Bladder and Prostate

PAYA Urologic Oncology Course , Colorado Spring 2022

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A peds urologist’s journey with care of kids with bladder and prostate rhabdomyosarcoma…….

Overview

- **BACKGROUND**
  - **EPIDEMIOLOGY**

- **RISK STRATIFICATION**
  - **TNM PRE-TREATMENT STAGING CLASSIFICATION**
  - **GROUPING CLASSIFICATION**
  - **PATHOLOGY/HISTOLOGY**
  - **RISK STRATIFICATION SCHEMA**

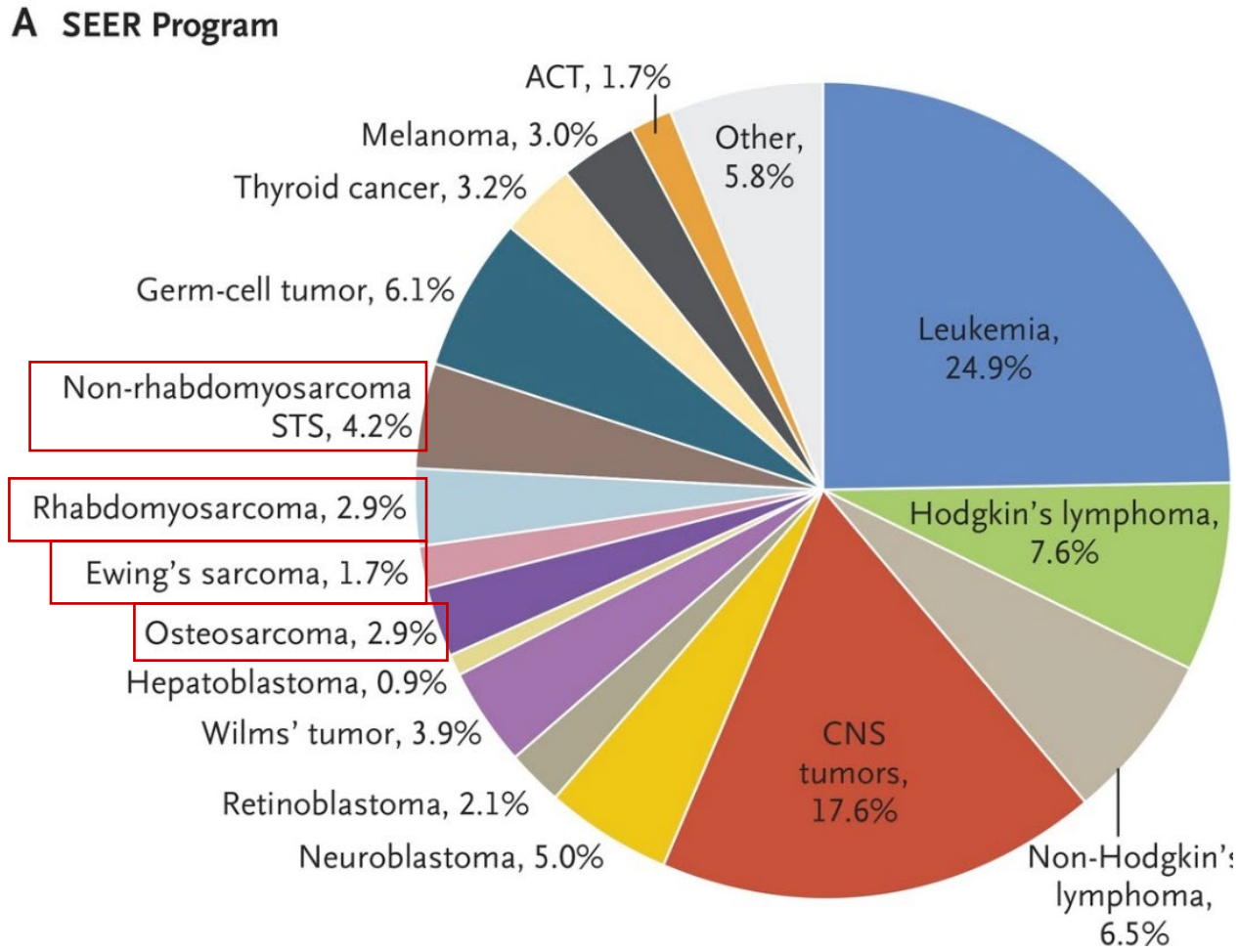
- **TREATMENT BASED ON RISK STRATIFICATION**
  - **Chemo**
  - **Surgery**
  - **XRT**

Basics and Background

Bladder and Prostate Tumors

Rhabdomyosarcoma (RMS) is the most common pediatric soft-tissue sarcoma.

