Predictive Markers for Brain Metastases in Lung Cancer

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Introduction

- Lung cancer - most common cause of brain metastases
- 30-50% of lung cancer patients will develop brain metastases
- Fifty per cent of lung cancer brain metastases occur at disease presentation
  - 50–60% as the only site of distant disease
  - Multiple lesions
  - One third of patients - solitary

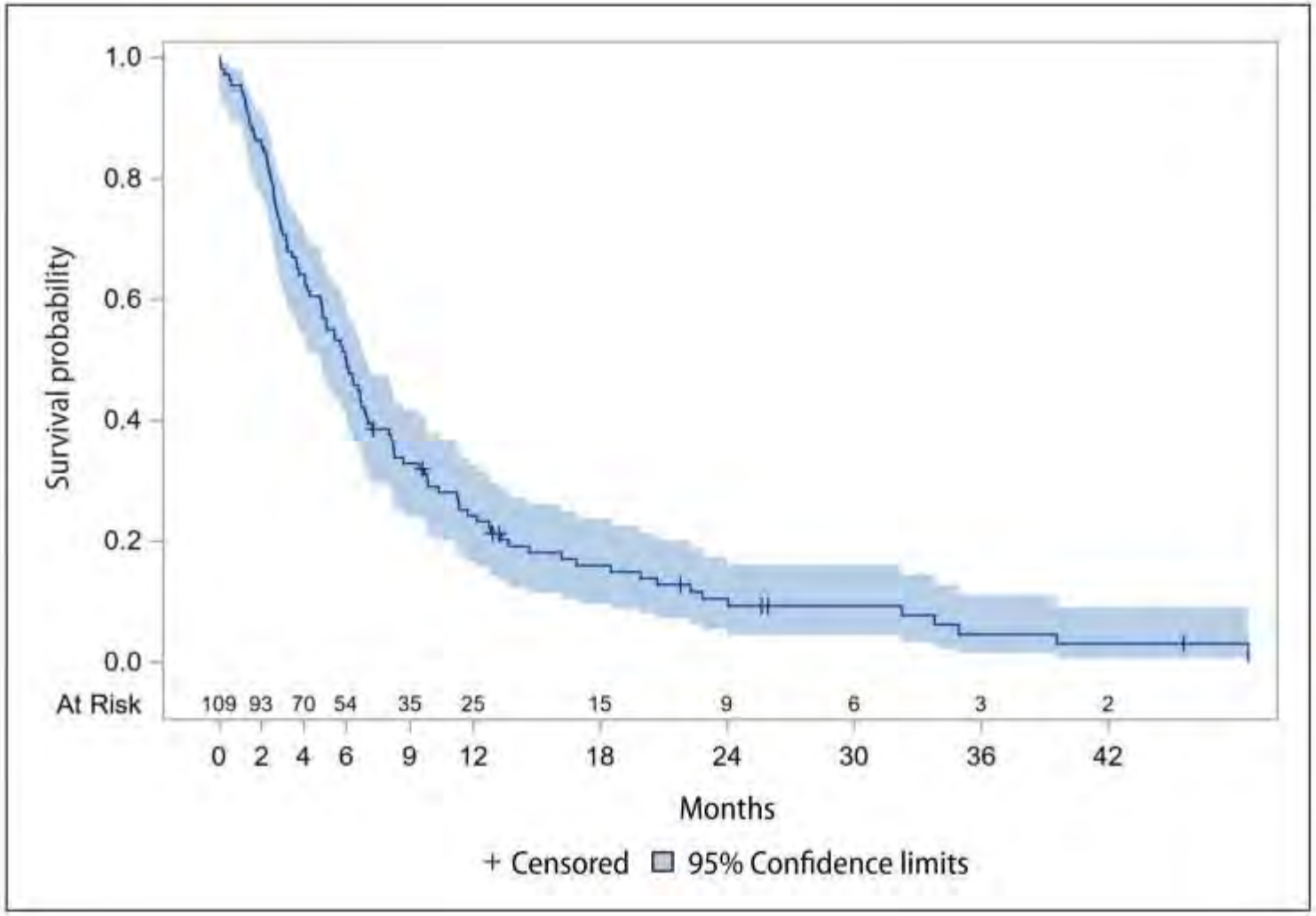
Preusser M. ESMO Open 2018;3:e000262.

Outcomes

- Poor prognosis
- Retrospective analysis of 109 patients with brain metastases treated with stereotactic radiation
- 1-2 brain lesions (94%)
- 50% - undetectable or controlled extracranial disease
- Median OS - 6.1 months.
- 12-month survival rate - 24%

Gunnarsson K. Rep Pract Oncol Radiother. 2022 Jul 29;27(3):410-418.

Outcomes



Gunnarsson K. Rep Pract Oncol Radiother. 2022 Jul 29;27(3):410-418.

Prognosis

- Graded Prognostic Assessment
- 1888 patients with NSCLC; 299 patients with SCLC

	0	0.5	1
Age (yrs)	>60	50-60	<50
KPS	<70	70–80	90–100
ECM	Present		Absent
No. of lesions	>3	2–3	1

Sperduto PW. Int J Radiat Oncol Biol Phys. 2010 Jul 1;77(3):655-61.

Prognosis

- Median survival (months) based on GPA

	Overall	0-1	1.5-2.5	3	3.5-4	P value
NSCLC	7.00 (6.53-7.50)	3.02 (2.6-3.84)	6.53 (5.90-7.10)	11.33 (9.43-13.10)	14.78 (11.79-18.80)	<.0001
SCLC	4.90 (4.30-6.20)	2.79 (2.04-3.12)	5.30 (4.63-6.83)	9.63 (7.50-14.95)	17.05 (6.10-27.43)	<.0001

Sperduto PW. Int J Radiat Oncol Biol Phys. 2010 Jul 1;77(3):655-61.

Economic Burden

- Retrospective analyses - US commercial administrative claims data - lung cancer registry and mortality records from the Social Security Administration Death Master File (2005-2010)
- 584 patients
  - Brain metastases (n=247)

Ganguli A. Value Health. 2011:14;A440-A441

Economic Burden

- Average health care costs following diagnosis of brain metastases - 23% higher ($184,872 vs. $150,931; p = 0.010)
  - 25% higher hospitalization costs $46,871 vs. $37,504; p.082);
  - 23% higher ambulatory costs, ($121,224 vs. $98,276; p0.033);
  - 23% higher retail pharmacy costs, ($13,282 vs. $10,774; p = 0.118).
- Patients with brain metastases
  - More hospitalizations (2.4 vs.1.9; p = 0.005),
  - ER visits (2.7 vs. 2.2; p = 0.067),
  - Ambulatory encounters (111 vs. 92; p = 0.005) from initial diagnosis

Ganguli A. Value Health. 2011:14;A440-A441

Pathogenesis

- Hematogenous spread
- Usually located at the junction of gray matter and white matter
- Distribution follows the relative rate and blood flow in each area
  - Cerebrum – 80%
  - Cerebellum – 15%
  - Brainstem – 5%

