University of Kentucky
Department of Urology

RMS – Basics & Background

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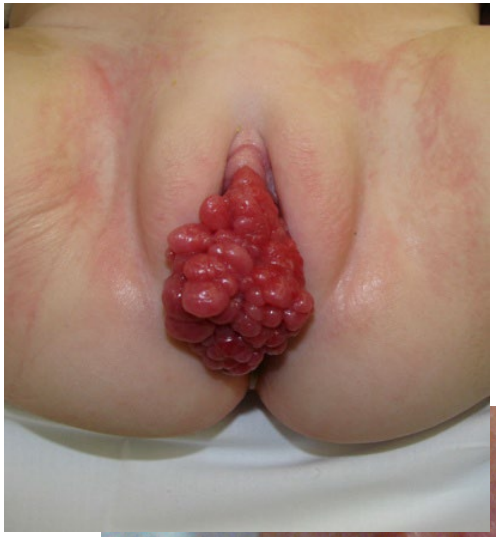
Amanda F. Saltzman MD
Associate Professor, Department of Urology & Pediatrics

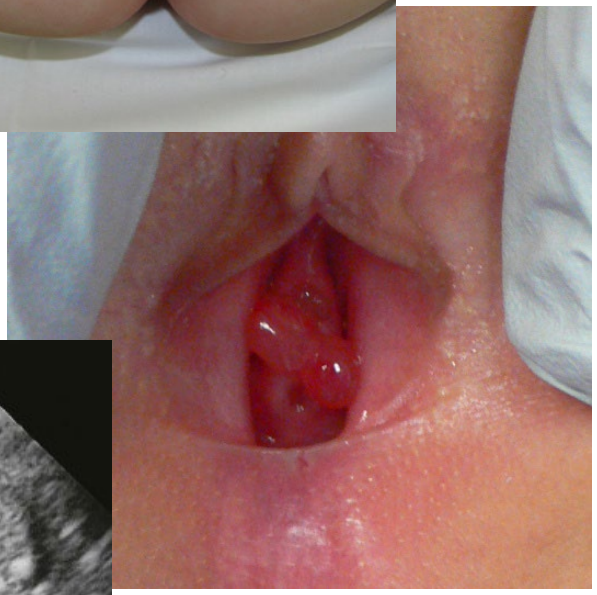
Objectives

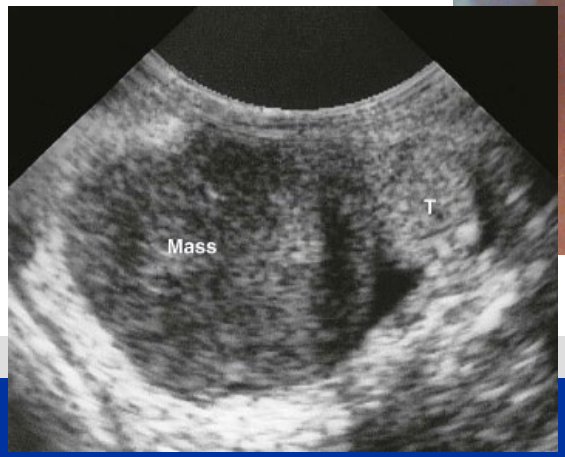
1. Introduction/Epidemiology
2. “Lingo”
3. Treatment backbones
    i. Chemotherapy
    ii. Local control
4. COG vs SIOP

Clinical Presentation

- Pelvic RMS
  - Hematuria
  - Urinary obstruction, stranguria
  - Constipation
  - Extrusion of tissue, vaginal discharge
- Para-testicular RMS
  - Painless scrotal mass







