Spinal Cord Glioma

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Case

- 22 year old female with no relevant PMH presented with a one month history of mid-back pain and a small area of numbness on her knee.
- ROS: Positive for gradually progressive bilateral lower extremity weakness and paresthesia.
  - No bladder or bowel dysfunction.
  - No saddle anesthesia

Case

- SH: No previous surgeries
- FH: No family history of cancer or neurologic disorders.
- SH: Nonsmoker, no alcohol use, no drug use
- Medications: None
- Exam: 3/5 strength in the bilateral lower extremities, otherwise unremarkable

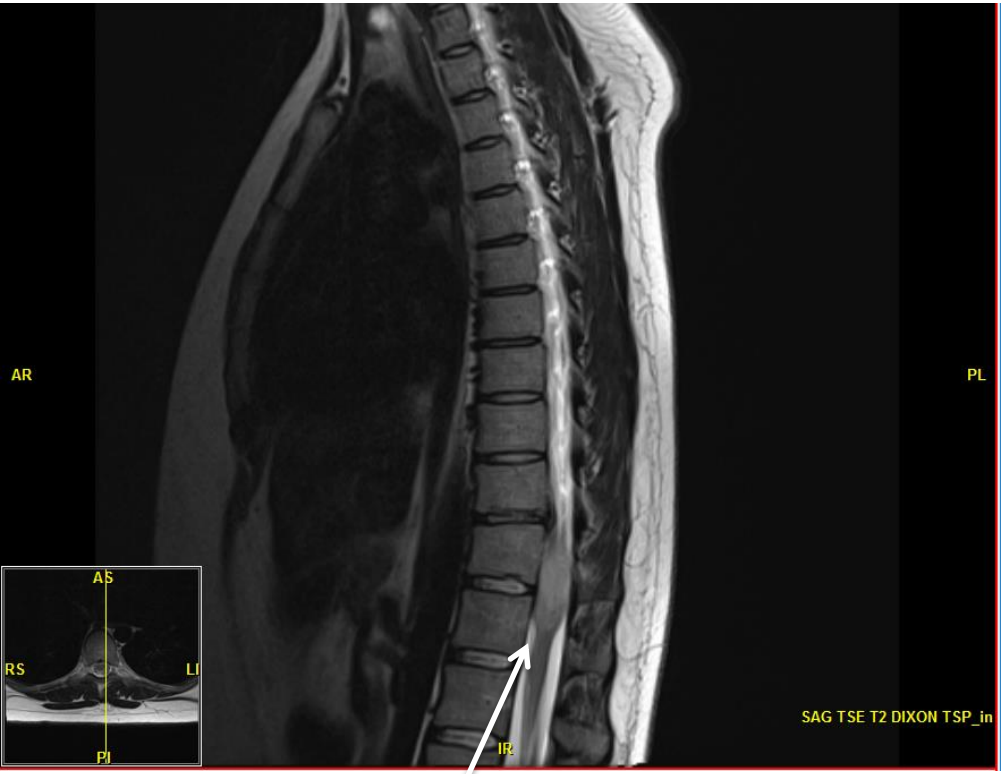
Case

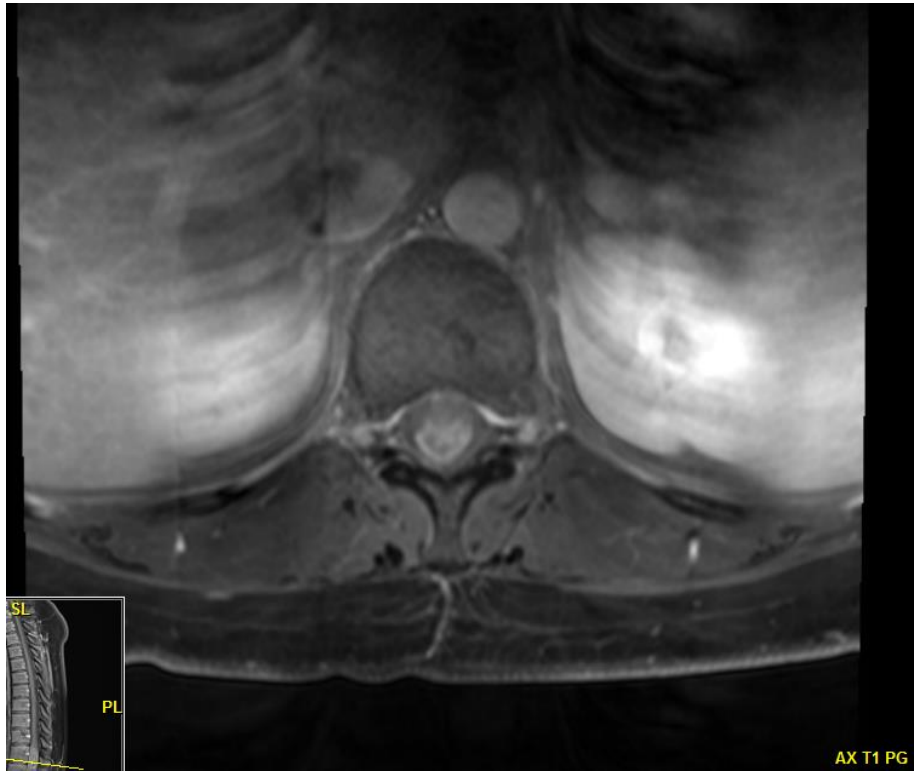
- Given her continued progressive symptoms despite conservative treatment with physical therapy, an MRI was obtained

Case

- MR of the thoracic spine
  - T11-T12 centrally located intramedullary expanding lesion with well defined borders and mild heterogeneous enhancement
  - Radiographically consistent with ependymoma
- MR of the brain, cervical spine, and lumbar spine were negative

