Rhabdomyosarcoma (RMS)

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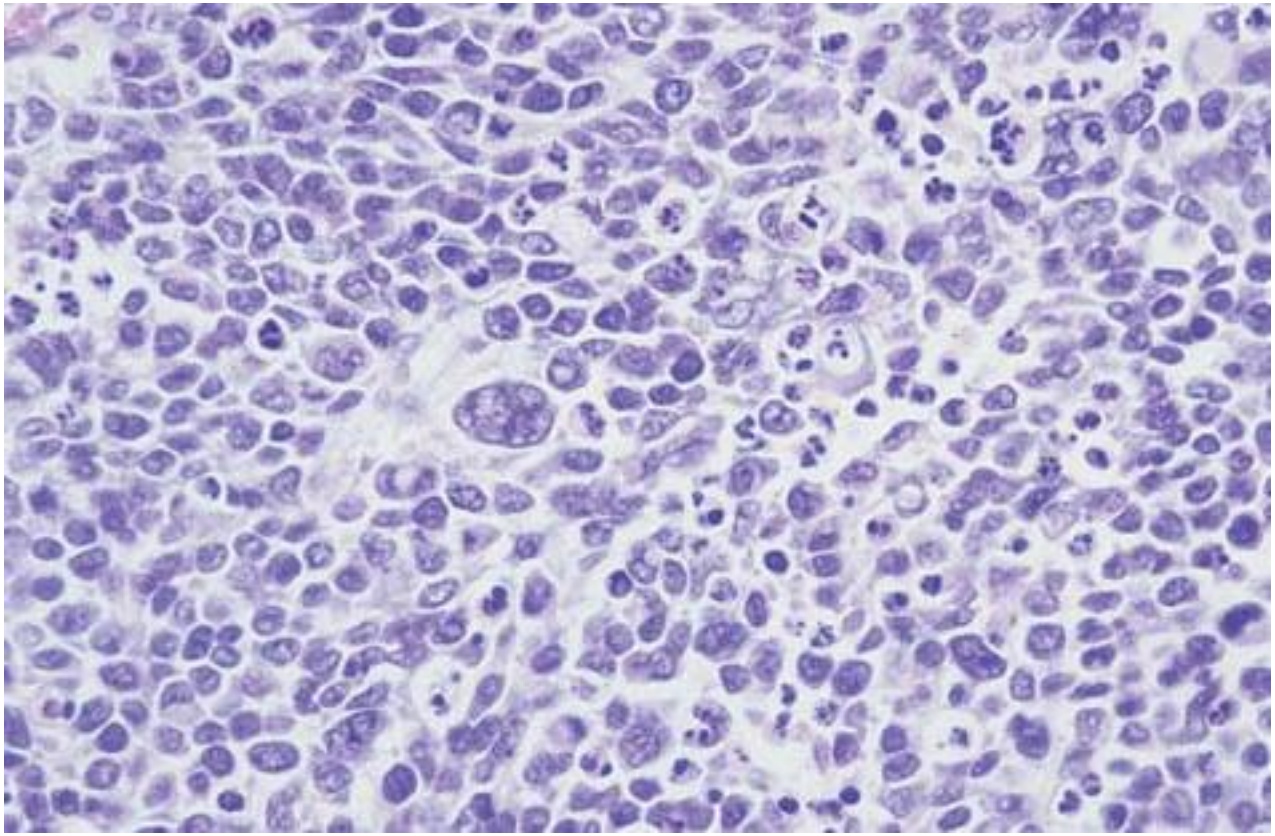
Epidemiology

- RMS is the **most common pediatric soft tissue sarcoma**
  - 40% of all pediatric soft tissue sarcomas
  - 350 cases/year in the USA

- Slight male predominance
- Peak age is between 2 – 5 years of age

Pathology: What is the differential?



Pathology

- This is a **small round blue cell tumor**
  - **MR LEMONS (**mnemonic**)**: Melanoma, rhabdomyosarcoma, lymphoma, Ewing's sarcoma, medulloblastoma, olfactory (esthesioneuroblastomas), neuroblastoma, small cell carcinoma

- Generally, RMS is divided into 3 histologic subtypes (arranged from the most favorable to the least favorable prognosis)
  - **Embryonal (75% of RMS cases)**
    - Includes botryoid and spindle variants
  - **Alveolar (25% of RMS cases)**
  - **Pleomorphic / Undifferentiated**

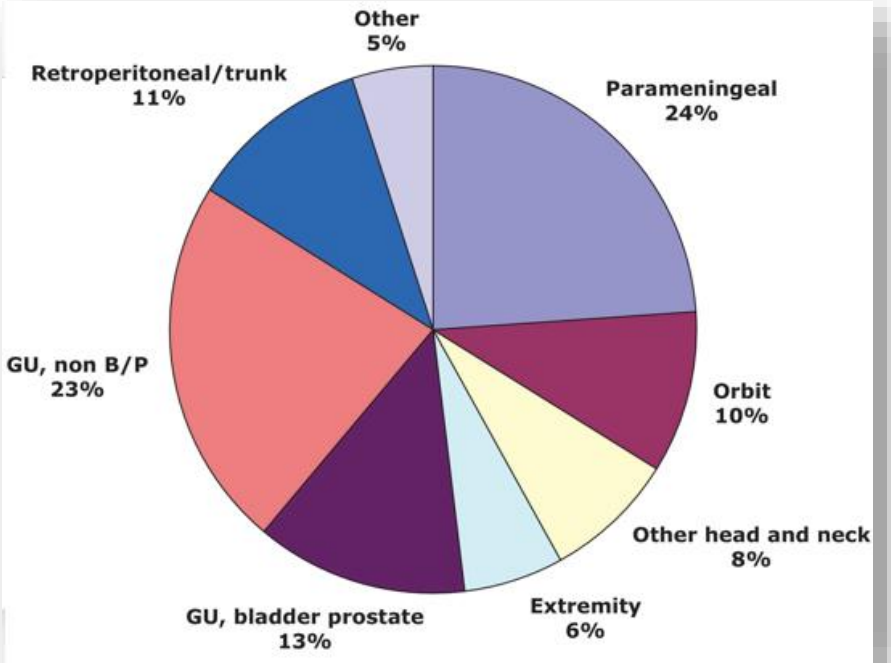
Genetics

- **Embryonal**
  - Loss of heterozygosity of **11p15.5**

- **Alveolar**
  - Translocations of:
    - **t(2:13)**
      - Chromosome 2: PAX3
      - Chromosome 13: FOX01 (Forkhead box protein O1, also called FKHR or FORKHEAD)
    - **t(1:13)**
      - Chromosome 1: PAX7
      - Chromosome 13: FOX01 (Forkhead box protein O1, also called FKHR or FORKHEAD)
  - These translocations result in **PAX-FOXO1 Fusion Genes** = **Forkhead fusion patients have a worse prognosis**

Anatomic Sites

- RMS can occur almost anywhere in the body
- The **head and neck region** is the most common site of RMS
  - This includes para-meningeal head and neck, non para-meningeal head and neck, orbit
- The GU tract is second most common



Clinical Presentation and Workup

- RMS usually presents as an **asymptomatic mass**, but this is site dependent

- Universal:
  - H&P with CBC, CMP, LFTs, UA
  - **CT/MRI of the primary site**
  - **PET CT** (or CT CAP and bone scan)

