Emerging Novel Diagnostic and Therapeutic Approaches for Leptomeningeal Metastases

AUGUST 8 | 6:15-7:15 PM | BALLROOM DEF

Presented at the SNO/ASCO CNS Conference

Sheraton Downtown Denver

GREG FULLER, MD, PHD

SEEMA NAGPAL, MD

JONATHAN T. YANG, MD, PHD

ANDREW BRENNER, MD, PHD

Neuropathology of Leptomeningeal Metastatic Disease

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To better understand

Leptomeningeal Metastatsis

we must understand the

structure of the **Meninges**

Our understanding of the Meninges has significantly changed since the time we were in medical school!

There are 2 recent discoveries that will likely impact our concept and treatment of LMD in the near future

The first is a *newly discovered*

4^{th} Meningeal Layer!

“SLYM”

PMID 36603070

Science 2023

BRAIN ANATOMY

A mesothelium divides the subarachnoid space into functional compartments

Kjeld Møllgård[1]*†, Felix R. M. Beinlich[2]†, Peter Kusk[2]†, Leo M. Miyakoshi[2]†, Christine Delle[2], Virginia Plá[2], Natalie L. Hauglund[2], Tina Esmail[2], Martin K. Rasmussen[2], Ryszard S. Gomolka[2], Yuki Mori[2], Maiken Nedergaard[3]*

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Subarachnoid Lymphatic-like Membrane (SLYM)

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Subarachnoid Lymphatic-like Membrane (SLYM)

The central nervous system is lined by meninges, classically known as dura, arachnoid, and pia mater. We show the existence of a fourth meningeal layer that compartmentalizes the subarachnoid space in the mouse and human brain, designated the subarachnoid lymphatic-like membrane (SLYM).

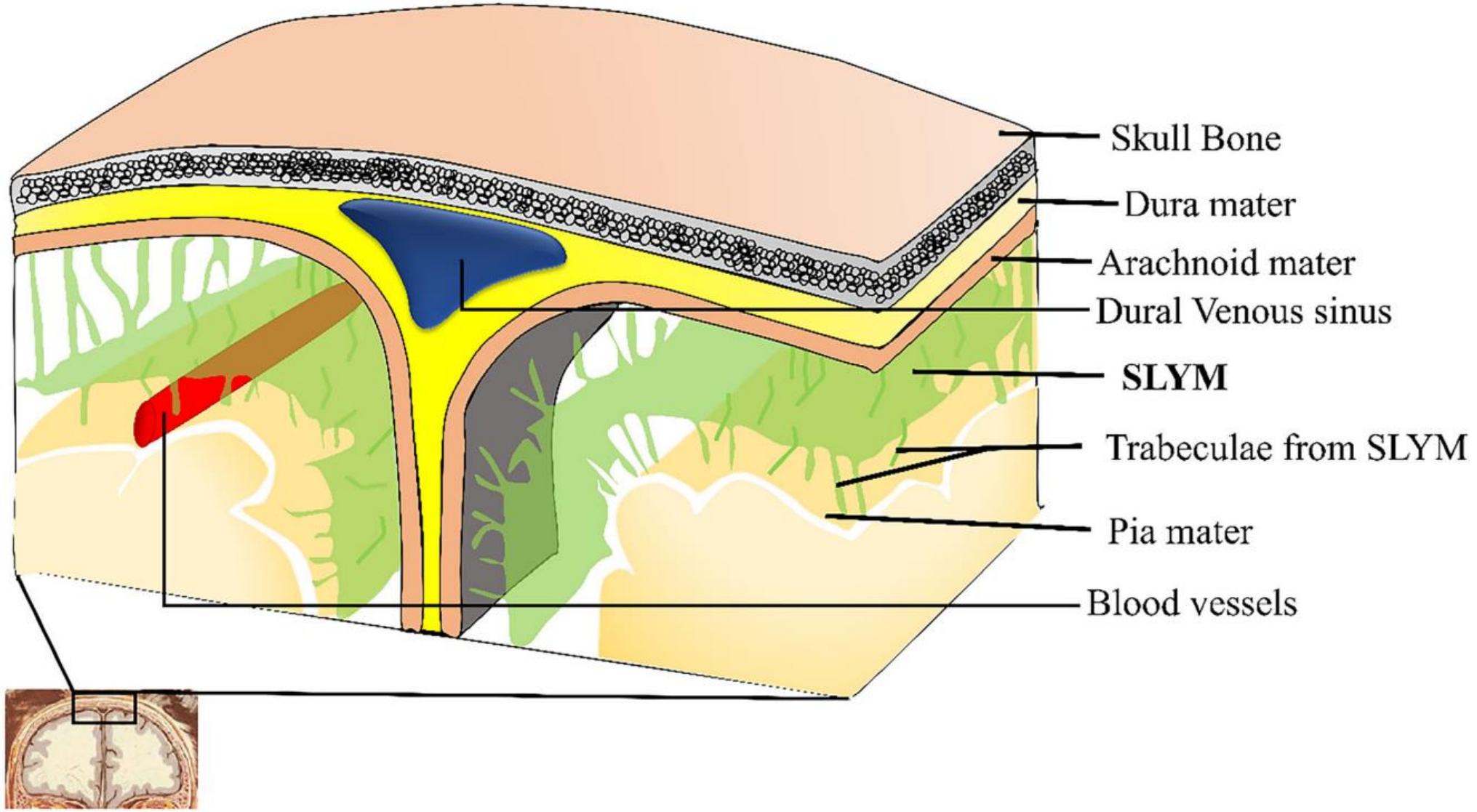

FIGURE 1 Revised meningeal arrangement in the brain. Recently, Møllgård et al. reported the existence of a new leptomeningeal layer in mice and human brains between the arachnoid and pia, dividing the subarachnoid space containing CSF into superficial outer and deep inner compartments. The new meningeal layer is a one—to two-cell thick mesothelial membrane, not allowing the passage of moieties more than one μm in size and three kilodaltons in weight. Thus, it creates two distinct functional compartments. They described vessels primarily located in the inner compartment (Møllgård et al., 2023).

Anat Record 2024
PMID 38924700

SLYM Essential Points

- SLYM partitions the SAS, which has major implications for the CNS glymphatic system

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- SLYM partitions the SAS, which has major implications for the CNS glymphatic system
- SLYM is an immune cell-rich membrane, which has major implications for LMD immunotherapy

2nd Recently Evolving Meningeal Concept

Subpial Space/Perivascular Compartment

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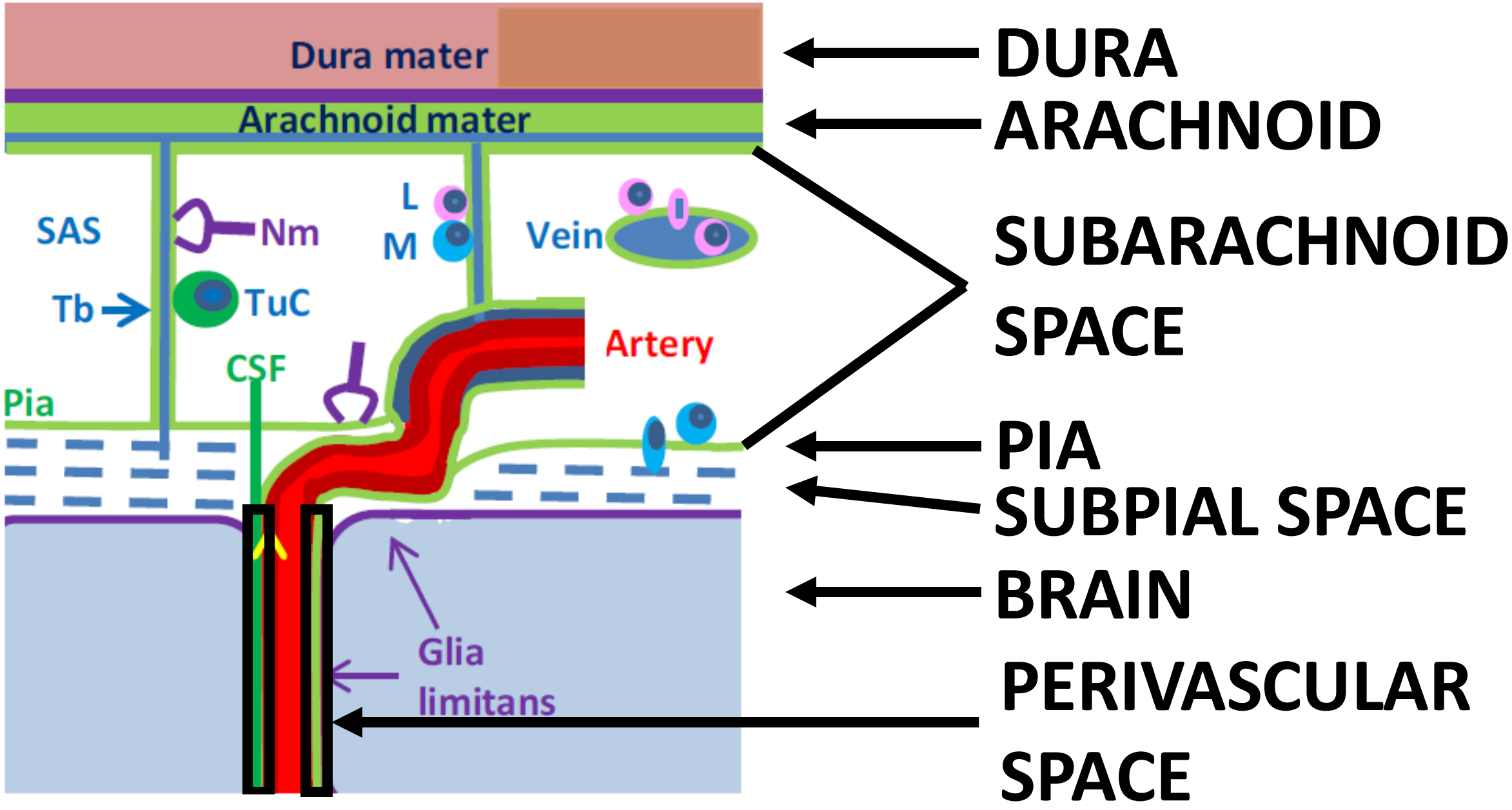
Subpial Space/Perivascular Compartment

CNS Extravascular Migratory Metastasis

(CNS EVMM)



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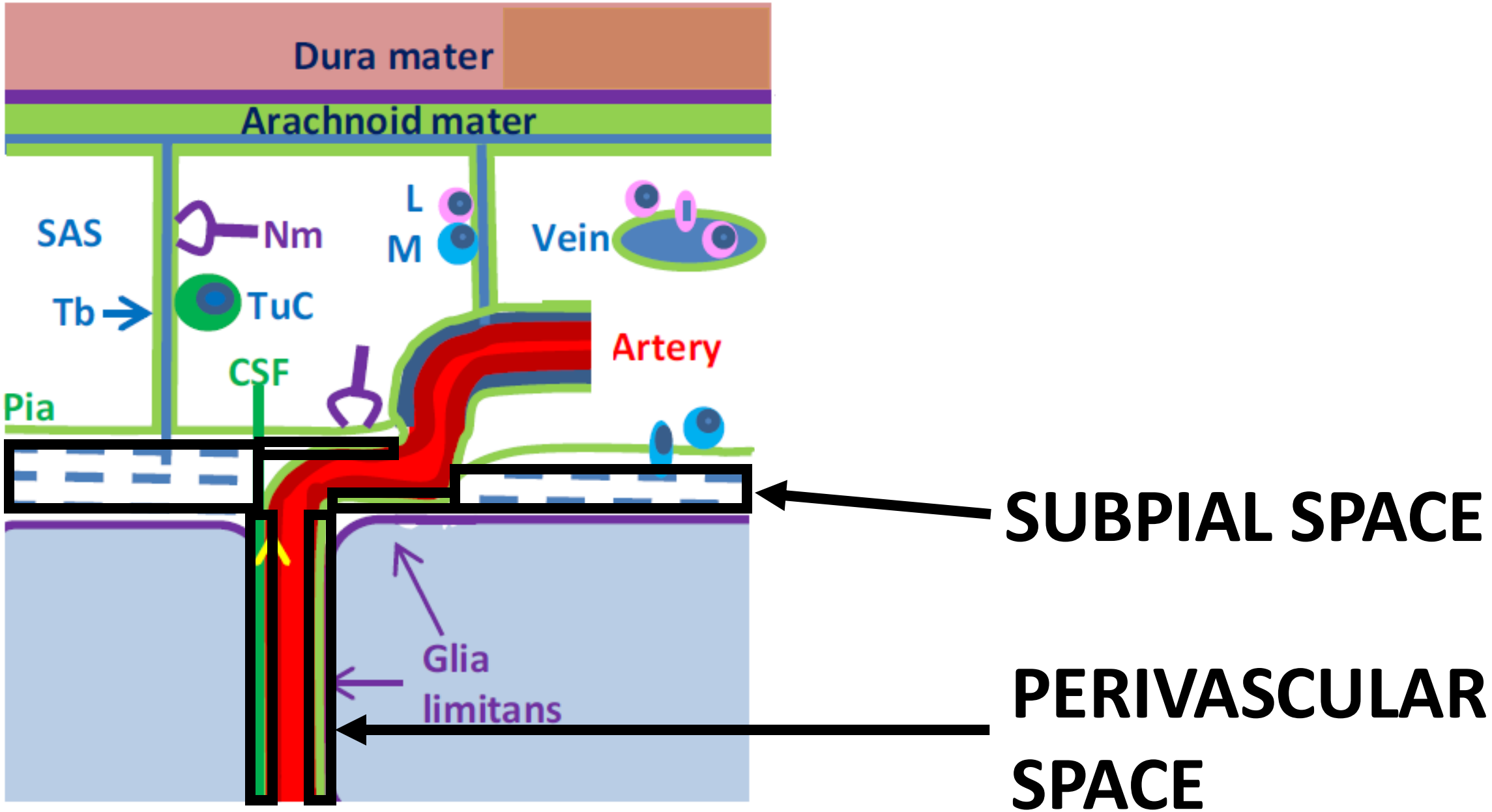

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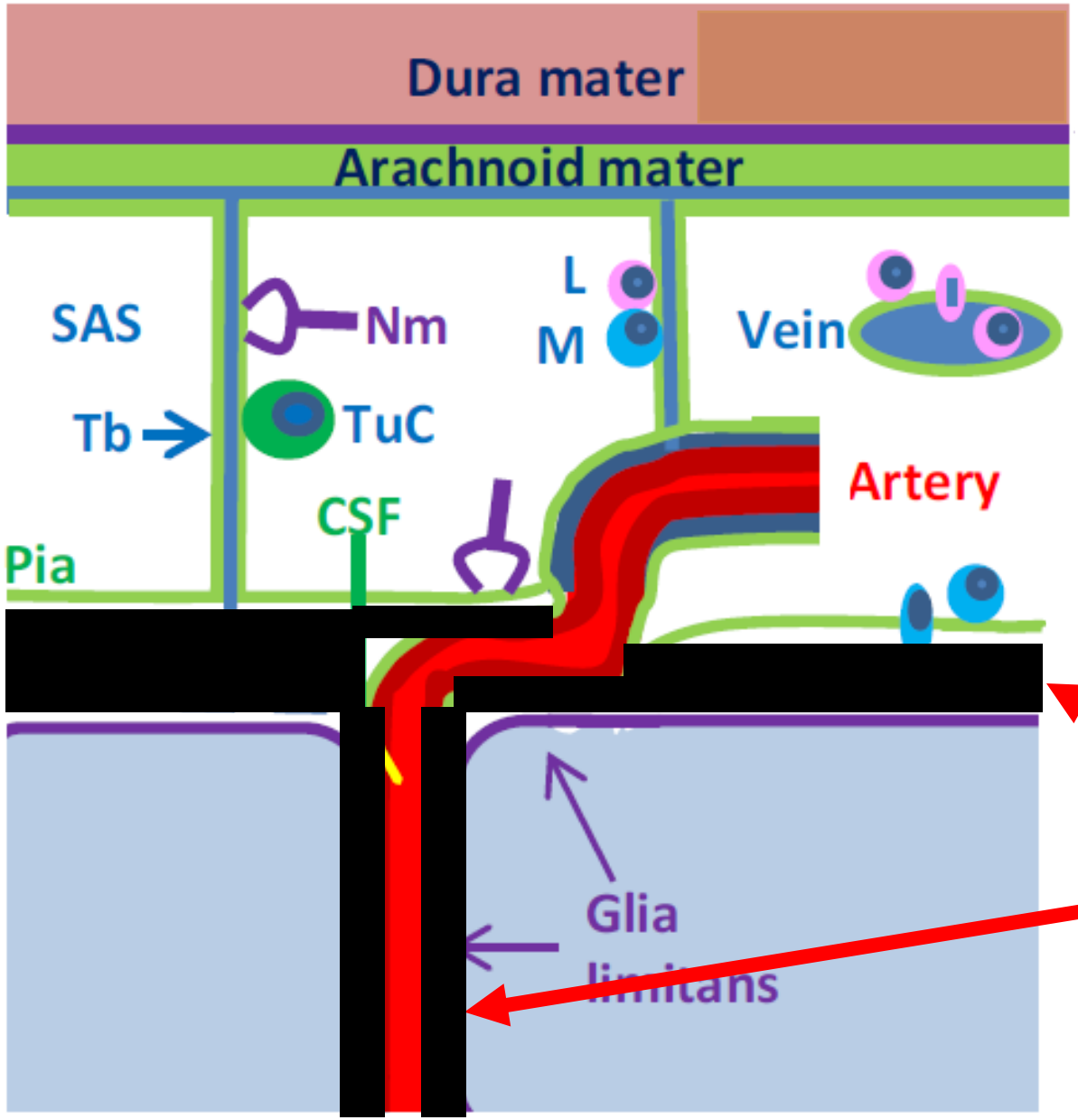

SUBPIAL / PERIVASCULAR COMPARTMENT!

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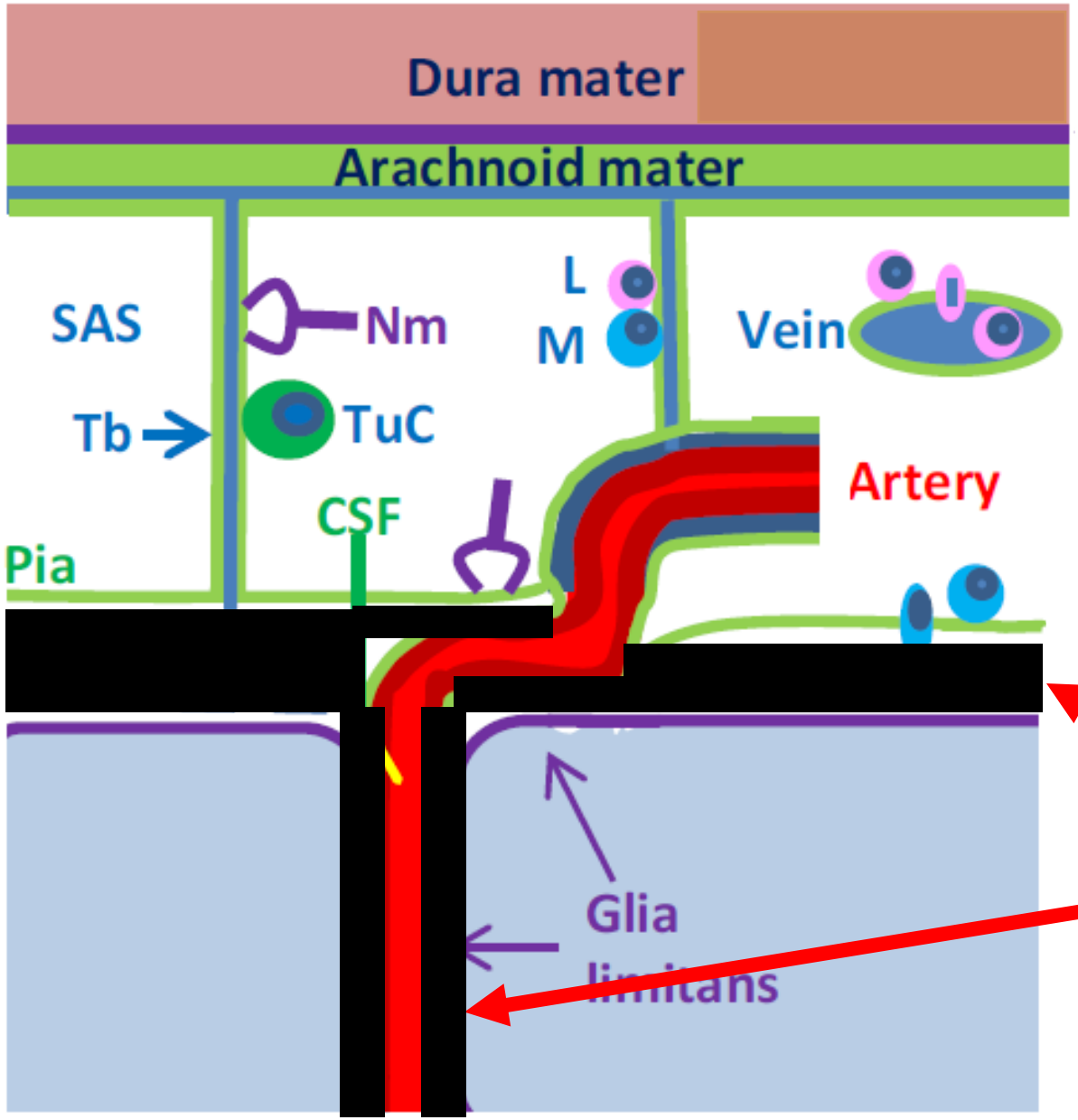

There is a process, termed **Extravascular Migratory Metastasis (EVMM)**, in which **cancer cells exit the blood vessels** in the cerebral cortex gray matter ribbon **into the perivascular space**, and then **travel along the vascular tree**, ultimately reaching the space just beneath the pia mater **(subpial space).**

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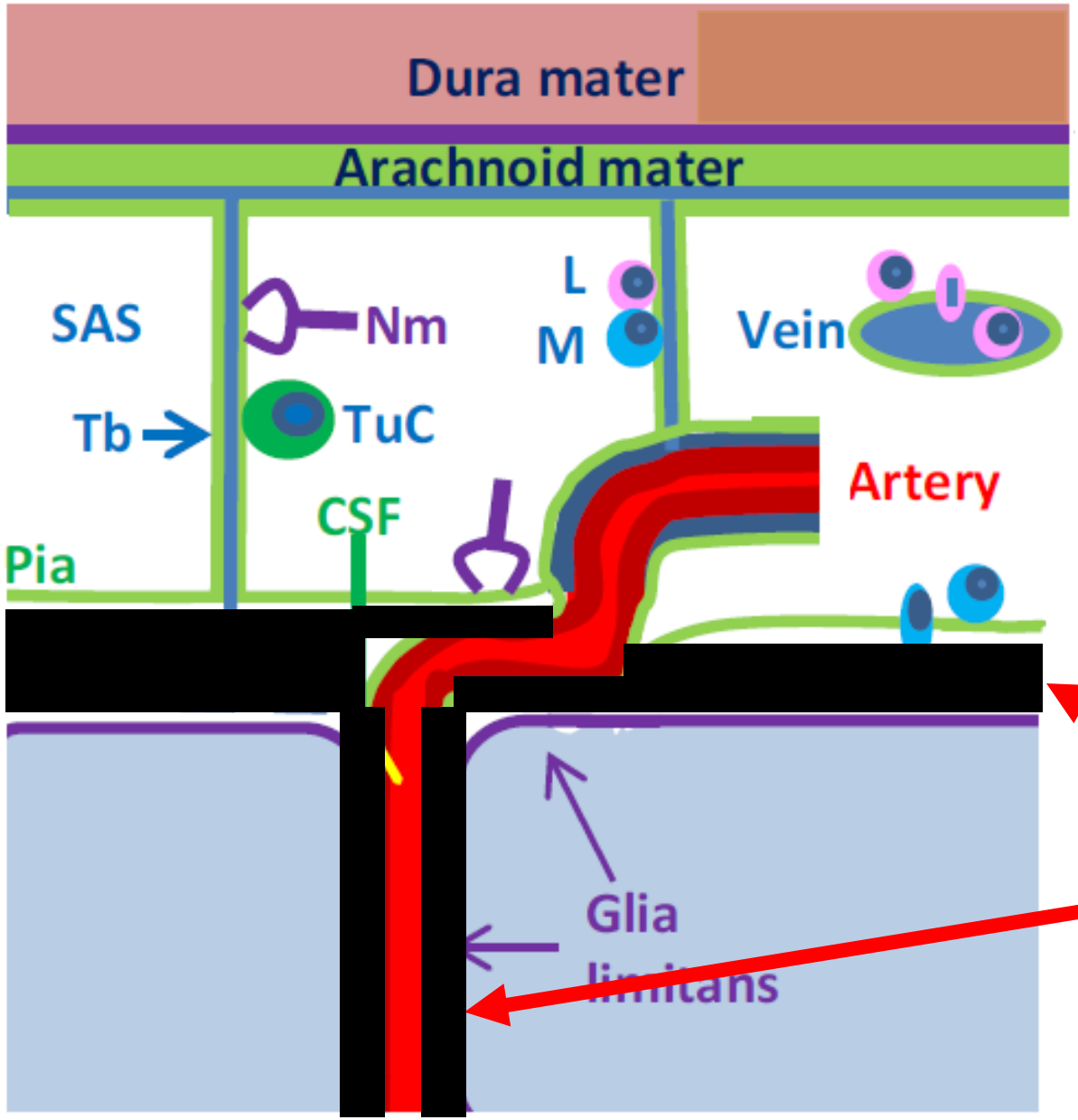

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Extravascular Migratory Metastasis

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Cerebral Cortex - from SAS to Gray/White Junction

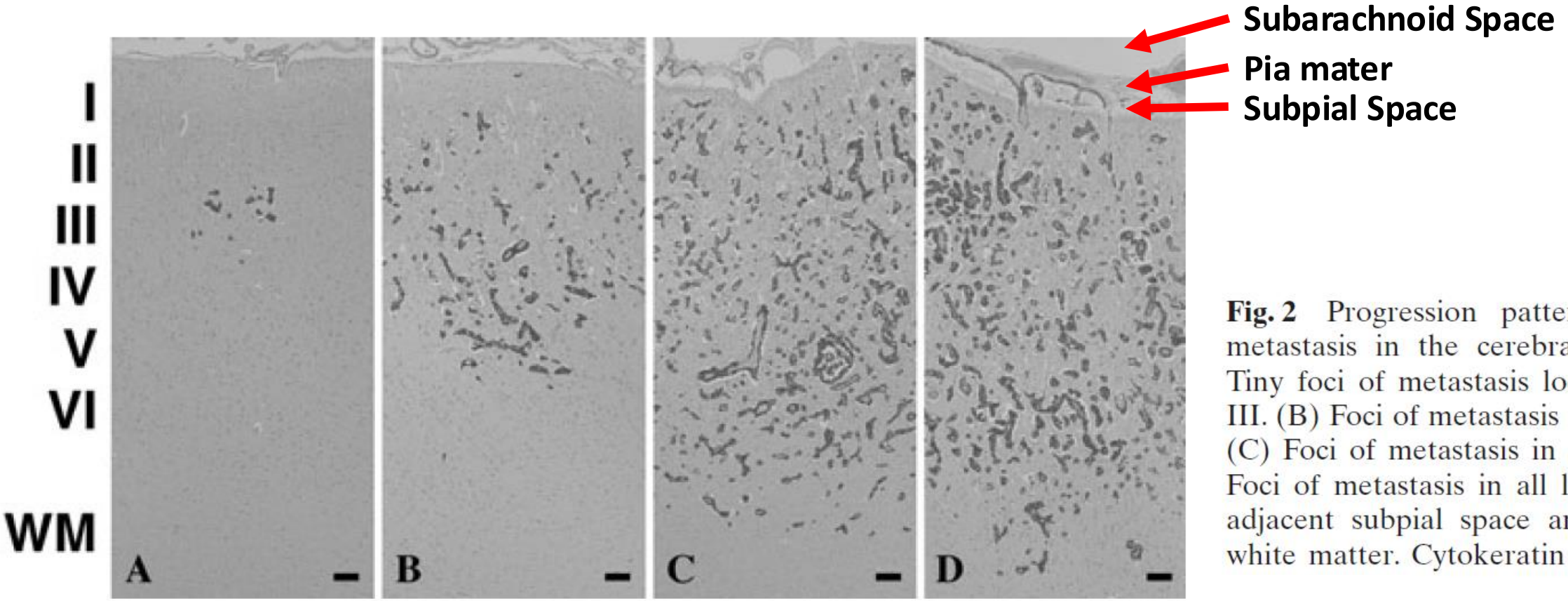
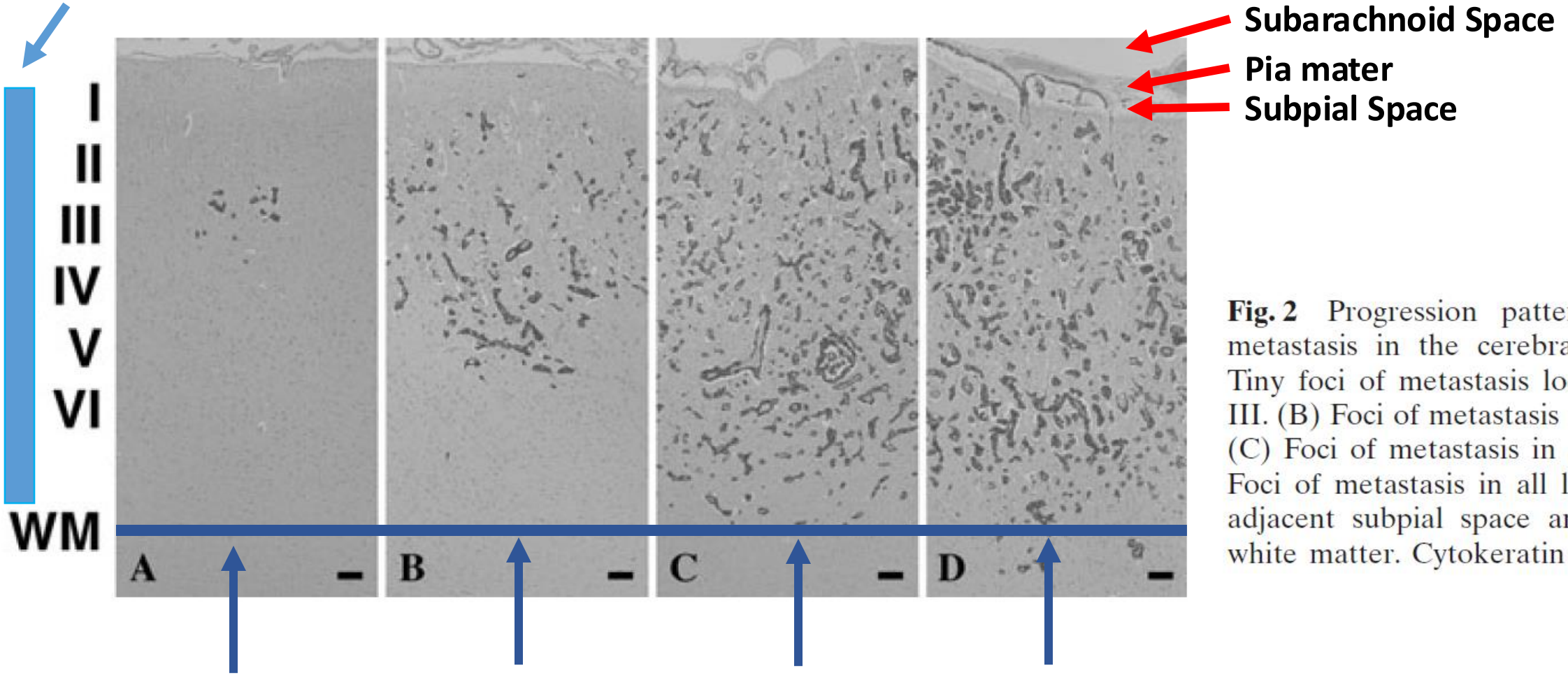


Fig. 2 Progression pattern of cancer metastasis in the cerebral cortex. (A) Tiny foci of metastasis located in layer III. (B) Foci of metastasis in layers II–V. (C) Foci of metastasis in all layers. (D) Foci of metastasis in all layers and the adjacent subpial space and subcortical white matter. Cytokeratin immunostain.

Modified from Neuropathol 2007 PMID 17899695

Cerebral Cortex - from SAS to Gray/White Junction

Cortical Gray Ribbon (6 laminae in neocortex, I-VI)



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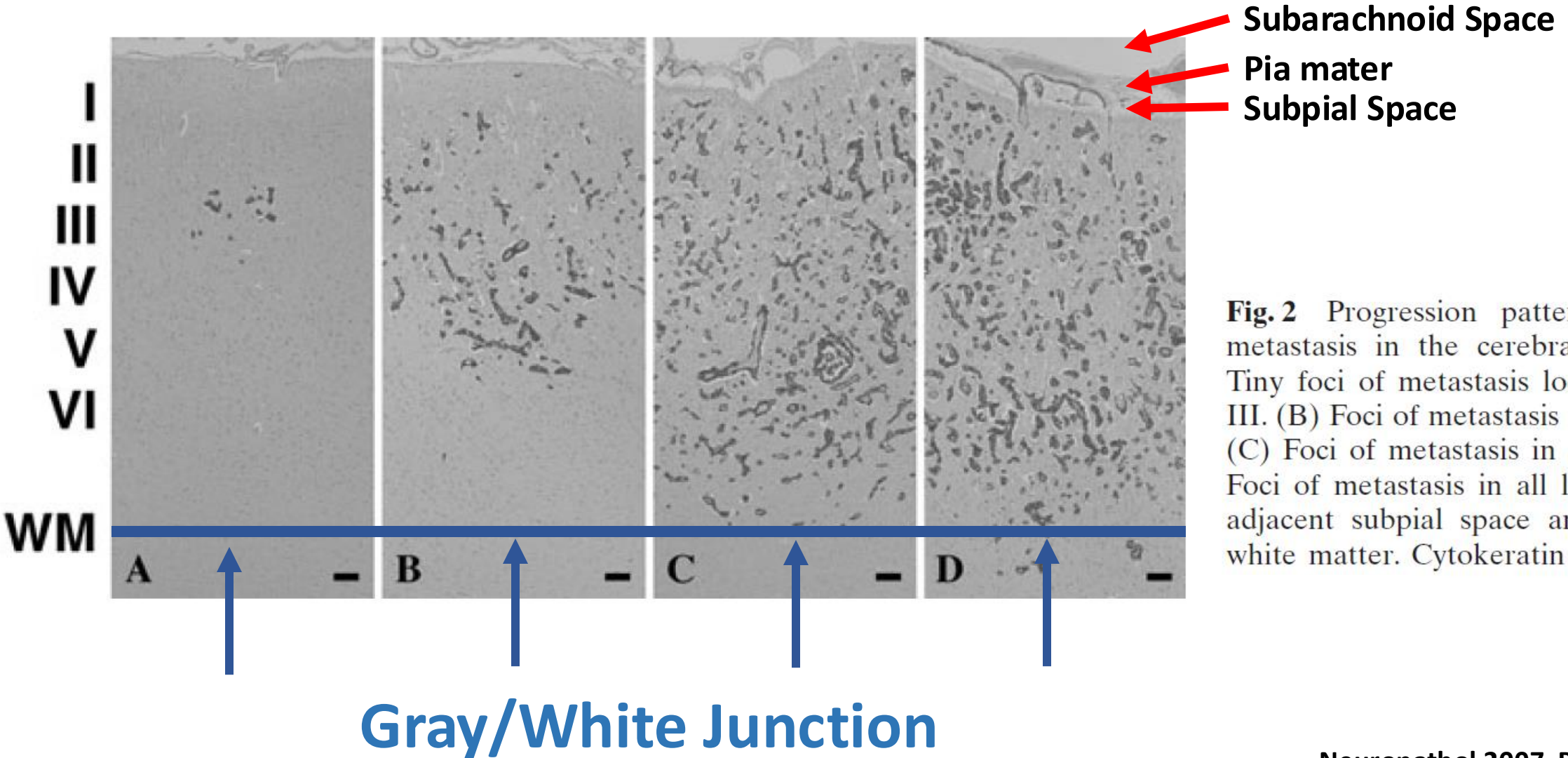
EVMM BEGINS INTRACORTICALLY! (*NOT at the gray/white junction*)



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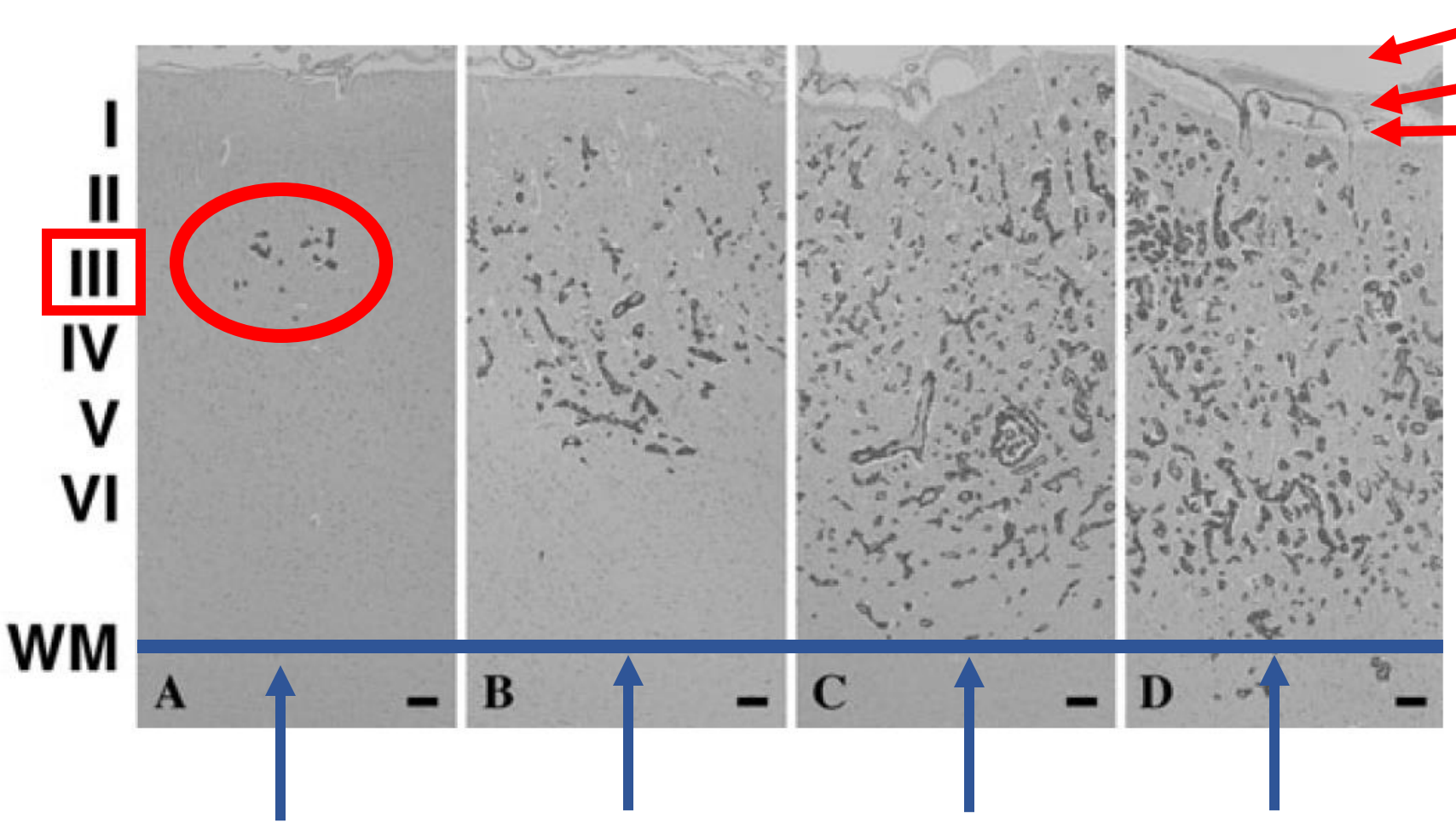