Bladder and Prostate location specifically is the most common primary GU site of RMS and accounts for about 5% of all RMS

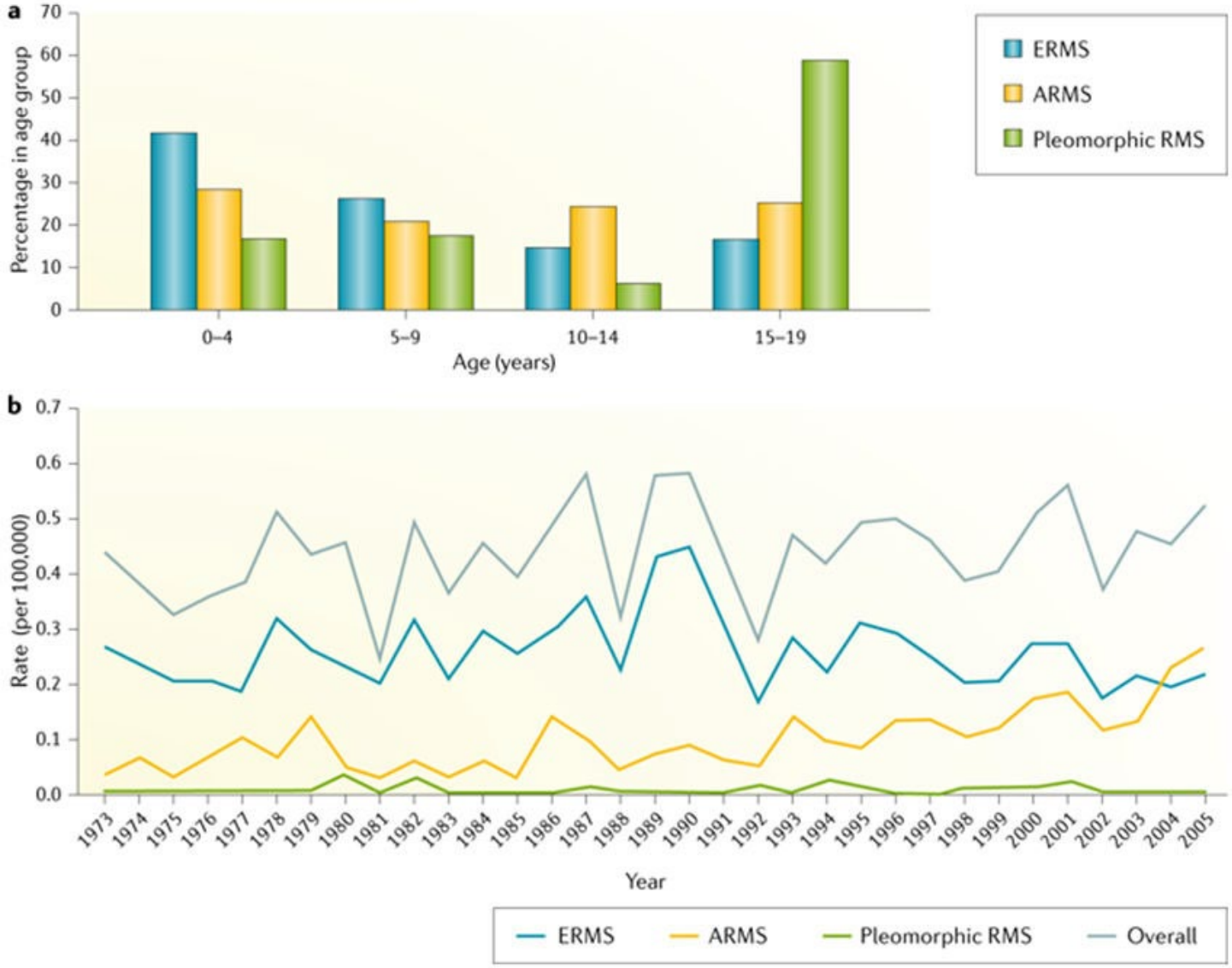


Frequency of Pediatric Cancer Types among Patients Younger than 20 Years of Age

Zhang J et al. N Engl J Med 2015;373:2336-2346.