  - **Biopsy the primary site**
  - **Bone marrow biopsy**

- Site Dependent
  - Lumbar puncture if parameningeal tumor (if CSF positive, obtain MR spine)
  - Sentinel lymph node biopsy for extremity cases
  - Ipsilateral retroperitoneal lymph node dissection for paratesticular sites in boys age greater than 10

Risk Stratification

- In RMS, there is **pre-operative staging** and **post-operative grouping**
  - Combining these will lead to a **risk group** (**low, intermediate, high**) which will determine treatment

- **Staging**
  - TNM not often used
  - Depends on site, size, and nodal involvement
    - There are favorable sites and unfavorable sites

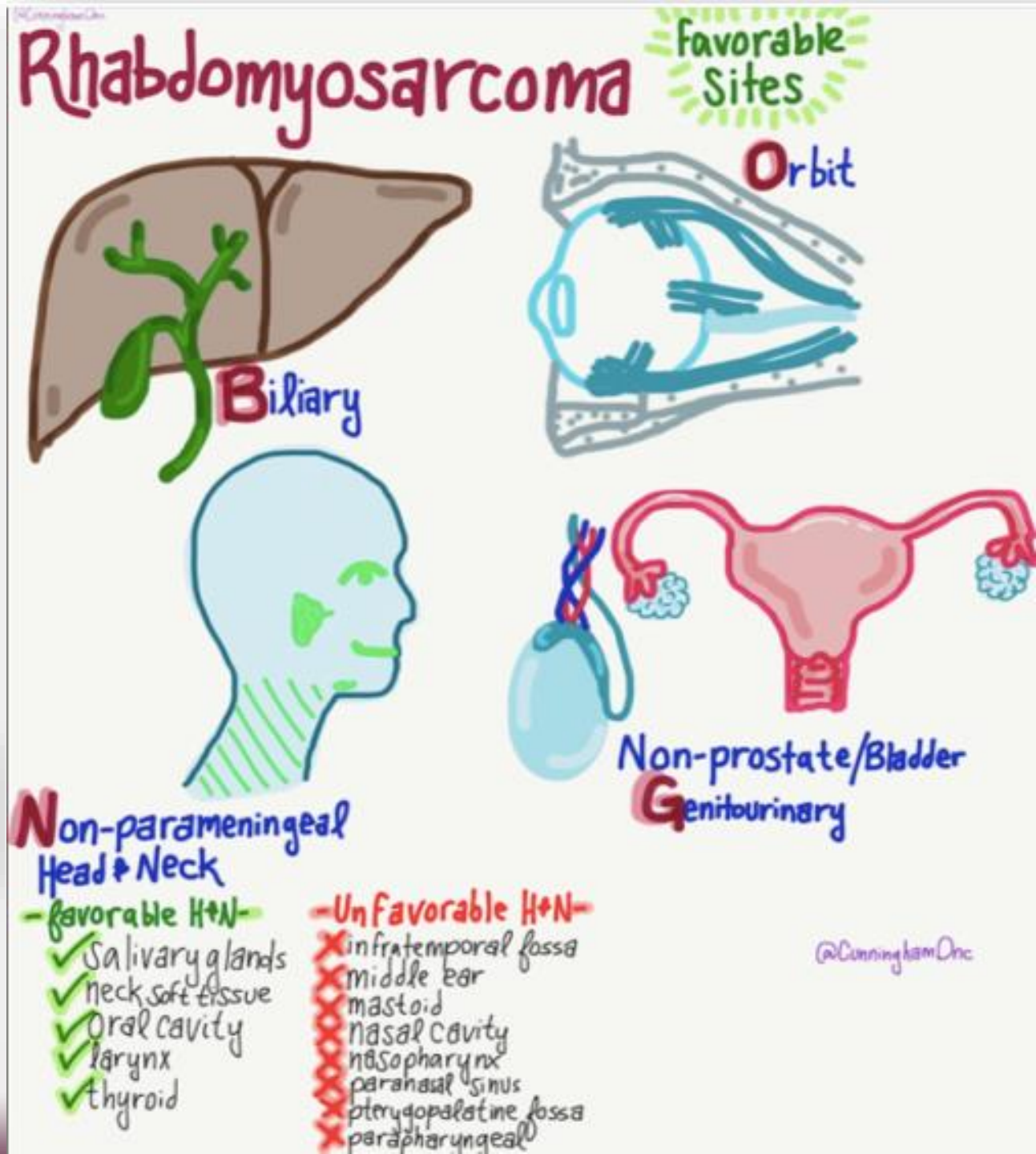
- **Grouping**
  - Depends on possible extent of surgical resection; *the group is assigned at the time of initial diagnosis*

Staging

TABLE 56.5: IRSG Staging System					
Stage	**Sites**	**Size**	**N**	**M**	**3-yr Failure-Free Survival[19]**
I: Favorable site	Orbit Head and Neck (non-PM) GU (non-bladder/prostate) Biliary tract	Any size	Any N	M0	86%
II: Unfavorable site, N0 and ≤5 cm	Bladder/Prostate Extremity Parameningeal Other (including: RP, perineal, perianal, intrathoracic, GI) Liver (nonbiliary)	≤5 cm	N0 or Nx	M0	80%
III: Unfavorable site, >5 cm or node-positive	Same as Stage II	≤5 cm	N1	M0	68%
		>5 cm	Any N	M0	
IV: Metastatic	All	Any size	Any N	M1	25%

T1, Confined to anatomic site of origin; T2, Extension and/or fixation to surrounding tissue; a, ≤5 cm in diameter; b, >5 cm in diameter; N0, Not clinically involved; N1, Clinically involved; Nx, Clinical status unknown; M0, No distant metastases; M1, Distant metastases.

Staging: Remember the favorable sites by the mnemonic **BONG**



Danielle A. Cunningham, MD

Grouping

- Remember, depends **on possible extent** of surgical resection; *the group is assigned at the time of* **initial diagnosis**
  - *If a patient is deemed unresectable, has a great response to chemotherapy, and then has a gross total resection…this patient remains at Group 3*

TABLE 56.6: IRSG Grouping Classification	
Group I	Localized disease, completely resected A: Confined to muscle or organ of origin B: Infiltration outside the muscle or organ of origin
Group II	*Gross total resection with:* A: Microscopic residual disease B: Regional LN spread, completely resected C: Regional LN resected with microscopic residual
Group III	*Incomplete resection with gross residual disease* A: After biopsy only B: After major resection (>50%)
Group IV	Distant metastasis at onset

COG Risk Stratification

- Stage 4, Group 4 is High Risk
  - Unless you are fusion negative and less than 10 years old
- Alveolar is Intermediate Risk
- For Embryonal, to fall into low risk….you must fusion negative AND:
  - All BONG
  - Not BONG, Not Gross Residual

