MAYO CLINIC

PRECISION IN PROXIMITY

A MAYO CLINIC APPROACH TO CHORDOMA TREATMENTS UTILIZING PROTON THERAPY

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GLOSSARY

PRESENTATION TERMS

- **ARIA:** Varian Record and Verify System
- **AYA:** Adolescent and Young Adult
- **CToR (CT on Rails):** CT imaging machine in treatment room
- **RS or ERS (Range Shifter or Extended Range Shifter):** Beam modifying devices, shifts range of beam
- **LET (Linear Energy Transfer):** The energy deposited by an ionizing particle per unit of path length through the medium.
- **MC (Monte Carlo):** Dose calculation model simulating particle-by-particle interactions in patient
- **MeV:** Megaelectron Volt
- **MFO:** Multi-Field Optimization
- **SFO:** Single Field Optimization
- **OTV (Optimization Target Volume):** Structure created to aid in target optimization
- **PSQA:** Patient-Specific Quality Assurance
- **STV (Scanning Target Volume):** Created per field, indicates area for proton spot map
- **SOP:** Standard Operating Procedure
- **VAC (Vacuum):** Beam line without any beam modifiers (RS or ERS)

LEARNING OBJECTIVES

- Describe chordomas, including their histologic features, the standard of care, and the role of radiation therapy in management
- Explain an approach to treating chordoma patients using proton therapy near serial structures, including beam selection, optimization, and robustness
- Describe strategies to mitigate biological enhancement per the Mayo Clinic biological model
- Discuss delivery and monitoring methods to ensure optimal outcomes

CHORDOMAS

CHARACTERISTICS

- Chordoma is a rare type of bone cancer that starts in the bones of the spine or the skull.
- Chordomas are different from other bone tumors for reasons including where they grow, how they start and who they affect. Chordomas have a notochord origin.
- The notochord is an early developmental structure that helps form the spine before birth. About 1 in 1 million people, the leftover cells eventually become cancerous.
- Chordomas usually grow slowly.
- Chordomas can grow anywhere along the spine. But they often grow in two locations. The first is the clivus or skull base. The second is the sacrum. Chordomas also can grow in the mobile spine.
- Chordomas can happen at any age. But they most often affect adults ages 40 to 60.

CHORDOMAS

CLINICAL INTERVENTION

- Surgery is usually the main treatment. However, chordomas can be hard to remove fully. This is because they grow very close to the spinal cord, blood vessels, nerves and brain. If tumor-free margins can't be obtained, surgery is followed by high-dose radiation therapy.
- Proton therapy has quickly become the modality of choice to treat these tumors given high dose and steep fall off.
- Chordomas are locally aggressive, "sticky" tumors that are difficult to fully eradicate due to their tendency to wrap around critical structures like the brainstem, spinal cord, and major nerves.
- More than half of all chordoma tumors grow again after initial treatment. Chordoma is a high-recurrence tumor >50% recurrence rate overall. Local recurrence is the dominant pattern.
- Multiple recurrences over time are common Recurrence can occur years after treatment, requiring long-term surveillance.
- A Mayo Clinic study published in Neurosurgical Focus found that patients receiving proton-based therapy had a 40% likelihood of tumor recurrence, compared with an 88% chance of recurrence for patients who received standard photon radiation therapy.

CHORDOMAS

MAYO CLINIC APPROACH

- Diagnostic workup MRI of the involved site with contrast. CT for evaluation of bony involvement and surgical planning. We don’t typically get a biopsy as the imaging often points us in the correct direction (although if needed we will get a biopsy)
- Surgery is the cornerstone of treatment. This is especially important if the tumor is compressing the brainstem.
- Goal is gross total or maximal safe resection, recognizing that negative margins are often difficult because of proximity to critical neurovascular structures.
- For skull-base lesions, subtotal resection is common, while for sacral/mobile spine disease, en bloc (removing an entire targeted mass in one single piece, fully encased in its surrounding tissue or scar shell) resection may be attempted when anatomically feasible.
- Postoperative, high-resolution postoperative MRI is obtained to assess residual disease and define the radiation target.
- Chordomas generally require dose-escalated treatment, typically: ~70 Gy(RBE) after GTR ~78 Gy(RBE) to residual disease. At Mayo Clinic, proton therapy is considered the preferred modality to achieve the desired RBE.
- To date there is not a proven role for systemic therapy. We are hoping in the future we will have systemic therapy.

