

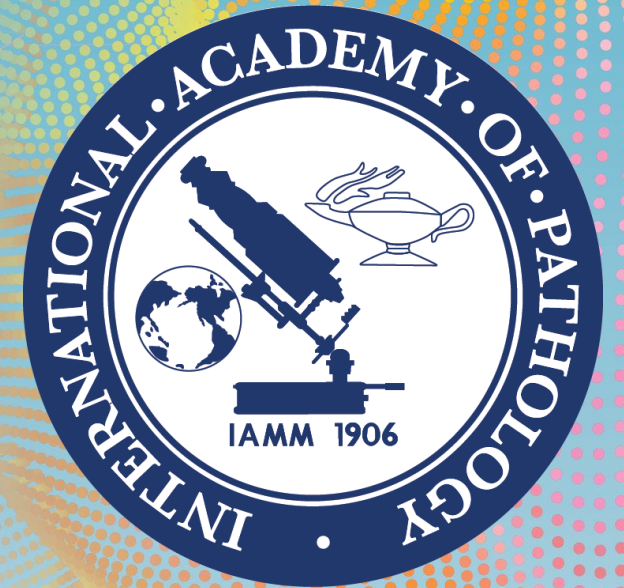
Improving the Grading of cSCC

A/Prof Andrew Dettrick

Sunshine Coast University Hospital

Sunshine Coast University, Health Sciences

Sullivan Nicolaides Pathology, Sunshine Coast



Disclosure of Relevant Financial Relationships

No relevant financial relationships

Why?

2019

87M

Right forehead excision by GP

“Scar with adjacent moderately-differentiated SCC. Deep invasion with deep margin involved. No PNI/LVI.”

@ 3 months

Re-excision

*“Residual/recurrent **Poorly-Differentiated** SCC, invading subcutis, **8mm thick**, deep margin 1.2mm.”*

@ 12 months

Neck lump

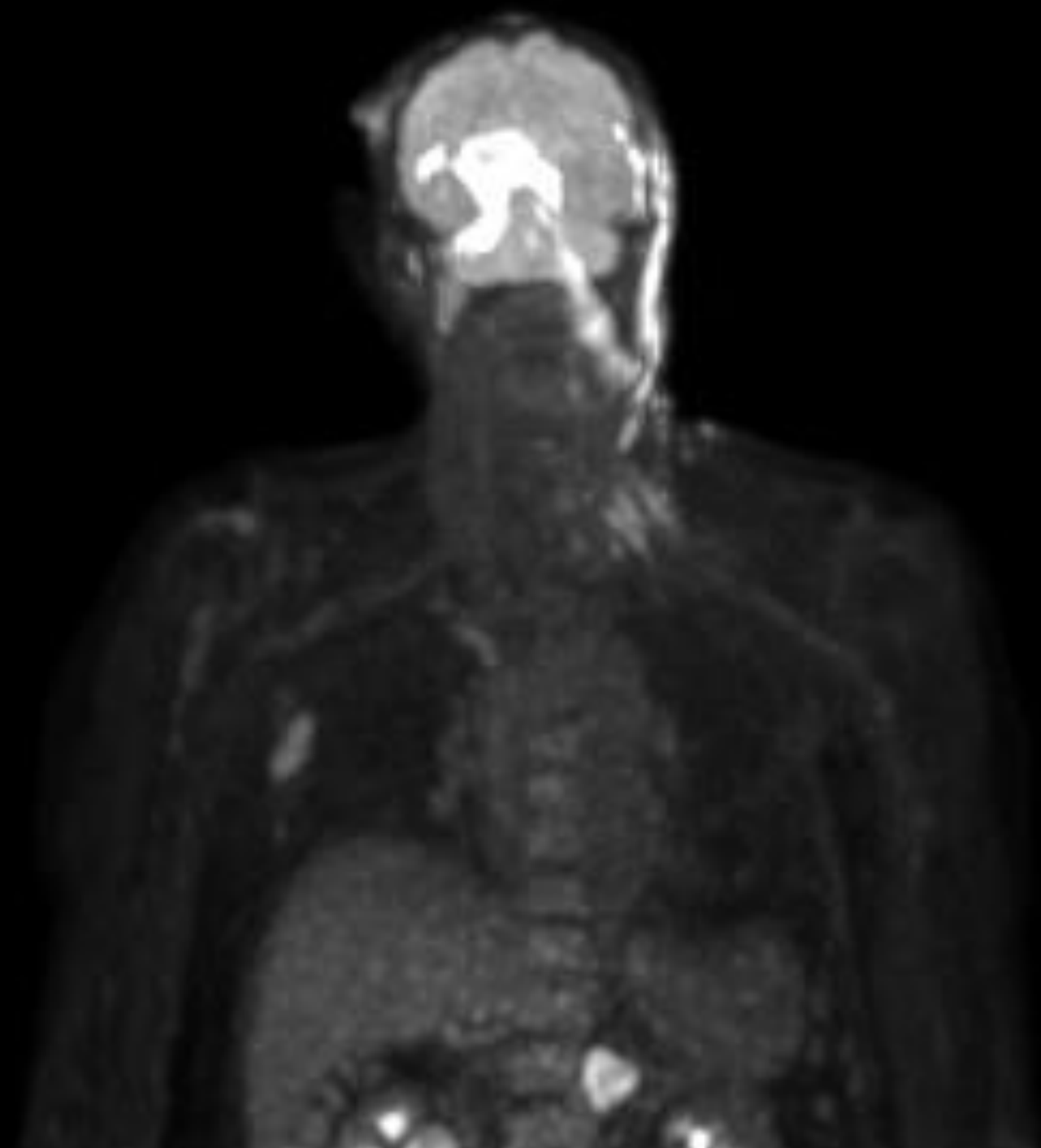
Re-re-excision + parotid + modified radical neck

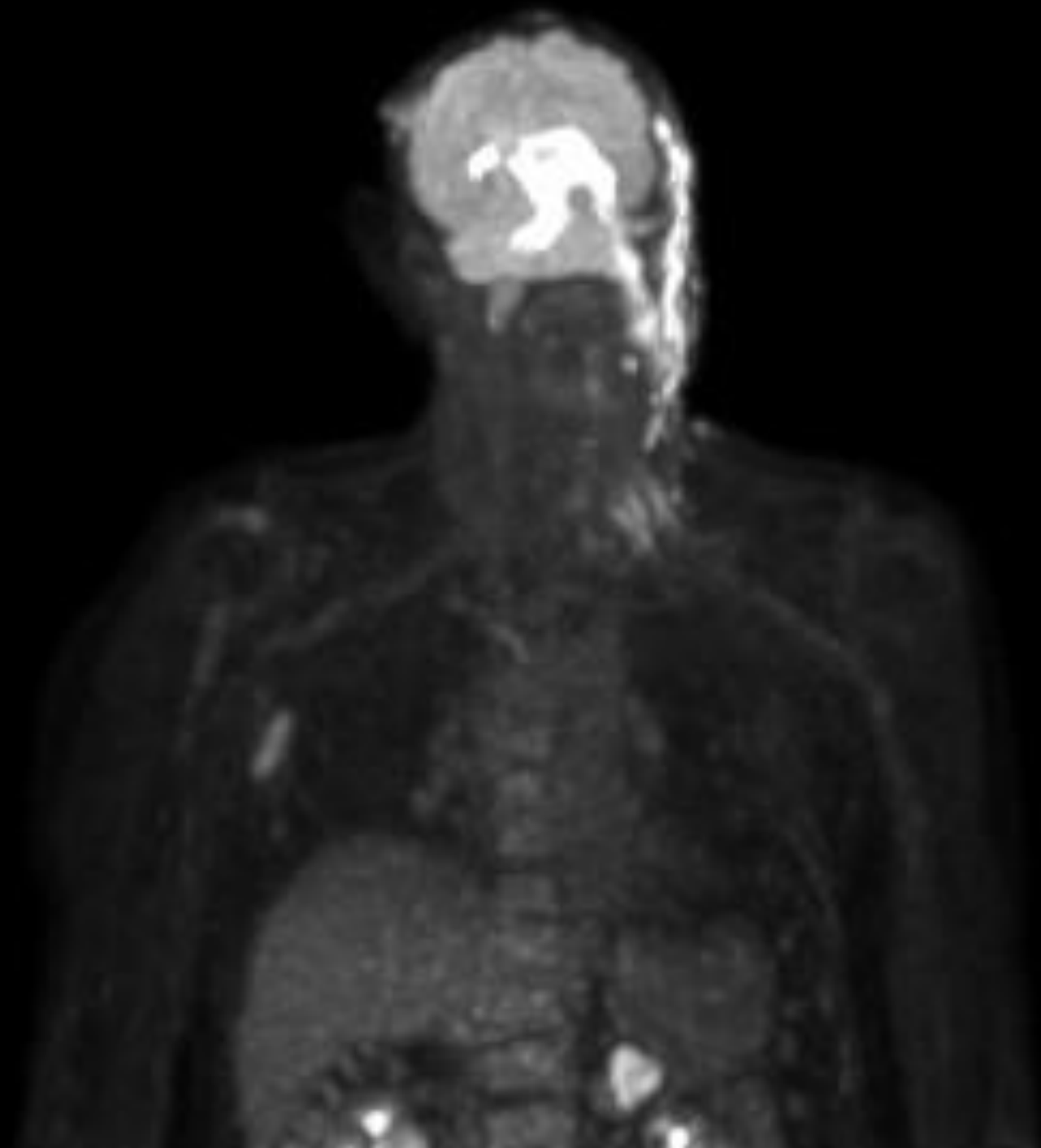
“Multifocal subcut + soft tissue deposits + 5/48 nodes, margin focally involved”

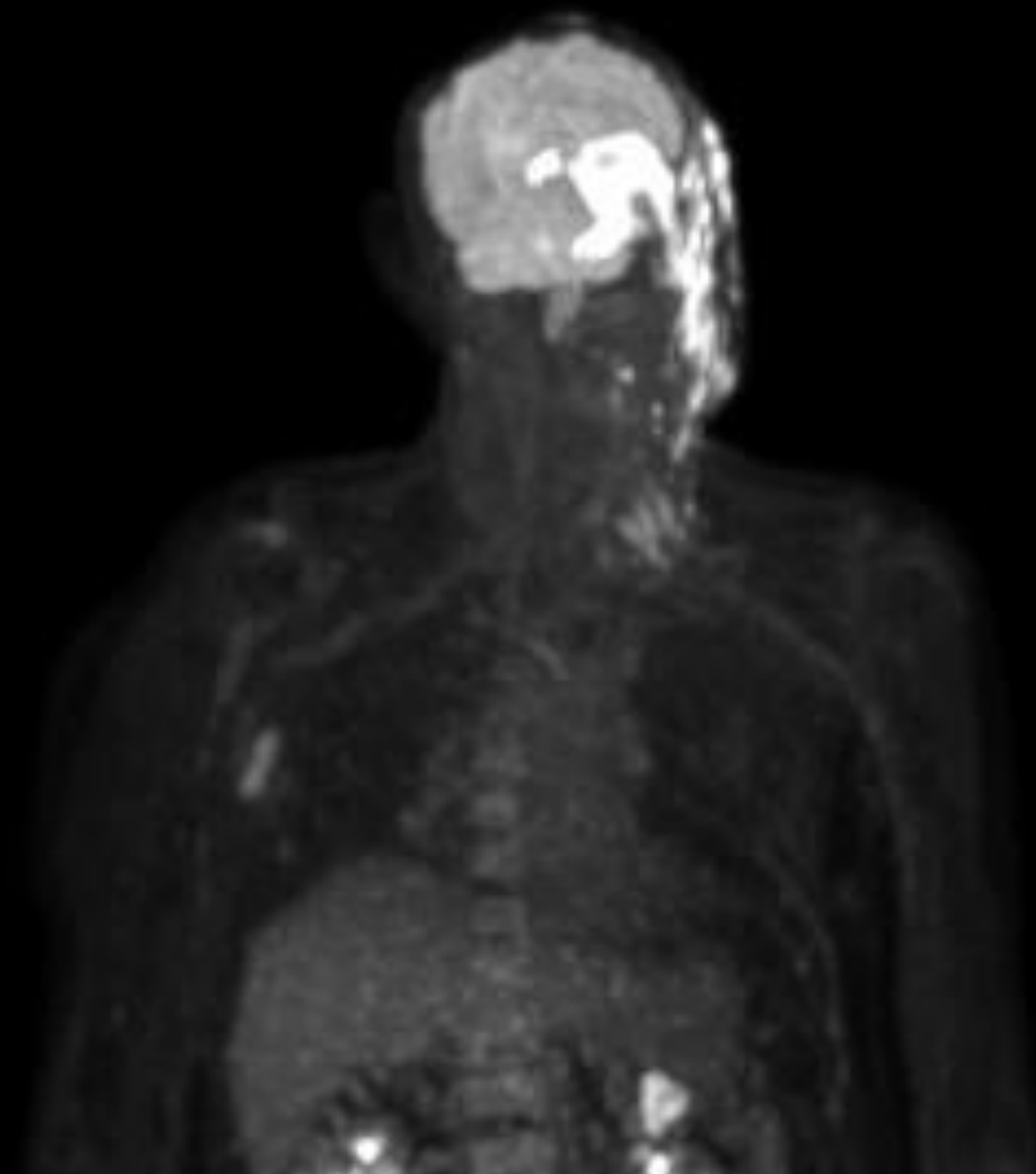
Adjuvant rads

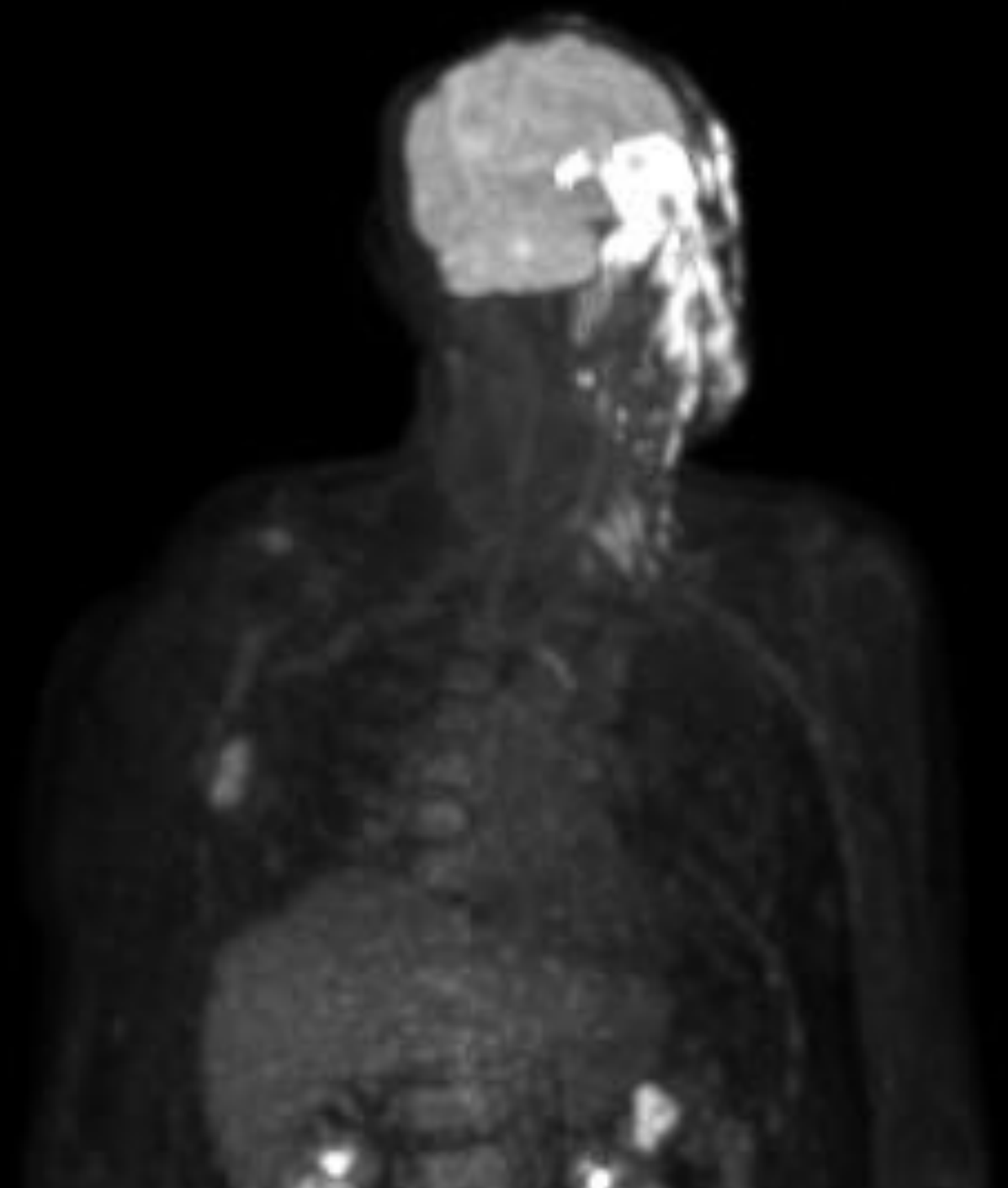
60Gy in 20#

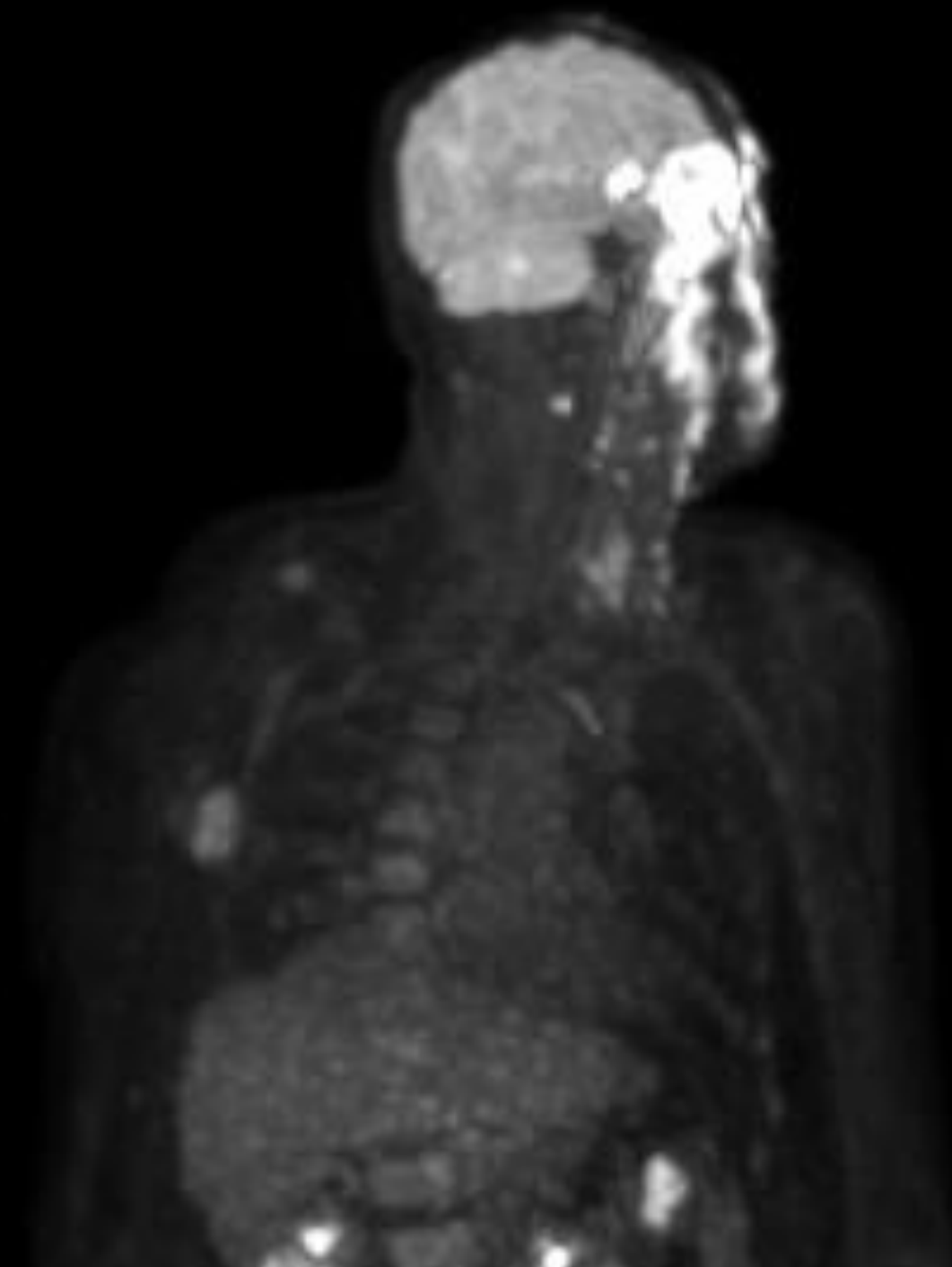
36 days later...

