Pediatric Medulloblastoma

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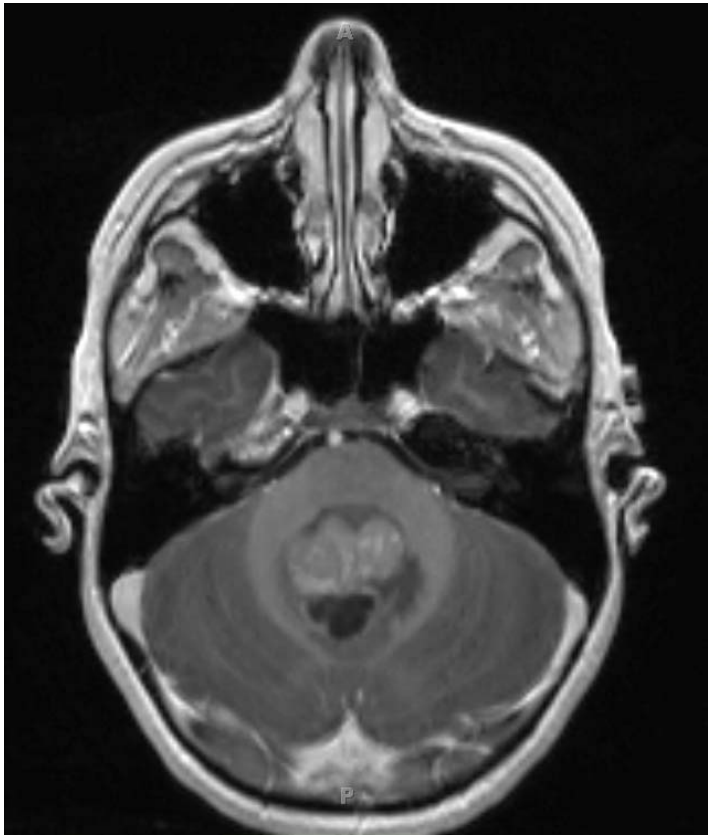
Case Presentation

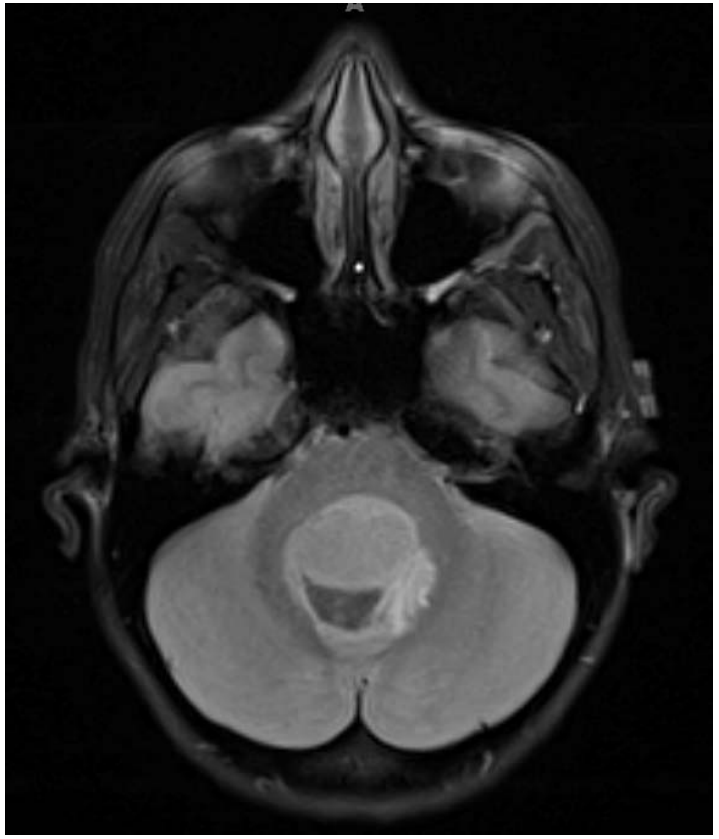
- 9 yo presented to the ED with 3 month history of intermittent headache associated with abdominal pain and vomiting
  - Head CT revealed a 3 cm posterior fossa mass with 6 mm tonsillar herniation
- PMH
  - An episode of ileus at 18 months
  - Otherwise unremarkable