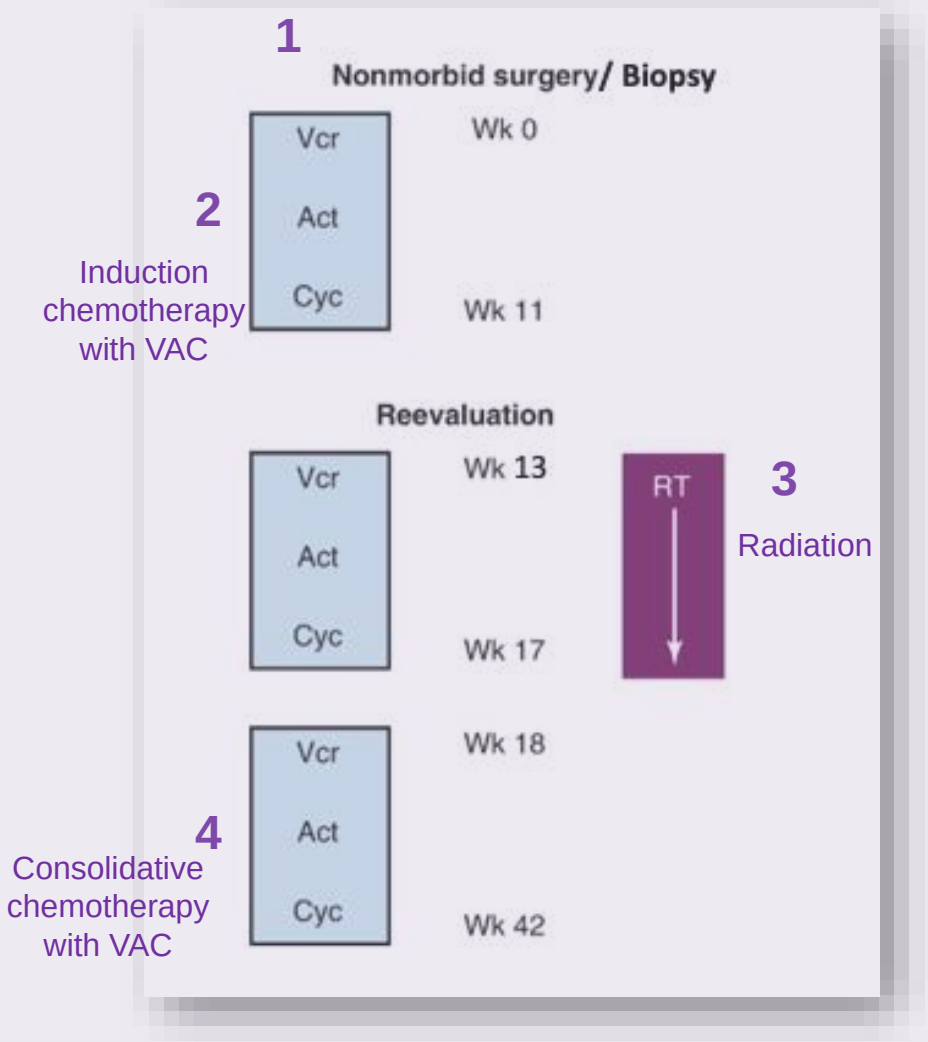
Table 60.7: Risk Stratification Based on Pre-Op Staging + Post-Op Grouping

Risk Group	Involved Groups
Low (~35%)	Favorable histology (embryonal) *and* PAX/FOX01 fusion negative *and* – Favorable site (stage I): groups I–III – Unfavorable site (stages II–III): groups I–II
Intermediate (~50%)	– Favorable histology (embryonal), PAX/FOX01 fusion negative, unfavorable site (stages II–III): groups III – Favorable histology (embryonal), PAX/FOX01 fusion positive, any site (stages I–III): groups I to III – Unfavorable histology (alveolar), PAX/FOX01 fusion positive or negative, any site (stages I–III): groups I–III – Stage IV, group IV, PAX/FOX01 fusion negative, <10 years old
High (~15%)	– Stage IV, group IV, PAX/FOX01 fusion negative, ≥10 years old – Stage IV, group IV, PAX/FOX01 fusion positive, any age

Source: Adapted from American Cancer Society. Rhabdomyosarcoma. 2020. https://www.cancer.org/cancer/rhabdomyosarcoma.html

Introduction to Treatment

This will vary based on risk group and protocol used



Introduction to Treatment

1. Non-Morbid **Surgery** (**if this is not possible, a simple incisional biopsy will do; this tumor is radiosensitive so do not handicap the patient!**)
   - If possible: complete excision with 5 mm margins
   - Extremity RMS must have at least sentinel lymph node biopsy
   - Paratesticular RMS in boys > 10 years should have a retroperitoneal lymph node dissection

Delayed Primary Excision (DPE)

- The rational for DPE is:
  - For tumors that are unresectable at diagnosis, **the chemotherapy will cause tumor shrinkage**: 1) making it **resectable** 2) with the resection, **allowing a lower dose of radiation**
  - This was explored on **COG D9803**
    - In an attempt to potentially reduce the dose of RT given to patients with intermediate-risk RMS whose tumors were unresectable at diagnosis, select patients were treated with induction chemotherapy followed by DPE prior to RT.
    - Those who achieved gross total resection at the time of DPE were then eligible for reduced dose RT
      - 36 Gy if the tumor was completely resected
      - 41.4 Gy for microscopic residual
      - 50.4 Gy for those without DPE or with DPE in which gross residual disease remained postoperatively.
    - Local control following DPE and reduced dose RT was similar to historic results after higher doses of definitive RT.

