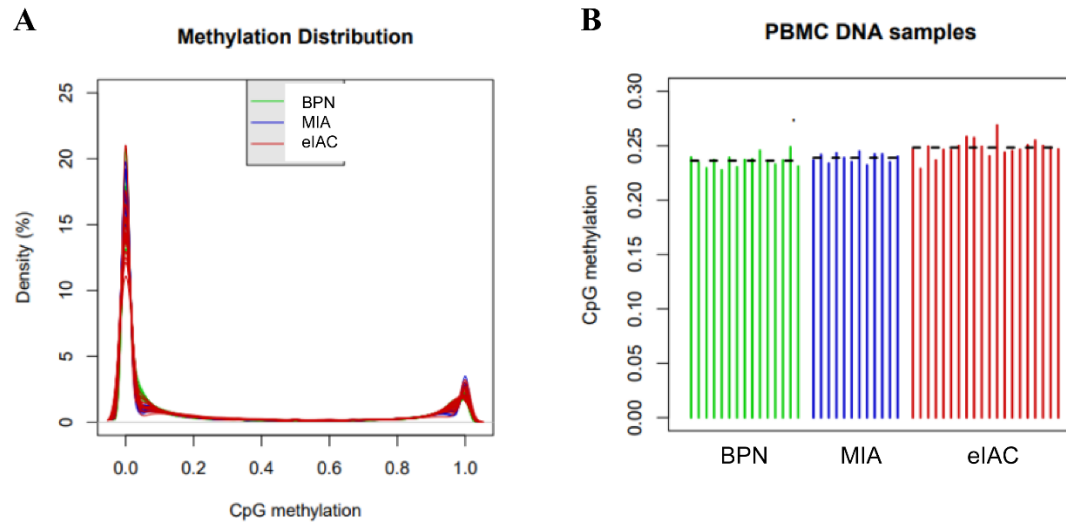


Supplementary Information

This Supplementary Information File includes:

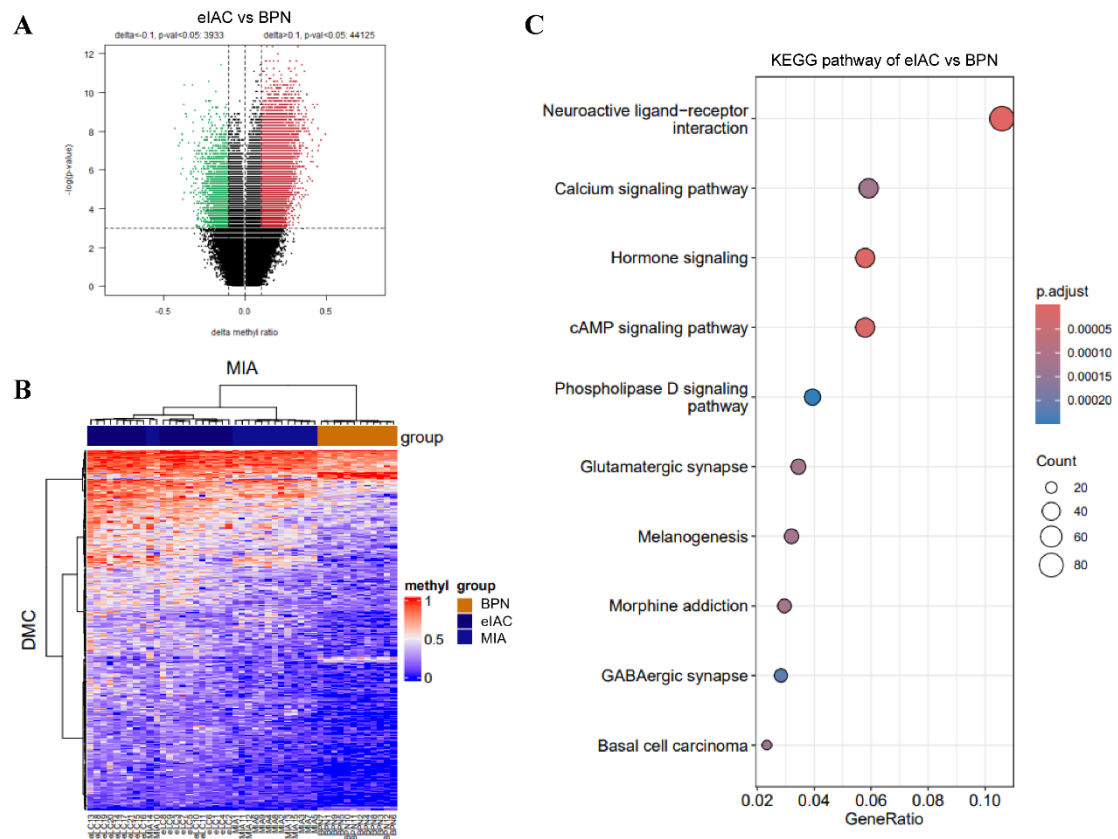
Supplementary Figures 1-7

Supplementary Tables 1-10



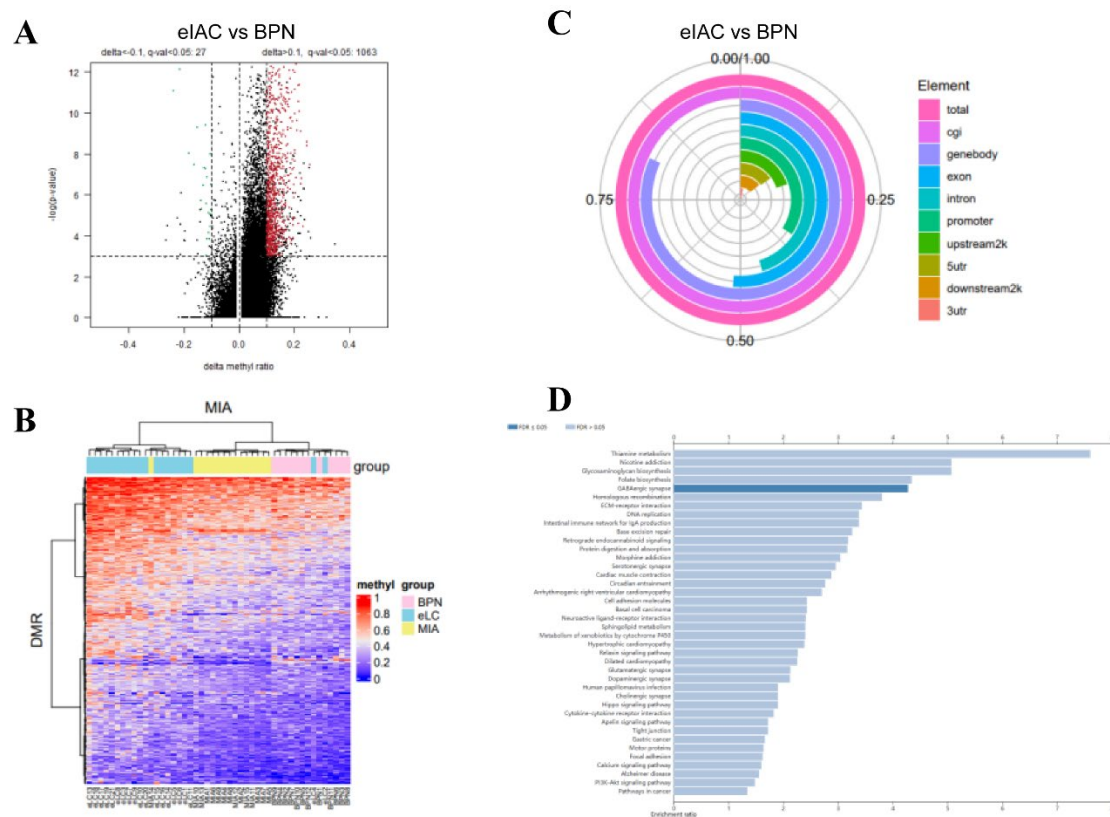
Supplementary Fig. 1 Genome-wide DNA methylation landscape in PBMCs across pulmonary nodule subtypes.

(A) Density curves of CpG methylation levels in PBMCs among the BPN, MIA, and eIAC groups. (B) Mean DNA methylation levels in PBMCs of the BPN, MIA, and eIAC groups.



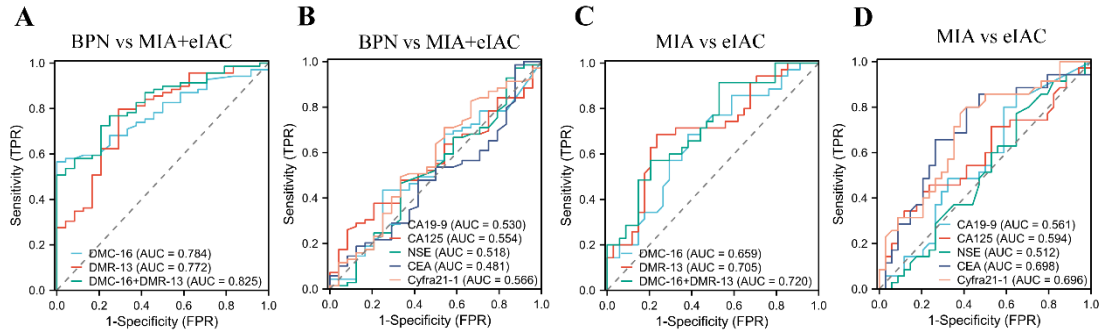
Supplementary Fig. 2 Identification of DMCs in eIAC versus BPN comparisons by Methylo-me-seq.

(A) Volcano plots presented DMCs in eIAC versus BPN comparisons. (B) Heatmaps presented DMCs in eIAC versus BPN comparisons. (C) KEGG analysis of the genes that were modified by DMCs identified in eIAC versus BPN comparisons.



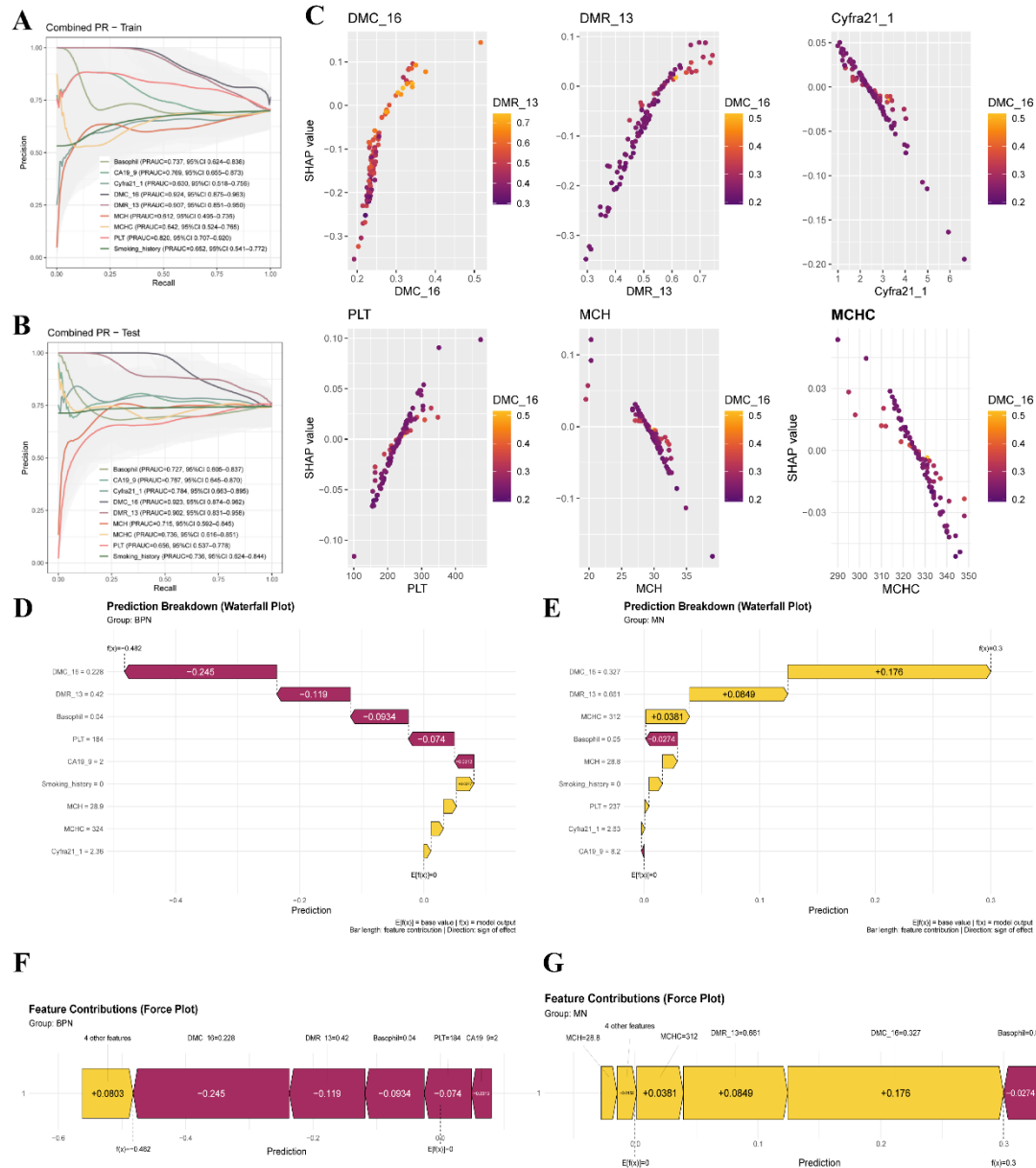
Supplementary Fig. 3 Identification of DMRs in eIAC versus BPN comparisons by Methylome-seq.