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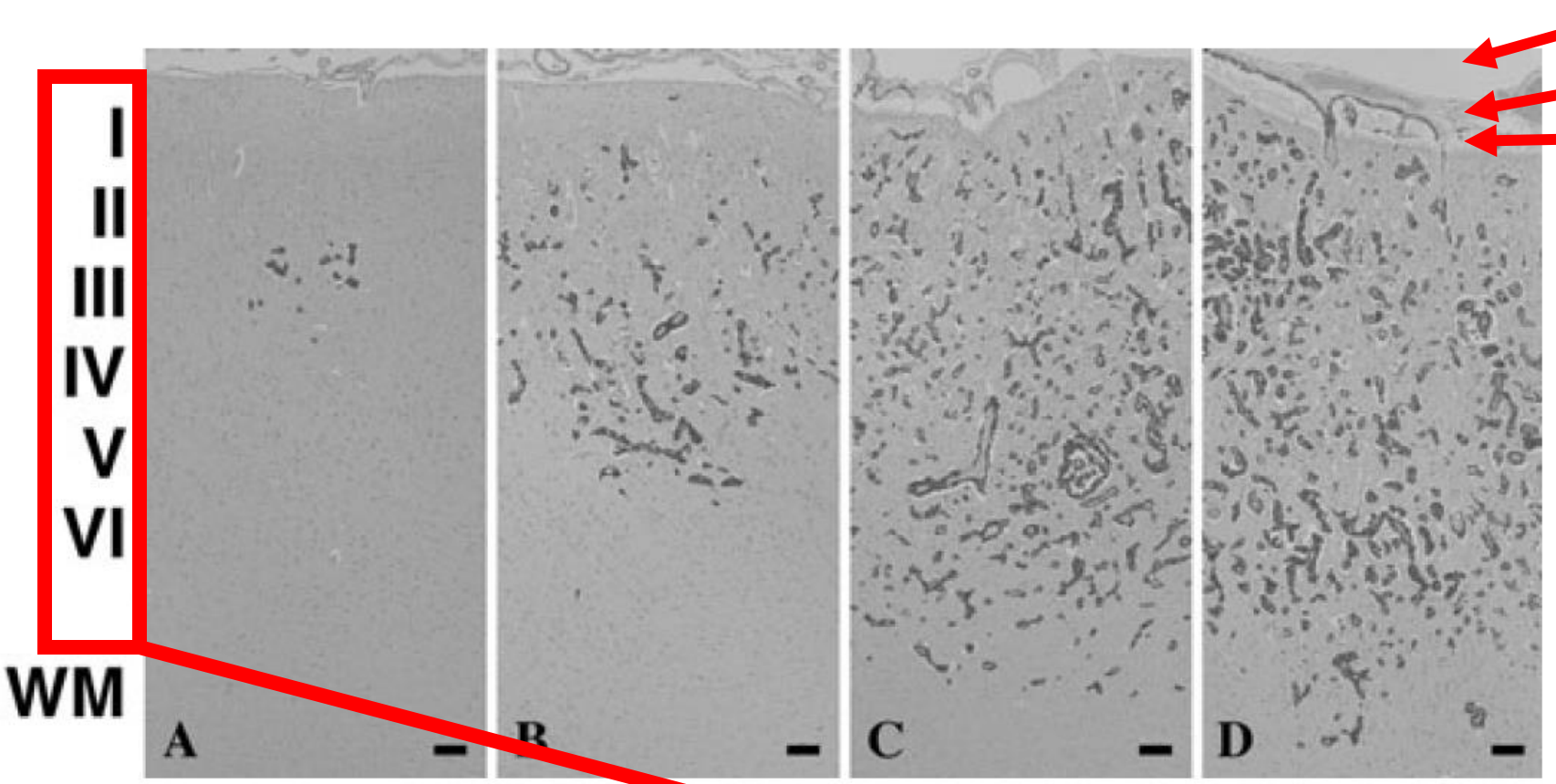

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Cortical gray ribbon thickness (I – VI) = 2.5mm

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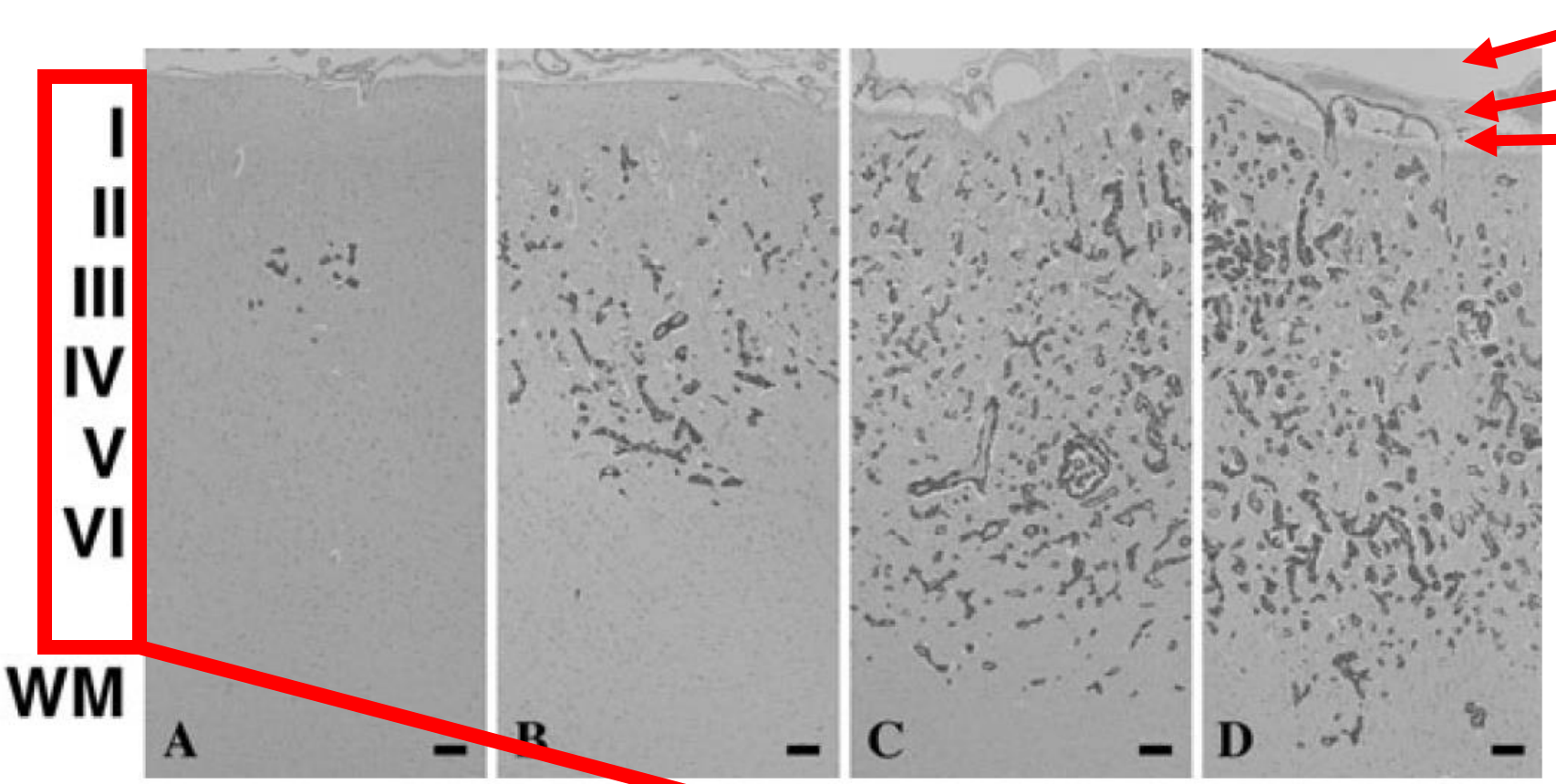

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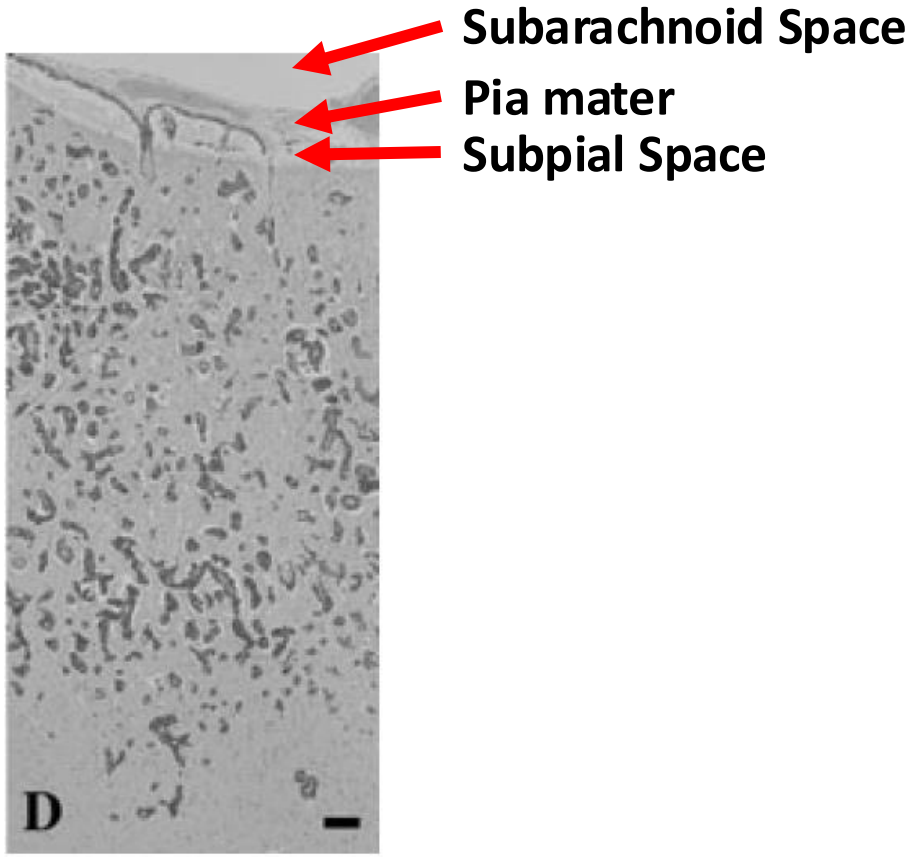

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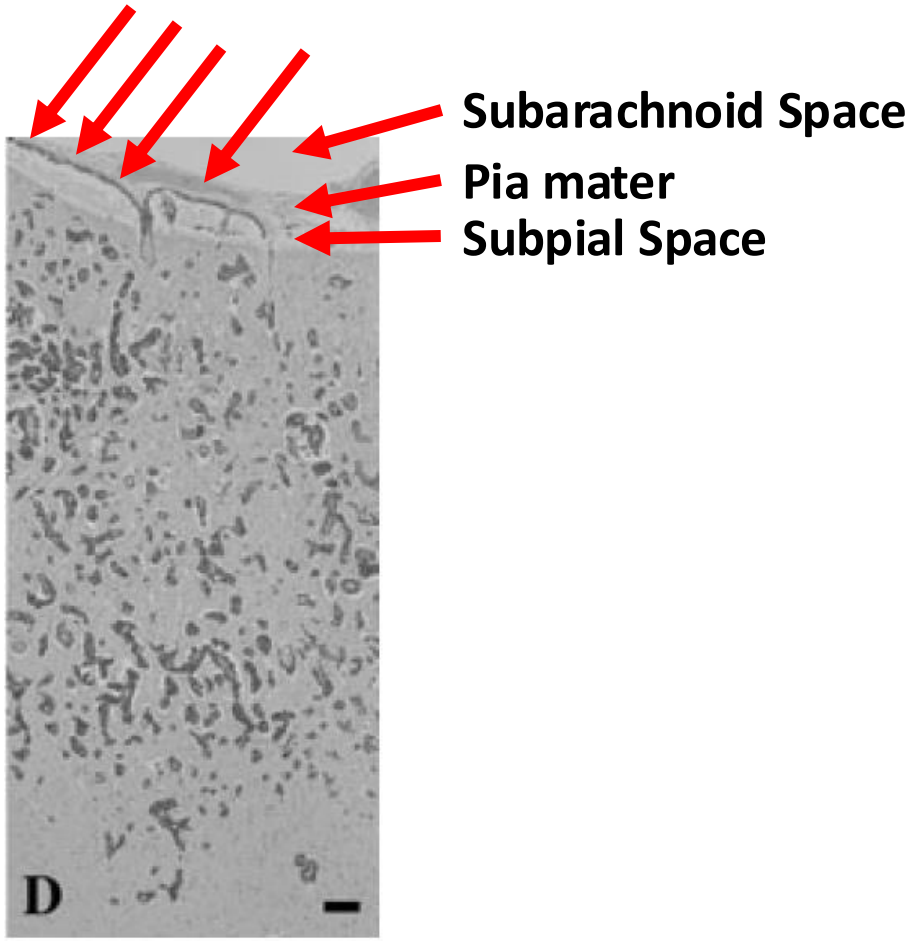

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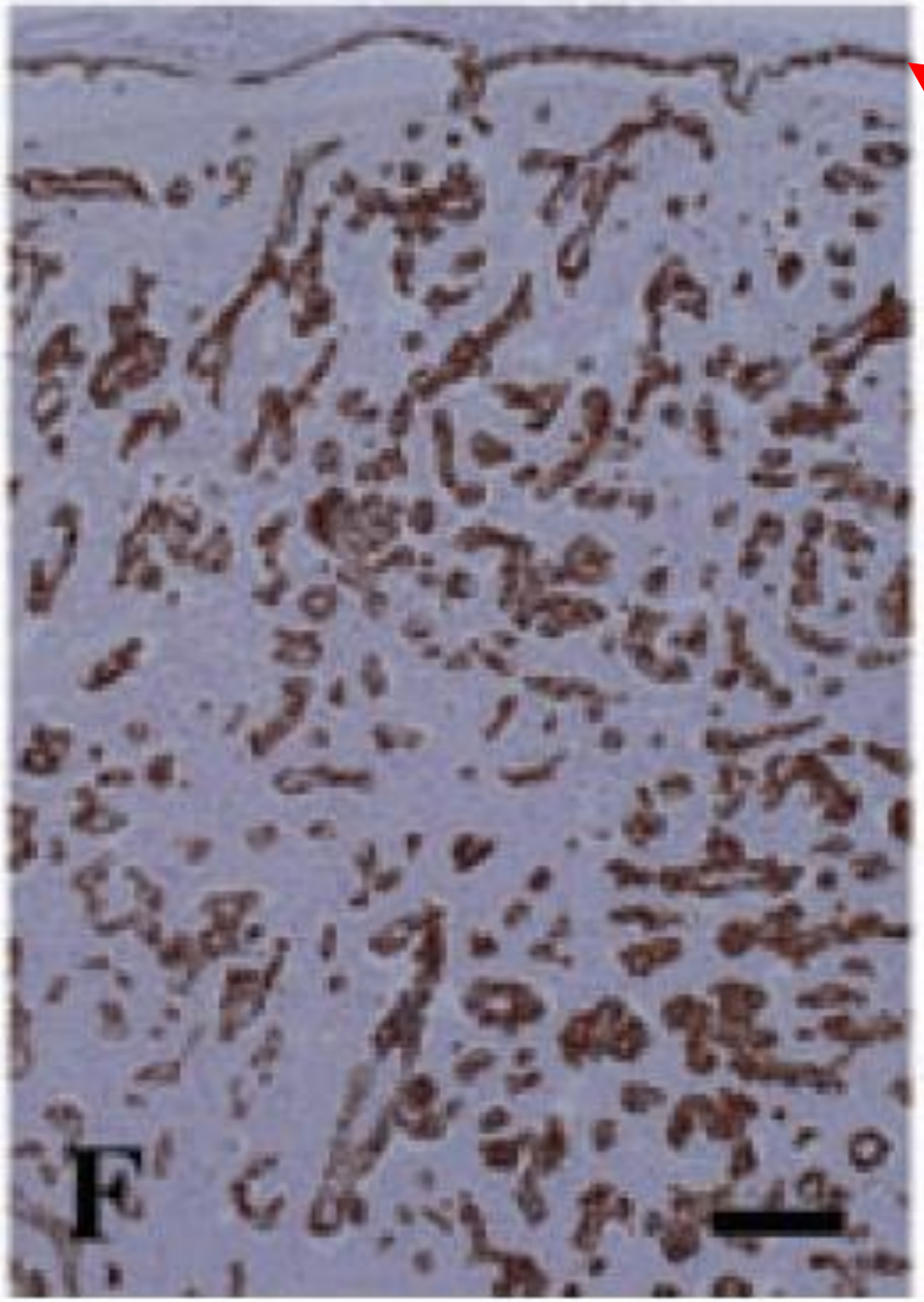

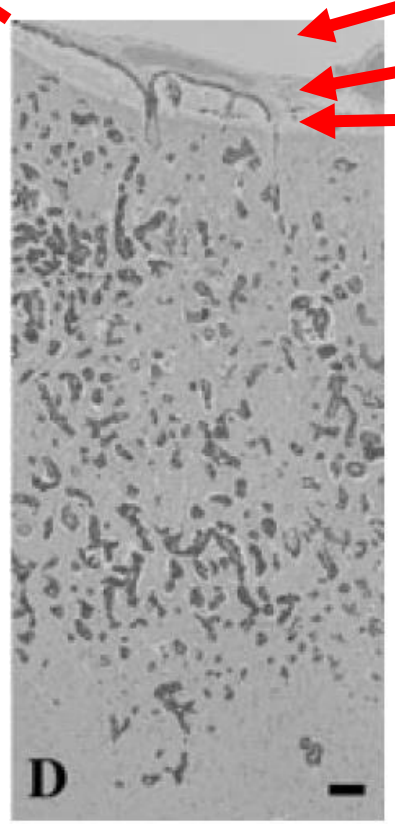

Subarachnoid Space

Pia mater

Subpial Space

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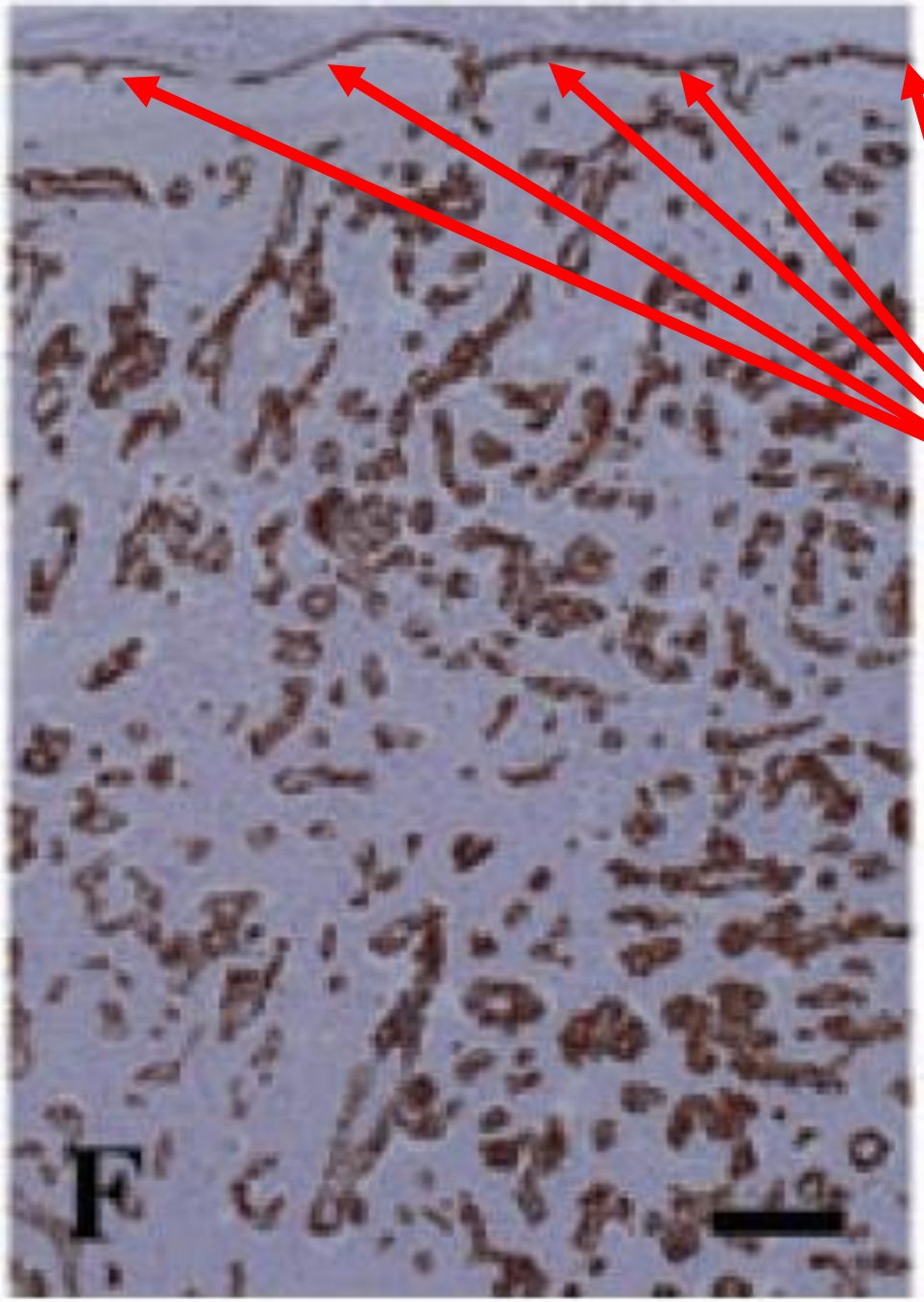
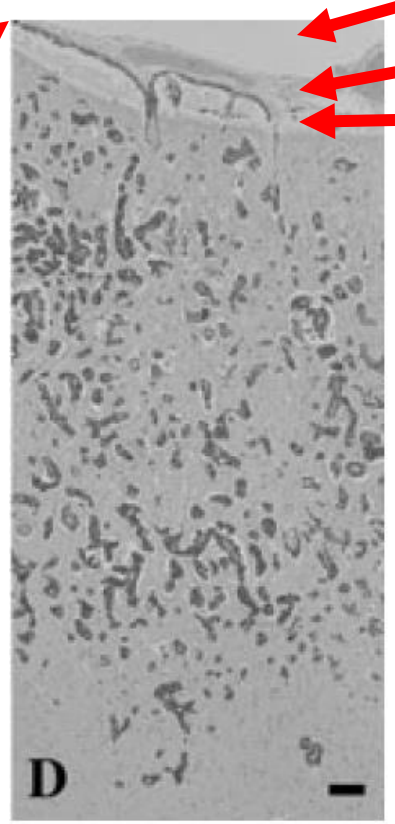


Metastatic Tumor in the Subpial Space!



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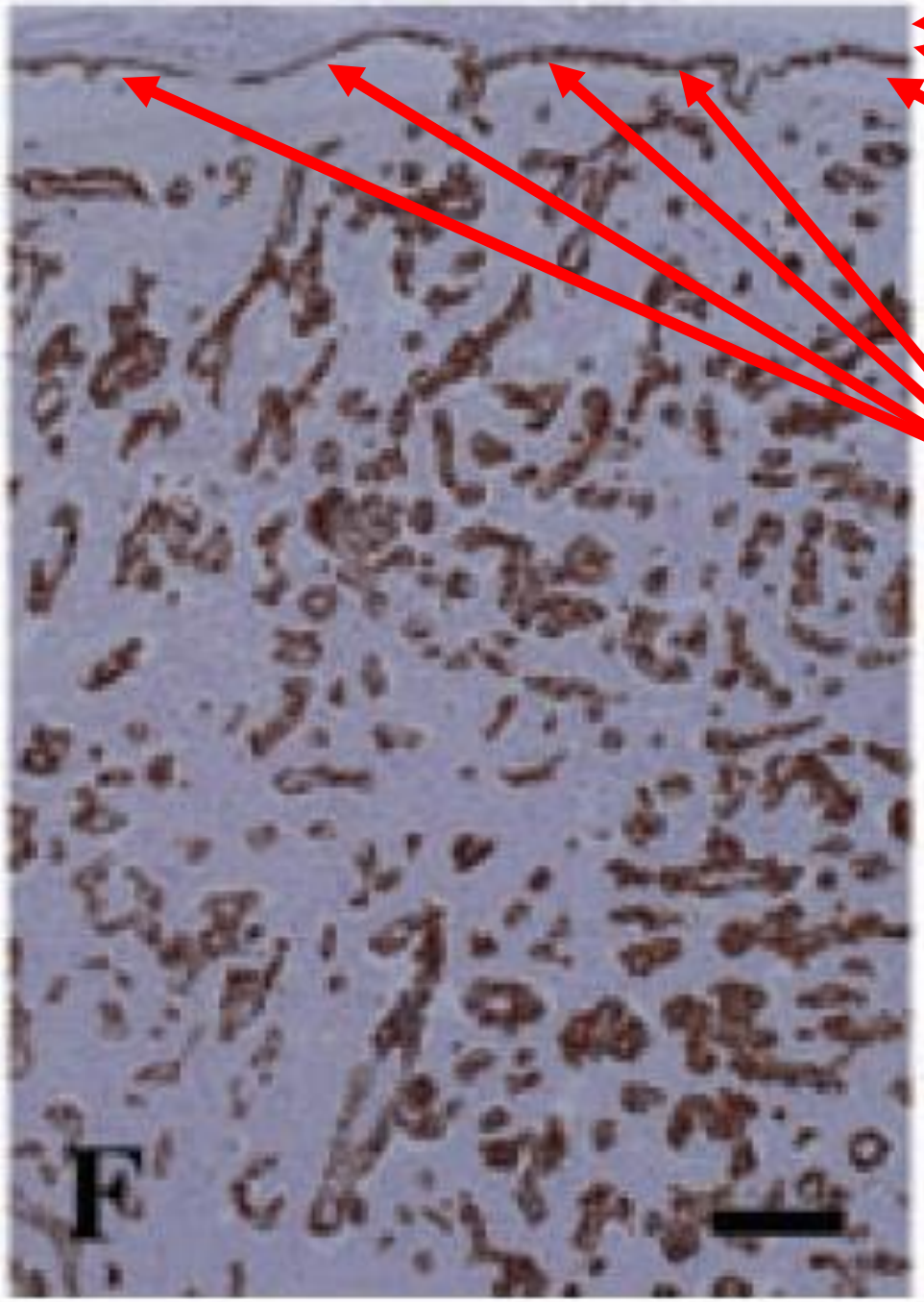

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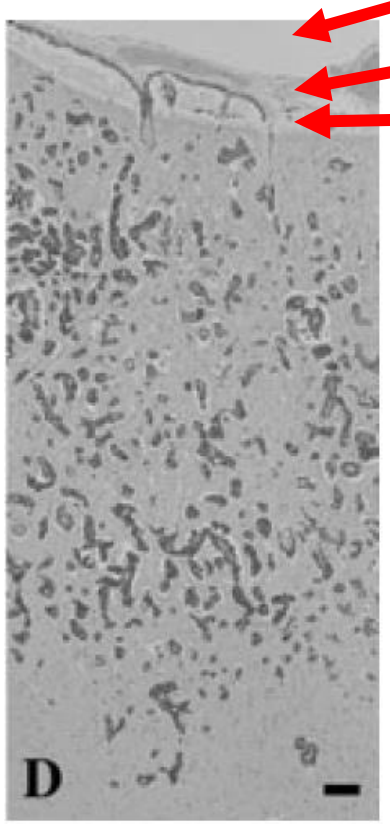

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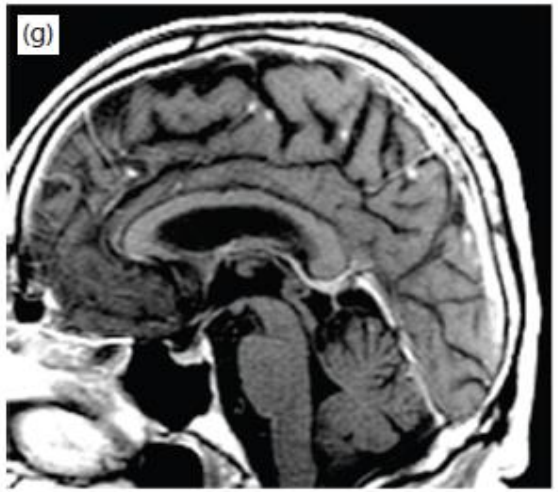
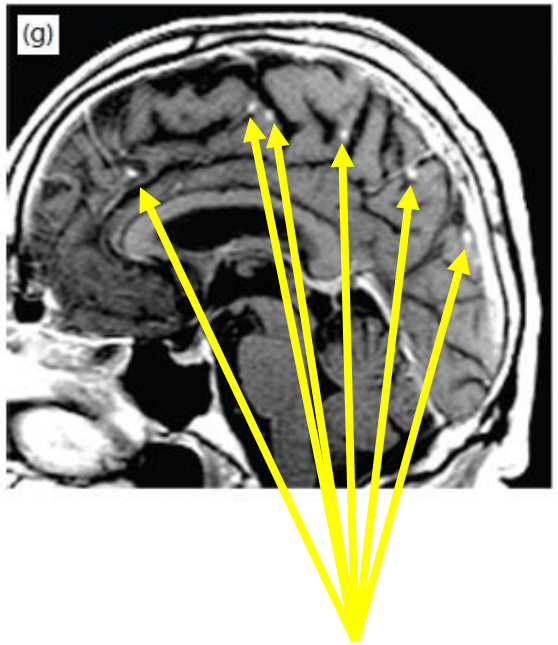


Cykowski MD, Ballester LY, Fuller GN. Metastatic Disease. Greenfields Neuropathology, **10E 2024** ISBN: 1032481374 ISBN13: 9781032481371



Metastatic tumor foci in the superficial gray matter cortical ribbon

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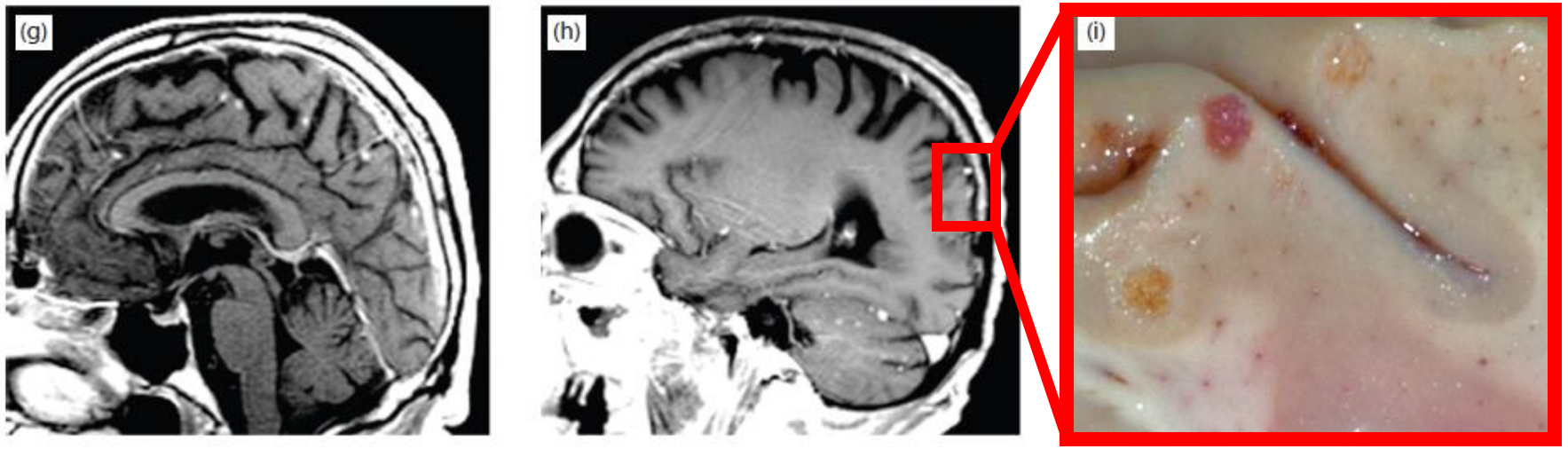

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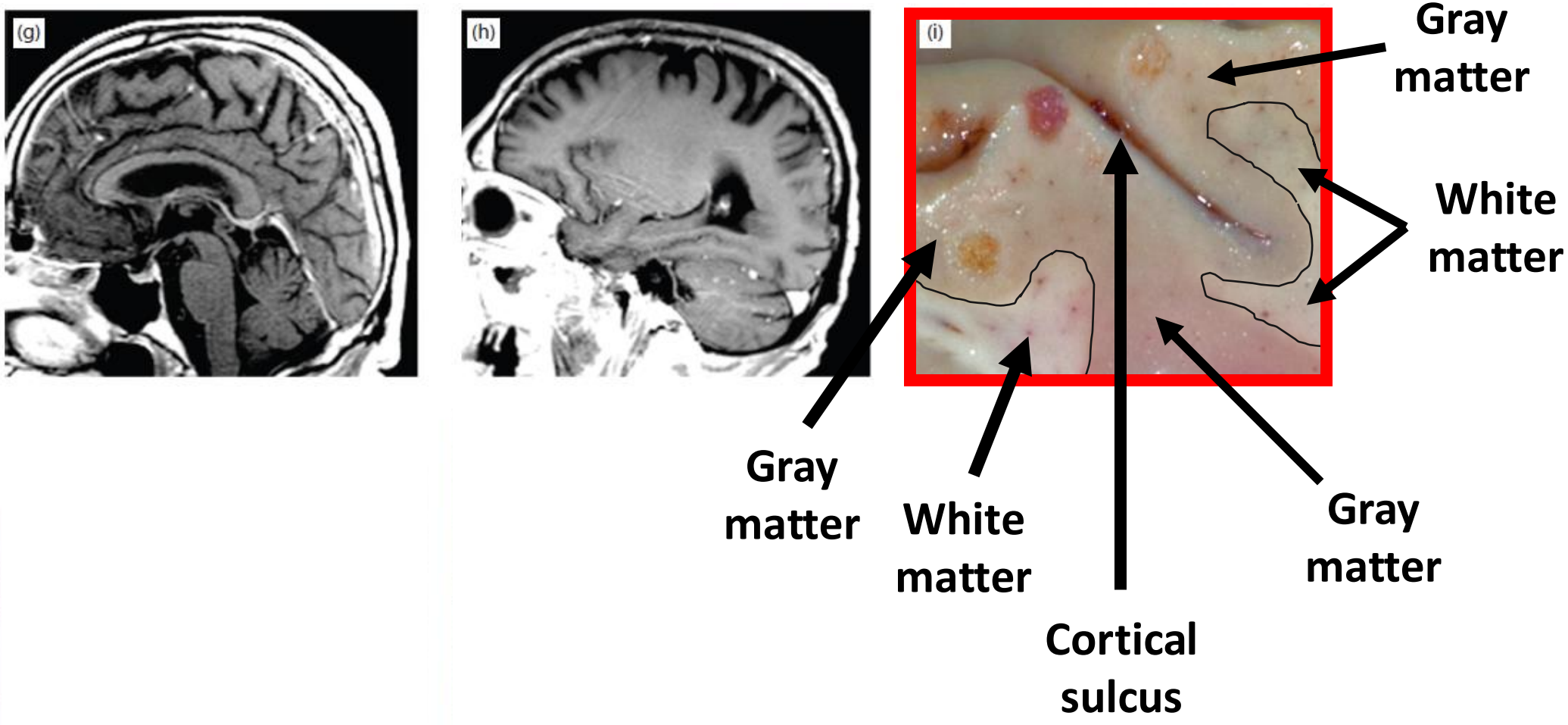

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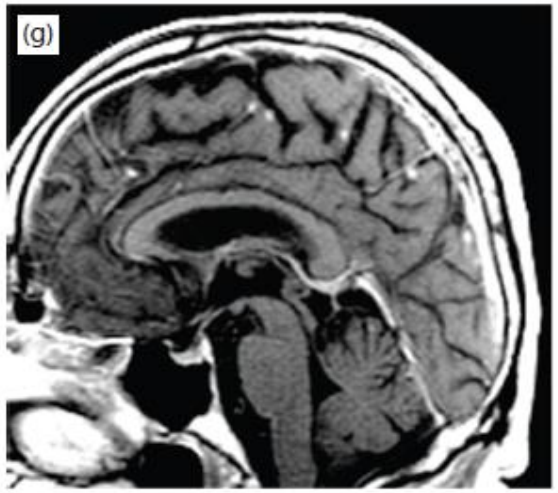

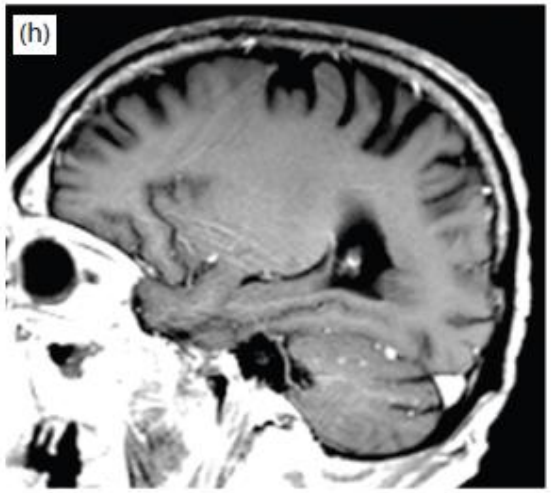

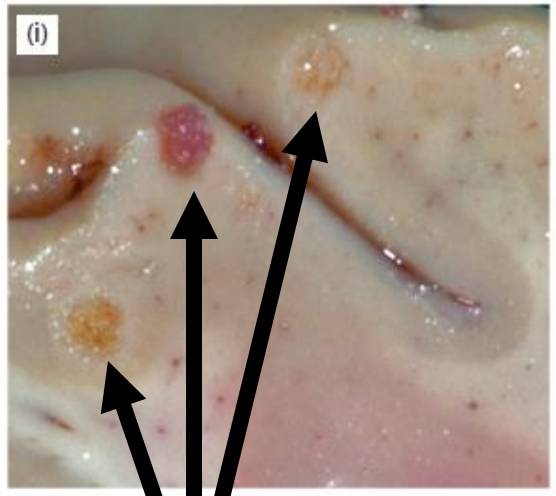

EVMM Metastatic Lesions in the gray cortical ribbon

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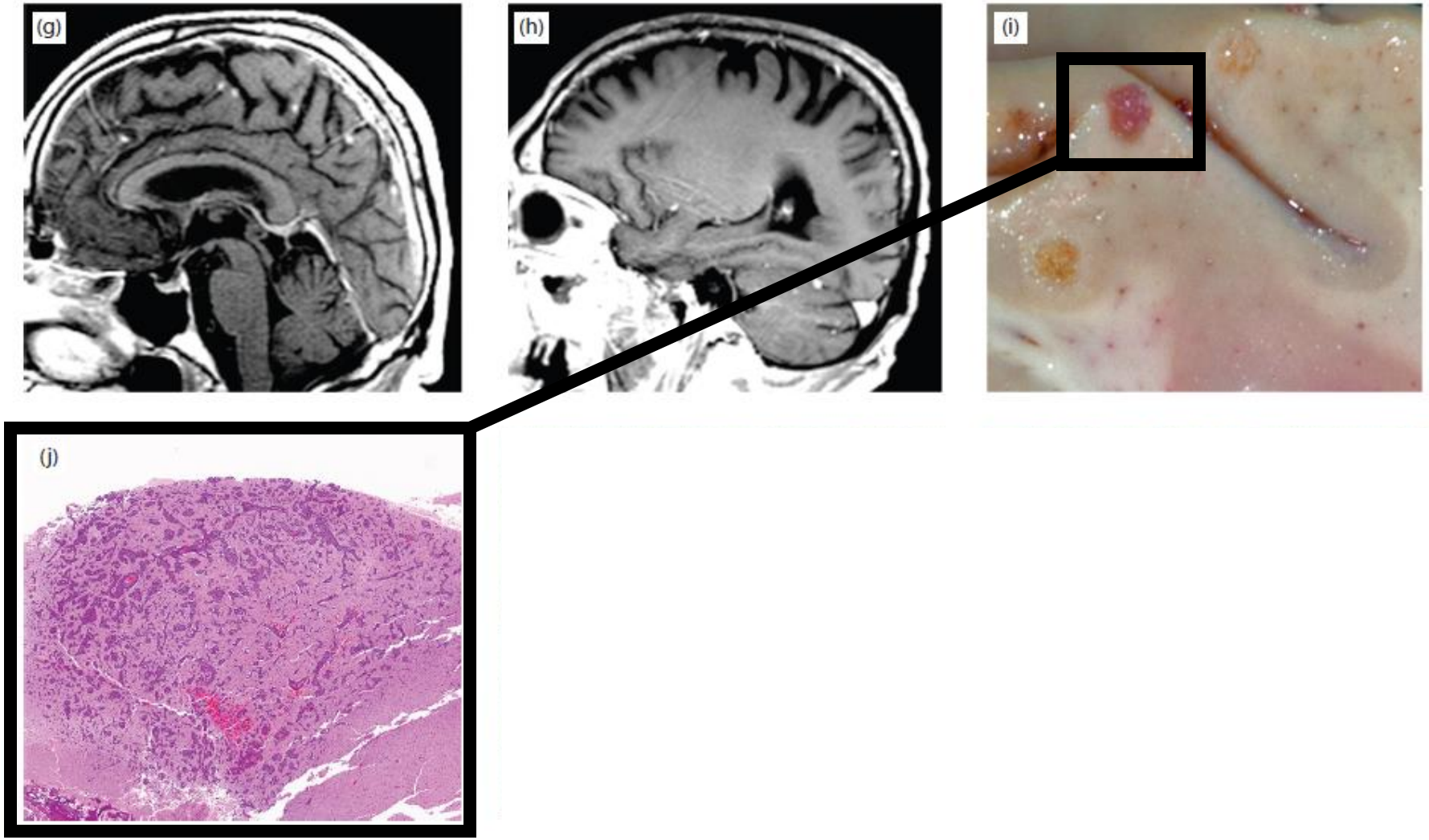