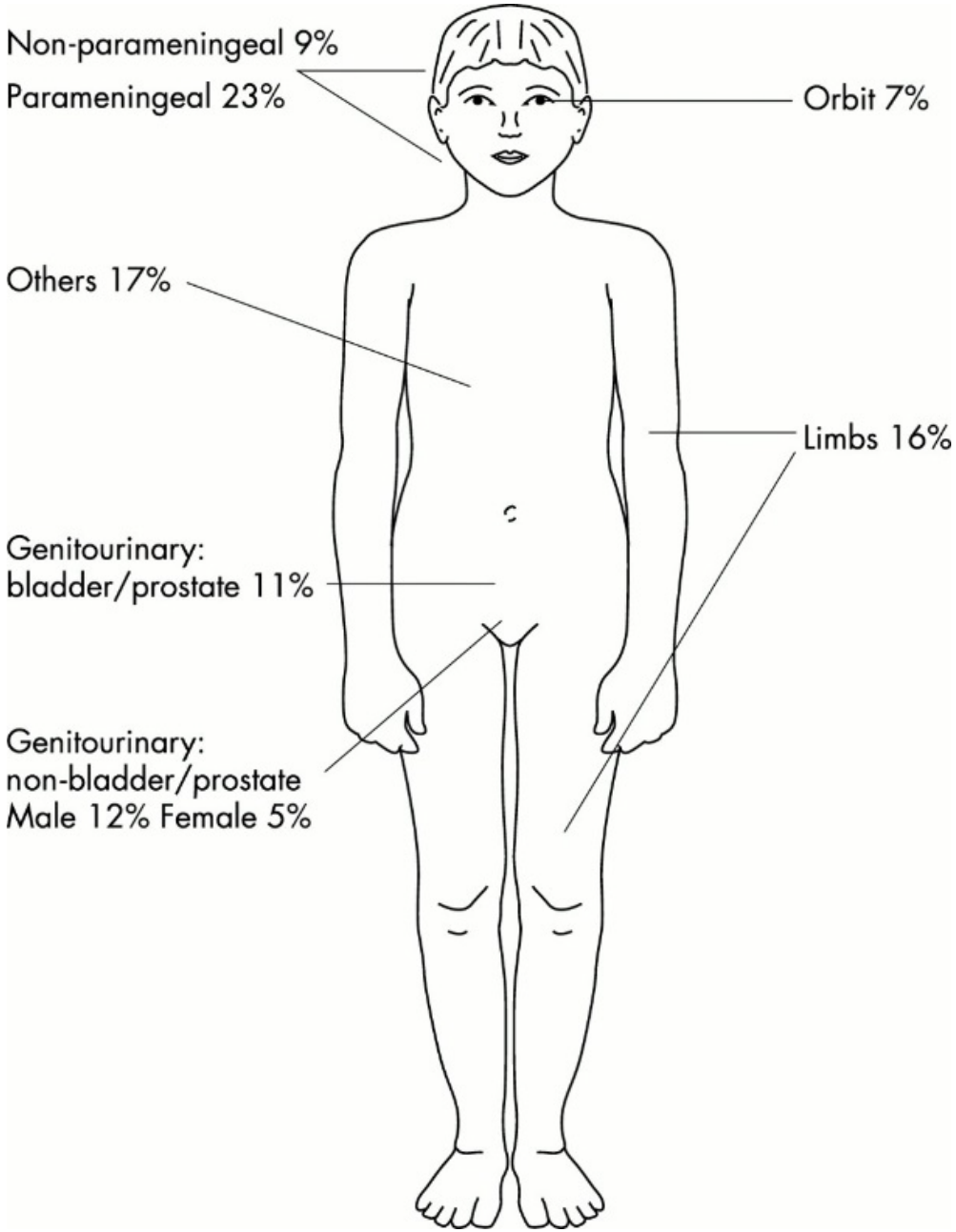
RMS incidence varies with age and subtype

There is a bimodal age distribution, with peaks in the first decade (> 50% of cases, median age 2 years, mostly embryonal or botryoid RMS) followed by a peak during adolescence (mostly alveolar RMS) .



Rhabdomyosarcoma (RMS)

- Approximately 15–20%of all RMS arise from the genitourinary (GU) system.
- GU sites that can be affected by RMS include:
  - the female genital tract (vagina, uterus, cervix), paratestis, bladder/prostate (BP)
- **BP location specifically is the most common primary GU site of RMS and accounts for about 5% of all RMS**



McDowell BMJ, 2002

GU RMS Epidemiology

- **BP location specifically is the most common primary GU site of RMS and accounts for about 5% of all RMS**

- About three quarters of all GU RMS will be diagnosed in the first 5 years of life, with a male predominance.

- Age of diagnosis is an important risk factor—age < 1 year or > 10 years has an event free survival (EFS) of 53% compared to 71%for those aged 1–9 years