(A) Volcano plots presented DMRs in eIAC versus BPN comparisons. (B) Heatmaps presented DMRs in eIAC versus BPN comparisons. (C) Genomic distribution of DMRs identified in eIAC versus BPN comparisons. (D) KEGG analysis of the genes that were modified by DMRs identified in eIAC versus BPN comparisons.



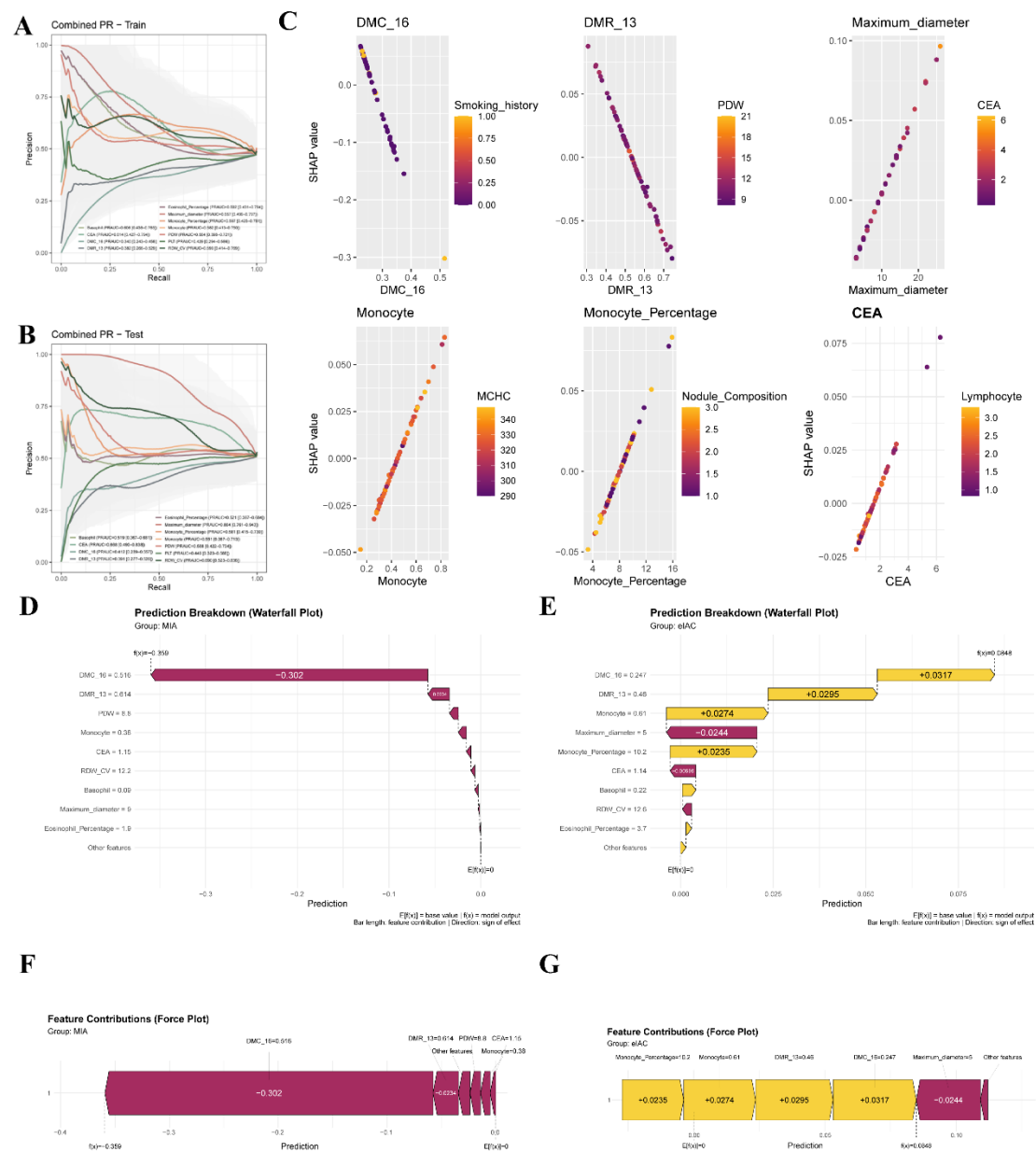
Supplementary Fig. 4 ROC of various biomarkers in the Test cohort.

(A) ROC curves to identify MIA from BPN and eIAC patients using PBMCs DNA methylation signatures in the Test cohort. (B) ROC curves to identify MIA from BPN and eIAC patients using conventional serum tumor biomarkers in the Test cohort. (C) ROC curves to identify MIA from BPN patients using PBMCs DNA methylation signatures in the Test cohort. (D) ROC curves to identify MIA from eIAC patients using conventional serum tumor biomarkers in the Test cohort.