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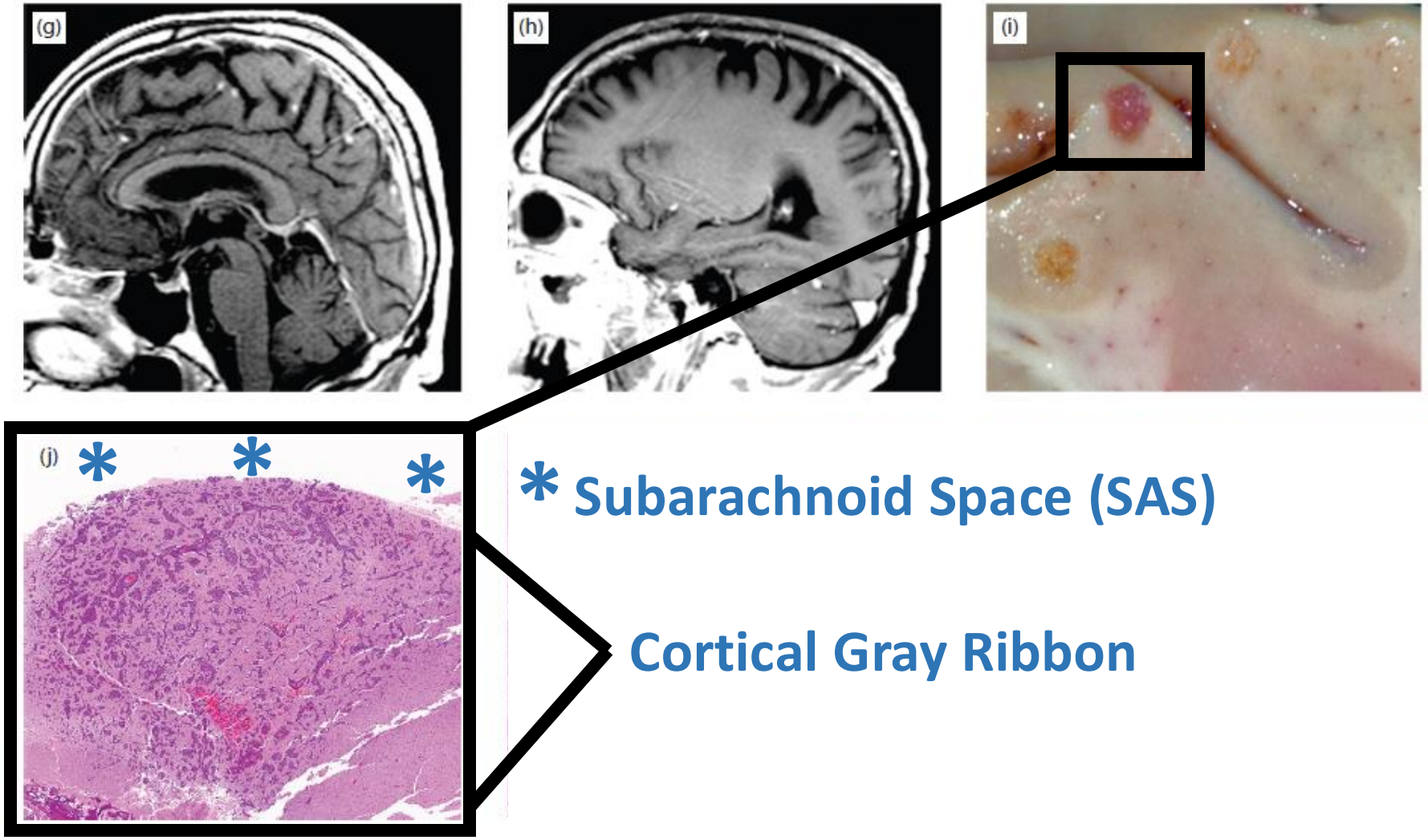

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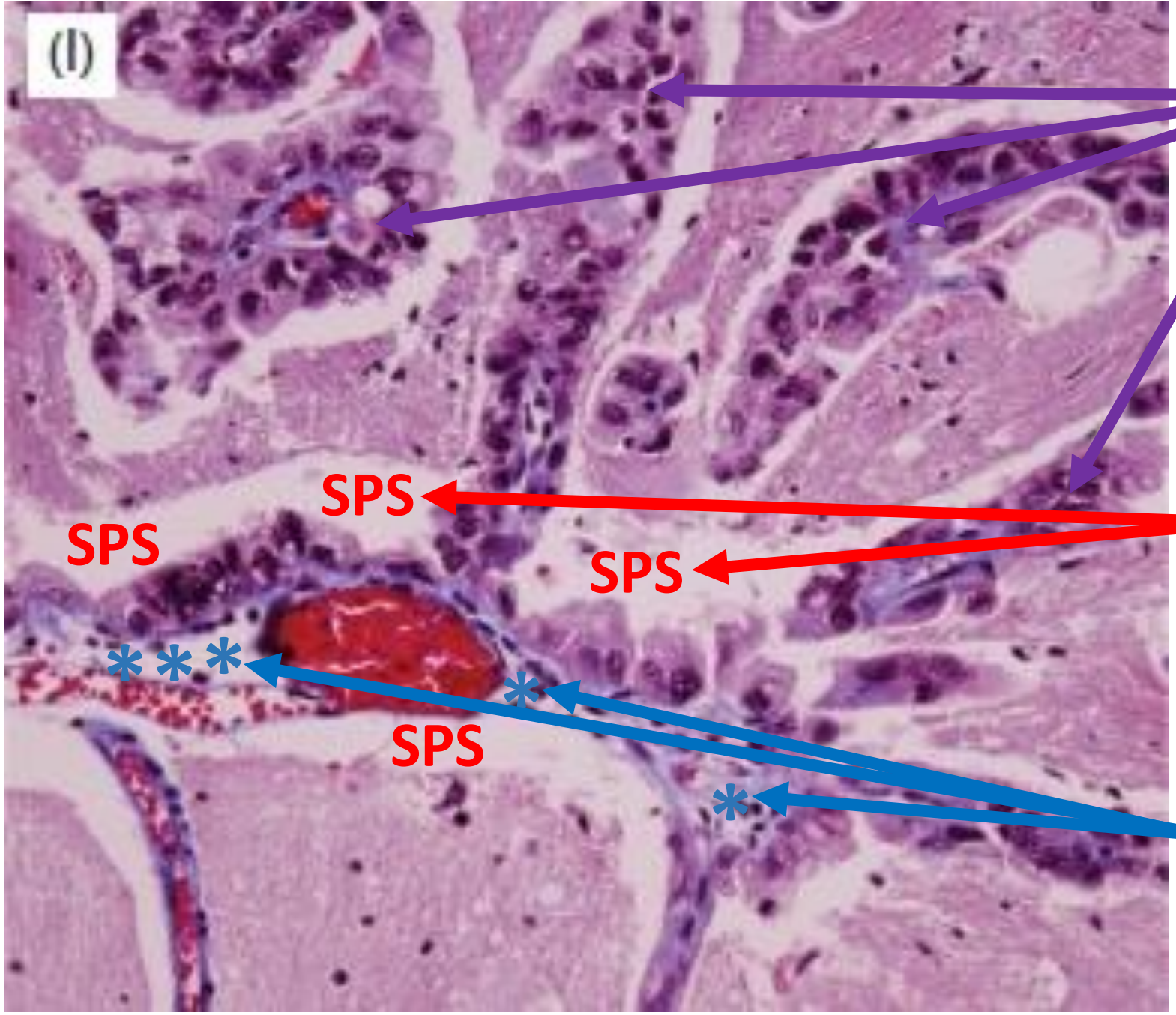

Metastatic Tumor in Perivascular Space Compartment

Subpial Space Compartment

* Subarachnoid Space Compartment

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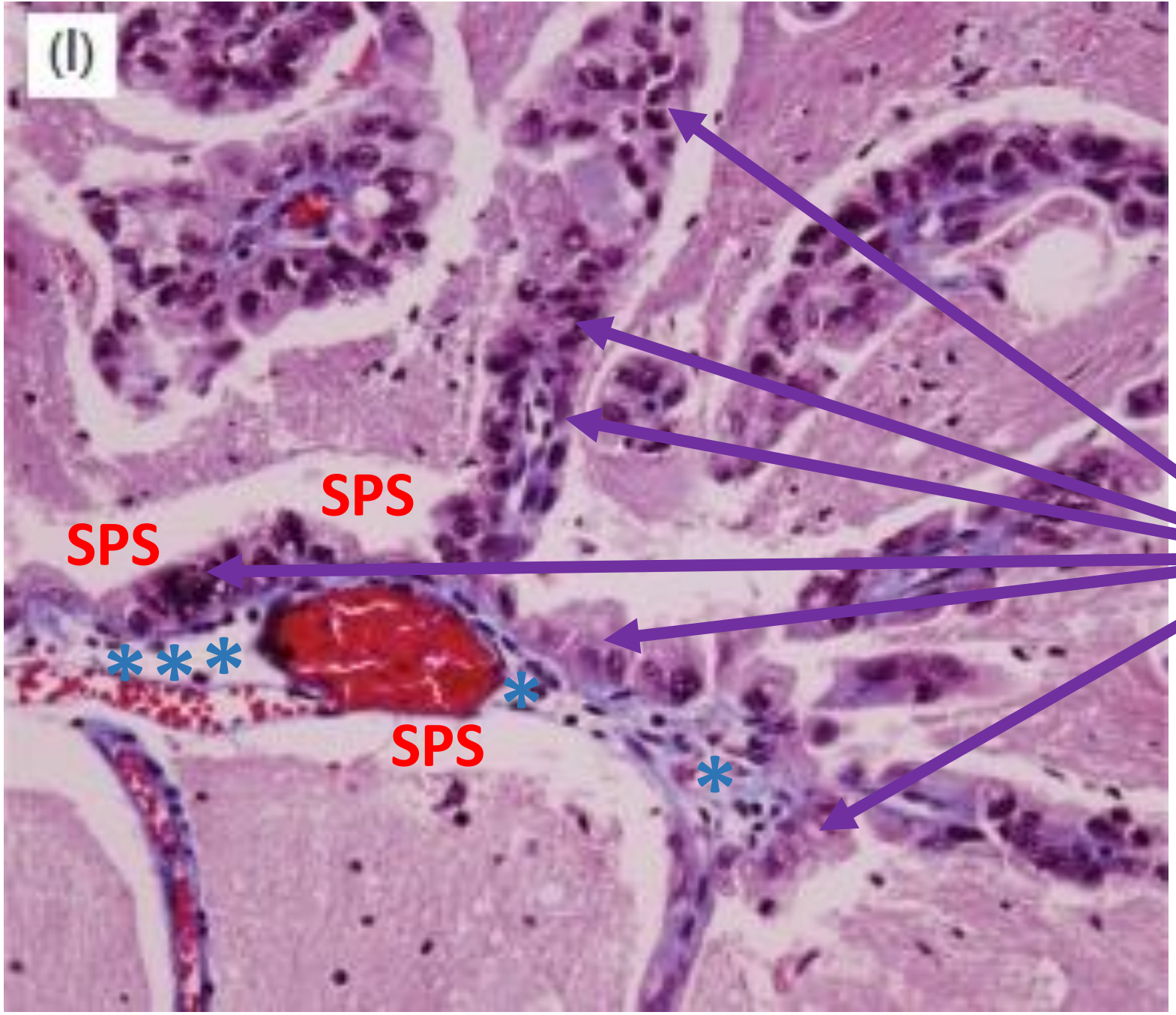

Extravascular Migratory Metastasis (EVMM)

Metastatic Tumor in Perivascular Space/Subpial Space Compartment

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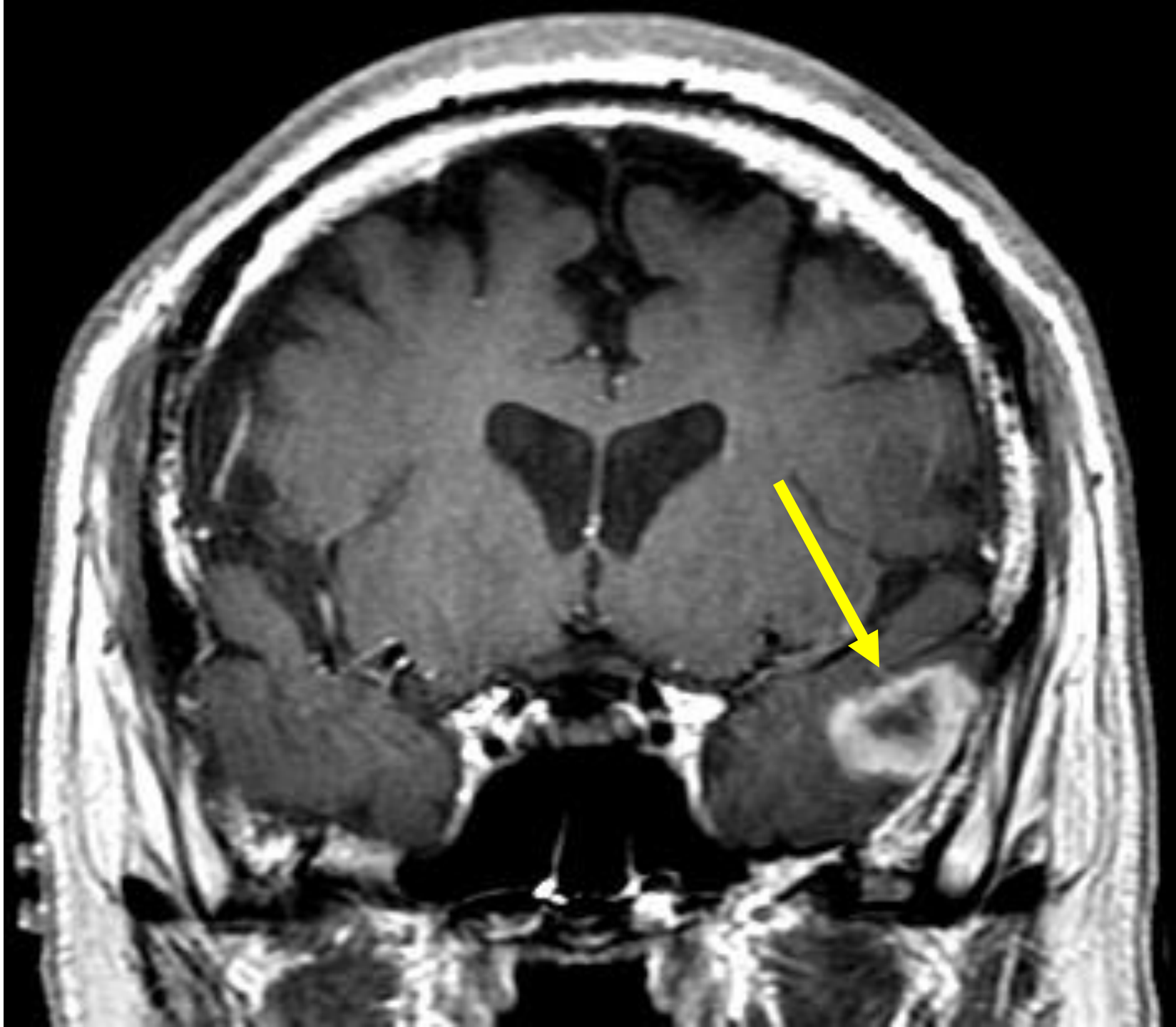
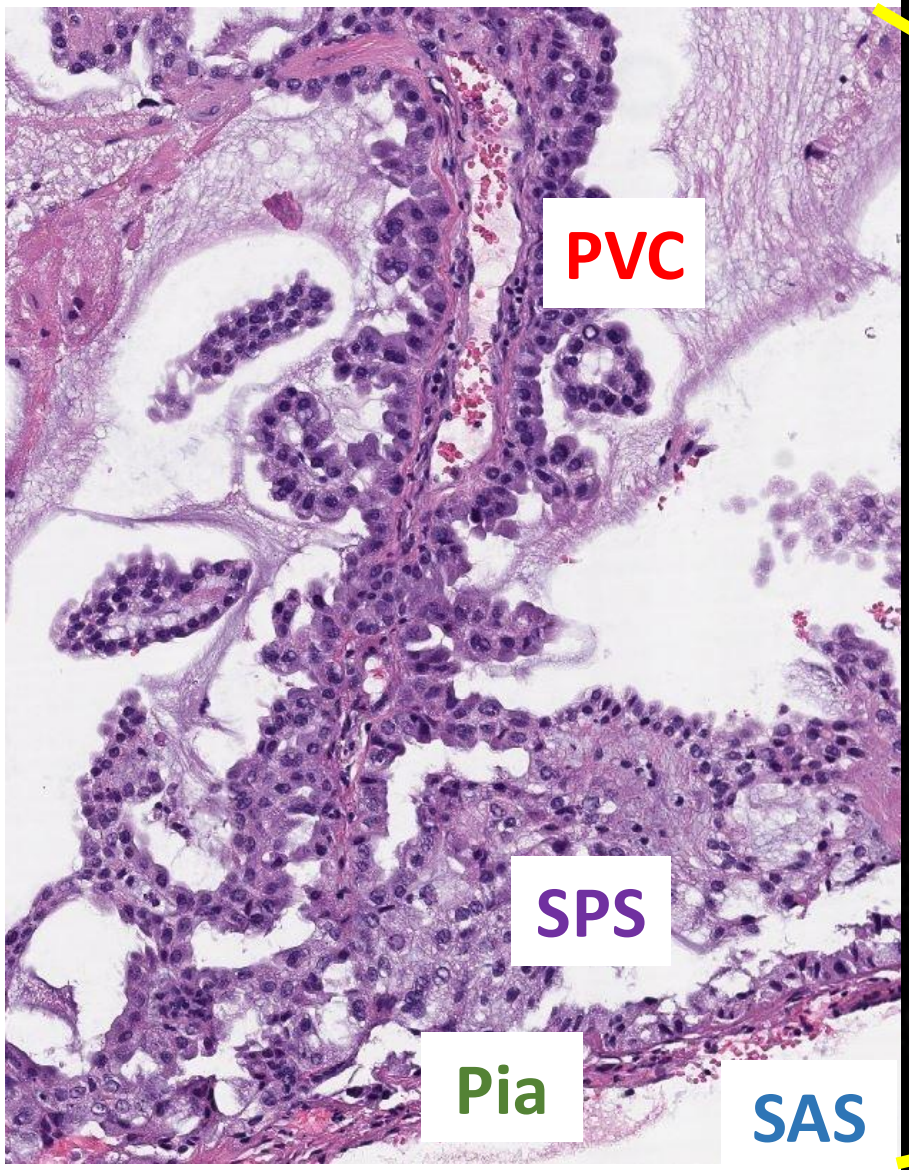
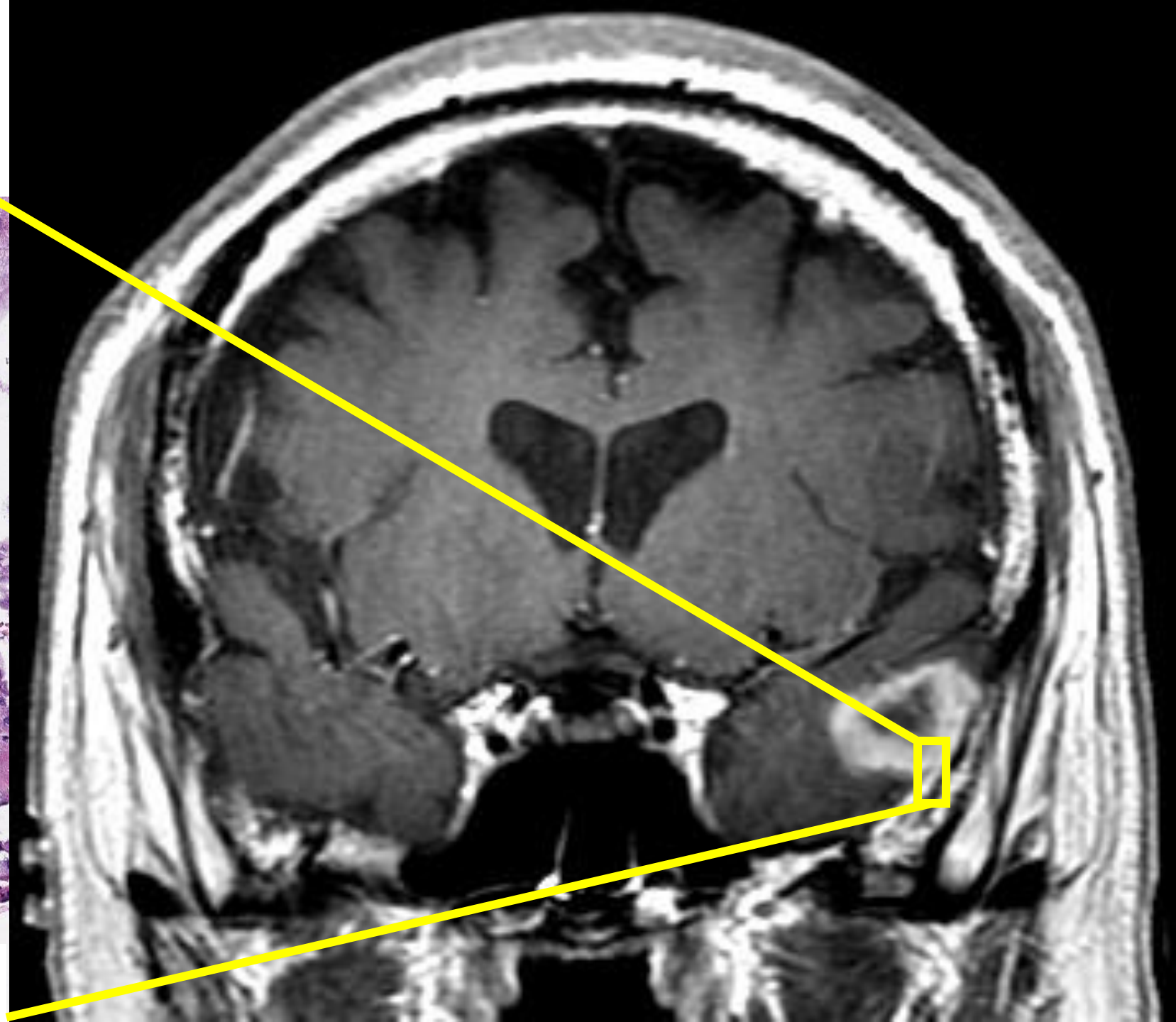
Lung Mucinous Adenoca



Lung Mucinous Adenoca

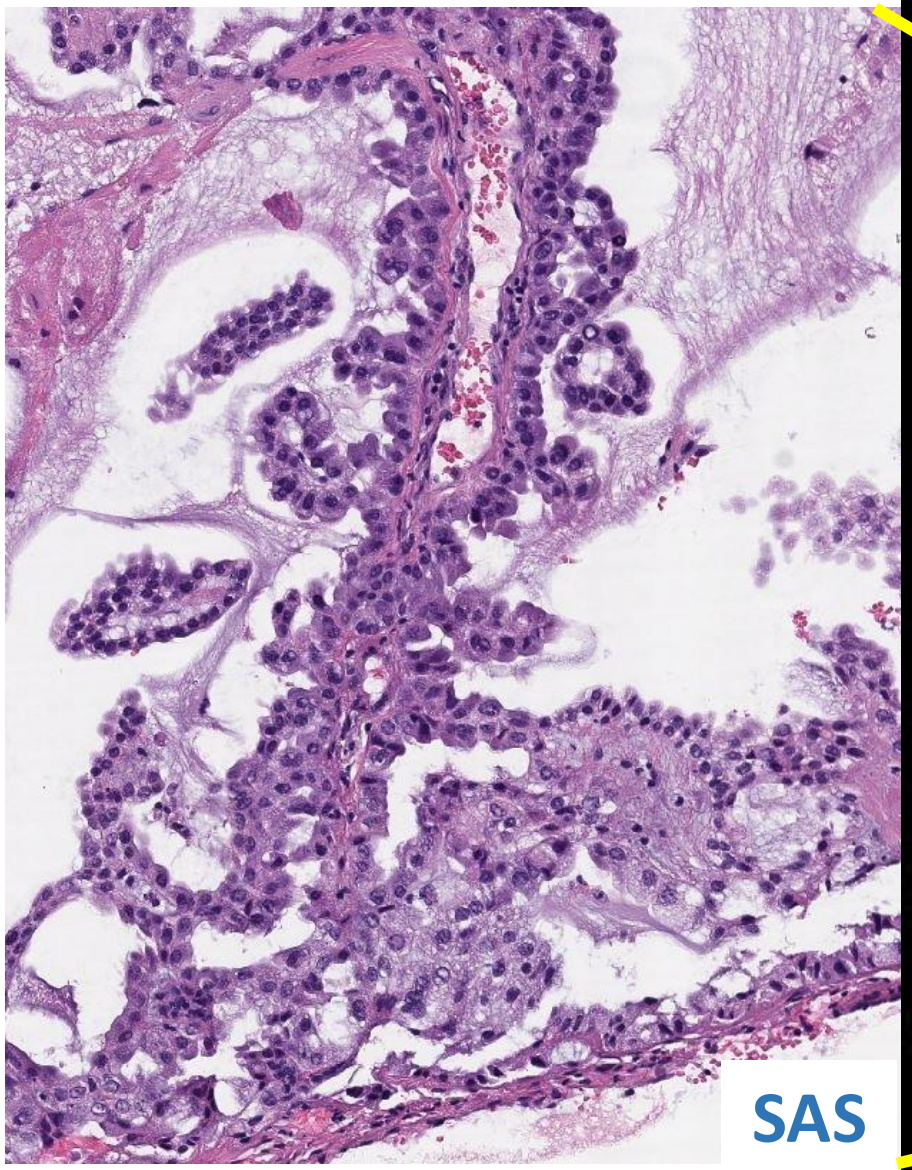
EVMM





Lung Mucinous Adenoca

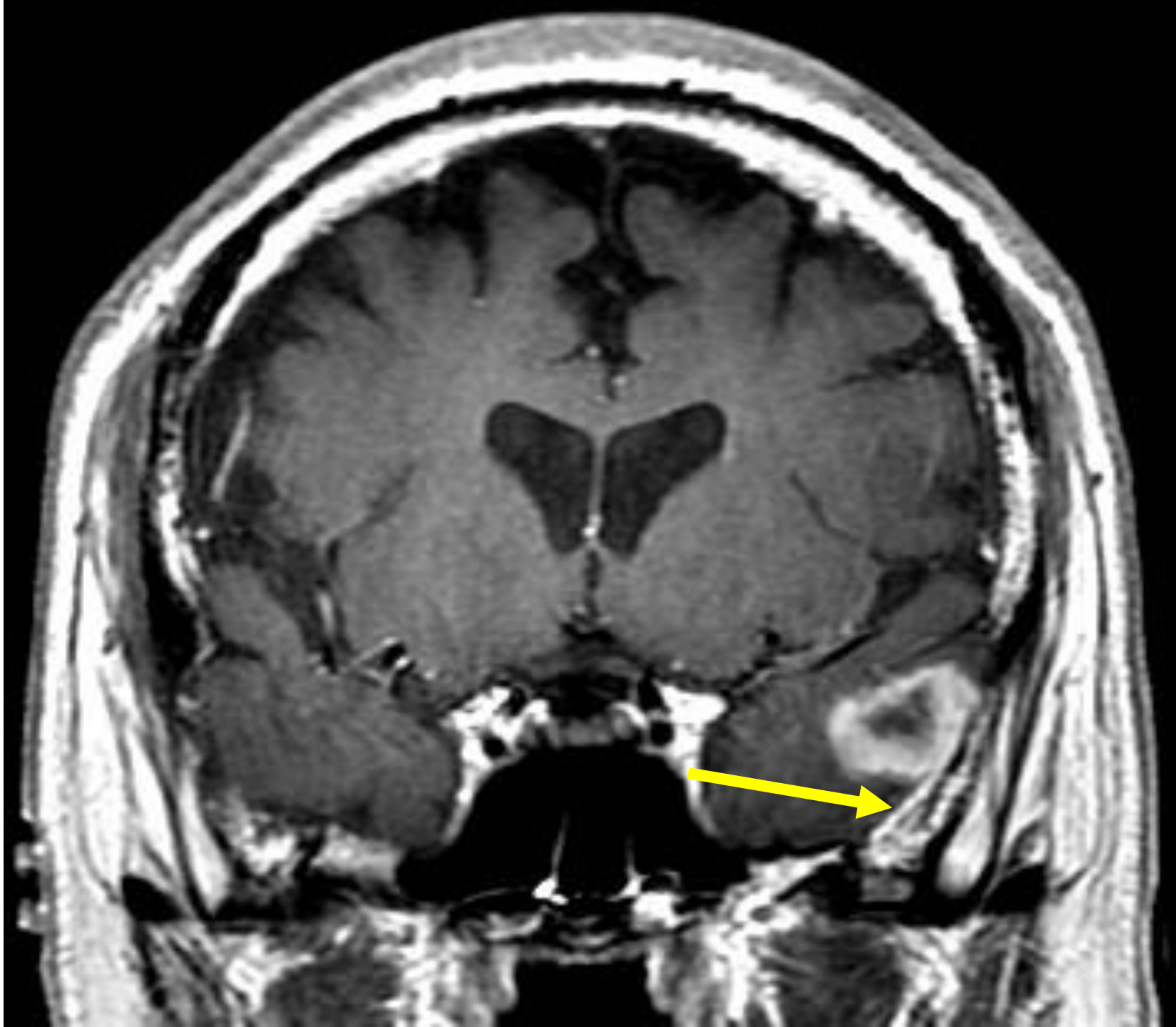
EVMM



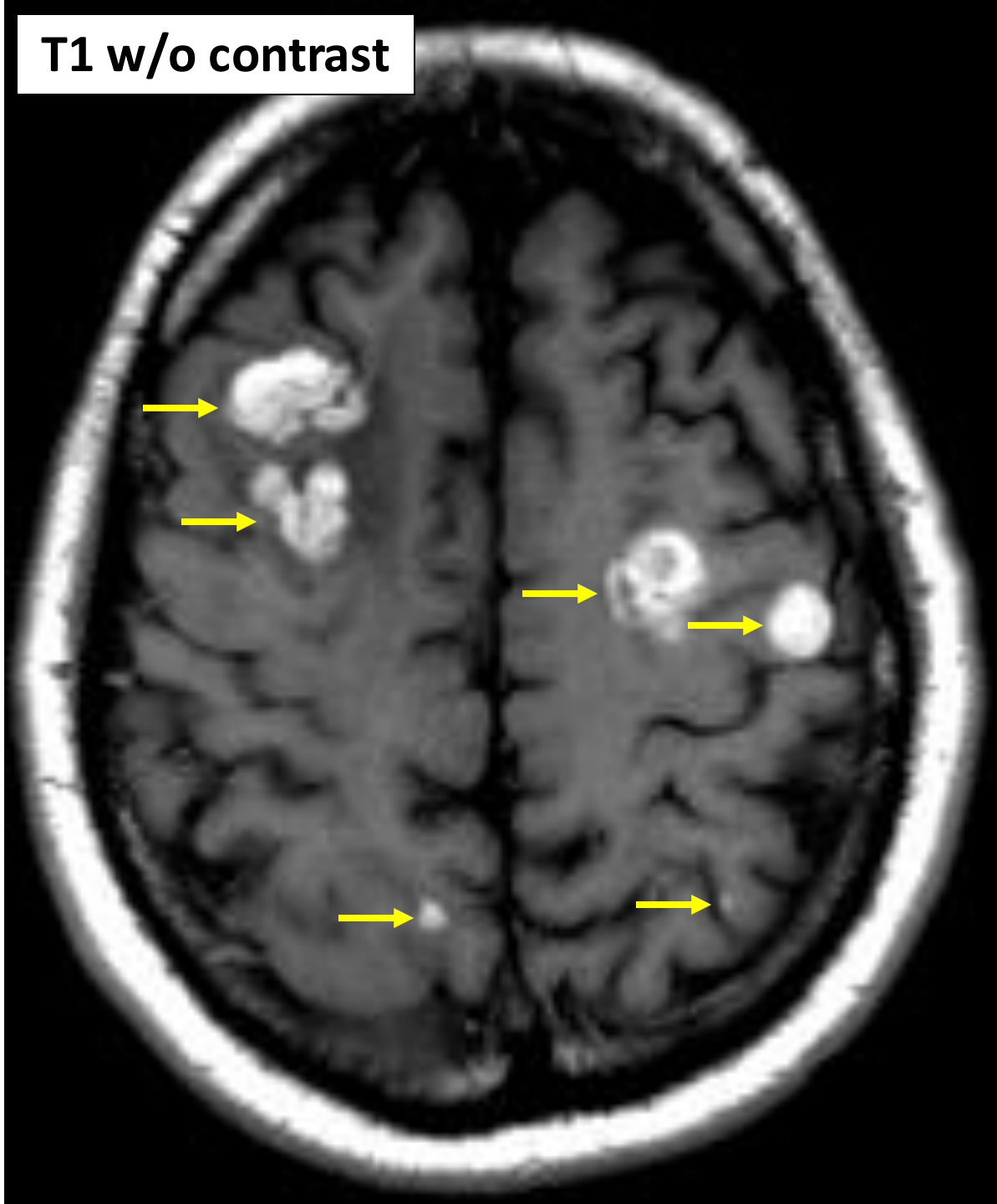
SAS

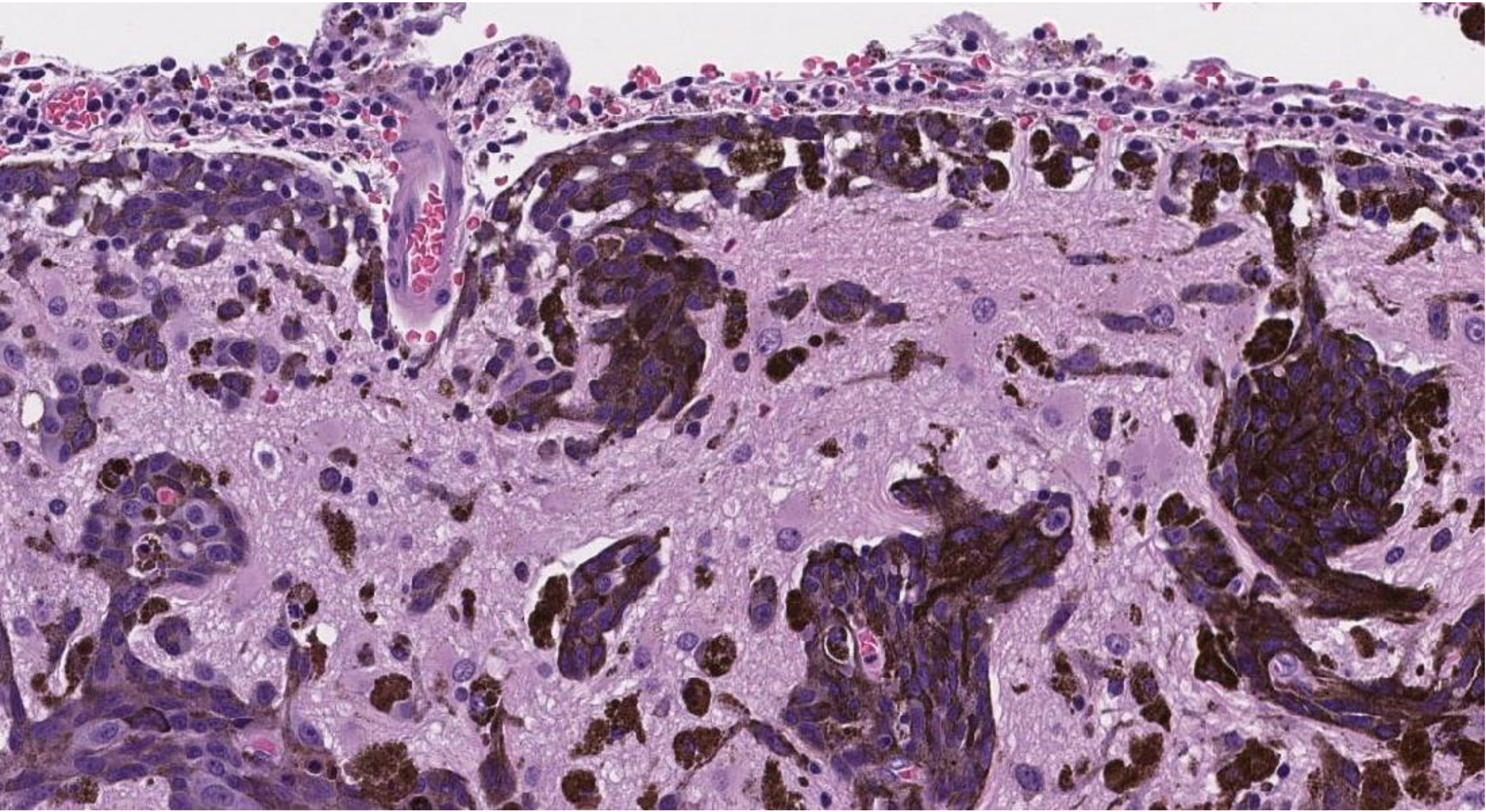
Lung Mucinous Adenoca

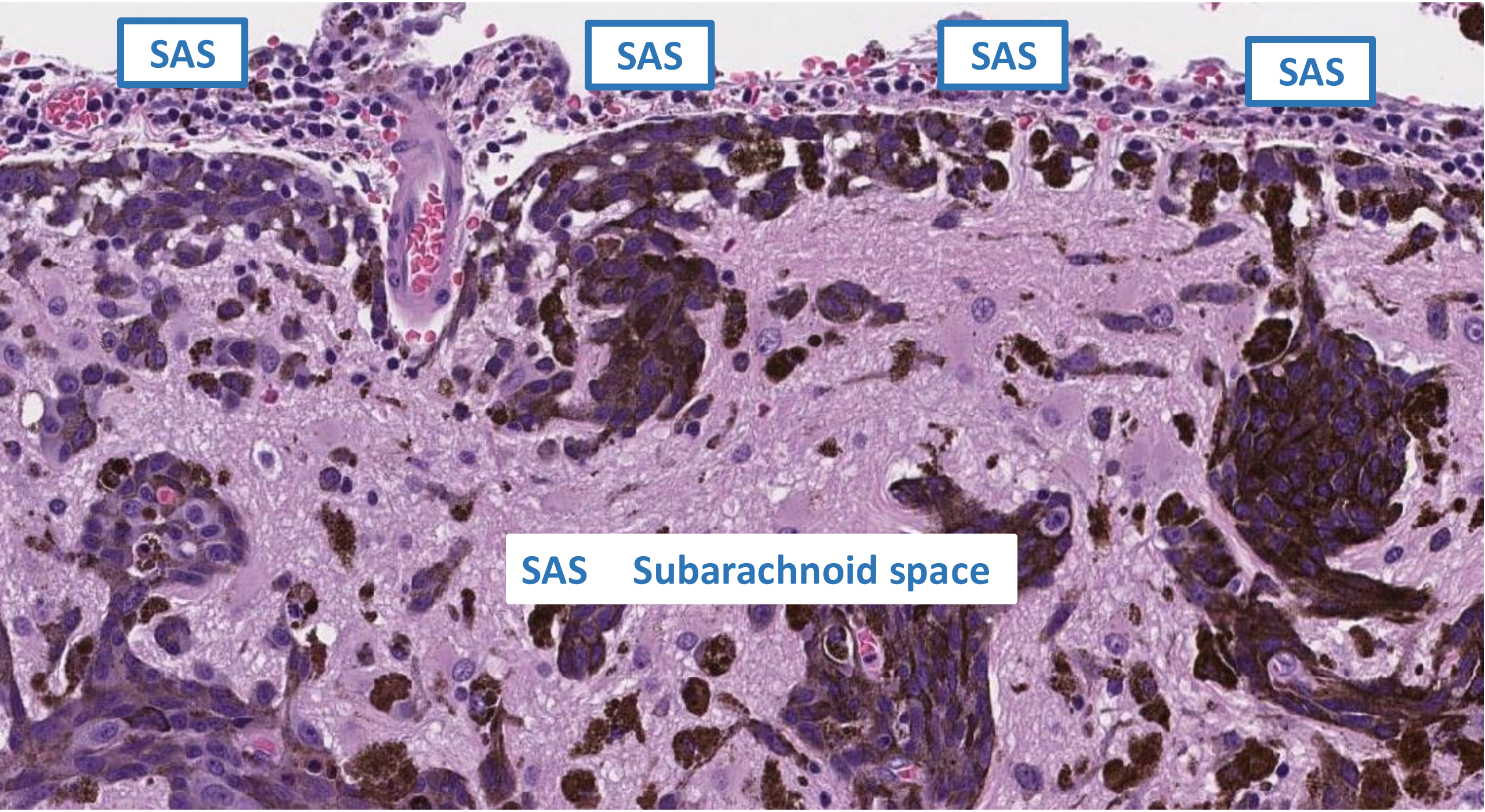
EVMM in the subpial space mimics LMD!