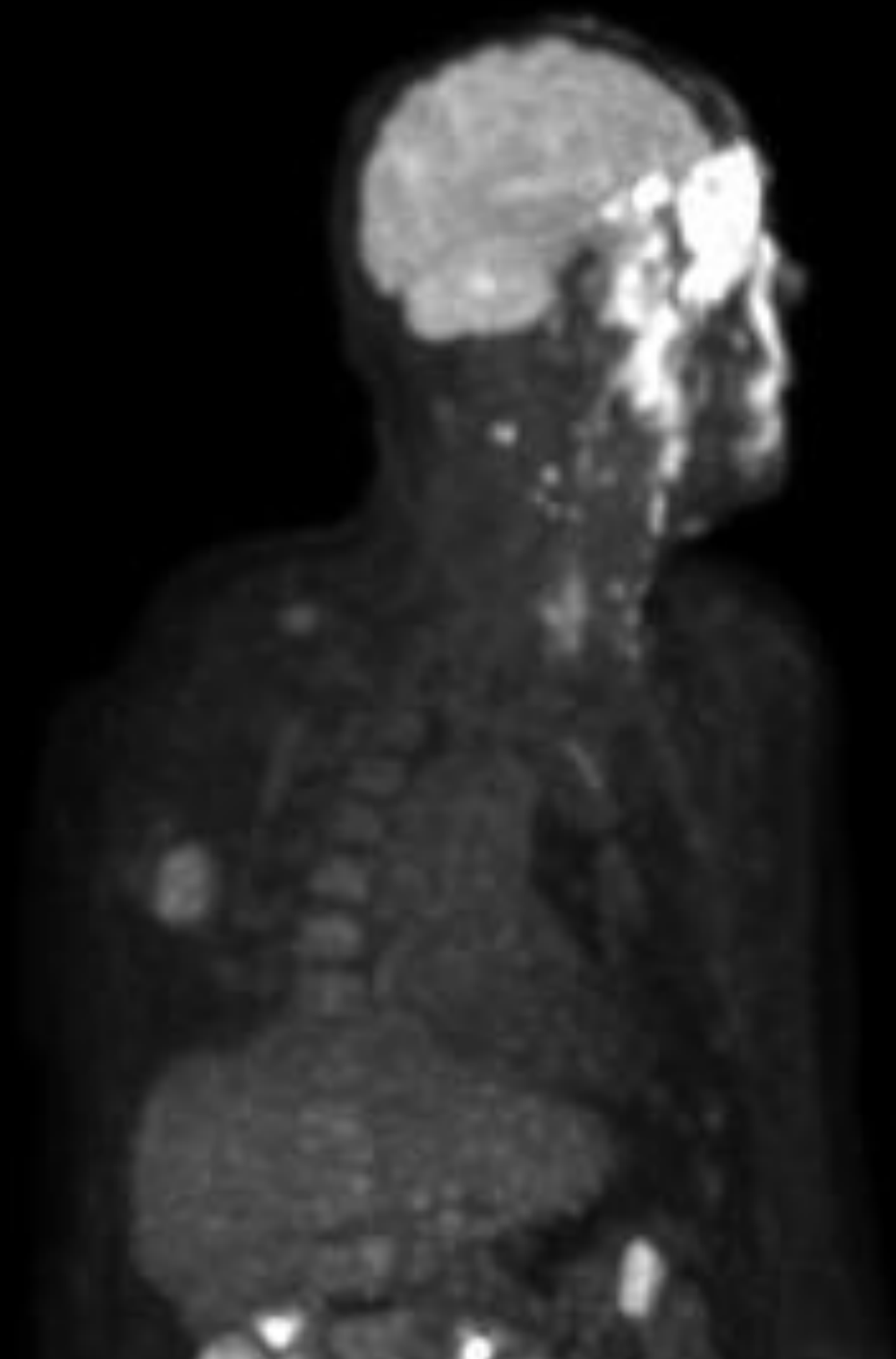


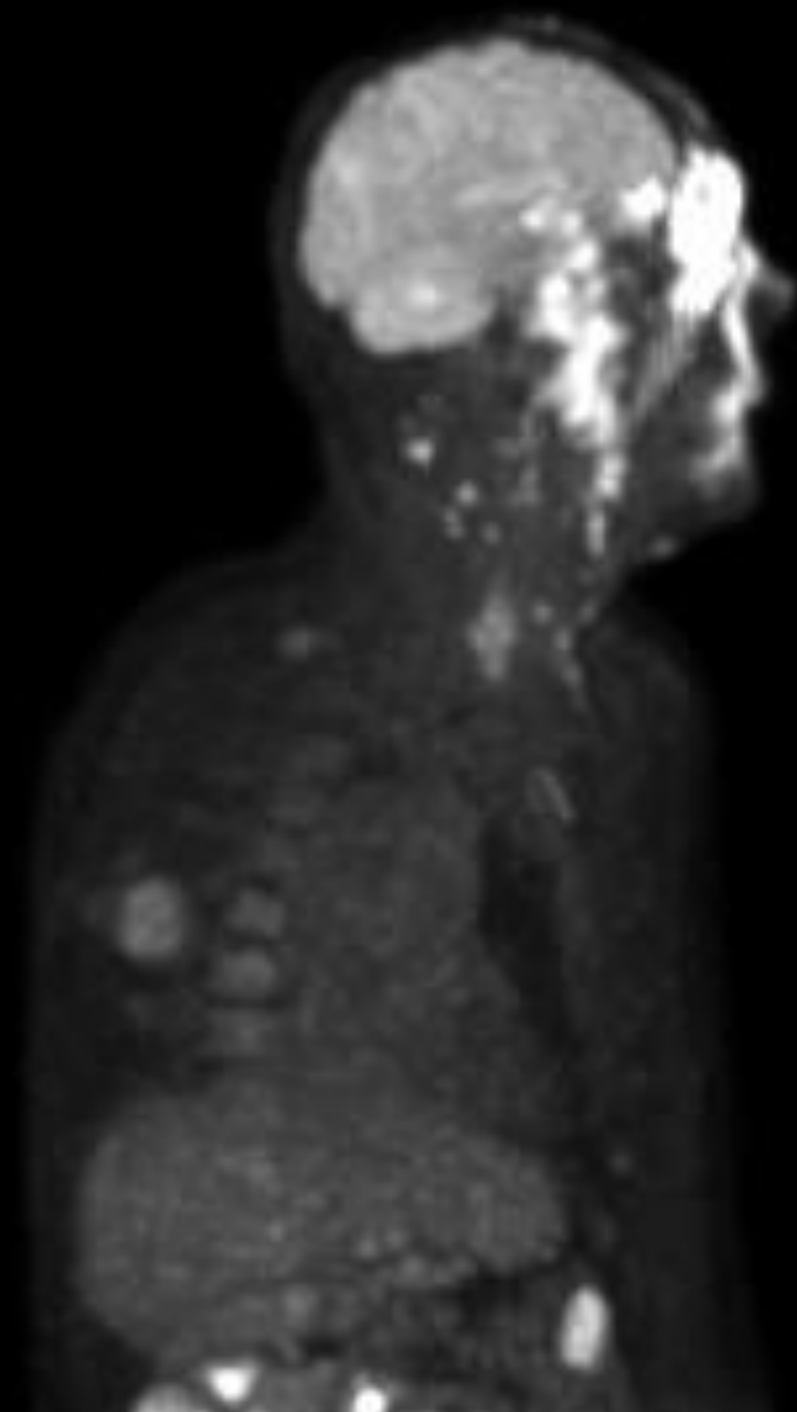


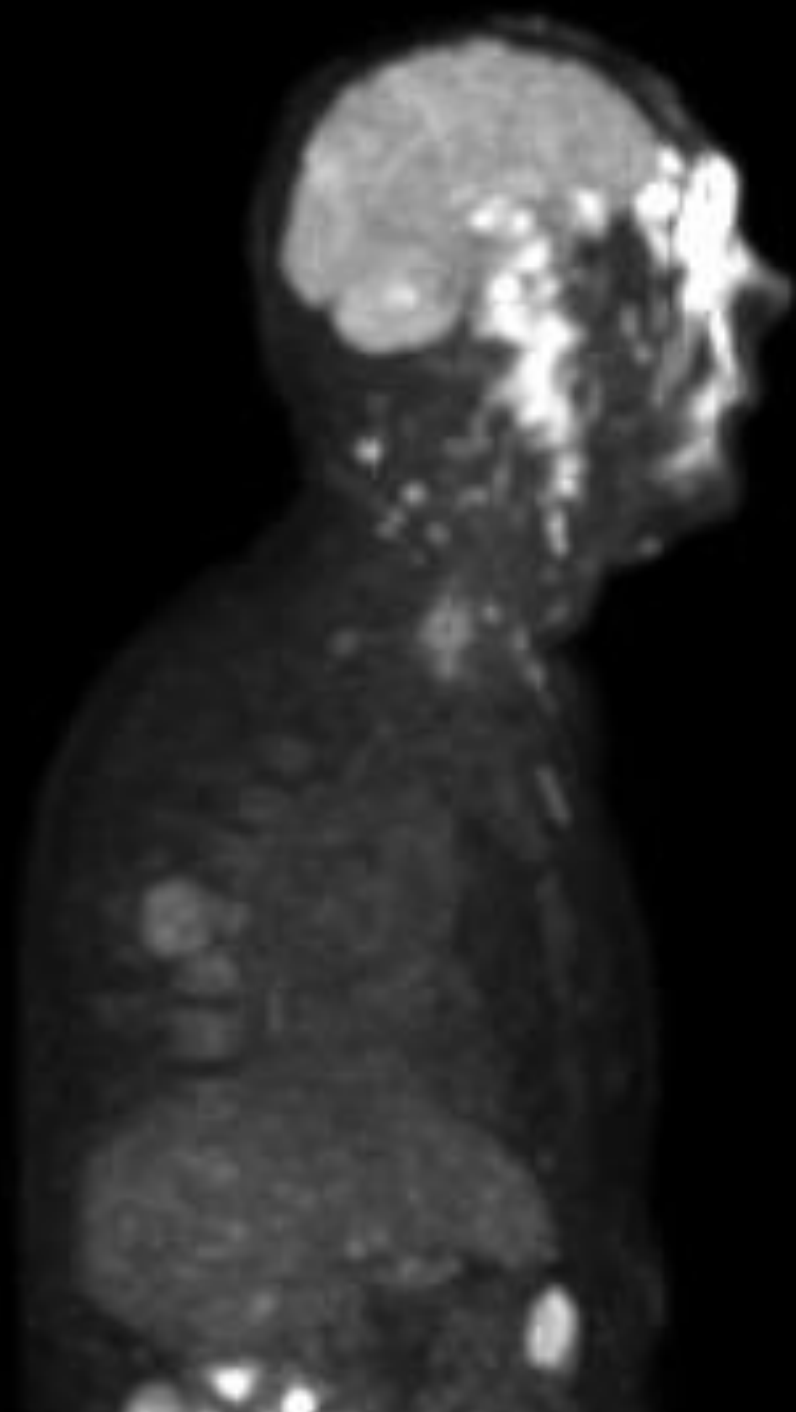


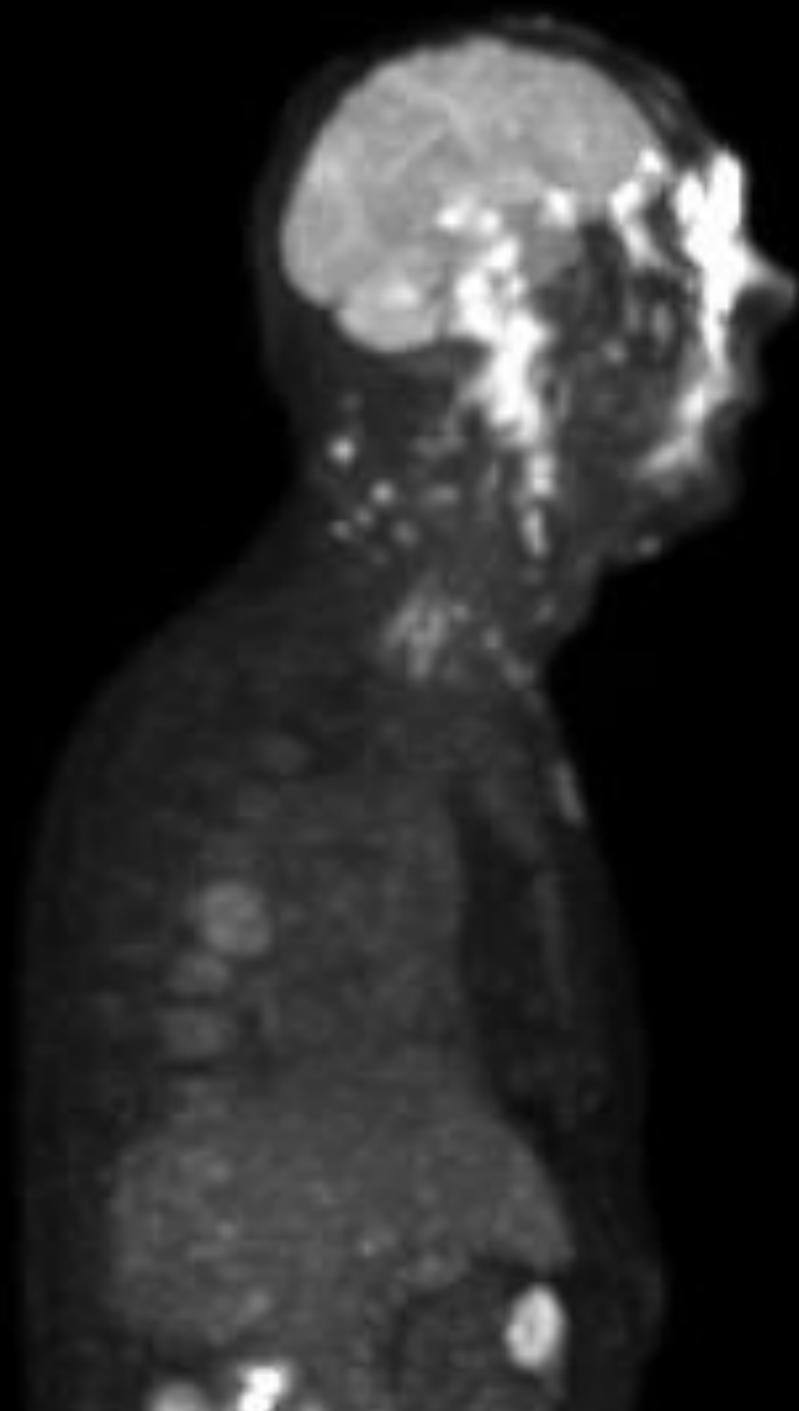


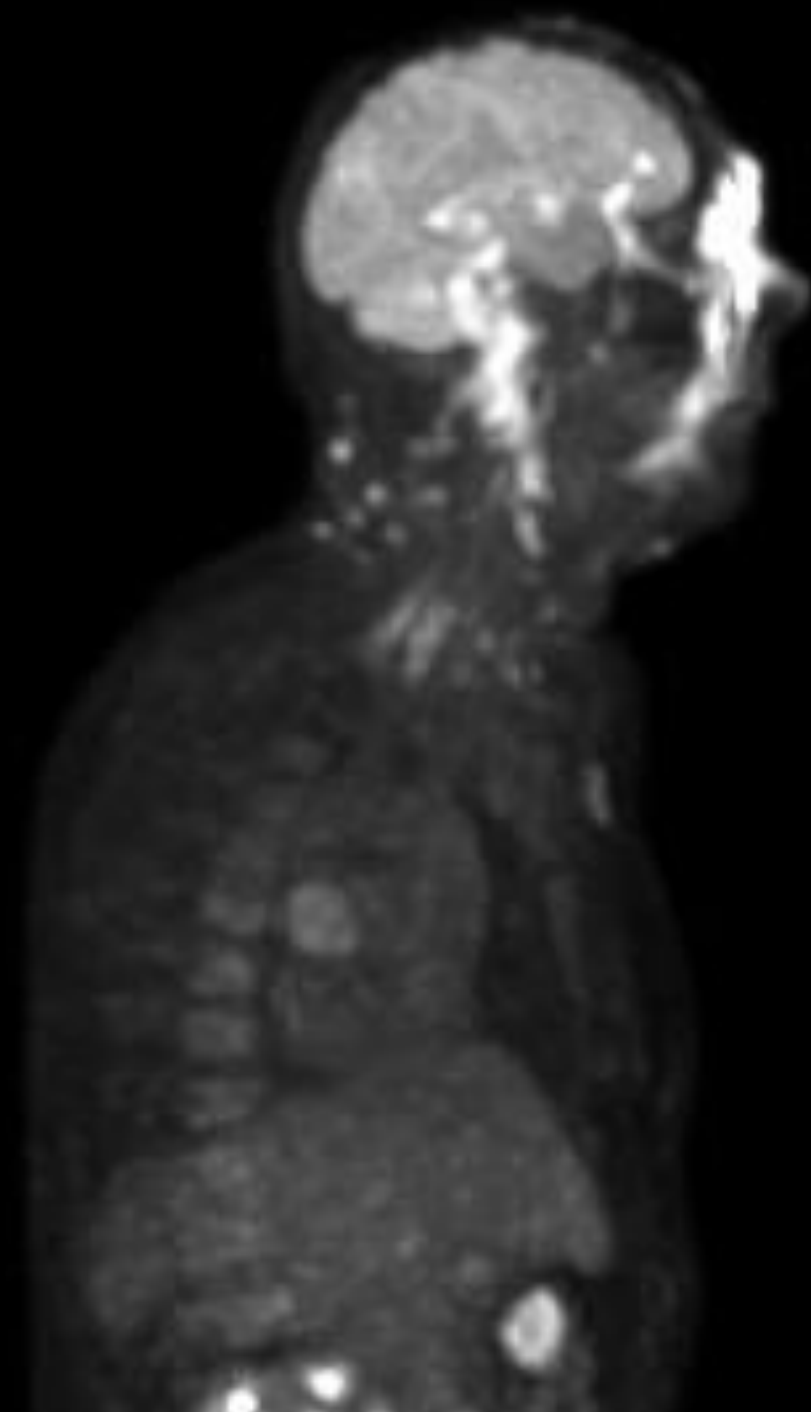


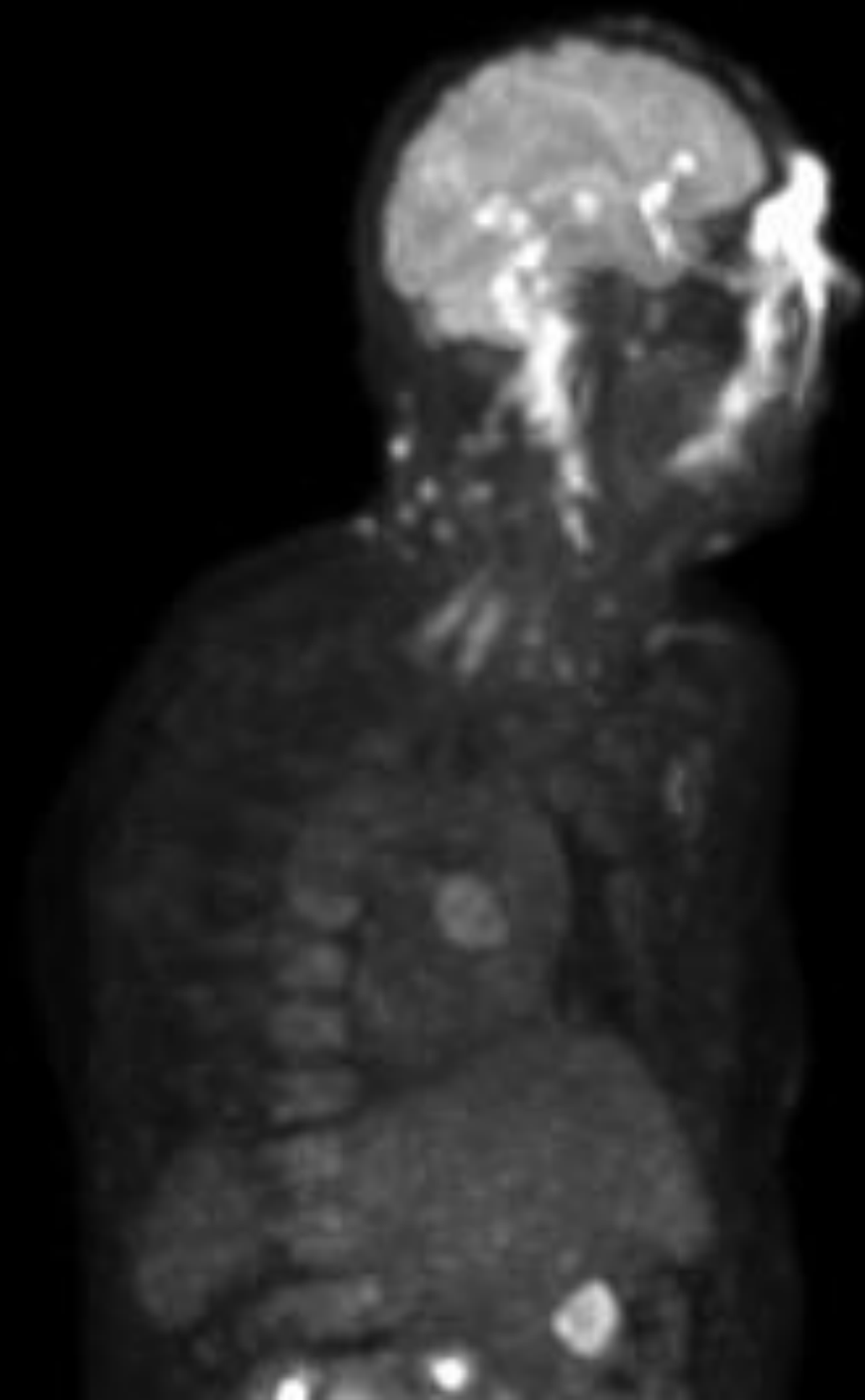


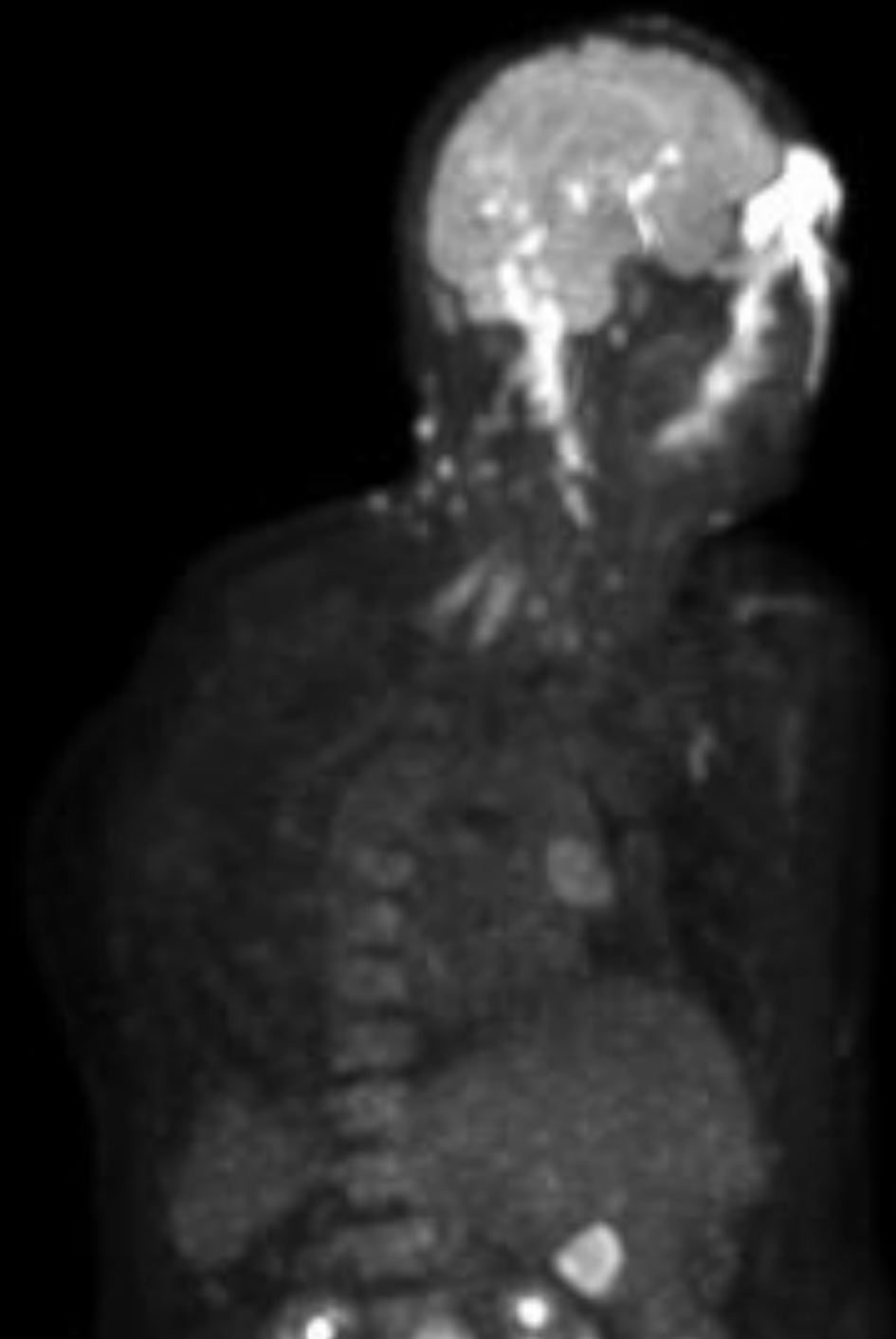


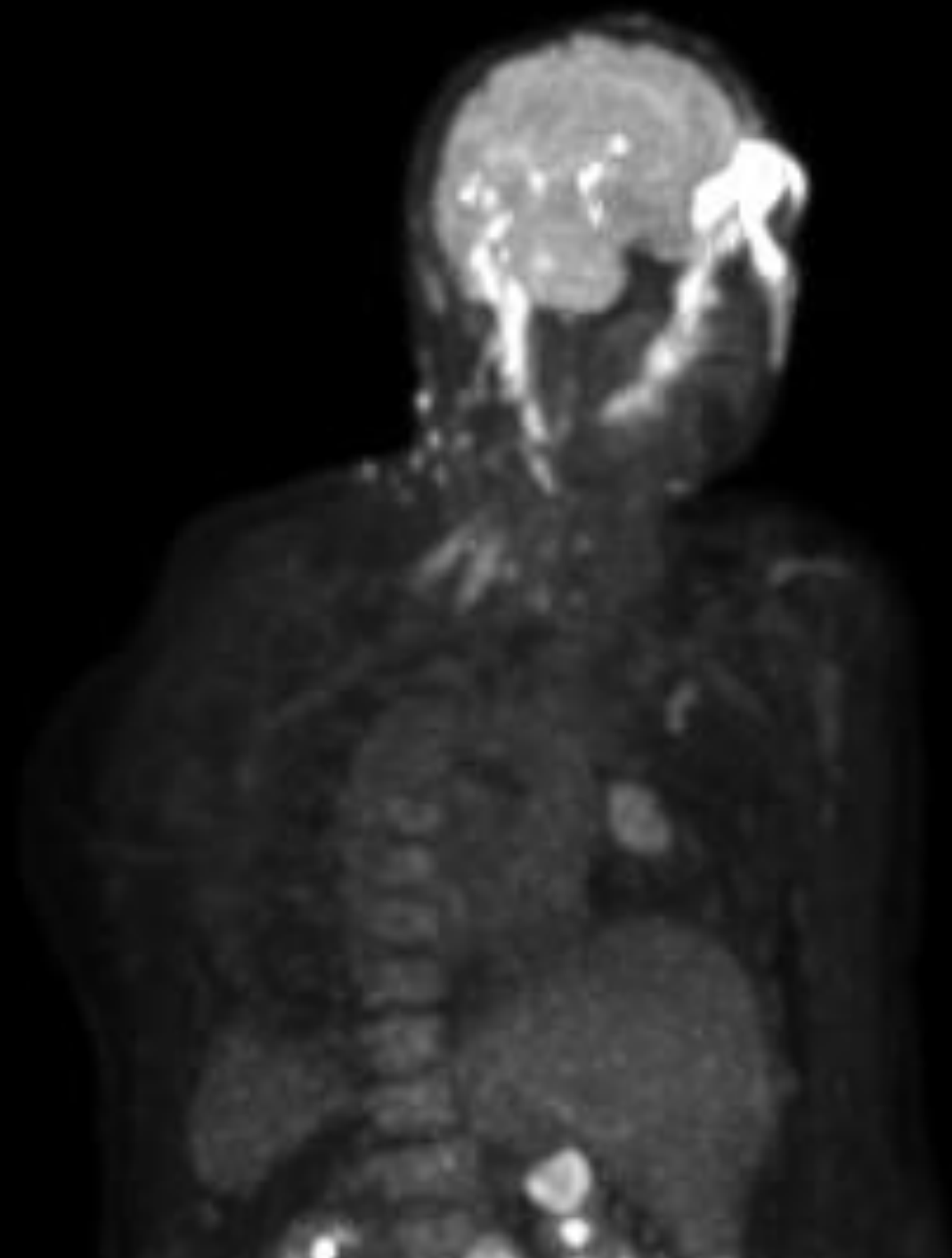