COG D9803

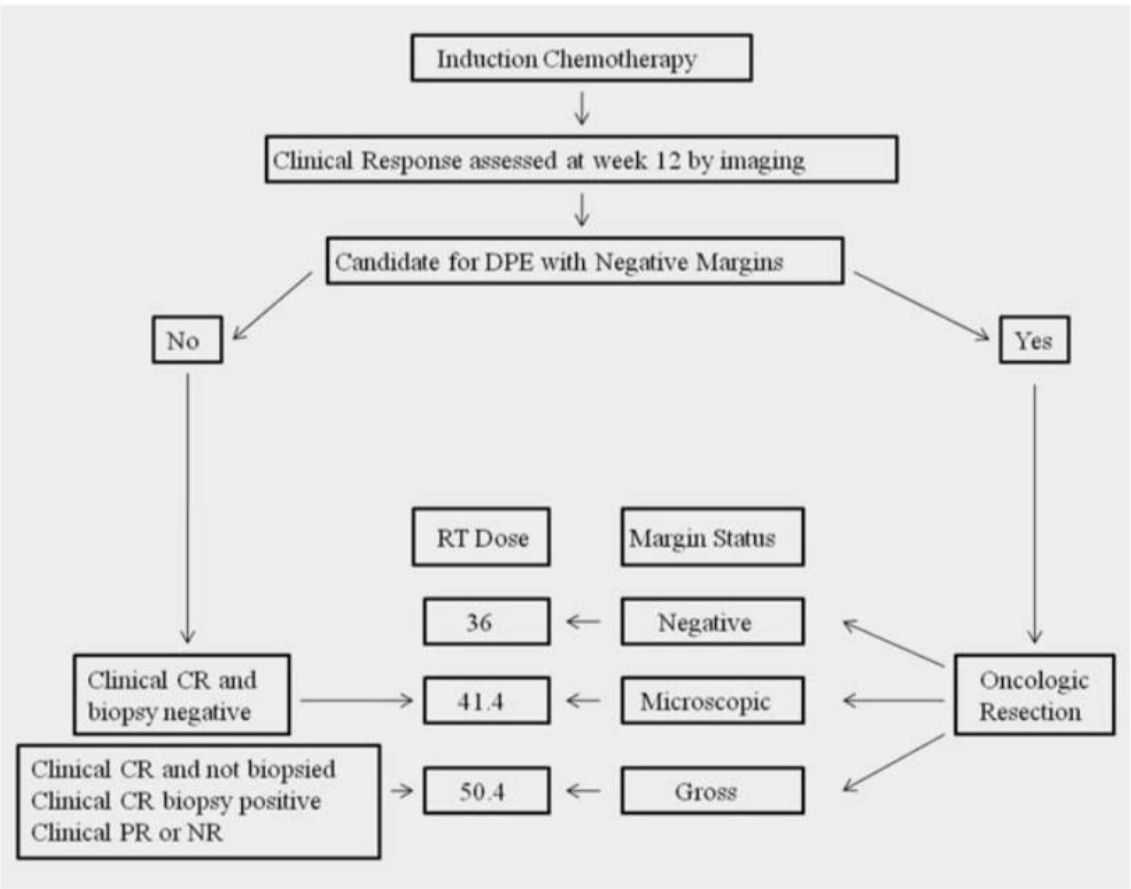


Figure 1. Local control algorithm for COG D9803. Delayed primary excision (DPE), complete response (CR), partial response (PR) and radiation therapy (RT).

2) Chemotherapy

- Chemotherapy
  - **VAC** based; this will vary on protocol
    - Vincristine
    - Actinomycin-D
    - Cyclophosphamide

3) Radiation - Doses

Clinical Group	Dose
I, Embryonal or FOX01 fusion negative	0 Gy
I, FOX01 fusion positive	36 Gy
II	36 Gy
III, < 5 cm	50.4 Gy
III, > 5 cm	59.4 Gy

Notes:

***Omission of radiation is only allowed for node negative patients**

***A complete response (CR) will receive 36 Gy**

***A cone-down is allowed if the dose exceeds 36 Gy; pre-chemotherapy volume will receive 36 Gy, post-chemotherapy volume will receive the higher dose**

***A CR in the orbit will receive 45 Gy; otherwise 50.4 Gy**

3) Radiation – Doses post DPE

	Total Dose - Gy		post DPE - Dose Gy		
Clinical Group	if no CR at Week 9**	if CR at Week 9**	if GTR post DPE with negative margin	if GTR post DPE with microscopic margin	if post DPE, gross residual disease
I, FOXO1 +	36	36	N/A	N/A	N/A
II	36	36	N/A	N/A	N/A
III, ≤5cm*	50.4	36	36	41.4	50.4
III, >5cm*	59.4	36	36	41.4	59.4

CR response doses

A positive margin will require slight dose escalation

Gross disease doses

3) Radiation - Target Volumes

- Radiation Target Volumes
  - GTV1
    - **The volume is defined as disease <u>prior</u> to any surgical debulking or chemotherapy***
      - Post-operative radiation: tumor bed and any bone or soft tissue that was involved with the tumor prior to surgical resection
      - Definitive Radiation: tumor prior to any chemotherapy
  - CTV1
    - GTV + 1 cm
    - When lymph nodes are clinically or pathologically involved with tumor, the entire lymph node drainage chain should be included in the CTV.
  - PTV1
    - Minimum of 0.3 cm

3) Radiation - Target Volumes

- Radiation Target Volumes 2: these volumes are utilized when the prescription dose is higher than 36 Gy
  - GTV2
    - **The volume is defined as disease <u>after</u> chemotherapy (this is the cone-down)**
  - CTV2
    - GTV + 1 cm
  - PTV2
    - Minimum of 0.3 cm depending on immobilization

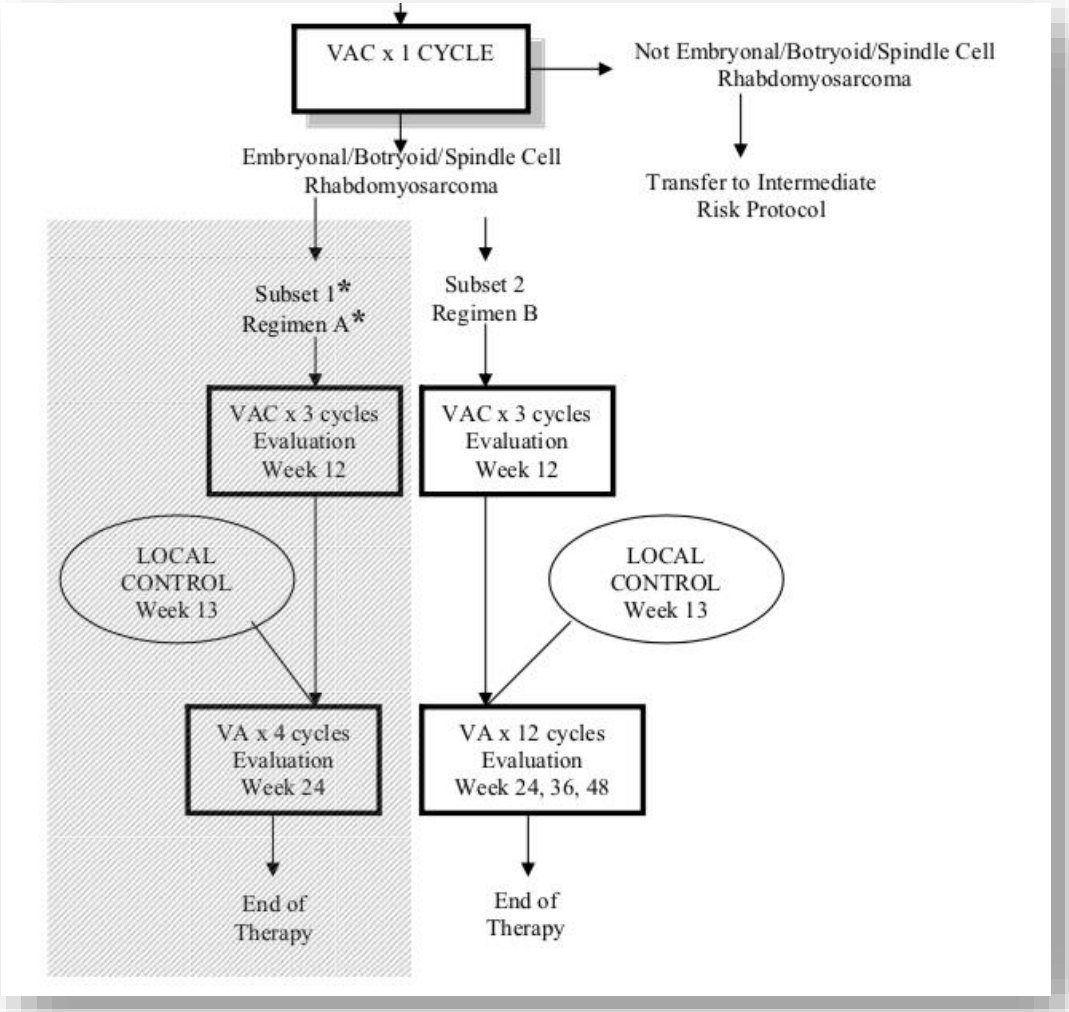
3) Radiation Timing

- Radiation Timing
  - Low and Intermediate Risk = Week 13
  - High Risk = Week 20