PROTONS AT MAYO CLINIC

EQUIPMENT

- Equipment
  - Hitachi
  - 4, ½ Gantries
  - 2 CToR
  - 2 Full Gantries
- Treatment Planning
  - MIM
  - Eclipse
  - ARIA
  - In-house 2nd check system, PSQA System

PROTONS AT MAYO CLINIC

PLANNING CHARACTERISTICS

- Beam Energies
  - 97 total (71-230 MeV; 4-32 cm depth)
- Variety of range shifting devices
- Single field optimization vs. Multi-field optimization
- Planning Targets: CTV+Robust Evaluation
- Monte Carlo Dose
  - 2nd check of dose with MC algorithm
  - Accuracy
- RBE
  - 1.1

Machine	Spot Size	Range (cm)	Field Size
VAC	4 mm	4-32 cm	30 x 40
ERS45	6 mm	0-27.5 cm	25 x 30
RS 25	6 mm	1.5-29.5 cm	30 x 40
RS 45	6 mm	0-27.5 cm	30 x 40

PROTONS AT MAYO CLINIC

PLANNING SOP

- We do not use PTVs. Instead, we use robust optimization on the CTV. We define robustness parameters per site standards and simulate shifts of isocenter in three dimensions as well as systematic differences in proton range.
- Our department has developed a GPU-accelerated, in-house Monte Carlo dose calculation platform
  - Monte Carlo dose algorithms simulate particle-by-particle interactions of each individual proton with the medium (patient).
  - Used as a second check of the dose calculated by the primary Eclipse dose optimization system.
  - When discrepancies between Eclipse and Monte Carlo dose are present, Monte Carlo is the more accurate representation of the “true” dose.
- Unlike MV x-rays, in which the RBE is nearly always 1, protons exhibit a marked increase in RBE toward the end of their range. This is due to the increased linear energy transfer (LET) of protons at the end of range.
  - Proton RBE is a function of many parameters, including LET, dose per fraction, and alpha/beta ratio.
  - All our dose calculation algorithms (Eclipse and Monte Carlo) already include a uniform RBE factor of 1.1.

PROTONS AT MAYO CLINIC

RBE MODELING

- How do we assess RBE?
  - We developed a surrogate RBE model.
- Mechanically, this is a simple LET-based adjustment applied to the physical dose. Biological Dose equals Physical Dose times a function of LET. Higher-LET regions get scaled up to reflect potentially higher biological effect, and notably the model is independent of alpha/beta and independent of fractionation.
- This is a very simple model. The reason we keep it simple is practical. More complex models require additional assumptions that are not realistic in the clinical setting. This one is intentionally simple so that it is fast, reproducible, and usable on every plan.
- What the model does capture is the expected trend: higher LET points to higher biological effect. We care about identifying risk locations, not exact values — and that is enough to flag end-of-range hotspots, brainstem and spinal cord risk, and pediatric sensitivity concerns.
- Clinically, the value is that physical dose can look completely acceptable while biologic hotspots still exist underneath. This makes those visible, enables small targeted plan changes, and adds a conservative safety layer to plan evaluation.