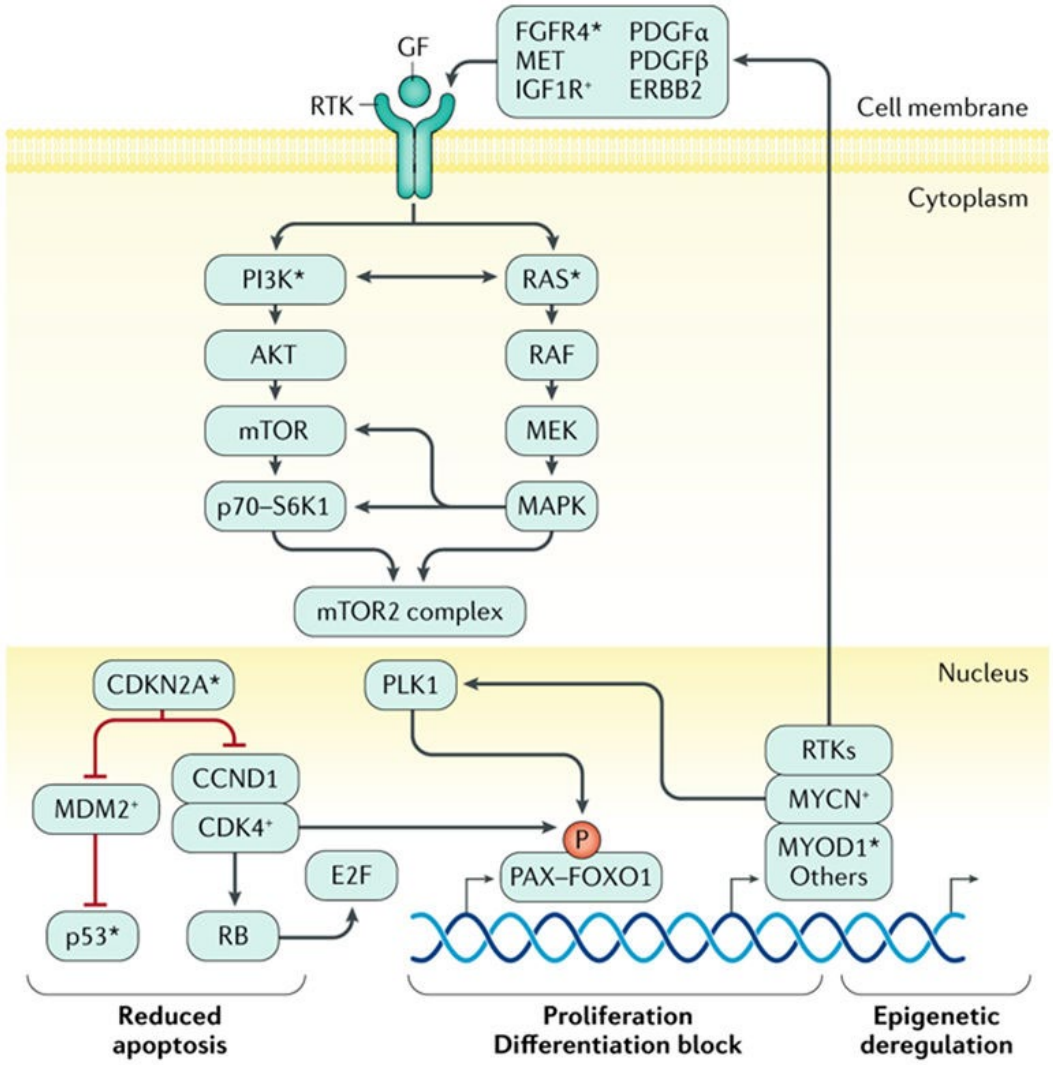
RMS 5-Year Survival By Site

Primary Site	Number of Patients	Survival at 5 Years (%)
Orbit	107	95
Superficial head and neck (nonparameningeal)	106	78
Cranial parameningeal	134	74
Genitourinary (excluding bladder/prostate)	158	89
Bladder/prostate	**104**	**81**
Extremity	156	74
Trunk, abdomen, perineum, etc.	147	67
Biliary	25	78

https://www.cancer.gov/types/soft-tissue-sarcoma/hp/rhabdomyosarcoma-treatment-pdq#link/_778_toc

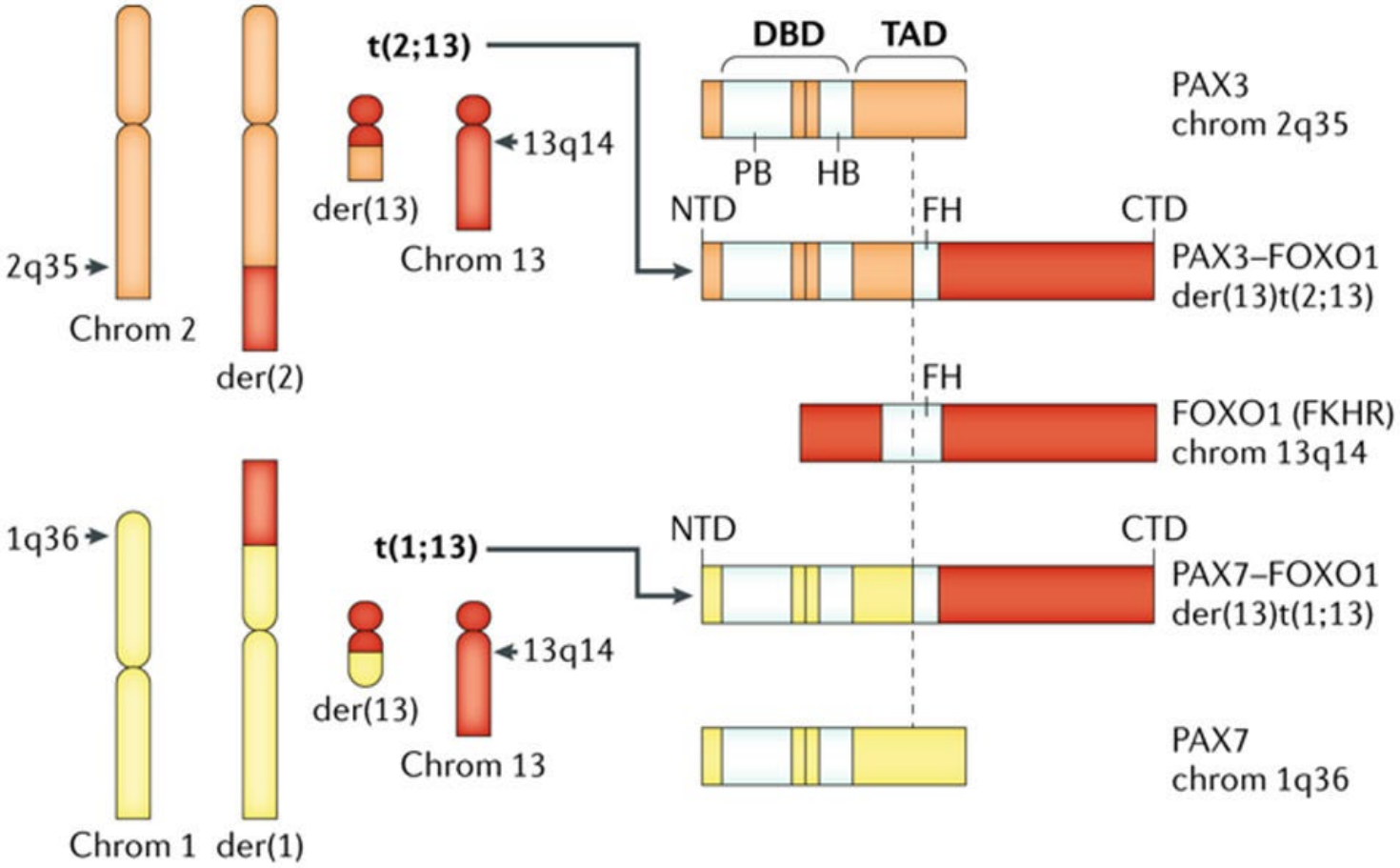
Key functional pathways are perturbed in RMS