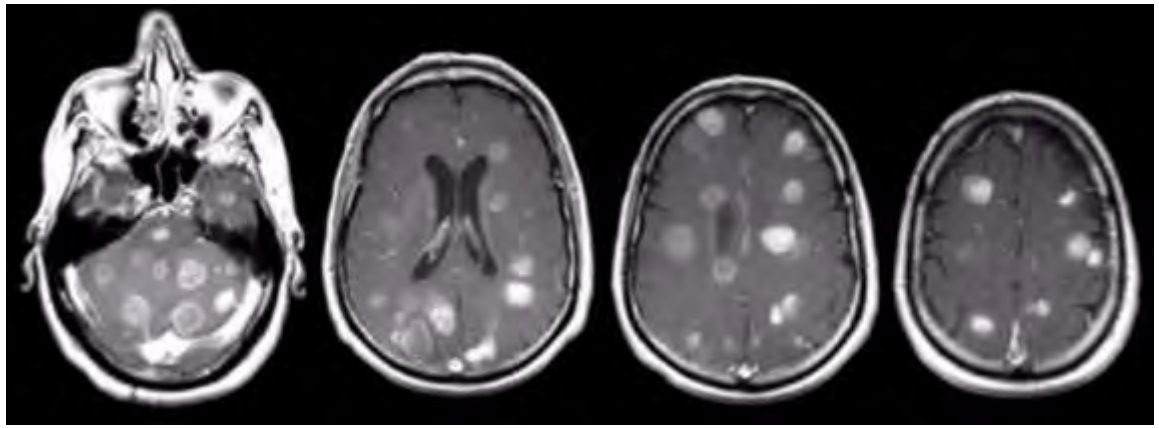
Loeffler JS. UpToDate. Last updated September 30, 2022

Clinical Features

- Headache – 40-50%
  - More common with multiple lesions, posterior fossa lesions
- Focal neurologic dysfunction – 20-40%
- Cognitive dysfunction – 30-35%
- Seizures – 10-20%
- Stroke-like symptoms – 5-10%

Loeffler JS. UpToDate. Last updated September 30, 2022

Imaging studies



Predictive factors for brain metastases

- Single institution study
- 975 patients following surgery for early-stage lung cancer
- Distant metastasis – 207 patients
  - Brain metastasis (n = 60)
  - Isolated brain metastasis (n = 26; 43%)
- 5-year actuarial risk of developing brain metastasis – 10%

Hubbs JL. Cancer 2010;116:5038–46.

Predictive factors for brain metastases

- Risk factors for developing brain metastasis on multivariate analysis
  - Younger age (hazard ratio, 1.03/year)
  - Larger tumor size (HR, 1.26/cm)
  - Lymphovascular space invasion(HR, 1.87)
  - Hilar lymph node involvement (HR, 1.18)

Hubbs JL. Cancer 2010;116:5038–46.

Predictive factors for brain metastases

- Meta-analysis of 43 studies
- Clinical factors
  - Female (OR =1.32, 95% CI: 1.17-1.49, P<0.00001)
  - Adenocarcinoma (OR =2.34, 95% CI: 1.76-3.11, P<0.00001)
  - Advanced stage (OR =1.48, 95% CI: 1.01-2.17, P=0.04);
  - EGFR mutation (OR =1.88, 95% CI: 1.26-2.80, P=0.002)
  - KRAS mutation (OR =2.99, 95% CI: 1.82-4.91, P<0.00001)

Chen S. Ann Palliat Med. 2021 Apr;10(4):3657-3672.

Predictive factors for brain metastases

- Serum biomarkers
  - CEA (WMD - 10.94; P<0.00001)
  - CA 19-9 (WMD - 20.23; P<0.0001)
  - Neuron-specific enolase (WMD – 9.66; P<0.00001)
  - CA 125 (WMD - 22.39; P=0.0005)
  - CYFRA 21-1 (WMD - 1.78; p=0.04)

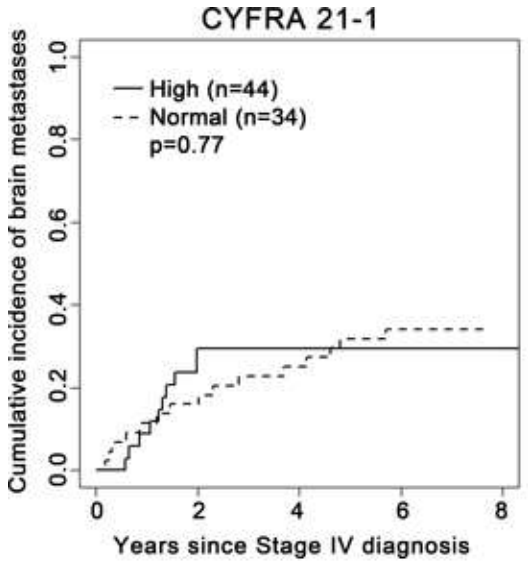
Chen S. Ann Palliat Med. 2021 Apr;10(4):3657-3672.

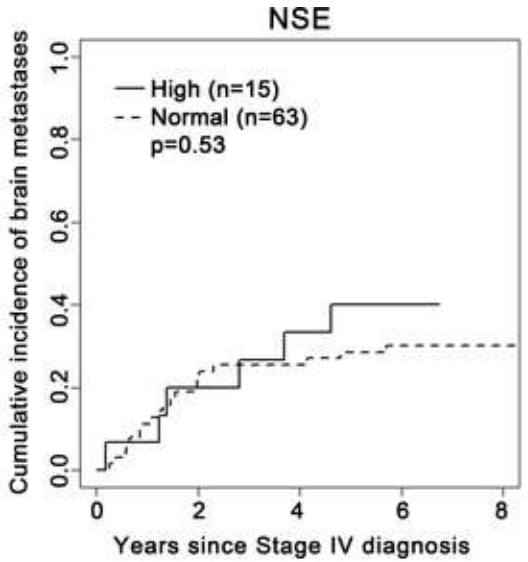
Predictive factors for brain metastases

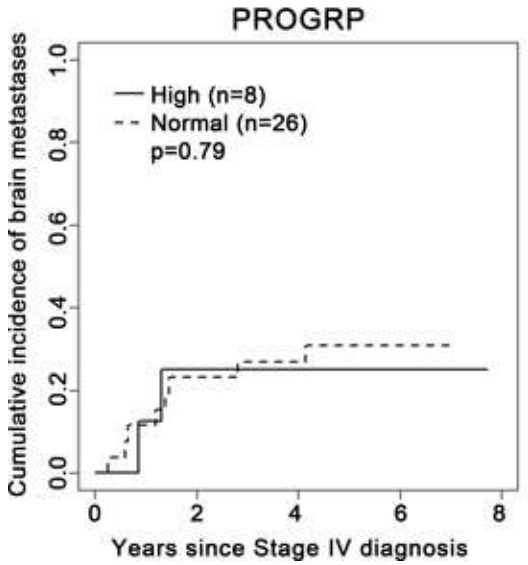
- Prospective single center study – stage IV NSCLC patients (n=118)
- Brain metastases (n=57; 48%)
  - Baseline (n=31; 26%)
  - Subsequent (n=26; 22%)
- Age <65 years - only clinical factor associated with brain metastasis at baseline (OR 3.00; p = 0.02)

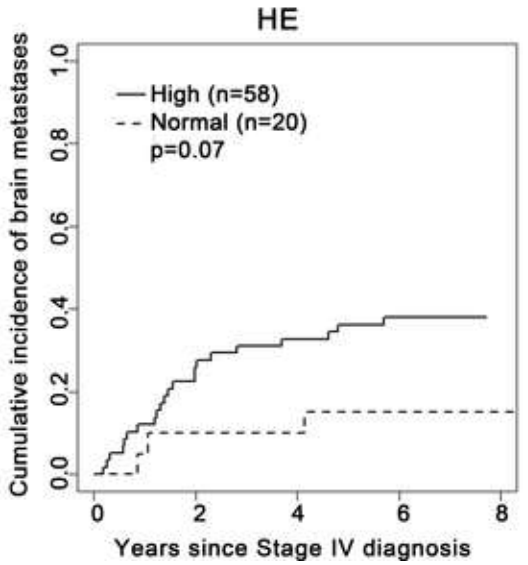
Li BT. PLoS ONE 11(1): e0146063.