MRI





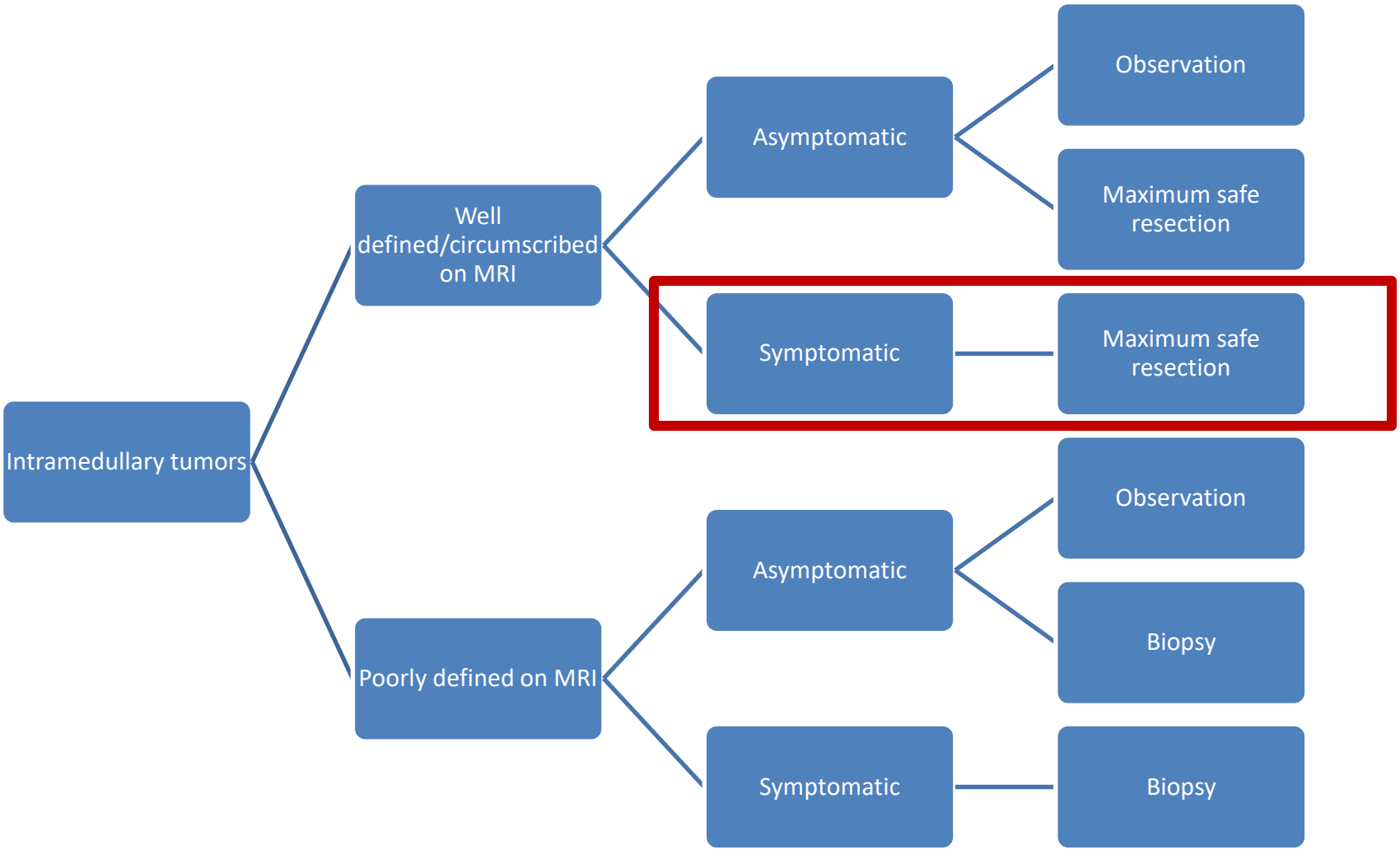
T2 imaging: Centrally located mass with well defined borders

Most consistent with ependymoma

Workup (NCCN v3.2019)

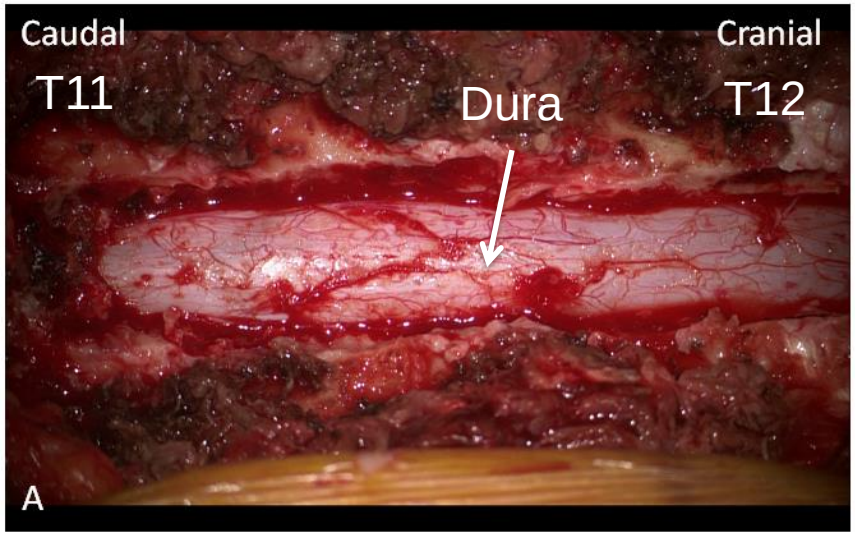
- Spine MRI (cervical, thoracic, and lumbar)
- CT myelogram if MRI is contraindicated