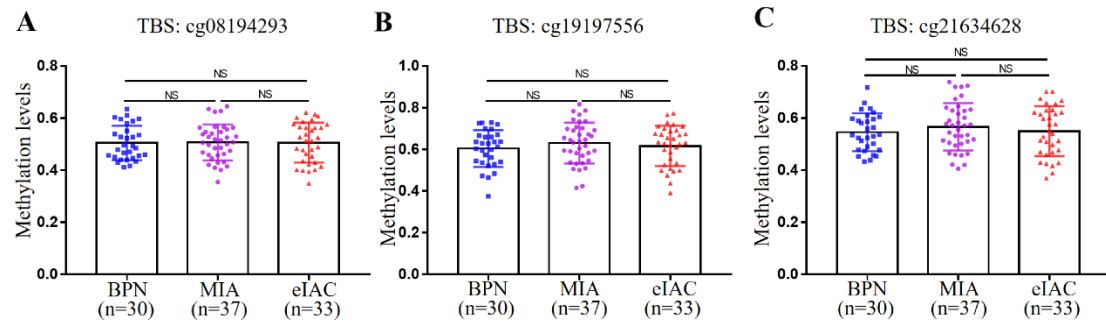
Supplementary Fig. 5 Supplementary information for SurgMalig model.

(A-B) PR curves performance of SurgMalig model with different features in the Train cohort (A) and Test cohort (B). (C) Scatter plot of SHAP values for each feature in the SurgMalig model. (D-E) Waterfal plot for one BPN (D) patient and one MN (E) patient in the SurgMaligmodel. (F-G) Force plot for one BPN (F) patient and one MN (G) patient in the SurgMaligmodel.



Supplementary Fig. 6 Supplementary information for ResectGuide model.

(A-B) PR curves Performance of ResectGuide model with different features in the Train cohort (A) and Test cohort (B). (C) Scatter plot of SHAP values for each feature in the ResectGuide model. (D-E) Waterfal plot for one MIA (D) patient and one IAC (E) patient in the ResectGuide model. (F-G) Force plot for one MIA (F) patient and one IAC (G) patient in the ResectGuide model.



Supplementary Fig. 7 Detection of DMCs targets screened by other study.

(A-C) TBS results of cg08194293 (A), cg19197556 (B) and cg21634628 (C) in the train cohort. Data are shown as mean $\pm$ SD; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; NS, no significance. P values were determined by a two-sided Mann-Whitney U test.

Supplementary Table 1. Clinicopathological characteristics of participants in the Discovery cohort.

Characteristics	BPN (n=12)	MIA (n=15)	eIAC (n=20)	<i>P</i> value ^a	<i>P</i> value ^b	<i>P</i> value ^c
Age, y, mean ± SD	46.5±8.2	43.3±11.2	49.7±11.4	0.408	0.108	0.414
Gender, n (%)						
Male	9 (75.0)	9 (60.0)	14 (70.0)	0.411	0.538	0.760
Female	3 (25.0)	6 (40.0)	6 (30.0)			
Smoking history, n (%)						
Never	9 (75.0)	13 (86.7)	12 (60.0)	0.438	0.084	0.387
Ever/current	3 (25.0)	2 (13.3)	8 (40.0)			
Size (mm), n (%)						
<10	6 (50.0)	10 (66.7)	9 (45.0)	0.381	0.203	0.784
≥10	6 (50.0)	5 (33.3)	11 (55.0)			
Type, n (%)						
Solid	0 (0.0)	3 (20.0)	6 (30.0)	0.115	0.245	0.106
Part-solid	9 (75.0)	6 (40.0)	11 (55.0)			
Ground-glass	3 (25.0)	6 (40.0)	3 (15.0)			
Clinical stage, n (%)						
IA1	-	15 (100.0)	0 (0.0)	-	-	-
IA2	-	-	10 (50.0)			
IA3	-	-	2 (10.0)			
IB	-	-	6 (30.0)			
II	-	-	2 (10.0)			

P value^a was calculated between MIA versus BPN group

P value^b was calculated between MIA versus eIAC group

P value^c was calculated between BPN versus eIAC group

P values were determined by Chi-Square test.

Supplementary Table 2. Clinicopathological characteristics of participants in the Train cohort.

Characteristics	BPN (n=30)	MIA (n=37)	eIAC (n=33)	<i>P</i> value ^a	<i>P</i> value ^b	<i>P</i> value ^c
Age, y, mean ± SD	51.4±11.7	49.9±11.6	51.5±12.0	0.606	0.573	0.969
Gender, n (%)						
Male	13 (43.3)	12 (32.4)	14 (42.4)	0.359	0.388	0.944
Female	17 (56.7)	25 (67.6)	19 (57.6)			
Smoking history, n (%)						
Never	21 (70.0)	33 (89.2)	27 (81.8)	0.131	0.790	0.234
Ever/current	7 (30.0)	4 (10.8)	4 (12.1)			
Size (mm), n (%)						
<10	15 (50.0)	27 (73.0)	17 (51.5)	0.053	0.064	0.906
≥10	15 (50.0)	10 (27.0)	16 (48.5)			
Type, n (%)						
Solid	11 (36.7)	9 (24.3)	11 (33.3)	0.016	0.271	0.382
Part-solid	15 (50.0)	11 (29.7)	13 (39.4)			
Ground-glass	4 (13.3)	17 (46.0)	9 (27.3)			
Clinical stage, n (%)						
IA1	-	37 (100.0)	11 (13.1)	-	-	-
IA2	-	-	11 (13.1)			
IA3	-	-	48 (57.1)			
IB	-	-	14 (16.7)			
Monocyte, 10 ⁹ /L, mean ± SD	1.93±0.62	1.97±0.54	1.89±0.56	0.794	0.569	0.796
Lymphocyte, 10 ⁹ /L, mean ± SD	0.43±0.14	0.42±0.14	0.48±0.13	0.867	0.097	0.157

P value^a was calculated between MIA versus BPN group

P value^b was calculated between MIA versus eIAC group

P value^c was calculated between BPN versus eIAC group

P values of Monocyte and Lymphocyte were determined by a two-sided Mann–Whitney U test, others indicators *P* values were determined by Chi-Square test.

Supplementary Table 3. Clinicopathological characteristics of participants in the Test cohort.