MRI

T1 post contrast



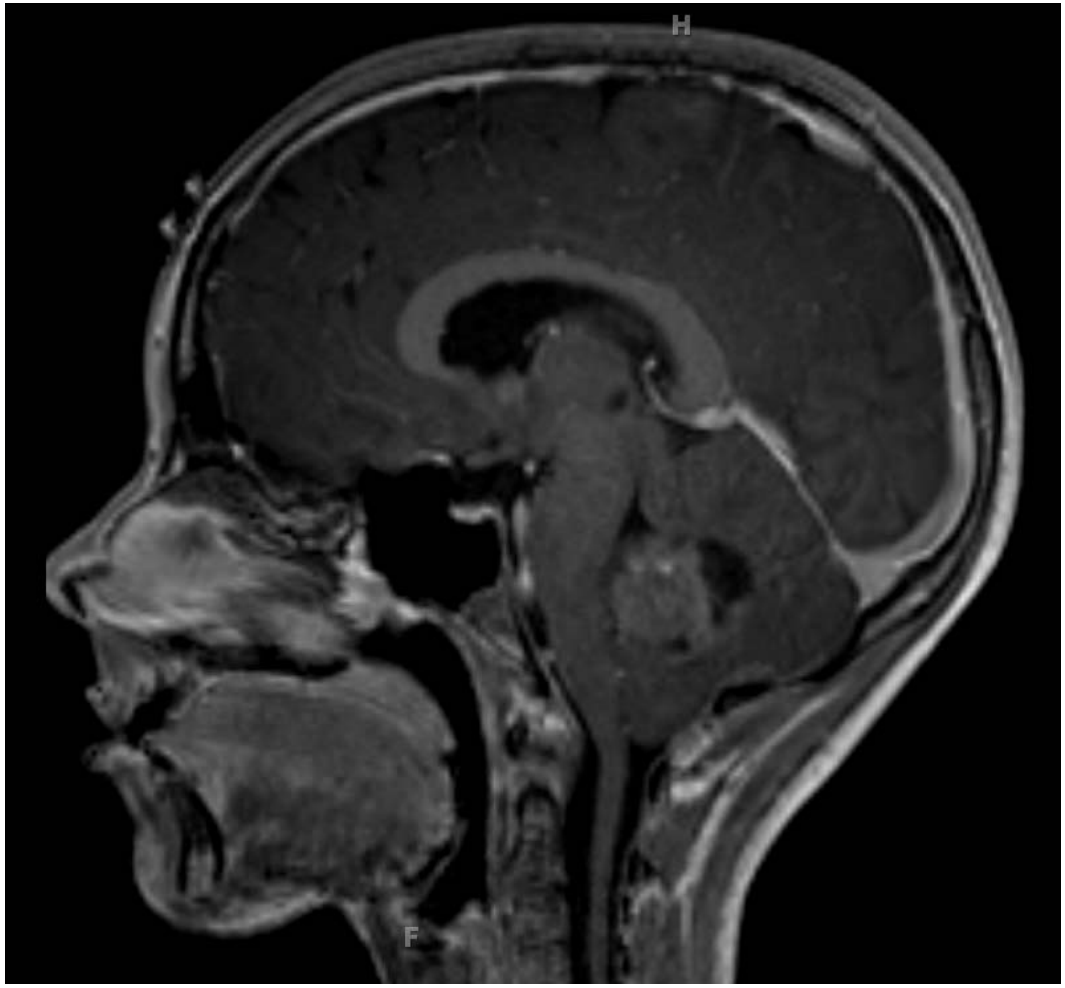
T2 FLAIR



Brain MRI revealed a heterogeneously enhancing 2.4 x 2.2 x 3.0 cm mass in the posterior fossa centered around the 4th ventricle.

MRI

T1 post contrast



There was descent of cerebellar tonsils through the foramen magnum (7mm below plane of the foramen magnum)

Diffusion weighted imaging (not shown) revealed restricted diffusion, suggesting high cellularity.

