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RMS – Key Surgical Topics

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Objectives

1. Approaching new RMS patient
2. Local Control
    i. XRT vs radical surgery
    ii. PRE, DPE
    iii. Special circumstances
3. Recent/Current COG Trials
4. Novel Therapies

Approaching a New RMS

- In general, keep a broad differential
  - Think of what all needs to be done for staging
  - Think multi-disciplinarily:
    - Oncology
    - Urology
    - Radiation Oncology
    - Radiology
    - Pathology
    - Onco-fertility
    - Genetics
- **The operation is the easiest part!**

Approaching a New RMS

- Imaging
  - Ideally start with an US
    - Look for location, appearance of lesion, impact on surrounding structures
    - What next level imaging is needed?
- Labs
  - CMP, CBC, Coags
  - For para-testicular consider αFP, βhCG and LDH

Approaching a New RMS

- More imaging versus surgery for tissue diagnosis?
  - Can be hard to say, worth a multidisciplinary discussion
  - Going straight to getting tissue can have impact of making a case group III automatically if oncology gives chemotherapy

- Para-testis → likely radical inguinal orchiectomy then more imaging
- Pelvic → likely imaging and then biopsy, rarely resection, and then more imaging

Additional Workup for Staging

- CT CAP
- Bone marrow biopsies
- Bone scan vs PET

Treatment

- Combination of chemotherapy, surgery and XRT
- ”Local control” refers to managing site of primary tumor
  - This may be upfront or after neoadjuvant chemotherapy
  - Can be surgical or with XRT
  - Surgical option depends on how “easily” this is done/how disfiguring this may be upfront
  - Worse EFS but same OS without this component
- Must obtain tissue diagnosis regardless

Surgery in RMS

- Potential Timing of Surgery:
  - At diagnosis
  - After biopsy but before chemotherapy (PRE)
  - After chemotherapy (DPE)
  - After chemotherapy and radiation for salvage
- Consider combining procedures
  - BM biopsy, port, etc.
- Send specimens fresh (no formalin)

Initial Diagnostic Strategies

- Paratestis mass → inguinal exploration
  - If low suspicion for malignancy → excise with frozen section*
  - If high suspicion for malignancy → radical orchiectomy
  - If tumor adherent to scrotal skin, excise bit of scrotum attached to tumor with specimen

- Pelvic mass → biopsy
  - Can consider complete excision if tumor is resectable…

* Specific steps to accomplish this, described in COG protocols (draping, intraop FS, changing instruments, etc.)

Case Example

- 8 yo M referred to you after scrotal orchiectomy → RMS
- Otherwise workup normal, no mets
- What now?

- Important to explore groin and complete radical orchiectomy (get proximal cord out)
  - Consider scrotal scar excision
  - Can combine with port, BM biopsies

"Resectability"

- Generally, pelvic RMS are unresectable at the outset
- Advantages of complete upfront resection:
  - Make patient group I → avoid XRT
- Disadvantages of complete upfront resection:
  - Highly morbid if requires exenteration
  - FS margin reliability is low
  - If +margin after resection → worst of both worlds
- COG qualifies surgery often, endorsing only if possible "without loss of form or function"

Biopsy Strategies

- Endoscopic/TURBT
- Transrectal/transperineal US guided using biopsy gun
  - Take LOTS of cores
- Laparoscopic/open
  - Consider LN sampling
  - If residual tumor remains, mark with metal clips
- Consider potential seeding with approach

Example – 3y M with B/P RMS, M0

- Can't be stage I
- Will require chemotherapy after tissue diagnosis
- Which tissue diagnosis/local control strategy is best?

- Biopsy only → group IIIa
  - Will get XRT → radiation cystitis, SMN risk, bowel issues, etc.