Characteristics	BPN (n=24)	MIA (n=34)	eIAC (n=35)	<i>P</i> value ^a	<i>P</i> value ^b	<i>P</i> value ^c
Age, y, mean ± SD	52.0±15.5	48.2±11.9	52.4±12.9	0.304	0.169	0.906
Gender, n (%)						
Male	10 (41.7)	10 (29.4)	11 (31.4)	0.334	0.856	0.420
Female	14 (58.3)	24 (70.6)	24 (68.6)			
Smoking history, n (%)						
Never	19 (79.2)	30 (88.2)	30 (85.7)	0.347	0.755	0.510
Ever/current	5 (20.8)	4 (11.8)	5 (14.3)			
Size (mm), n (%)						
<10	12 (50.0)	23 (67.6)	10 (28.6)	0.176	0.001	0.095
≥10	12 (50.0)	11 (32.4)	25 (71.4)			
Type, n (%)						
Solid	8 (33.3)	5 (14.7)	8 (22.9)	0.095	0.401	0.593
Part-solid	9 (37.5)	10 (29.4)	13 (37.1)			
Ground-glass	7 (29.2)	19 (55.9)	14 (40.0)			
Clinical stage, n (%)						
IA1	-	34 (100.0)	10 (28.6)	-	-	-
IA2	-	-	18 (51.4)			
IA3	-	-	5 (14.3)			
IB	-	-	2(5.7)			
II	-	-	0 (0.0)			
Monocyte, 10 ⁹ /L, mean ± SD	1.93±0.42	1.92±0.50	1.97±0.88	0.988	0.806	0.830
Lymphocyte, 10 ⁹ /L, mean ± SD	0.43±0.12	0.46±0.14	0.46±0.17	0.429	0.433	0.994

P value^a was calculated between MIA versus BPN group

P value^b was calculated between MIA versus eIAC group

P value^c was calculated between BPN versus eIAC group

P values of Monocyte and Lymphocyte were determined by a two-sided Mann–Whitney U test, others indicators *P* values were determined by Chi-Square test.

Supplementary Table 4. Distribution of methylation in each sample via Methylome-seq.

Sample	Total_CpG	Covered_CpG	Mean	SD	Min	Q25	Median	Q75	Max
MIA1	4045187	3572606	0.197	0.335	0.000	0.000	0.000	0.200	1.000
MIA2	4045187	3654069	0.190	0.338	0.000	0.000	0.000	0.167	1.000
MIA3	4045187	3736469	0.176	0.330	0.000	0.000	0.000	0.118	1.000
MIA4	4045187	3667590	0.191	0.334	0.000	0.000	0.000	0.182	1.000
MIA5	4045187	3714595	0.182	0.334	0.000	0.000	0.000	0.133	1.000
MIA6	4045187	3858454	0.191	0.332	0.000	0.000	0.000	0.174	1.000
MIA7	4045187	3792178	0.176	0.331	0.000	0.000	0.000	0.111	1.000
MIA8	4045187	3570393	0.196	0.337	0.000	0.000	0.000	0.200	1.000
MIA9	4045187	3589043	0.195	0.336	0.000	0.000	0.000	0.200	1.000
MIA10	4045187	3627047	0.196	0.333	0.000	0.000	0.000	0.200	1.000
MIA11	4045187	3565021	0.186	0.336	0.000	0.000	0.000	0.154	1.000
MIA12	4045187	3474090	0.186	0.334	0.000	0.000	0.000	0.167	1.000
MIA13	4045187	3718303	0.182	0.334	0.000	0.000	0.000	0.143	1.000
MIA14	4045187	3795734	0.199	0.335	0.000	0.000	0.000	0.217	1.000
MIA15	4045187	3933375	0.180	0.329	0.000	0.000	0.000	0.135	1.000
BPN1	4045187	3236717	0.206	0.348	0.000	0.000	0.000	0.233	1.000
BPN2	4045187	3127152	0.207	0.354	0.000	0.000	0.000	0.214	1.000
BPN3	4045187	3064564	0.203	0.353	0.000	0.000	0.000	0.200	1.000
BPN4	4045187	2819770	0.234	0.367	0.000	0.000	0.000	0.375	1.000
BPN5	4045187	2889591	0.211	0.357	0.000	0.000	0.000	0.231	1.000
BPN6	4045187	2956162	0.211	0.358	0.000	0.000	0.000	0.250	1.000
BPN7	4045187	2990718	0.219	0.357	0.000	0.000	0.000	0.273	1.000
BPN8	4045187	3103165	0.197	0.349	0.000	0.000	0.000	0.174	1.000
BPN9	4045187	2423166	0.248	0.383	0.000	0.000	0.000	0.433	1.000
BPN10	4045187	2920915	0.218	0.358	0.000	0.000	0.000	0.267	1.000
BPN11	4045187	3206466	0.194	0.348	0.000	0.000	0.000	0.167	1.000
BPN12	4045187	2690200	0.221	0.361	0.000	0.000	0.000	0.286	1.000
eIAC1	4045187	3418758	0.205	0.344	0.000	0.000	0.000	0.222	1.000
eIAC2	4045187	3285766	0.189	0.343	0.000	0.000	0.000	0.150	1.000
eIAC3	4045187	1927958	0.320	0.408	0.000	0.000	0.032	0.800	1.000
eIAC4	4045187	3520666	0.198	0.341	0.000	0.000	0.000	0.200	1.000
eIAC5	4045187	2577145	0.250	0.377	0.000	0.000	0.000	0.455	1.000
eIAC6	4045187	3238703	0.220	0.352	0.000	0.000	0.000	0.300	1.000
eIAC7	4045187	1866648	0.344	0.412	0.000	0.000	0.077	0.833	1.000
eIAC8	4045187	2638062	0.276	0.382	0.000	0.000	0.000	0.593	1.000
eIAC9	4045187	2747033	0.268	0.376	0.000	0.000	0.000	0.536	1.000
eIAC10	4045187	2859884	0.232	0.366	0.000	0.000	0.000	0.333	1.000
eIAC11	4045187	3034035	0.206	0.351	0.000	0.000	0.000	0.214	1.000
eIAC13	4045187	3144845	0.248	0.363	0.000	0.000	0.000	0.409	1.000
eIAC14	4045187	3389529	0.211	0.350	0.000	0.000	0.000	0.250	1.000
eIAC15	4045187	3355099	0.204	0.352	0.000	0.000	0.000	0.200	1.000

eIAC16	4045187	3667679	0.196	0.342	0.000	0.000	0.000	0.176	1.000
eIAC17	4045187	3244644	0.217	0.358	0.000	0.000	0.000	0.250	1.000
eIAC18	4045187	3132295	0.239	0.365	0.000	0.000	0.000	0.389	1.000
eIAC19	4045187	2896521	0.239	0.370	0.000	0.000	0.000	0.375	1.000
eIAC20	4045187	2614352	0.214	0.361	0.000	0.000	0.000	0.280	1.000
eIAC21	4045187	3015652	0.228	0.366	0.000	0.000	0.000	0.303	1.000

Supplementary Table 5. Methylation of common 21 DMCs across groups via Methylome-seq.