PATIENT 0

Male, Pediatric
Diagnosis: Chordoma
Resection: C-spine + Halo
Case Presentation

TECHNIQUE REFINEMENT

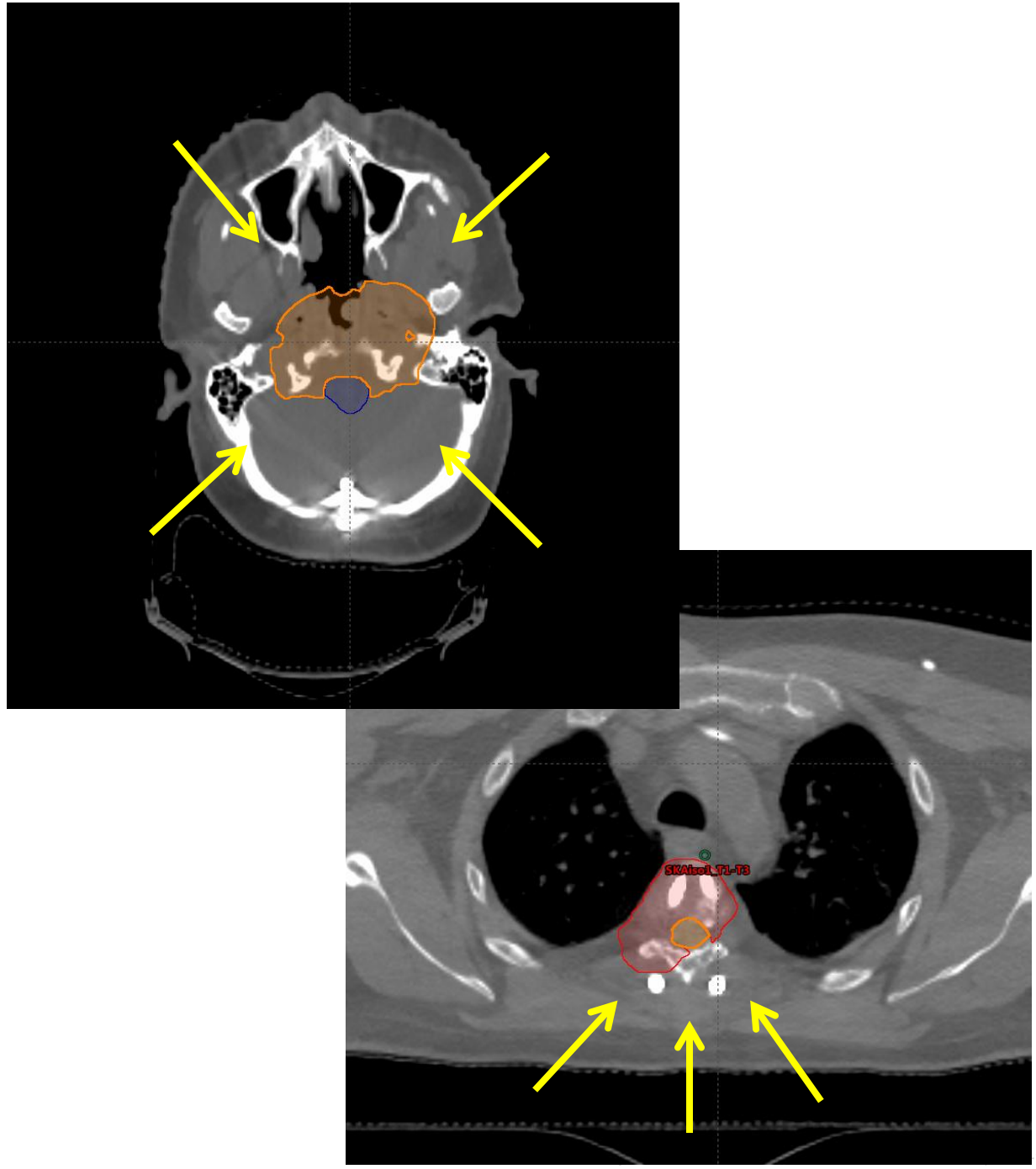
WHERE ARE WE NOW?

- Continued to refine plan characteristics such as:
  - Beam Arrangement
  - Scanning Target Volume
  - Optimization strategy
  - Robustness criteria
- Patient Examples
  - Chordoma (Clivus, C-Spine, T-Spine)
  - Metastatic Retreatment areas
- Guidelines and Caveats

PLAN CHARACTERISTICS

BEAM ARRANGEMENT

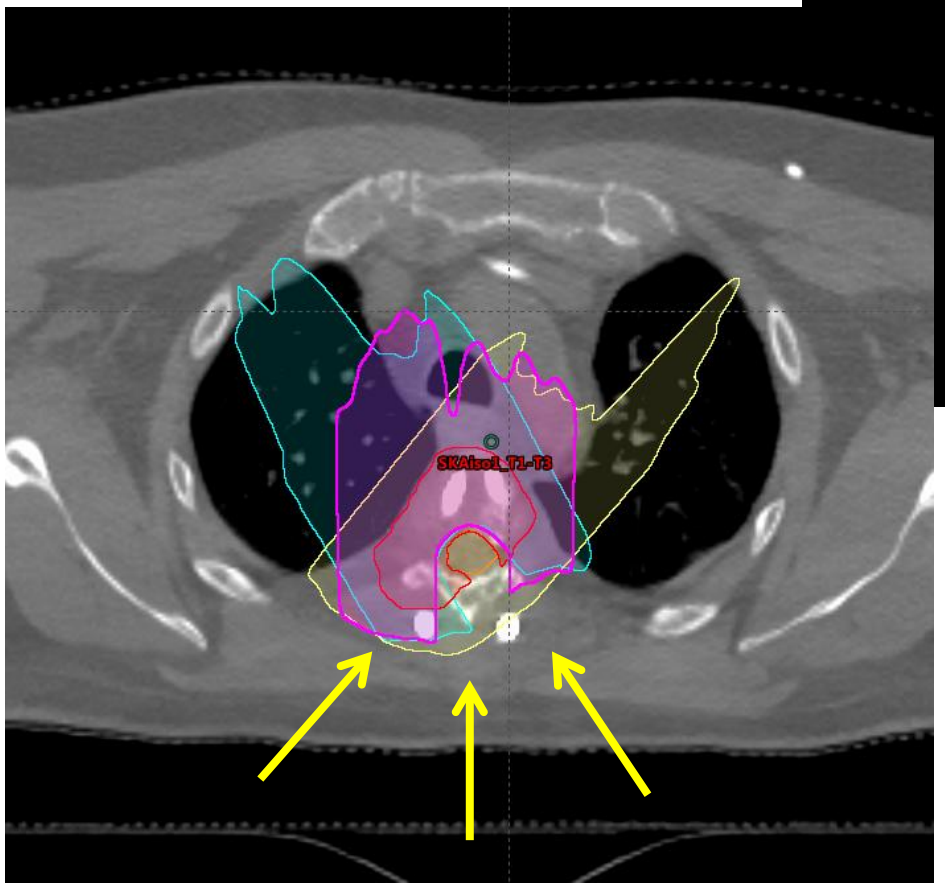
- “X” Technique or modified “X” work
  - 4 fields allow optimal coverage of CTV and biologic mitigation
  - 3 fields can be used if volume does not wrap around the OAR
  - MFO