In FP RMS, chromosomal translocations result in PAX3–FOXO1 or PAX7–FOXO1 fusion genes.



PAX–FOXO1 fusion gene drives RMS formation

PAX/FOXO1 fusion status is recognized as a more important prognostic factor compared to histologic subtypes, and now will be utilized instead of histology for risk stratification in current and future treatment protocols.



Aberrant gene expression

Aberrant gene expression in RMS

Cause of aberrant gene expression	Gene	Effect	Invasion/ Migration	Proliferation	Transformation	Survival
PAX3/7–FOXO1 fusion protein	*CDH3*/P-Cadherin	Upregulation	++	++	–	–
	CNR1	Upregulation	++	–	–	–
	CXCR4	Upregulation	++	++	–	–
	FGFR4	Upregulation	–	++	–	–
		Mutation	–	++	++	–
	IGF2	Upregulation and/or loss of imprinting	–	++	++	++
	MET	Upregulation	++	++	–	++
	MYCN	Upregulation and/or amplification	–	++	++	–
	TFAP2B	Upregulation	++	–	–	++
Somatic mutation	*TP53*	Loss of Function	–	–	–	++
12q13-15	*MDM2*	Amplification	–	–	–	++
	CDK4	Amplification	–	++	–	–
13q31-32	miR-17-92	Amplification	–	++	–	++
	GPC5	Amplification	–	++	–	–

++, process is upregulated; –, no effect.

Heritable syndromes associated with an increased risk of RMS

Syndrome	Phenotype	Associated gene(s)	References
Li-Fraumeni	Cancer susceptibility syndrome	*TP53*	31
Neurofibromatosis type 1	Systemic effects	*NF1*	32,33
DICER1	Cancer susceptibility syndrome	*DICER1*	37
Costello	Systemic effects	*HRAS*	34,35
Noonan	Systemic effects	*BRAF; KRAS; NRAS; PTPN11; RAF1; SOS1*	34
Beckwith-Wiedemann syndrome	Overgrowth disorder	*IGF2; CDKN1C; H19; KCNQ1OT1*	36

Environmental and other risk factors associated with RMS development

Risk factor	OR (95% CI)	Reference[a]
Birth defects	2.4 (0.9–6.5)	33
Prenatal X-ray exposure	1.9 (1.1–3.4)	25
Maternal drug use	3.1 (1.4–6.7)	42
Paternal drug use	2.0 (1.3–3.3)	42
Childhood allergies	0.6 (0.4–0.9)	44
Use of fertility medications	0.7 (0.2–2.3)	43
Vaginal bleeding during pregnancy	1.8 (1.1–2.7)	43
Premature birth	2.5 (0.7–8.5)	43
First–degree relative with ERMS	2.4 (1.5–3.9)[b]	45
First-degree relative with ARMS	1.0 (0.3–3.5)	45
Paternal exposure to Agent Orange	1.7 (0.6–5.4)	234

Presentation

- Presentation usually involves some combination of hematuria, stranguria (slow, painful voiding), frequency, and urinary retention.
- In young boys who present with urinary retention, RMS must be considered and ruled out.
- This same presentation in a young girl would also be suspicious for urethral or vaginal RMS.
- BP RMS is often large at presentation and may be felt on abdominal

and/or rectal examination.