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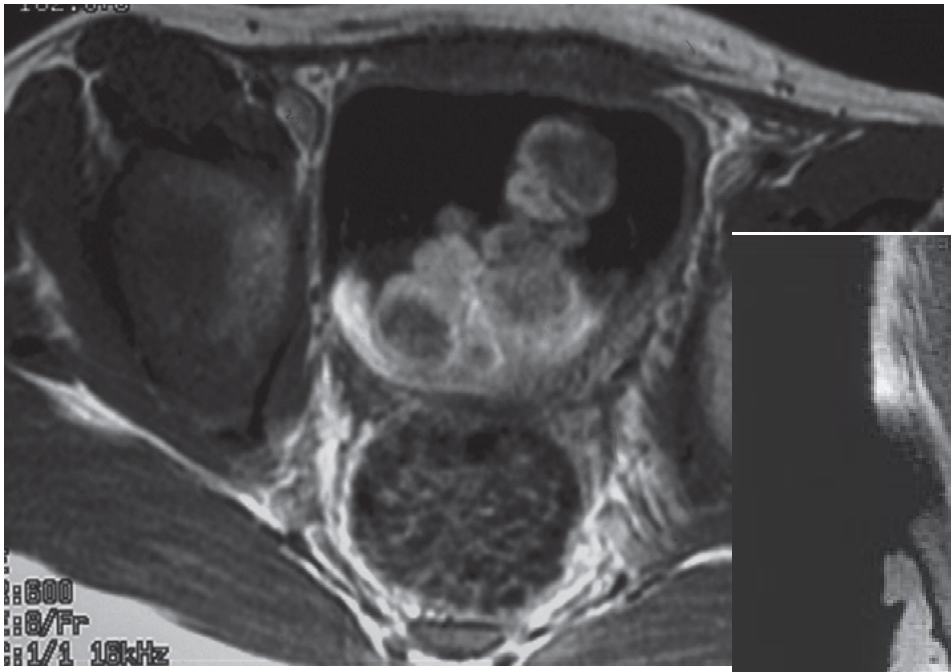