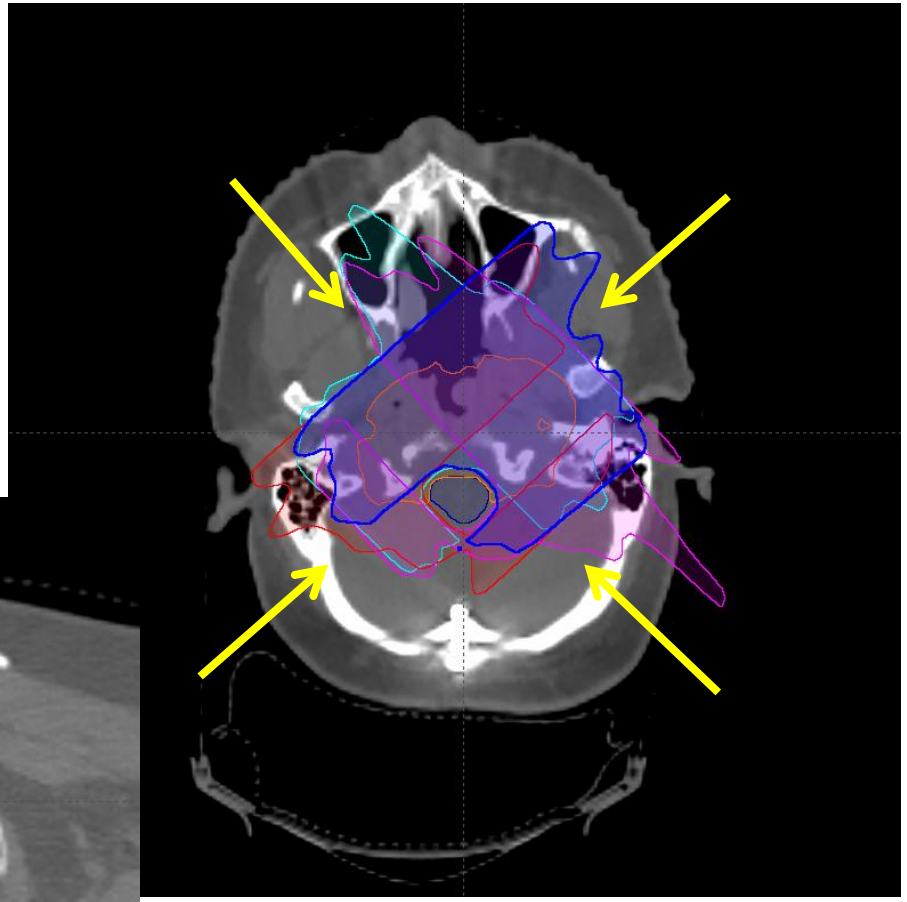


PLAN CHARACTERISTICS

SCANNING TARGET VOLUME

- New technique for cropping STV
- New Approach
  - Crop only the proximal beam path of the STV
  - Allow STV to treat all other areas of the target
  - Some corners of CTV are cut out of the cropped STV and are covered by none of the STVs. This is acceptable because the penumbra and combination of doses from the other fields fills this in.
- Caveat
  - At least 2 beams need to be able to treat each area of CTV
  - Depending on the target and arrangement, you may not crop proximal range of ALL beams