Predictive factors for brain metastases









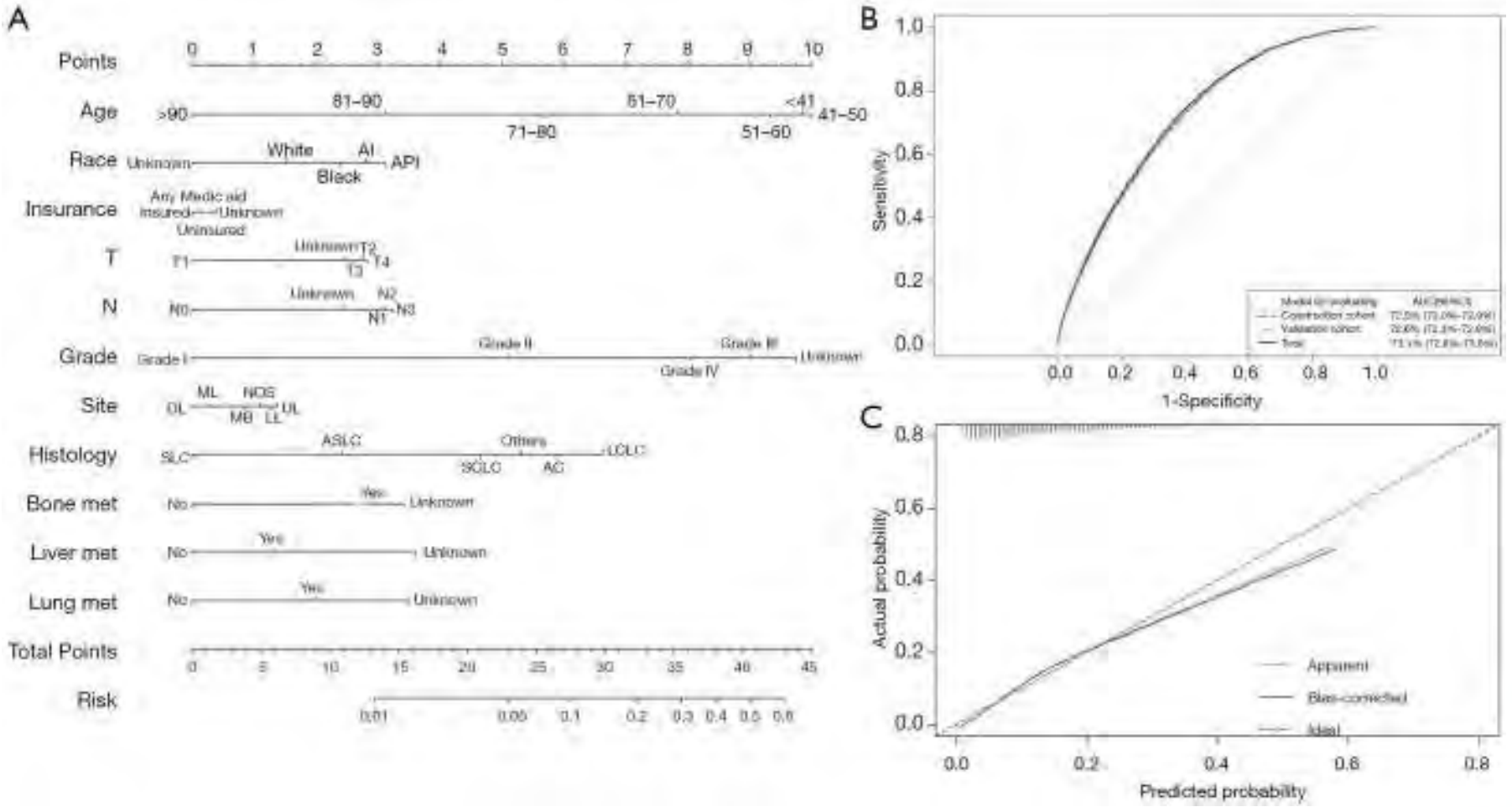
Li BT. PLoS ONE 11(1): e0146063.

Predictive nomogram for brain metastases

- 266,522 LC cases diagnosed between 2010 and 2016 were selected from the SEER cohort.
- Risk factors for developing BM - univariable and multivariable logistic and Cox regression analysis
- Nomograms were constructed based on risk factors.
- Nomogram performance was evaluated with ROC curve, or C-index and calibration curve.

Zuo C. Transl Cancer Res. 2021 Jan; 10(1):22–37.

Predictive nomogram for brain metastases



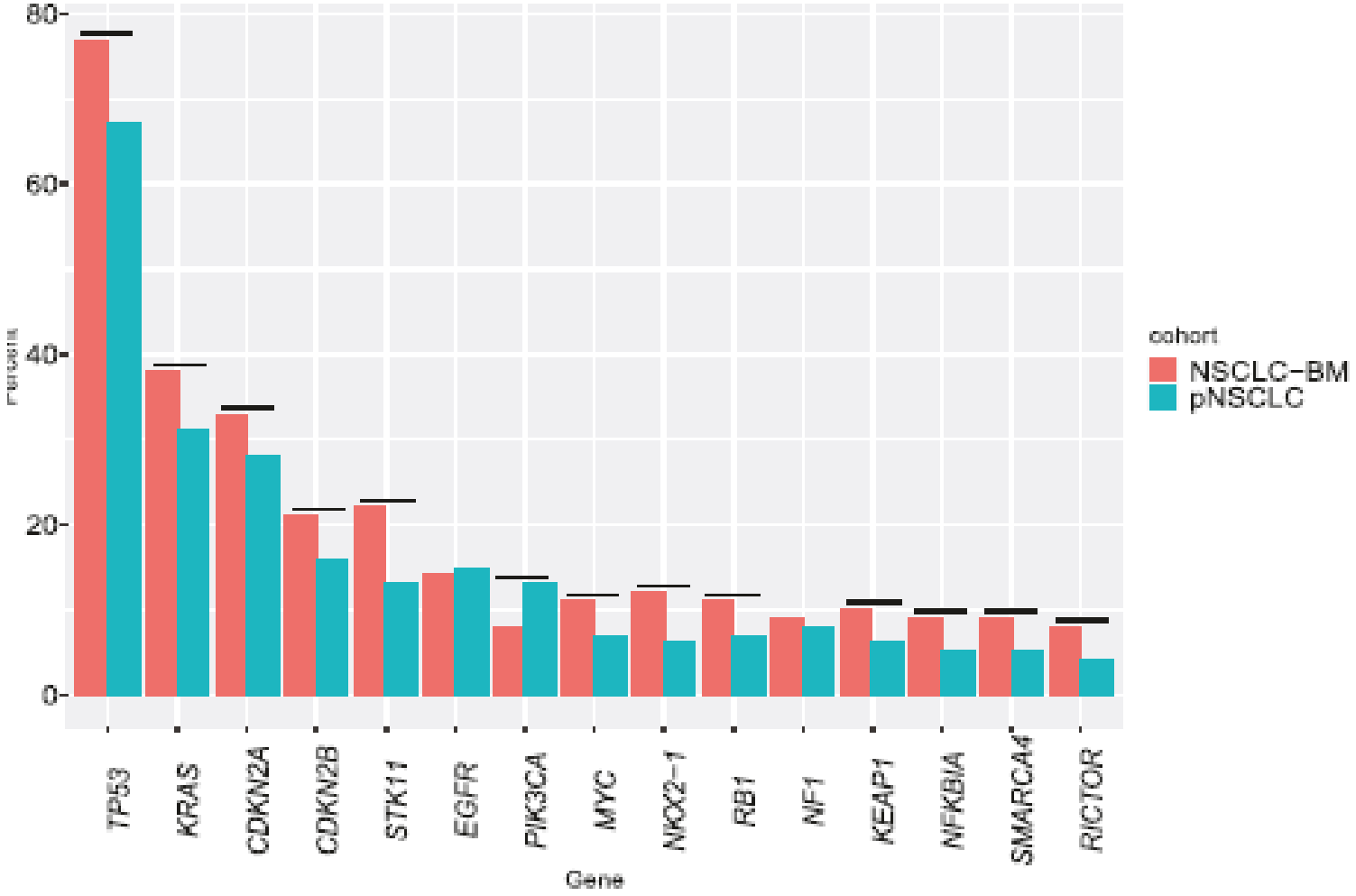
Zuo C. Transl Cancer Res. 2021 Jan; 10(1): 22–37