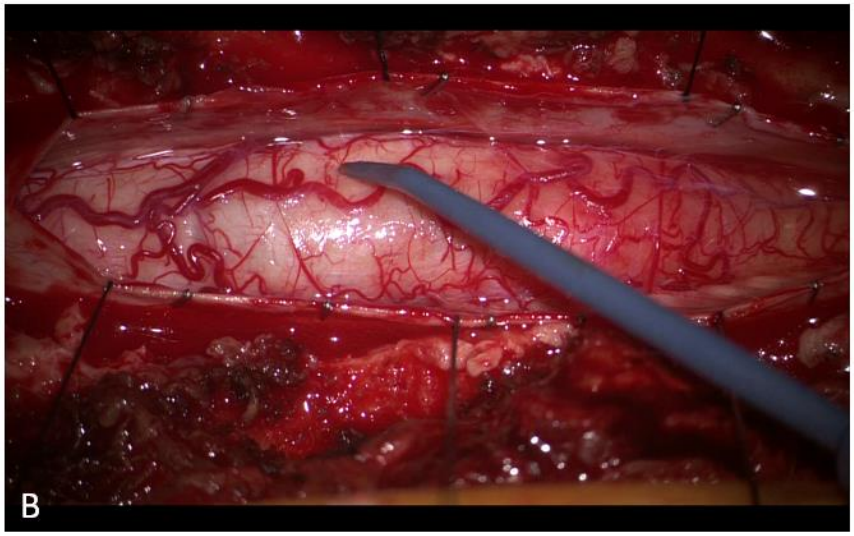
Treatment options (per NCCN)

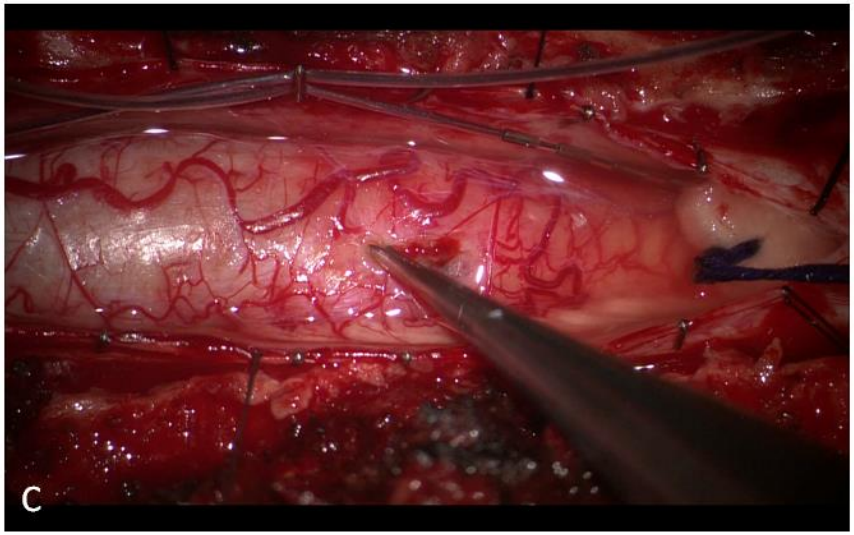


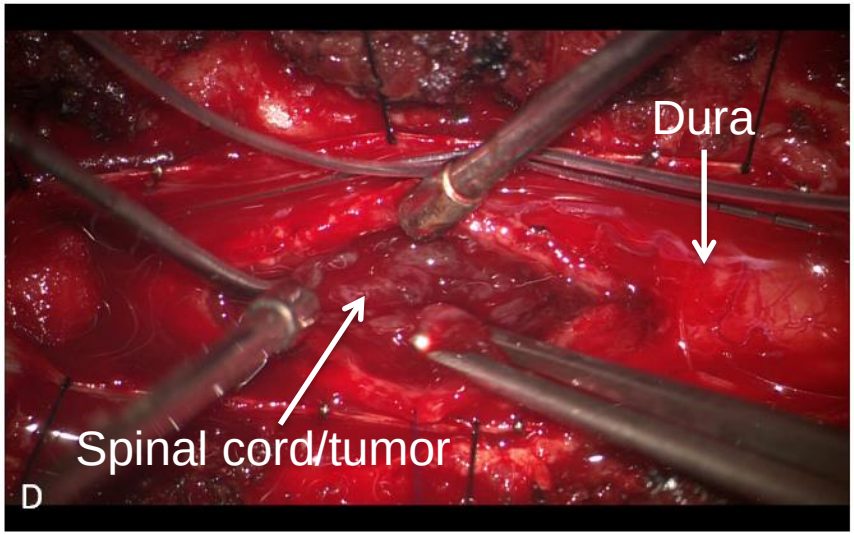
Case

- She underwent T11-T12 laminectomy and intramedullary spinal cord tumor resection
  - Postoperative course was uncomplicated
  - Per surgeon: 60% removed
- Pathology: Diffuse midline glioma (WHO grade IV)
  - H3K27-M mutant
  - ATRX retained, IDH-1 negative, high Ki67
  - MGMT not performed