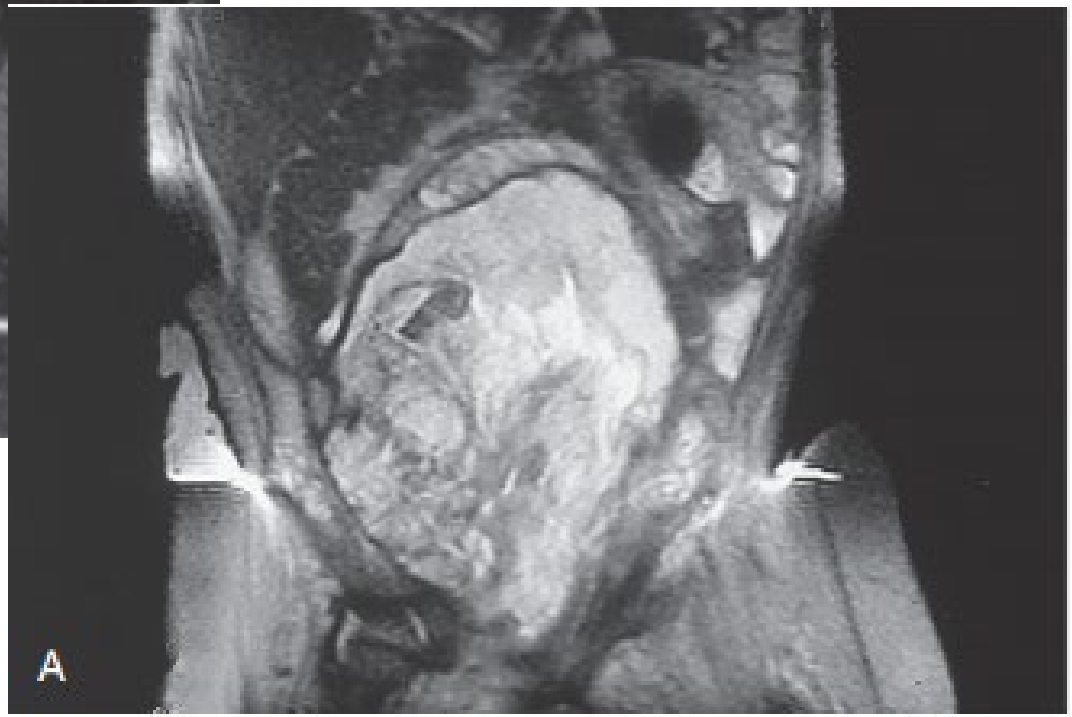
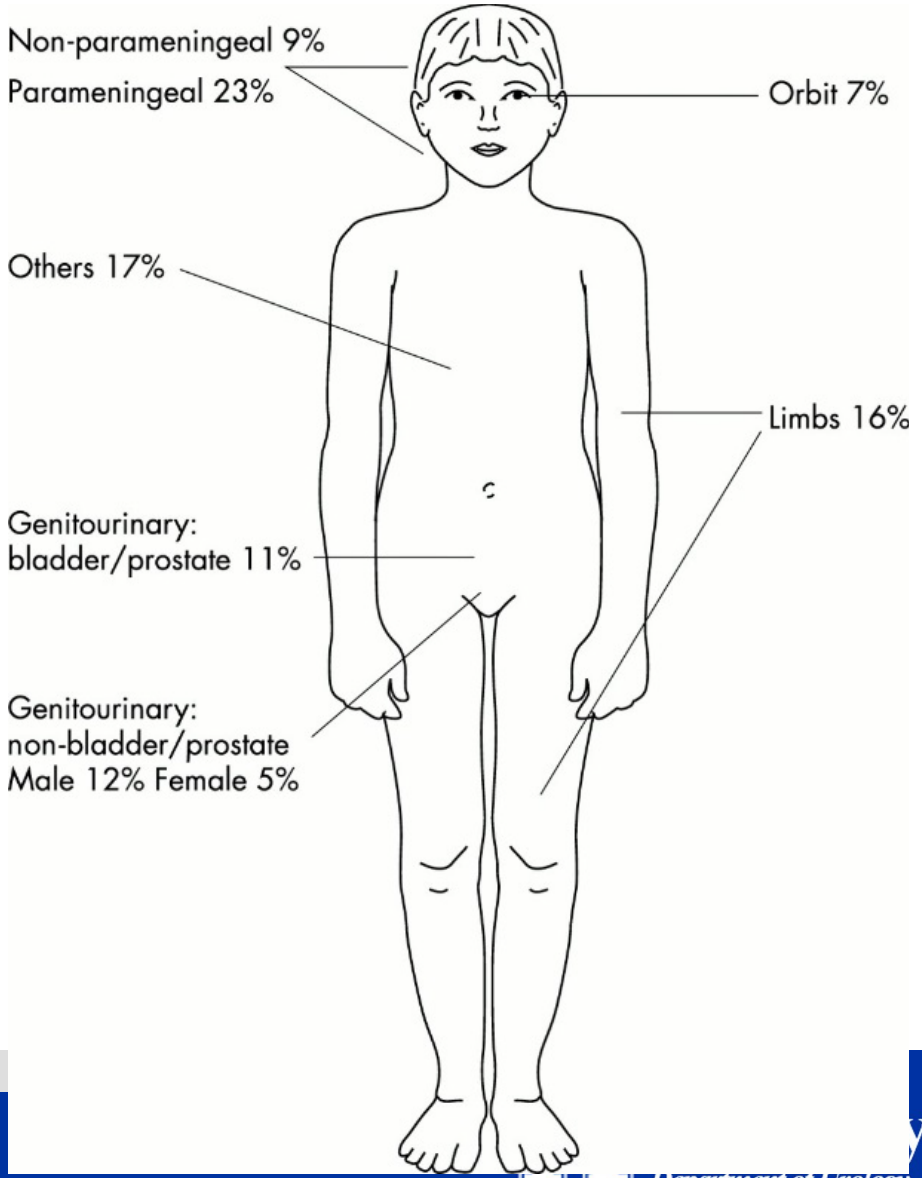