Genomic analyses

- 3035 NSCLC-BM tested with comprehensive genomic profiling compared to a separate cohort of 7277 primary NSCLC (pNSCLC) specimens
- Clinical factors
  - Female (54.6% vs. 51%, P=0.001)
  - Median age (62 vs. 69 yrs, P=1.1E-156)
  - Adenocarcinoma (69.5% vs. 60.4%, P=1.0E-17);
  - LCNEC (2.6% vs. 1.1%, P=3.9E-07)
  - Squamous cell carcinoma (6.9% vs. 25.5%, P=3.0E -118)

Huang RSP. Oncologist. 2022;27(10):839-848.

Genomic analyses of brain metastases



Huang RSP. Oncologist. 2022;27(10):839-848.

Genomic analyses of brain metastases

- Targetable alterations

Biomarker	NSCLC-BM	NSCLC	P-value
ALK fusion	2.7%	1.7%	0.02
MET exon 14 skipping mutations	1%	2.3%	1.1E-04
KRAS mutations	35.7%	29.6%	4.3E-08
K-ras G12C	15.2%	11.7%	5.9E-05
MET amplification	4.4%	2.3%	1.4E-06
TMB–high	55.4%	33.6%	1.3E-91
STK11 mutations	17.7%	11.6%	1.5E-14
KEAP 1 mutations	8.9%	5.3%	8.5E-10

Huang RSP. Oncologist. 2022;27(10):839-848..

Risk factors for brain metastases

- Retrospective study
- Patients who underwent testing for EGFR (n=1522)
- EGFR mutation (n=432; 30%)
- Brain metastases (n=236; 15.5%)
  - No EGFR mutation (n=143/1070; 13.3%)
  - EGFR mutation (n=93/432; 20.6%)
- Higher likelihood of an EGFR mutation among patients with brain metastases (OR: 1.8; P < .001).

Bhatt VR. J Glob Oncol. 2017 Jun; 3(3): 208–217.

Risk factors for brain metastases

Effect	Variable	OR (95% CI)	P value
Sex	Female v. Male	1.13 (0.87, 1.48)	NS
Ethnicity	Asian v. White/other	2.14 (1.16, 3.95)	0.02
Smoking	No v. Yes	2.75 (2.04, 3.72)	<0.001
Alcohol	No v. Yes	1.61 (1.07, 2.41)	0.02
Stage	IV v. I/II	1.76 (0.33, 9.35)	NS
	III v. I/II	0.51 (0.14, 1.90)	
Adenocarcinoma	Yes v. No	3.07 (1.87, 5.03)	<0.001
Metastatic disease	Brain v. Extracranial	1.85 (1.34, 2.54)	<0.001
	None v. Extracranial	1.64 (0.46, 5.83)	NS

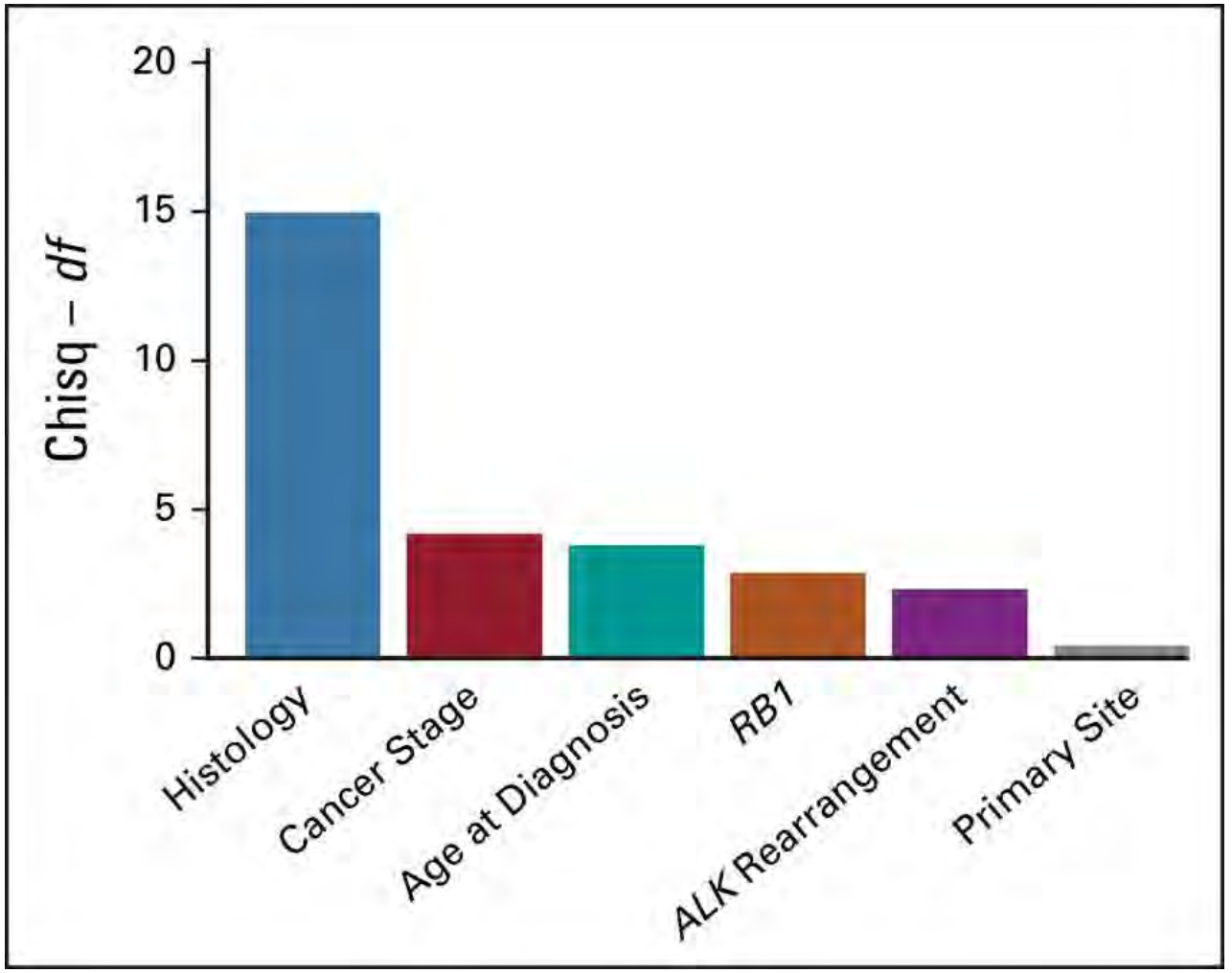
Bhatt VR. J Glob Oncol. 2017 Jun; 3(3): 208–217.

Clinicogenetic predictors for brain metastases

- Retrospective study
- A penalized regression competing risk model
- 330 patients diagnosed with lung cancer between 01/2014 and 06/2019 and followed through 06/2021
- Main outcome - time from the diagnosis of distant metastatic disease to the development of brain metastasis, death, or censoring.