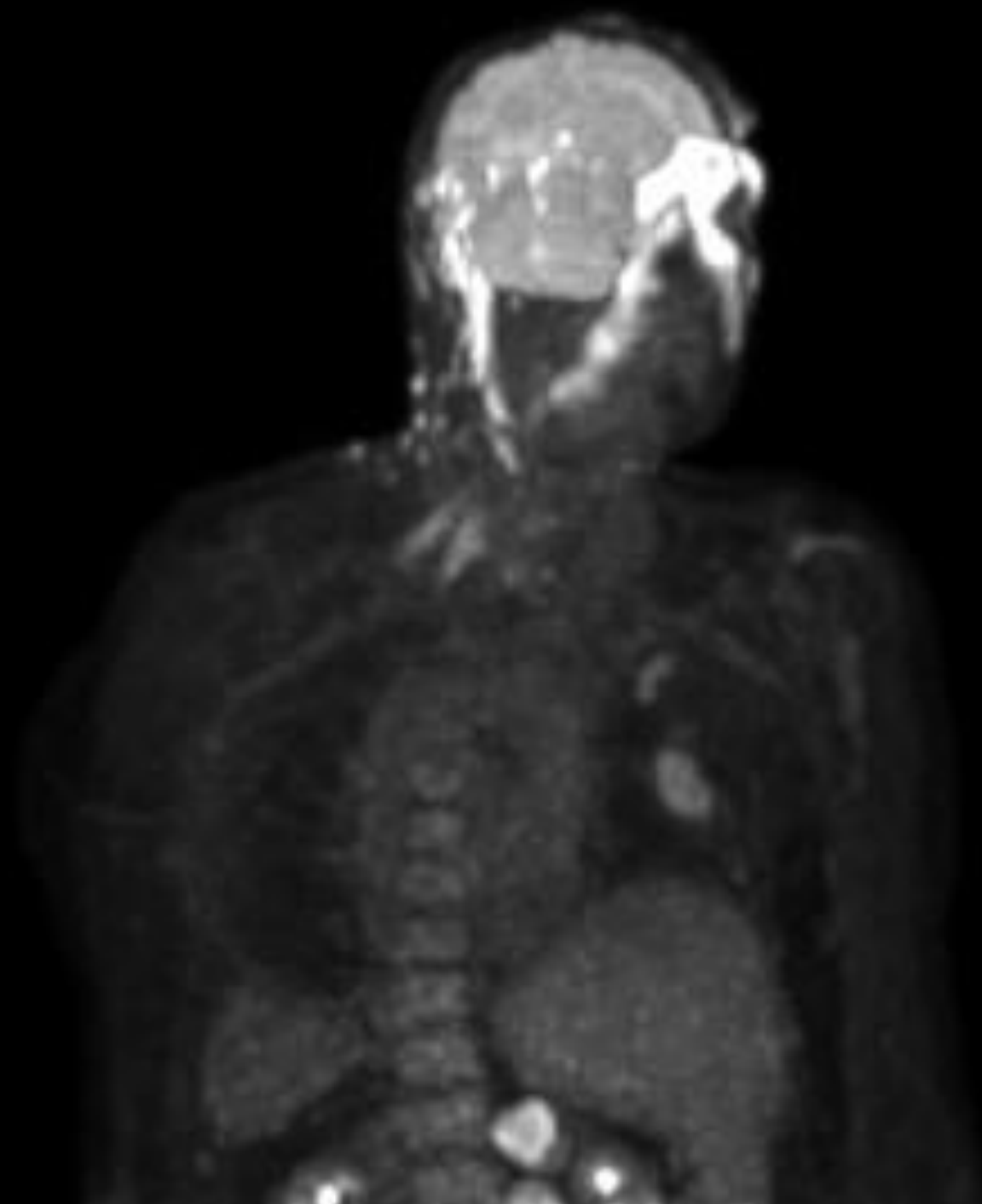


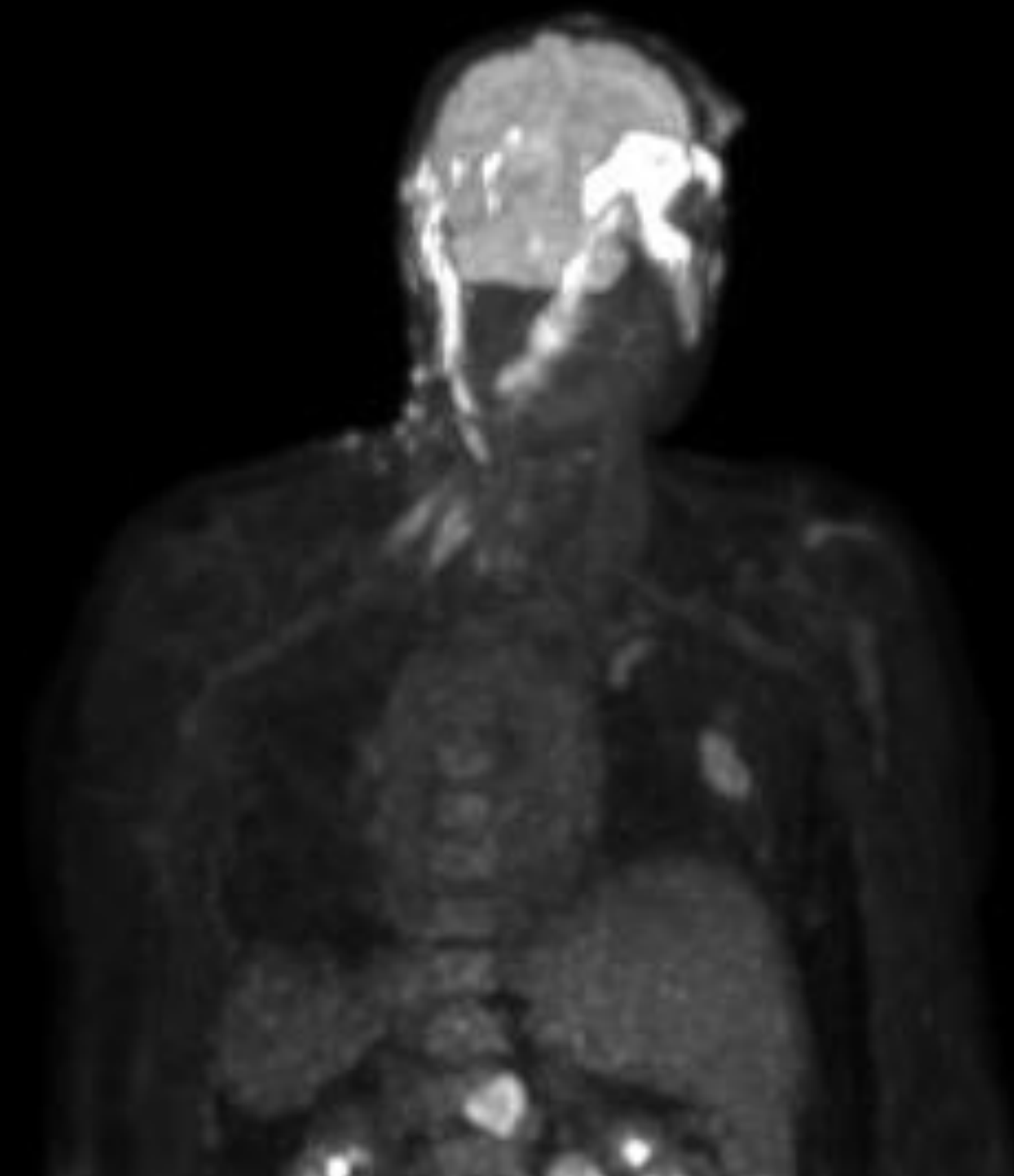


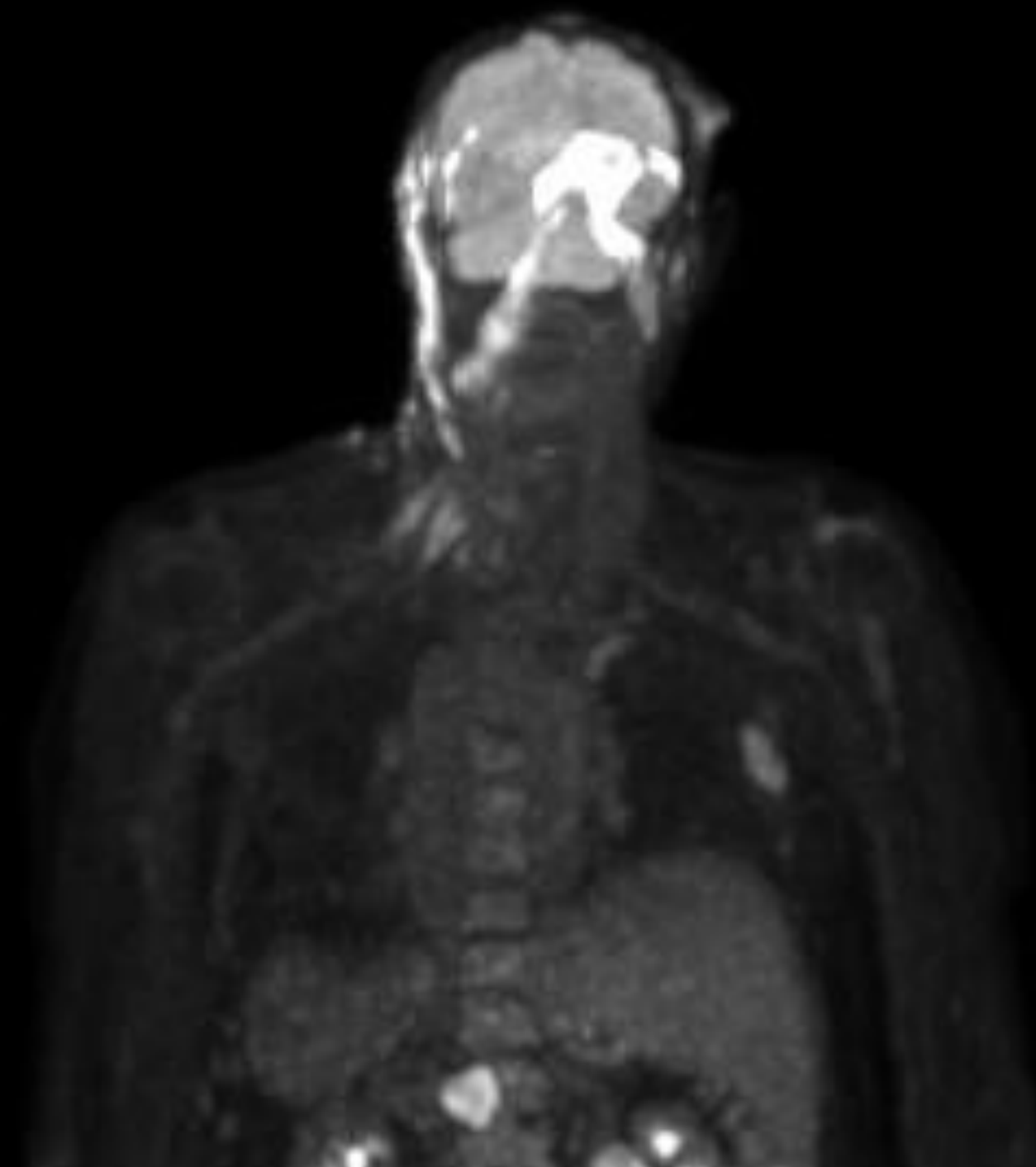


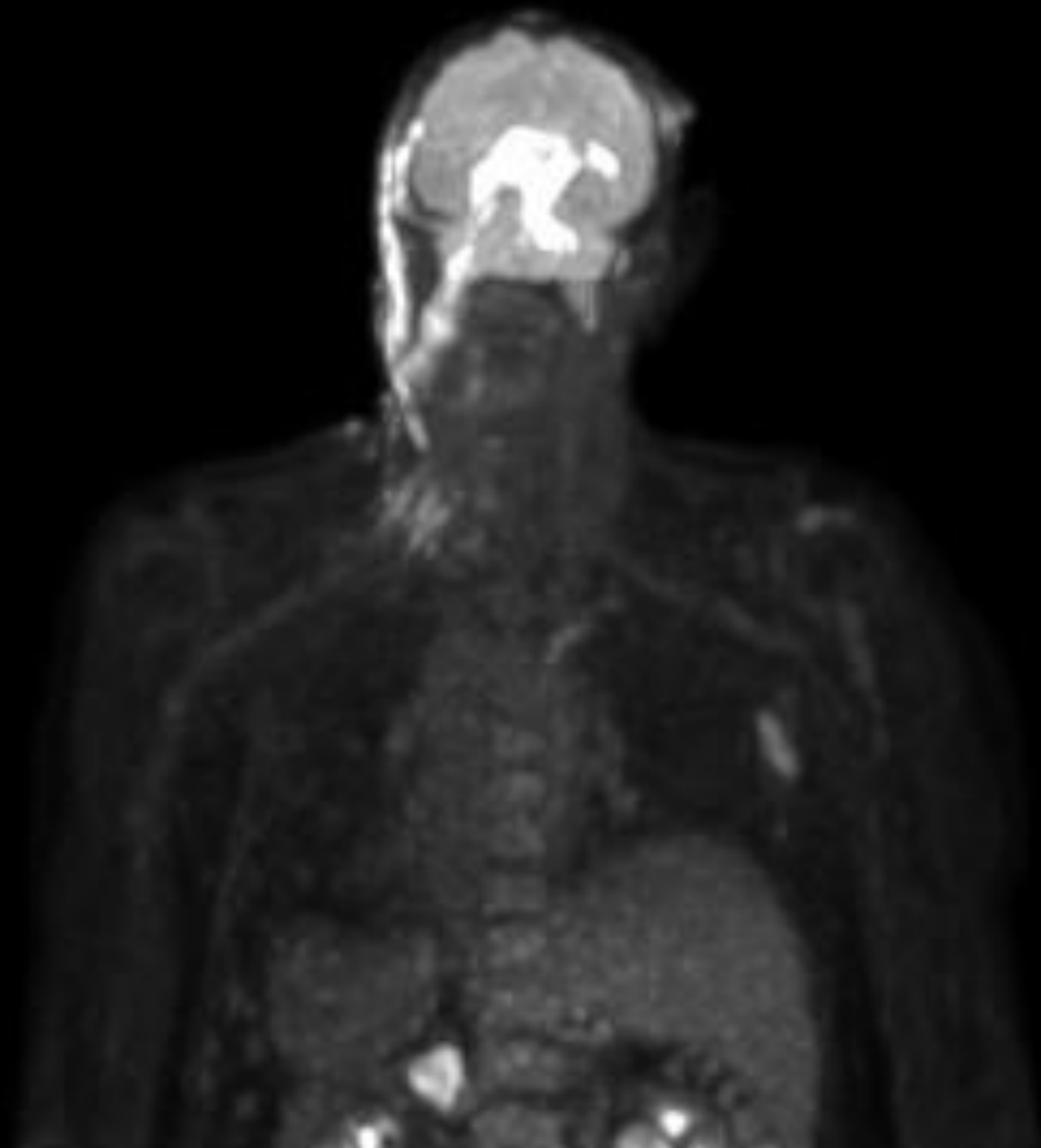


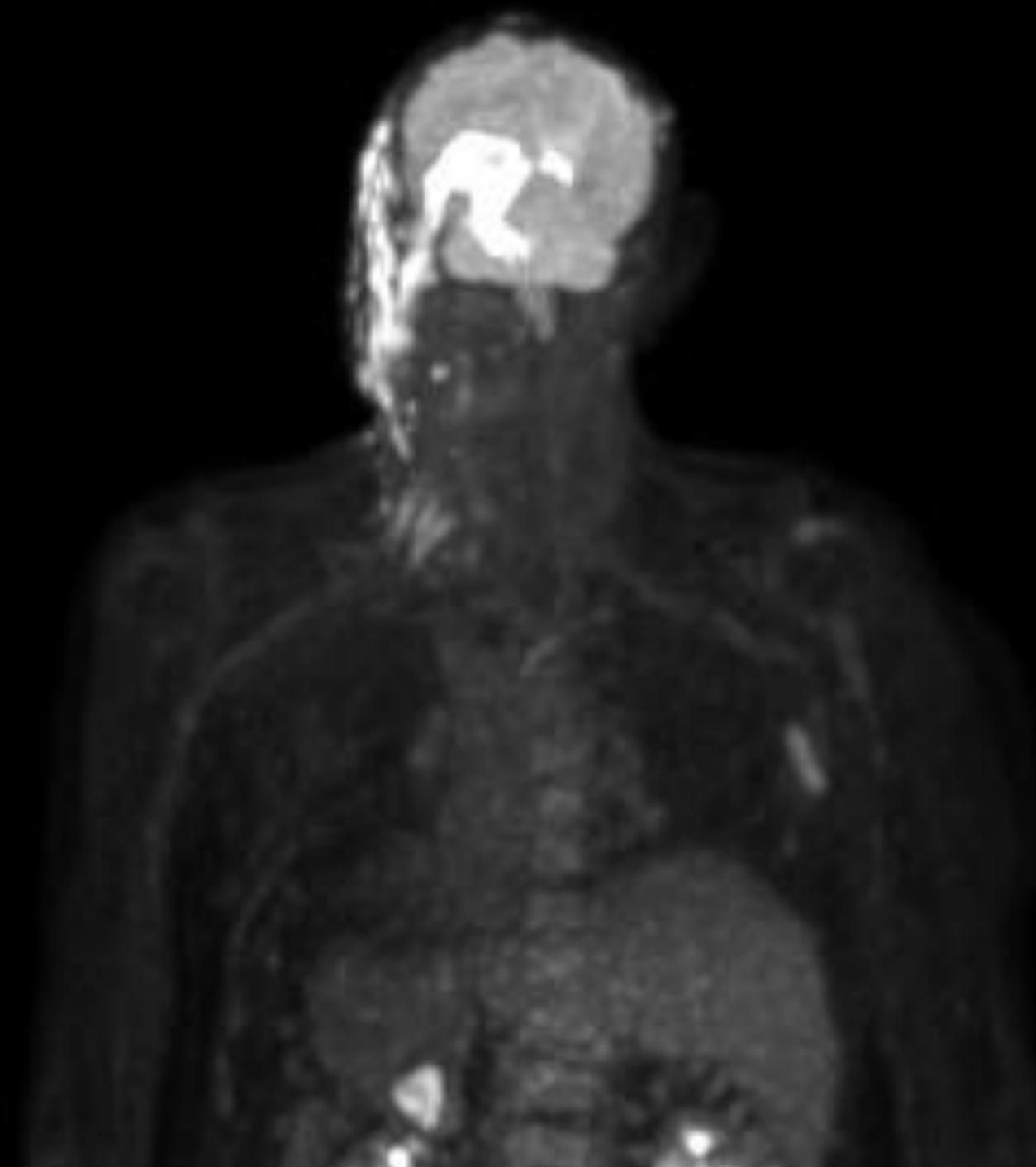


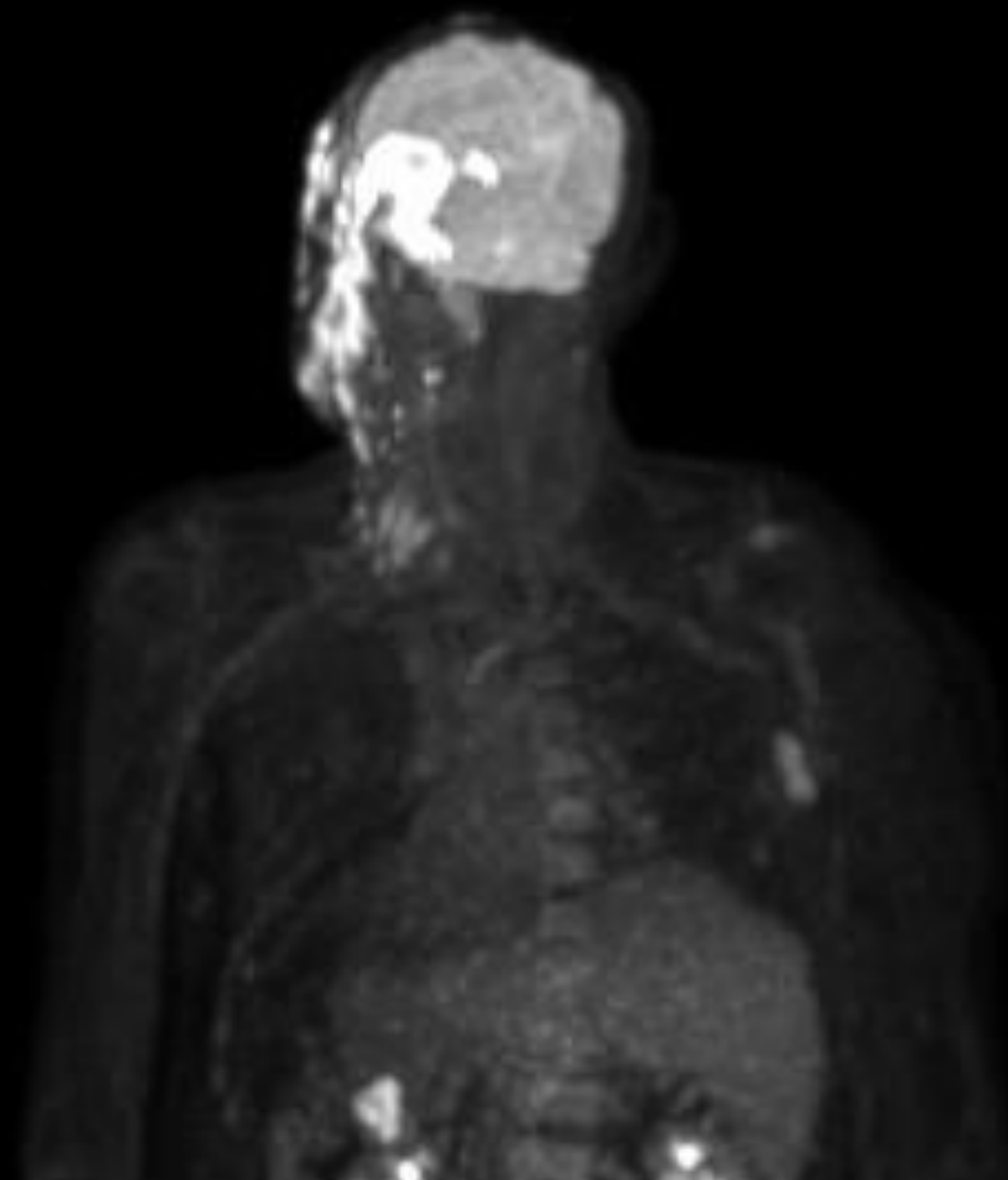


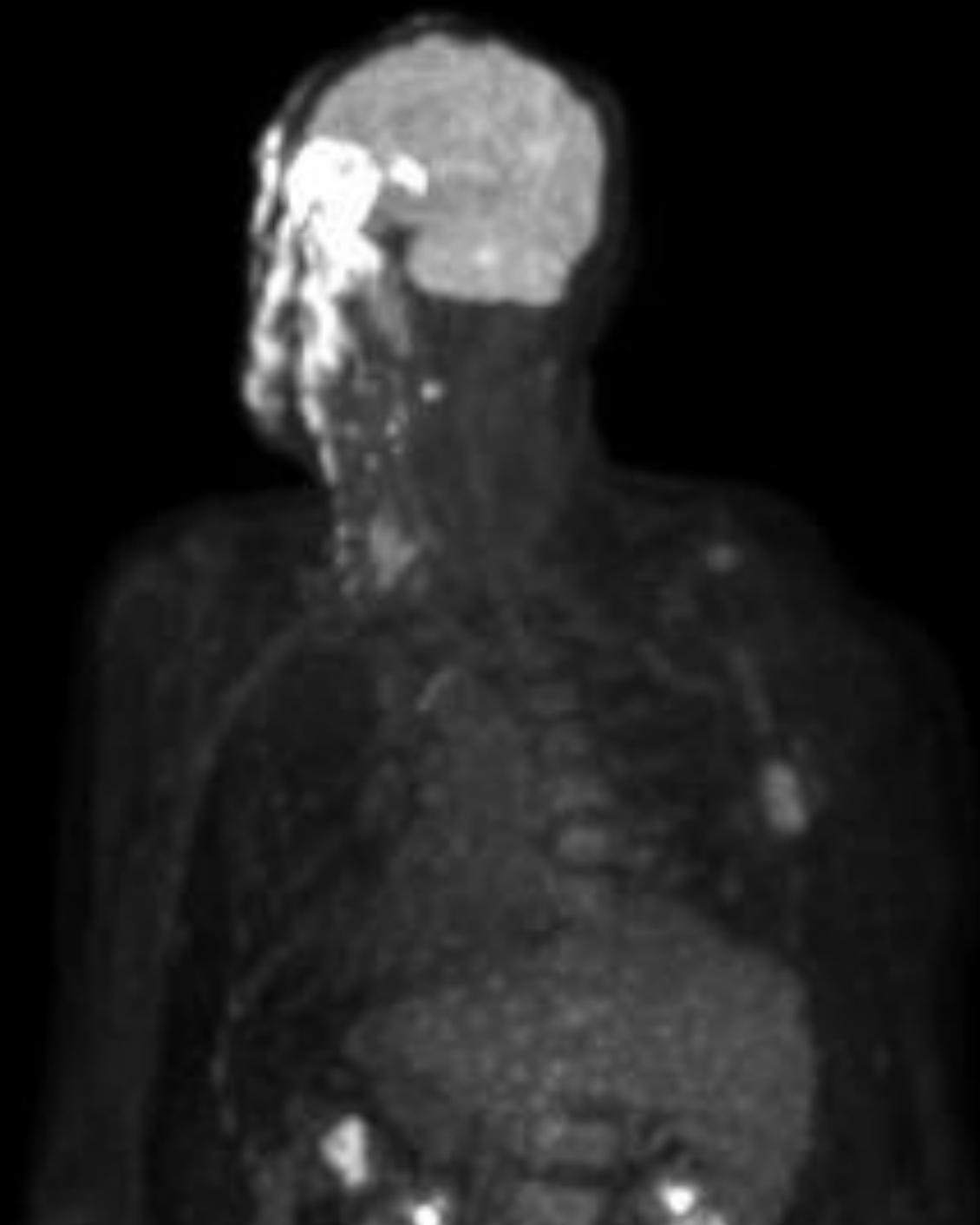


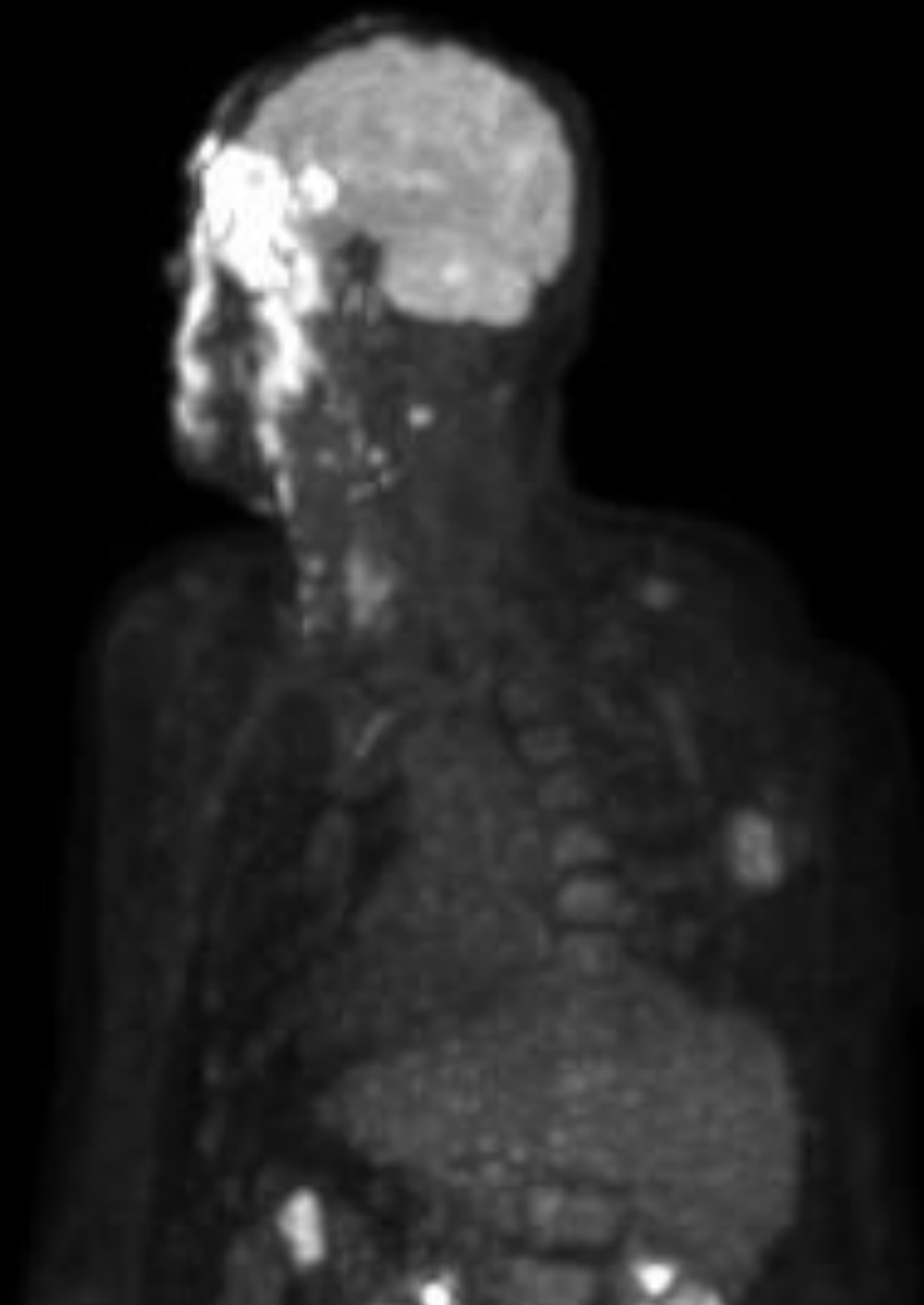


