



Controversies in Bladder/Prostate RMS – Local Control

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Disclosure

- None
- This will be COG-centric...

Objectives

1. Introduction
2. COG vs. SIOP
3. Local Control Options (XRT, PRE, DPE, etc.)
4. Novel Therapies:
 - i. Proton Therapy
 - ii. Brachytherapy
 - iii. Upfront Surgery

Treatment

- Combination of chemotherapy, surgery and XRT
- "Local control" refers to managing site of primary tumor
 - This may be upfront or after neoadjuvant chemotherapy
 - 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

Local Control

Surgery

- Excision of the primary tumor up front without causing major functional or cosmetic deficits
- If Group 1 → no need for XRT
- Can consider re-excision after starting therapy (DPE)

Radiation

- Typically begins 3-15 weeks; 3600-5040 cGy
- Frequently have residual mass after radiation (20%)
 - No change in recurrence with/out mass

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 → group II
 - Urinary diversion, infertility, ED

Collaborative Group Study

- IRSG → COG North America
- SIOP Europe/rest of world
- Historically → early radical surgical excision everywhere
- Details on treatment varies, survival is about the same

Collaborative Group Study

COG	Topic Difference	SIOP
<ul style="list-style-type: none">• Minimize surgical morbidity/disfigurement• Emphasize organ preservation	Study Goal	<ul style="list-style-type: none">• Minimizes use of local control with chemotherapy intensification

Collaborative Group Study

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Collaborative Group Study

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<ul style="list-style-type: none"> EFS 	Endpoint	<ul style="list-style-type: none"> OS
<ul style="list-style-type: none"> Accept more toxic initial treatment to avoid salvage therapy 	Salvage	<ul style="list-style-type: none"> Accept lower EFS and higher salvage rates

Collaborative Group Study

COG		Site	SIOP	
5yEFS	5y OS		5y EFS	5y OS

Collaborative Group Study

COG		Site	SIOP	
5yEFS	5y OS		5y EFS	5y OS
78%	84%	All RMS	57%	71%

Collaborative Group Study

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5yEFS	5y OS		5y EFS	5y OS
78%	84%	All RMS	57%	71%
79%	86%	B/P RMS	64%	94%

Collaborative Group Study

COG		Site	SIOP	
5yEFS	5y OS		5y EFS	5y OS
78%	84%	All RMS	57%	71%
79%	86%	B/P RMS	64%	94%
83%	90%	Non-B/P RMS	82%	94%

- No statistical differences for B/P based on protocol

Surgery in RMS

- Potential Timing of Surgery:
 - At diagnosis
 - After biopsy but before chemotherapy (PRE)
 - After chemotherapy
 - Second Look Operation, SLO or DPE
 - After chemotherapy and radiation for salvage local control

“Resectability”

- Generally, pelvic RMS are unresectable at the outset
- Advantages of complete upfront resection:
 - Make patient group I and avoid radiation provided - margins
- Disadvantages of complete upfront resection:
 - Highly morbid if requires exenteration
 - FS margin reliability is low
 - If still with positive margins after resection → worst of both worlds

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

Surgical Timing - DPE

- DPE = delayed primary excision
- Allows for surgical excision with – margin after chemotherapy to reduce dose of XRT given
- Per guidelines, +margin → standard dose XRT
- Margin Negative → 36 Gy
- Gross Disease/+ margin → 50.4 Gy

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

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

- 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 Ses
- 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 encouraging but not prime time 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?

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...

- COG and SIOP protocols have equivalent outcomes
- I prefer XRT for local control unless very 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

Conclusion

- COG vs. SIOP – just different, neither clearly “better”
- 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 in improving QoL long-term outcomes for these patients

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