ID	Alternative name	Chromosome	Start	End	MIA	BPN	eIAC
chr1_31586928_31586929	DMC-1	chr1	31586928	31586929	0.627	0.977	0.867
chr1_45803745_45803746	DMC-2	chr1	45803745	45803746	0.254	0.553	0.714
chr1_45803756_45803757	DMC-3	chr1	45803756	45803757	0.277	0.596	0.749
chr2_91442251_91442252	DMC-4	chr2	91442251	91442252	0.201	0.553	0.414
chr2_11466249_8_114662499	DMC-5	chr2	114662498	114662499	0.198	0.700	0.407
chr7_94656502_94656503	DMC-6	chr7	94656502	94656503	0.618	0.966	0.791
chr7_94656523_94656524	DMC-7	chr7	94656523	94656524	0.645	0.932	0.805
chr8_64369557_64369558	DMC-8	chr8	64369557	64369558	0.407	0.055	0.239
chr8_14009865_8_140098659	DMC-9	chr8	140098658	140098659	0.598	0.978	0.835
chr8_14120931_0_141209311	DMC-10	chr8	141209310	141209311	0.875	0.175	0.541
chr9_13728096_4_137280965	DMC-11	chr9	137280964	137280965	0.424	0.893	0.696
chr10_8035282_8035283	DMC-12	chr10	8035282	8035283	0.423	0.859	0.590
chr11_396999_397000	DMC-13	chr11	396999	397000	0.323	0.913	0.631
chr12_1029563_17_102956318	DMC-14	chr12	102956317	102956318	0.290	0.696	0.500
chr14_6128010_3_61280104	DMC-15	chr14	61280103	61280104	0.366	0.932	0.647
chr17_3404033_7_34040338	DMC-16	chr17	34040337	34040338	0.959	0.711	0.855
chr18_8014747_1_80147472	DMC-17	chr18	80147471	80147472	0.736	0.986	0.858
chr19_1632666_4_16326665	DMC-18	chr19	16326664	16326665	0.546	0.994	0.813
chr20_5358175_3_53581754	DMC-19	chr20	53581753	53581754	0.530	0.949	0.777
chr20_5358186_0_53581861	DMC-20	chr20	53581860	53581861	0.254	0.706	0.503

chr22_4606128	DMC-21	chr22	46061284	46061285	0.690	0.955	0.826
4_46061285							

Supplementary Table 6. Methylation of common 35 DMRs across groups via Methylome-seq.

ID	Alternative name	Chromosome	Start	End	MIA	BPN	eIAC
chr1_54356350_54356400	DMR-1	chr1	54356350	54356400	0.420	0.067	0.225
chr1_67134700_67134750	DMR-2	chr1	67134700	67134750	0.363	0.107	0.260
chr1_121395950_121396000	DMR-3	chr1	121395950	121396000	0.311	0.577	0.456
chr1_121396150_121396200	DMR-4	chr1	121396150	121396200	0.108	0.360	0.256
chr1_144323100_144323150	DMR-5	chr1	144323100	144323150	0.340	0.611	0.503
chr1_144323900_144323950	DMR-6	chr1	144323900	144323950	0.111	0.382	0.280
chr1_144642550_144642600	DMR-7	chr1	144642550	144642600	0.131	0.375	0.253
chr1_227887700_227887750	DMR-8	chr1	227887700	227887750	0.394	0.139	0.279
chr1_235651000_235651050	DMR-9	chr1	235651000	235651050	0.461	0.216	0.361
chr11_397200_397250	DMR-10	chr11	397200	397250	0.607	0.827	0.722
chr11_46347650_46347700	DMR-11	chr11	46347650	46347700	0.356	0.484	0.611
chr11_65786300_65786350	DMR-12	chr11	65786300	65786350	0.579	0.304	0.445
chr12_49389200_49389250	DMR-13	chr12	49389200	49389250	0.626	0.335	0.479
chr12_49389350_49389400	DMR-14	chr12	49389350	49389400	0.791	0.503	0.674
chr12_49389250_49389300	DMR-15	chr12	49389250	49389300	0.716	0.416	0.588
chr12_102956300_102956350	DMR-16	chr12	102956300	102956350	0.258	0.532	0.422
chr14_100826550_100826600	DMR-17	chr14	100826550	100826600	0.591	0.225	0.457
chr14_105529850_105529900	DMR-18	chr14	105529850	105529900	0.389	0.504	0.634
chr16_3443100_3443150	DMR-19	chr16	3443100	3443150	0.624	0.162	0.389
chr16_22536200_22536250	DMR-20	chr16	22536200	22536250	0.788	0.289	0.547

chr16_3156960 0_31569650	DMR-21	chr16	31569600	31569650	0.074	0.484	0.358
chr17_7885200 _7885250	DMR-22	chr17	7885200	7885250	0.364	0.626	0.729
chr17_3282260 0_32822650	DMR-23	chr17	32822600	32822650	0.180	0.324	0.425
chr17_4435390 0_44353950	DMR-24	chr17	44353900	44353950	0.109	0.221	0.351
chr17_4435395 0_44354000	DMR-25	chr17	44353950	44354000	0.142	0.295	0.494
chr17_4435405 0_44354100	DMR-26	chr17	44354050	44354100	0.162	0.313	0.469
chr17_4435410 0_44354150	DMR-27	chr17	44354100	44354150	0.143	0.250	0.427
chr17_7804090 0_78040950	DMR-28	chr17	78040900	78040950	0.402	0.653	0.538
chr17_7804100 0_78041050	DMR-29	chr17	78041000	78041050	0.521	0.788	0.668
chr18_5532190 0_55321950	DMR-30	chr18	55321900	55321950	0.050	0.394	0.258
chr18_8014740 0_80147450	DMR-31	chr18	80147400	80147450	0.572	0.904	0.785
chr19_1466000 _1466050	DMR-32	chr19	1466000	1466050	0.283	0.403	0.536
chr19_1911070 0_19110750	DMR-33	chr19	19110700	19110750	0.248	0.391	0.517
chr19_2921305 0_29213100	DMR-34	chr19	29213050	29213100	0.153	0.277	0.611
chr19_2921300 0_29213050	DMR-35	chr19	29213000	29213050	0.209	0.436	0.704

Supplementary Table 7. Primer sequence of DMCs and DMRs for TBS.