  - Patients with cord compression, visual loss, intracranial extension, cranial neuropathies = Day 0 per ARST 0431
    - However, in many cases emergent chemotherapy will relieve symptoms as quickly as radiation and delaying radiation should be assessed on a case by case basis

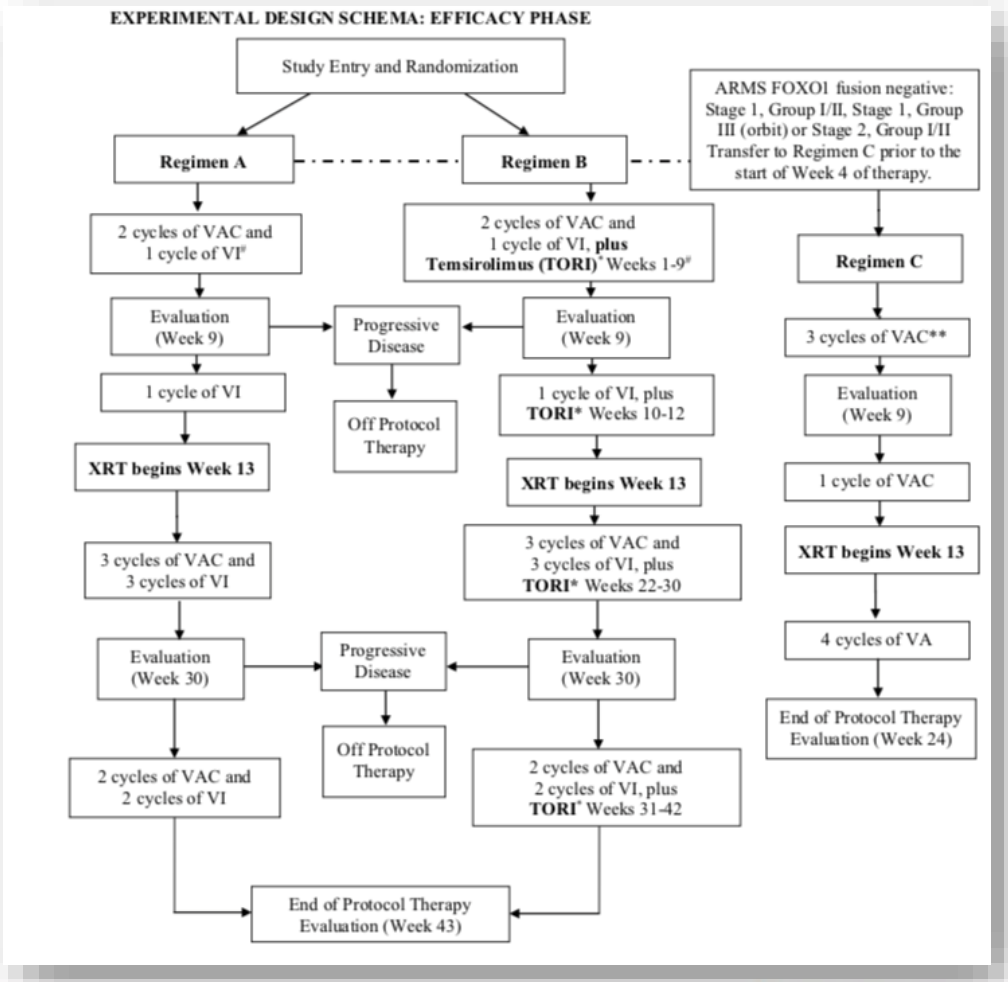
ARST 0331 – Low Risk Protocol

1. Biopsy/Surgery
2. VAC chemotherapy
3. **XRT** starts at week **13**
4. VA chemotherapy



ARST 1431 – Intermediate Risk Protocol

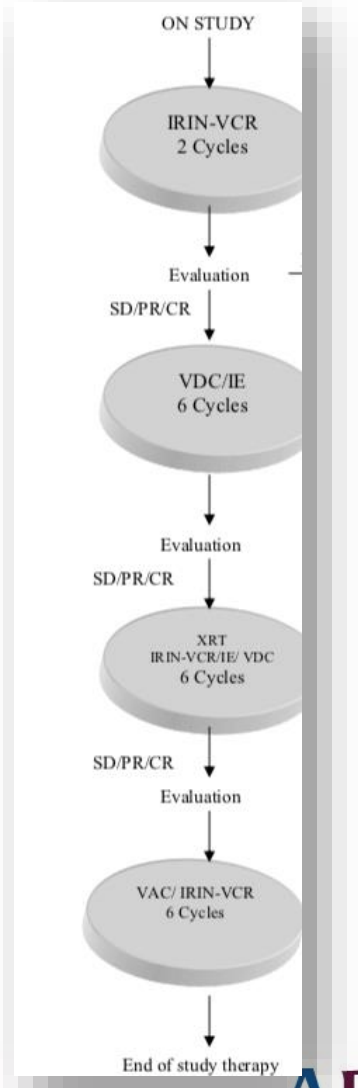
1. Biopsy/Surgery
2. VAC chemotherapy (this study also this study investigates use of temsirolimus (an mTOR inhibitor))
3. **XRT** starts at week **13** (allowed for DPE)
4. Consolidation chemotherapy



ARST 0431– High Risk Protocol

- **Local control is achieved by radiation;** resection is rarely indicated

- Week 1-6
  - Vincristine/irinotecan
- Week 7 to 19
  - Vincristine/doxorubicin/cyclophosphamide alternating with etoposide/ifosfamide
- **Week 20** - 25
  - **Radiation** with vincristine/irinotecan
- Week 26 – 34
  - Vincristine/doxorubicin/cyclophosphamide alternating with etoposide/ifosfamide
- Week 38 - 46
  - Vincristine/dactinomycin/cyclophosphamide
- Week 47 – 62
  - vincristine/irinotecan



Management of Metastatic Disease in ARST 0431

- All radiation, primary site and metastatic disease, is given at week 20

- All metastatic sites will receive radiation regardless of their response

- Pulmonary Mets
  - 15 Gy in 10 fx whole lung irradiation (WLI), with a boost to any gross residual to 50.4 Gy

Prognosis - Event Free Survival (EFS)

- **Low Risk** EFS = 90%
- **Intermediate Risk** EFS = 70%
- **High Risk** EFS = Less than 30%
  - Remember, these are the metastatic patients

Follow - Up

- **Year 1**
  - MRI q3 months of primary site
  - CT Chest q3 months (with imaging of any metastatic sites)
- **Year 2 -3**
  - MRI q4 months of primary site
  - CT Chest q4 months (with imaging of any metastatic sites)
- **Year 4 -5**
  - MRI q6 months of primary site
  - CT Chest q6 months (with imaging of any metastatic sites)