Presentation

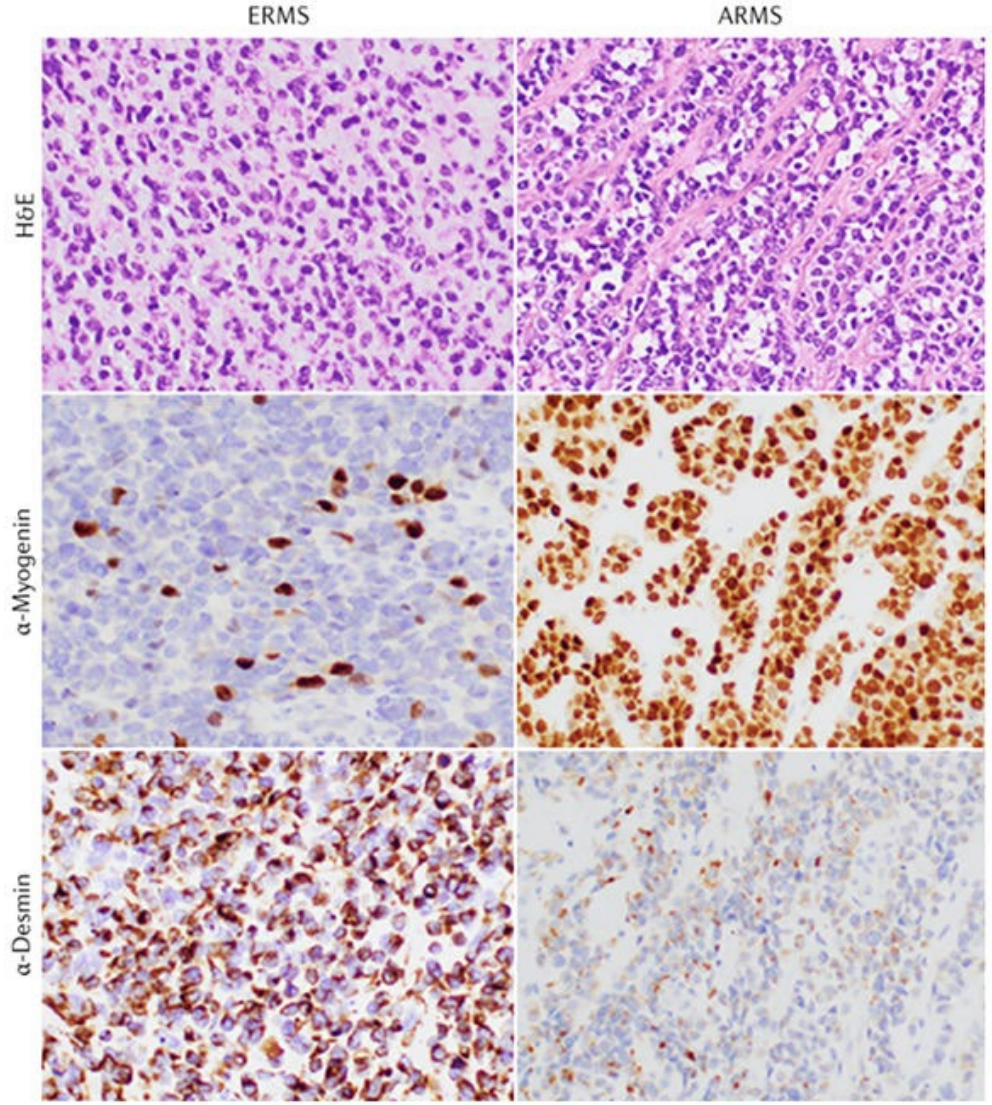
- Bladder lesions tend to be botryoid on the trigone or bladder neck.
- Prostate primaries tend to be large solid and sessile masses.

Evaluation

- Imaging
  - Ultrasound-→ MRI or CT primary site (abdomen and Pelvis for GU)→CT chest→ (PET-CT whole body may have a role)
- FISH/RT-PCR for FOXO1 fusion (important prognostic factor)
- Biopsy of primary site +/- concerning lymph nodes

Rhabdomyosarcoma classification: Histology and fusion status

ERMS and ARMS can be distinguished based on histopathology features



Two distinct histologic and molecular subtypes:

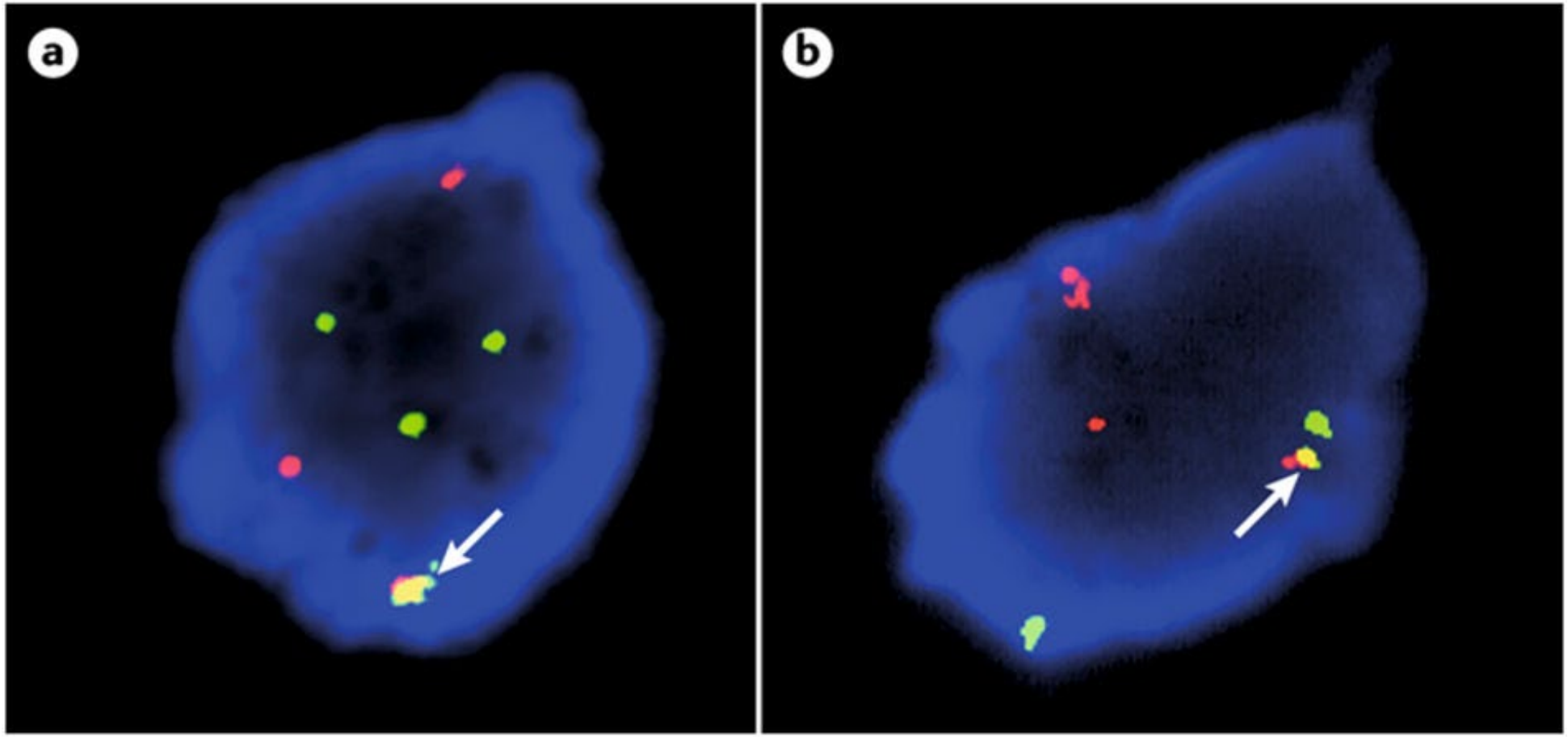
- **<u>Embryonal</u> RMS resembles skeletal muscle during embryonic development**
- <u>Alveolar</u> RMS is a prototypic SRBCT
- Desmin and Myogenin (not shown): markers of skeletal muscle differentiation

ERMS and ARMS
can be distinguished based on histopathology features

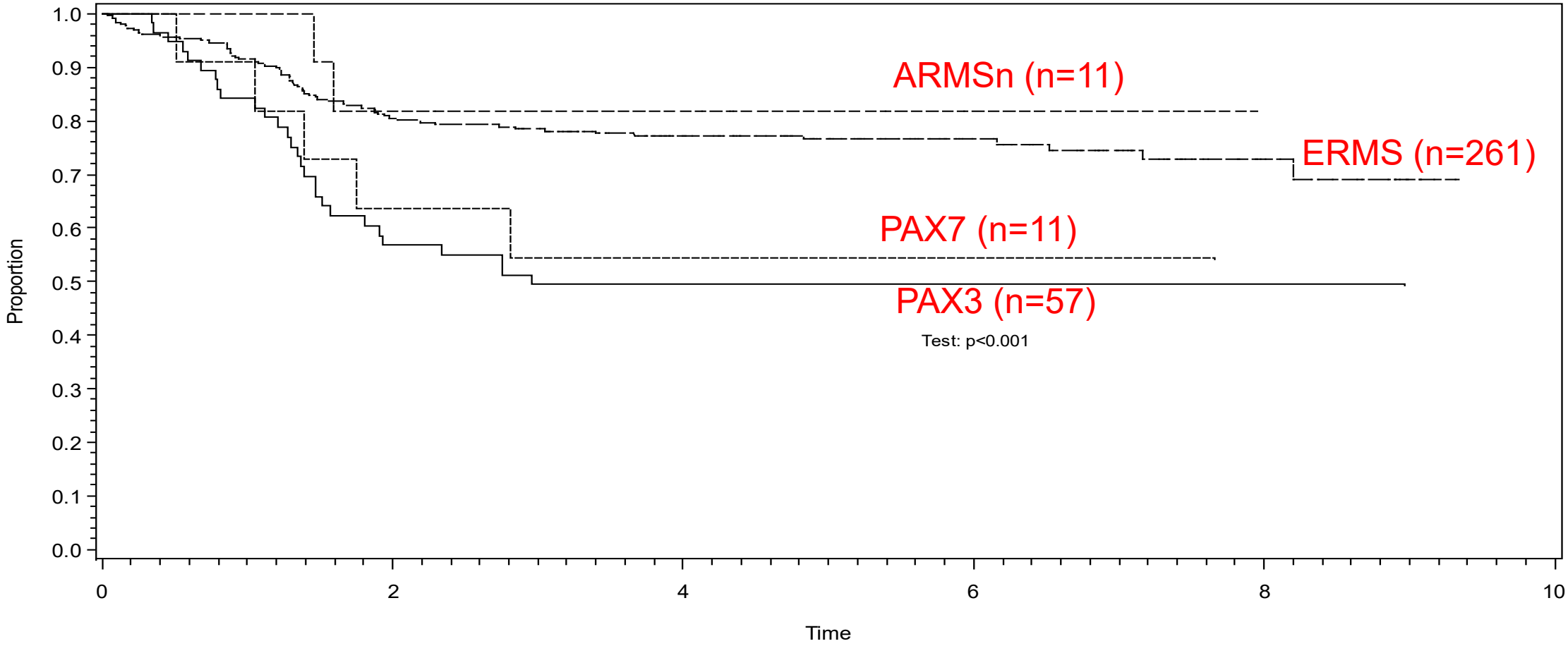
- **Embryonal is the most common (90%), especially in the GU system, and includes subtypes of botryoid and spindle cell.**
- **Embryonal RMS is more common in younger patients and has a better prognosis.**
- **No translocations have been consistently identified in embryonal RMS.**