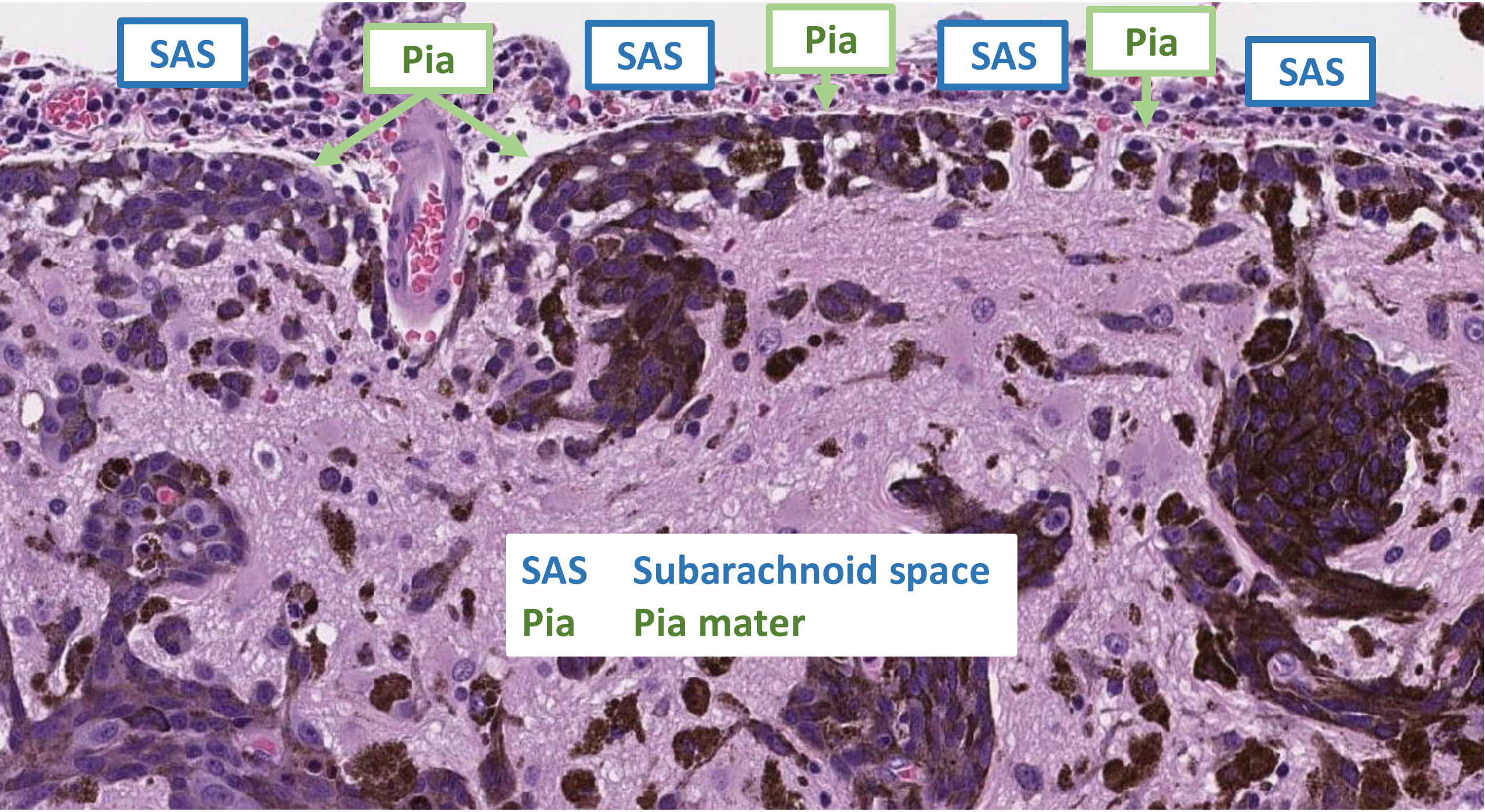


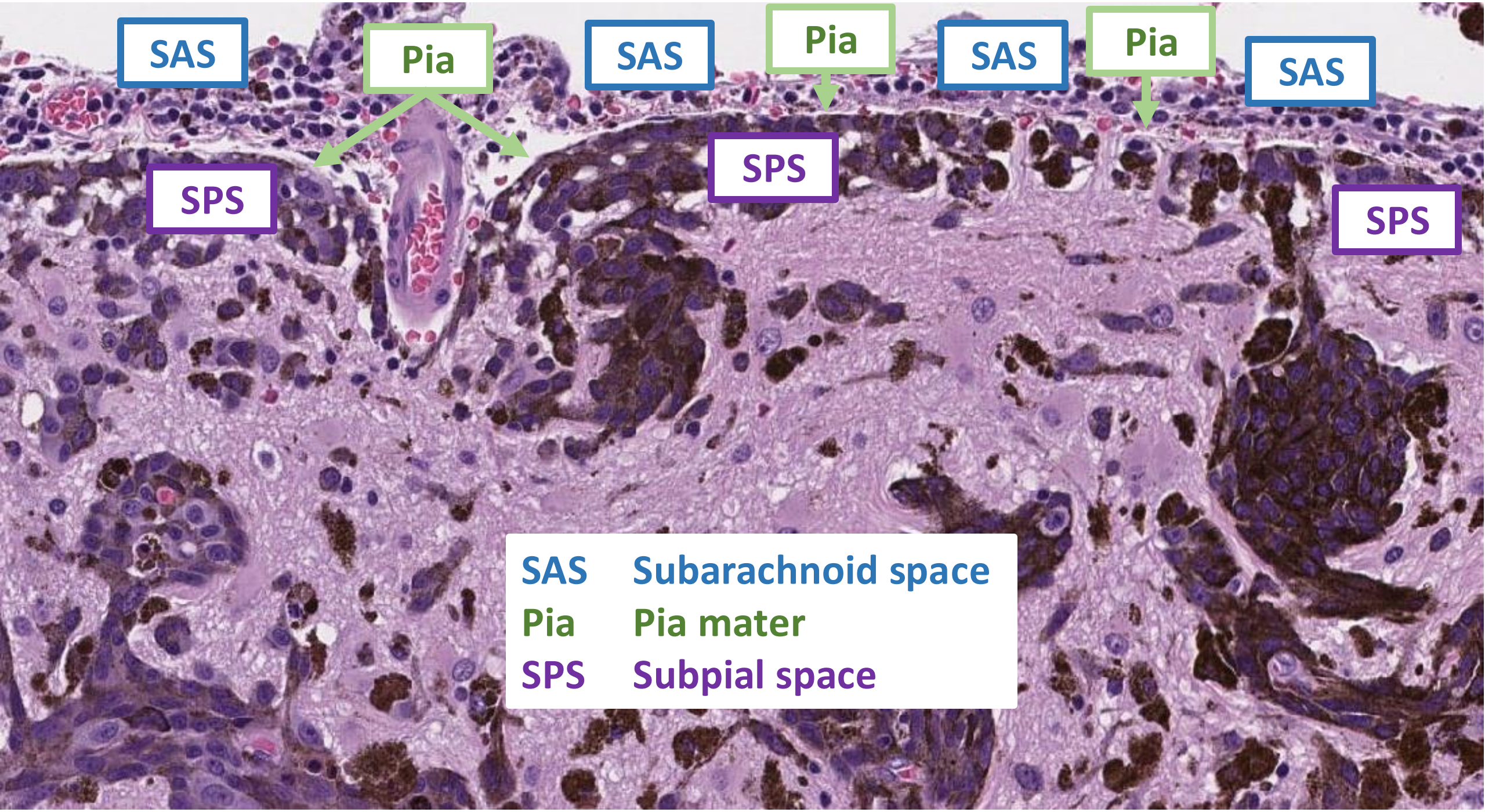
Metastatic Melanoma

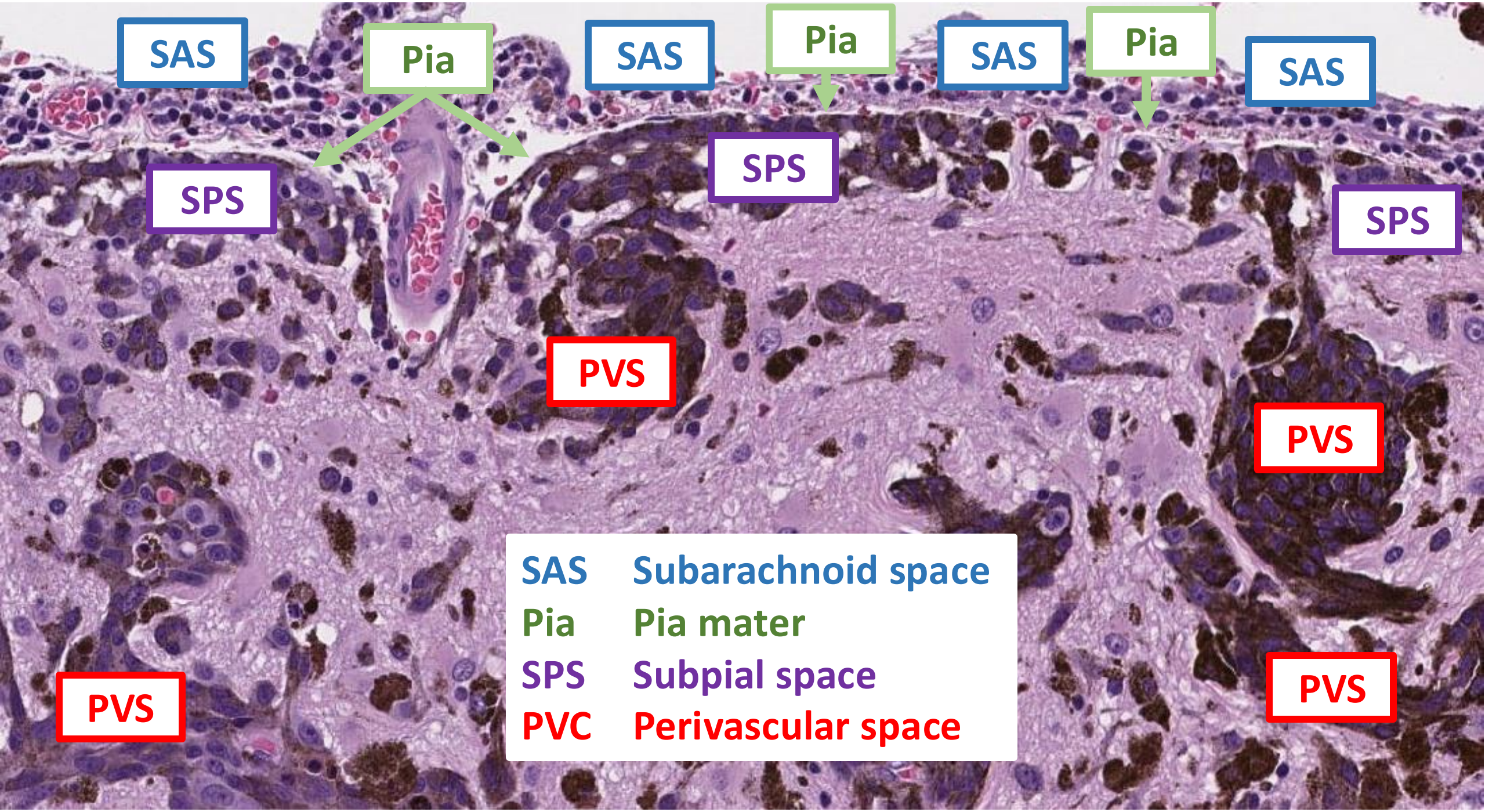


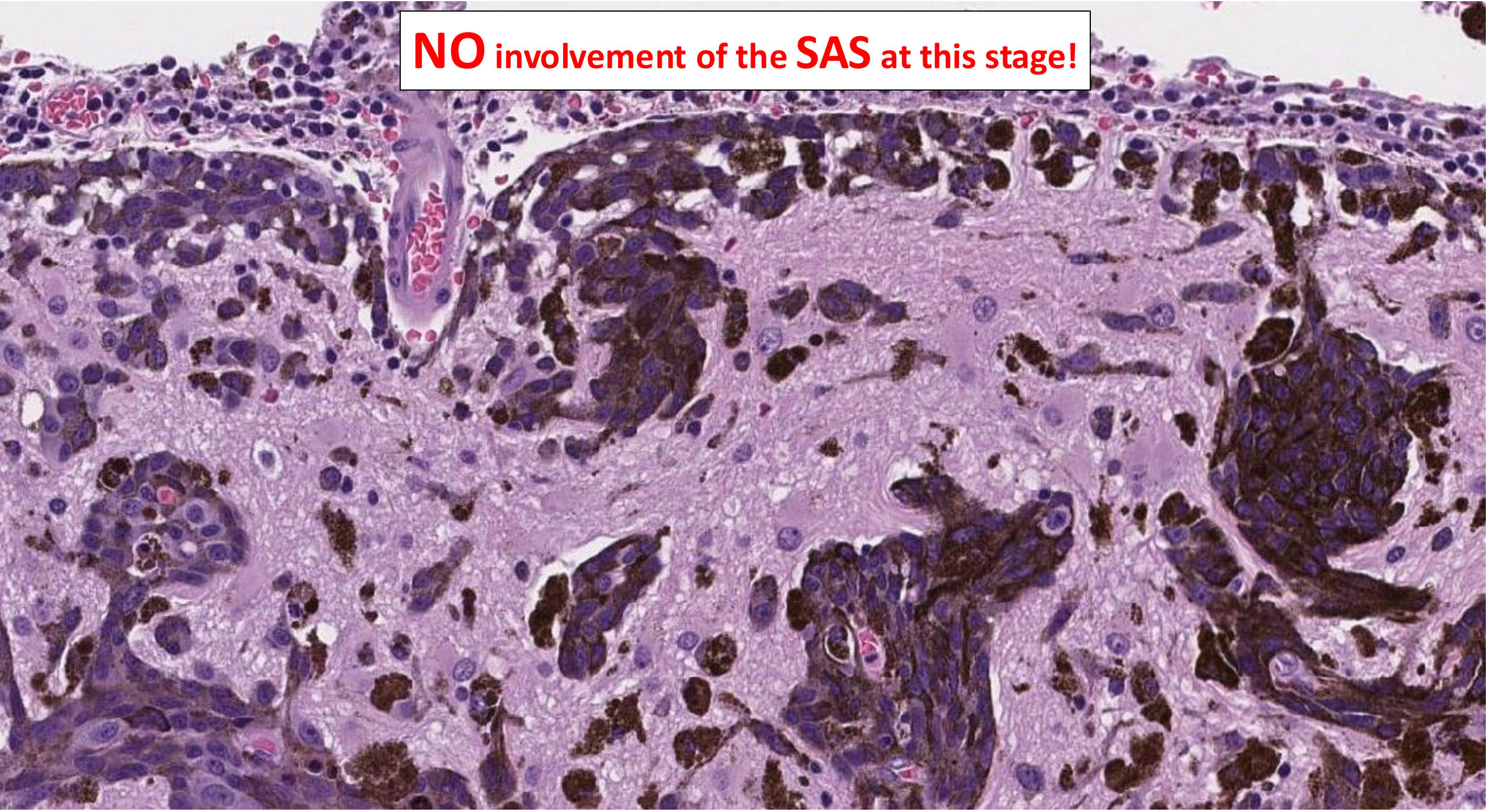


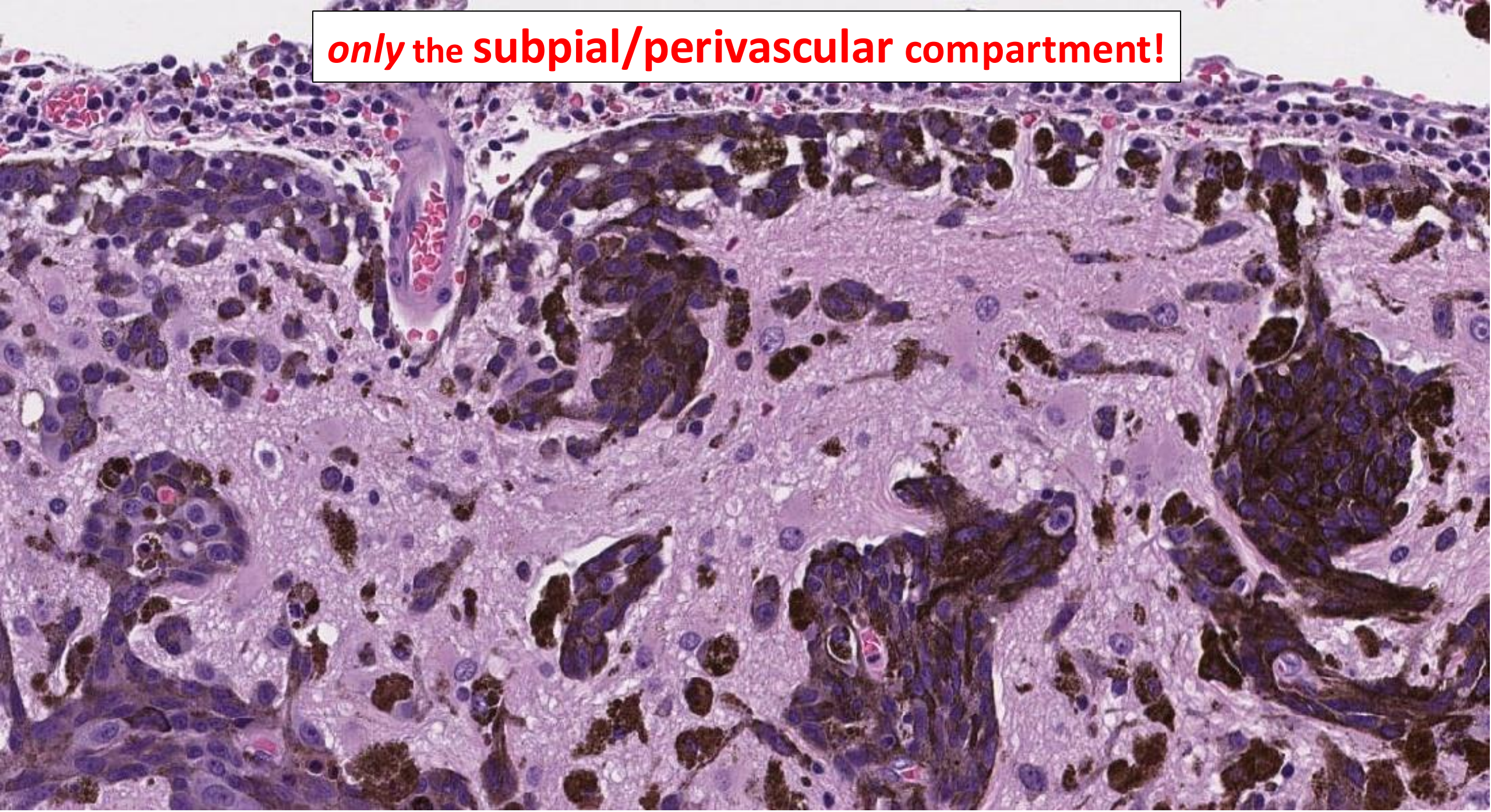

SAS
SAS
SAS
SAS
SAS Subarachnoid space


SAS
Pia
SAS
Pia
SAS
Pia
SAS
SAS Subarachnoid space
Pia Pia mater

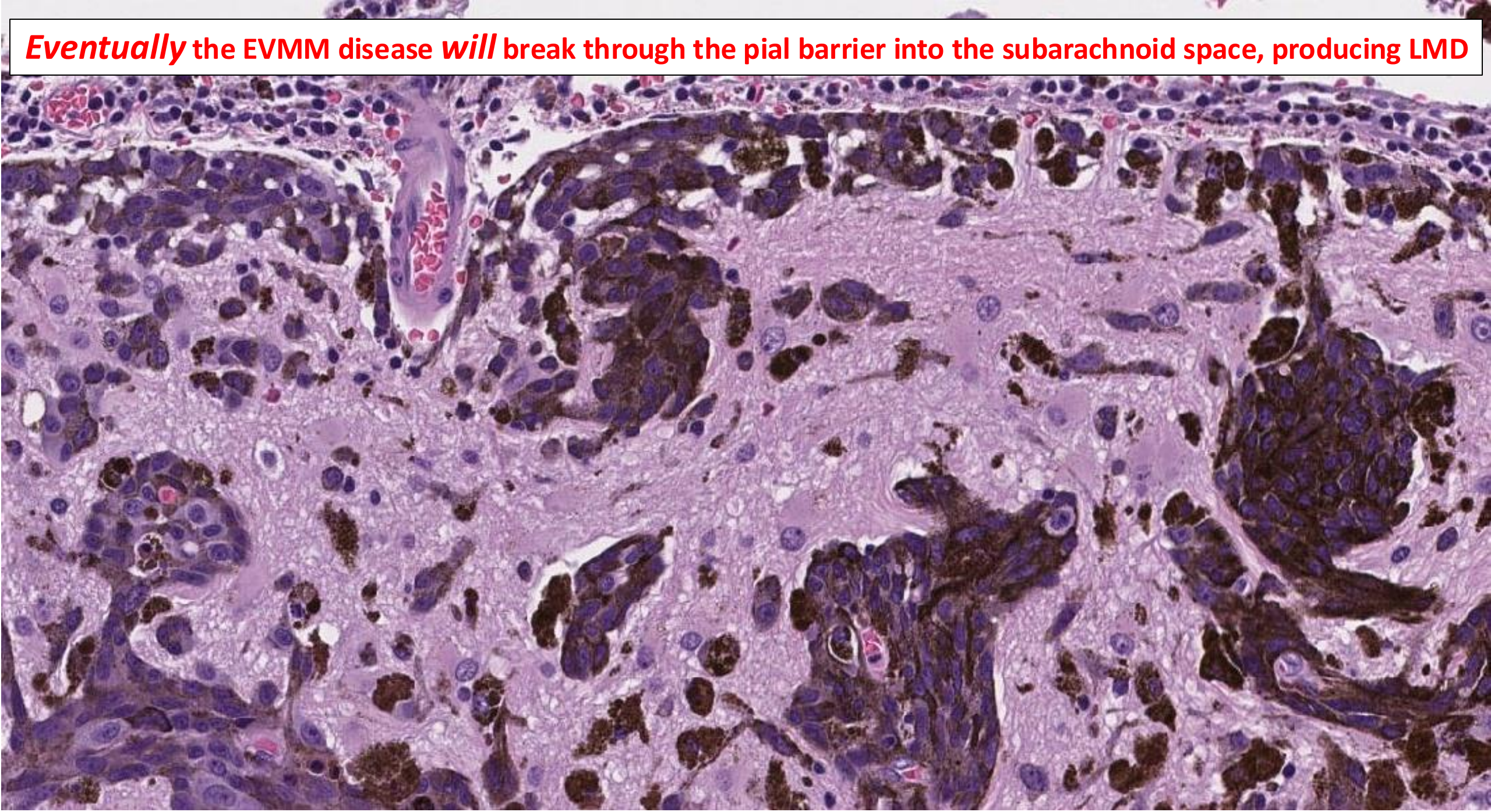

SAS
Pia
SAS
Pia
SAS
Pia
SAS
SPS
SPS
SPS
SAS Subarachnoid space
Pia Pia mater
SPS Subpial space


SAS
Pia
SAS
Pia
SAS
Pia
SAS
SPS
SPS
SPS
PVS
PVS
PVS
PVS
SAS Subarachnoid space
Pia Pia mater
SPS Subpial space
PVC Perivascular space


NO involvement of the SAS at this stage!


only the subpial/perivascular compartment!

Eventually **the EVMM disease *will* break through the pial barrier into the subarachnoid space, producing LMD**



Prevalence of LM/Subpial/PVS Compartment Metastatic Disease

Prevalence of SUPERFICIAL* Metastatic Disease

*SAS + 2.5mm cortical ribbon

BJC British Journal of Cancer

www.nature.com/bjc

BJC 2020
PMC7591856

ARTICLE

Molecular Diagnostics

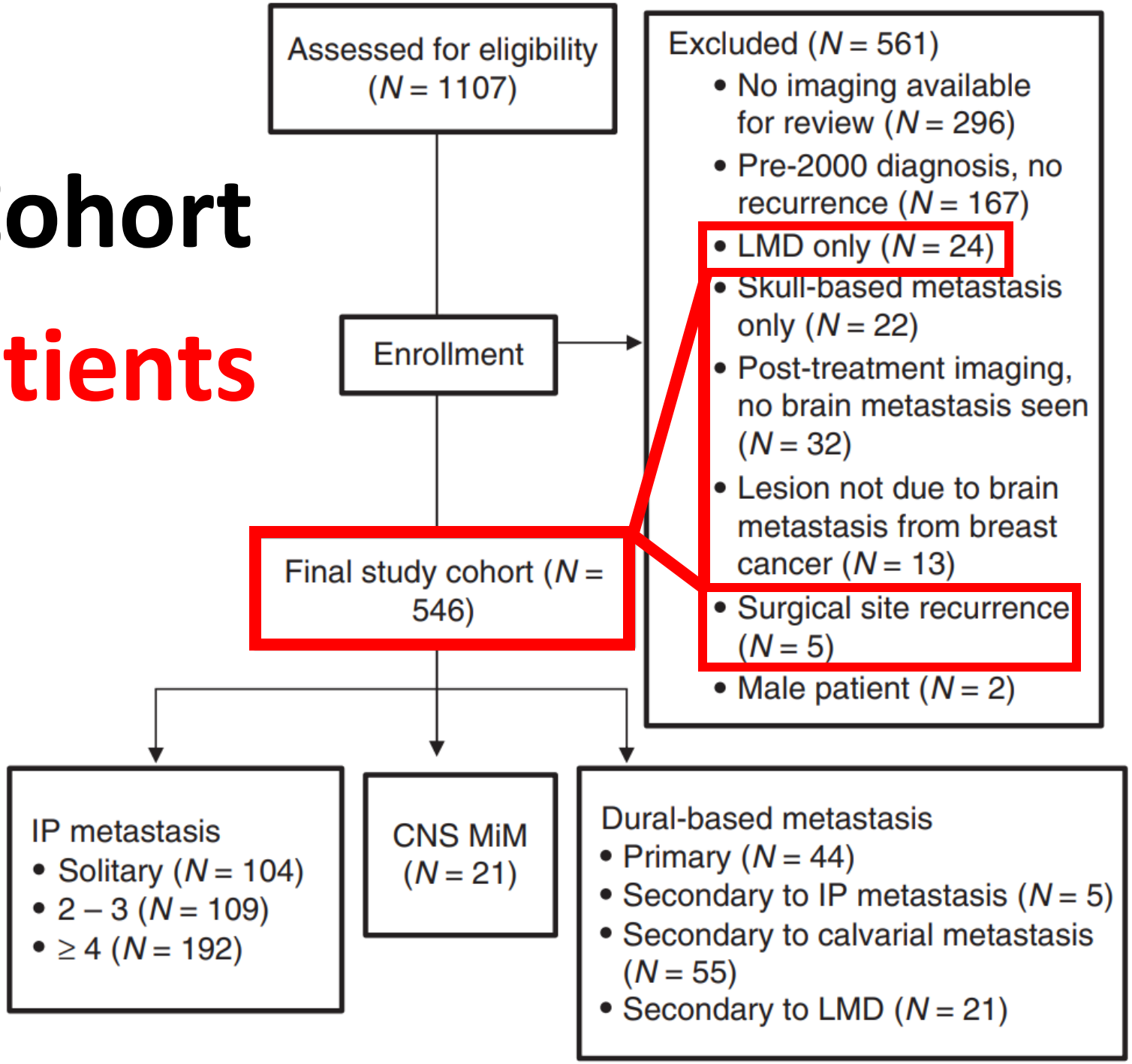
Central nervous system miliary metastasis in breast cancer: a case series analysis and proposed identification criteria of a rare metastasis subtype

Sami I. Bashour[1], Nuhad K. Ibrahim[1], Donald F. Schomer[2], Kenneth R. Hess[3], Chao Gao[1,4], Debu Tripathy[1] and Gregory N. Fuller[5]

BJC 2020
PMC7591856

Study Cohort

575 patients



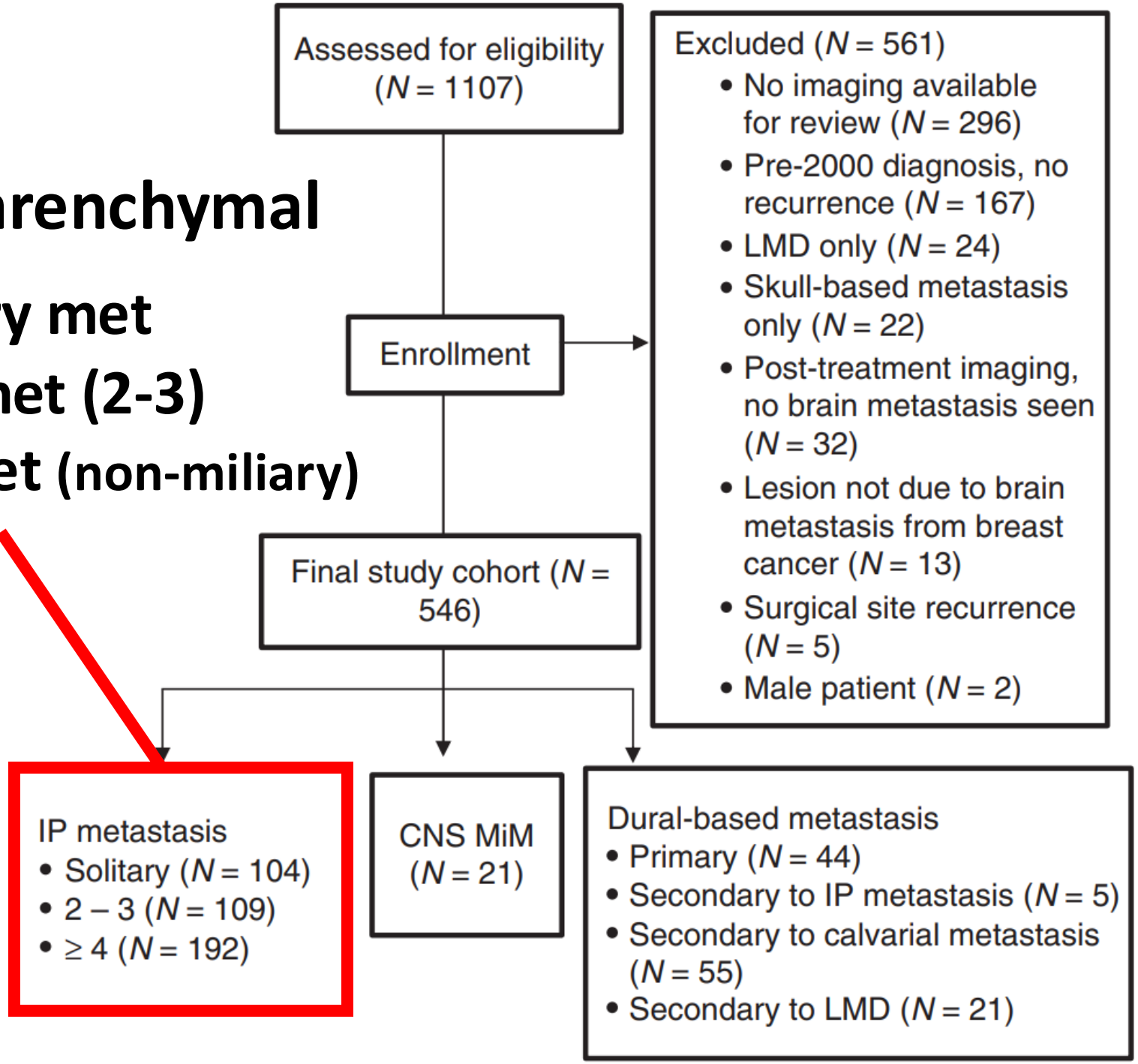
BJC 2020
PMC7591856

70% Intraparenchymal

50% Solitary met

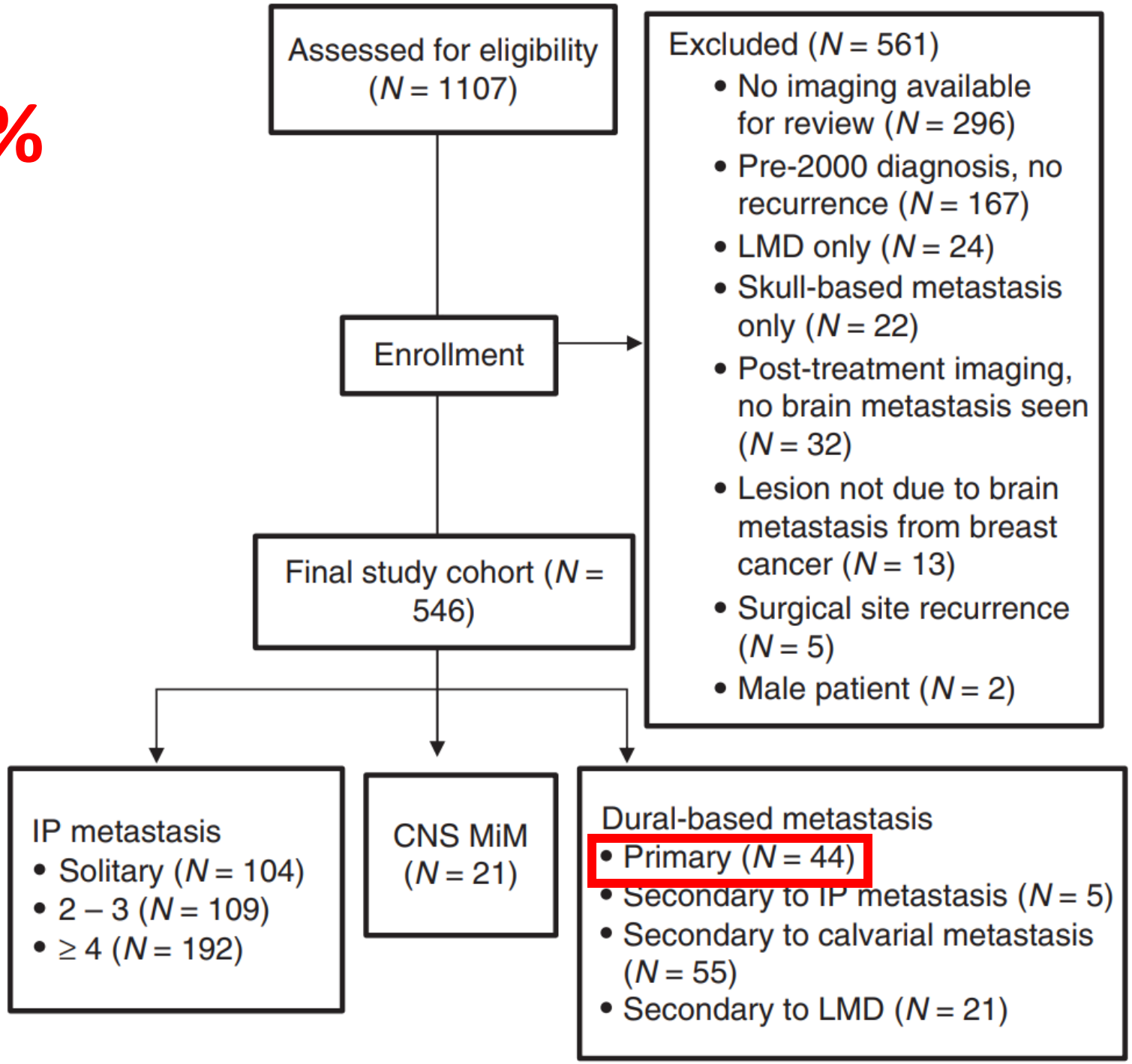
25% Oligomet (2-3)

25% Polymet (non-miliary)



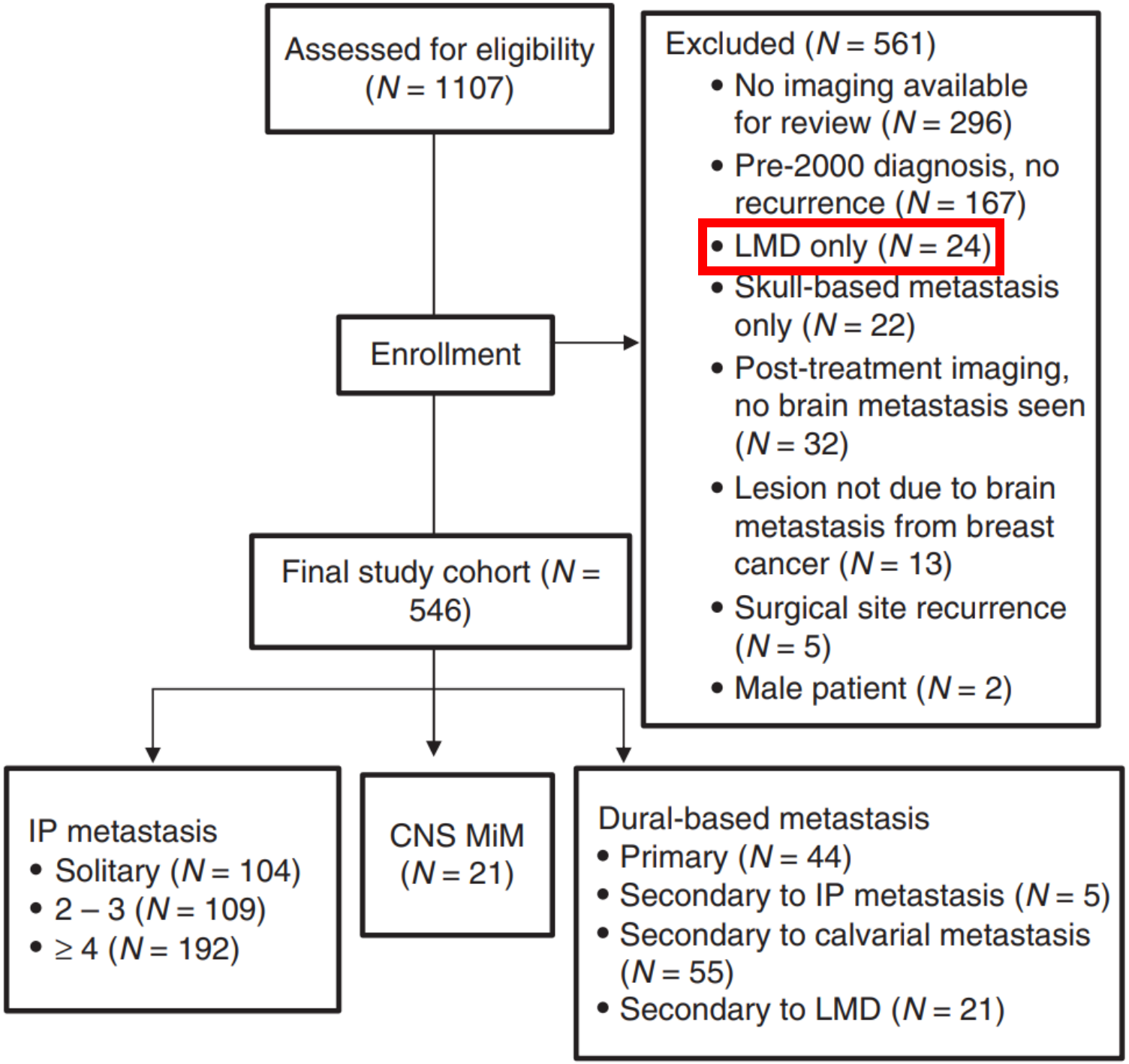
Dura 8%

BJC 2020
PMC7591856



LM **4%**

BJC 2020
PMC7591856



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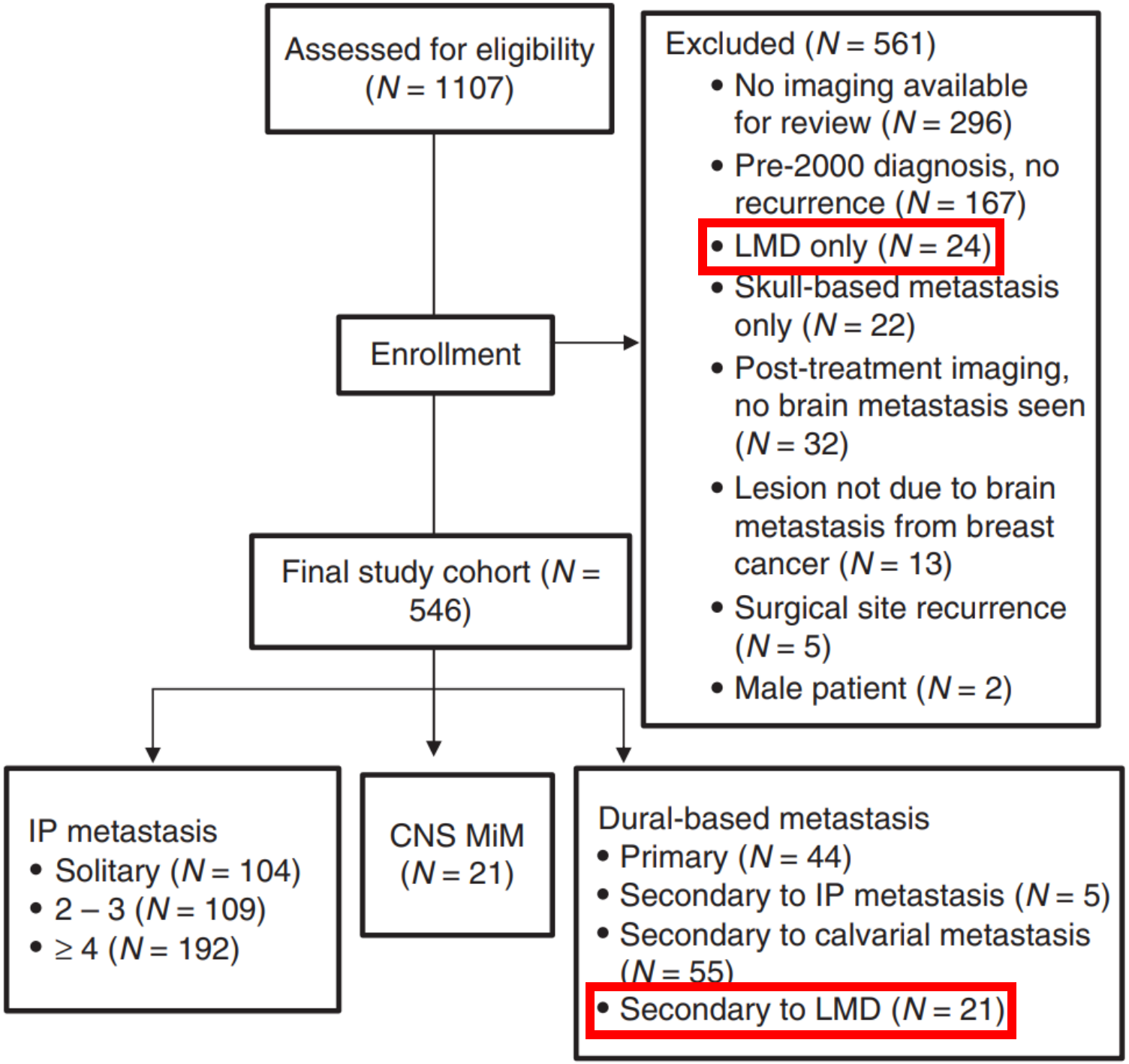
LM **4%**