Treatment

- Surgical resection was performed
- MRI on POD #1 revealed no residual disease
- Pathology: medulloblastoma, grade IV, without large cell/anaplastic features. Beta-catenin staining was negative
- CSF cytology > 14 days postop was negative for malignant cells
- Baseline labs, audiometry, IQ testing were all within normal limits

- **Diagnosis: Standard Risk Medulloblastoma**

Epidemiology

- Most common childhood malignant brain tumor
- 20% of pediatric CNS tumors
- ~ 550 cases per year in the US
- Median age of presentation is 5-7 yo
- 75% occur in children < 15 yo
- More common in males (~2:1)

Presentation

- Increased intracranial pressure: headaches, nausea, vomiting
- Cerebellar involvement: ataxic gait
- In infants: loss of milestones, increased head circumference, head tilt due to CN IV palsy
- Clinical exam: papilledema, nystagmus, CN abnormalities (VI most common → "setting sun" sign with downward gaze)
- 50-75% have <3 months of symptoms

Work Up

- Complete history
- Complete physical exam with focus on neurological exam, fundus exam (for papilledema)
- Labs: CBC, CMP
- Imaging: Head CT and Brain MRI
- Ancillary tests prior to treatment:
  - Audiometry
  - IQ testing
  - Serum TSH and growth hormone

Workup: CSF

- 30-40% have CSF spread at the time of diagnosis
- CSF sampling is rarely obtained prior to surgery given the risk of herniation in the setting of increased ICP
- If not obtained pre-operatively, must wait 10-14 days after surgery to avoid false-positive findings from surgical debris

Imaging Recommendations

- Pre-op MRI brain and spinal cord (post-op spine can give false positives) should be performed
- Timing of imaging is important:
  - Post-op MRI brain within 48 hours
  - If MRI of spine not performed pre-op, then must wait 10-14 days after surgery to avoid false positives

Typical Imaging Findings

- CT: hyperdense on noncontrast CT (reflecting high cellularity), enhances with contrast
- MRI: well defined, solid, T1 hypointense, T2 hyperintense mass; often compresses 4th ventricle

DDx of posterior fossa mass in a child

- Medulloblastoma
- Astrocytoma (usually pilocytic astrocytoma, i.e. JPA)
- Ependymoma
- Atypical teratoid rhabdoid tumor (ATRT)

Histology

- Small round blue cell tumor
- Most common embryonal tumor of the CNS (others include PNETs, ATRT)
- Molecularly distinct from PNETs
- 40% have Homer-Wright rosettes
- Most stain + for neuron-specific enolase, synaptophysin, and nestin

Other small round blue cell tumors

- **LEARN NMR**
  - **L**ymphoma
  - **E**wing's
  - **A**cute lymphoblastic leukemia
  - **R**habdomyosarcoma
  - **N**euroblastoma
  - **N**euroepithelioma
  - **M**edulloblastoma
  - **R**etinoblastoma

Histology - Prognostic Factors

Poor prognosis

- Large cell/anaplastic variant
- Diploid DNA
- LOH 17p
- p53 mutation
- Low TrkC (tyrosine kinase that mediates neuronal differentiation)
- Her-2 Neu positive

Better prognosis

- Desmoplastic variant
- High TrkC expression
- β-catenin nucleopositivity

Histology

- Variants of medulloblastoma
  - Classic: most common
  - Nodular/desmoplastic: best prognosis, can be treated with surgery and chemotherapy alone
  - Large cell/anaplastic: most aggressive, always treat under high risk paradigm
- This traditional classification will likely be phased out in favor of molecular classification (next slide)

Prognostic Factors

- Risk stratification based on molecular profile
  - Group 1 (~10%): **Wnt/β-catenin pathway**, excellent prognosis, 5 yr OS 95%, usually "classic" histology
  - Group 2 (~30%): **Hedgehog pathway**, good prognosis, peaks in infancy and young adults
  - Group 3 (~25%): **c-MYC amplification**, poor prognosis, 5 yr OS only 50%
  - Group 4 (~35%): **neuronal signature** expression, peaks in childhood, 5 yr OS 50%

* Although being studied, molecular analysis is not currently part of routine pathologic evaluation

Modified Chang's Staging

- T1: tumor < 3 cm in diameter
- T2: tumor ≥ 3 cm in diameter
- T3a: tumor > 3 cm and with extension into aqueduct of sylvius or foramen of luschka
- T3b: tumor > 3 cm and with unequivocal extension into brainstem
- T4: tumor > 3 cm with extension past the aqueduct of sylvius or past foramen magnum