- Radical cystoprostatectomy with -margins -LNs → group I
  - Urinary diversion, infertility, ED

Surgical Timing - PRE

- Pre-chemotherapy re-excision
- Aims for group reduction
- If after biopsy and dx, complete resection is possible with minimal morbidity → re-excise completely **before** chemotherapy begins

- Most commonly with small bladder dome lesion that can be resected with partial cystectomy and LN sampling
- Commonly applied to non-BP GU RMS
- <50% of BP RMS cases achieve –margin with upfront surgery
  - Resist the temptation to offer early extirpative surgery

Case example

Surgical Timing - DPE

- DPE = delayed primary excision
- Done after chemotherapy as local control
- Goal is for complete excision **with** – margin to reduce dose of XRT
  - Debulking does not help

- Per guidelines, +margin → standard dose XRT (50.4Gy)
- Neg margin → 36 Gy

Benefit of DPE…

- Retrospective analysis of 369 int risk RMS patients
  - 136 B/P
- DPE → decreased XRT and same/improved survival
  - Driven by parameningeal/non-B/P/non-extremity pts
- No difference for B/P patients
  - Many had R1 or R2 resection → was this "good" surgery?
  - Highlights importance of R0 goal if this path is chosen

XRT in Very Young Children

- Special carve out for babies <24mos in COG XRT protocols

- Late effects can be devastating to growing skeleton
- Permanent
- May be seen years after treatment
- Greater potential for growth loss

- Careful consideration for young patients

Diversion After Radical Surgery

- Generally perform incontinent diversion
  - Ureterostomies vs. conduit
- Intraop FS very unreliable if considering orthotopic diversion
  - Have been reported in Italy

Residual Mass after Chemo/XRT

- About 20% of cases; does not seem to affect outcomes
- May required second look operation to assess the response and potentially surgical control
- Mature rhabdomyoblasts can be easily confused with active disease (particularly on frozen section)
  - Recurrence after this is low, but deaths have been reported
  - Observation alone

Example – 3y M with B/P RMS, M0

Scenario 1:

- Biopsy only → VAC → radical surgery for local control
  - Surgery will decrease, not eliminate need for postop XRT
  - If – margin → lower dose XRT
  - If + margin → regular dose XRT
  - Now has surgery AND lower vs. full dose XRT risks…
  - What type of reconstruction?

Scenario 2:

- Biopsy only → VAC → XRT for local control
  - May have residual mass after?
  - May have XRT-related symptoms?
  - Can always have more surgery later if issues arise…

My Thoughts…

- XRT vs surgery (COG vs SIOP) have equivalent outcomes
  - Pick least bad option with family
- I prefer XRT for local control unless young infants
- Even if bladder function deteriorates and reconstruction is undertaken → chance for no further surgery
- Having a bladder, no matter how defunctionalized, preserves the UVJ and provides a plate for augmentation/APV over complete neobladder construction

ARST 0331

- Low risk RMS (embryonal)
- VA with lower doses of cyclophosphamide ± reduced XRT
  - Stage I/II, group I/II → VAC x 12 weeks, VA x12 weeks + XRT
  - Stage I, group III or stage III, group I/II → VAC x12 weeks, VA x36 weeks + XRT
- Subset 1 did great (population for ARST 2032)
- Subset 2 had suboptimal outcomes → now intermediate risk

ARST 2032 (multi group study)

- Very low risk and low risk fusion – RMS
  - VLR = fusion -, stage I/group I, *MYOD1/TP53* wild type
  - LR = fusion -, stage I/group II or stage II/group I or II with *MYOD1/TP53* wild type
  - *MYOD1* or *TP531* + → regimen M
- Evaluate FFS with dose/therapy reduction
  - VLR → VA x24 weeks
  - LR → VAC x12 weeks, VA x12 weeks

D 9803

- Intermediate risk RMS
- Outcomes comparing VAC vs VAC/VTC
- VAC/VTC did not improve FFS or OS
- VAC remained standard
- Emphasized surgery >> XRT for local control