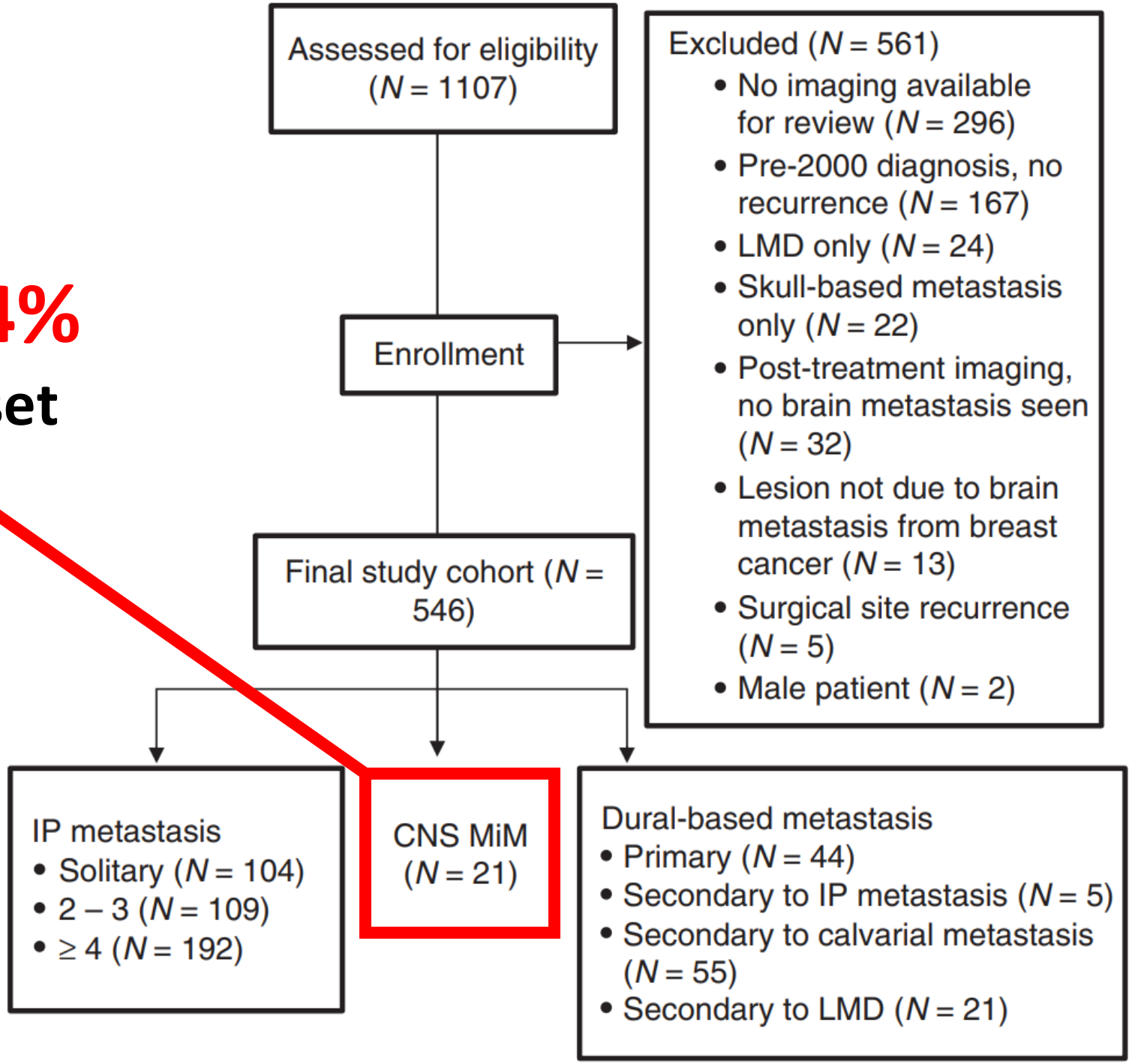
LM+ **4%**



BJC 2020
PMC7591856

EVMM 4%

Miliary subset



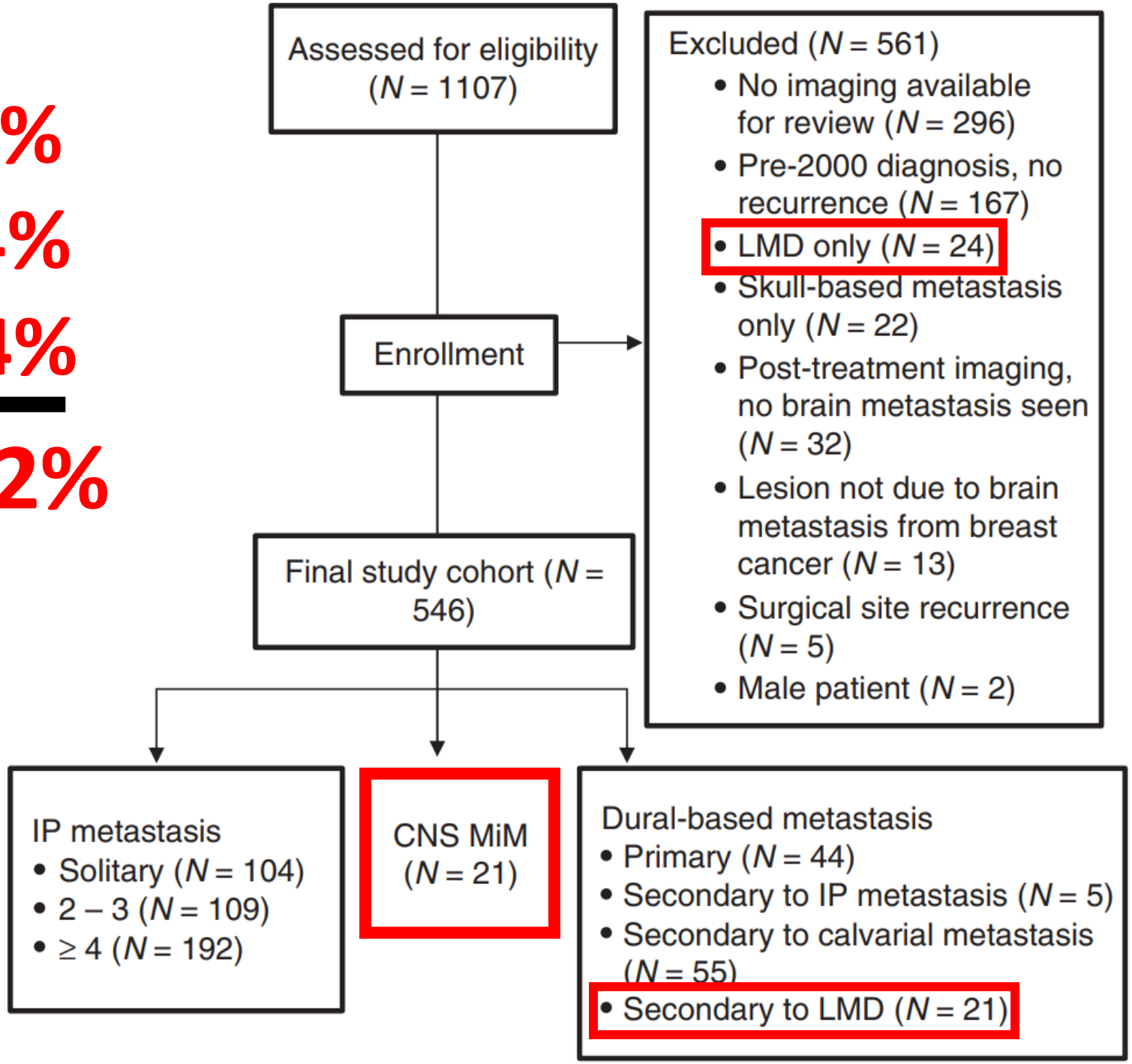
BJC 2020
PMC7591856

LM 4%

LM^{+} 4%

EVMM 4%

LM^{T} 12%



“Take Home” Points

Take Home Points

- **New 4th Meningeal Layer: Subarachnoid Lymphatic-like Membrane (SLYM)**

Take Home Points

- New 4th Meningeal Layer: Subarachnoid Lymphatic-like Membrane (SLYM)

- **Extravascular Migratory Metastasis: An "in transit" stage of LMD in a subset**

Update on CSF Diagnostics in LMD:

Because all that enhances ISN'T cancer

Seema Nagpal, MD
Clinical Professor of Neurology, Neurosurgery and Neurosciences
August 2024

Disclosures

There are no FDA approved medications specifically for brain metastases…***except tucatinib,*** which includes brain met patients!

Medications for brain metastases discussed are technically off label (except tucatinib)

I have research funding from BPGBio, Servier, Novocure, ABM Therapuetics, Biocept (RIP), VBI

I have consulted for Novocure, Biocept, Servier, Bayer, Mirati, Midatech, Kiyatec, Enclear

Other Disclosures

When I started giving LM talks in 2010:

Median OS for metastatic melanoma with brain mets was 3 months

I had about 30 slides

We had first generation drugs, with CNS responses, but no clinical trials

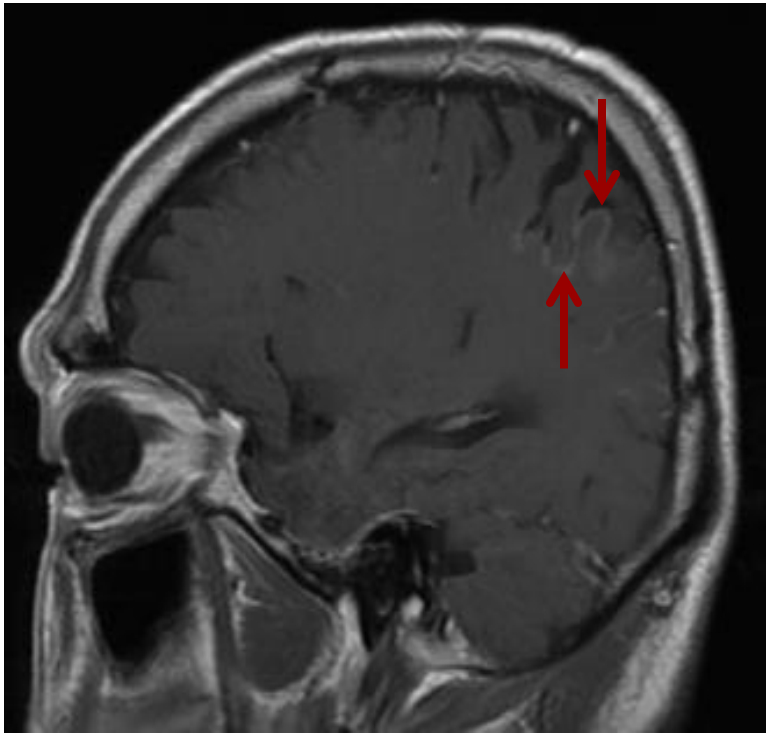
Breath became air…in March 2015
3rd Generation Osi was approved in November 2015

I have 200+ LM slides

Leptomeningeal Metastases:

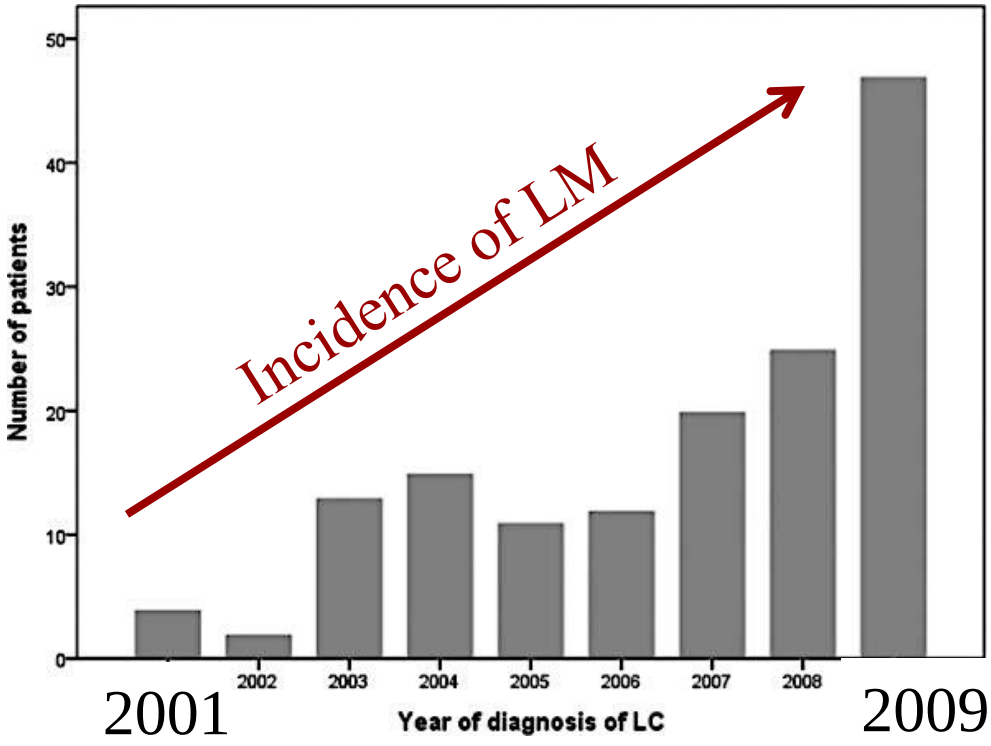
(brief reminder of the clinical disease)

- Occurs in 5-8% of cancer patients
- Nausea, vomiting, headache, seizures, *non-descript "doing poorly"*
- Diagnosis is frequently missed
- Present at autopsy in almost 20% of patients with neurologic signs or symptoms
- **Median OS 14 weeks in lung CA (2013)**
- Death from ICP or from CN involvement



Leptomeningeal Metastases:

Increasing incidence in NSCLC



Possible Explanations

- Patients live long enough
- Variable CNS drug activity
- Increasing sensitivity of MRI & MDs
- Do treatments encourage development of LM? (yes)

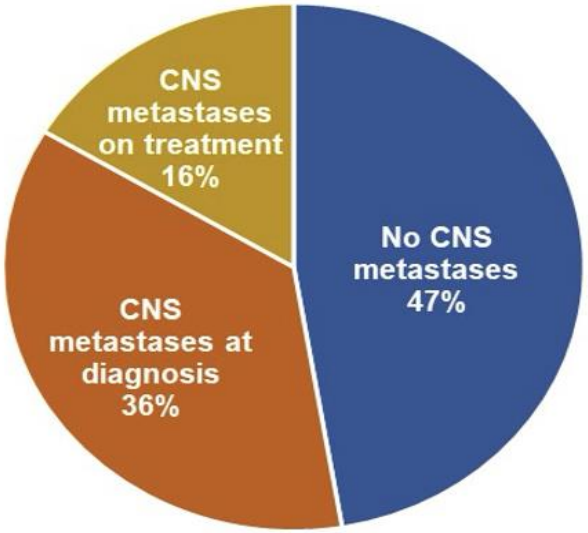
Lee S, et al. *Leptomeningeal Carcinomatosis in Non-Small-Cell Lung Cancer Patients: Impact on Survival and Correlated Prognostic Factors*. Journal of Thoracic Oncology. 8(2):185-191, February 2013.

Leptomeningeal Metastases:

Increasing incidence in NSCLC

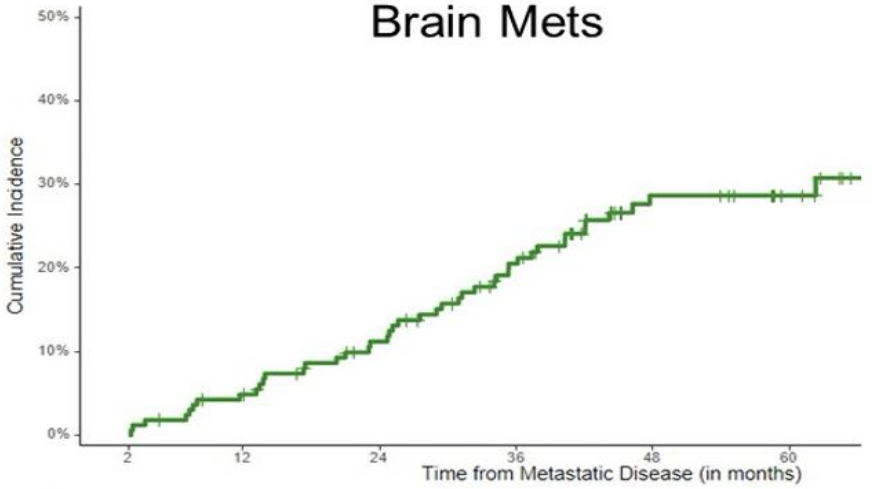
CNS Metastases in EGFR+ NSCLC

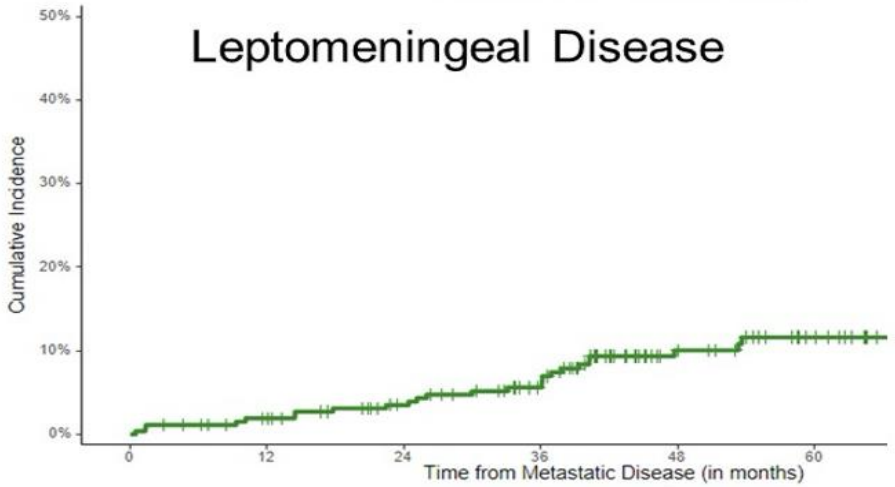
Cases at MSK (2014-2022)



LMD cumulative incidence:
@1yr: 4.9%
@5yrs: 12%

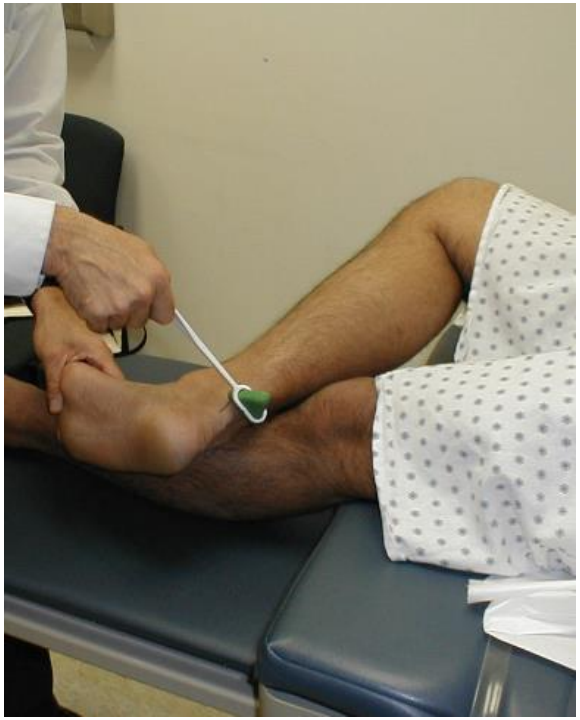
Cumulative Incidence

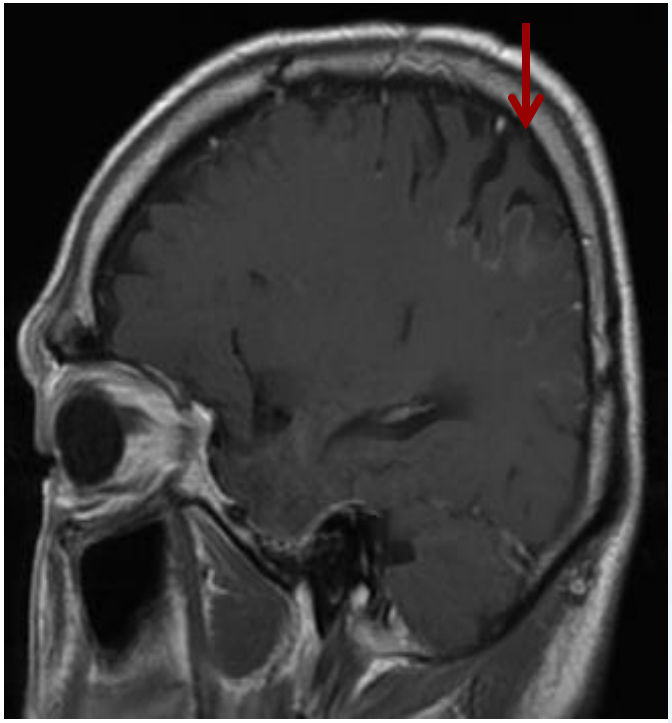


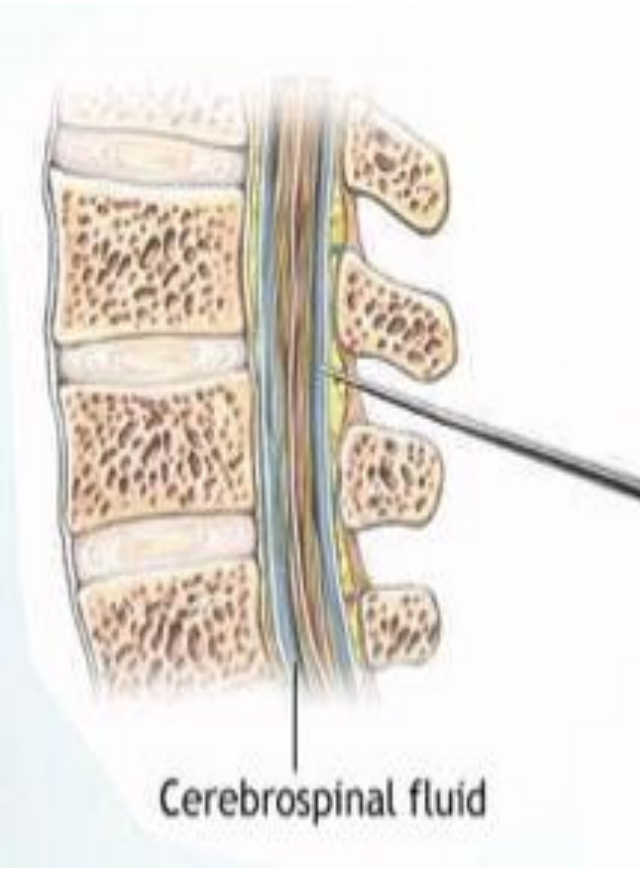


Soria, et al *NEJM 2018*

Diagnosing LMD







Recognizing the Signs and Symptoms

In a series of 187 patients:

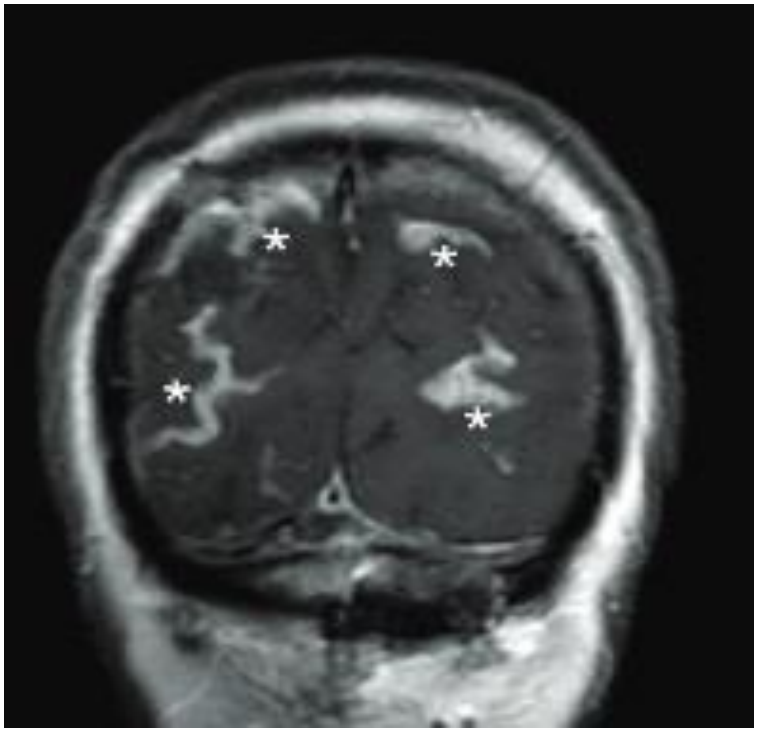
- 24% of patients have S/S referrable to cortex, cerebellum or spine
- Headache
- Confusion
- Nausea/Vomiting
- Diplopia
- Cerebellar dysfunction
- Back pain
- Leg weakness

Cancer.ie cacexia

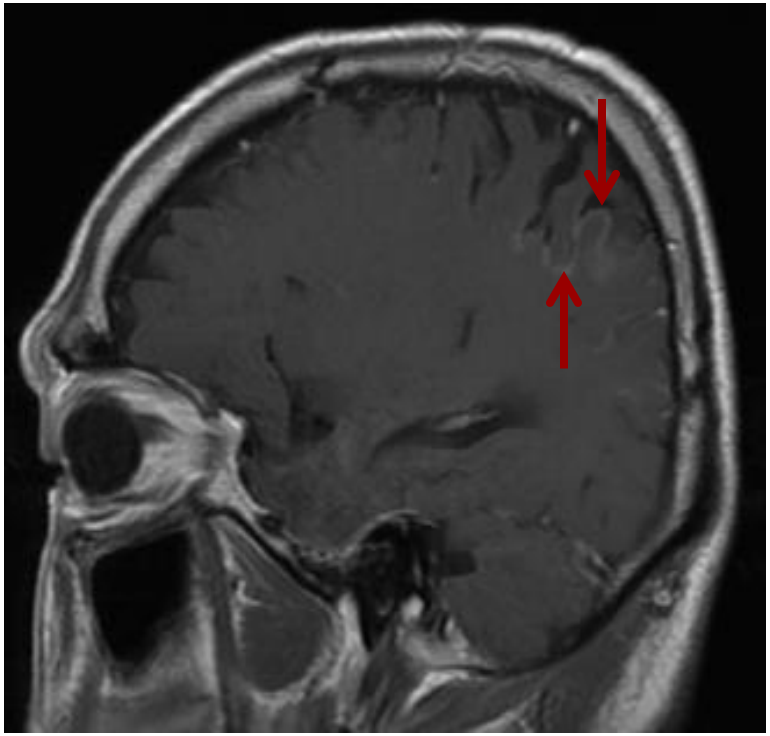
Clarke J. Neurology 2010

MRI is around 75% sensitive

…with low interrater reliability!



Rarely, bulky and obvious…



More often subtle and easy to miss

Lee S, et al. **Leptomeningeal Carcinomatosis in Non-Small-Cell Lung Cancer Patients: Impact on Survival and Correlated Prognostic Factors.** Journal of Thoracic Oncology. 8(2):185-191, February 2013.

MRI is around 75% sensitive

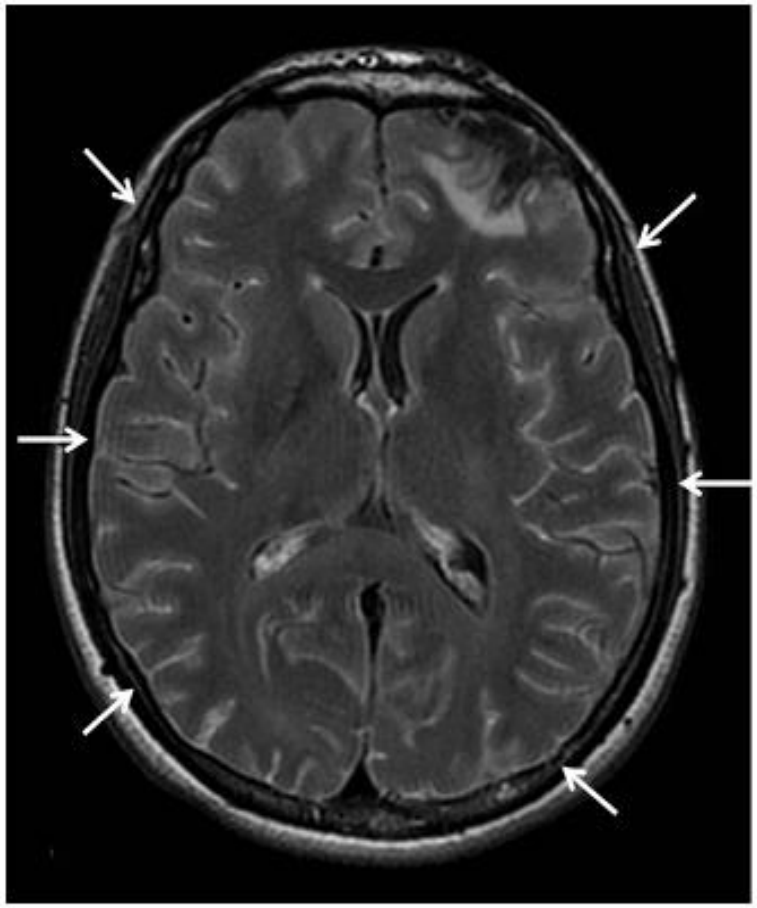
…for solid tumors

Table 2 Comparison of diagnostic tools

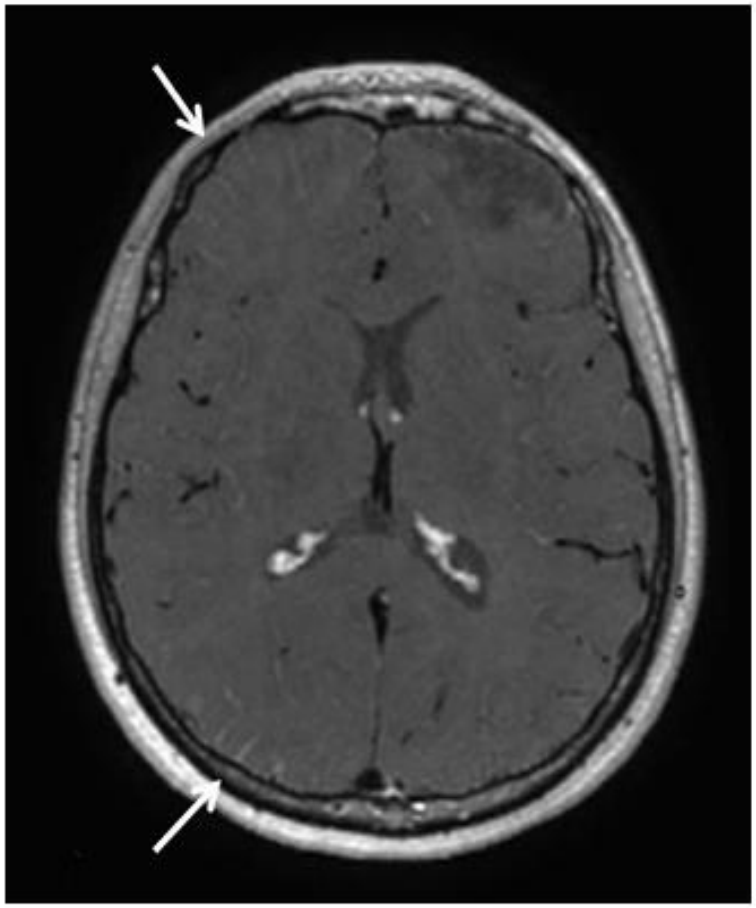
	Diagnostic tool		Overall, count (%)	Hematopoietic, count (%)	Solid, count (%)	*p* Value
	Cytology	MRI				
Cytology and MRI (seg ≥1), n = 93	+	+	45 (48)	12 (36)	33 (55)	0.08
	−	+	14 (15)	4 (12)	10 (17)	
	+	−	34 (37)	17 (52)	17 (28)	
Cytology and full MRI n, =48	+	+	26 (54)	6 (46)	20 (57)	0.42
	−	+	10 (21)	2 (15)	8 (23)	
	+	−	12 (25)	5 (38)	7 (20)	

Clarke J. Neurology 2010

Using Alternate Sequences May Increase Sensitivity

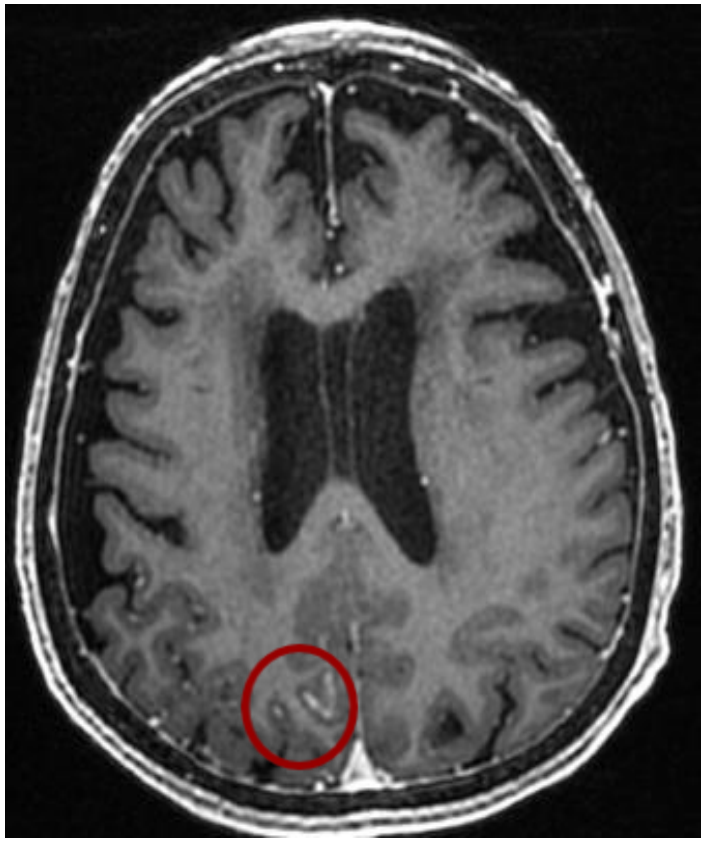


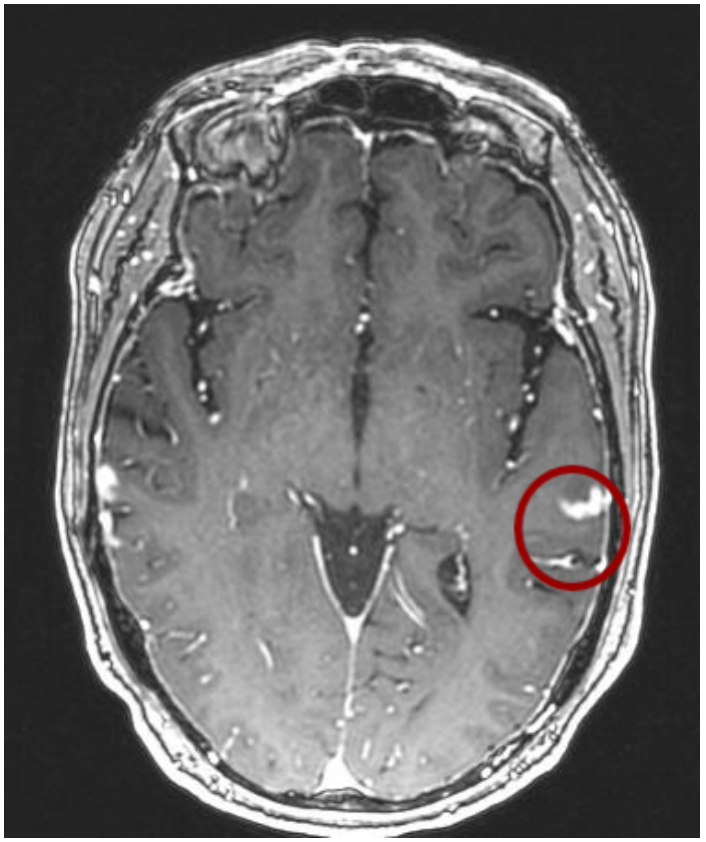
T2 FLAIR post-gadolinium



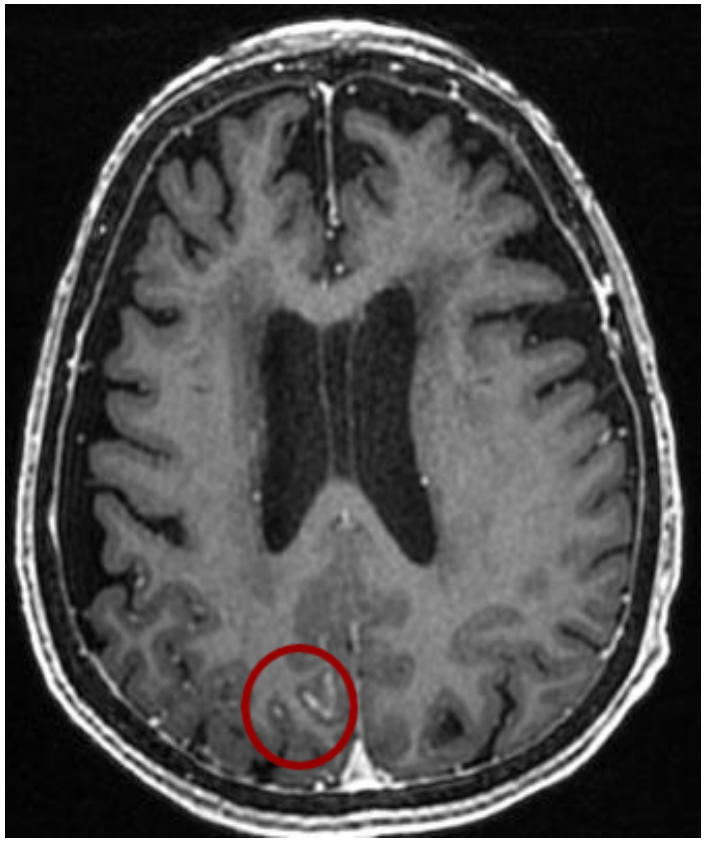
T1 w GRE

But, MRI is still *non-specific*!