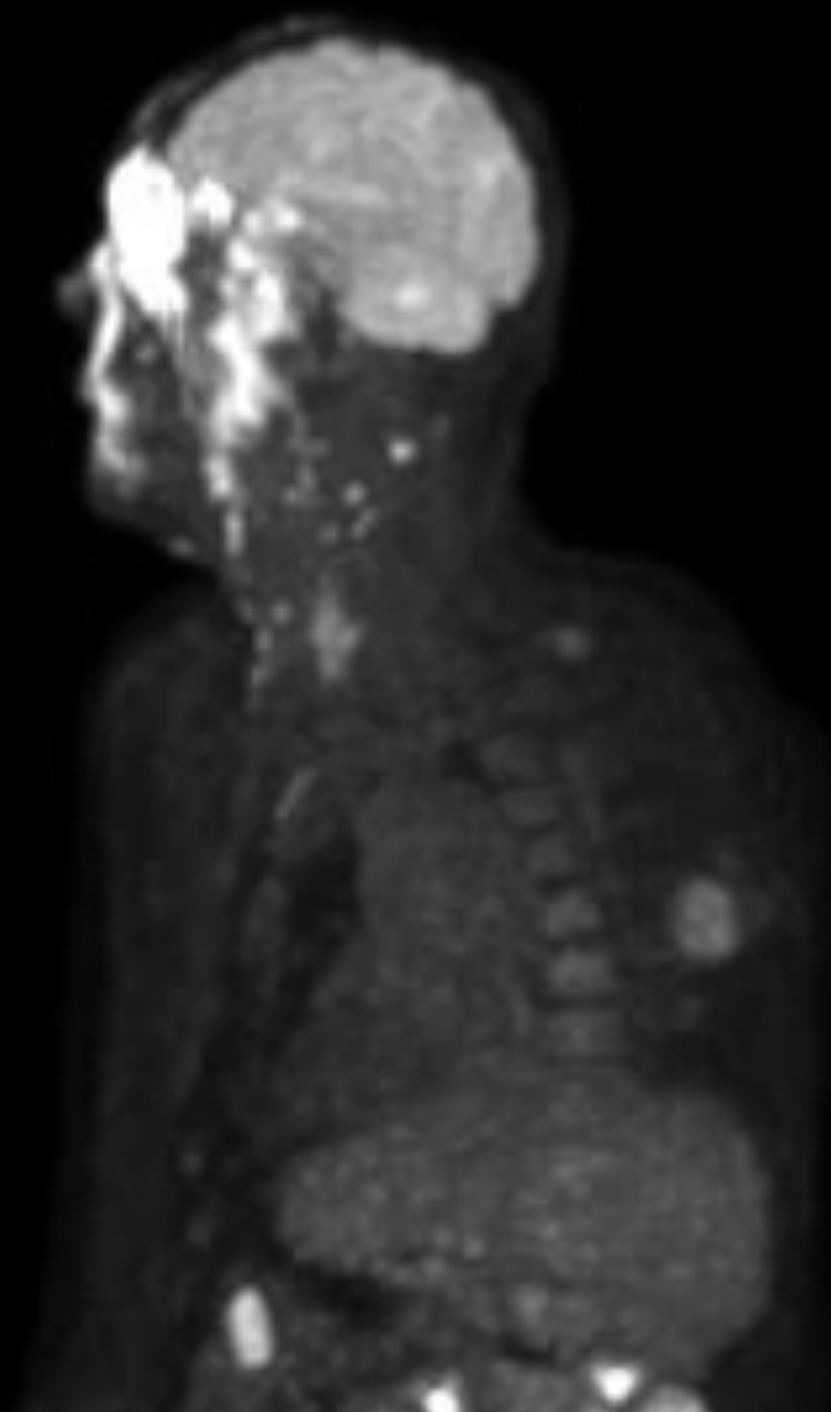


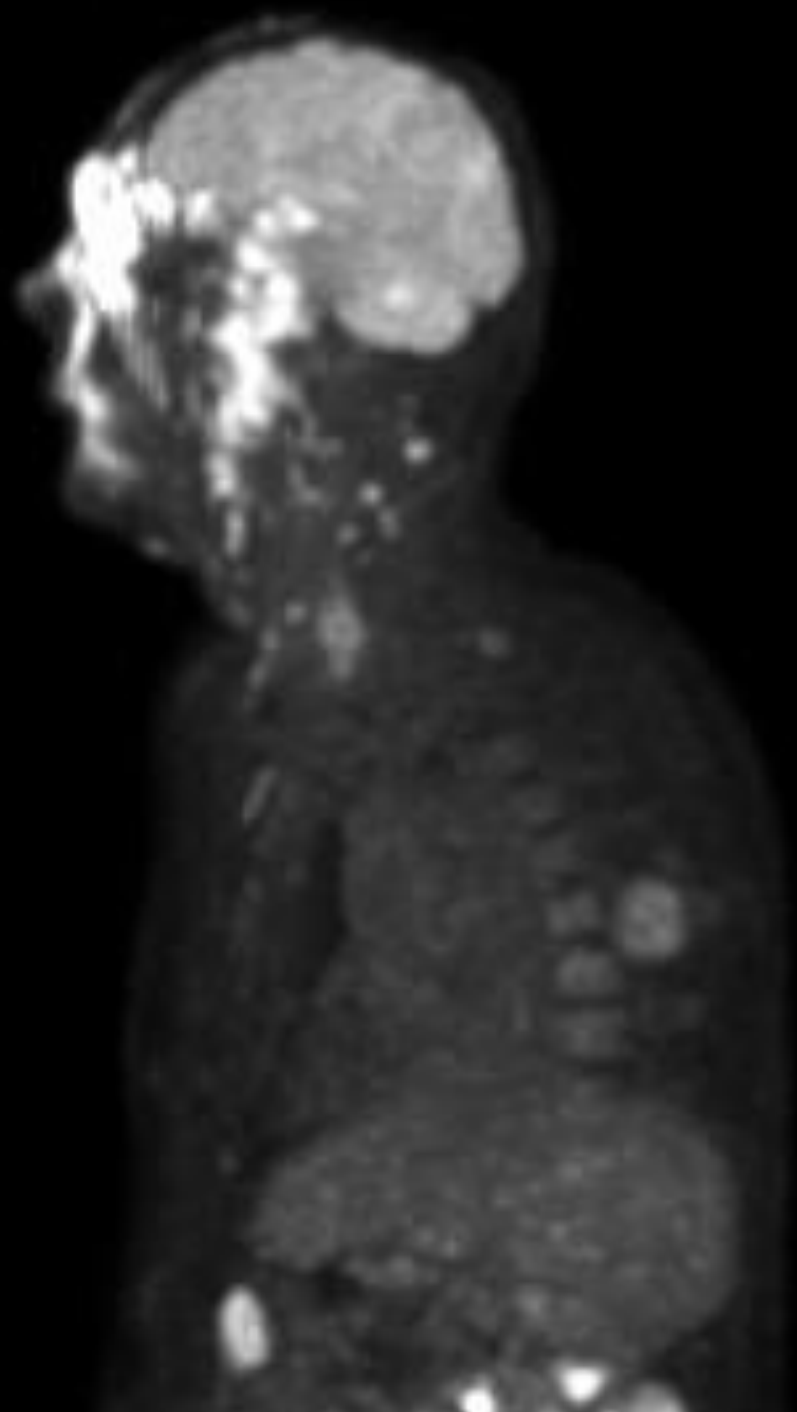


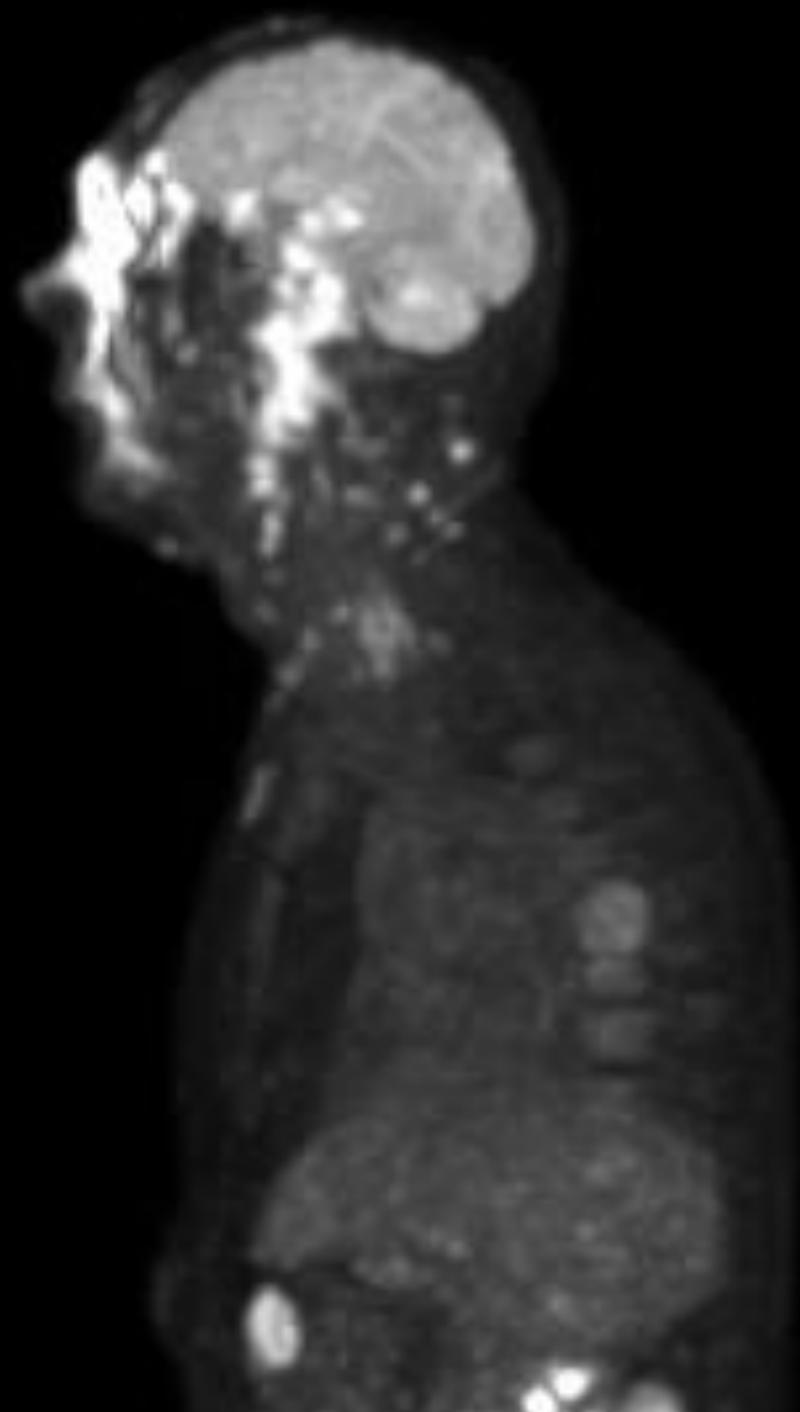


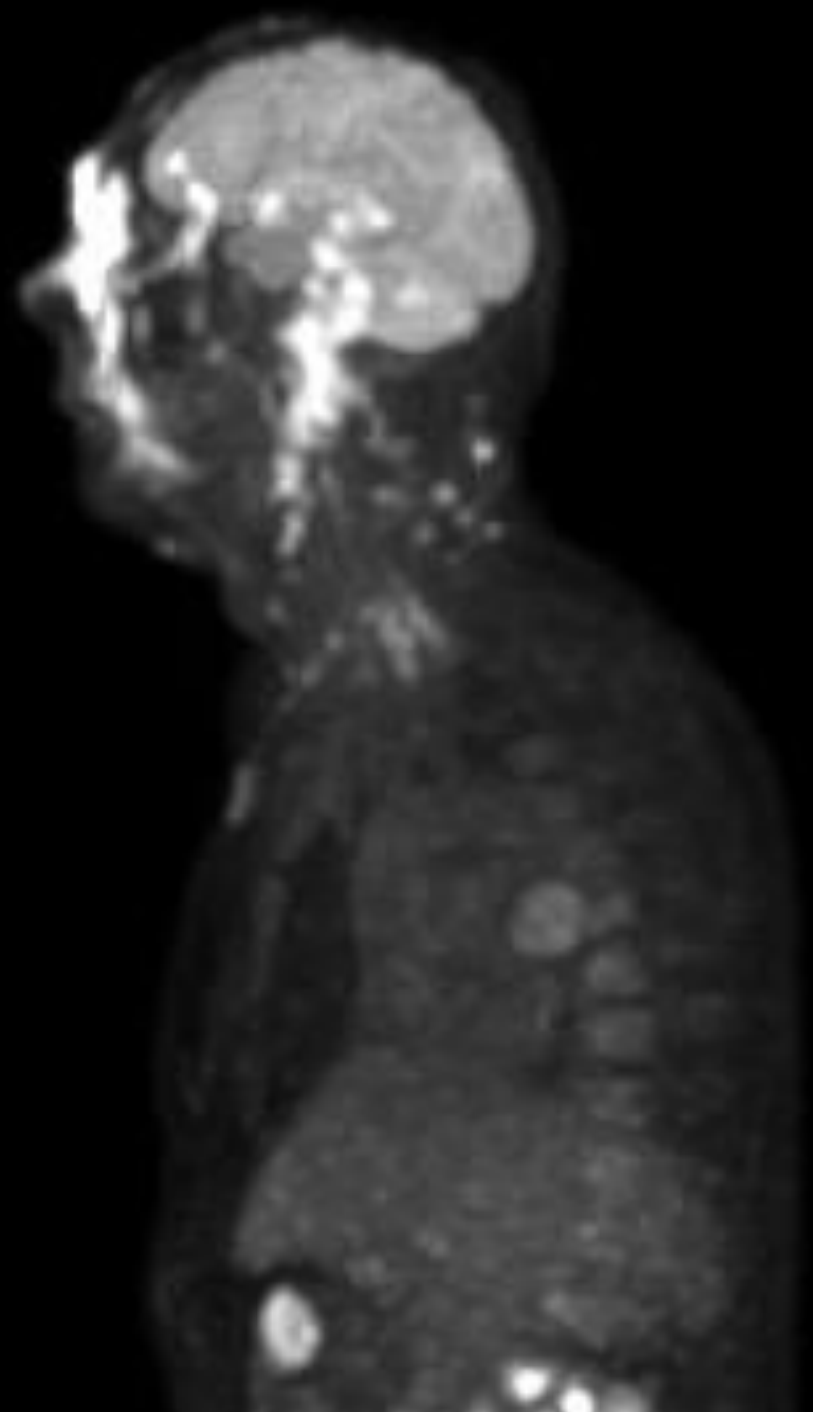


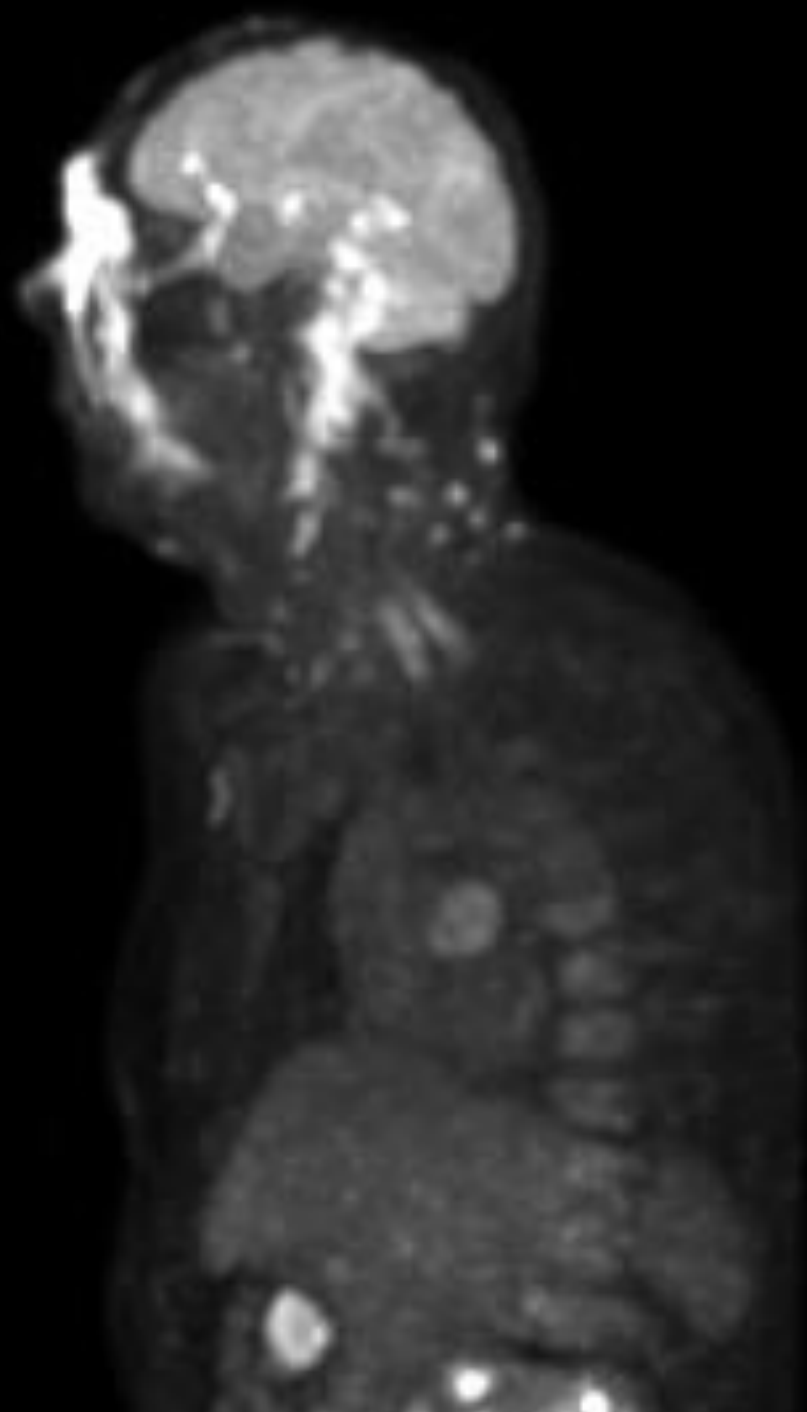


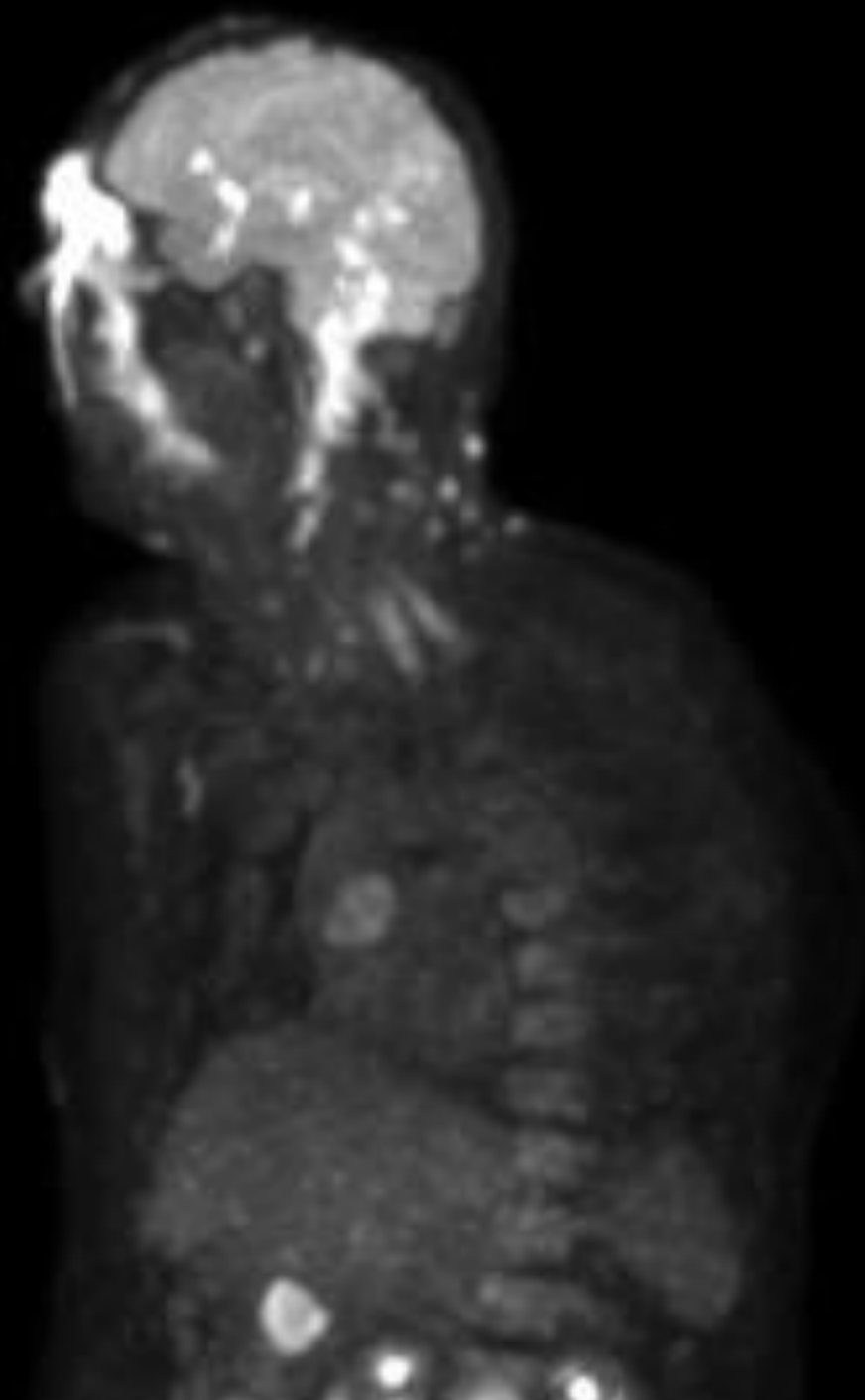


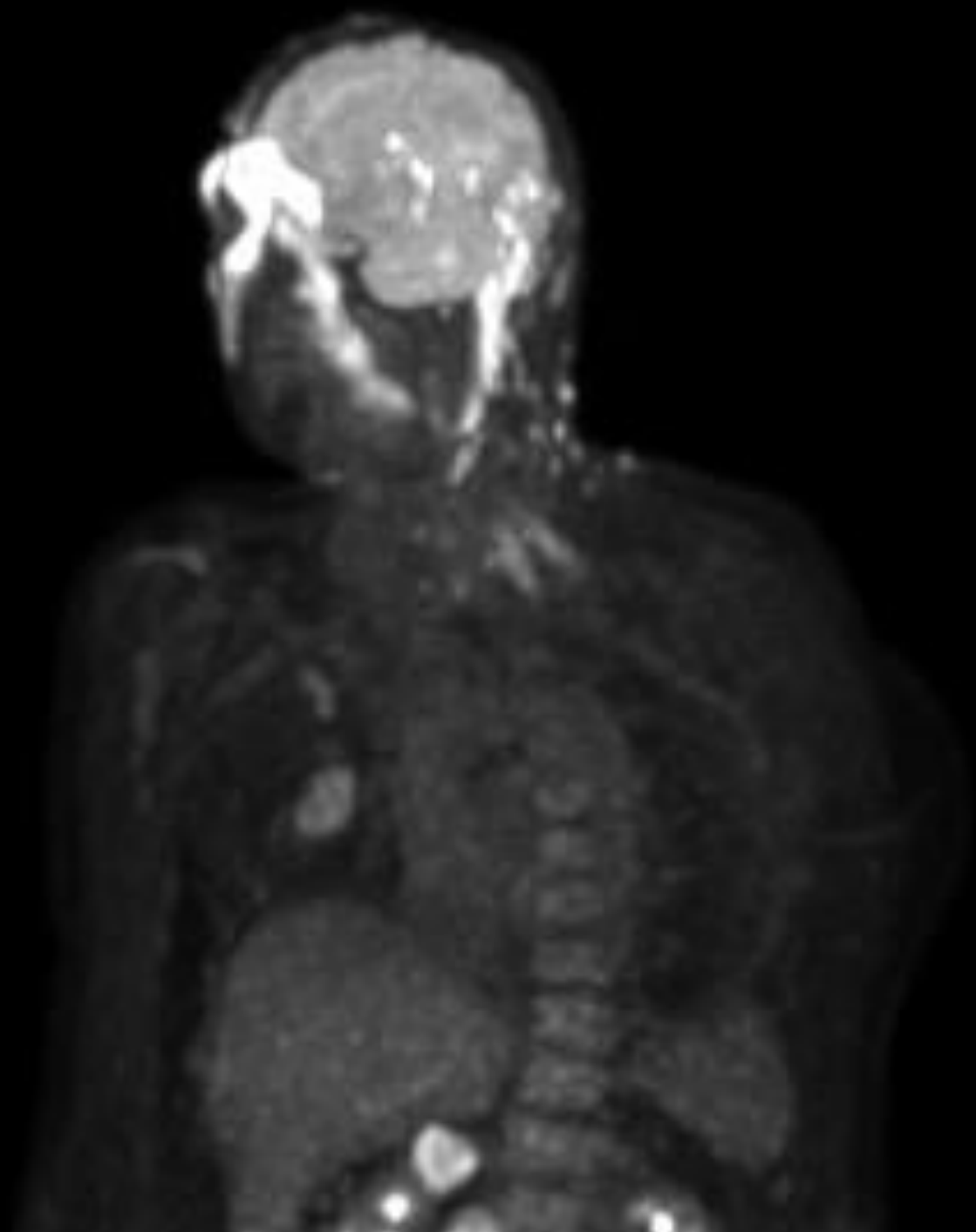