Caudal
Cranial
T11
Dura
T12
A

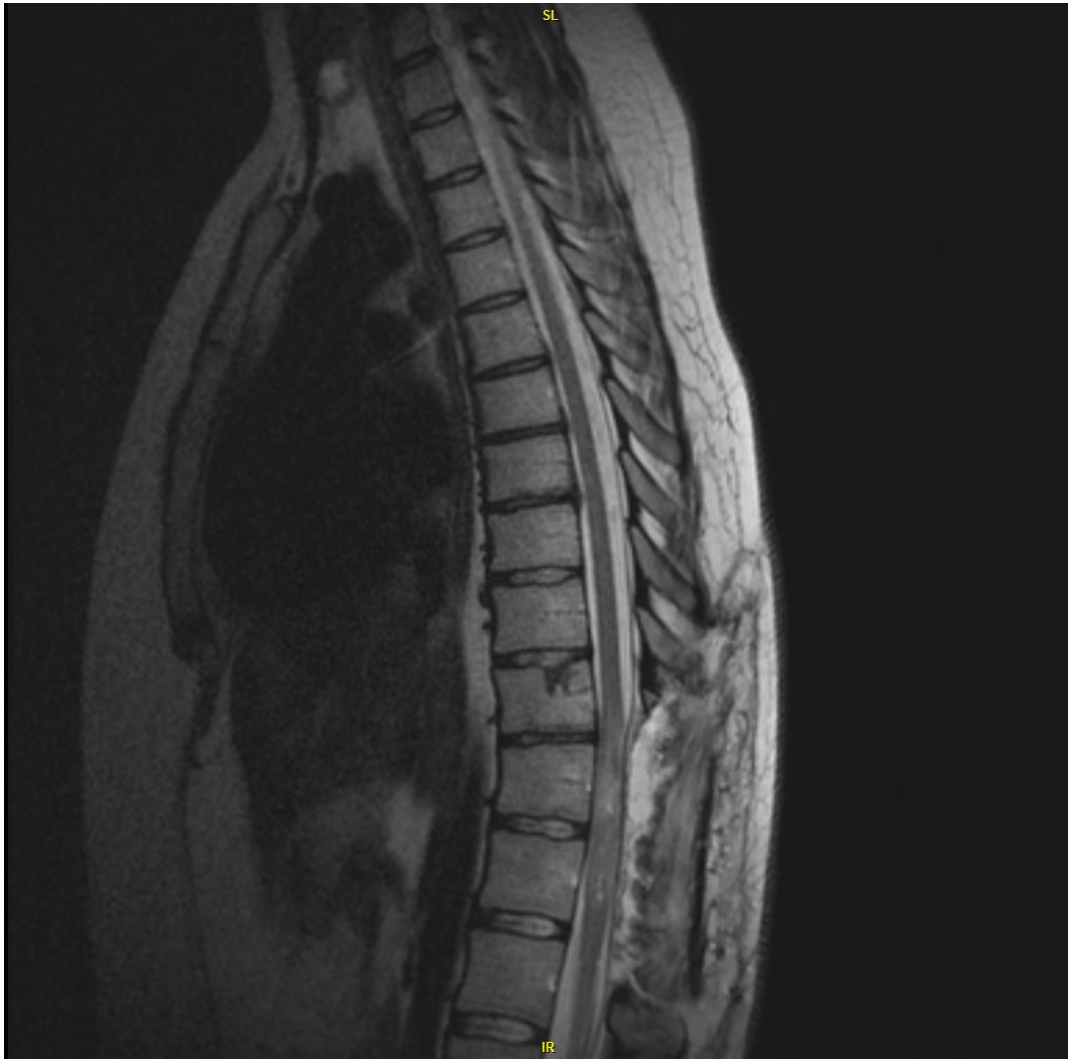

B


C


Dura
Spinal cord/tumor
D

Postoperative MRI

- 1 month post-op
- Significant decrease in size of abnormality, although enhancement remains
- Suggesting subtotal resection