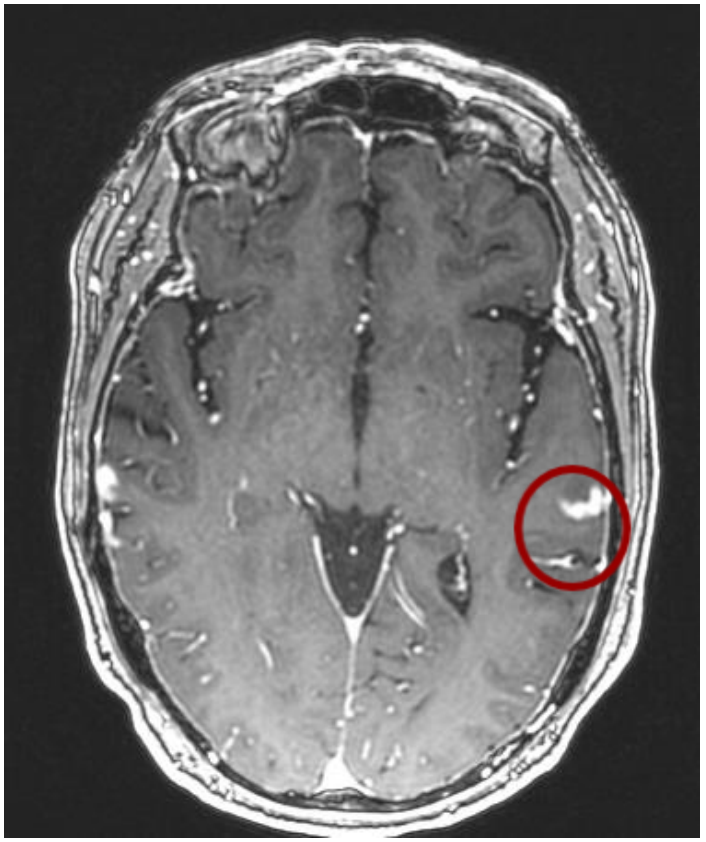




But, MRI is still *non-specific*!



Inflammatory Cerebral Amyloid in a patient w 5 primary cancers



Chronic Lymphocytic Meningitis in a patient with remote hx of breast CA

Pathologic diagnosis from CSF is the gold standard

No. of patients	Type of fluid	Percent cytologically positive per sample				Authors
		First	Second	Third	>Three (no.)	
126	CSF	75%	92%	94%	95% (10)	Balm and Hammack[43] (1996)
68	CSF	57%	69%	76%	90% (?)	Fizazi et al.[45] (1996)
35	CSF	91%	97%			Jayson et al.[46] (1994)
34	CSF	94%			100% (?)	Nakagawa et al.[44] (1992)
44	CSF	91%	98%	100%		Boogerd et al.[39] (1991)
63	CSF	71%	92%	100%		Kaplan et al.[42] (1990)
90	CSF	54%	84%	86%	87% (7)	Wasserstrom et al.[2] (1982)
25	CSF	92%	100%			Yap et al.[5] (1978)
47	CSF	45%	64%	72%	74% (6)	Olson et al.[3] (1974)
532	All CSF studies	71%	86%	90%	93%	
55	Pleural	60%	92%	97%	100% (5)	Garcia et al.[47] (1994)
472	Pleural[a]	91%	93%	93%		Johnston[50] (1985)
64	Pleural	59%	65%	70%		Winkelmann and Pfitzer[49] (1981)
95	Pleural	53%	64%	69%	73% (≥ 4)	Salyer et al.[48] (1975)
282	Blood	92%	99%	100%		Weinstein et al.[51] (1983)
80	Blood	80%	89%	99%		Washington[52] (1975)

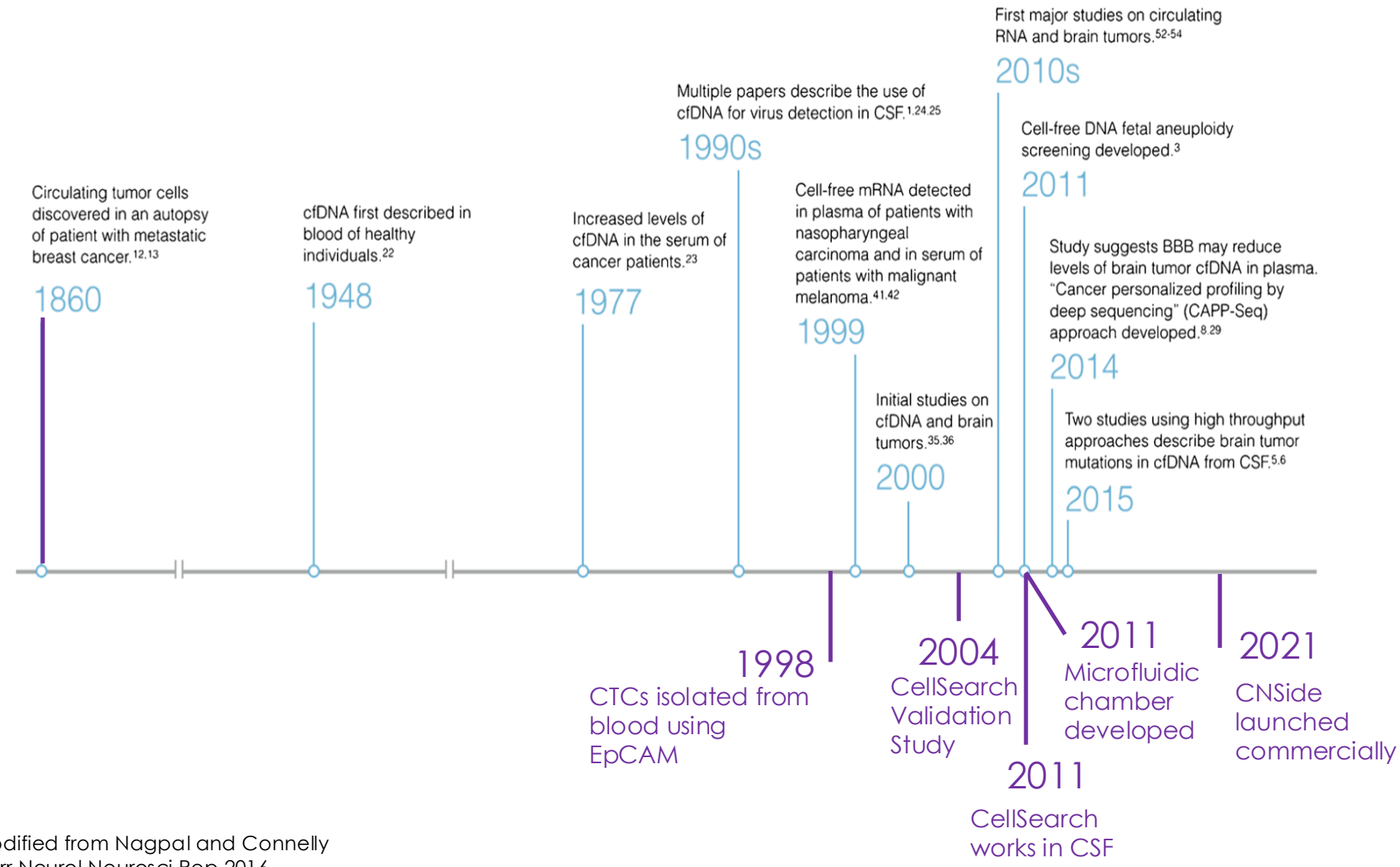
Single LP is about 60-70% sensitive for solid tumor.

The solution?

Multiple lumbar punctures

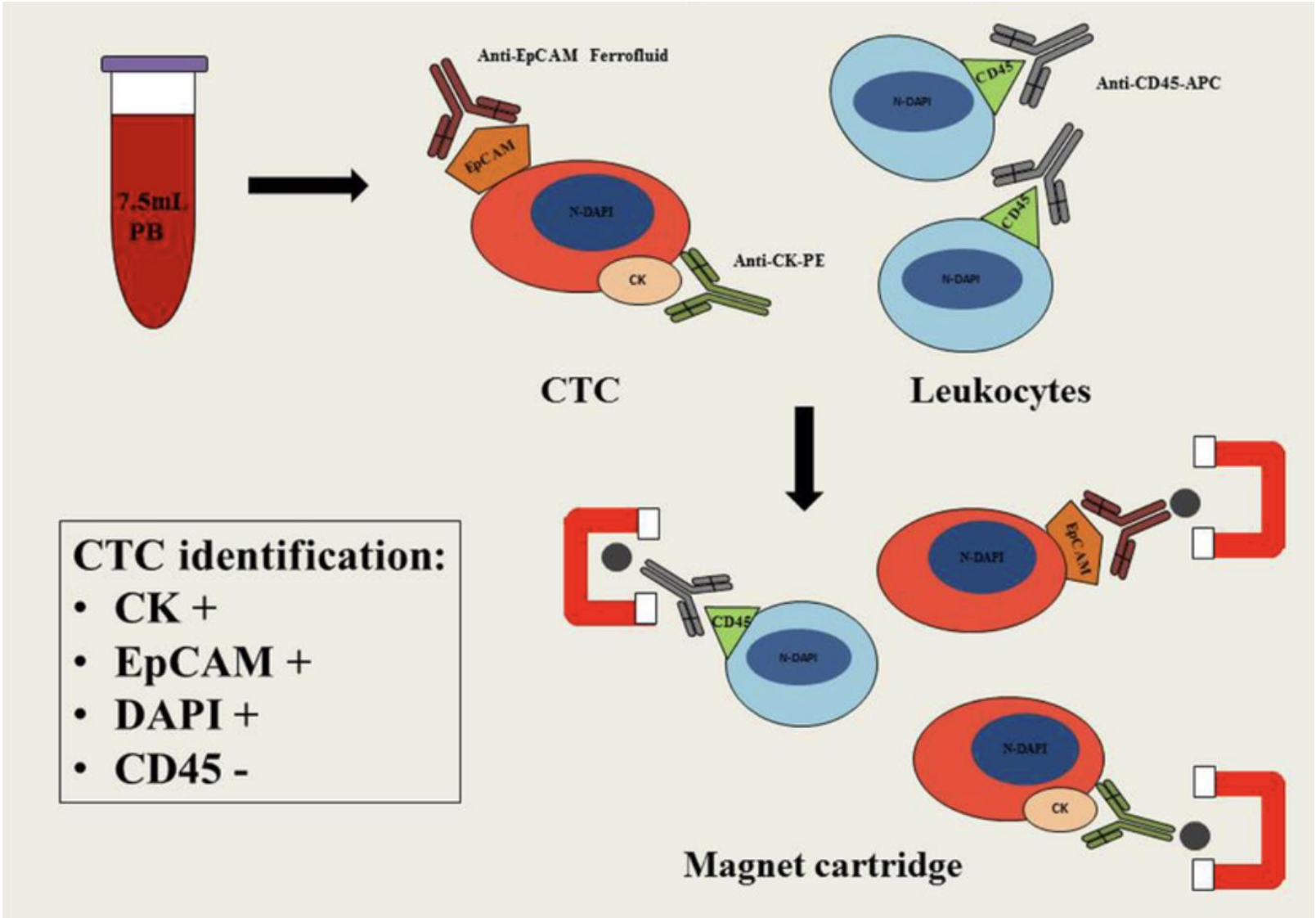
Glantz et al. Cancer 1998

A history of "liquid biopsies"



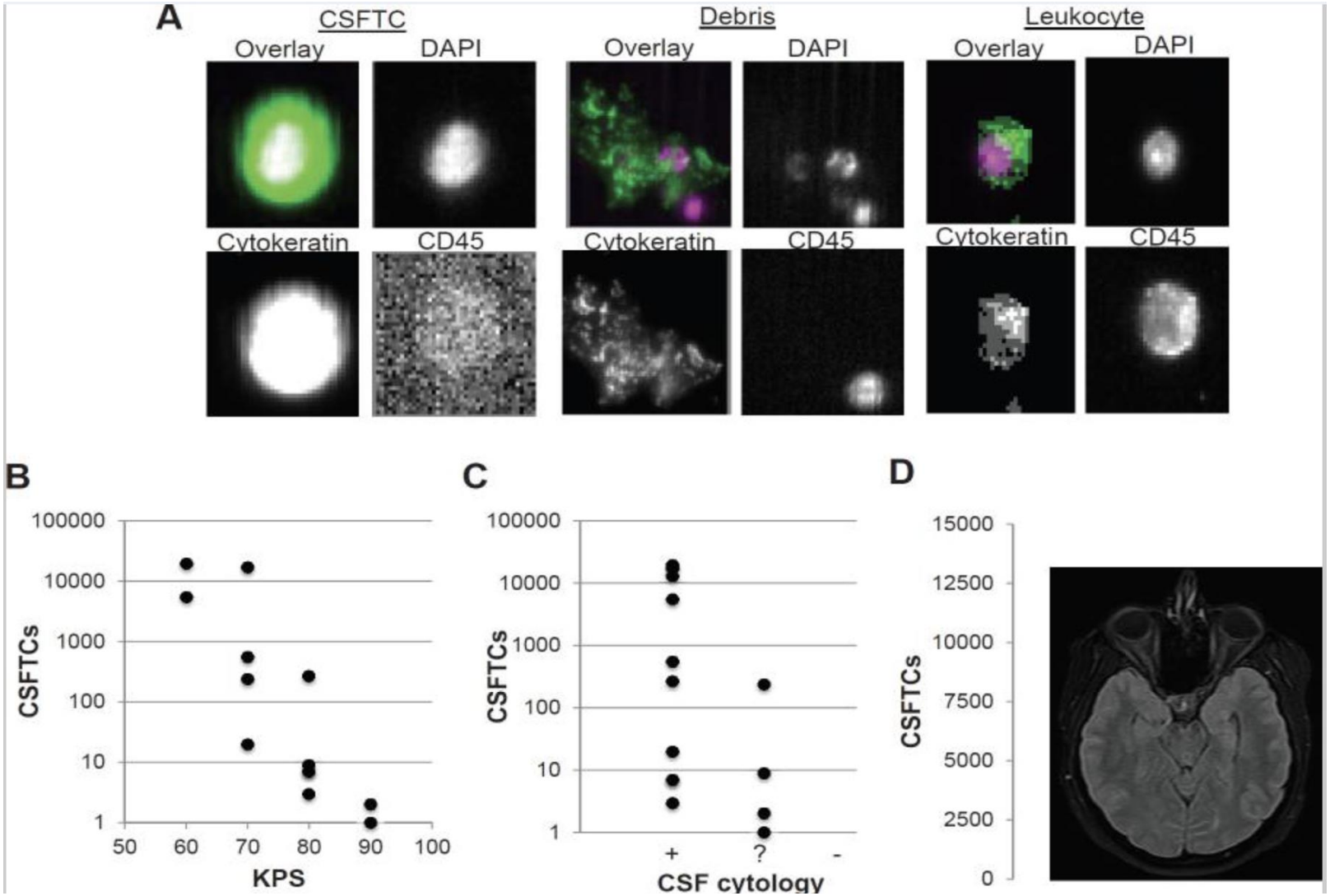
Modified from Nagpal and Connelly
Curr Neurol Neurosci Rep 2016

CellSearch: *Isolating CTCs using EpCAM*



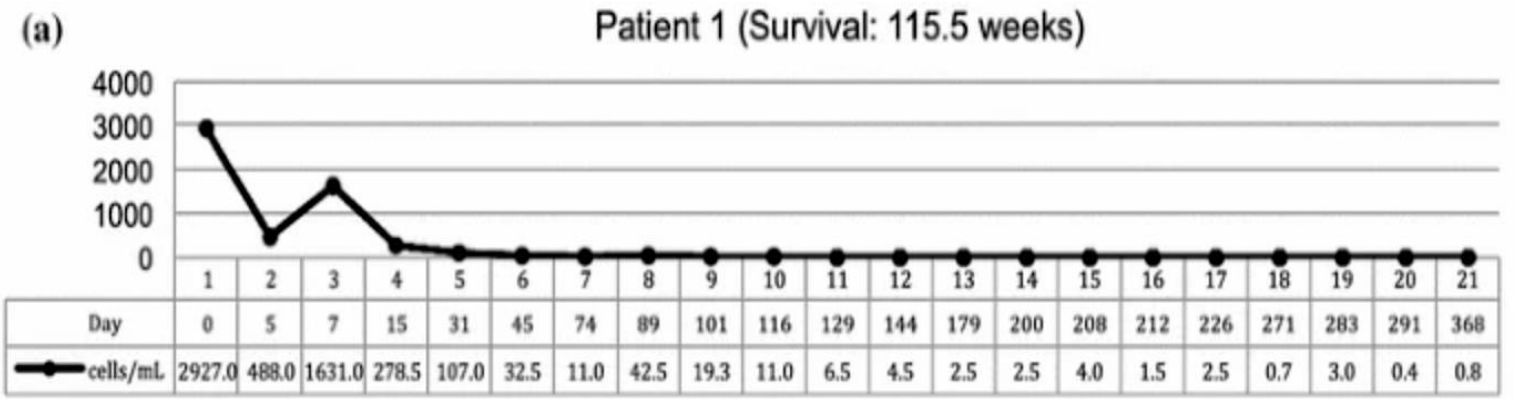
Atriuini et al. Frontiers in Onc 2014

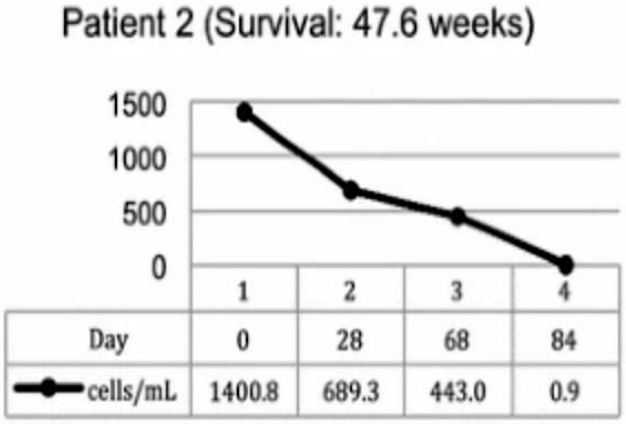
CellSearch: *Isolating CTCs in CSF*

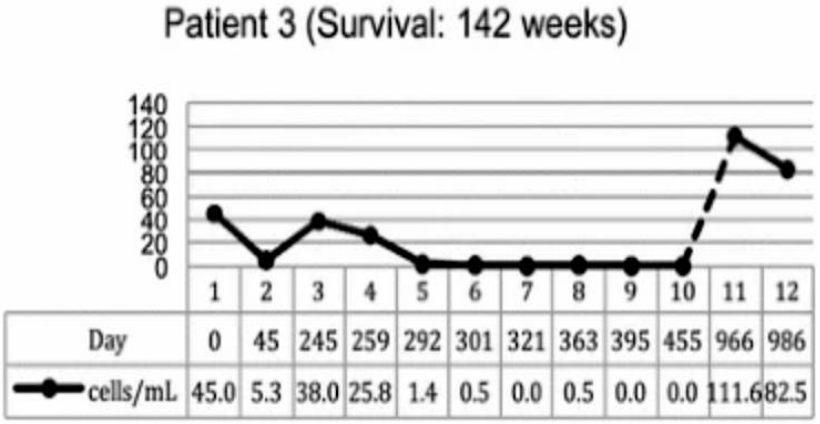


Patel AS Oncotarget 2011

CTCs correlate with clinical course

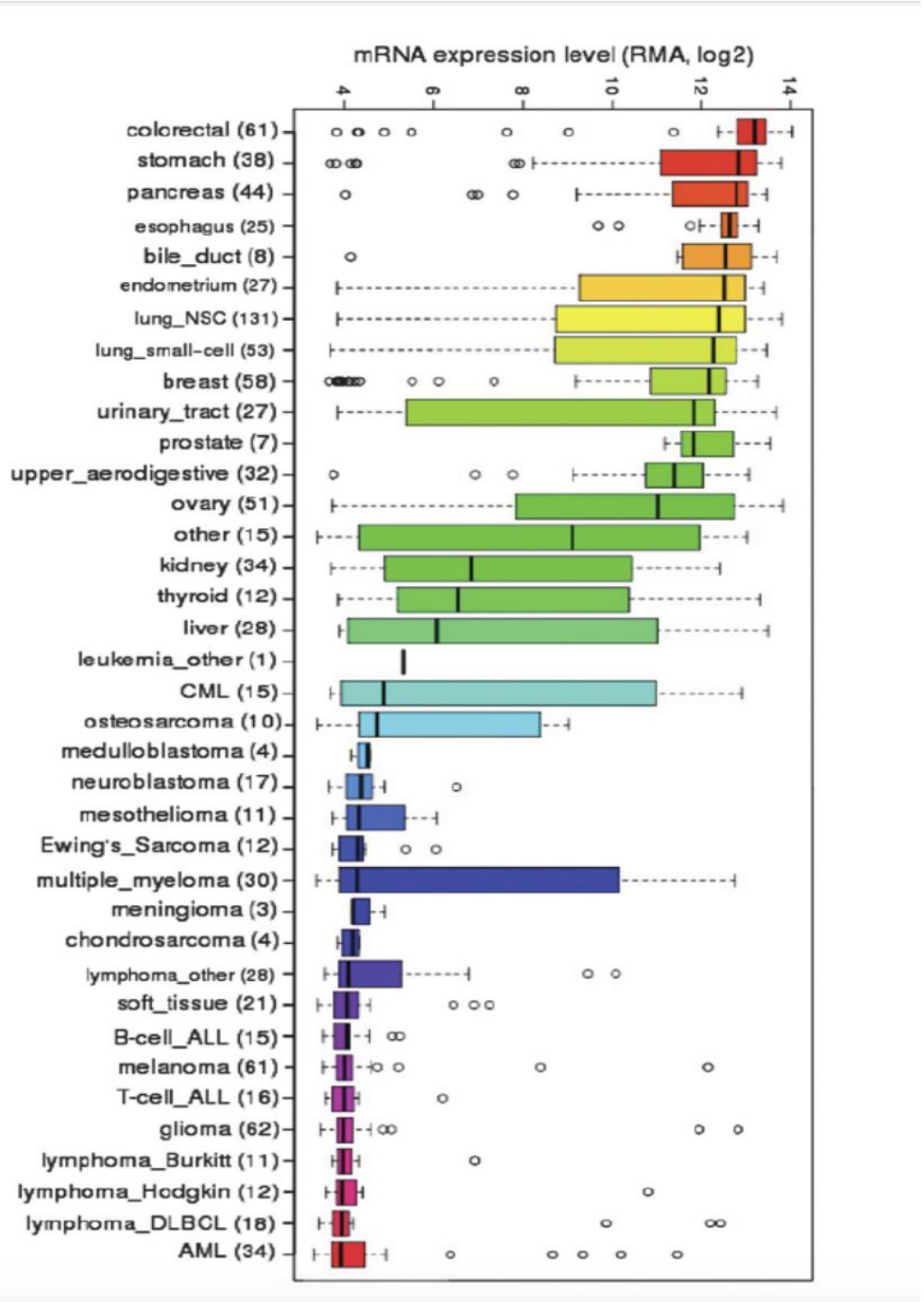






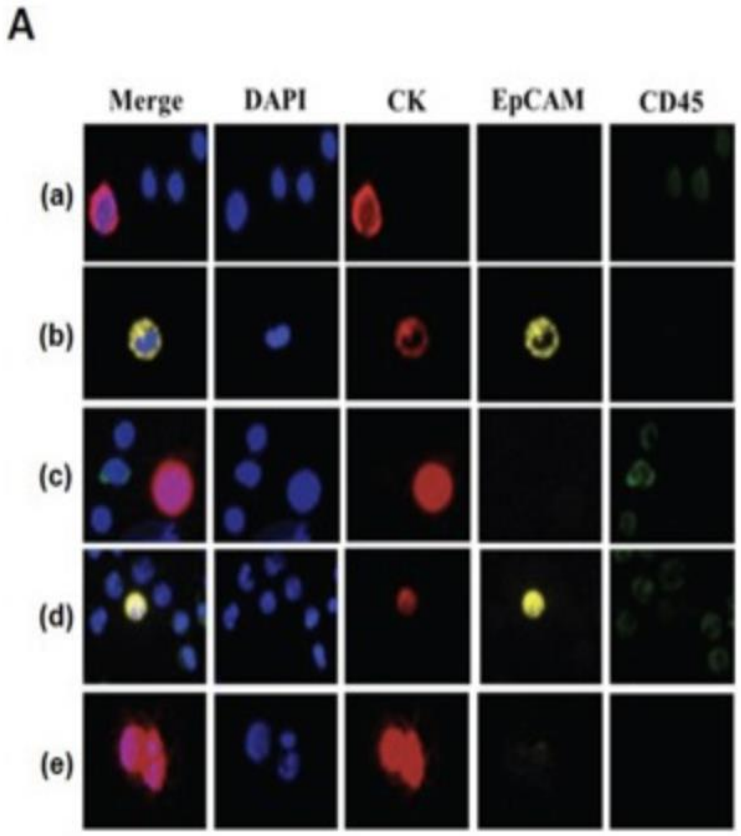
Lee JS Breast CA Res and Treat 2015

Many cancers loose EpCAM or don't express it

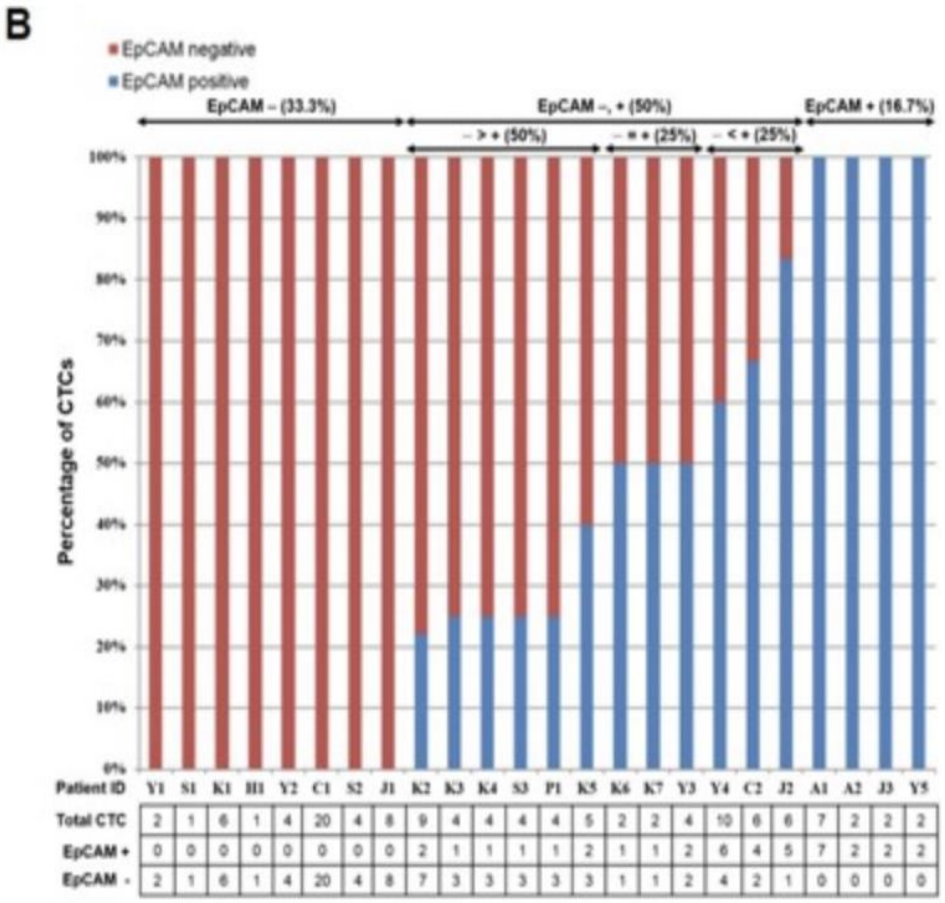


Ward K Molec and Clin Onc 2015

EpCAM based assays leave many patients out



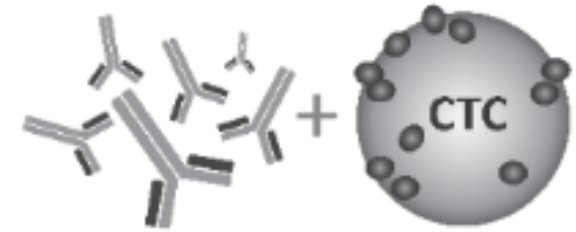
32 breast cancer patients

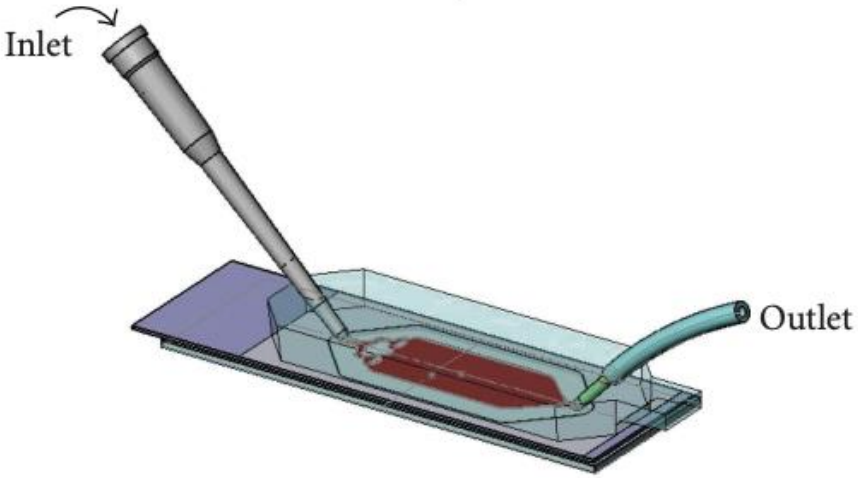


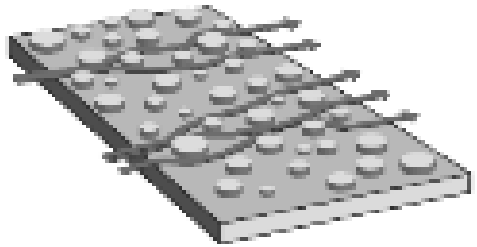
EpCAM negative
EpCAM positive

Hyun KA Oncotarget 2016

Microfluidic chamber with a multi-Ab cocktail







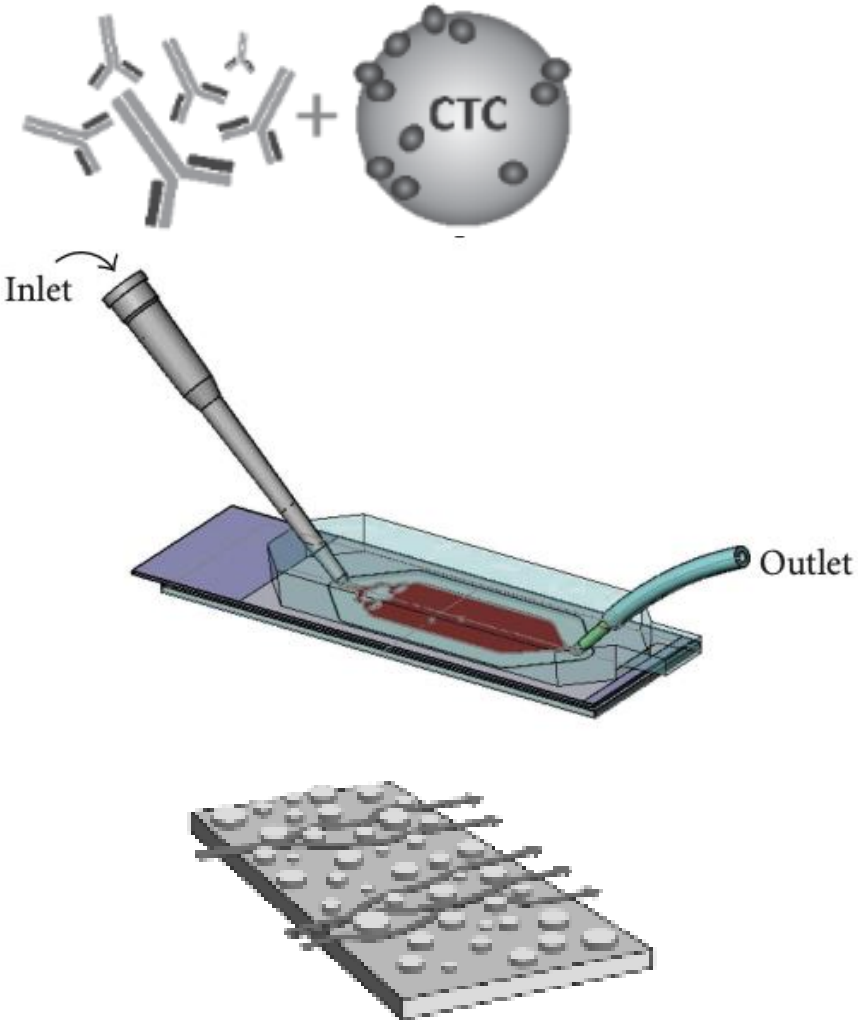
Initial Antibody Cocktail

Ep-CAM
Trop-2
Anti-Met C
Anti-Folate binding protein (MOV18)
Anti-N-cadherin (GC-4)
Anti-CD318
Anti-mesenchymal stem cell antigen
Anti-HER2
Anti-EGFR

*Designed for CTCs in Blood

Mikolajczyk J Onc 2011

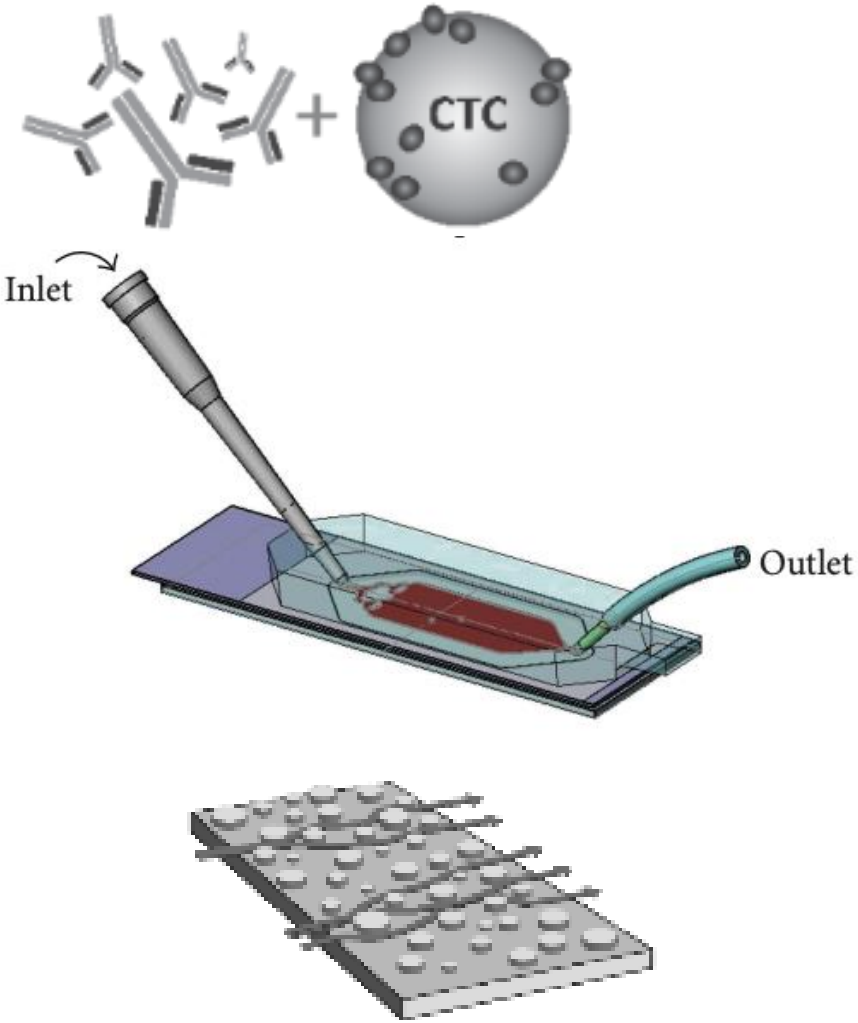
Multi-Ab Cocktail Captures More CTCs

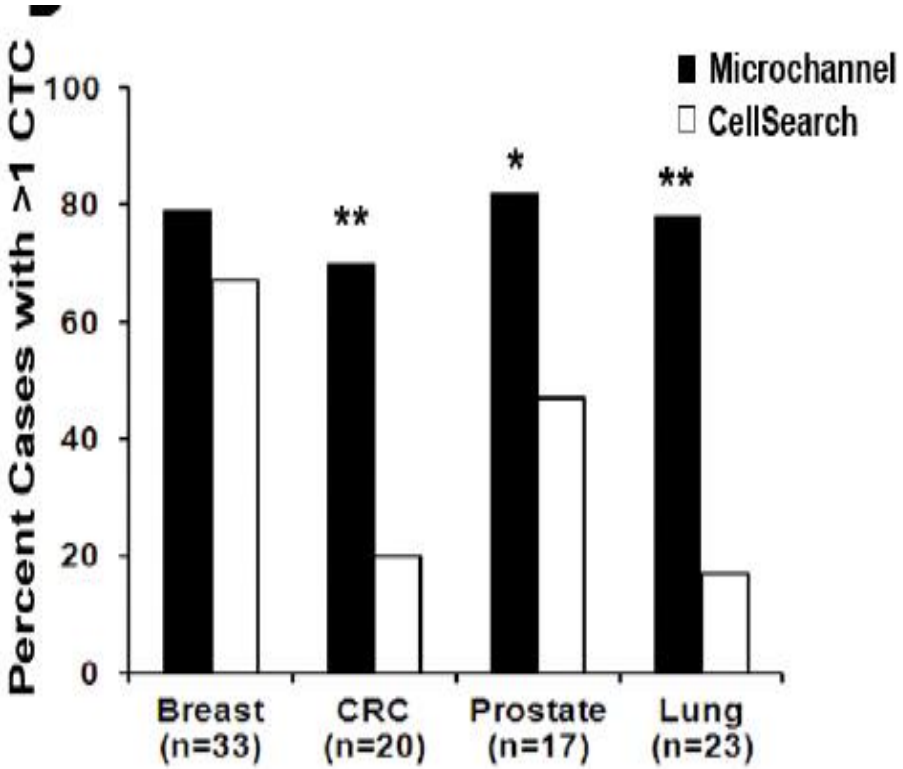


Tumor type	Anti-EpCAM only	Antibody mix
Breast	0	1
Prostate	37	33
Breast	8	25
Lung	0	0
Breast	8	12
Breast	94	115
Breast	0	1
Prostate	57	97
Prostate	0	0
Colorectal	0	1
Breast	6	16
Lung	1	2
Breast	13	22
Breast	54	72
Breast	0	0
Breast	0	1

Mikolajczyk J Onc 2011

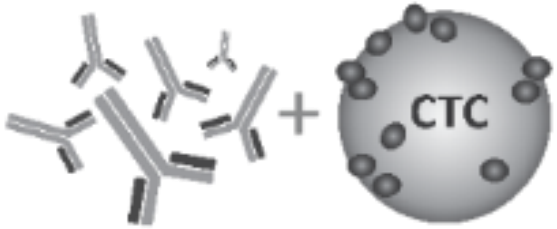
Multi-Ab Cocktail Captures More CTCs

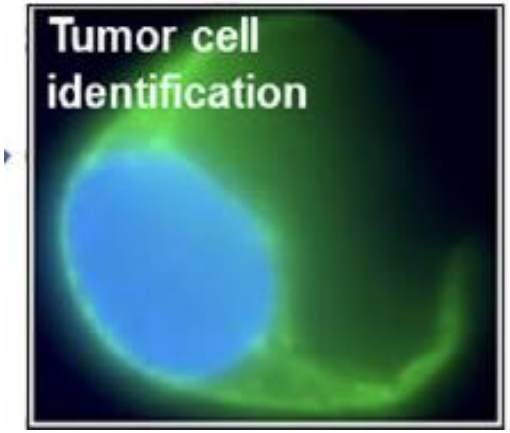


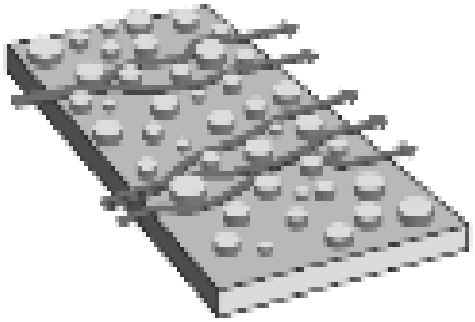


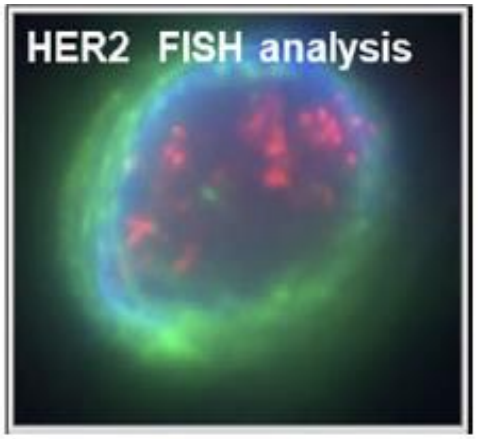
Pecot Cancer Discov 2011

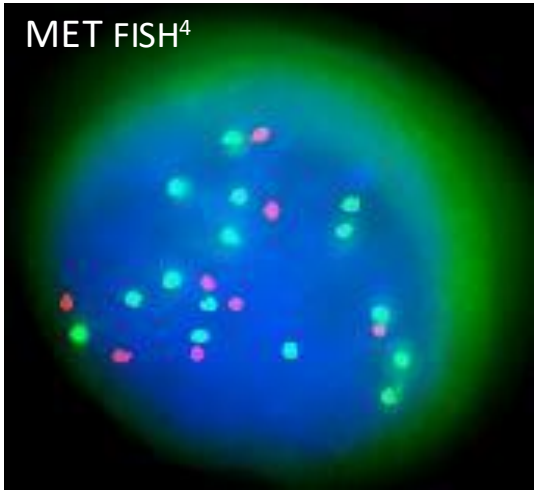
9000+ “pegs” allow staining and co-localization











These are targetable!