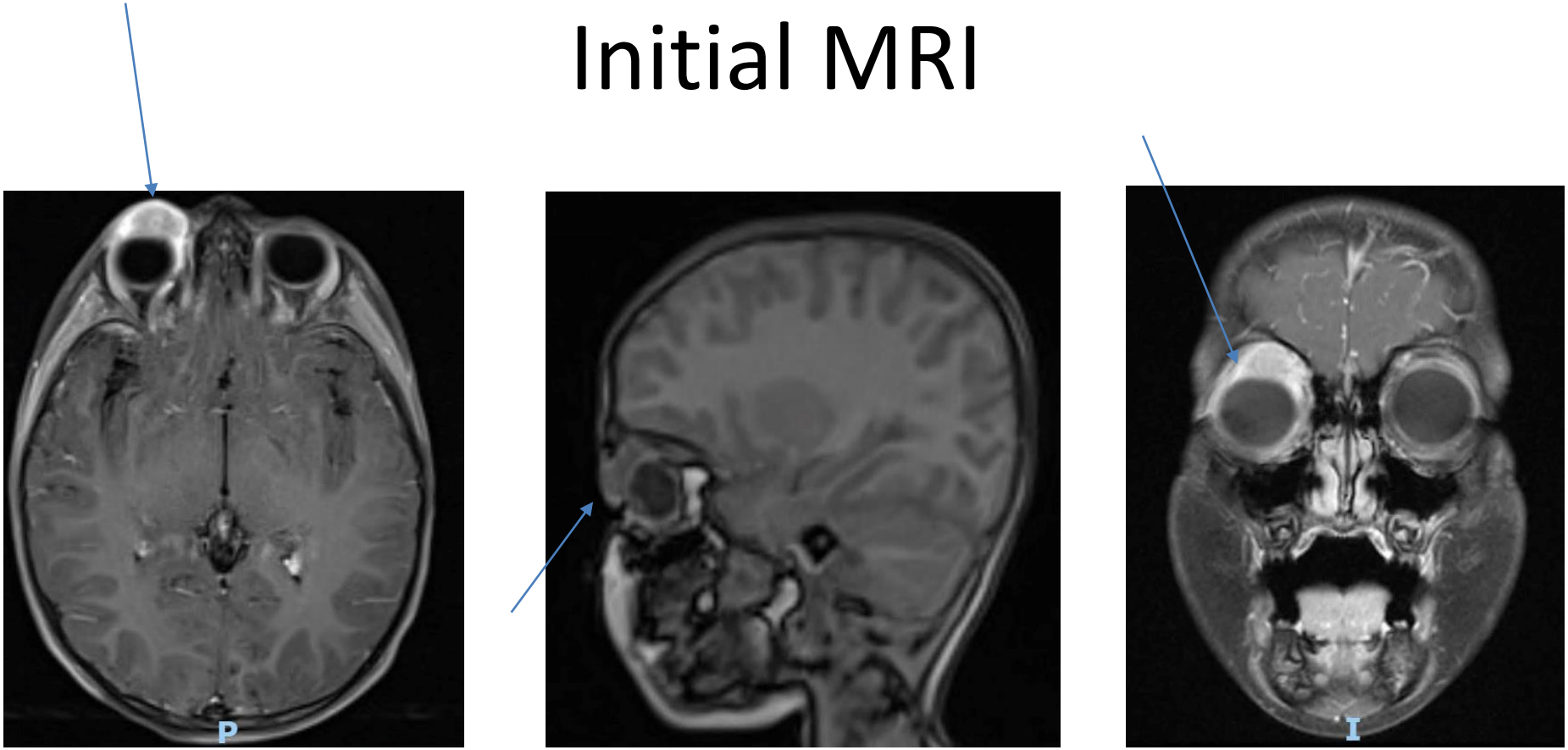
Case

Case Presentation

- 4 year old boy who presented with swelling of his right upper eyelid
  - Parents noted a mass here a few days prior to presentation

- After initial infectious workup, MRI was ordered

Initial MRI



MRI showed a nonspecific mass anterior and superior to the right globe measuring 2cm

Case Presentation

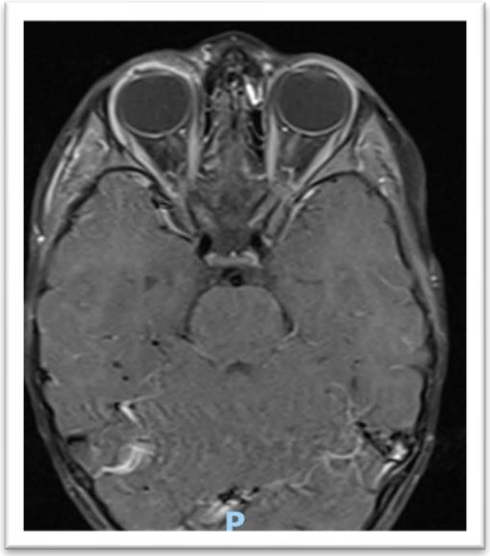
- Incisional biopsy was performed with pathology returning for:
  - **Rhabdomyosarcoma**
  - Spindle cell variant (**Embryonal**), FOXO1 fusion negative

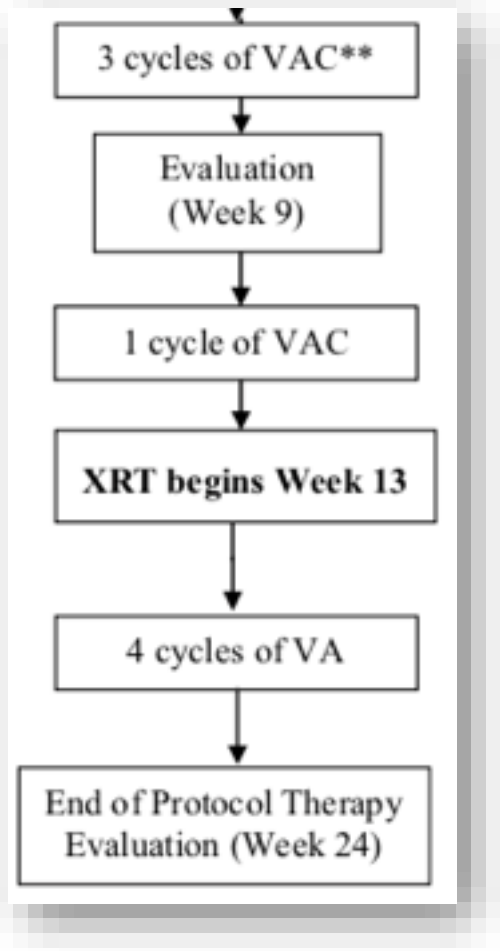
- **PET CT negative** apart from primary site
- **A bone marrow biopsy is usually indicated**; however, per ARST1431: patients with embryonal RMS who have non-invasive tumors that <5 cm without nodal disease, bone marrow biopsy is not indicated

- **Stage: 1 (BONG)**
- **Group: 3 (Unresectable)**
- **Risk Group: Low**

Case Presentation

- Treatment was started with 4 cycles induction VAC, local control with radiation, followed by 4 cycles VA (as per the low risk protocol)
- At time of simulation for XRT, there was complete resolution of the orbital mass
- We planned to treat **the pre-chemotherapy tumor volume to 45 Gy in 25 fractions (orbital dose)** using VMAT, starting with week 13 of chemotherapy