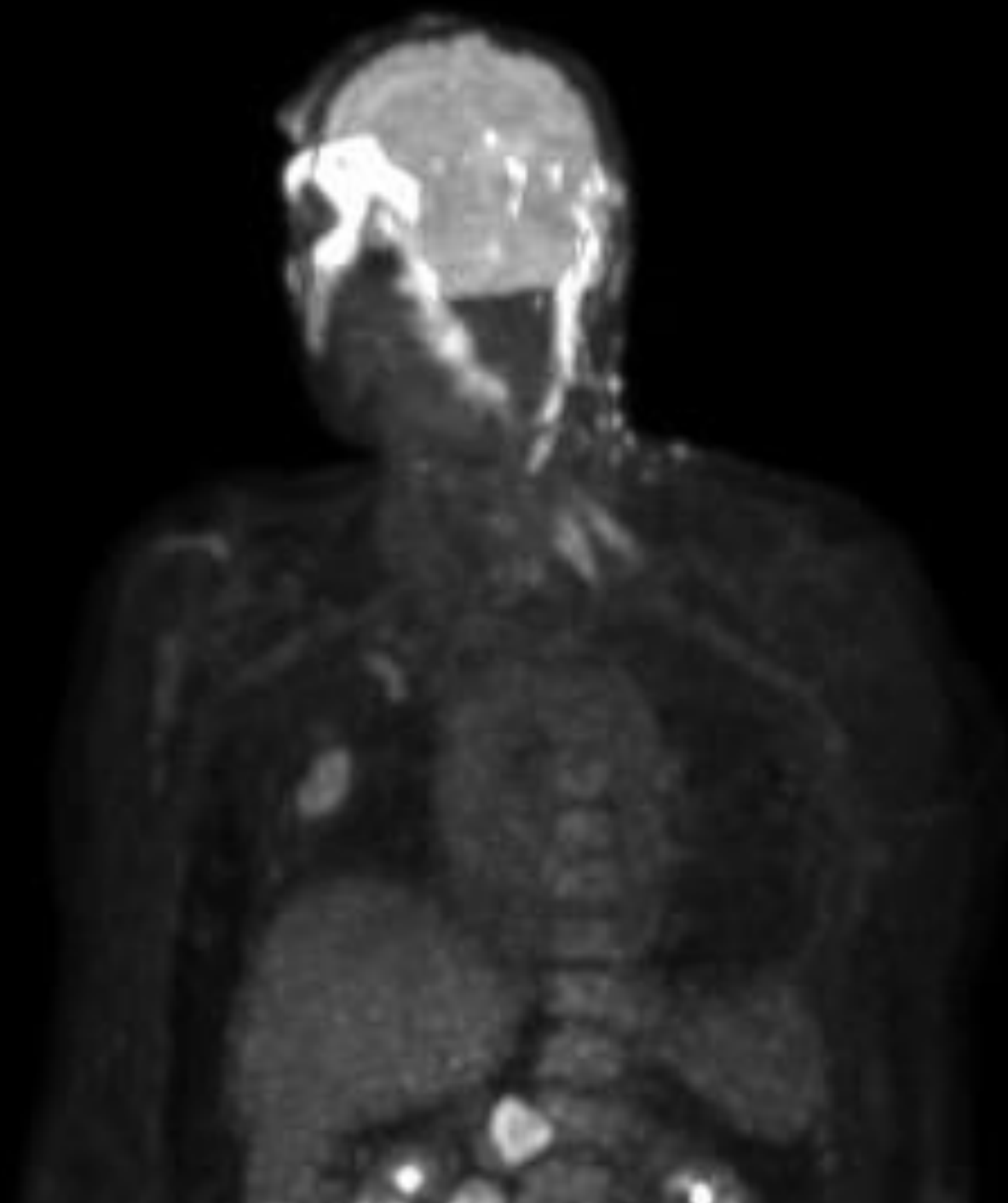


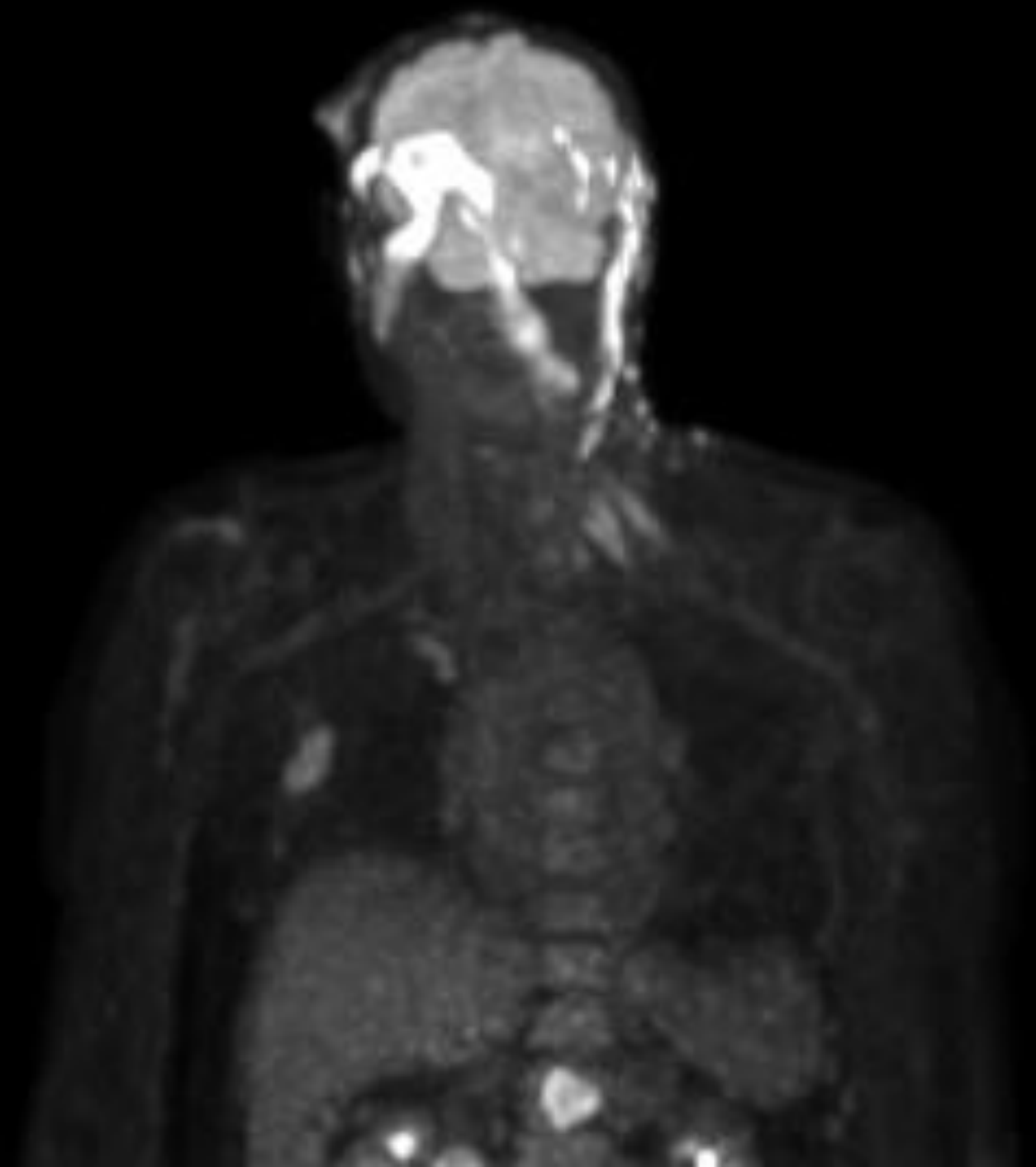


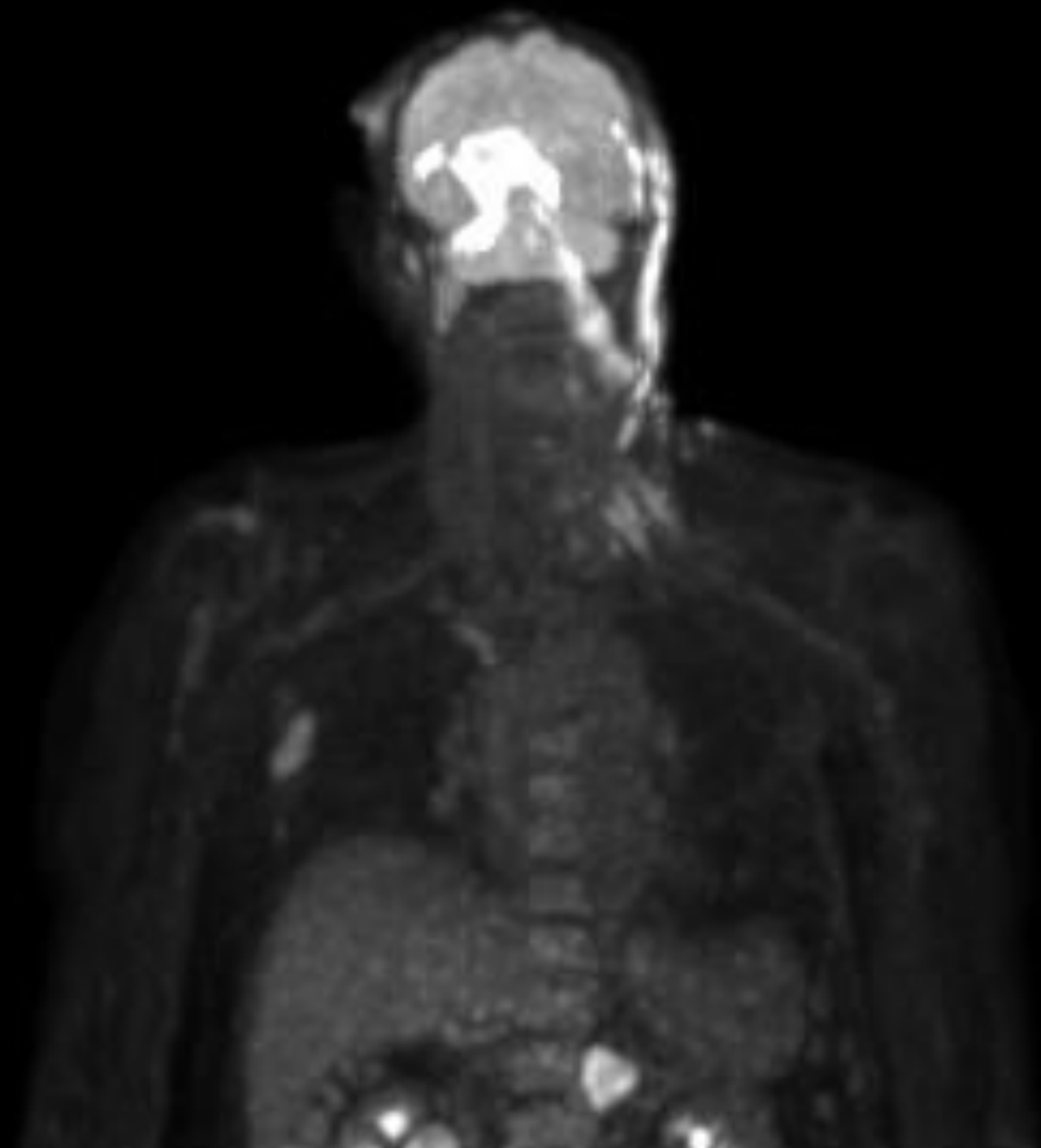




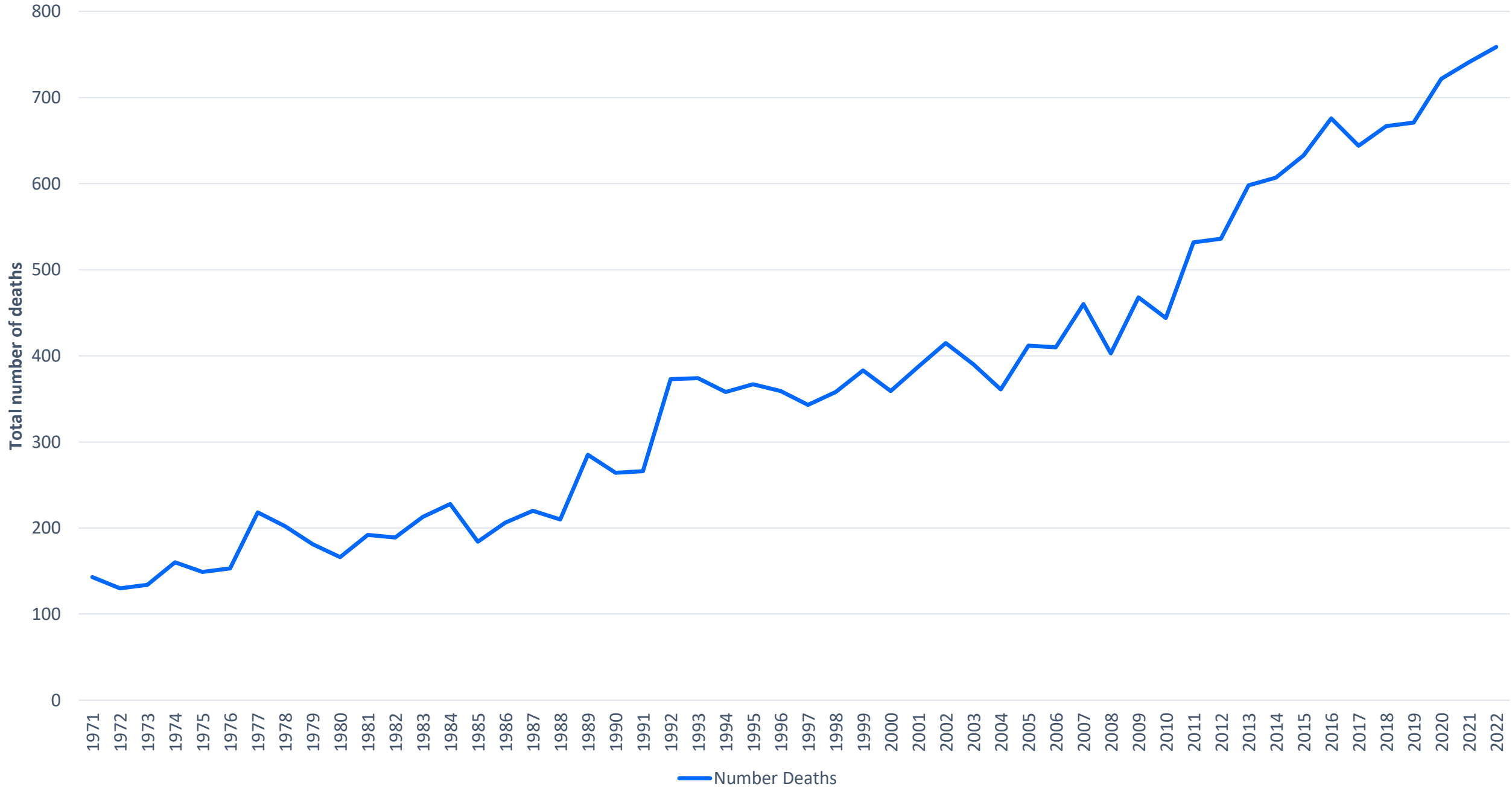




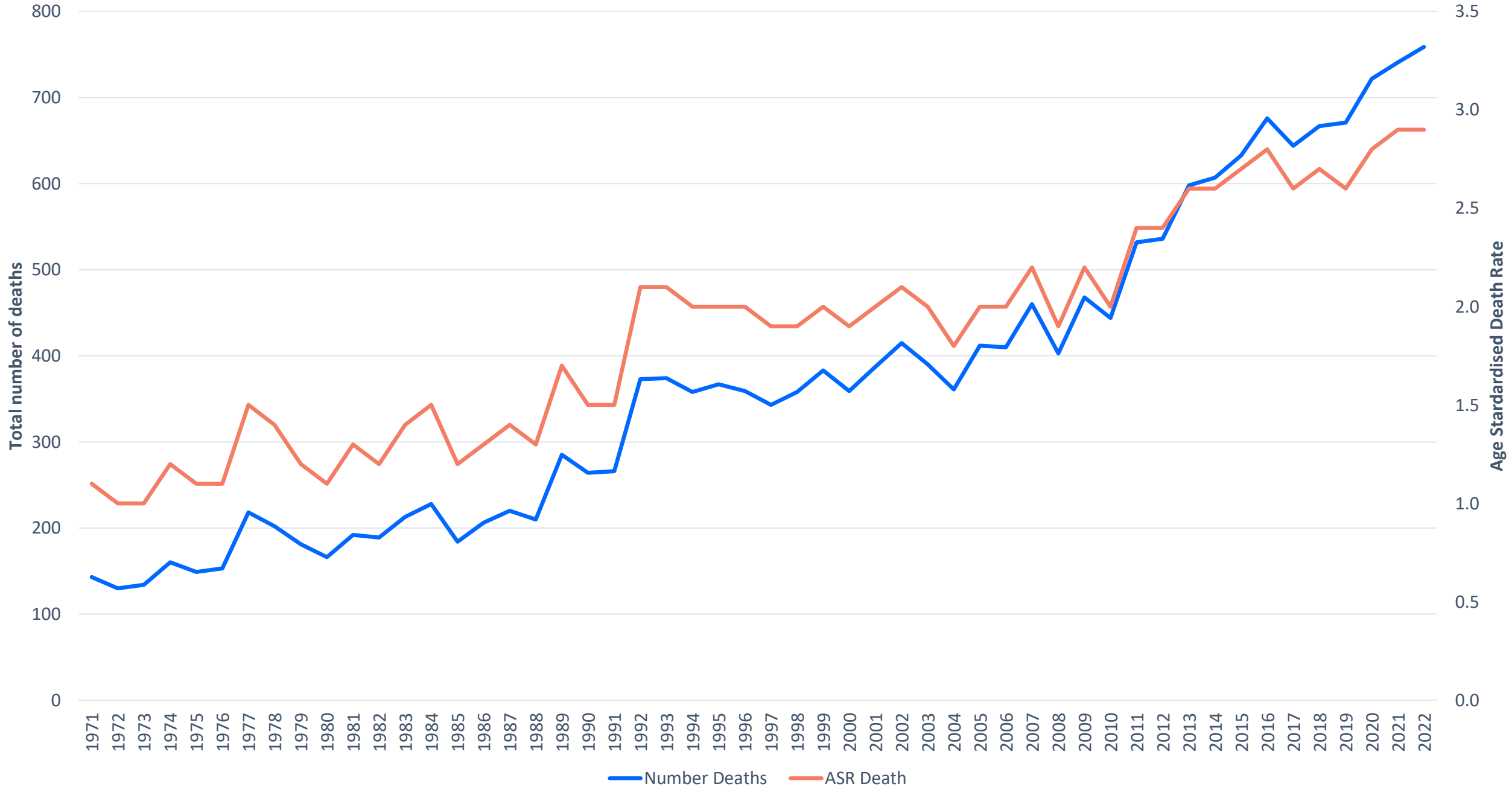




NMSC Deaths Australia (ABS data)



NMSC Deaths Australia (ABS data)



Skin Cancer Epidemic

Increasing burden NMSC*

World: ~1,200,000 cases

Australia: 271-593/100,000

NMSC → more hospital admission than any other cancer

Skin Cancer → ~1,000,000 episodes of primary care

Deaths NMSC*

World: ~63,000 (*more than melanoma*)

Aust: ~800

**includes cSCC and all others except melanoma*

**no registry data for cSCC alone*

...so overall prognosis very good.