Modified Chang's Staging

- M0: no evidence of gross subarachnoid or hematogenous metastases
- M1: microscopic CSF involvement
- M2: gross nodular seeding intracranially beyond the primary site (in cerebellar/cerebral subarachnoid space, 3rd ventricle, or lateral ventricle(s)
- M3: gross nodular seeding of spinal subarachnoid space
- M4: metastases outside cerebrospinal axis

Risk Stratification

Features	Standard Risk (2/3)	High Risk (1/3)
Age	≥ 3 years old	< 3 years old
Extent of resection	< 1.5cm^2 residual disease after resection	Subtotal resection, 1.5cm^2 residual tumor
M-stage*	M0 by craniospinal MRI and CSF	M+; leptomeningial seeding

* Note: M stage is prognostic, T stage is not

Surgical definitions

- Near total resection (NTR): < 1.5cm^2 residual tumor on post-op MRI
- Subtotal resection (STR): 51-90% resection
- Bx only: < 50% resection
  - Tumor biopsy is NOT necessary; patients should go straight to surgery
- 5-yr EFS is worse in STR vs. GTR/NTR

Surgery risks

- Posterior fossa syndrome
  - 10-15% of cases
  - May occur 12-24 hours postop and improves over several months
  - SAME
    - **S**wallowing dysfunction
    - **A**taxia
    - **M**utism
    - **E**motional lability

Principals of Radiation

- In patients > 3 yo post-op RT with concurrent vincristine is delivered to the entire craniospinal axis followed by a posterior fossa or tumor bed boost
- Proton therapy, IMRT, or 3-D conformal therapy are acceptable treatment modalities
- Pre-op and post op MRIs of brain and spine are required for accurate target volume delineation

Principals of Radiation

- Dose of RT based upon risk grouping:
  - Standard risk patients treated with 23.4 Gy in 13 fractions followed by posterior fossa/tumor bed boost to 54-56 Gy
  - High risk patients treated with 36-39.6 Gy in 20-22 fractions followed by posterior fossa boost to 54-56 Gy
    - Spine mets also receive boost and final dose depends on location:
      - 40-45 Gy at level of the cord
      - 50.4 Gy if below the cord

Chemotherapy

- Radiation is delivered with concurrent vincristine
- Adjuvant chemotherapy is standard of care
- Chemotherapy can also be given for younger patients in order to delay RT, as the toxicity profile for patients <3 yo who get radiation is worse than for older children

Treatment Paradigm - Standard risk

- Max safe resection → RT with concurrent weekly vincristine → adjuvant chemo with 8 cycles of cisplatin / CCNU (i.e. lomustine) / vincristine
- RT is CSI 23.4 Gy with posterior fossa or tumor bed boost to 54 Gy
- OS at 5 years: 86%, EFS: 81% (CCG / POG A9961)

Treatment Paradigm - High risk (> 3yo)

- Similar to standard risk pts except RT is the following:
  - CSI dose is 36 Gy - 39.6 Gy rather than 23.4 Gy
  - Entire posterior fossa boost to 54 Gy
  - RT with concurrent vincristine followed by adjuvant chemotherapy (similar to standard risk)
- POG 9031 demonstrated those with M1 disease had 5 yr EFS of 65%

Treatment paradigm: < 3 yo

- By definition, always high risk if < 3 yo
- Surgery followed by intensive chemotherapy is primary treatment
- RT reserved for salvage therapy

Craniospinal Irradiation

- Goals: Achieve uniform dose throughout the subarachnoid space
- Spine field(s) delivered with PA beam
- Cranial fields delivered with opposed laterals
- Cranial and spine fields must be matched
  - The collimator and couch must be rotated during delivery of cranial fields in order to account for beam divergence
- Moving junction (i.e. gap and feather) is often used between fields to minimize areas of potential underdose/overdose

Craniospinal Irradiation

- Specific approach varies by institution
- Setup
  - Prone or Supine
  - Immobilize with a reproducible setup
    - Body immobilization with alpha cradle, vac lock bag, etc.
    - Aquaplast mask for head immobilization; neck hyperextended to avoid divergence of PA beam through mouth
    - CT sim
    - Anesthesia may be required