Wu J. JCO Precis Oncol. 2022 Oct;6:e2200220.

Clinicogenetic predictors for brain metastases



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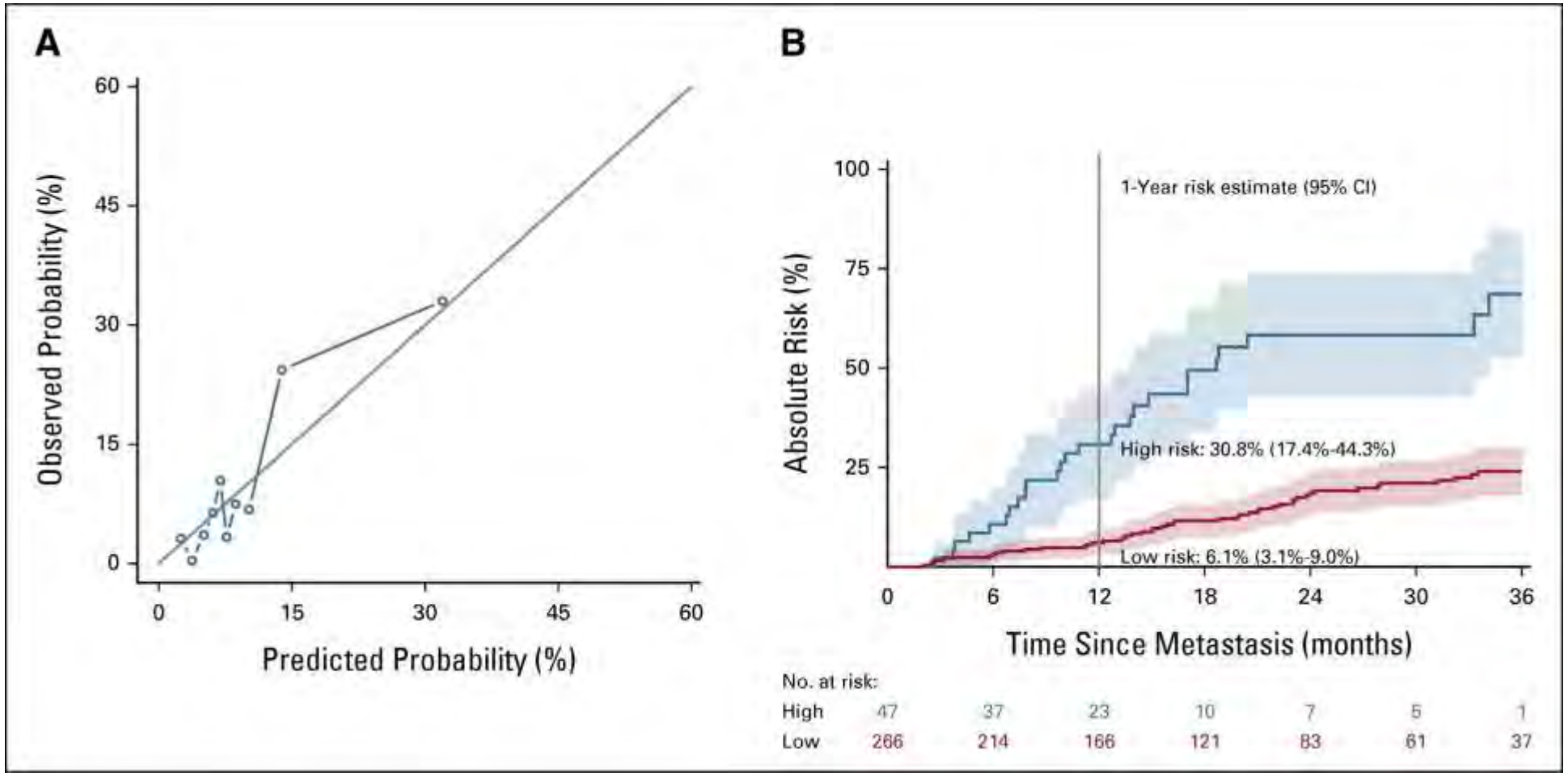
Clinicogenetic predictors for brain metastases



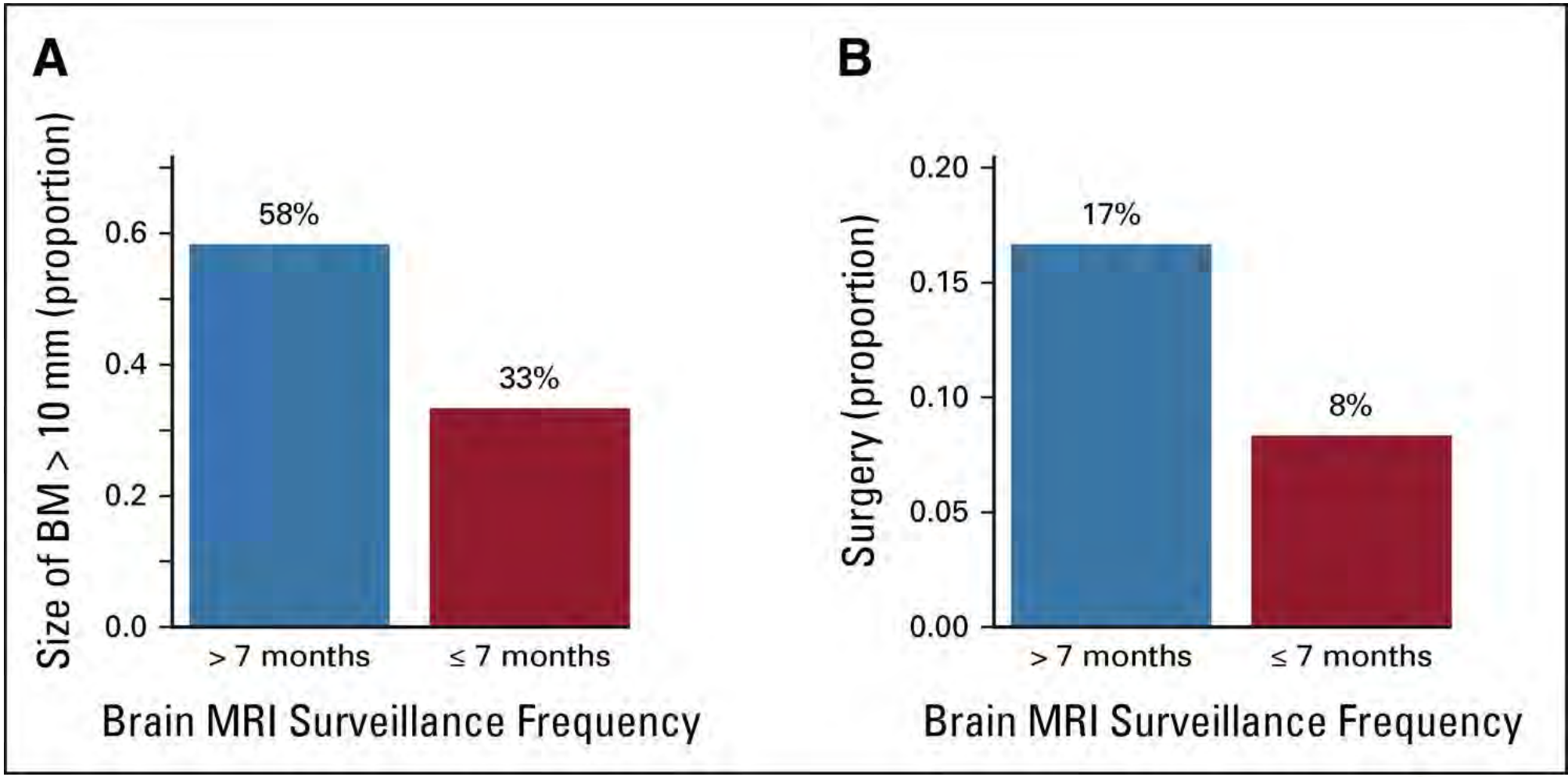
Wu J. JCO Precis Oncol. 2022 Oct;6:e2200220.