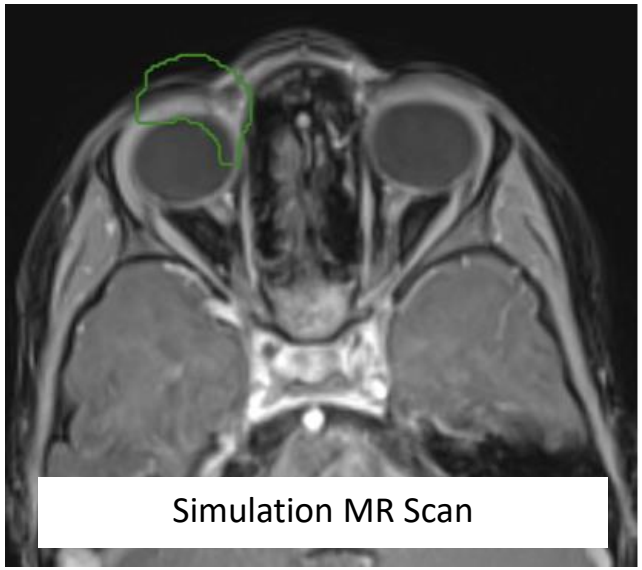
Radiation Simulation

- CT
- MRI with and without contrast
- Facemask
- Anesthesia was required (due to young age)

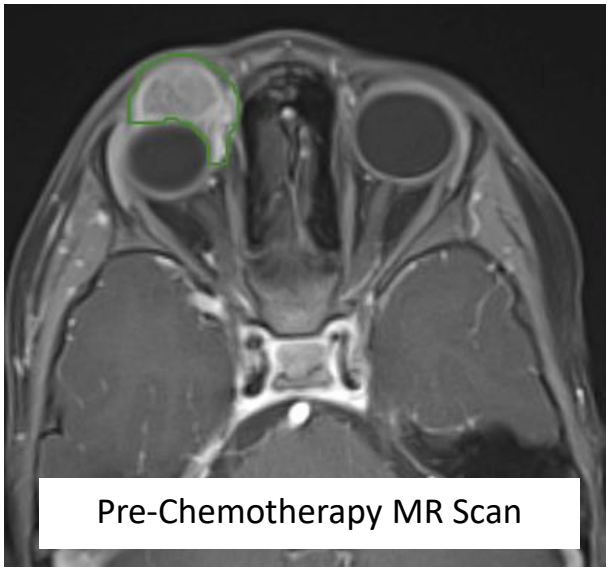
- Given the superficial location of the tumor, a 1 cm bolus was used