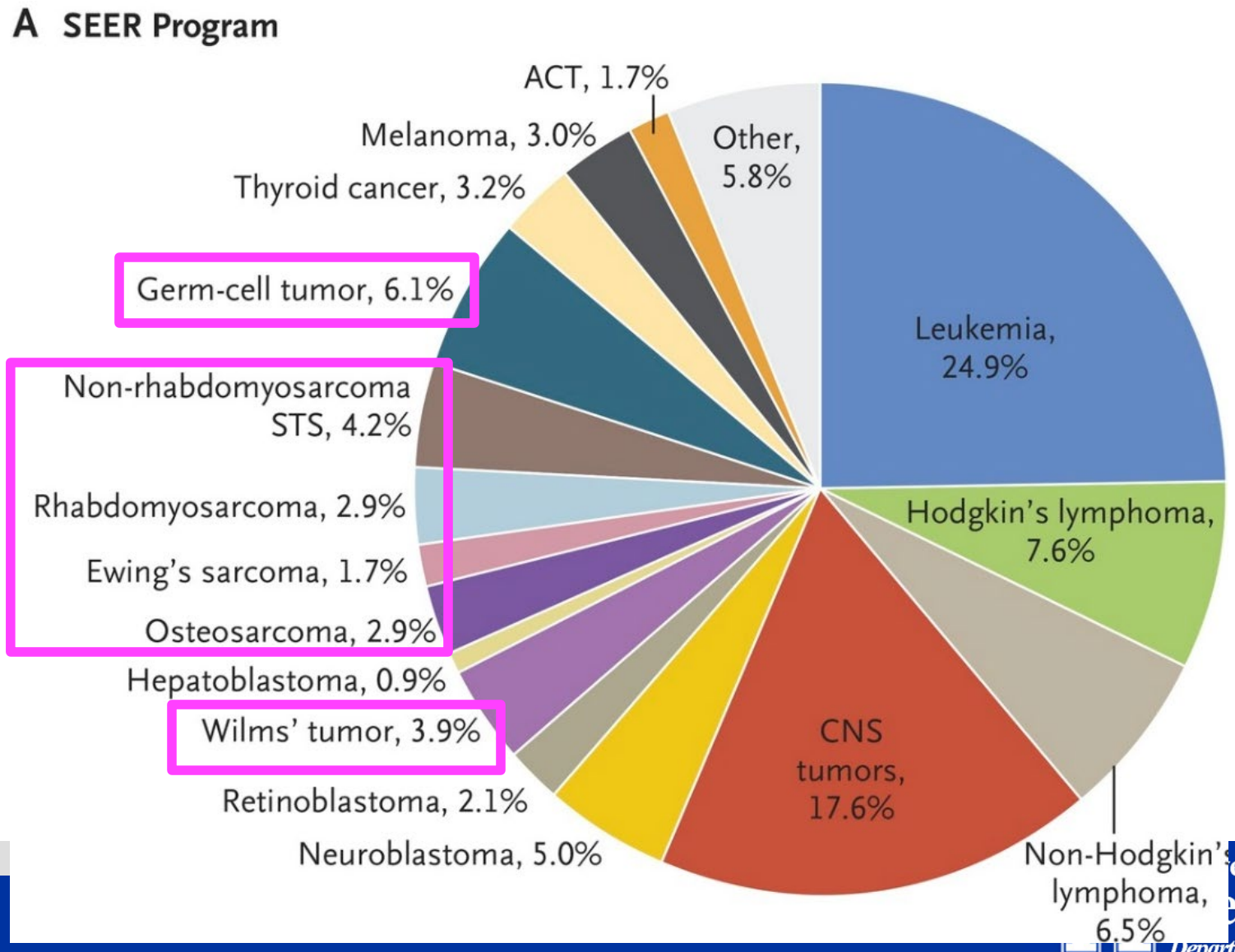


Introduction

- RMS develops from striated muscle tissue
- Can occur anywhere in body
  - Site affects prognosis
  - Site affects treatment
- 15-20% of all RMS arises from GU system
  - BP site is most common; 5% of all RMS



Epidemiology



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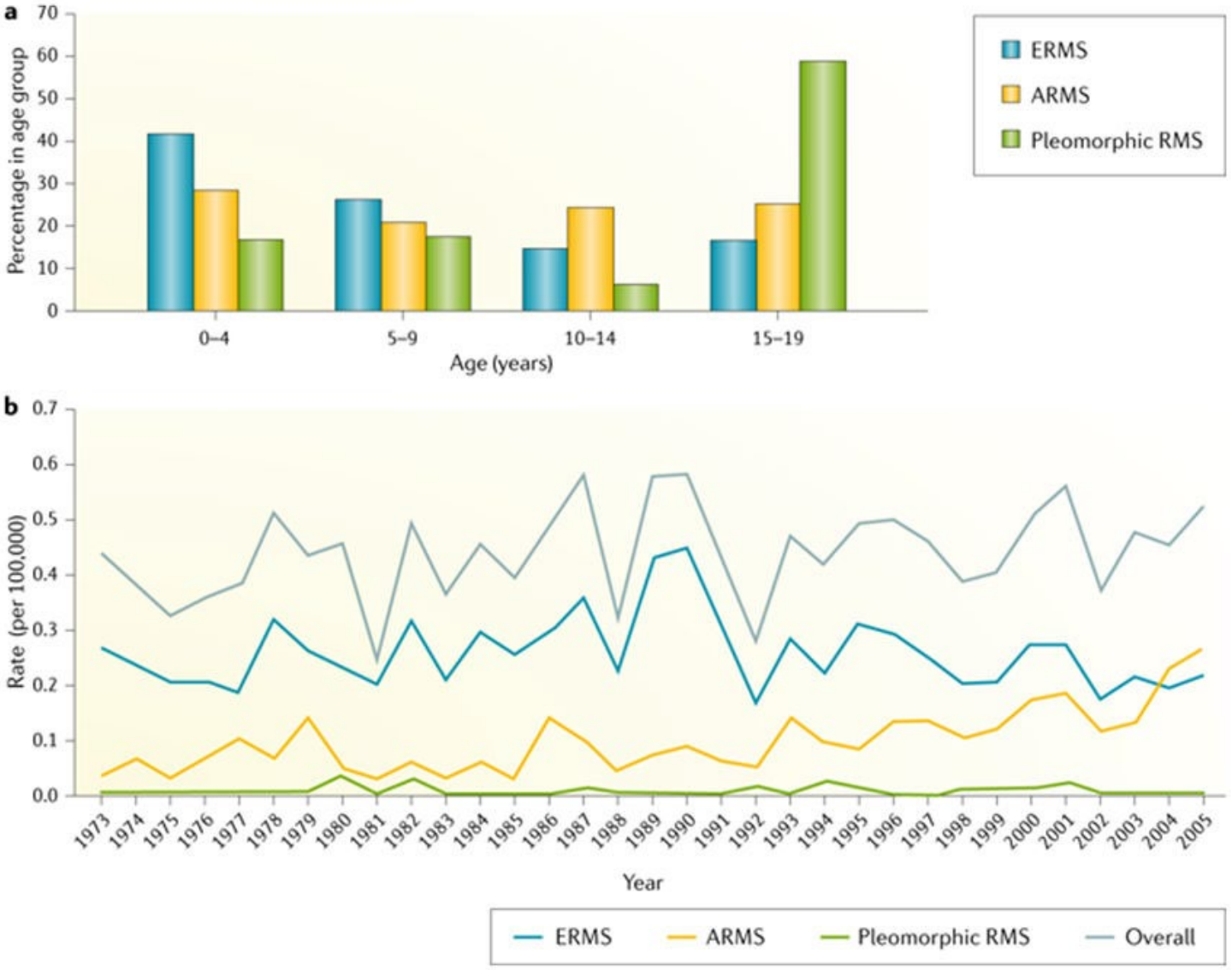