Clinicogenetic predictors for brain metastases

- 48 high-risk patients - 24 patients (50%) developed brain metastasis
- 12 patients (50%) - brain metastasis detected more than 7 months after last brain MRI (or date of metastasis, whichever was later
- Patients who missed this 7-month brain MRI surveillance opportunity window - larger brain metastasis (58% v 33%, >10 mm; OR, 2.80; CI, 0.51 to 13).
- Patients who missed the window - more likely to undergo surgery (17% v 8%, odds ratio, 2.2; CI, 0.22 to 34).

Wu J. JCO Precis Oncol. 2022 Oct;6:e2200220.

Clinicogenetic predictors for brain metastases



Wu J. JCO Precis Oncol. 2022 Oct;6:e2200220.

Risk factors in SCLC

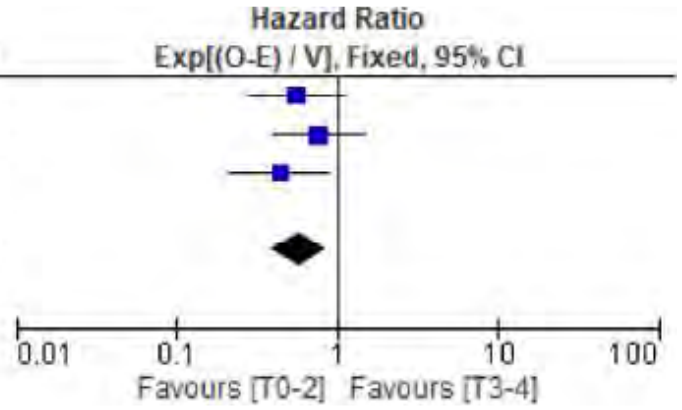
- Meta-analysis of 57 studies (13,188 patients)
- Factors associated with brain metastases
  - Higher T stage (≥T3) (HR = 1.72, 95% CI: 1.16–2.56; P = 0.007)
  - Male sex (HR = 1.24, 95% CI: 0.99–1.54; P = 0.06)
- Factors protective against brain metastases
  - Limited stage disease (HR = 0.34, 95% CI: 0.17–0.67; p = 0.002)
  - Older age (≥65) (HR = 0.70, 95% CI: 0.54–0.92; P = 0.01)
  - Better PS (0–1) (HR = 0.66, 95% CI: 0.42–1.02; P = 0.06)

Zeng H. Front. Oncol., 10 June 2022 https://doi.org/10.3389/fonc.2022.889161.

Risk factors in SCLC

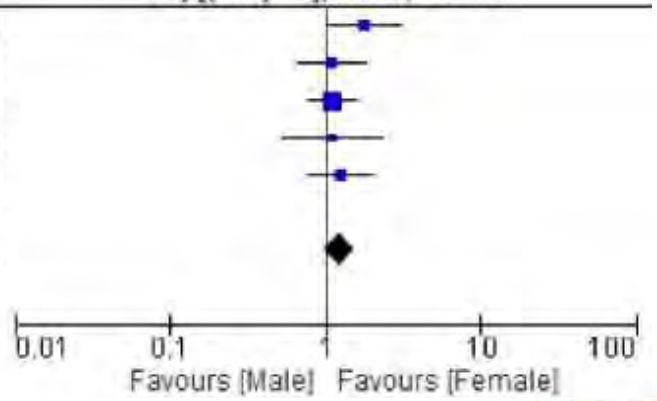
Study or Subgroup	T0-2 Events	T0-2 Total	T3-4 Events	T3-4 Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
203.Kim,2019	0	193	0	41	-4.65	8.01	32.8%	0.56 [0.28, 1.12]
34. Bernhardt, 2017	0	0	0	0	-2.42	8.82	36.1%	0.76 [0.39, 1.47]
519. Zheng, 2018	0	67	0	60	-6.21	7.58	31.1%	0.44 [0.22, 0.90]
Total (95% CI)		**260**		**101**			**100.0%**	**0.58 [0.39, 0.86]**
Total events	0		0					

Heterogeneity: Chi² = 1.23, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 2.69 (P = 0.007)



Study or Subgroup	Male Events	Male Total	Female Events	Female Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
368.Roengvoraphoj, 2017	40	110	18	69	8	13.74	17.1%	1.79 [1.05, 3.04]
377. Sahmoun, 2005	0	138	0	71	1.59	15.22	18.9%	1.11 [0.67, 1.83]
439.Suzuki, 2018	0	142	0	151	2.91	28.13	34.9%	1.11 [0.77, 1.60]
514.Zeng, 2017	27	129	9	46	0.81	6.98	8.7%	1.12 [0.53, 2.36]
80.Chen, 2016	0	171	0	33	3.73	16.48	20.5%	1.25 [0.77, 2.03]
Total (95% CI)		**690**		**370**			**100.0%**	**1.24 [0.99, 1.54]**
Total events	67		27					

Heterogeneity: Chi² = 2.46, df = 4 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.90 (P = 0.06)

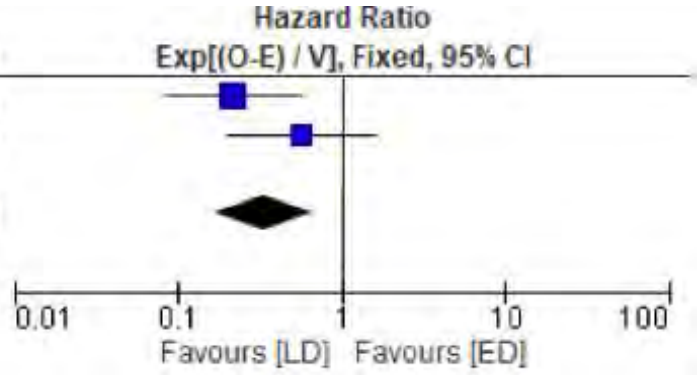


Zeng H. Front. Oncol., 10 June 2022 https://doi.org/10.3389/fonc.2022.889161.

Protective factors in SCLC

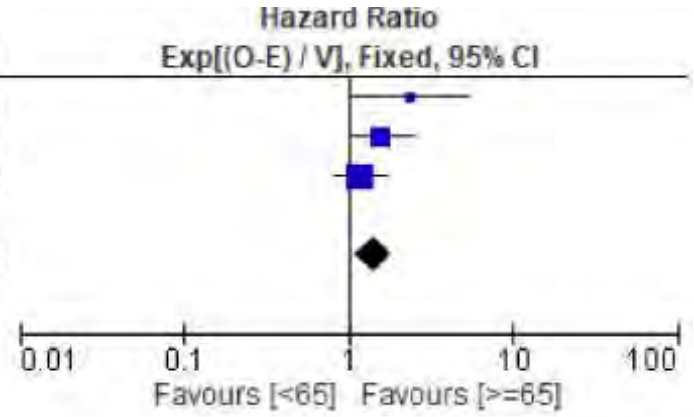
Study or Subgroup	LD Events	LD Total	ED Events	ED Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
377. Sahmoun, 2005	27	33	71	176	-6.6	4.31	54.2%	0.22 [0.08, 0.56]
514.Zeng, 2017	30	155	6	20	-2.06	3.64	45.8%	0.57 [0.20, 1.59]
Total (95% CI)		**188**		**196**			**100.0%**	**0.34 [0.17, 0.67]**
Total events	57		77					