Target	Forward Primer Sequence (5' to 3')	Reverse Primer Sequence (5' to 3')
DMC-1	GTTTAGTTTGGGGYGAGAGGGTTAT	TCAATAATAACCCATATCCTCCATAC
DMC-2	GTTTTTTTYGTGAGGAGYGTAGAGGA	TAACCRAACRAACTCCCTAAACCACC
DMC-3	GTTTTTTTYGTGAGGAGYGTAGAGGA	TAACCRAACRAACTCCCTAAACCACC
DMC-4	GTGYGTTTTTTTGGGGATTTTGT	CRCCRAAAACCAAAATCATAAAAAACC
DMC-5	GGAGTTGTAGAGAAGTTTTATTTTGT	CTTCATTTCCRAAACTAAATCTCTAAAC
DMC-6	TTGAGGAGAATAGYGGAGAAGGTTTA	CATACTCACCACRCRAAACTCCTCT
DMC-7	TTGAGGAGAATAGYGGAGAAGGTTTA	CATACTCACCACRCRAAACTCCTCT
DMC-9	AGTTAGTTTTAGTGTATGGTTTATAGTA	CACTAAACCTAACTAATATCRTCCTCTAC
DMC-10	ATGGYTTTTGTAGATAAGATAGTTGT	CCCCTCCCCTACACTAAATTTATTC
DMC-11	GGGAAGGTGTTTTGGGYGTTTTTGYGTTATGTT	AAACTACCRAATACRTCCCAAACACC
DMC-12	GTTATTAAGTTTTGYGTAGTAGAGTTGG	TACTCTATATTAATAAAAAATTACCTTAAATATC AC
DMC-13	GTGYTTGGGTAYGGGGTGTTTAGTTTA	ATCATAATCRACCCRACTCCCAACCC
DMC-14	TAAAGAGATGGGGTTTATTGTTGGT	TACCCAAACRTCTTCCTAAACCTTC
DMC-15	AGAAGTAGGAGGGATTTTGGAAAGT	ATAACAAAAACCCCTTCCTAAACATC
DMC-16	GGAATYTTGGTGTTTAGGATTTGT	CCCCTACCTCCCAACCRACAAATCT
DMC-17	GTTTGTTTTTAGTTGGTATAAGTTGTTAAG	AACTACTAACTACRCTACCATTATAAAC
DMC-18	AATGTTGGAGAGAGGGTGTATGTTTA	TTACCCTACATCCCCAACTCCCCCA
DMC-19	GTGYTATTYGGAGTAGTGAGTGGGT	CTTCCAAACTTAACAATACTACCA
DMC-20	GTGYTATTYGGAGTAGTGAGTGGGT	CTTCCAAACTTAACAATACTACCA
DMC-21	TATYGGGAYGGGTAGAATTTTTTAAATG	CCRCTCTACCRAAAAACTAAAACTC
DMR-1	GGGTGAAAGTTTATAGTTGAATAAATAG	ATTCCCATCTCCTTTACAACCTCTAC
DMR-2	AAGTTTATTAATATTTAGTTTAGAAGATGTAAAGG	TTTACATAAACRACCTTTCTATCCCC
DMR-3	GAGTTAAGTTTATTTATATTTTGTGTTTGGTTG	CCTAACRCCRAAAAAACACAAAACAAC
DMR-5	AGGGTTTTAGTTYGTTTYGGTTTTTGA	AAACAAAAAATAATCCACRACRAAAAAA ACC
DMR-6	TAGTTTTTGTATATTYGTGTTTTGGTTTTTGT	ACRAAAAAATCRCTATAACAAAAAACAAAA ACC
DMR-7	GTAAAAGTYGTGGYGAGTAAAAAGT	ACACACTCRCCRCCTTAACCTTTTAC
DMR-8	GTTTTTTTGGGGYGTTTAGGAAGGG	CTACCCAAACTCRACTTCRAAATCTTA
DMR-9	GGTAAGATTTGTAGAAAAGGAGGTTA	CAAAAATCTAAACAACAAACRCCCTATATC
DMR-10	TTTAGTTTTAGTYGGGTAGGGGGGT	TAACCTCAAAAACRACCCCRACACTACC
DMR-12	GTTTATTGGTTAAGATAYGGGGGTTT	AAATCCCAAAACTTAACATAACAACCTC
DMR-13	GTTTAAAGTTGGAAGGATTTYGTTTAGTT	CTAATCTACCTCCTCAATTAACAAAC
DMR-14	GTTTAAAGTTGGAAGGATTTYGTTTAGTT	CTAATCTACCTCCTCAATTAACAAAC
DMR-15	GTTTAAAGTTGGAAGGATTTYGTTTAGTT	CTAATCTACCTCCTCAATTAACAAAC
DMR-16	TAAAGAGATGGGGTTTATTGTTTGGT	TACCCAAACRTCTTCCTAAACCTTC
DMR-17	AAGGGTGGGTGGGTGGTAGGGATTT	CCTAATTCATAAAACACRAAAAAACATC
DMR-18	TTTTGGGGYGTAGAGATATYGGGTGGT	CCCAAAACACRAAACTCRAAACACCTAT
DMR-19	GTTTAGGAGTATTTTATTATAATAGGTATGTTTA	ATCCCTTAAAAACTATTCTCTCCCC
DMR-20	TGAGATGGAATTATTTTYGAATTAAGAGG	CTCCRCCTCTTAAATTCRAATAATAAATTC