How to identify the high risk cases ?

Stage

cSCC Early/localised:

- Excellent (91-95% complete cure)

cSCC with nodal mets:

- Pretty bad
 - (5y OS 22-80%)*
 - (median 52%)

(*see appx)

Clinical PF

Tumour diameter

Tumour site

Bone invasion

Symptomatic PNI

Rapid growth*

Recurrence

Immunosuppression

(others...)

Histo PF

HR-PNI

Poor differentiation (PD)*

Deep invasion*

LVI*

Special variant histology*

(*more research needed)

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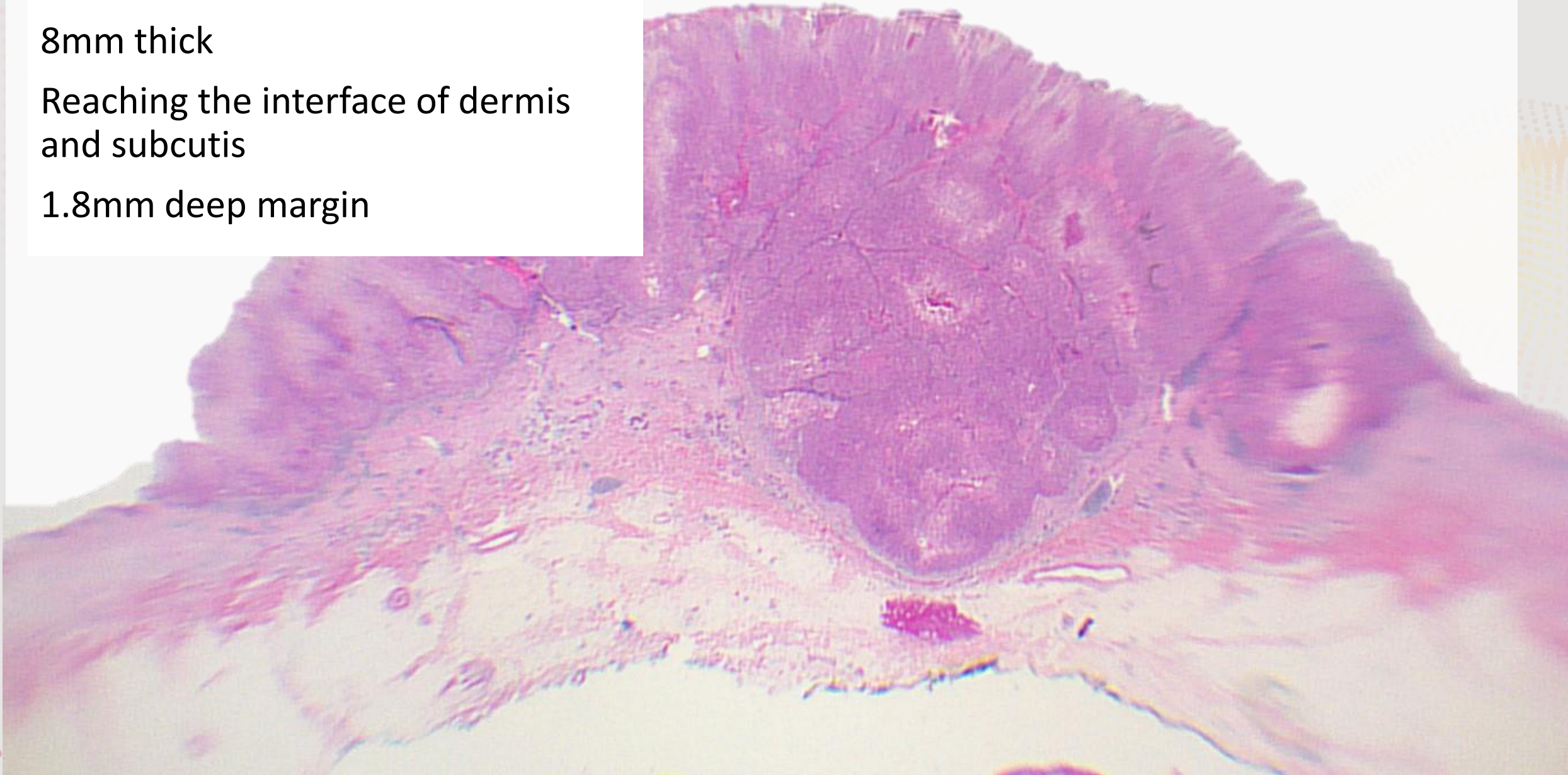
(*more research needed)

Poorly-differentiated

8mm thick

Reaching the interface of dermis
and subcutis

1.8mm deep margin



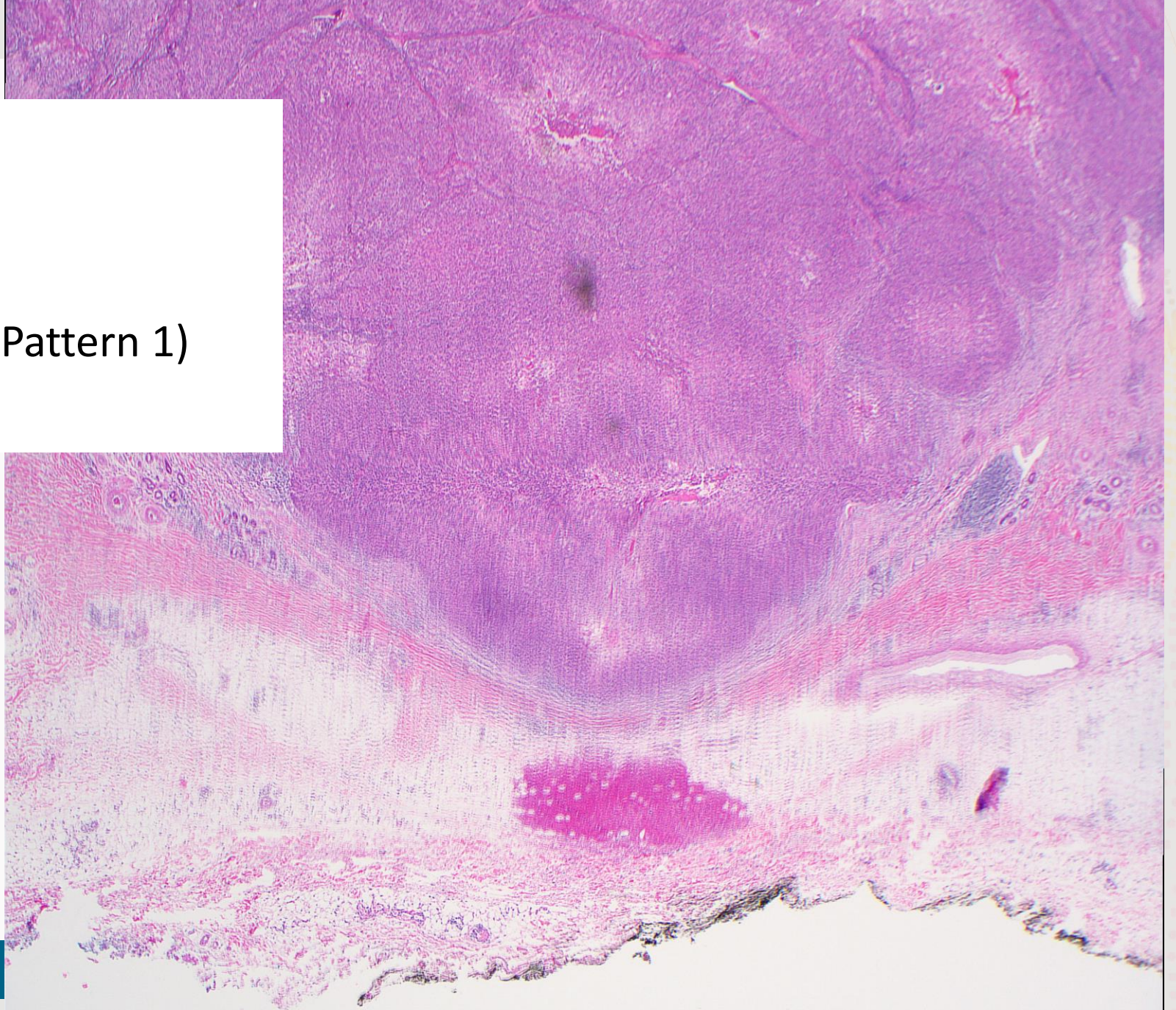
NOT a High-Risk cSCC

Moderately-differentiated

DOI ~4-5mm

Expanding/pushing invasion (Pattern 1)

NOT invading subcutis

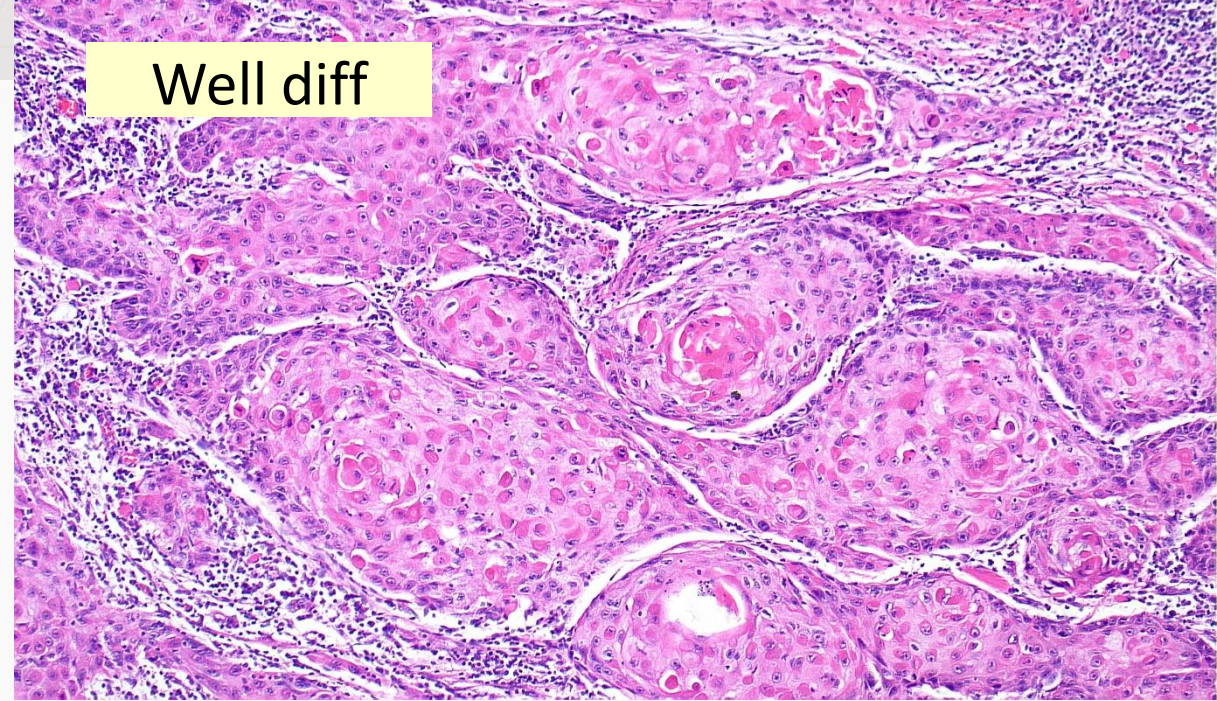


Grading cSCC

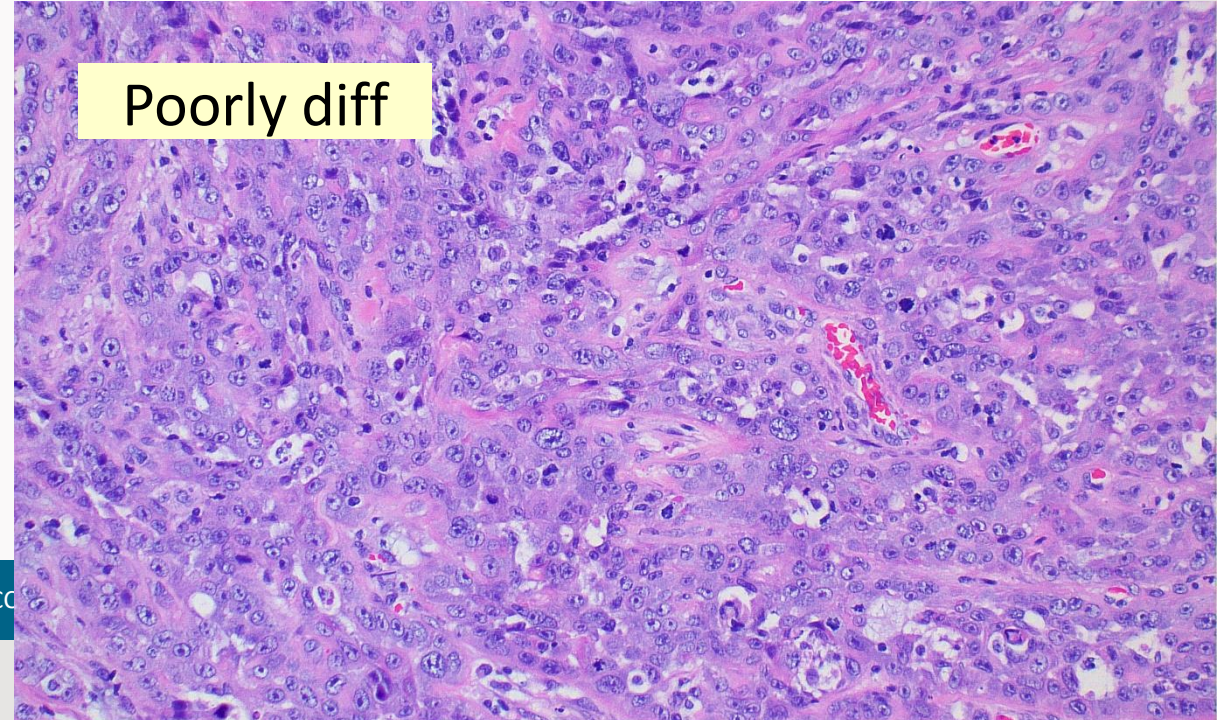
“Poorly-Differentiated” is part of definition of High Risk cSCC

Treatment decisions often based on finding of PD (CCA, NCCN, AAD, European, British)

Well diff



Poorly diff



Grading cSCC

Broders grading

1914 (!)

Probs first ever 'personalised medicine'

4-tier (generally used a 3-tier)

Not well defined

Black and white microphotographs (better in the second paper)

Lip SCCs (probably not cSCC)

*Interobserver agreement not good

Dr Albert Broders



Grading cSCC

Broders grading

1914 (!)

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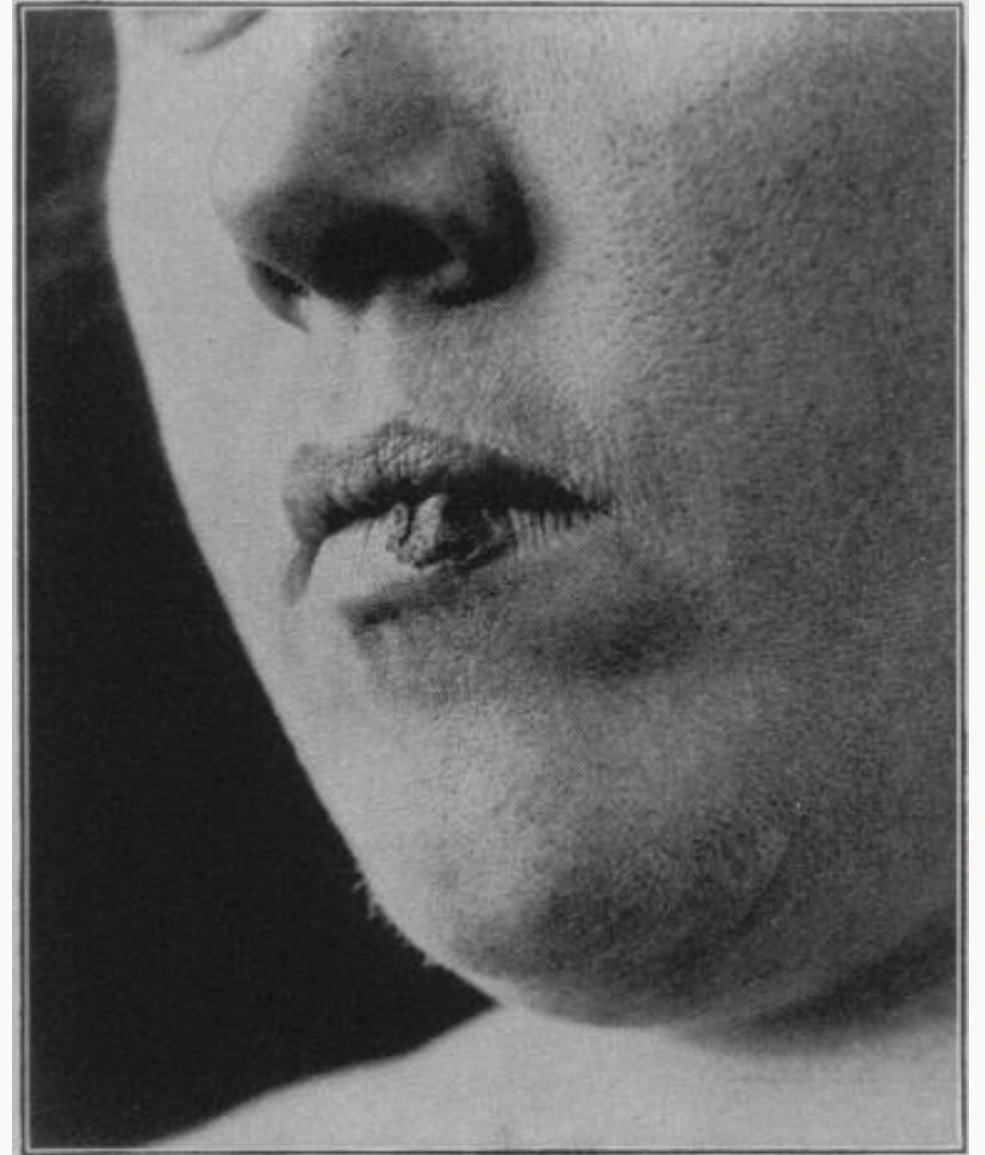
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Lip SCCs (probably not cSCC)

**Interobserver agreement not good*



Grading cSCC

Interobserver Agreement ?