Mikolajczyk J Onc 2011
Kumthekar Front Onc 2024

CNSide appears more sensitive than cytology in a small NSCLC series

Table 2. Comparison of CSF tumor cell capture between CNSide AND Cytology

Puri et al

Patient Number	LMD (±)	Number of CSF Draw	LP/Ommaya (O)	Number of Months Between CSF draws	Cytology (Positive, Negative, Atypical)	CNSide	
						Detected/Not Detected	Cells/mL
6	+	1	O	0	Positive	Detected	15
		2		1.8	Positive	Detected	525
8	+	1		0	Negative	Not detected	0
		2	O	8	Negative	Detected	0.3
		3		27	Negative	Detected	1
		4		30	Negative	Not detected	0
9	+	1*		0	Negative	Detected	13
		2		1.4	Negative	Detected	7
		3	LP	2.7	Negative	Detected	11
		4		6	Negative	Detected	7
		5		21	Negative	Detected	85
		6		22	Negative	Detected	210
10	+	1*		0	Negative	Detected	58
		2	O	1	Positive	Detected	383
		3		2	Positive	Detected	151
		4		2.6	Positive	Detected	514
11	+	1*		0	Positive	Detected	19
		2		0.7	Positive	Detected	43
		3		1.4	Positive	Detected	12
		4	O	2.4	Positive	Detected	7
		5		4	Negative	Detected	5
		6		6	Negative	Detected	5
		7		9	Positive	Detected	17
		8		10.6	Negative	Not detected	0
12	+	1*	LP	NA	Negative	Detected	4
13	–	1*	LP	NA	Negative	Not detected	0
14	–	1		NA	Negative	Not detected	0
		2	LP	NA	Negative	Not detected	0
		3		NA	Negative	Not detected	0
15	–	1*	LP	NA	Negative	Not detected	0

15 NSCLC patients

CTCs detected in 88% of samples compared to 40% by cytology

CTCs NOT detected in the 3 patients who never had confirmatory cytology

Puri JNOA 2024

CNSide appears more sensitive than cytology in a larger series

Table 3. Comparison of CNSide™ with Cytology Based on EANO Criteria

EANO classification	Positive			Negative
	Confirmed	Probable	Possible	Lack of evidence
Cytology positive	23 (100%)	0 (0%)	0 (0%)	0 (0%)
Cytology negative	0 (0%)	19 (100%)	40 (100%)	5 (100%)
CNSide™ positive	23 (100%)	12 (63%)	34 (84%)	0 (0%)
CNSide™ negative	0 (0%)	7* (37%)	6* (16%)	5 (100%)

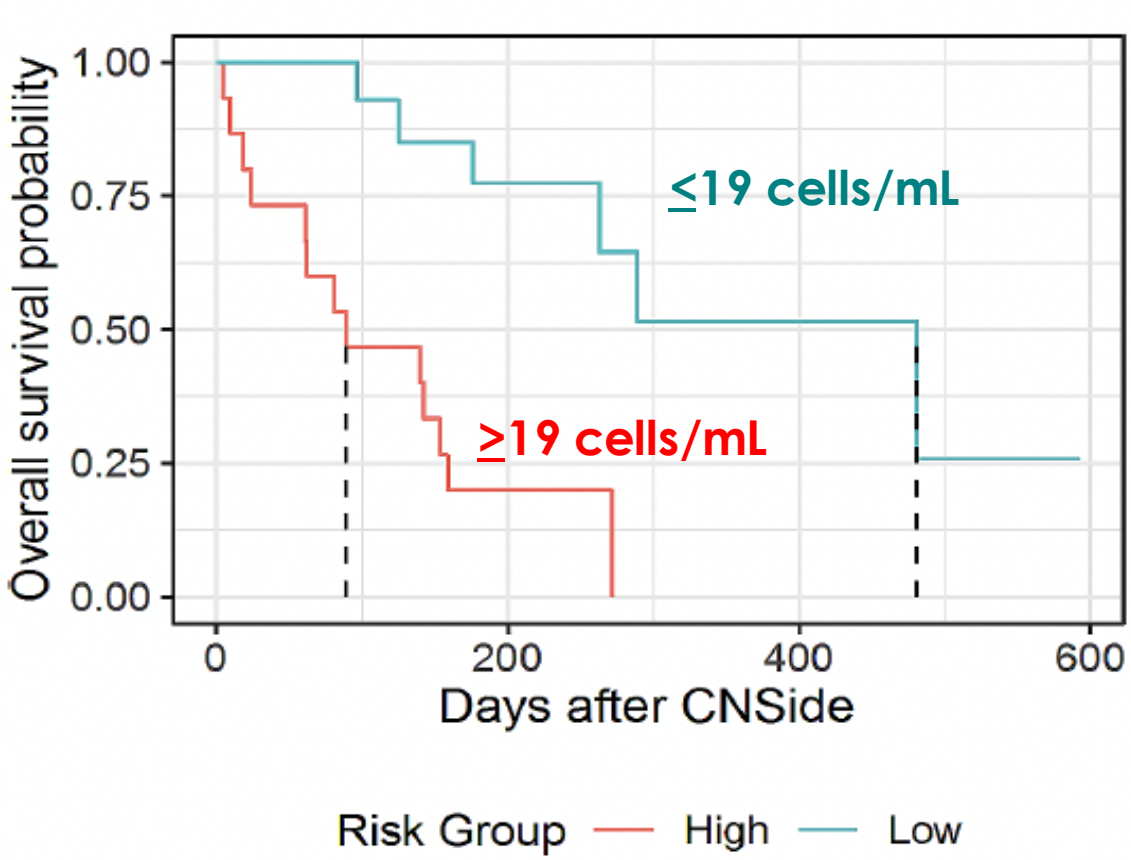
EANO criteria	**Cytology positive (*N* = 23)**	**MRI + C/F (*N* = 19)**	**MRI (*N* = 40)**	**No findings (*N* = 5)**
Test Characteristic	Statistic estimate		95% Confidence interval	
Sensitivity	63.9%		48.2–79.6%	
Specificity	100%		100%	
PPV	100%		100%	
NPV	80.0%		69.8-89.5%	

EANO: European Association of Neuro-Oncology.
*Thirteen additional cases detected by CNSide™ among EANO "probable" and "possible" cohorts.

87 consecutive patients
Mostly breast and lung
28% had cytology + CSF, ALL identified by CNSide
13 additional cases of LMD identified by CNSide

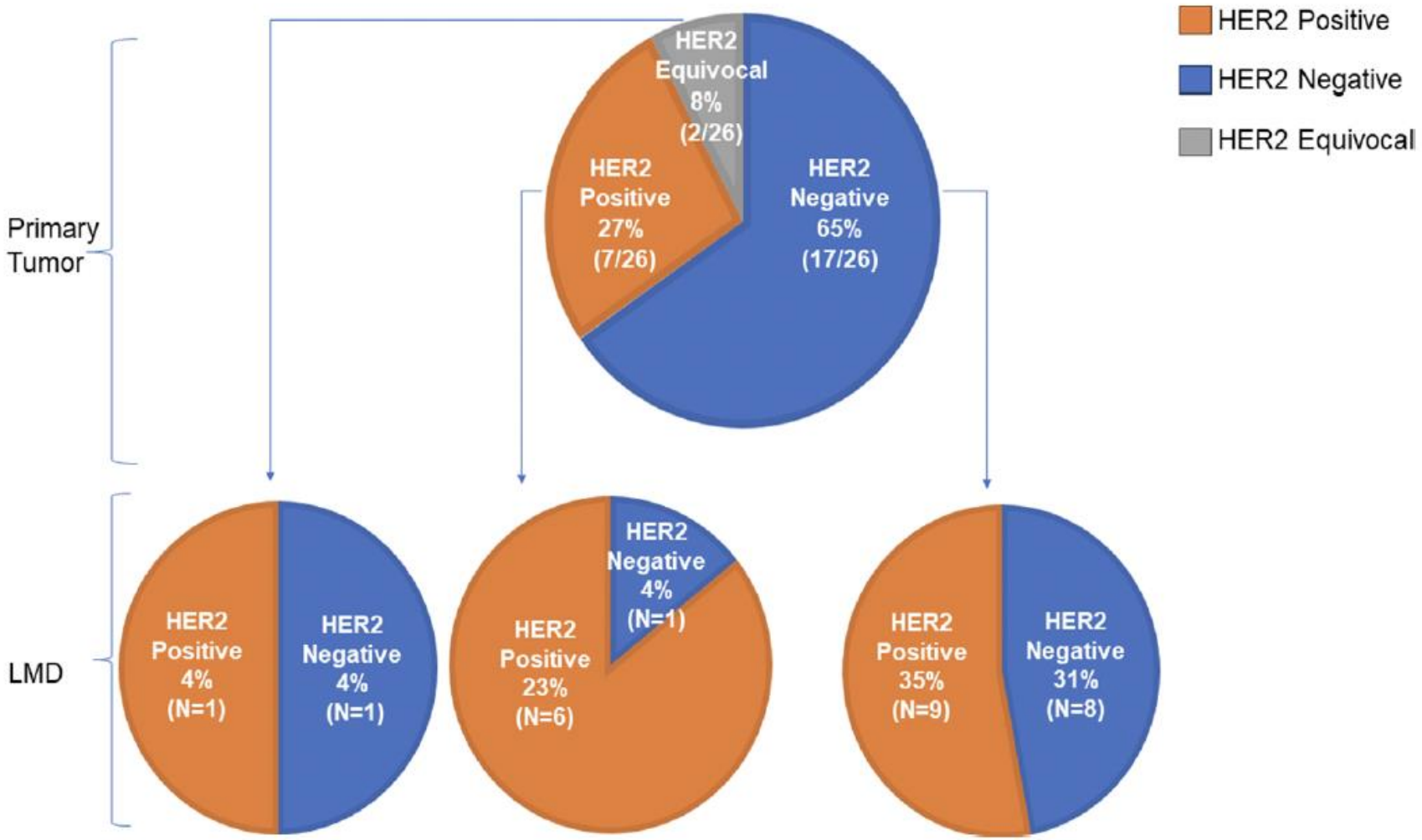
Appel et al JNOA 2024

CTCs by CNSide correlate with survival



Barbour JNO 2024

CNSide Confirms the HER2 "FLIP" on CTCs

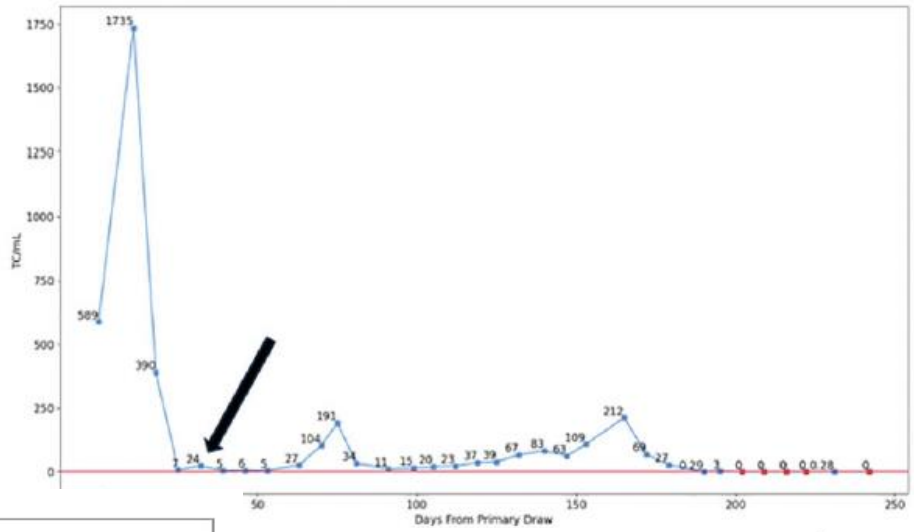


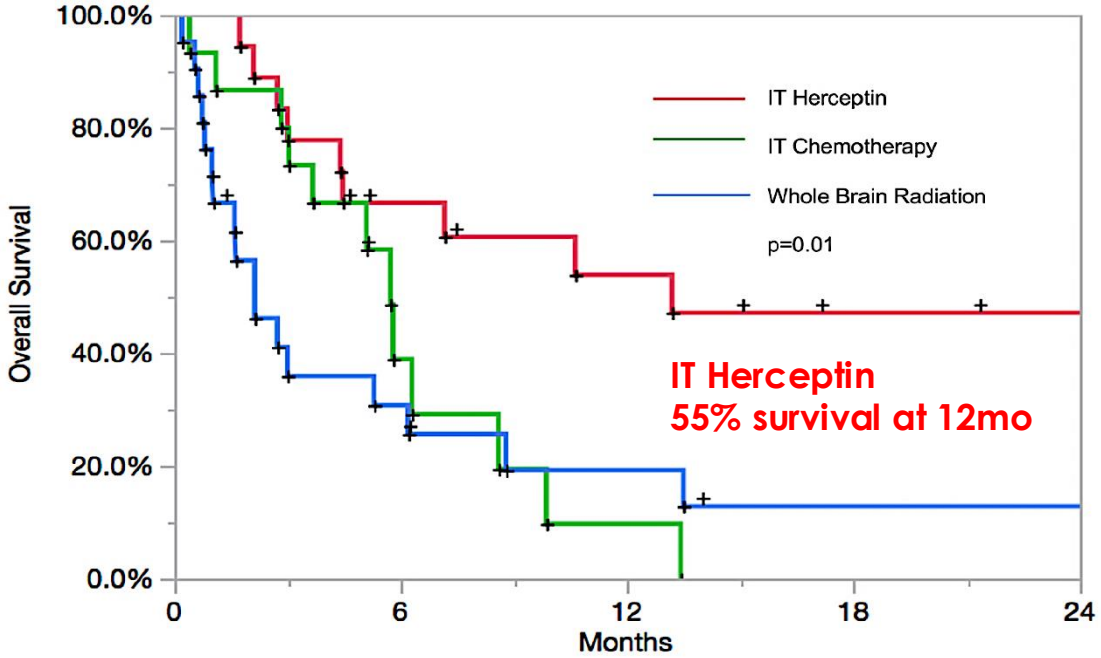
Kumthekar JNO 2024

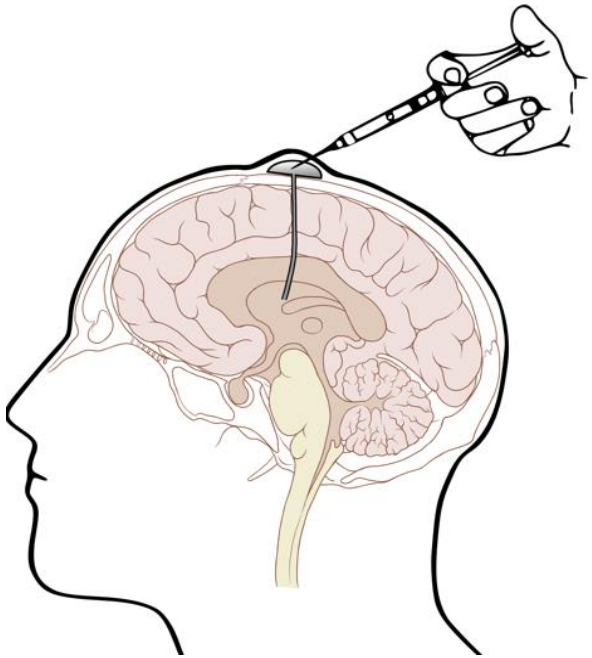
CNSide Supports Clinical Decision Making

Ability to test HER2 on CTCs can provide meaningful treatment alternatives for patients

Kumthekar JNO 2024

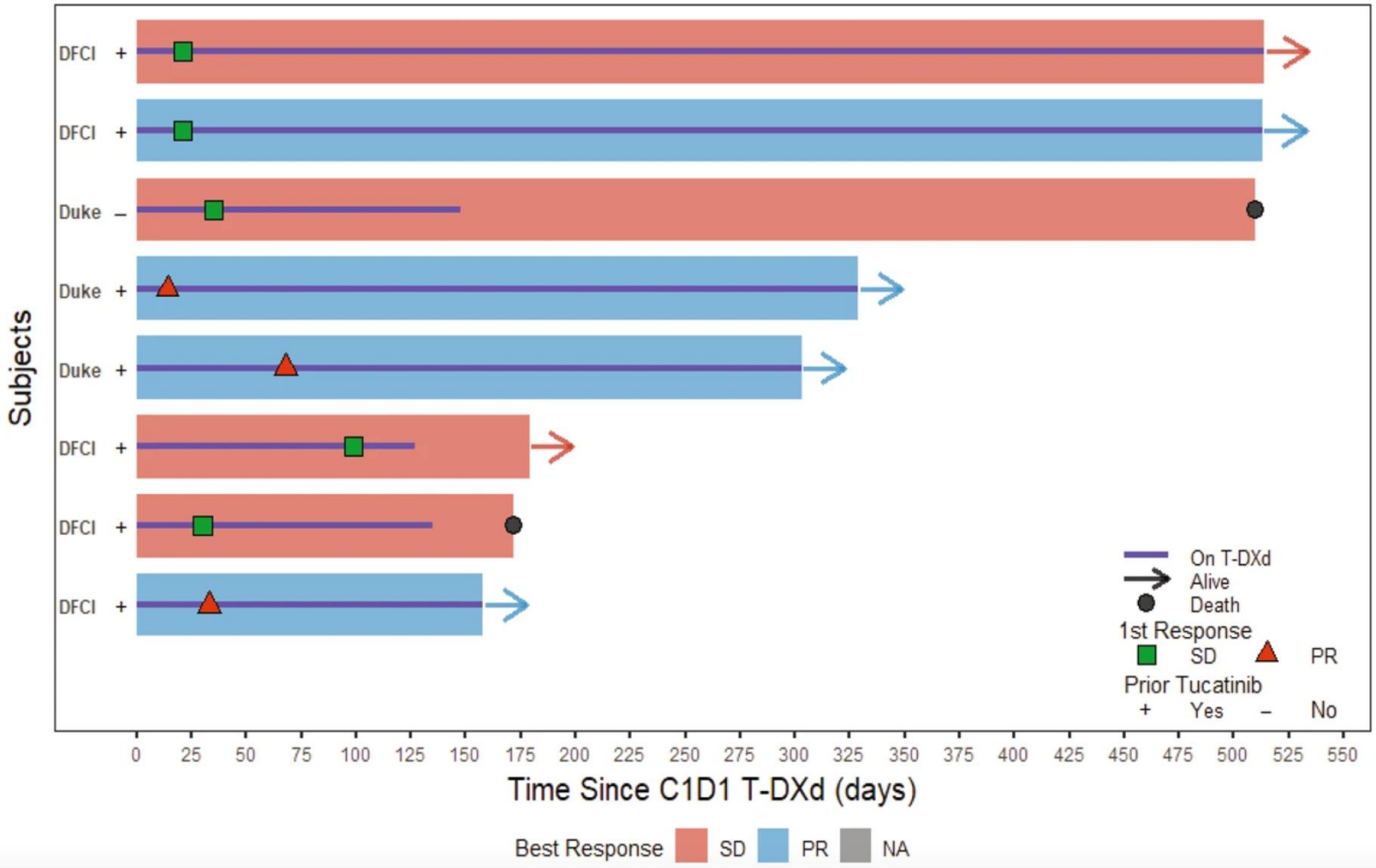






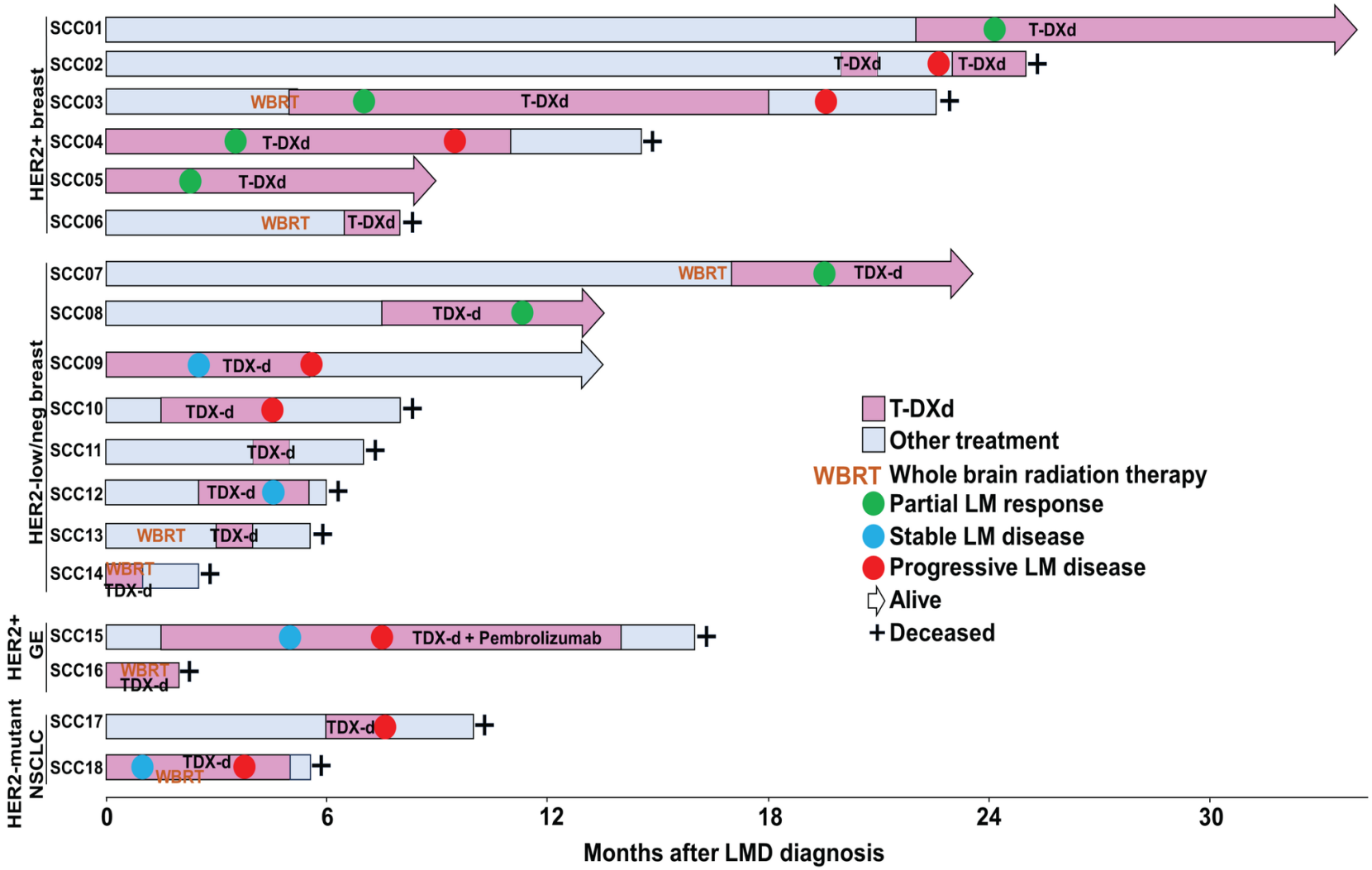
Figuraet al. Breast Cancer Research and Treatment (2019).

Enhurtu in HER2+ LMD:
Trastuzumab deruxtecan

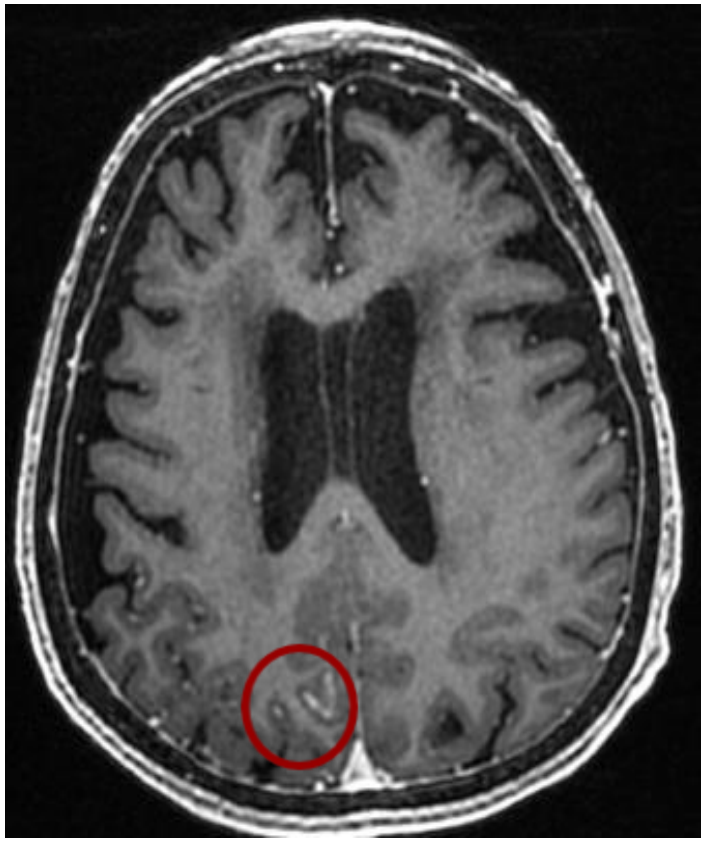


Enhurtu in LMD at Stanford:

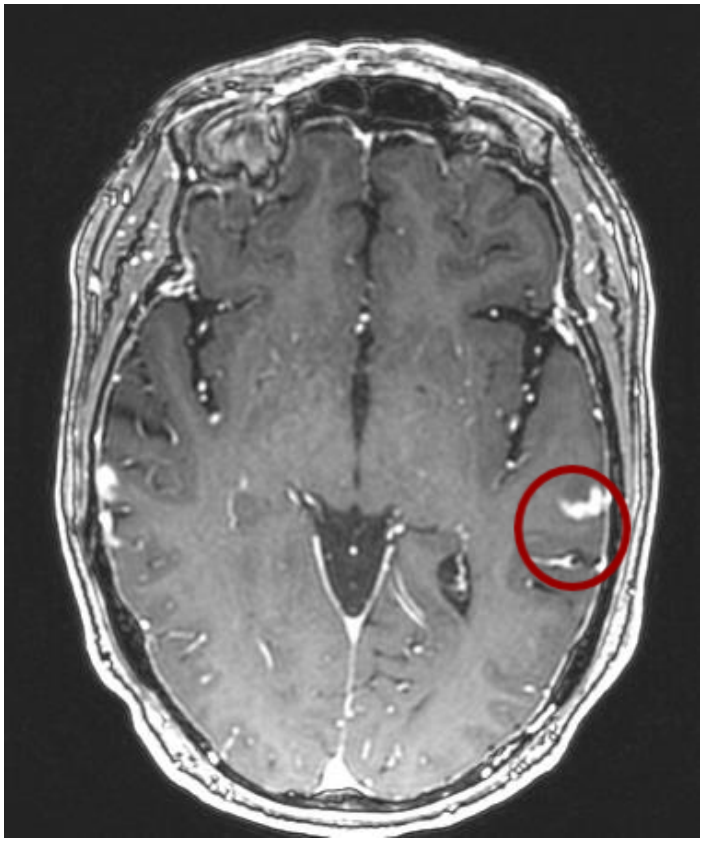
(we extrapolated)



Negative predictive capacity helps avoid toxic therapy



Inflammatory Cerebral Amyloid in a patient w 5 primary cancers



Chronic Lymphocytic Meningitis in a patient with remote hx of breast CA

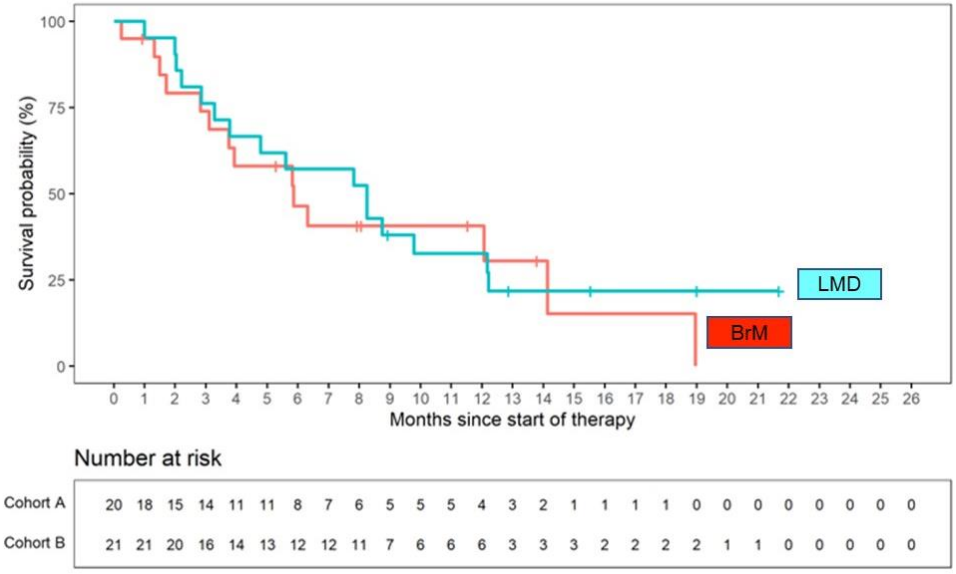
ASCO 2024:

Amivantinab + Lazertinib add PFS and Survival Benefit

Progression-free Survival:

Brain mets cohort: median 5.9 months (95% CI: 2.8-14.1)

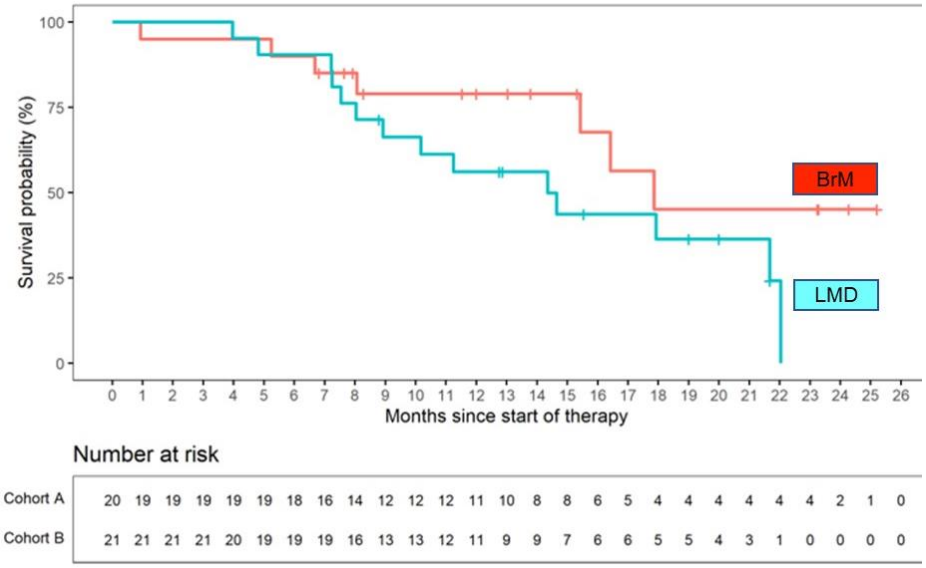
LMD cohort: median 8.3 months (95% CI: 3.3-12.2)



Overall Survival:

Brain mets cohort: median 17.9 months (95% CI: 15.4-NR)

LMD cohort: median 14.4 months (95% CI: 8.0-NR)

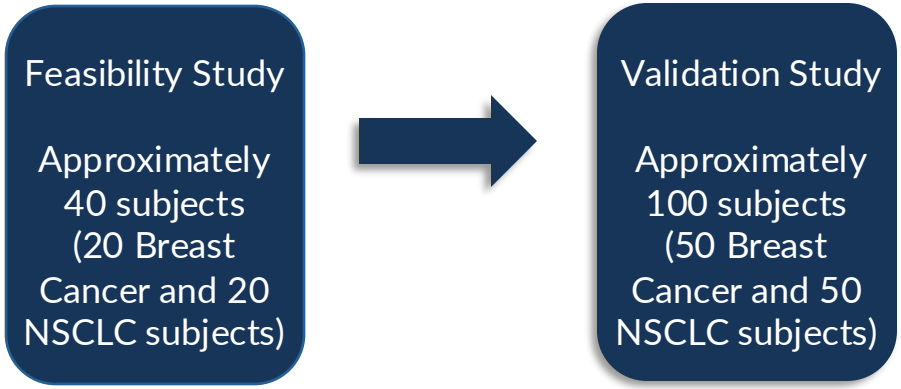


CNSide can detect MET amplification and EGFR mutations

The FORESEE Study: establishing clinical utility

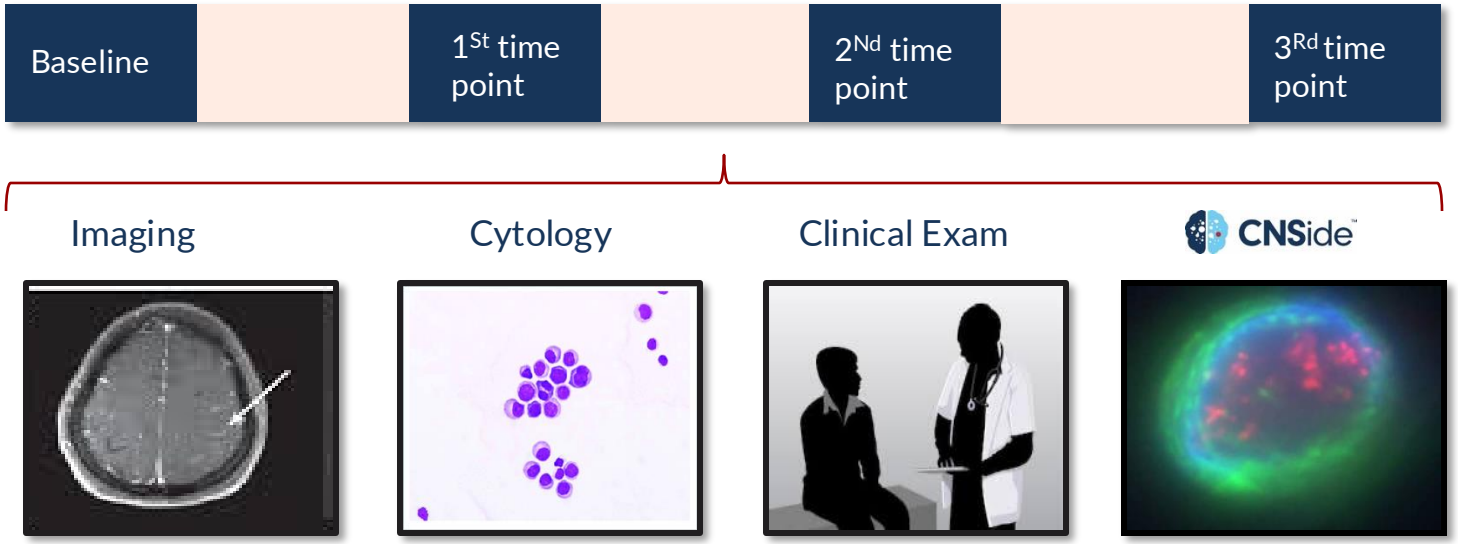
- Establish how CNSide is clinically useful in the management of LM
  - Feasibility study: obtain wide range of data on how CNSide is used (i.e., detection & enumeration of tumor cells, actionable biomarkers)
  - Validation study: validate endpoints that were measured in the feasibility study in larger cohort
    - Validation study design could be altered based on results of feasibility study

Study design:



Trial Schema

- Observational multi-site Study in the US
- At baseline and three consecutive time points Imaging, Cytology, Clinical evaluation and CNSide results will be collected
- At each time point, treatment decisions will be assessed via a questionnaire completed by Physician
- Treatment is per Physician's choice



Study End Points

- Primary Endpoint
  - Measure the impact of CNSide in combination with MRI, Cytology and Clinical Evaluation on clinical treatment decisions made by Physicians

Where did this design come from?

Trial Name[1]	Clinical treatment decision end point	NCT number
Treatment Decision Impact of OncotypeDX™ in HR+, N- Breast Cancer Patients (SWITCH)	Impact of the OncotypeDx Recurrence score on the treatment recommendation made	NCT01446185
Genomic Grade Index (GGI): Feasibility in Routine Practice and Impact on Treatment Decisions in Early Breast Cancer	The impact of Genomic Grade Index results on adjuvant treatment decision	NCT01916837
Measuring the Impact of MammaPrint on Adjuvant and Neoadjuvant Treatment in Breast Cancer Patients: A Prospective Registry (IMPACt)	Change in Treatment Decision	NCT02670577
Prospective Clinical Utility Study to Assess the Impact of Decipher on Treatment Decisions After Surgery (PRO-IMPACT)	Number of participants for which the Decipher test changes the urologist's and patient's treatment plan choices	NCT02080689

The future is bright

(so put on your sunglasses)

- EGFR: Erlotinib, osimeritinib, lazertinib
- ALK/ROS1:Ceritinib, alectinib, brigatinib, lorlatinib
- BRAF/MEK: Vemurafenib, dabrafenib, encorafinib
- HER2: Lapatinib, neratinib, tucatinib, T- dx
- IDH: vorasidenib
- PD-1/PDL-1Abs (too many to list!)
- NTRK: entrectinib, laro, repo
- KRAS: adagrasib
- MET: campatinib, tepotinib
- RET: selpercatinib
- HER3 Drugs?

Better testing means smarter treatment and better outcomes

Neuro-oncology:

combating therapeutic nihilism

2.5 years from diagnosis of LM from HER2+ breast CA
WBRT + IT trastuzumab (lived 4.5 years post dx!!)

Learning Points

- LMD is an increasing problem for our patients
- New testing modalities will help us diagnose and track disease
- There are multiple drugs in the pipeline that have CNS activity and are options!
- Not all that enhances is LMD…when in doubt, poke

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Radiation-Based Therapeutic Approaches to Leptomeningeal Metastasis

Jonathan T. Yang, MD, PhD
Director of Clinical Research
NYU Brain and Spine Tumor Center

Disclosures

Employer: NYU School of Medicine

Research funding: AstraZeneca, Kazia Therapeutics, Natera, Debiopharm, Cantex Therapeutics, Biocept

Consulting/Advisory Board: AstraZeneca, Debiopharm, Galera Therapeutics, Nanocan Therapeutics, Plus Therapeutics

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Radiation Therapy for the Management of Leptomeningeal Metastasis (LM)

- **Long served as a pillar in the management of LM**

- **For patients with select primary CNS malignancies, craniospinal irradiation is considered the standard-of-care for patients with known or at risk of leptomeningeal dissemination with goal of disease control and cure.**
  - Medulloblastoma
  - Intracranial and spinal ependymoma
  - CNS germ cell tumors

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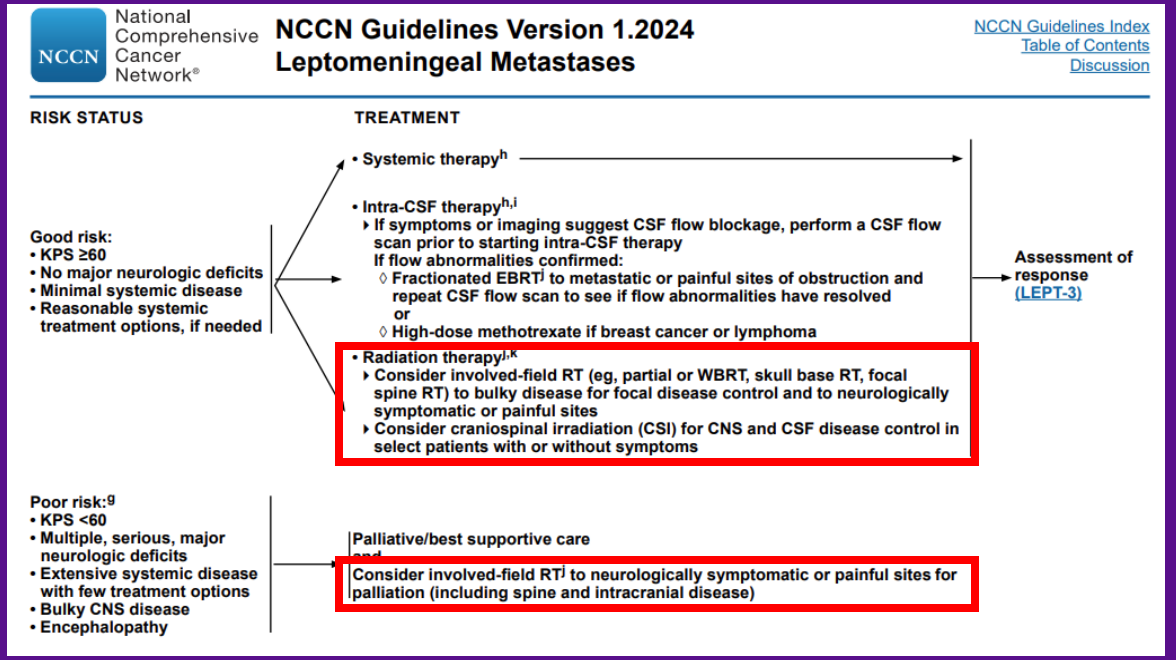
Radiation Therapy for the Management of LM

- Long served as a pillar in the management of LM
- For patients with leptomeningeal dissemination from solid tumors, palliative radiation therapy has an essential role for symptom management and disease control.