DMR-21	GAGGGTGGTGGTGATGATGGTGGTTT	AAAAACAATAAAATCRAACRAAAAACCCAAAA AAC
DMR-26	GTGYGGTTTTYGTGTTGTTGGGTTT	CAACCTAAACTCRAACRTAAATATCCAC
DMR-27	GTGYGGTTTTYGTGTTGTTGGGTTT	CAACCTAAACTCRAACRTAAATATCCAC
DMR-28	TTTGGAGTAGAAAGGGTATTGTTTAG	CACCTCRCRTACACAACCTACCTCTAC
DMR-29	TTTGGAGTAGAAAGGGTATTGTTTAG	CACCTCRCRTACACAACCTACCTCTAC
DMR-30	ATATGTAAAGTAGGAAGAGATTATTTTGG	CATTATTCRAAAAACTAATAAAAAACCCCTC
DMR-31	GTTTGTTTTTTAGTTGGTATAAGTTGTTAAG	AACTACTAACTACRCTACCATTATAAAC
DMR-32	TAGTTTGGGAGATTYGGGATAGGAGG	CTACCRCTATTAAAACTATCRTTAAAAAACTA AC
DMR-33	GGTAGTTTTATTTTTTYGAGYGATGATT	CCAATTCATACTCAAACCTTTATAAAAAAC
DMR-34	TYGGTTGAGGAAGGGTYGTTTtaggt	TCCCTATAACCRACCTTAACRATTAAAAAC
DMR-35	TYGGTTGAGGAAGGGTYGTTTtaggt	TCCCTATAACCRACCTTAACRATTAAAAAC

Supplementary Table 8. The sensitivity and specificity of various biomarkers in the Train cohort.

Distinction	Biomarker	Sensitivity	Specificity	PPV	NPV	Cutoff	AUC	95% CI
BPN vs MIA+elAC	DMC-16	0.933	0.543	0.950	0.467	0.245	0.830	0.749 – 0.911
	DMR-13	0.933	0.543	0.950	0.467	0.519	0.775	0.686 – 0.865
	DMC-16+DMR-13	0.867	0.671	0.922	0.531	0.770	0.853	0.778 – 0.928
	CA19-9	0.933	0.286	0.909	0.359	13.350	0.556	0.441 – 0.672
	CA125	0.600	0.557	0.765	0.367	9.070	0.538	0.413 – 0.663
	NSE	0.600	0.500	0.745	0.340	11.750	0.510	0.386 – 0.635
	CEA	0.533	0.657	0.767	0.400	1.125	0.534	0.396 – 0.672
	Cyfra21-1	0.967	0.271	0.950	0.363	1.675	0.614	0.495 – 0.733
MIA vs elAC	DMC-16	0.970	0.459	0.944	0.615	0.280	0.744	0.630 – 0.859
	DMR-13	0.727	0.595	0.710	0.615	0.542	0.666	0.538 – 0.794
	DMC-16+DMR-13	0.970	0.459	0.944	0.615	0.998	0.753	0.640 – 0.866
	CA19-9	0.545	0.514	0.559	0.500	8.050	0.475	0.337 – 0.612
	CA125	0.545	0.730	0.643	0.643	7.840	0.564	0.423 – 0.705
	NSE	0.394	0.730	0.574	0.565	10.150	0.526	0.388 – 0.664
	CEA	0.485	0.838	0.646	0.727	1.695	0.624	0.489 – 0.760
	Cyfra21-1	0.879	0.270	0.714	0.518	3.105	0.520	0.382 – 0.657

Supplementary Table 9. The sensitivity and specificity of various biomarkers in the Test cohort.

Distinction	Biomarker	Sensitivity	Specificity	PPV	NPV	Cutoff	AUC	95% CI
BPN vs MIA+elAC	DMC-16	0.565	1.000	1.000	0.444	0.345	0.784	0.692 – 0.875
	DMR-13	0.797	0.708	0.887	0.548	0.612	0.772	0.662 – 0.883
	DMC-16+DMR-13	0.768	0.750	0.898	0.529	0.700	0.825	0.740 – 0.911
	CA19-9	0.435	0.750	0.833	0.316	11.500	0.530	0.395 – 0.666
	CA125	0.261	0.917	0.900	0.301	15.400	0.554	0.429 – 0.680
	NSE	0.464	0.667	0.800	0.302	12.950	0.518	0.377 – 0.658
	CEA	0.986	0.125	0.767	0.750	0.385	0.481	0.346 – 0.615
	Cyfra21-1	0.710	0.458	0.790	0.355	1.935	0.566	0.427 – 0.705
MIA vs elAC	DMC-16	0.686	0.618	0.649	0.657	0.365	0.659	0.529 – 0.789
	DMR-13	0.686	0.765	0.750	0.703	0.664	0.705	0.580 – 0.831
	DMC-16+DMR-13	0.914	0.471	0.640	0.842	0.367	0.720	0.600 – 0.840
	CA19-9	0.314	0.912	0.583	0.667	5.600	0.561	0.422 – 0.699
	CA125	0.314	0.912	0.786	0.564	7.875	0.594	0.458 – 0.731
	NSE	0.771	0.353	0.551	0.600	10.700	0.512	0.372 – 0.651
	CEA	0.657	0.735	0.719	0.676	1.535	0.698	0.570 – 0.826
	Cyfra21-1	0.771	0.618	0.675	0.724	2.135	0.696	0.570 – 0.822

Supplementary Table 10. Performance of SurgMalig Model and ResectGuide Model in the Train and Test cohorts.

Model	Cohort	Algorithm	AUC	PRAUC	Accuracy	Classification Error	Sensitivity	Specificity	Precision	PPV	NPV	Recall	F1_Score
SurgMalig Model	Train	Lasso+S											
		tepglm[foward]	0.926	0.970	0.860	0.140	0.843	0.900	0.952	0.952	0.711	0.843	0.894
SurgMalig Model	Test	Lasso+S											
		tepglm[foward]	0.806	0.934	0.742	0.258	0.710	0.833	0.925	0.925	0.500	0.710	0.803
ResectGuide Model	Train	Enet[alpha=0.2]	0.862	0.881	0.814	0.186	0.636	0.973	0.955	0.955	0.750	0.636	0.764
ResectGuide Model	Test	Enet[alpha=0.2]	0.843	0.862	0.783	0.217	0.629	0.941	0.917	0.917	0.711	0.629	0.746