Literature review

Only 6 studies

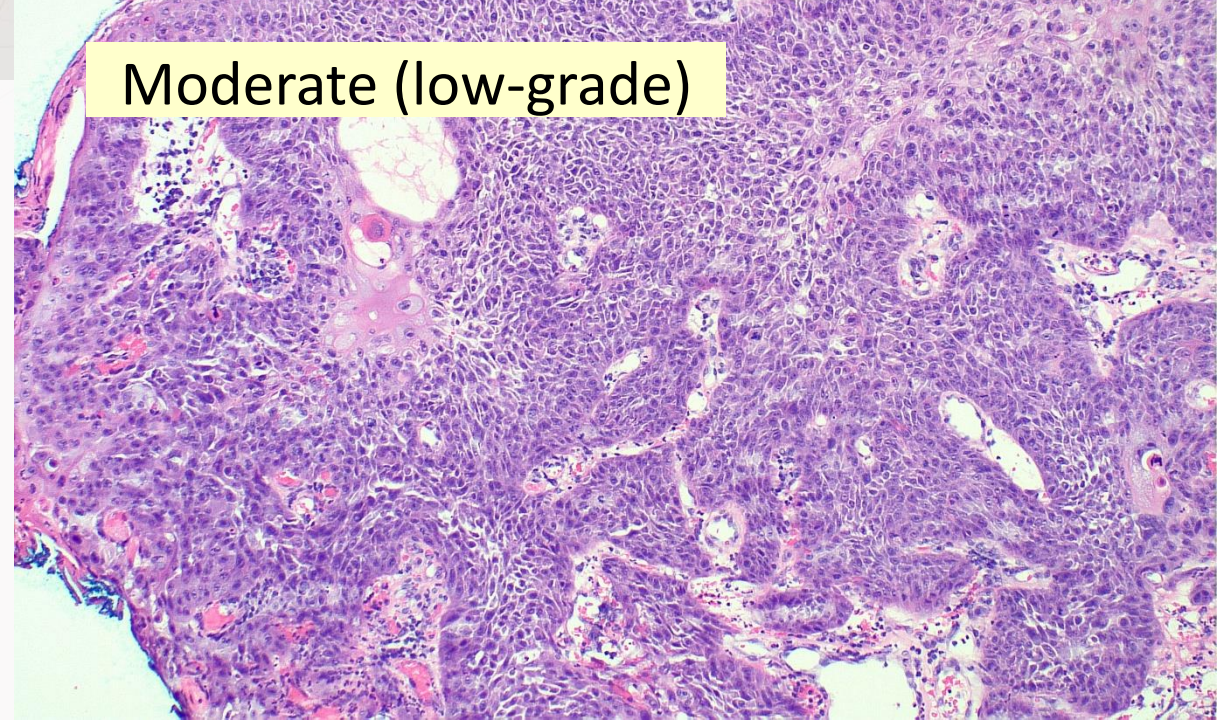
Definitions of grading system used?

- 3 x Broders
- 1 x Brandwein-Gensler (mSCC)
- 2 x No definition

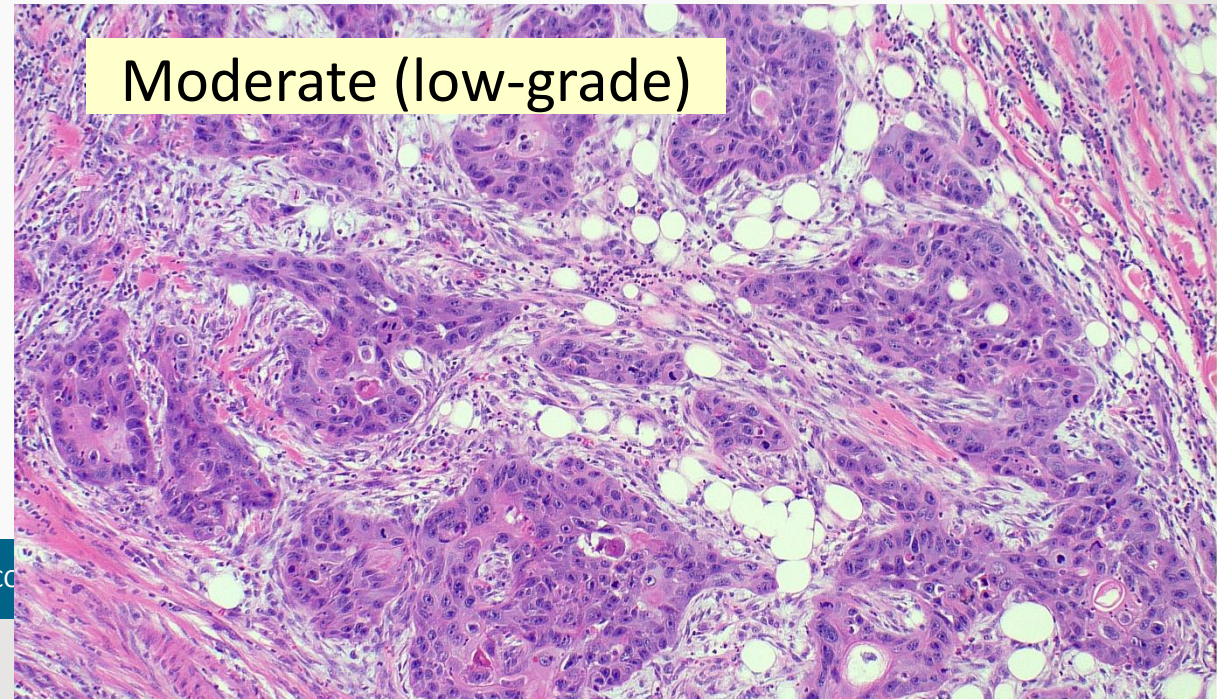
$K = 0.25-0.65$ (*minimal to moderate)

(*study designs variable)

Moderate (low-grade)



Moderate (low-grade)



RCPA St

Grade

S3.02 HISTO (*Only

- GX:
- G1:
- G2:
- G3:
- G4:
- Not a

Histological tumour grade for squamous cell carcinoma / WHO risk category must be recorded.

CS3.02a

A histologic grading system¹⁴ is most applicable to cutaneous squamous cell carcinoma (cSCC) and is described here. The current international consensus is to report the highest grade within the tumour irrespective of its proportion. This approach is also advocated by the National Comprehensive Cancer Network (NCCN)¹⁵ and is used in Royal College of Pathologists (RCPa) United Kingdom primary SCC and regional lymph node dataset¹⁶ as well as other RCPA datasets such as that of oral cavity.¹⁷

Well-differentiated SCCs resemble their normal counterparts. The SCC frequently shows easily recognisable and often abundant keratinisation. The epithelium is obviously squamous and intercellular bridges (prickles) are readily apparent. There is minimal nuclear pleomorphism and mitoses are rare.

Moderately differentiated SCCs show greater architectural complexity and cytologic atypia. Usually, there is less keratin formation which is often limited to the formation of keratin pearls and scattered keratinised cells. Anisonucleosis and nuclear pleomorphism are more pronounced. Mitotic figures are easily identified.

Poorly differentiated SCCs may show sheets and nests of markedly atypical cells. Intercellular bridges and intracytoplasmic keratinisation may be present focally. Mitoses are frequent. In some instances, immunohistochemistry (IHC) with squamous markers such as CK5/6 or p40 may be required to exclude differential diagnoses such as melanoma. Poor differentiation is an independent adverse prognostic factor for cutaneous SCC.¹⁸

Sarcomatoid/spindle cell carcinoma: tumours that show a prominent pleomorphic spindle cell component with or desmoplastic or myxoid stroma. These tumours generally require an immunohistochemical panel to distinguish between carcinoma, melanoma, angiosarcoma and pleomorphic dermal sarcoma. While these are designated as poorly differentiated SCC, a comment regarding the sarcomatoid/spindle cell appearance should be included. This is particularly useful in selecting appropriate IHC in the future if the SCC recurs or metastasises.

Our study

IOA of “usual practice”

Vs 2-Tier system

Pathologists with a range of experience (2
Dermpath, 1 x AP, 1 x Gen Path)

79 Consecutive cases, 1 rep slide

2 rounds (3 months apart)

Round 1: Grade “as per usual”

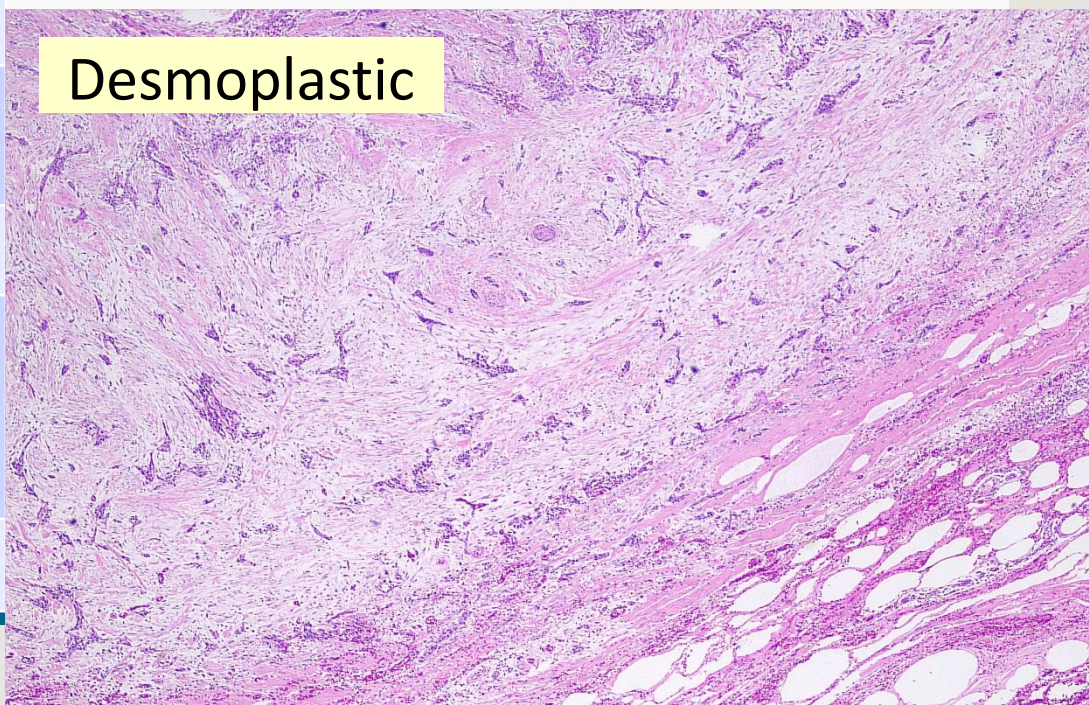
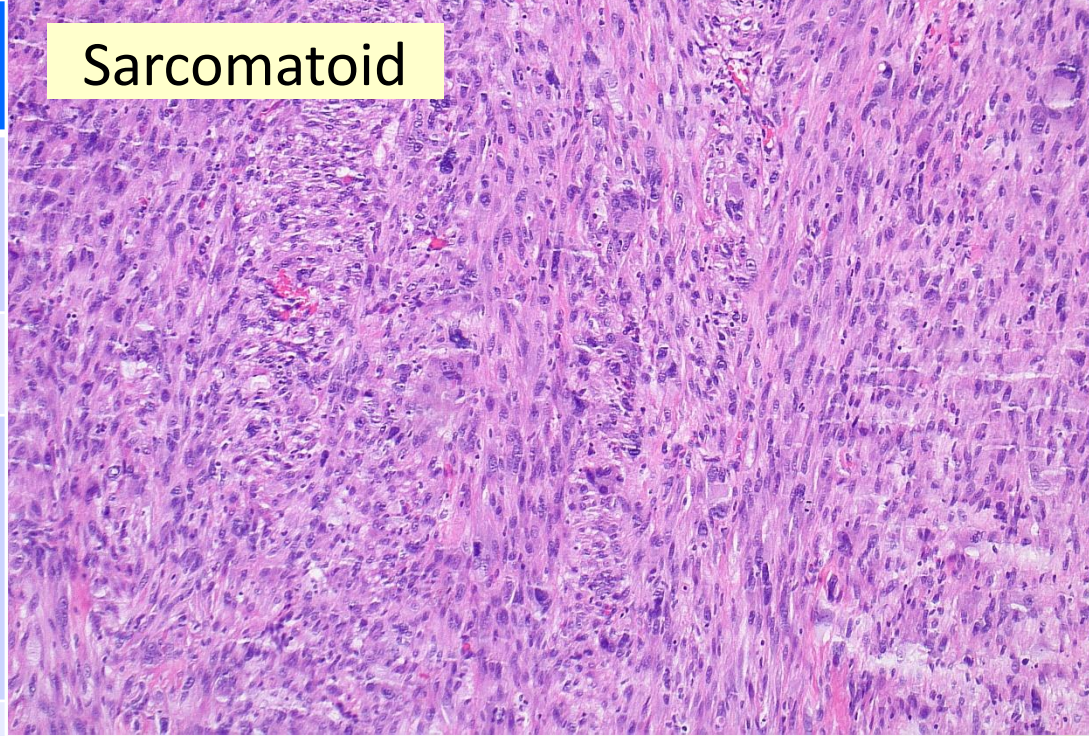
Circulated Grading Guide (+ images)

Round 2: 2-Tier grade

Demographics	Average Age (range)	74 years (43 - 94)
	Male: Female (% male)	61:18 (77% male)
Grade on original report	Well	22 (28%)
	Moderate	37 (47%)
	Poor	17 (22%)
	Undifferentiated or sarcomatoid	1 (1.3%)
	Not graded	2 (2.5%)
Sites	Head and neck	63 (80%)
	Below the clavicle	16 (20%)

HREC Reference: LNR/2022/QGC/87507

Histological criteria	SC Low Grade	SC High Grade
	(Incorporates traditional well to moderately differentiated or Broders 1 and 2)	(Incorporates traditional poorly differentiated and undifferentiated or Broders 3 and 4)
	Must show ALL of the following criteria	May show ANY of the following criteria
Degree of squamous differentiation	Majority (>25%) of the tumour shows squamous differentiation identifiable using routine H&E (large pink cells with central nuclei, intercellular bridges, keratinisation)	Focal (<25%) or absent squamous differentiation on H&E
Mitoses	“Low”: mitoses are sparse or occasional	“High”: mitoses are frequent and easy to find
Undifferentiated / Immunohistochemistry required for diagnosis	No	Yes
Worst pattern of infiltration (low power assessment)	Expanding	Infiltrative / tumour budding
Spindle cell differentiation	Absent	Any component of spindle cell differentiation (including sarcomatoid, carcinosarcomatous or metaplastic)
Specific uncommon histological variants:	Absent	Adenosquamous, acantholytic, desmoplastic



Results

	Usual Practice	2-Tier Grading
InterObserver Agreement	Observers used 3 or 4 grades	Observers attempted to follow training guide
IOA Overall	Minimal* Fleiss K = 0.304 (95% CI 0.240-0.368, P<0.001)	
IOA Between Pairs		

*(*McHugh 2012, % data that are reliable <20%)*

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IOA Between Pairs	Cohen K = 0.173 to 0.533	

(*McHugh 2012, % data that are reliable <20%)

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IOA Between Pairs	Cohen K = 0.173 to 0.533	Cohen K = 0.344 to 0.662

(*McHugh 2012, % data that are reliable <20%)

Concatenation alone ?

Round 1 grades were converted into a 2-tier scale:

(if range of differentiation given, highest grade was accepted)

Fleiss K = 0.633

(95% CI 0.541-0.725, P=<0.001)

→ Moderate!

→ and better than after training! (cf K = 0.517)

Round 1 grade	2-Tier Conversion
Well differentiated	Low-grade
Moderately differentiated	
Poorly differentiated	High-grade
Undifferentiated or sarcomatoid	

Limitations / Future directions

Guide clearly needs improvement

- Fully illustrated with WSI ideal

Training set/session?

Aiming for Moderate to Strong agreement (K = 0.6-0.9 please)

Then test 2-Tier Grading System in a set with long-term follow up data (to establish prognostic significance)



Acknowledgements

A/Prof Duncan Lambie

Dr Amy Power

Dr Fiona Tang

Dr Karien Treurnicht

Dr Chandan Jadhav

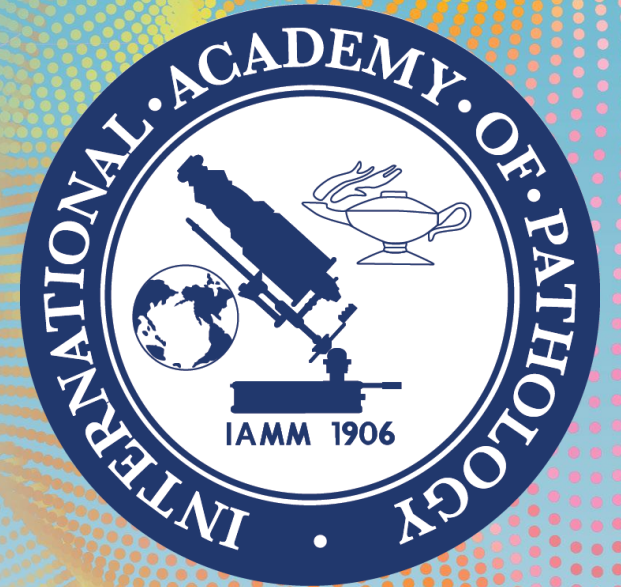
Dr Rebecca Donkin

Dr Ryan Livingston

Mr Daniel Meloncelli



Appx



Appendix: Studies of survival in HNcSCC with nodal metastasis, last 25y, with adequate data

Study	Design	Cases	Comments	Country	5y DSS	5y OS	5y DFS/ PFS	Other measures/comments
Kraus 1998 ⁹²	Retro	45	Single site, 1984-1995	US	-	22%	34%	Memorial Sloan Kettering.
Veness 2005 ⁷⁴	Retro	167	Single site, 1980-2002	Aust	58%	50%		Westmead Hospital.
Oddone 2009 ⁷⁶	Retro	250	Single site, unknown dates			78%		Westmead Hospital; possible overlap of included cases.
Givi 2011 ⁷⁵	Retro	51	Single site, 1993-2007	US	-	30%		Memorial Sloan Kettering; possible selection bias.
Pramana 2012 ⁷⁷	Retro	75	Single site, 1994-2008	Aust	66%	52%		St George Hospital Kogarah; only parotids included.
Mizrachi 2013 ⁷⁰	Retro	71	Single site, 1990-2008	Israel	78%	52%		Rabin Medical Centre.
Shao 2014 ⁷⁴	Retro	160	Single site, 1989-2010	NZ	77%	48%		Parotids only.
Schmidt 2015 ⁷²	Retro	113	Single surgeon, 1998-2011	Aust	83%	80%	75%	Selection bias likely; excluded cases with distant metastasis; only includes surgical cases; OS fell to <50% by 10y. Single regional centre (Toowoomba).
McDowell 2016 ⁷¹	Retro	132	Parotid metastases only	Aust	64%	44%	37%	Peter MacCallum Cancer Centre.
Hirshoren 2017 ⁷³	Retro	149	Single site, 2001-2014	Aust	-	50%		Peter MacCallum Cancer Centre; included surgical patients with curative intent; possible overlap of included cases.
Bobin 2018 ⁹³	Retro	35	Single site; Parotid metastases only	France	59%	35%		Small number of cases
Lam 2018 ⁹³	Retro	46	Single site, 1986-2016	Aust	-	50%		Westmead Hospital; possible overlap of included cases; immunocompromised patients only.

Study	Study Characteristics			Intervention			Outcomes			
	Study type	Population (inclusion/exclusion)	No. cases	Grading system used (3/4 tier). Observers.	No. of rates	Spread of grades	Interobserver Agreement		Intraobserver Agreement	Other findings
							Kappa*	%Agree		
Wechslerl 2001	Interobserver reliability, retro, observational, within the HELIOS study.	Europe. Multicentre. Cancer registry, 20-70yo.	111	4-tiers. 3 General Pathologists, 7 Dermato-pathologists.	2 (from panel of 10)	Not clear as no consensus grade given	0.65 (weighted) (96% CI, 0.50-0.80)	59%	NS	Agreement about diagnosis of malignancy was good.
Jagdeo 2007	Interobserver reliability study, prospective, 6 years.	USA. Multicentre. Veterans, face and ears.	47	Broders, 3-tier. Pathologists.	2	Not provided	0.25 (95% CI, 0.20-0.32)	62%	NS	
Agar 2015	Interobserver reliability, retro, observational.	NZ. Single centre. Known metastatic cases.	49	Brandwein's system from mSCC, not classic cSCC grading. ³⁰ Pathologists.	2	W 4, M 29, PD 16	NS	90%	NS	Primary tumors were hard to identify; high proportion of metastases with WPOI pattern 4.
Fujimoto 2019	Interobserver reliability, retro, observational.	Japan. Multicentre. Median age 81 (40-96), no immunosuppressed patients, common cSCC (excluding eyelid, inner lip, anogenital)	48	Broders, 3-tier. Pathologists.	6	W 13, M 29, PD 6	0.332 (median)	NS	NS	Tumor budding has higher kappa than grade
Prezzano 2021	Interobserver reliability, retro, observational.	USA. Single centre. No pop details provided.	131	Broders, 3-tier. 3 Mohs surgeons & 3 Dermato-pathologists.	6	W 50, M 45, PD 36	Round 1: 0.56 (0.59 for poor vs nonpoor) Round 2: 0.60	NS	0.70 (after training)	Agreement was better for well v non-well than it was for poor v non-poor
Nash 2022	Interobserver and intraobserver reliability, retro, observational, survey of reporting habits.	USA. No pop details provided.	45	No details provided. Dermato-pathologists.	21	Not provided	0.5306 (95% CI, 0.5110-0.5502)	NS	Range 0.3077-0.8414	Test-retest agreement problematic for a subset of observers

Deaths from Melanoma Vs NMSC

- 2001-2021

— Melanoma
— NMSC