Advantages to Prone vs. Supine

Prone

- Direct visualization of light fields for spine field setup (therapists often prefer prone)

Supine

- Often more comfortable for the patient; potentially less movement during treatment
- Easy airway access for patients requiring sedation

Traditional Prone Technique

- Sim and place spine fields first:
  - SSD setup (cranial fields will be SAD)
  - Borders
    - Superior: C4-C7 (while avoiding exit dose through oral cavity)
    - Inferior: establish termination of thecal sac as determined by MRI (~S2) and cover 1-2 cm inferiorly.
    - Lateral: cover the recesses of the entire vertebral bodies with at least 1 cm margin on either side. Must cover the sacral foramina (“spade” shape)

Traditional Prone Technique

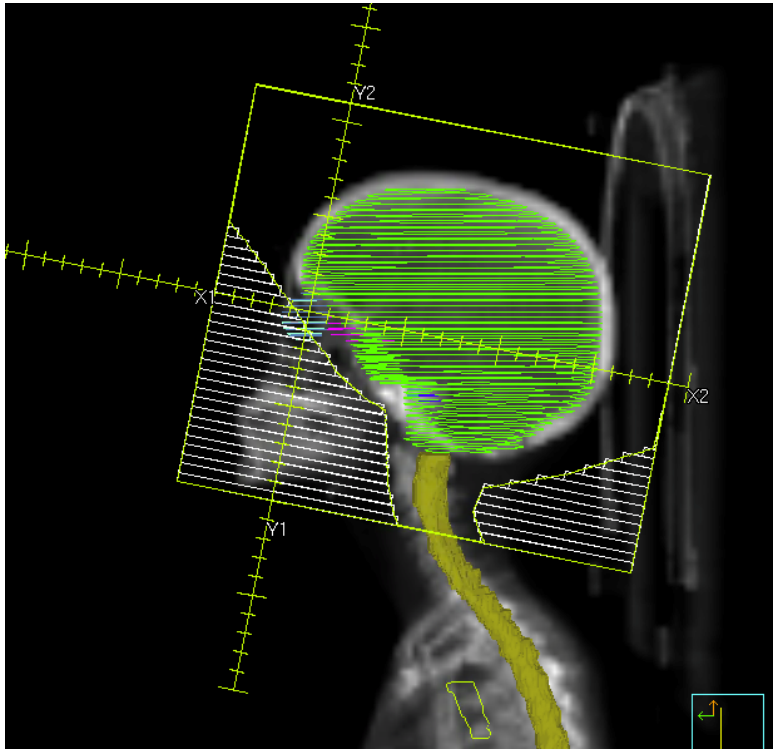
- Spine field:
  - Number of spine fields
    - Young children: entire spine can often be encompassed in one field
    - In older children, may need two adjacent fields
  - Try to avoid extending SSD because this increases exit dose
  - Matching adjacent spinal fields: There will be a gap at the skin with adjacent field borders matching at the anterior surface of the spinal canal (some institutions match at the depth of mid-spinal cord)

Traditional Prone Technique

- Brain and upper cervical spine are treated with lateral fields
  - SAD setup
  - Place isocenter in midline in same coronal plane as spine field to avoid ant/post shifts during treatment
  - Must have coverage of cribriform plate (0.5 – 1cm to block edge)
  - Try to minimize dose to eye and lens

Traditional Prone Technique

- Brain and upper cervical spine are treated with opposed lateral fields
  - Borders
    - Sup and post: flash
    - 0.5-1 cm margin on cribriform plate (must contour)
    - 1 cm margin inferior to middle cranial fossa
    - 1 cm margin anterior to vertebral bodies



Traditional Prone Technique

Technique for matching brain and spine field:

- In order for the cranial field to match diverging spine fields, the collimator must rotate
- Angle of collimator rotation can be calculated with the following equation:

$$\theta_{coll} = \arctan (L_1/2*SSD)$$

L_1= length of posterior spine field

SSD = source to surface distance of posterior spine field

Traditional Prone Technique

Technique for matching brain and spine field:

- In order for the spine field to match diverging cranial fields, couch must rotate **toward the gantry**
- Angle of "couch kick" can be calculated with the following equation:

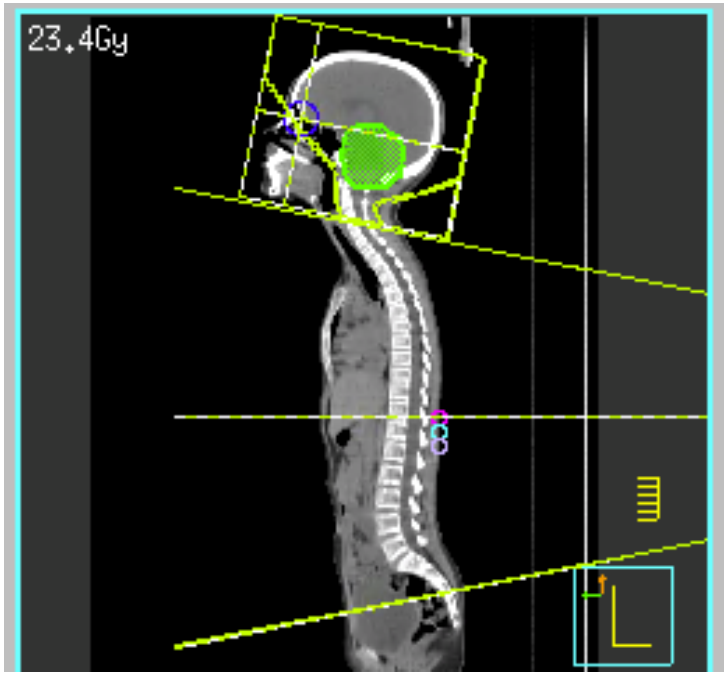
$$\theta_{couch} = \arctan(L_2/2*SAD)$$

L_2= length of lateral cranial field

SAD = source to axis distance of lateral cranial field

The Case: CSI

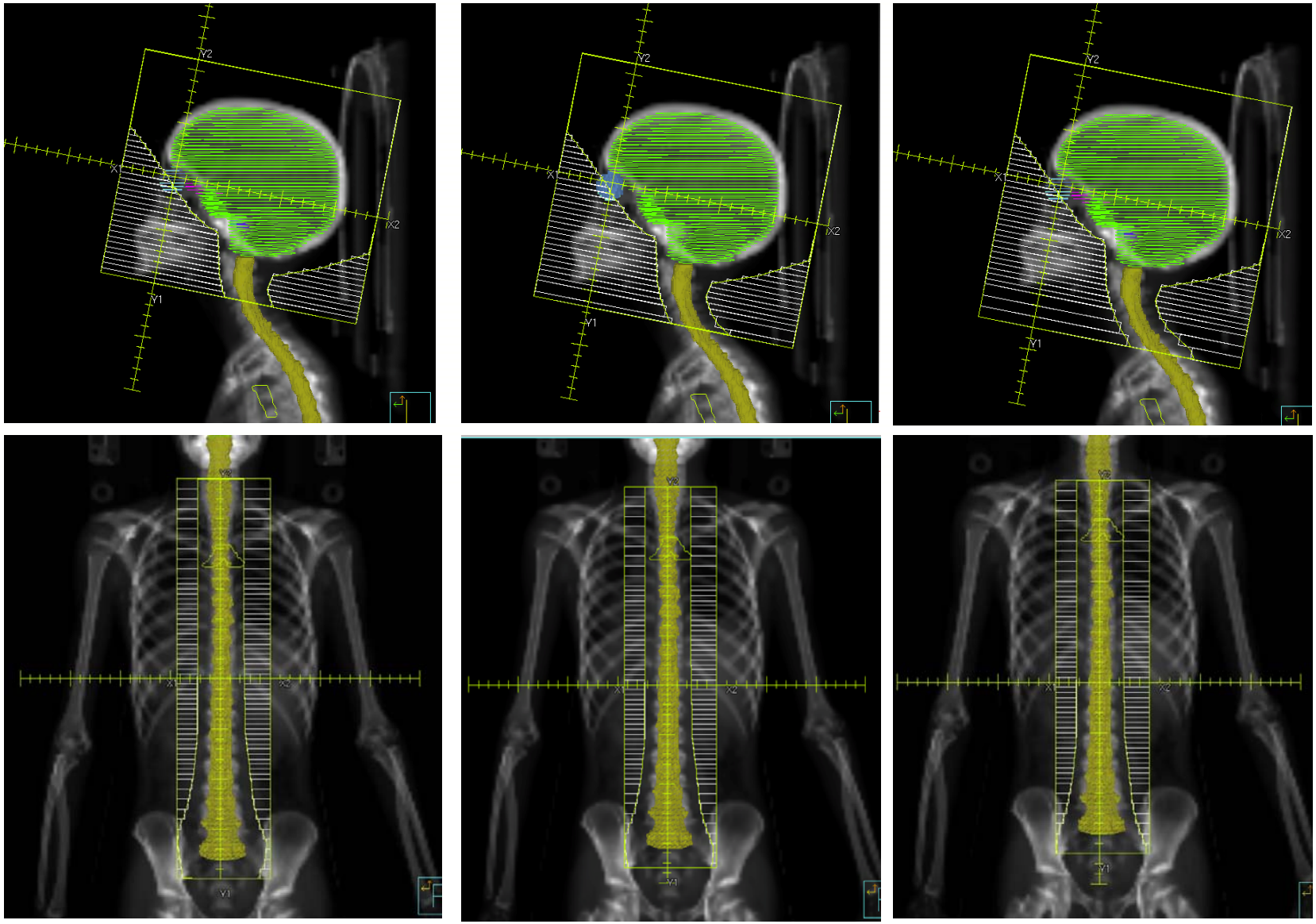
- Our patient was treated CSI to 23.4 Gy in the supine position