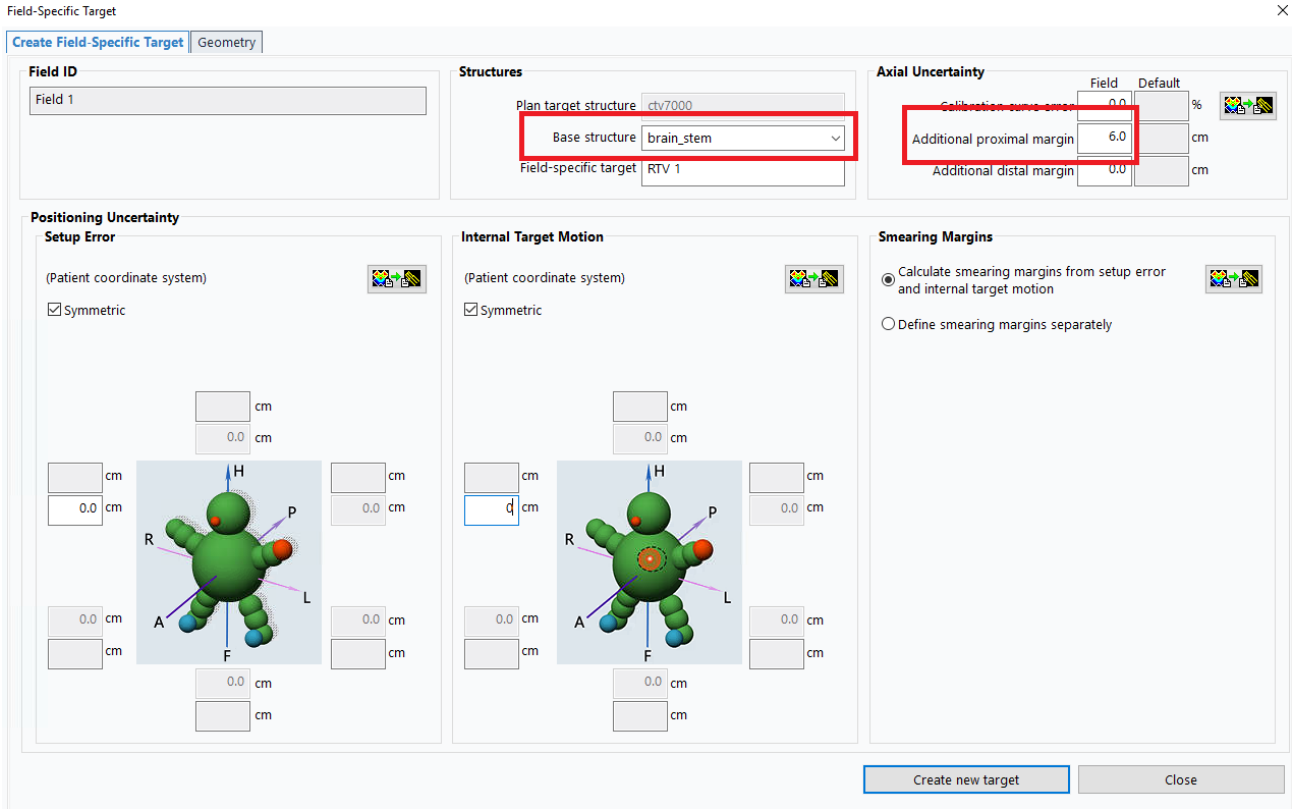




PLAN CHARACTERISTICS

SCANNING TARGET VOLUME-ECLIPSE TIPS

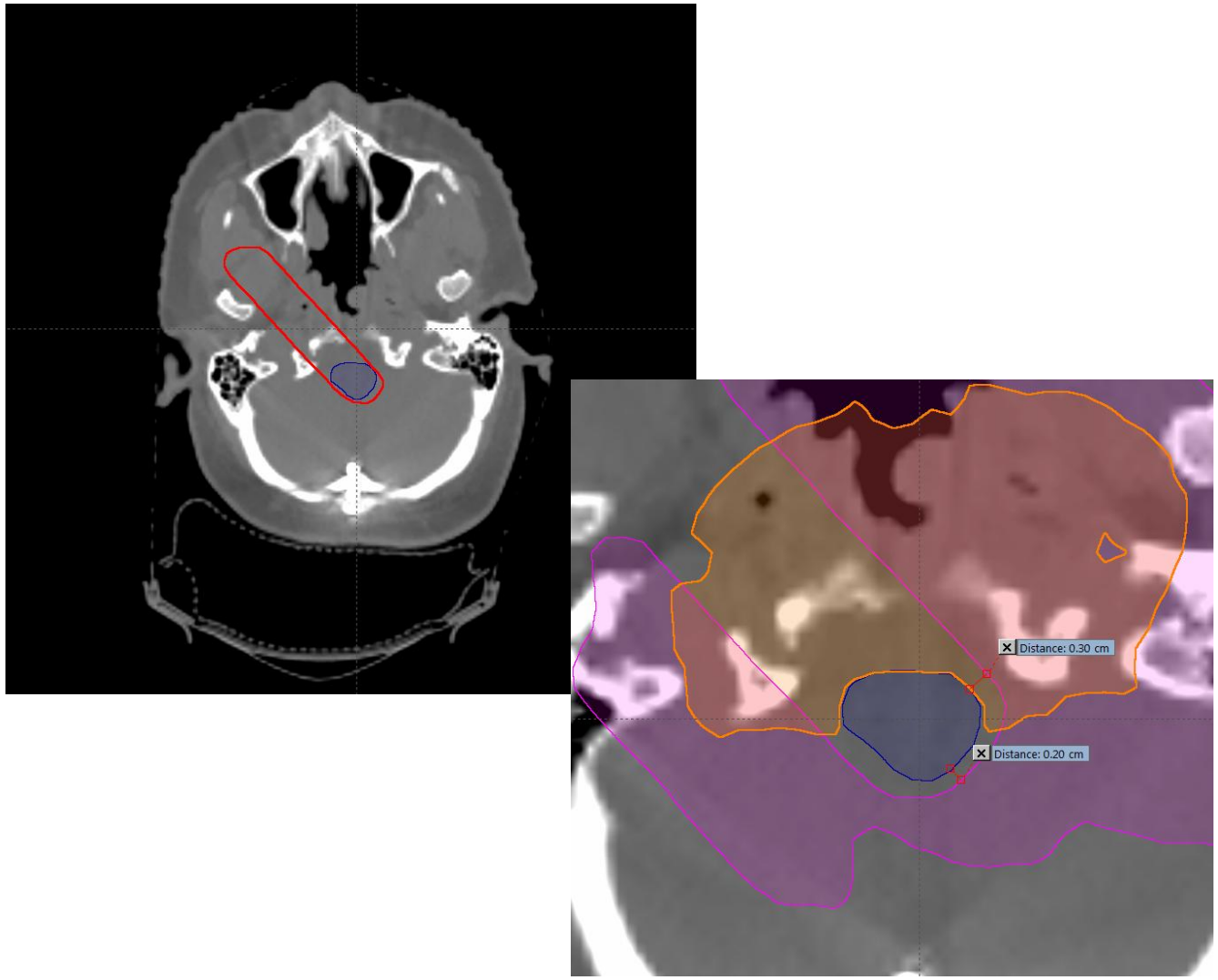
- Create Proximal Avoidance
  - Base Structure = OAR
  - ≥6cm proximal margin (must extend through end of STV)
  - Set all other margins to 0
- Create STV as normal
  - Follow general approach (positioning uncertainty, calibration curve uncertainty)