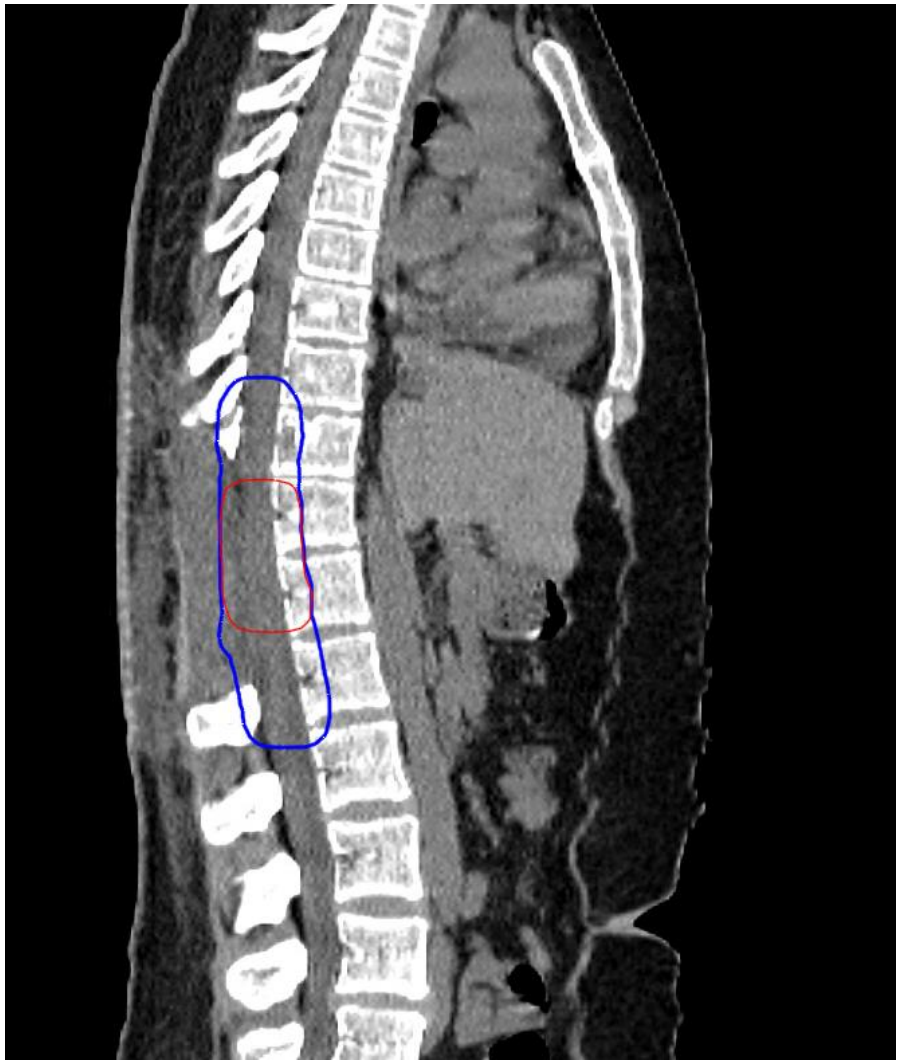


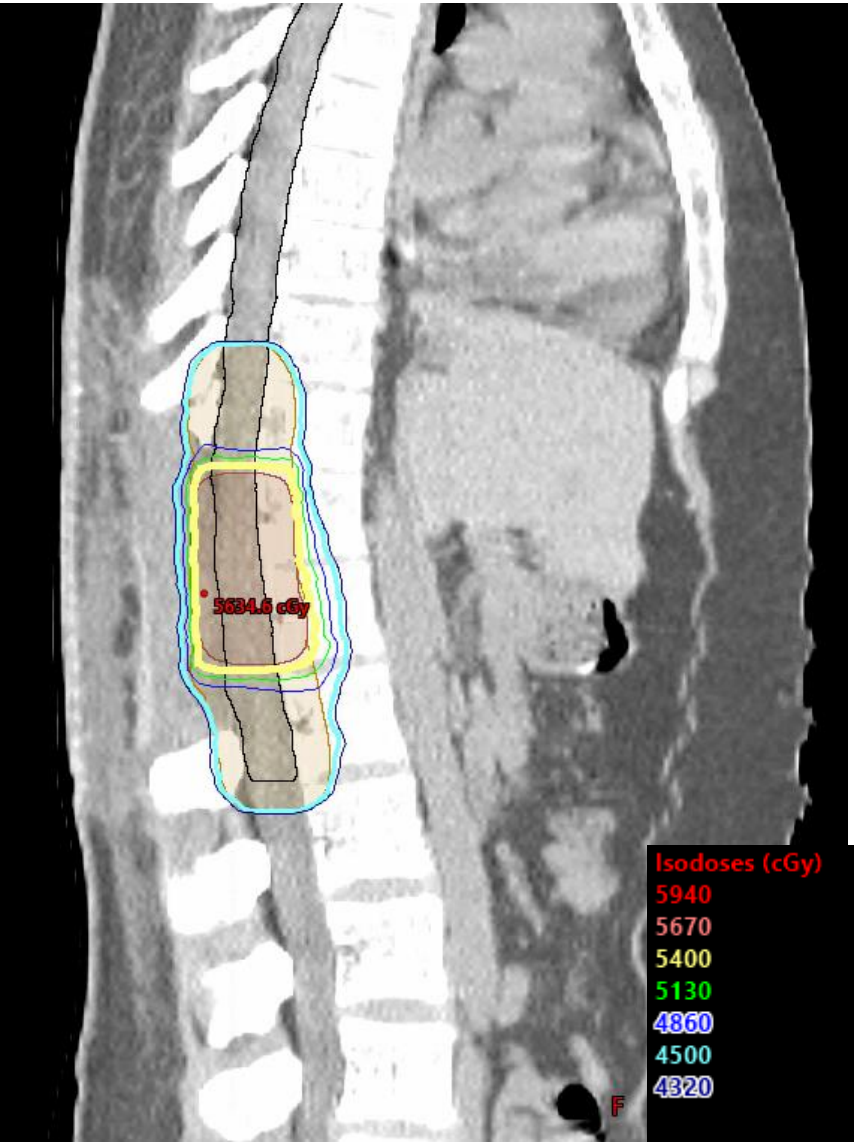
Adjuvant Treatment

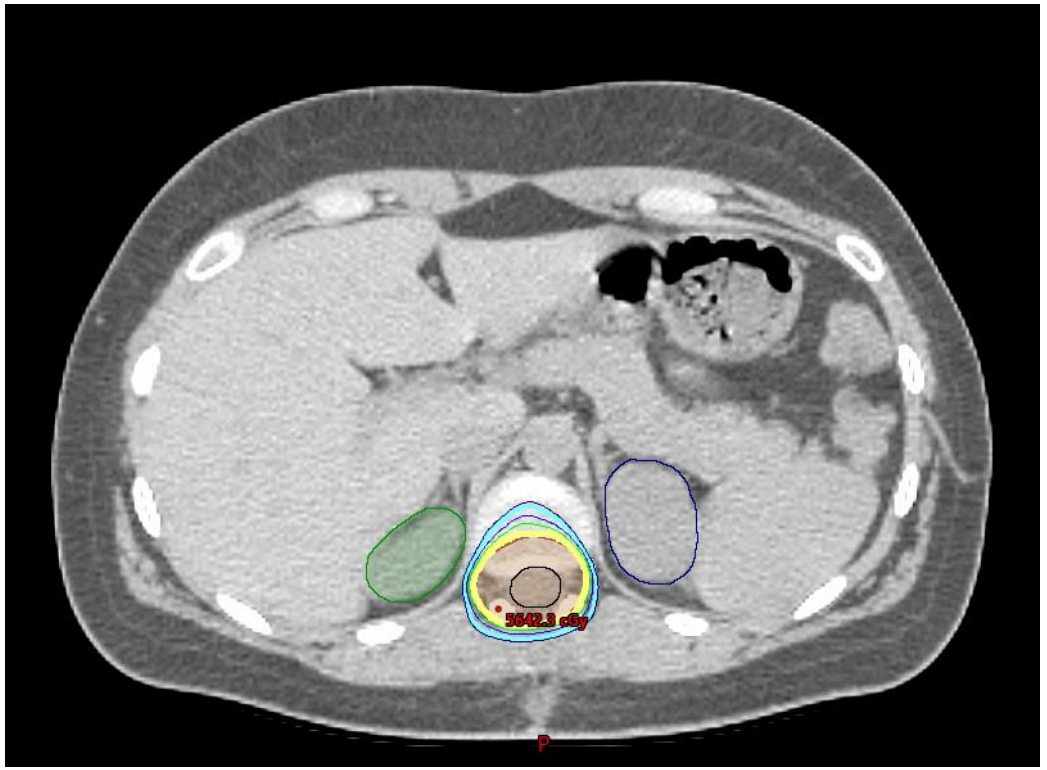
- **Multidisciplinary approach**
- Clinical trials if available
- Temozolomide with radiation therapy (as per glioblastoma)
  - Pregnancy test!
  - Fertility counseling
    - Please see manuscript by Ghadjar et al for an excellent review on fertility preservation (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4341866/pdf/13014_2015_Article_353.pdf)