The “gap and feather” technique

- Rather than rotating the couch to match divergence of cranial beam, a gap of 0.5 cm is placed between the brain and spine field each day (collimator is still rotated).
- Feathering “spreads out” the cold spot at the gap between the brain and spine fields, as well as any cold spots in the cord due to skin gap when more than one spine field is required.
- Feathering is accomplished with the use of asymmetric jaws.
  - For cranial fields: open caudal border of cranial field by 1cm each day, cycle every 3 days.
  - For spine fields: shift isocenter(s) caudally by 1cm for each day; adjust blocks for each day accordingly.

Day 1 Day 2 Day 3



The Case: Tumor Bed Boost

After CSI to 23.4 Gy, patient received limited target boost to tumor bed with IMRT photons to a total dose of 54 Gy

- GTV:
  - tumor bed + gross residual disease, including T1 signal abnormality with and without contrast
  - Do not include surgical defects visible on post-op MRI that did not contain disease on pre-op MRI
- CTV:
  - GTV + 1 – 1.5 cm
  - excluding bone, tentorium, and entirety of brainstem (however, brain stem immediately adjacent to tumor bed should be included as this is an area of potential microscropic disease)
- PTV:
  - CTV + 3 – 5 mm

Standard Risk: Tumor Bed vs. Posterior Fossa Boost

- Current COG protocol (ACNS 0331) is comparing posterior fossa boost vs. tumor bed boost in standard risk patients
- However, there is evidence available to support limiting the boost volume to the tumor bed
  - Failure rates within posterior fossa after tumor bed boost are comparable to historical experience with treating entire posterior fossa
    - Wolden et al., JCO, 2003 (PMID: 12915597)
    - Merchant et al., IJROBP, 2008 (PMID: 17892918)

Posterior fossa boost

- CTV = entire posterior fossa, including brainstem
- PTV = CTV + 3-5 mm (exclude pituitary unless involved)
- Bony Landmarks
  - Superior: 1 cm above the midpoint of a line drawn between the foramen magnum and the vertex
  - Anterior: posterior clinoids and anterior C1 (the pituitary should be blocked unless involved)
  - Inferior: C1-C2 junction
  - Posterior: internal occipital protuberance

RT late effects

- Decreased IQ
- Decreased growth
- Ototoxicity
- Hypopituitarism
- Secondary malignancy

Factors for decline in IQ after CSI

- Age < 7 yo (most imporant)
- Higher dose (36 Gy vs. 23.4 Gy)
- Higher IQ at baseline
- Female gender

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