Radiation Plan

- What do you want to contour as **GTV**?
  - Pre-chemotherapy volume



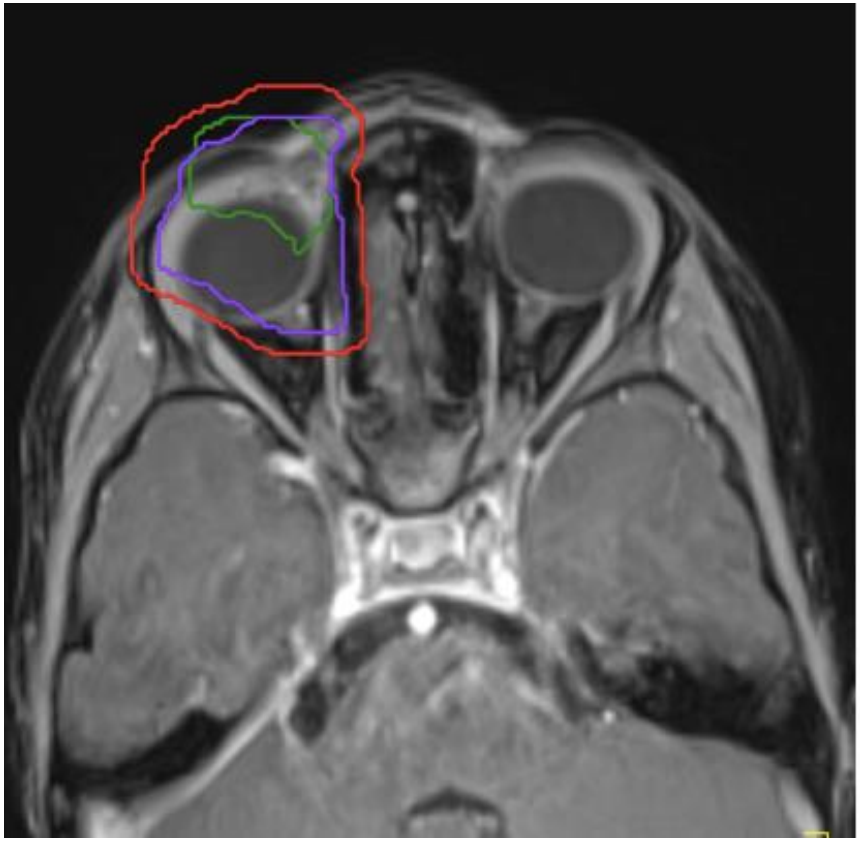
Simulation MR Scan



Pre-Chemotherapy MR Scan

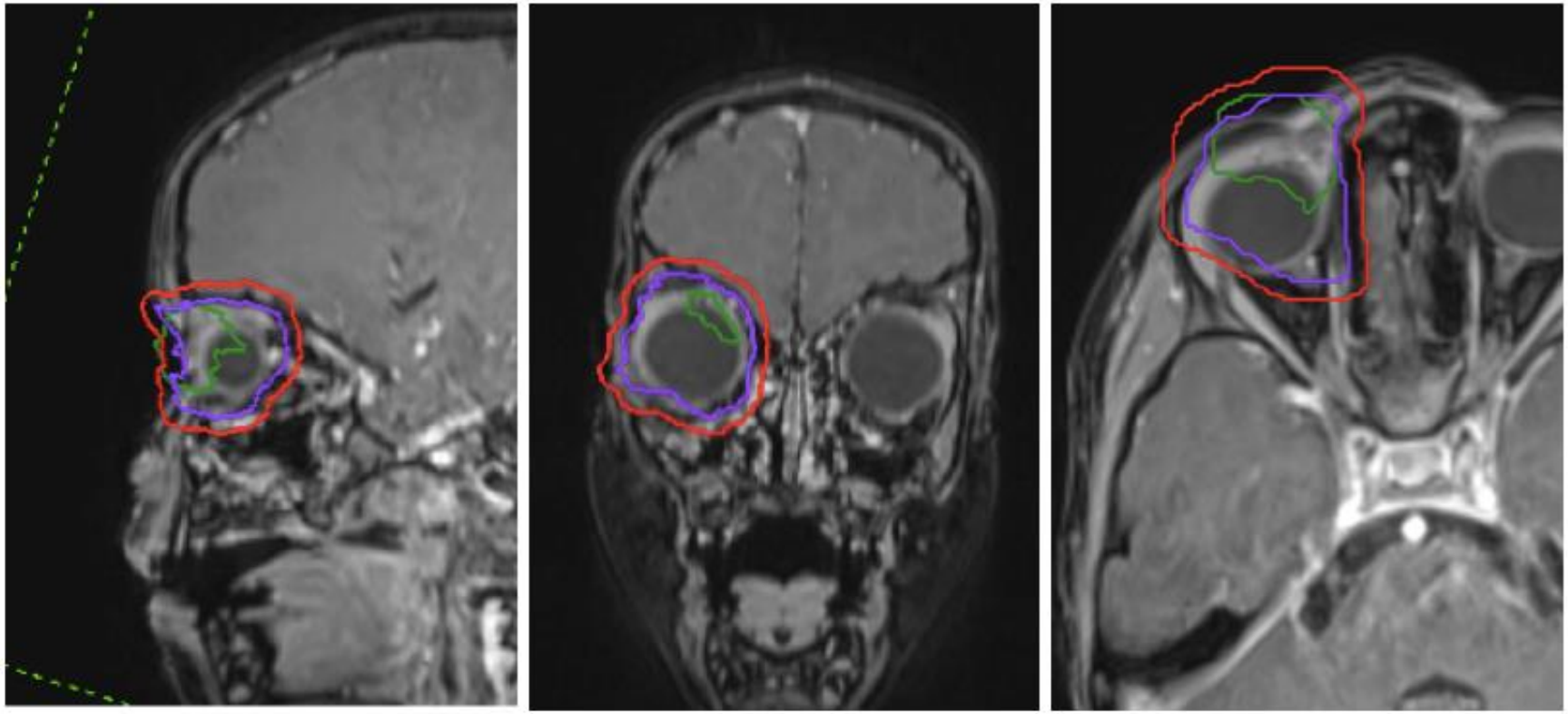
Radiation Plan

- What is the **CTV**?
  - 1 cm expansion from the GTV, anatomically constrained
- What is the **PTV**?
  - Minimum of 0.3 cm, depending on immobilization



Simulation MR Scan

Radiation Plan in 3 Dimensions



Dose Constraints from ARST1431

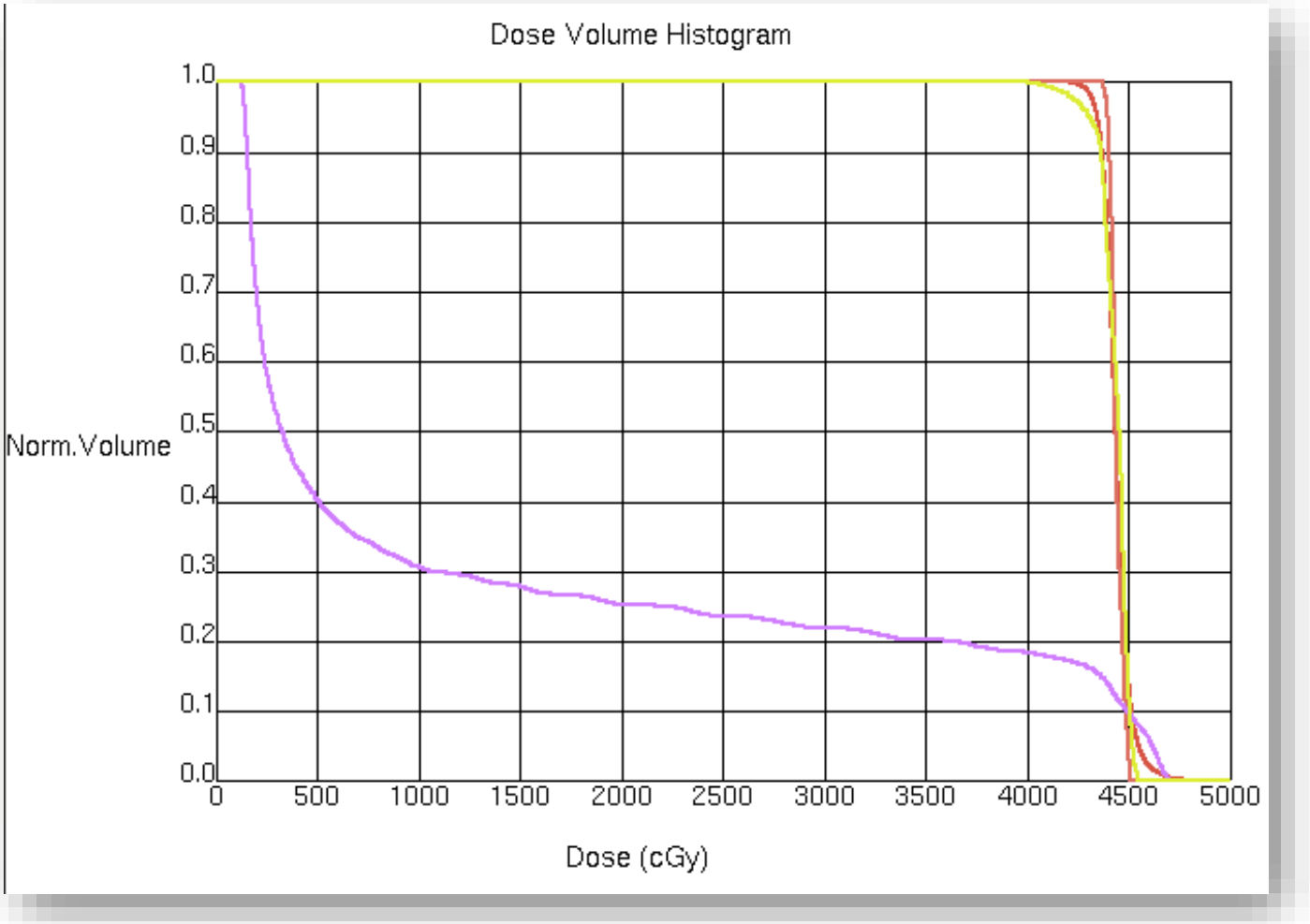
17.10 Organs at Risk for fractionated targets (not SBRT)

The organs at risk (OAR) guidelines in this section are recommendations. If the recommended doses to the OAR are exceeded because of target volume coverage requirements or other conditions, an explanation should be included in the quality assurance documentation. In some cases, photon IMRT may be the preferred treatment method to meet these recommendations and the required target volume coverage guidelines. Normal tissue tolerance is the same for photons and protons (proton dose measured in CGE).

17.10.1 Organs at risk dose recommendations

Organ	Volume (%)	Dose (Gy)
Single organs		
Bladder	100%	45
Heart	100%	30
Liver	100%	23.4
	50%	30
Rectum	100/%	45
Optic chiasm	100%	54
Small Bowel	50%	45
Spinal Cord	Any volume	45
Paired organs		
Kidney (bilateral)	50%	24
Kidney (bilateral)	100%	14.4
Lung (bilateral)	20%	20
Lung (bilateral)	100%	15
Optic nerve	100%	54
Lens	100%	14.4
Lacrimal Gland/Cornea	100%	41.4

Plan Evaluation



Plan Evaluation

- Is the PTV adequately covered? Yes
  - 98% of PTV45 receives prescription dose

- Did we respect all dose constraints? Yes and No
  - The right lacrimal gland and right lens dose constraints were exceeded due to given their location in the target volume. This will possibly lead to dry eyes, tearing, lens opacification with cataract formation
  - Right optic nerve received a max of 47 Gy, below constraint of 54 Gy

Side Effects

- **Acute side effects:**
  - Dry eye and possible redness of the eyelid
    - Given Aquaphor and artificial tears
  - Loss of eyelashes and eyebrows
    - They grow back to varying degrees

- **Late radiation side effects:**
  - Cataract formation, persistent dry eye, damage to the lacrimal gland and lacrimal duct, hypoplasia of the bony orbit, and risk of secondary radiation-induced malignancy.

Follow-up

- MRI orbit and CT chest without evidence of disease
- His hair, eyelashes, and eyebrows grew back
- He maintains close follow-up with ophthalmology

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