- Significant concerns about high dose cyclophosphamide and infertility

ARST 0531

- Intermediate risk RMS
- Eval outcomes with dose reduced cyclophosphamide
  - VAC vs VAC/VI
  - Emphasized XRT >> surgery for local control
- Local failure almost 30%
- Local failure, EFS, OS worse than D9803
- “VAC should remain standard”
- Secondary aim to look at bladder dysfunction…
  - Jon Routh trying to get these data

ARST 1431 (multi group)

- Current int risk study
  - Age <40y
  - Launched before 0531 data matured…
- VAC/VI vs VAC/VI ± temsirolimus x8-12 weeks
  - Emphasis on DPE and XRT boost to 59.4Gy if >5cm
- Uses fusion status, not histology
- Evaluating OS and EFS
  - Exploring difference between PAX3 vs PAX7 in fusion+
  - Does FDG-PET response correlate with survival?

Data expected soon

ARST 0431

- High risk RMS
  - Outcomes universally poor
- Chemotherapy/XRT intensification
- 56% OS, 38% EFS overall
  - Useful mainly in fusion – and age <10y (3y EFS 60-64%)
  - Not helpful for very high risk tumors
    - Stage IV fusion + (3y EFS 6-16%)
    - Stage IV fusion – and age ≥10y (3y EFS 32-38%)

ARST 2031 (multi group study)

- High risk RMS
  - Age <50y
  - Stage IV, group IV
  - All fusion +, only ≥10y fusion -
- Outcomes are universally bad in this group
- Comparing EFS between VAC/VINO-C_{PO} vs VINO-AC/VINO-C_{PO}

XRT Effects

- 40% of patients with BP RMS survive event free with apparently normally functioning bladders
- XRT dose affects bladder function, likely deteriorates over time
- Historical study, normal bladder function on UDS only in those who did not receive pelvic XRT
- Significant effects on growing skeleton
  - Permanent, continue years after treatment
  - Limb length discrepancy, facial asymmetry, halting of pelvic growth/gait anomalies
  - Young patients even more sensitive to AEs
- XRT effects have driven innovation…

Novel Therapies

1. Proton Beam
2. Brachytherapy
3. Urinary diversion

- Proton beam acceptable in COG protocols
- Brachy ok but limited availability
- Up front diversion controversial

Proton Beam

- Protons more exact, less “field effect”
- Not universally available

- Proton therapy allows improved targeting of the desired tissue in 3 dimensions
  - Energy/radiation is not delivered into surrounding areas
  - For children, the toxicity reduction is imperative
  - Appears to have equivalent disease control (especially for BP RMS) and limited treatment related AEs

- Appropriate substitute to standard XRT if available

Brachytherapy

- Initially looked at brachy + XRT or protons to decrease damage to surrounding tissues
- French group published using surgery + brachy as local control
  - 95 BP RMS patients age 28mo, mostly ERMS, f/u 64mo
  - Seeds implanted transperineally using plastic tubes
  - 12% relapsed at a median 14mo, 6.3% local only failures
  - 5y OS was 91% and 5y DFS was 84%(15)
  - 15% without relapse had brachy-related urinary issue requiring intervention (similar to XRT reports)
- This is ok per COG, mostly used for vaginal tumors
- Long-term data not available…yet

Diversion after Surgery

- Classically, radical cystoprostatectomy → incontinent diversion → continent diversion after durable survival
- Italian group reviewed their experience (n=11)
  - Immediate ileal neobladder vs. delayed continent diversion
- No patient with immediate reconstruction experienced upper tract deterioration, all continent
- All in the delayed group → CIC, rUTI, upper tract dilation
- Perhaps this may be feasible?

Conclusion

- Take time to think before rushing to the OR
  - Think three steps (years) ahead
- Beware of aggressive surgery in BP RMS; take time to think, prepare, counsel
  - Talk to peds onc, experts in field, pathologists, radiologists
- Look out for newer advances.data in improving QoL long-term outcomes for these patients

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