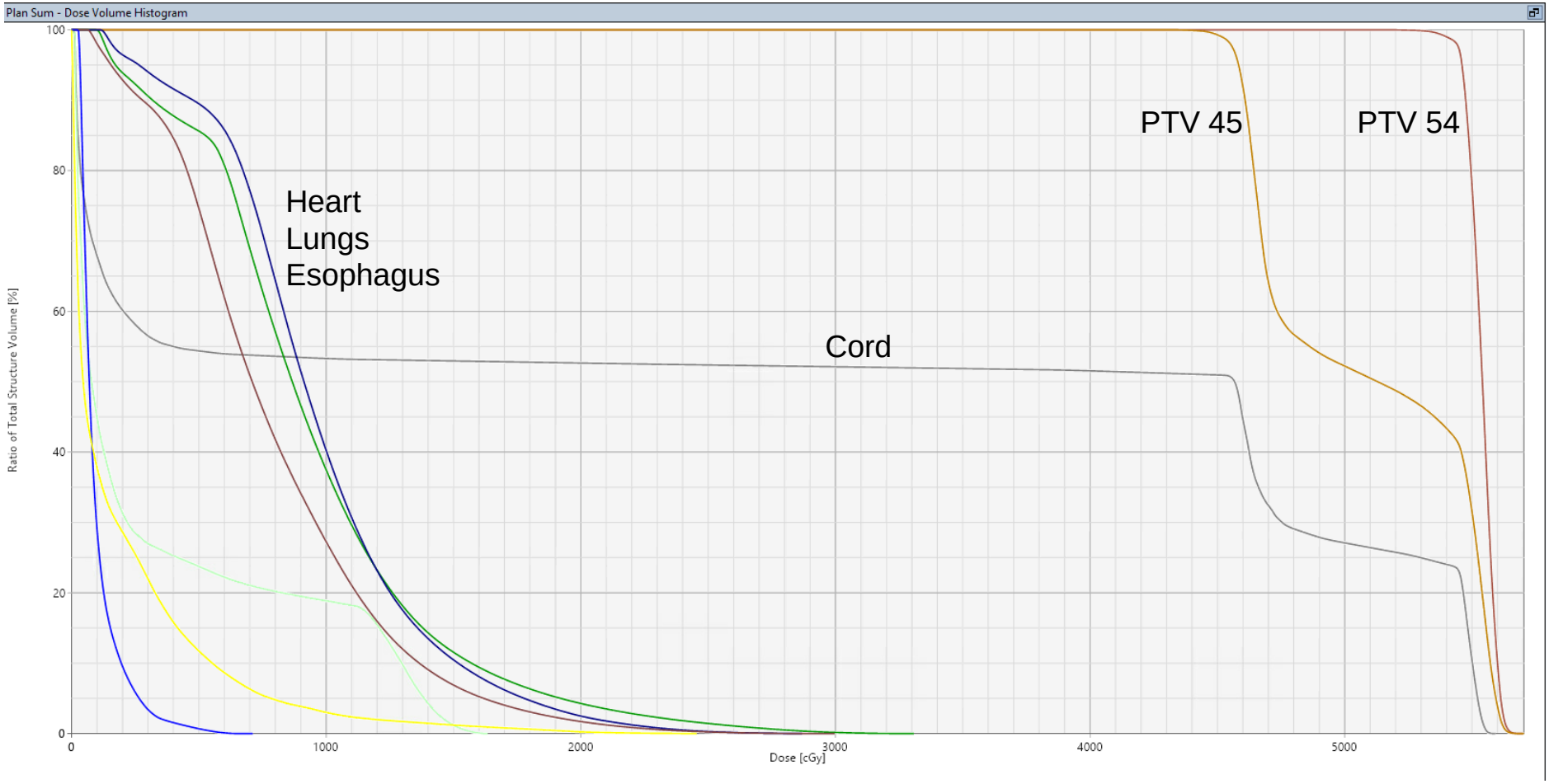
Adjuvant Radiation

- VMAT using 6MV photons
- 45 Gy in 25 fractions to low risk PTV followed by a 9 Gy boost to residual disease
- GTV: Gross tumor
  - CTV_45: GTV + 1.5 cm sup/inf expansion
  - PTV_45: CTV + 1 cm
- PTV_54: GTV +1 cm (CBCT used)
- Consider contouring ovaries (out of field in this patient)
- Minimize hot spot
  - Cord received a point dose of <56 Gy




5634.6 cGy
Isodoses (cGy)
5940
5670
5400
5130
4860
4500
4320
F


5642.3 cGy
P


Plan Sum - Dose Volume Histogram
Ratio of Total Structure Volume [%]
Dose [cGy]
0
20
40
60
80
100
0
1000
2000
3000
4000
5000
PTV 45
PTV 54
Heart
Lungs
Esophagus
Cord

Follow up

- She tolerated treatment well without significant toxicity
- She was started on Depakote by neuro-oncology given possible benefit in H3K27M gliomas (see Literature Review)
- She is continuing adjuvant temozolomide and tolerating well 1 month after radaition

SPINAL CORD GLIOMAS

Spinal Cord Gliomas

- Spinal cord malignancies account for 2-4% of all primary CNS cancers
  - High grade spinal cord gliomas account for 0.2% of all glioblastomas
- Typically treated similar to a GBM
  - Maximum total resection followed by adjuvant chemotherapy and radiation
  - Typically treated to 54 Gy (may treat to 60 Gy depending on disease site and institution)
  - Test for H3K27M when clinically indicated
    - Improved prognostic information, possible benefit with HDAC-inhibitors
- Local failures are most common
  - Most occur in-field within 2 years
- Most common cause of death: Sequelae from paraplegia (infection, etc)