Introduction

- 350 new pediatric cases of RMS per year in US
  - About 90 cases of GU origin
- 20% metastatic at diagnosis
  - Most likely site of spread is:
    - Lungs (40-50%)
    - Bone marrow (20-30%)
    - Lymph node (20%)
    - Bone (10%)
    - Visceral metastasis - uncommon at Dx but seen in 25% of terminal patients

5y Survival by Site

Site	# patients	5y OS
Orbit	107	95
Superficial head and neck	106	78
Cranial parameningeal	134	74
GU (except BP)	158	89
BP	104	81
Extremity	156	74
Trunk, abdomen, perineum, etc.	147	67
Biliary	25	78

Risk Factors for RMS Development

- Li-Fraumeni Syndrome (germline p53 mutations)
  - More prevalent in younger patients (<3 years)
- Neurofibromatosis-type I
- Beckwith-Wiedemann
  - Fetal overgrowth syndrome with 11p15 (IGF-2) abnormalities
- Noonan Syndrome
  - RAS-MAPK pathway
- Germline DICER-1 mutations
- Prior XRT and alkylating agent exposure increases risk

GU RMS

- Bladder, prostate, vagina, cervix, uterus, paratestis
- Male predominance
- 75% diagnosed by age 5y

- Age at diagnosis is important risk factor:
  - Age 1-9y → EFS 71%
  - Age <1y or >10y → EFS 53%

RMS "Lingo"

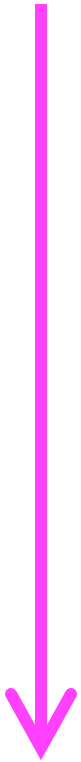
- Site
  - Favorable vs unfavorable
- Stage
  - Based on TNM system; pre-operative assignment
- Group
  - Based on completeness of resection BEFORE chemotherapy
- Histology
  - Alveolar vs. embryonal → new fusion status
- Risk
  - Low/intermediate/high

Site Classification

- Unfavorable
  - Bladder/prostate
  - Urachal
  - Retroperitoneal
- Favorable
  - Vaginal, uterine, vulvar
  - Paratesticular

Prognosis by Site

Most Favorable



Orbit/Head and Neck

GU - Paratestis, GYN (non-B/P)

GU - B/P, Urachal, Retroperitoneal

Parameningeal

Other

Extremity

Least favorable

Stage

- TNM system
  - Also incorporates site (favorable vs. unfavorable)
- Assigned PRE-operatively by surgeon

Stage	GU site	T	Size	N	M
I	Female genital tract Paratesticular	Any	Any	Any	M0
II	BP only	Any	a	N0 or Nx	M0
III	BP only	Any	a	N1	M0
			b	N0 or N1 or Nx	
IV	All	Any	Any	Any	M1

T1 confined to the anatomic site of origin
T2 extension and/or fixation to surrounding tissue
a ≤ 5cm
b >5 cm

Nx regional LNs not evaluated
N0 regional LNs not involved
N1 regional LNs involved

M0 no distant metastasis
M1 distant metastasis

Tips…

- BP is considered an unfavorable site → **cannot** be stage I

- Paratesticular and female genital tract is considered a favorable site → can **only** be stage I or IV

Group

- Based on COMPLETENESS of resection and nodal status

  BEFORE chemotherapy starts

- Should be “assigned” by surgeon at time of resection

Group

Group	Description
I	Localized disease, completely resected, regional LNs not involved
a	Confined to organ of origin
b	Contiguous involvement (infiltration through organ of origin)

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II	Total gross resection with evidence of regional spread
a	Grossly resected tumor with microscopic residual disease, no LN involvement
b	Regional disease with involved LNs, completely resected with no residual disease remaining
c	Regional disease with involved LNs, grossly resected, with microscopic residual and/or histologic involvement of the most distal regional LN in the dissection

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III	Incomplete resection with gross residual disease
a	After biopsy only
b	After gross resection (>50%) of primary tumor

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IV	Distant metastasis

Notes:

- **Regional LN biopsy or sampling for group I patients is highly advised if feasible**
- **LNs taken with the specimen must be examined, and if positive, place the patient in group IIb or higher**