PLAN CHARACTERISTICS

SCANNING TARGET VOLUME-ECLIPSE TIPS

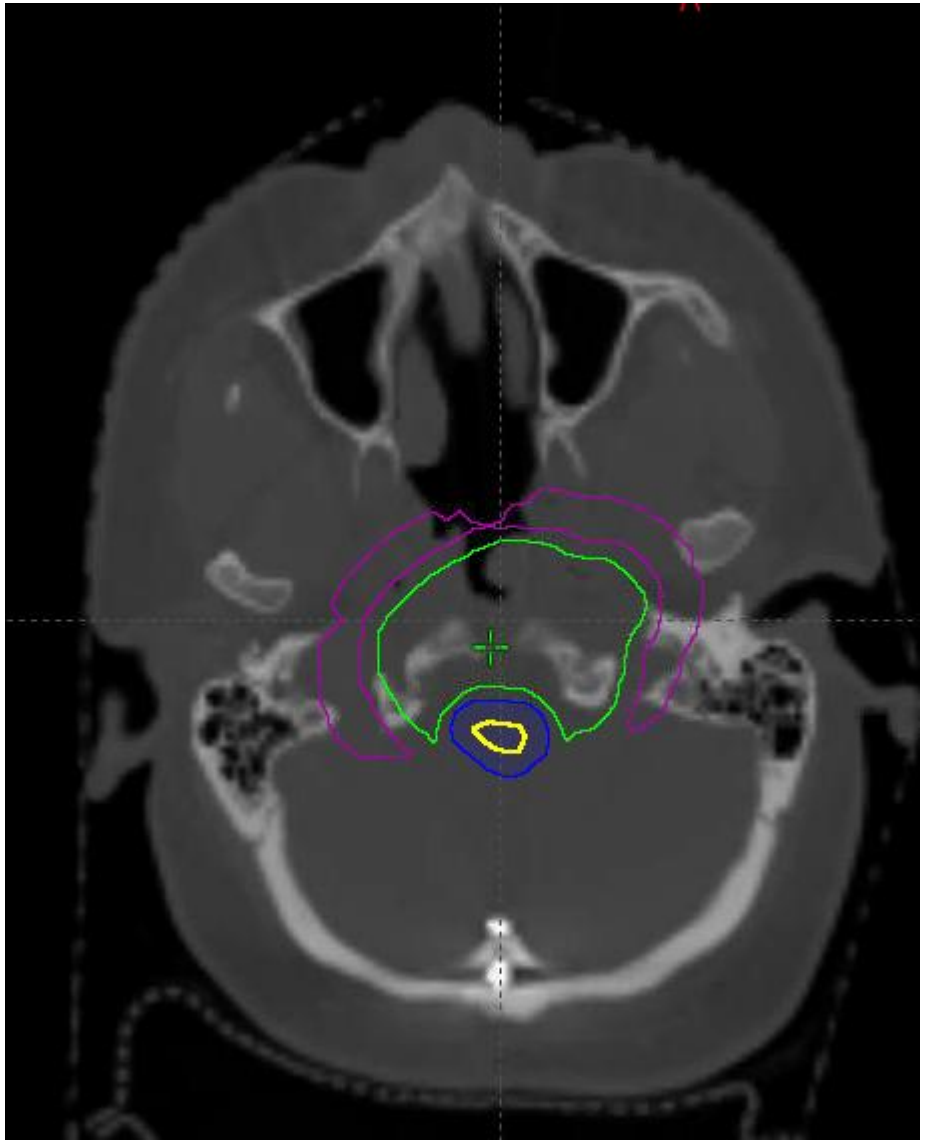
- Proximal Avoidance
  - Expand this proximal avoidance by 2mm circumferentially (1/2 spot size)
  - Crop from associated field STV
  - Do this for all beams
- General rule: CTVs are covered by at least 2 STVs



PLAN CHARACTERISTICS

OPTIMIZATION STRATEGY

- Create OTV (optimization target volume)
  - 2-3 mm expansion on each CTV
  - Cropping each CTV from each other as separate optimization structures
  - Crop out of brainstem or cord
    - If Rx exceeds constraints, crop +2mm to avoid surface dose
  - Create a brainstem/cord core
    - Crop 3-4 mm from the rind



PLAN CHARACTERISTICS

OPTIMIZATION STRATEGY

- Targets
  - Set lower objects 100cGy above target dose
  - Do not robustly optimize on high dose CTVs, ok on low dose CTVs
- Wrapped OAR
  - Set brainstem/cord to the max dose objective, set at higher priority than targets
  - Robustly optimize on brainstem/cord core
- Other OAR
  - Followed typical optimization strategy
  - Set monitoring objectives in optimization
- Biological enhancement
  - Beam angles/STVs should largely mitigate “pools” of dose
- Refine plan infinitely with hot/cold structures to address heterogeneity/areas of enhancement

PLAN CHARACTERISTICS

ROBUSTNESS

- 3mm, 3% Evaluation
- Target Robustness
  - OTVs
  - Robust optimization on low dose targets
  - Evaluate
- OAR Robustness
  - Wrapped OAR core priority

CLIVUS CHORDOMA

Female, AYA
Diagnosis: Chordoma
Resection: Clivus
Case Presentation

T-SPINE RETREAT

Male, Older Adult
Diagnosis: Unknown (Metastatic to Spine)
Resection: T-spine
Case Presentation