Clinical Pearls

- Spinal cord ends at L1-2 in adults
  - L3-4 in children
- 2/3 of spinal cord tumors are extramedullary
  - 1/3 intramedullary
- 90% are low grade (ependymomas)
  - Most commonly in lumbar/sacral spine
  - Present as well defined regions of enhancement, typically more central and symmetric
- Astrocytomas are most common in cervical or thoracic spine
  - Present as asymmetric expansion on MRI

Toxicities

- Radiation induced myelopathy presents as paresthesia, weakness, pain/temperature loss, or bladder and bowel dysfunction
  - 12-29 months after RT
- Risk of myelopathy (QUANTEC)
  - 54 Gy: <1%
  - 61 Gy: <10%
  - 13 Gy in 1 fraction (SRS): <1%
  - Cervical spine is less sensitive than thoracic spine (consider dose escalating to 60 Gy)

LITERATURE REVIEW

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 4, pp. 1060–1071, 2006

0360-3016/06/$–see front matter

doi:10.1016/j.ijrobp.2005.09.038

CLINICAL INVESTIGATION **Spinal Cord**

SPINAL CORD GLIOMAS: A MULTI-INSTITUTIONAL RETROSPECTIVE ANALYSIS

May Abdel-Wahab, M.D.,* Blessing Etuk, M.D.,* James Palermo, M.D.,†
Hiroki Shirato, M.D.,‡ John Kresl, M.D., Ph.D.,§ Ozlem Yapicier, M.D.,‖ Gail Walker, Ph.D.,¶
Bernd W. Scheithauer, M.D.,# Edward Shaw, M.D.,† Charles Lee, M.D.,**
Walter Curran, M.D.,†† Terry Thomas, M.Sc.,§ and Arnold Markoe, M.D.*

*Department of Radiation Oncology, University of Miami, Miami FL; †Department of Radiation Oncology, Wake Forest University School of Medicine, Wake Forest, NC; ‡Department of Radiation Oncology, Hokkaido University, Hokkaido, Japan; §Department of Radiation Oncology, Arizona Oncology Services at St Joseph's Hospital and Medical Center, and Cyberknife Center, Barrow Neurologic Institute, Phoenix, AZ; ‖Department of Pathology, Anadolu Health Care System, Kocaeli, Turkey; ¶University of Miami/Sylvester Comprehensive Cancer Center, Division of Biostatistics, Miami, FL; #Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; **Department of Radiation Oncology, Wayne State University, Detroit, MI; ††Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, PA

- Retrospective review of 183 patients treated with surgery vs surgery and PORT for spinal cord gliomas
- Included low, intermediate, and high grade tumors

Abdel-Wahab et al

- For astrocytoma
  - PFS was 42% at 5 years, 29% at 10 years, and 15% at 15 years
  - OS was 59% at 5 years, 53% at 10 years, and 32% at 15 years
- Of note, RT group had few complete resections when compared to surgery alone

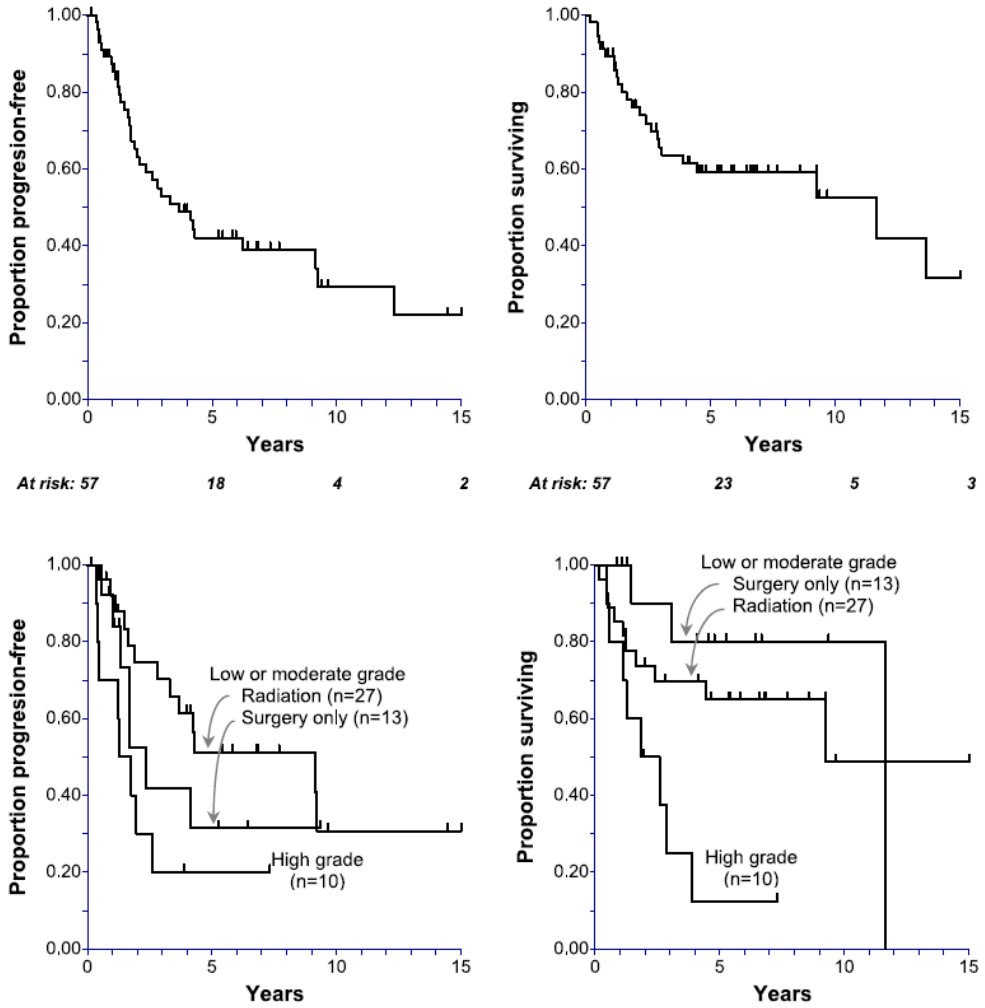


Fig. 2. Progression-free and overall survival in 57 astrocytoma patients by tumor grade and treatment.