Example – 3y M with B/P RMS, M0

- Can't be stage I
- Will require chemotherapy after tissue diagnosis

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

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

Prognosis by Stage and Group

Stage	3-yr EFS
1	86%
2	80%
3	68%
4	25%

Group	3-yr EFS
I	83%
II	86%
III	73%
IV	25%

Crist, et al. JCO, 2001
Brenneman et al, JCO, 2003

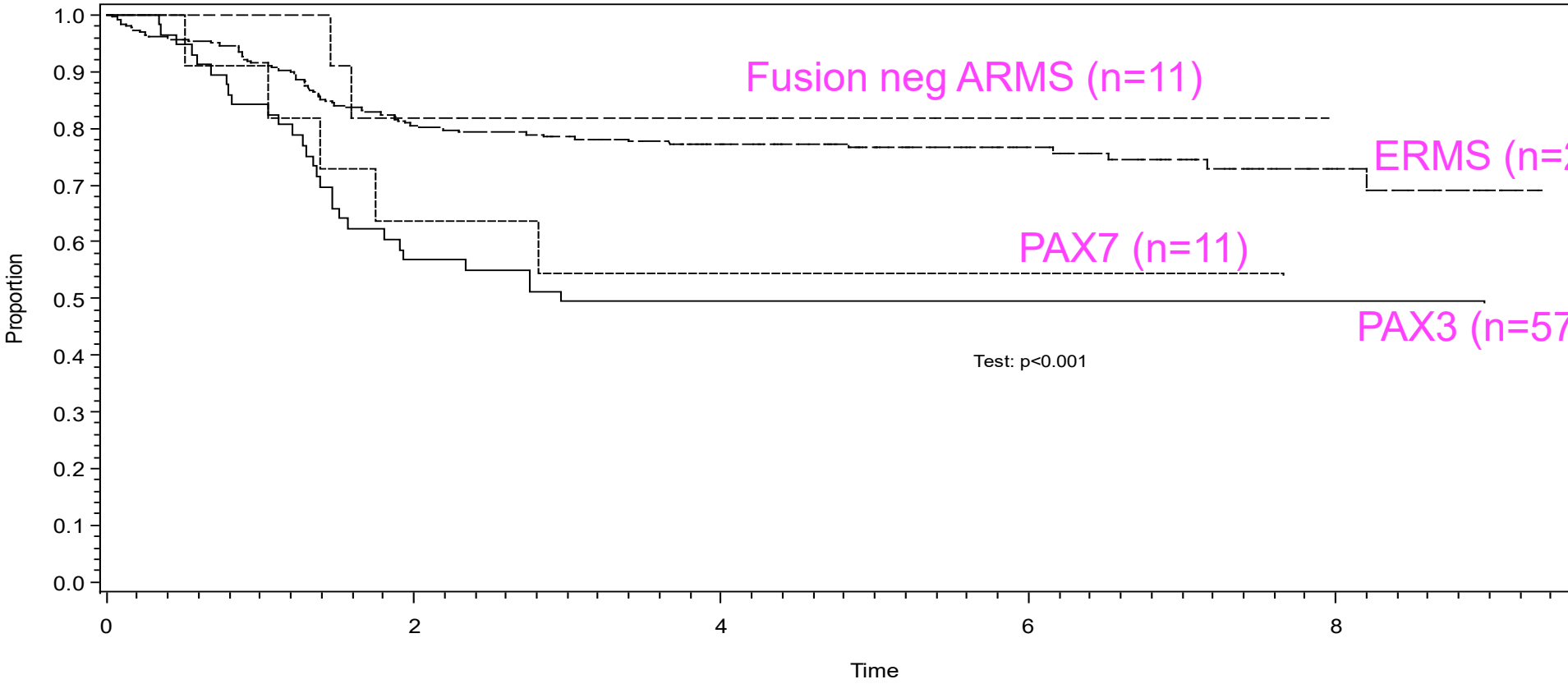
Histology

- Embryonal (ERMS) (90%); better prognosis
  - No consistent translocations
  - Further variants
    - Botryoid (very favorable) - vaginal/bladder in females
    - Spindle cell (very favorable) - paratesticular, orbit
- Alveolar (ARMS) (20%); worse prognosis
  - 2 common translocations