GUIDELINES

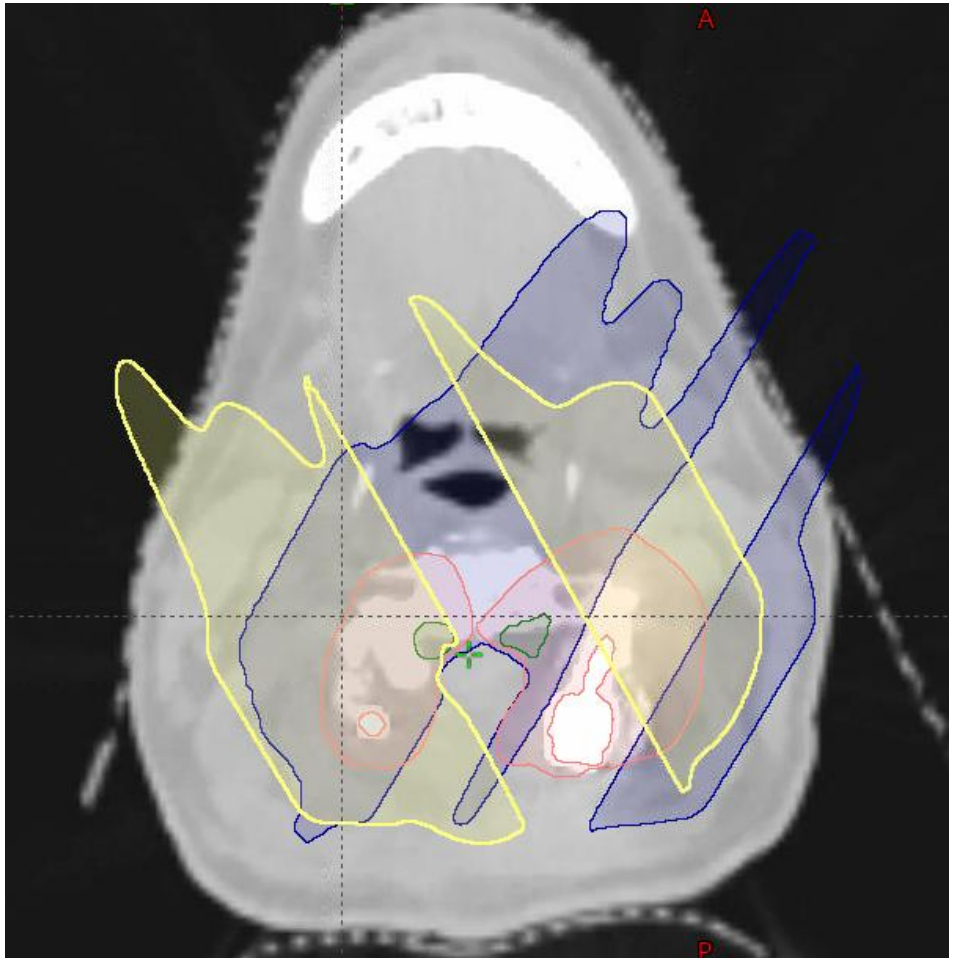
PATIENT-SPECIFIC CONSIDERATIONS

- Patient Selection
  - Dose escalation (high LET in target)
  - No enhancement in brainstem/OAR
  - Physical coverage is a priority
  - Ideal for cases with daily dose ≥180cGy
- STV modifications
  - May need to crop STV more from brainstem/OAR to avoid hot spots piling up on the edge depending on spot map

CAVEATS

PATIENT-SPECIFIC CONSIDERATIONS

- Hardware
  - Common in this patient population
  - Lengthy discussion with physics and physician
    - Develop standard of practice
- Biological Enhancement
  - In general, biologic enhancement is decreased with this technique
  - Some enhancement can still appear
- MONITOR, MONITOR, MONITOR!



SUMMARY

KEY TAKEAWAYS

- Chordomas are rare, locally aggressive notochord-origin tumors with >50% recurrence; surgery followed by high-dose radiation is the standard of care.
- Proton therapy is the preferred modality at Mayo Clinic, with ~40% recurrence versus ~88% reported for photon therapy.
- Planning uses robust CTV optimization (no PTVs), Monte Carlo second-check dose, and a uniform RBE of 1.1.
- A surrogate LET-based model flags end-of-range biologic hotspots that physical dose alone can hide.
- "X" or modified-X 3–4 field MFO beam arrangements cover the target while sparing wrapped organs at risk.
- Per-beam STVs are proximally cropped (≥6 cm avoidance + 2 mm / ½ spot size) to keep end-of-range dose off the brainstem and cord, with ≥2-beam CTV coverage maintained.
- OTV-based optimization with brainstem/cord core constraints prioritized above target objectives; robustness evaluated at 3 mm / 3%.
- Best suited to dose-escalated plans (≥180 cGy/fx); hardware and recurrent disease demand multidisciplinary discussion and continuous monitoring of biologic enhancement.