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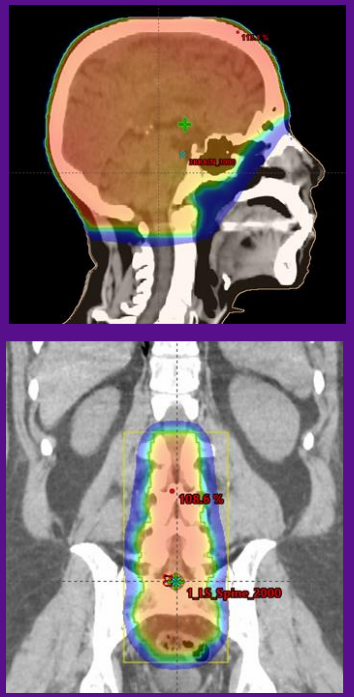
Goal-Directed Radiation Therapy for the Management LM

Symptom and local disease management → CNS and CSF disease control

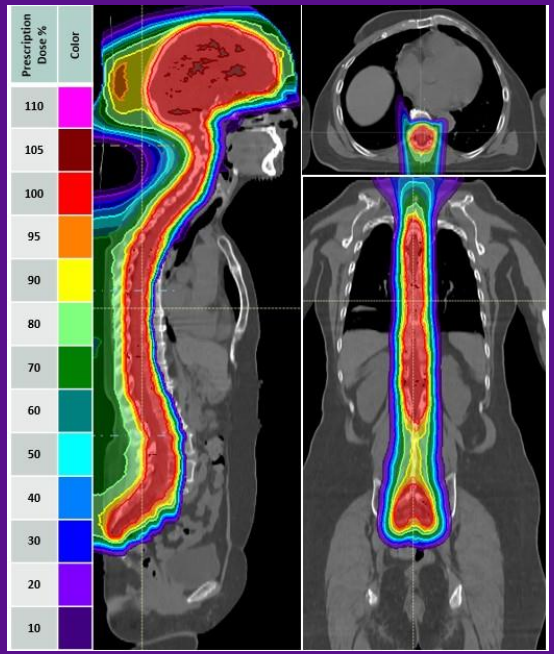
Involved-field radiotherapy (IFRT):

To manage and prevent symptoms in a specific location in the central nervous system (partial CNS compartment treatment)



Craniospinal irradiation (CSI):

To manage and prevent symptoms in the central nervous system, and to prolonged disease control in the central nervous system (comprehensive CNS compartment treatment)



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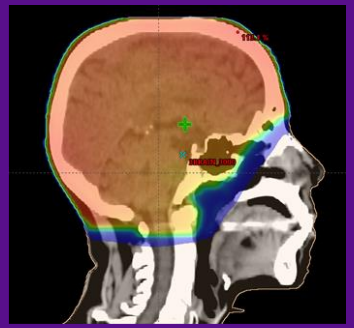
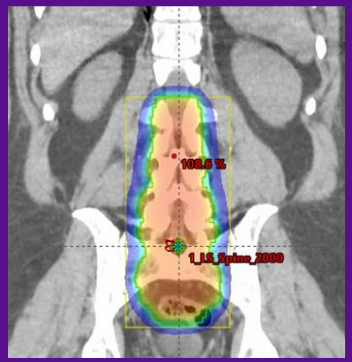
Goal-Directed Radiation Therapy for the Management LM

Symptom and local disease management → CNS and CSF disease control

Involved-field radiotherapy (IFRT):

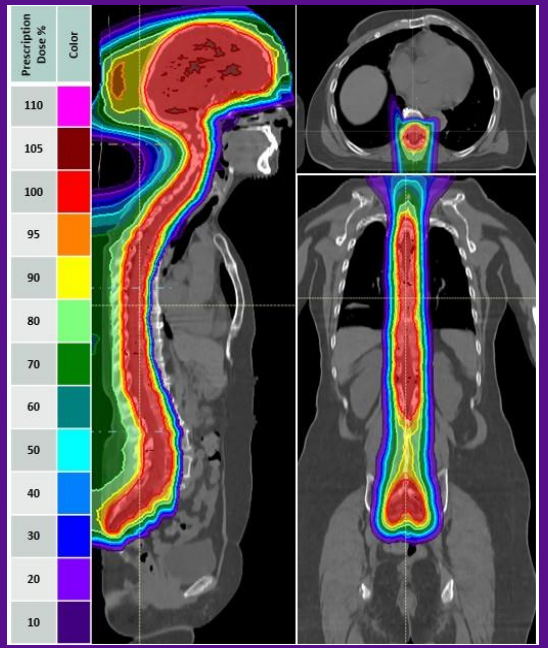
- Does not stop LM progression along the CNS axis and does not seem to improve survival
- Safe and effective in partially treating the CNS compartment





Craniospinal irradiation (CSI):

- Can potentially stop LM progression along the CNS axis and can potentially improve survival
- How do we safely treat the entire compartment in patients who tend to be heavily pretreated and needing to get back on systemic therapy quicky?



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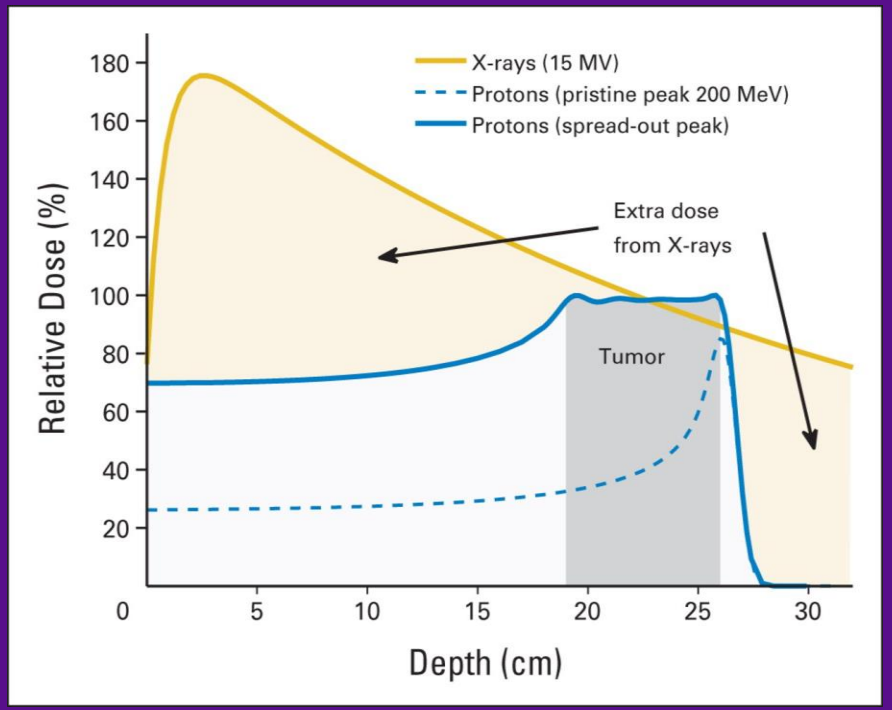
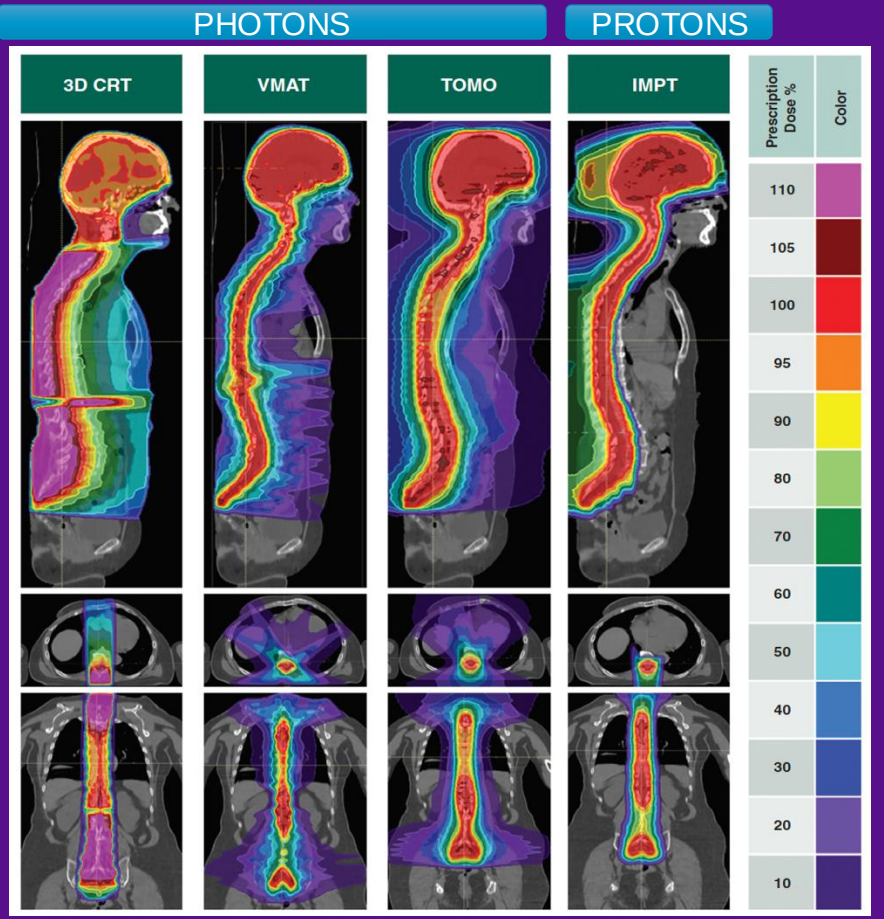
Lessons Learned from Traditional CSI Delivery Techniques

Study	Diagnosis	Patient number	Outcomes
Brown et al. 2014	Adult medulloblastoma	• 21 with 3DCRT photon CSI • 19 with proton CSI	Proton vs. Photon CSI: • >5% weight loss 16% vs. 64% • Grade 2+ nausea and vomiting 26% vs. 71% • Grade 3+ esophagitis 5% vs. 57%
Breen et al. 2024	Adult medulloblastoma	• 20 with photon CSI (9 with 3DCRT, 11 with IMRT) • 19 with proton CSI	Proton vs. Photon CSI: • acute dysphagia of any grade: 5% vs. 35% • weight loss during radiation: +1.0 vs. -2.8 kg
Harada et al. 2014	Solid tumors	17 with photon CSI	• 41%, 35% and 6% Grade 3-4 leukopenia, thrombocytopenia and anemia, respectively • 24% Grade 3-4 nausea and anorexia
El Shafie et al. 2019	Solid tumors	25 with tomortherapy photon CSI	32% with Grade 3 myelosuppression
Devecka et al 2020	Solid tumors	19 with photon CSI (3 with 3DCRT, 16 with tomotherapy)	9 patients did not complete RT, with 5 patients due to Grade 3-4 cytopenia

Differences Between Photon and Protons





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Mitin and Zietman. JCO 2014
Kotecha, La Rosa and Mehta Neuro Oncology 2024

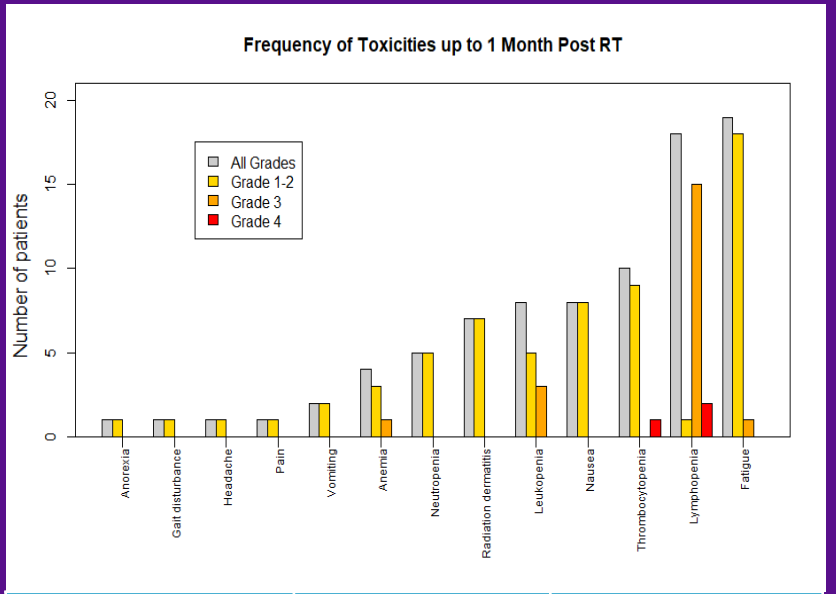
Proton CSI Phase I Trial

- **Between June 2018- April 2019, 21 patients enrolled**
- Median age 52 (30-67)
- Median KPS 70 (60-90)
- Most common histologies NSCLC (52%) and breast (33%)

- **1 patient was censored at 24 months**

- **Median OS= 9 months (95% CI: 6-22 months)**

- **Median CNS PFS= 7 months (95% CI: 5-13 months)**



Symptoms	Grade 3	Grade 4
Anemia	1 (5%)	0 (0%)
Leukopenia	3 (15%)	0 (0%)
Thrombocytopenia	0 (0%)	**1 (5%)**
Lymphopenia	15 (75%)	**2 (10%)**
Fatigue	**1 (5%)**	0 (0%)

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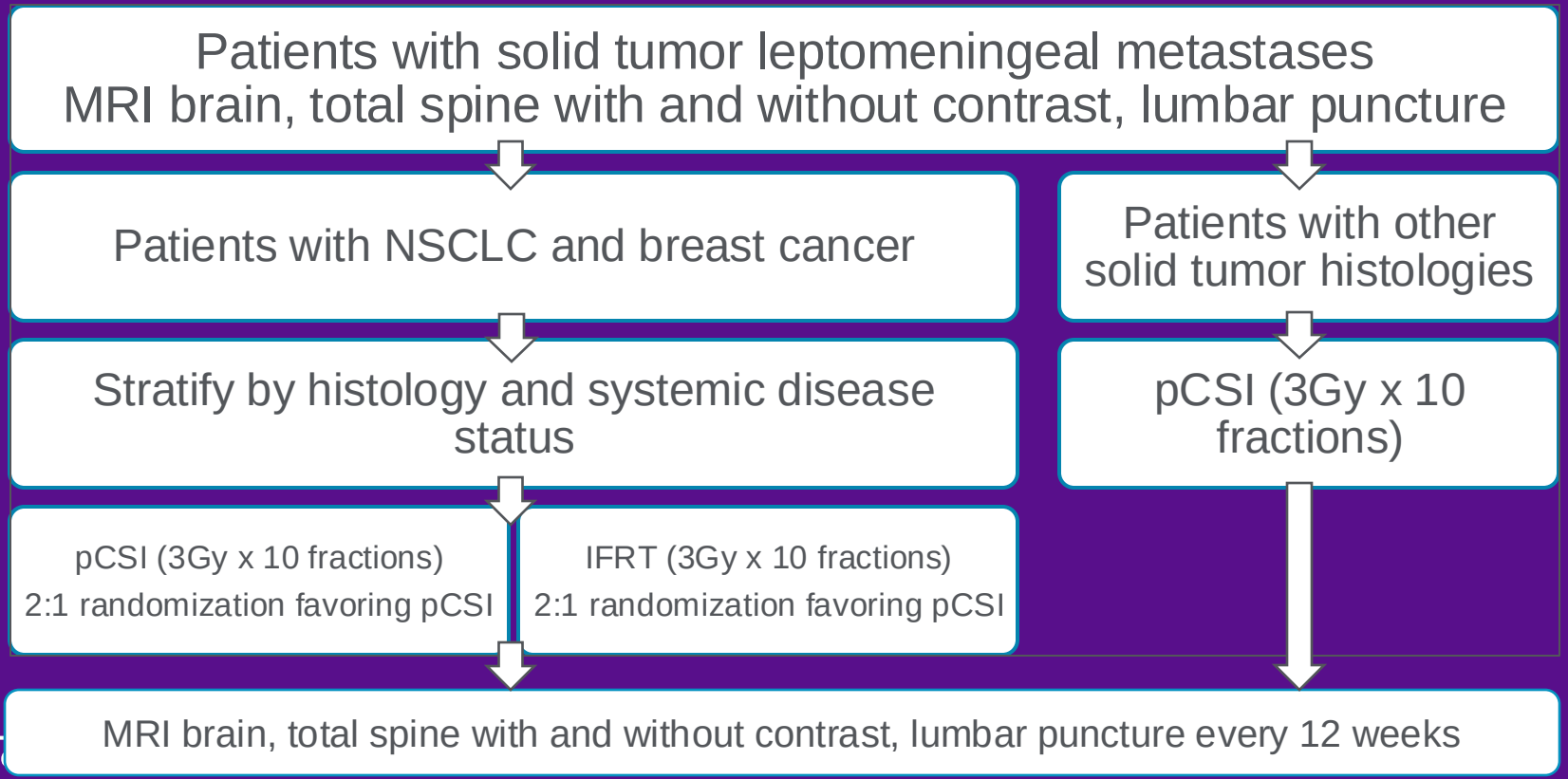
Yang et al., Neuro Oncology 2021

Randomized Phase II Trial of proton CSI vs. IFRT



Yang et al., JCO 2022

Phase II Trial- Randomized Groups

Characteristic	pCSI (N=42)	Photon IFRT (N=21)
Age (median, range)	56 (49-55)	61 (54-65)
Sex		
Female	34 (81%)	18 (86%)
Male	8 (19%)	3 (14%)
Primary Disease		
NSCLC	24 (57%)	12 (57%)
EGFR+	12 (29%)	7 (33%)
Breast	18 (43%)	9 (43%)
HER2+	6 (14%)	4 (19%)
Systemic Disease Status		
Active	22 (52%)	11 (52%)
Stable/None	20 (48%)	10 (48%)

Characteristic	pCSI (N=42)	Photon IFRT (N=21)
KPS (median, range)	80 (60-90)	80 (60-90)
Newly diagnosed LMD	35 (83%)	18 (86%)
At Enrollment		
Positive MRI	38 (91%)	21 (100%)
Positive Cytology	28 (67%)	11 (52%)
Positive CSF CTC	36 (86%)	17 (81%)
Brain Metastases		
Yes	28 (67%)	15 (71%)
No	14 (33%)	6 (29%)
Median Lines of Prior Systemic Therapy	2 (0-8)	2 (0-8)
IFRT Fields		
WBRT		9 (43%)
Spinal RT		1 (5%)
Both		8 (38%)

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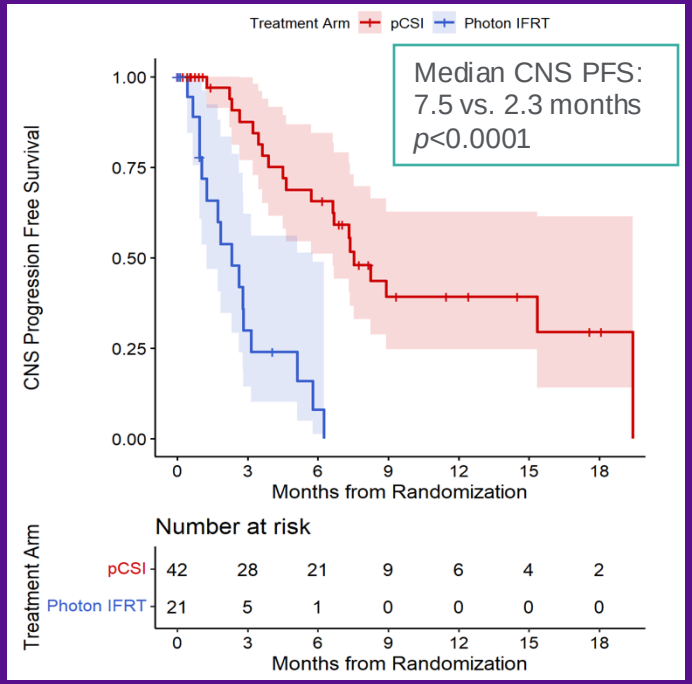
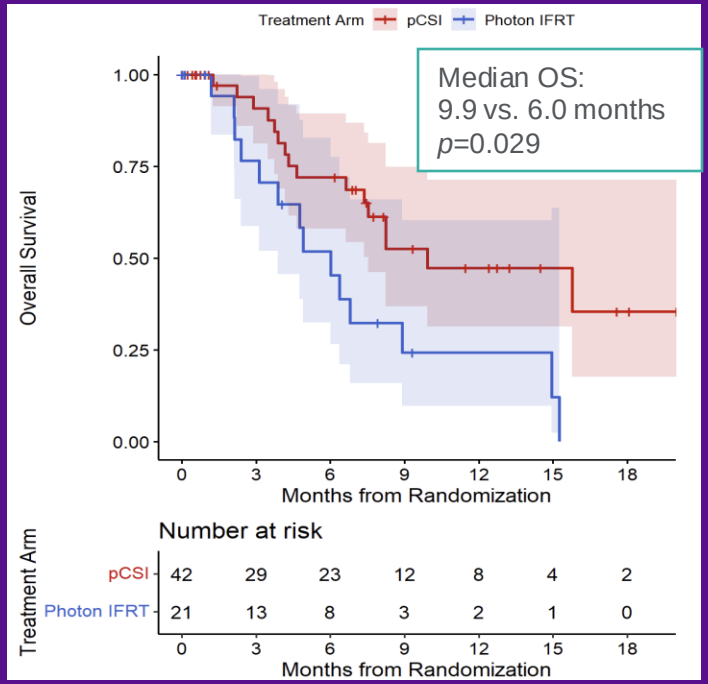
Yang et al., JCO 2022

Phase II Trial- Randomized Groups





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Yang et al., JCO 2022

Comparable High-Grade Toxicities

	Randomized pCSI group (N=42)		Randomized IFRT group (N=21)		Exploratory pCSI group (N=35)	
Symptoms	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Fatigue	1 (2%)		2 (10%)			
Gait Disturbance			1 (5%)			
Headache			1 (5%)		1 (3%)	
Muscle Weakness					1 (3%)	
Nausea					1 (3%)	
Pain	1 (2%)					
Vomiting	1 (2%)				1 (3%)	
Lymphopenia		4 (10%)		4 (19%)		6 (17%)

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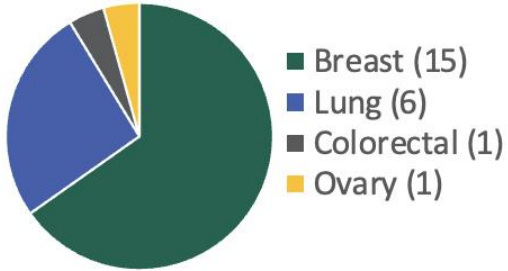
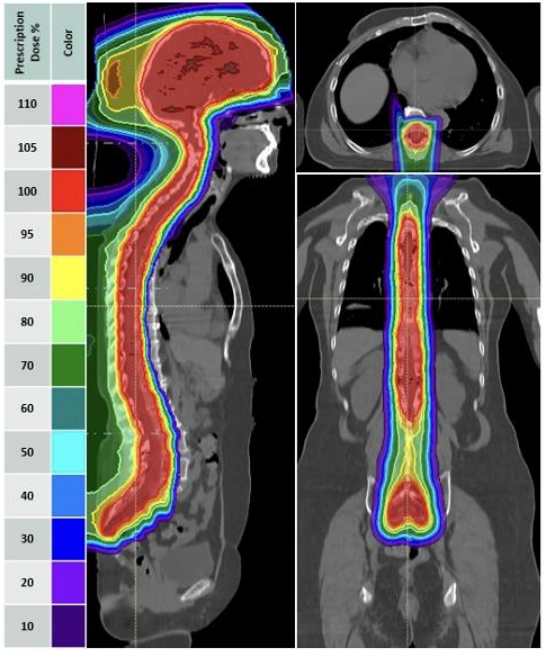
Yang et al., JCO 2022

Miami Cancer Institute Experience

- **23 patients** treated between 02/2022 and 11/2023.
- The median **age** was of 57 (range: 23-75).
- The median **KPS** was of 90 (range: 70-100).
- 13 patients (56.5%) were **Hispanic**.
- 14 patients had **prior RT** to brain or spine





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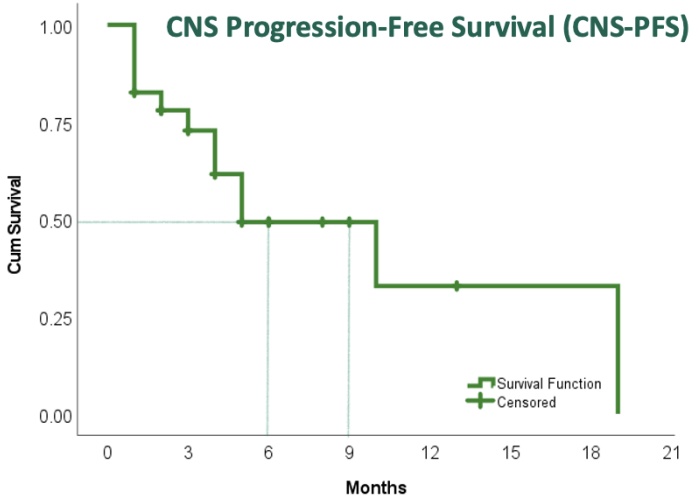
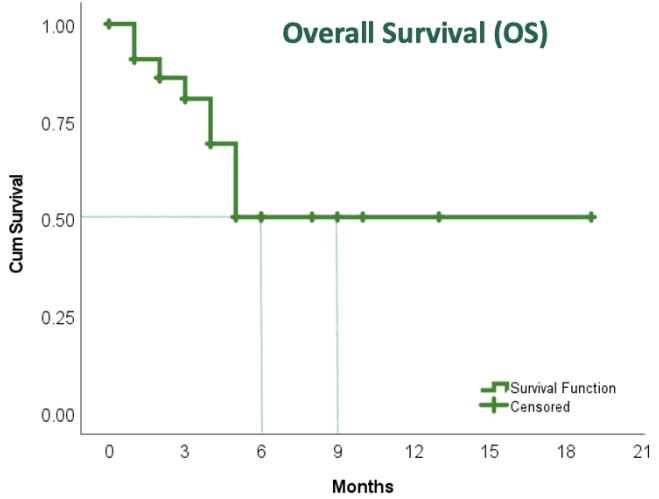
Results

- **Toxicity**: Nine (39.1%) Grade 2+, Grade 3 (2 lymphopenia and 1 thrombocytopenia)
- Estimated 9-month **CNS PFS** and **OS** were 50% and 50%, and respectively.





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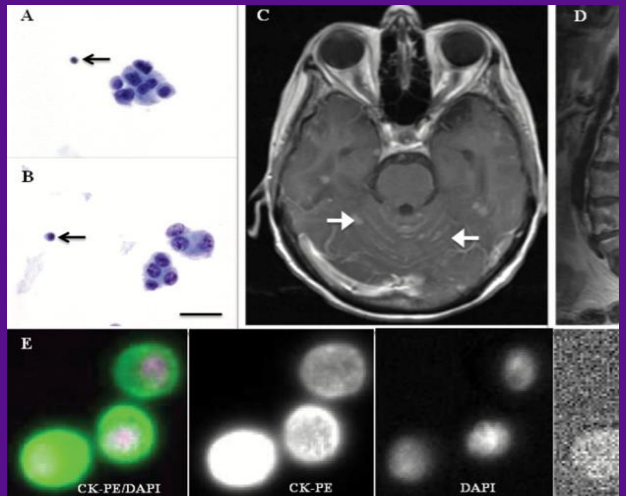
CSF Tumor Cells

- Tumor cells (TCs) in the CSF is a potential diagnostic and treatment response assessment tool
- In a prospective clinical trial evaluating intrathecal Trastuzumab for HER2+ epithelial cancer LM, dynamic changes in CSF TCs were observed with increased CSF TCs preceded MR changes with disease progression

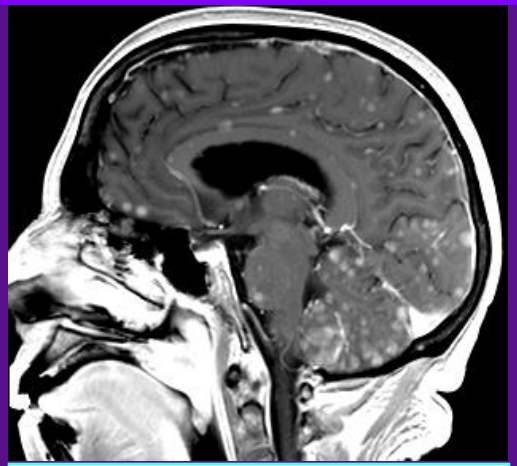


Lin et al. Neuro Oncol. 2017.
Diaz et al. Neuro-oncology Advances 2020
Wijetunga et al. Neuro-oncology Advances 2021

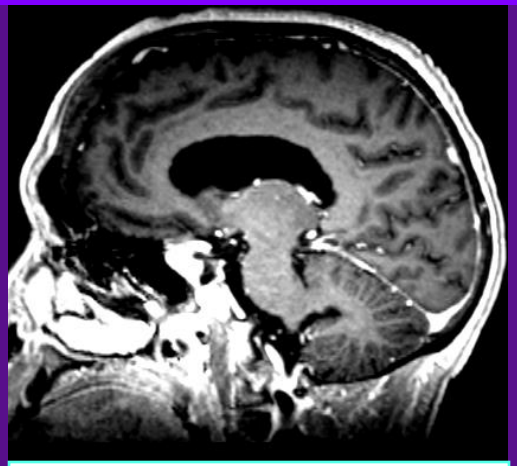
- Consecutive case series of 58 solid tumor LM patients who were treated with proton CSI between January 2018 and December 2020.
- **No increases in CSF TCs immediately after proton CSI**
- Most favorable group: **low baseline CSF TCs (**baseline CSF TC <53 cells/3mL, CellSearch), **median CNS PFS=12 months, OS= 17 months**)
- Favorable group: **high baseline CSF TCs, large CSF TCs decrease after proton CSI** (baseline CSF TC ≥53 cells/3mL and decrease ≥37 cells/3mL after proton CSI), **median CNS PFS=7 months, OS=11 months**)
- Unfavorable group: **high baseline CSF TCs, small CSF TCs decrease after proton CSI** (baseline CSF TC ≥53 cells/3mL and decrease<37 cells/3mL after proton CSI), **median CNS PFS=4 months, OS=5 months**

CSF Tumor Cells

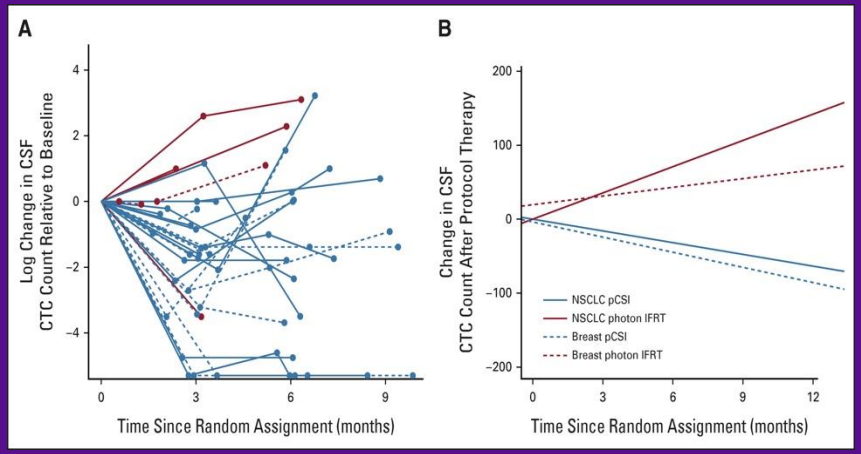
- In the phase II randomized trial, mean CSF TCs declined among patients treated with proton CSI and increased among patients treated with IFRT. For IFRT patients, the increase in CSF TCs was significantly associated with worse time to CNS progression, CNS PFS, and OS
- **Treating the entire CNS compartment is needed to meaningfully reduce the CSF disease burden**



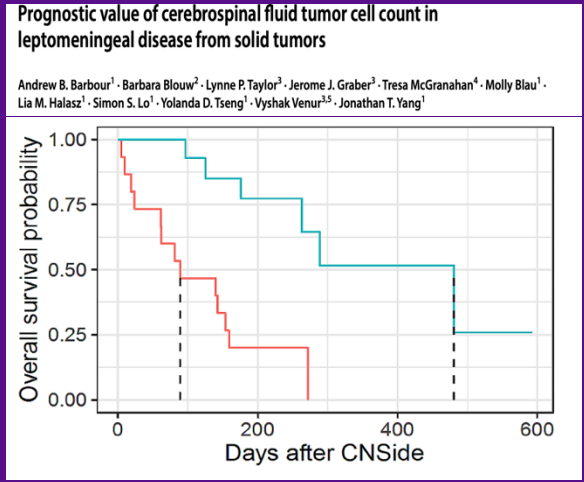
Pre-treatment MRI (extensive disease)
4,590 cells in total, and 1,092 per mL



8 weeks post-treatment (no measureable disease)
12 cells in total, and 2 per mL



Yang et al. JCO 2022
Barbour et al. Journal of NeuroOnc 2024
Example of MRI and CNSide numeration courtesy of Dr. Kotecha



Modern CSI Delivery for Solid Tumor LM

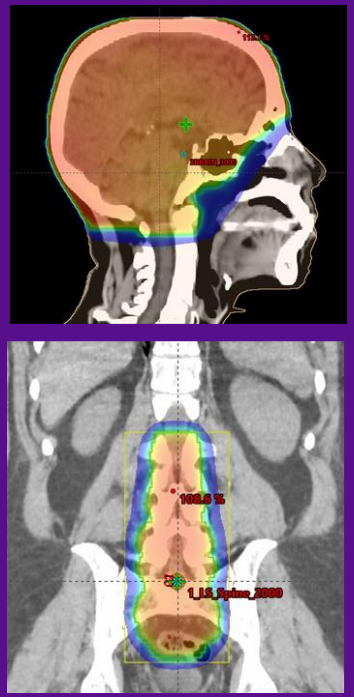
Study	Diagnosis	Patient number	Outcomes
Yang et al. 2021	Solid tumors	24 with **proton CSI**	5% and 10% Grade 4 thrombocytopenia and lymphopenia, respectively 5% Grade 3 fatigue Median CNS PFS=7.0 months, OS=8.0 months
Yang et al. 2022	Arms A and B: Breast cancer and NSCLC Arm C: all other solid tumors	Arms A and B: 42 with **proton CSI** 21 with IFRT Arm C: 35 with **proton CSI**	Arms A and B Proton CSI vs. IFRT: • Grade 3-4 toxicities low and comparable • Median CNS PFS: 2.3 vs. 7.5 months • Median OS: 6.0 vs. 9.9 months Arm C: Median CNS PFS=5.8 months OS=6.6 months
Kotecha et al. 2024	Solid tumors	23 with **proton CSI**	9% and 4% Grade 4 lymphopenia and thrombocytopenia respectively Median CNS PFS=9.0 months, OS=9 months
Perlow et al. 2024	Solid tumors	10 with **vertebral body sparing VMAT photon CSI**	No Grade 3 or above toxicities 1 patient with Grade 2 neutropenia, 9 with Grade 1 hematologic toxicity

Evolution of Radiation Therapy for Solid Tumor LM

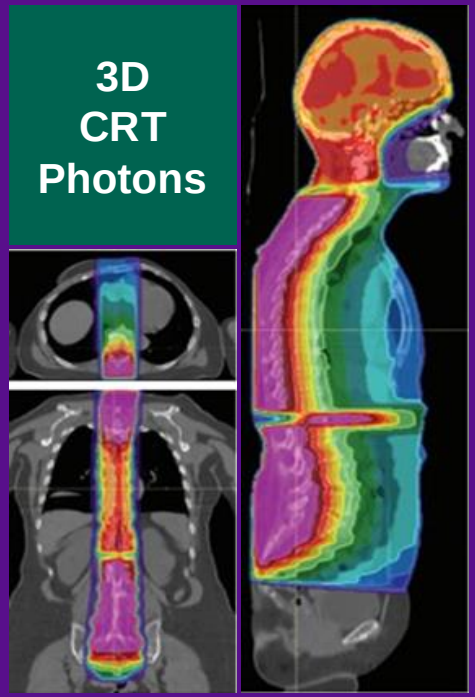
Partial CNS treatment

Traditional Comprehensive CNS treatment

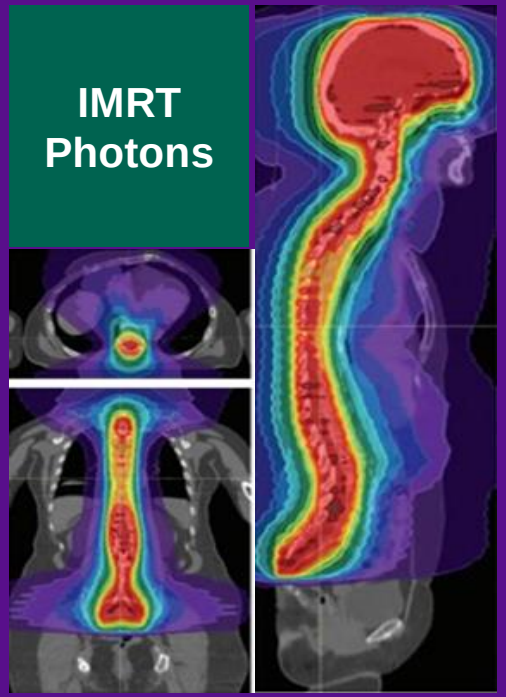
Modern Comprehensive CNS treatment



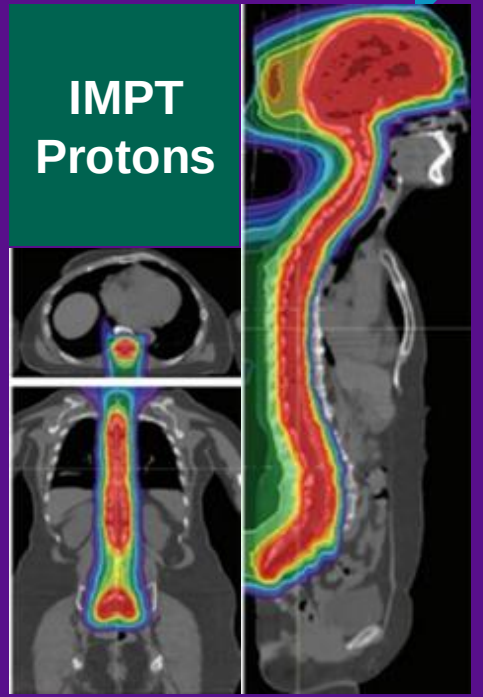
3D CRT Photons



IMRT Photons



IMPT Protons



Conclusions

- **Radiation therapy has long served as a pillar in the management of LM.**
- **For focal symptom and local CNS disease management, IFRT remains and important treatments for all patients with solid tumor LM.**
- **For CNS and CSF disease control, radiation to the entire CNS compartment is needed with potential improvement in patient survival.**
  - For external beam radiation therapy, modern and sophisticated radiation delivery techniques (proton CSI, vertebral body sparing VMAT photon CSI) are needed to adequately treat the CNS compartment while reduce/avoid radiation doses to bone marrow and anterior organs.
  - Other forms of targeted radiation delivery techniques to the entire CNS compartment, including intrathecal radionuclides such as rhenium (186Re) obisbemeda, should be investigated as patients may derive similar benefits as external beam radiation therapy to the entire CNS compartment.

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Thank you