Tumor Molecular Biology

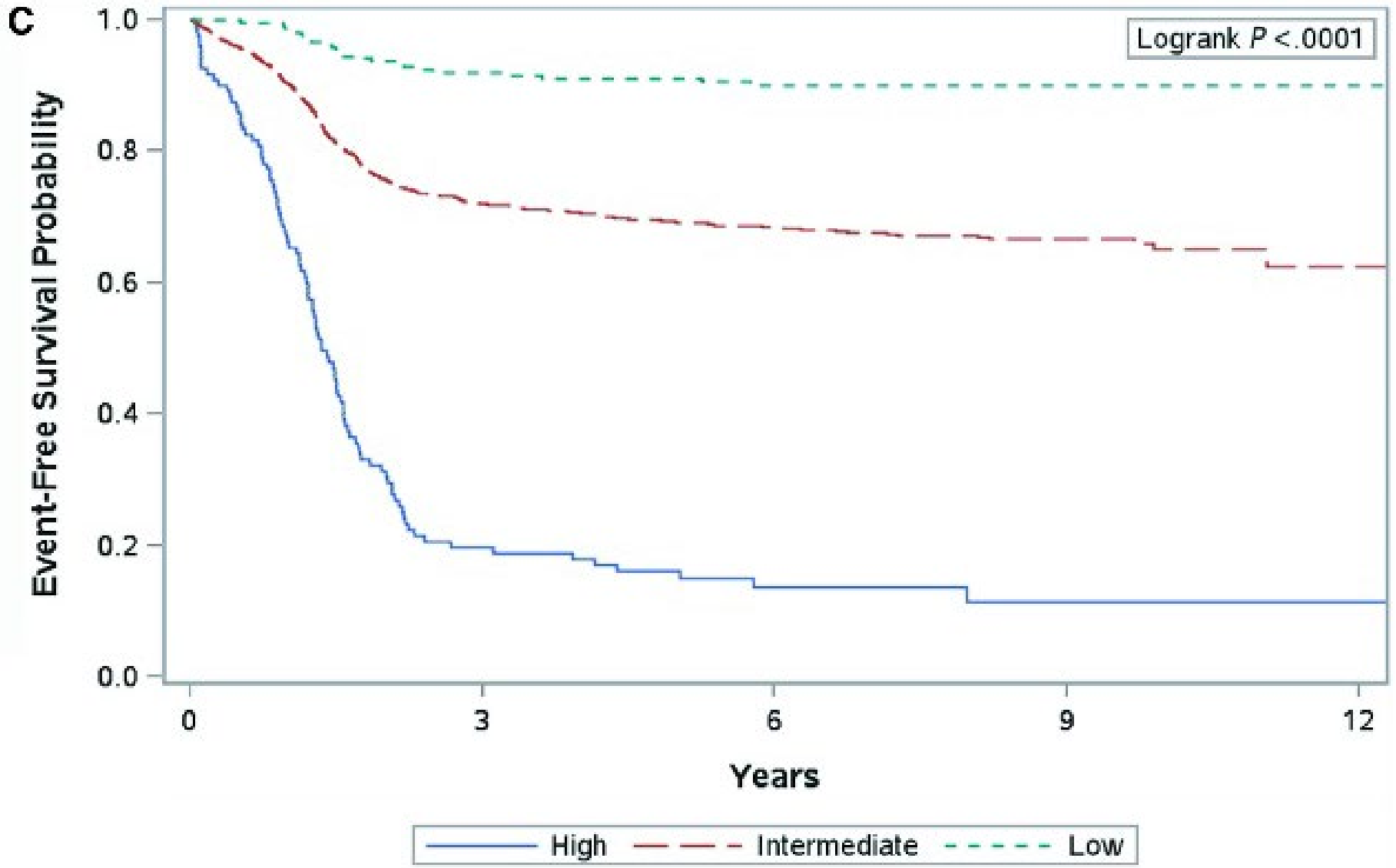
- Translocation or fusion ***Positive***
  - 70-80% ARMS
  - t(2;13) → PAX3-FOXO1 (60%)
    - Significantly poorer outcome, 4y OS 8%, older patients
  - t(1;13) → PAX7-FOXO1 (20%)
    - Better outcome compared to t(2;13) but worse than ERMS, 4y OS 75%, younger patients
- Translocation or fusion ***Negative***
  - Most often seen with ERMS
  - Fusion neg ARMS outcomes are indistinguishable from ERMS cases

Williamson et al. JCO 2010
Sorensen et al. JCO 2002


Fusion neg ARMS (n=11)
ERMS (n=
PAX7 (n=11)
PAX3 (n=57
Test: p<0.001
Proportion
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
Time