Heterogeneity: Chi² = 1.84, df = 1 (P = 0.18); I² = 46%
Test for overall effect: Z = 3.07 (P = 0.002)



Study or Subgroup	<65 Events	<65 Total	>=65 Events	>=65 Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
203.Kim,2019	0	0	0	0	5.15	5.91	11.1%	2.39 [1.07, 5.35]
376. Sahmoun, 2004	49	78	36	107	9.06	19.54	36.6%	1.59 [1.02, 2.48]
439.Suzuki, 2018	0	0	0	0	4.68	28	52.4%	1.18 [0.82, 1.71]
Total (95% CI)		**78**		**107**			**100.0%**	**1.42 [1.09, 1.86]**
Total events	49		36					

Heterogeneity: Chi² = 2.79, df = 2 (P = 0.25); I² = 28%
Test for overall effect: Z = 2.58 (P = 0.010)



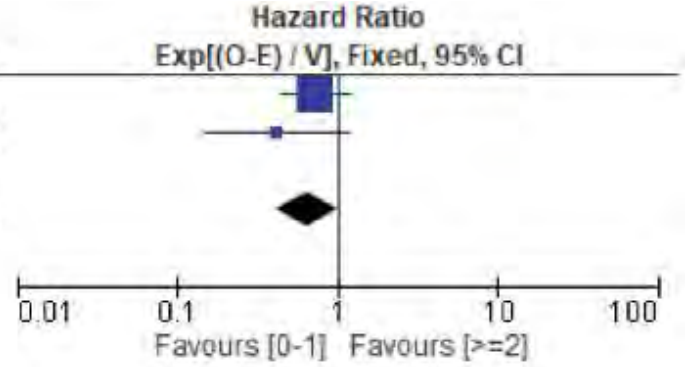
Zeng H. Front. Oncol., 10 June 2022 https://doi.org/10.3389/fonc.2022.889161.

Protective factors in SCLC

Study or Subgroup	0-1 Events	0-1 Total	>=2 Events	>=2 Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
439.Suzuki, 2018	0	239	0	54	-4.92	15.66	80.7%	0.73 [0.45, 1.20]
80.Chen, 2016	0	195	0	9	-3.25	3.75	19.3%	0.42 [0.15, 1.16]
Total (95% CI)		**434**		**63**			**100.0%**	**0.66 [0.42, 1.02]**
Total events	0		0					

Heterogeneity: $Chi^2 = 0.92$, $df = 1$ ($P = 0.34$); $I^2 = 0\%$

Test for overall effect: $Z = 1.85$ ($P = 0.06$)



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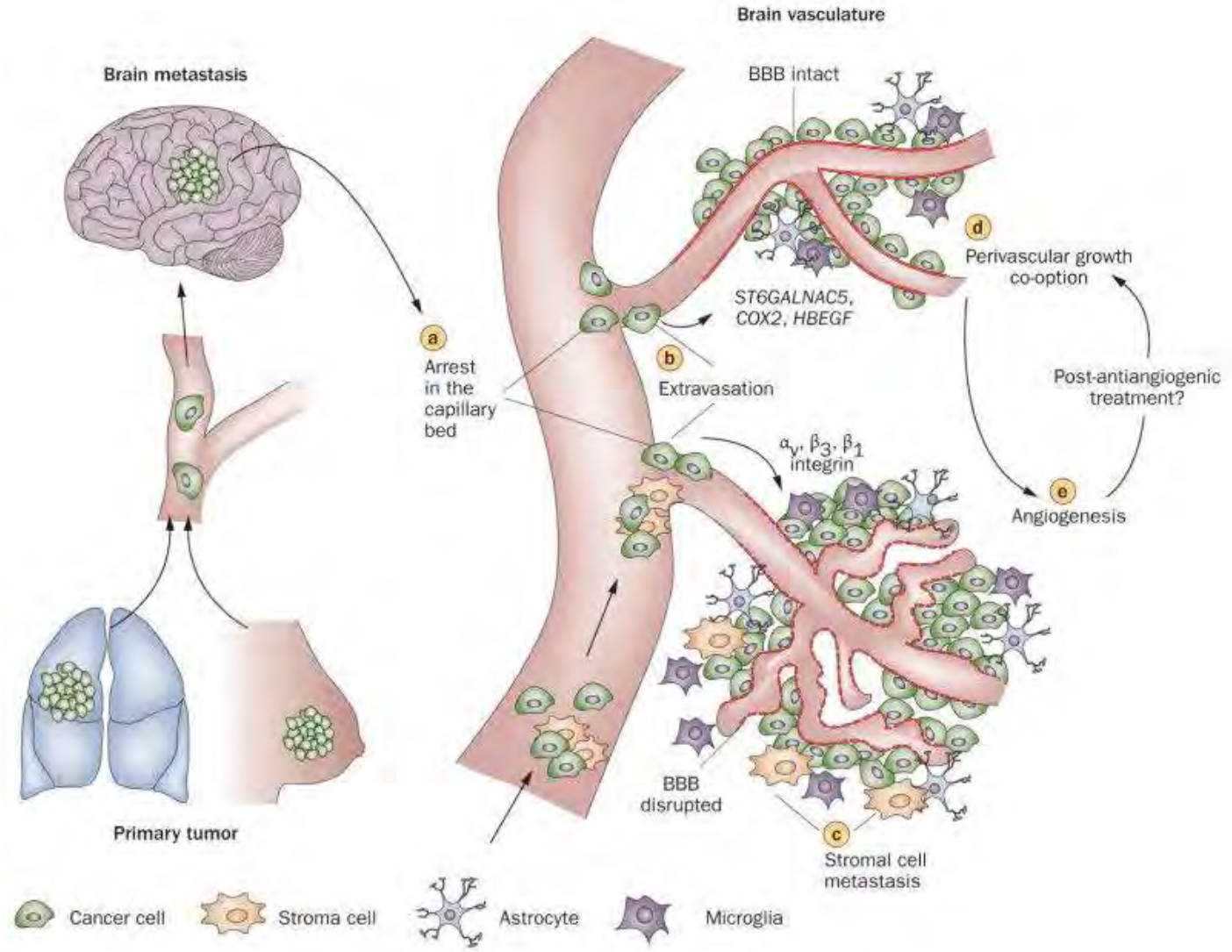
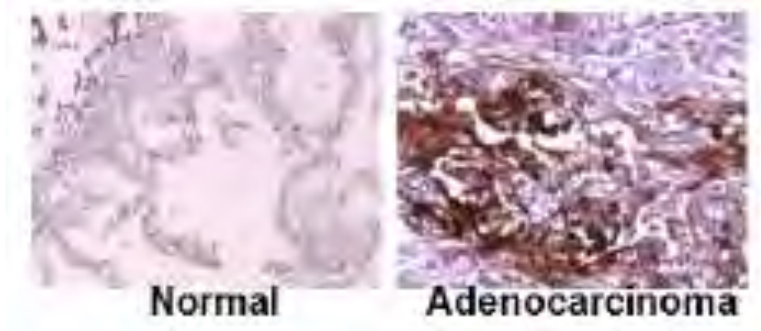
Pathogenesis of brain metastases

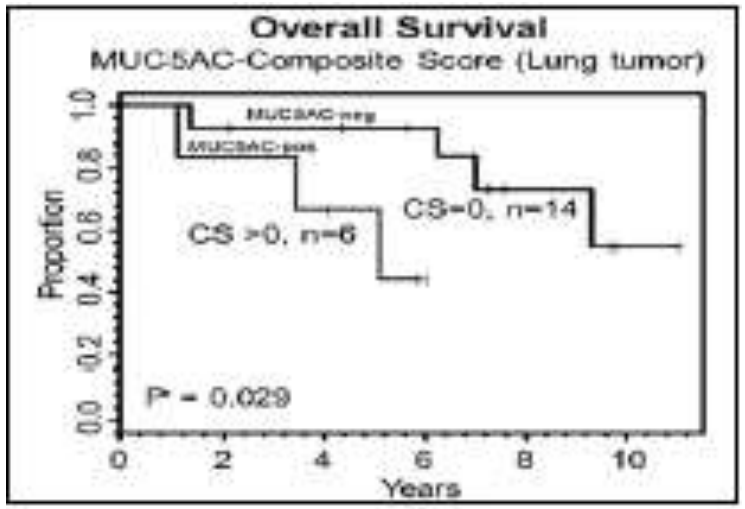


Eichler AF. Nat Rev Clin Oncol. 2011 Jun; 8(6): 344–356.