- Conclusion: PORT reduced progression in low and moderate grade astrocytomas

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journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Spinal cord glioblastoma: 25 years of experience from a single institution

Vijay Yanamadala [a,c,*], Robert M. Koffie [a,c], Ganesh M. Shankar [a,c], Jay I. Kumar [a,c], Quinlan D. Buchlak [a,c], Vidya Puthenpura [a], Matthew P. Frosch [b,c], Thomas M. Gudewicz [b,c], Lawrence F. Borges [a,c], John H. Shin [a,c]

[a] Department of Neurosurgery, Massachusetts General Hospital, 15 Parkman Street, WACC 021, Boston, MA 02115, USA
[b] Department of Pathology, Massachusetts General Hospital, Boston, MA, USA
[c] Harvard Medical School, Boston, MA, USA

- Single institution analysis of 6 patients with high grade spinal cord gliomas
- All patients underwent subtotal resection
  - 3 received postoperative radiation (54 Gy in 30 fractions)
  - 3 received postoperative chemo (temozolomide and bevacizumab)

Yanamadala et al

- At 3 month follow-up
  - KPS was stable in 50% of patients
  - All patients had decreased KPS at 1 year
- 100% overall survival at 1 year

Table 2
Outcomes for six patients with spinal cord glioblastoma

Patient outcomes	Metric
Follow-up mean [range], years	1.5 [1–3]
Neurological status (stable or improved ASIA score)	
Immediate post-operative	6
3 months	5
1 year	1
Functional status (stable or improved KPS)	
Immediate post-operative	5
3 months	3
1 year	0
Post-operative radiation	3
Post-operative chemotherapy	3
1 year survival	100% (6/6)

ASIA = American Spine Injury Association, KPS = Karnofsky Performance Status.

Conclusions from Yanamadala et al

There is an excellent 1 year survival, although with a decline in functional status, for patients with high grade spinal cord gliomas treated with subtotal resection +/- adjuvant chemoRT

Role of H3K27M?

- H3K27M: Substitution of lysine for methionine at position 27 in histone 3
  - Mutation in one of several H3 genes, including *H3F3A* or *HIST1H3B/C*
  - Almost always midline if present
  - Some evidence of improved outcomes with HDAC inhibitors (sodium valproate) in H3K27M tumors
    - Remains controversial
    - Largely based on pre-clinical studies and case reports
- Karremann et al published a study suggesting H3K27M as a poor prognostic factor for high grade gliomas in all regions of the CNS

JNS PEDIATRICS

LITERATURE REVIEW

J Neurosurg Pediatr 23:308–316, 2019

Impact of the H3K27M mutation on survival in pediatric high-grade glioma: a systematic review and meta-analysis

Victor M. Lu, MD,[1] Mohammed A. Alvi, MBBS,[2,3] Kerrie L. McDonald, PhD,[1] and David J. Daniels, MD, PhD[2]

[1]Prince of Wales Clinical School, The University of New South Wales, Sydney, Australia; and [2]Department of Neurologic Surgery and [3]Neuro-Informatics Laboratory, Mayo Clinic, Rochester, Minnesota

- Meta-analysis of 6 studies and 474 patients
- The presence of the mutation was associated with worse prognosis (HR 3.630) and a worse overall survival (by 2.3 years)

PLOS ONE

RESEARCH ARTICLE

Repurposing the anti-epileptic drug sodium valproate as an adjuvant treatment for diffuse intrinsic pontine glioma

Clare L. Killick-Cole[1]*, William G. B. Singleton[1,2], Alison S. Bienemann[1], Daniel J. Asby[1], Marcella J. Wyatt[1], Lisa J. Boulter[1], Neil U. Barua[1,2], Steven S. Gill[1,2]*

1 Functional Neurosurgery Research Group, School of Clinical Sciences, University of Bristol, Learning & Research Building, Southmead Hospital, Bristol, United Kingdom, **2** Department of Neurosurgery, North Bristol NHS Trust, Bristol, United Kingdom

- Sodium valproate causes dose-dependent decrease in DIPG cell line viability
- Valproate causes increase in acetylation of histone H3, reducing cell viability by induction of apoptosis
- Potentiates carboplatin
- **Conclusion:** Based on pre-clinical work, valproate may be used as an adjuvant treatment in DIPG

Case report

Prolonged survival in a patient with a cervical spine H3K27M-mutant diffuse midline glioma

Kelsey Peters,[1] Drew Pratt,[2] Carl Koschmann ,[3] Denise Leung[1]

- Case report of a 39 year old with cervical intramedullary H3K27M-mutated diffuse midline glioma
  - Underwent subtotal resection
  - Treated with 54 Gy and concurrent and adjuvant temozolomide
  - Started on valproic acid at time of disease progression (25 months after diagnosis)
  - Passed away at 31 months after diagnosis

Summary

- High grade spinal cord gliomas are rare
- H3K27M is a poor prognostic factor
- Treatment consists of biopsy/resection followed by radiation (54 Gy in 30 fx) and chemo (similar to GBM)
- Try to keep the spinal cord dose <54 Gy for <1% risk of myelopathy
- Most relapses occur in-field

References

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3. Killick-Cole CL, Singleton WGB, Bienemann AS, Asby DJ, Wyatt MJ, Boulter LJ, et al. Repurposing the anti-epileptic drug sodium valproate as an adjuvant treatment for diffuse intrinsic pontine glioma. *PLoS One* (2017) 12(5):e0176855. doi: 10.1371/journal.pone.0176855. PubMed PMID: 28542253; PubMed Central PMCID: PMCPMC5444593.

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Please provide feedback regarding this case or other ARROcases to arrocase@gmail.com