COG Risk

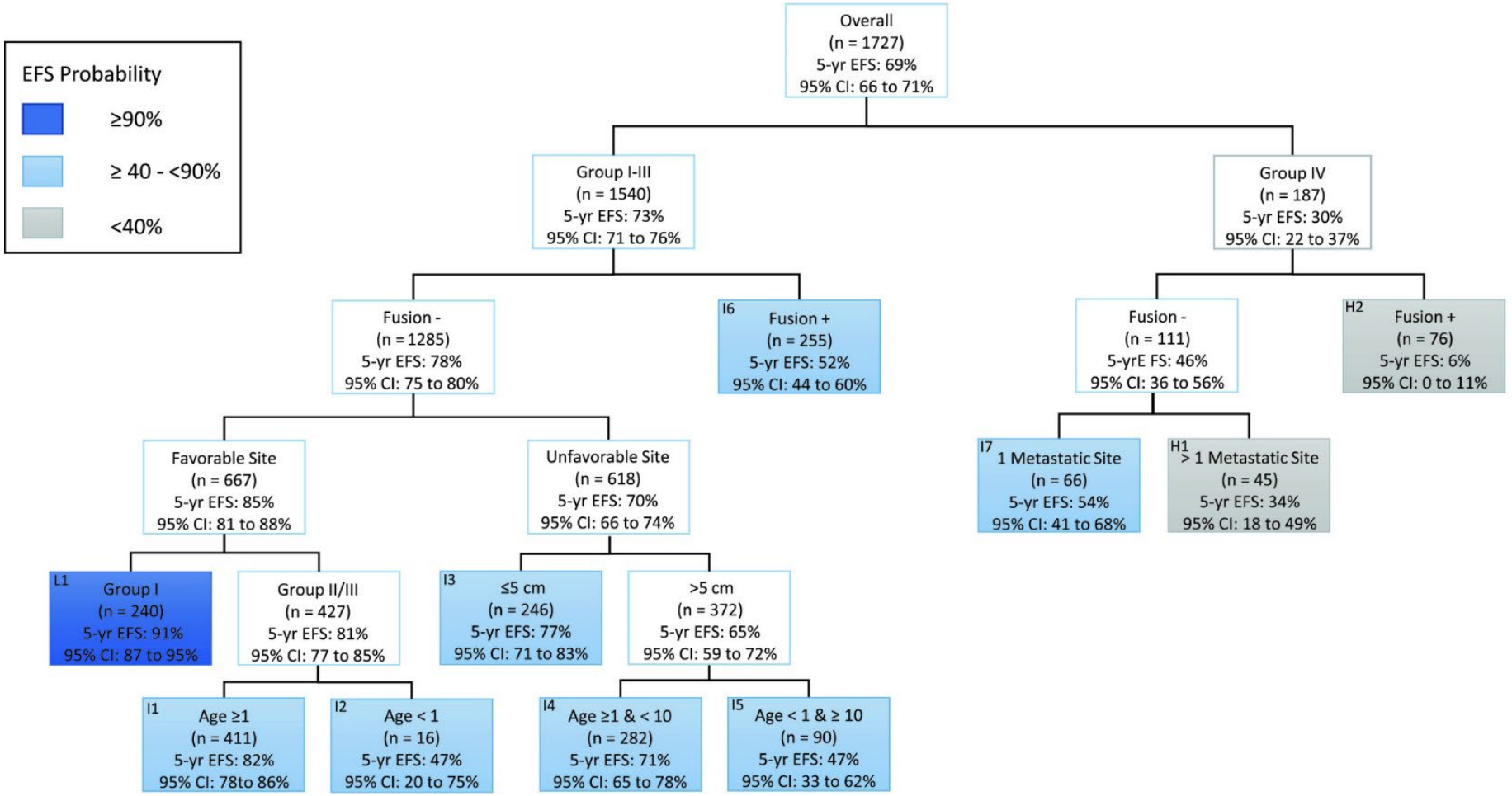
Risk category	Stage	Group	Fusion	3-year FFS
Low	I	I	neg	88%
	II	I		
	II	II		
	III	I		
	III	II		
Intermediate	II, III	I, II, III	pos	55-76%
	I, II, III	III	neg	
High	IV	IV	neg	<30%
	IV	IV	pos	



No. at Risk

High	121	22	10	2	1
Intermediate	1366	933	507	154	11
Low	240	211	152	50	4

Very Complicated…



Treatment

- Tissue diagnosis → chemotherapy → local control
  - Biopsy vs. resection
- "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

Chemotherapy

- Backbone of Rhabdo therapy is VAC (COG)
  - Vincristine, Actinomycin and Cyclophosphamide
  - SIOP uses IVA (ifosfomide instead of cyclophosphamide) ± anthracycline
- Other active drugs include:
  - Ifosfamide
  - Etoposide
  - Doxorubicin
  - Topotecan
  - Irinotecan
  - Temsirolimus

Collaborative Group Study

- IRSG → COG — North America
- SIOP — Europe/rest of world
- INSTRuCT — worldwide collaboration

- Historically → early radical surgical excision
- Details on treatment varies, survival is about the same

Collaborative Group Study

COG	Topic Difference	SIOP
• Minimize surgical morbidity/disfigurement • Emphasize organ preservation	**Study Goal**	• Minimizes use of local control with chemotherapy intensification

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• Minimize surgical morbidity/disfigurement • Emphasize organ preservation	**Study Goal**	• Minimizes use of local control with chemotherapy intensification
• XRT preferable	**Local Control**	• Surgery followed by XRT in select cases

Collaborative Group Study

COG	Topic Difference	SIOP
• Minimize surgical morbidity/disfigurement • Emphasize organ preservation	**Study Goal**	• Minimizes use of local control with upfront chemotherapy intensification
• XRT preferable	**Local Control**	• Surgery followed by XRT in select cases
• EFS	**Endpoint**	• OS

Collaborative Group Study

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• Minimize surgical morbidity/disfigurement • Emphasize organ preservation	**Study Goal**	• Minimizes use of local control with chemotherapy intensification
• XRT preferable	**Local Control**	• Surgery followed by XRT in select cases
• EFS	**Endpoint**	• OS
• Accept more toxic initial treatment to avoid salvage therapy	**Salvage**	• 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

COG		Site	SIOP	
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 based on protocol

INSTRuCT

- Multiple smaller groups studying a rare disease
  - Can’t ever generate numbers to make meaningful advancements
- Data commons to aggregate collected data
  - Harmonize definitions
  - Modeled after NBL
- Publish consensus statements/guidelines
- Allow for future joint projects

Conclusion

- Decisions and timing have major impact on therapy
  - Call your friends, load the boat, take time to think
- Nuances are complex
  - Keep a cheat sheet, refer to current protocols
- COG vs. SIOP – just different, neither clearly “better”
- INSTRuCT guidelines/future studies will likely be invaluable

amanda.saltzman@uky.edu
504-444-1443

@UKYurology @ UKYPedsUro @urosaltyMD

University of Kentucky
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