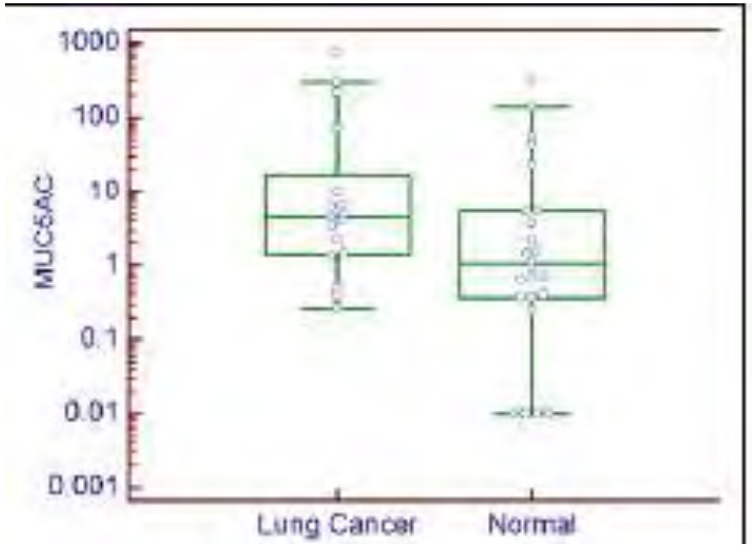
MUC5AC in lung cancer

Schematic representation of MUC5AC domains. The 5525 amino acid polypeptide backbone of MUC5AC is comprised of a central region having 9 Cysteine rich domains interspersed in with heavily O-glycosylated tandem repeat (TR) domains (8 amino acid repetitive consensus sequence).



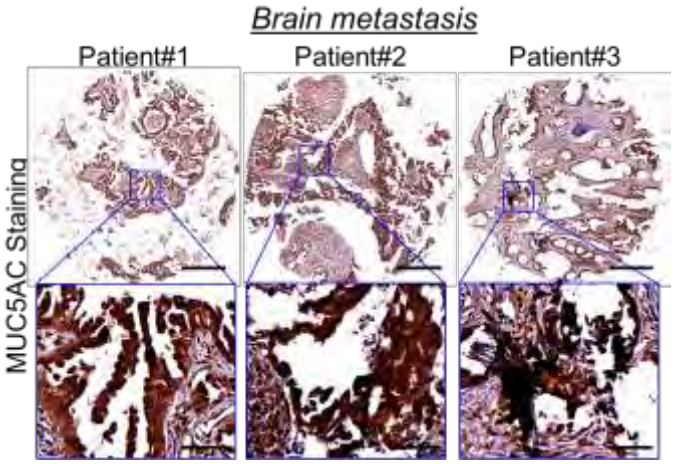


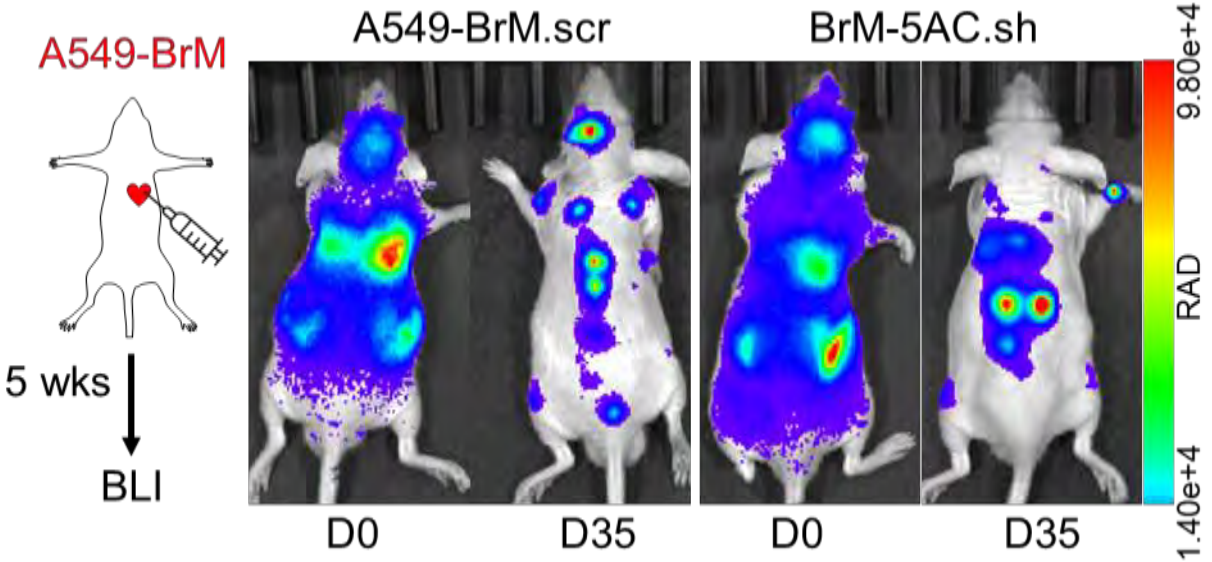
Lakshmanan I. Oncogene. 2016; 35(31): 4112–4121.

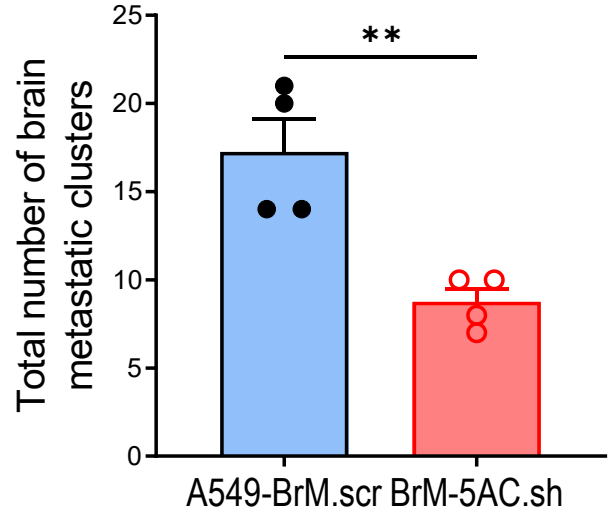


Median MUC5AC levels in lung cancer patients were higher than controls

MUC5AC in lung cancer brain metastases







Summary

- Female patients, adenocarcinoma histology, advanced stage increased risk of brain metastases
- Higher rates of several targetable genomic alterations - ALK fusions, KRAS G12C mutations, and MET amplifications; decreased frequency of MET exon14 skipping mutations
- No biomarkers can consistently predict for the development of brain metastases

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