- Alveolar carries a worse prognosis and is more common in older patients and those with extremity primary tumors [6].
- It has been associated with two translocations which are known to affect prognosis.
- Older patients, t(2;13) is frequently seen and is associated with a worse prognosis,
- Younger patients commonly have t(1;13) and a better prognosis than t(2;13) translocations
- But still much worse than embryonal RMS

PAX–FOXO1 translocation can be detected by FISH



FOX01 Fusion Status and Outcome



The presence of PAX-FOXO1 fusion drives unfavorable outcomes in children with RMS and is clinically and biologically different from fusion-negative ARMS and ERMS.

Risk Stratification

GU RMS

Staging uses the TNM system (clinical at the time of diagnosis, with histologic confirmation of RMS, generally BEFORE surgical intervention/assigned by the 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

Notes:

T1	Confined to the anatomic site of origin
T2	Extension and/or fixation to surrounding tissue
a	≤ 5 cm
b	> 5 cm
Nx	Regional LNs not evaluated
N0	Regional LNs not involved
N1	Regional LNs involved
M0	No distant metastasis
M1	Distant metastasis

BP is considered an unfavorable site and thus cannot be stage I

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

Grouping is based on pathologic histologic diagnosis (AFTER surgical intervention but BEFORE chemotherapy initiation)

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

Notes:

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

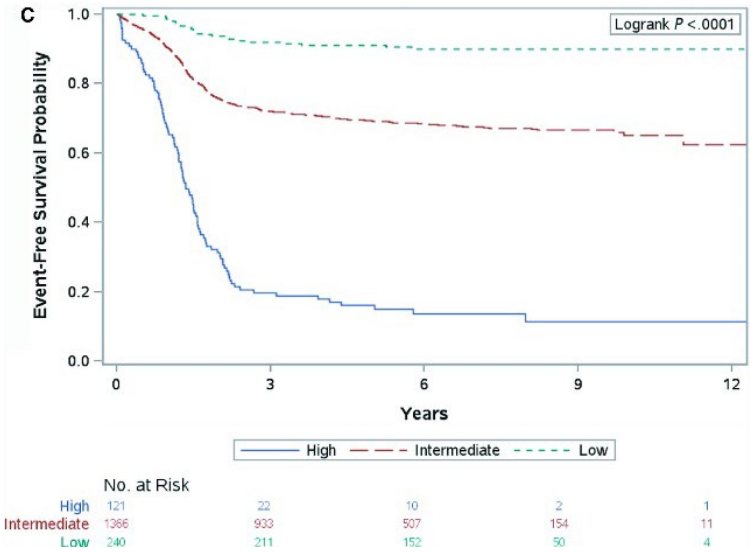
Risk Stratification for RMS

TABLE 3 Overall survival for terminal leaves from event-free survival tree

Risk group	Terminal leaf	Clinical group	Fusion status	Primary site	Age, years	Tumor size	Number of meta-static sites	5-year OS, %	95% CI of 5-year OS
Low	L1	I	Negative	Favorable	Any	Any	NA	99	97-100
Intermediate	I1	II/III	Negative	Favorable	≥1	Any	NA	93	90-96
	I2	II/III	Negative	Favorable	<1	Any	NA	80	59-100
	I3	I-III	Negative	Unfavorable	Any	≤5cm	NA	85	80-91
	I4	I-III	Negative	Unfavorable	≥1 or <10	>5cm	NA	81	75-86
	I5	I-III	Negative	Unfavorable	<1 or ≥10	>5cm	NA	61	46-75
	I6	I-III	Positive	Any	Any	Any	NA	65	58-73
	I7	IV	Negative	Any	Any	Any	1	70	57-82
High	H1	IV	Negative	Any	Any	Any	>1	40	24-56
	H2	IV	Positive	Any	Any	Any	Any	19	10-28

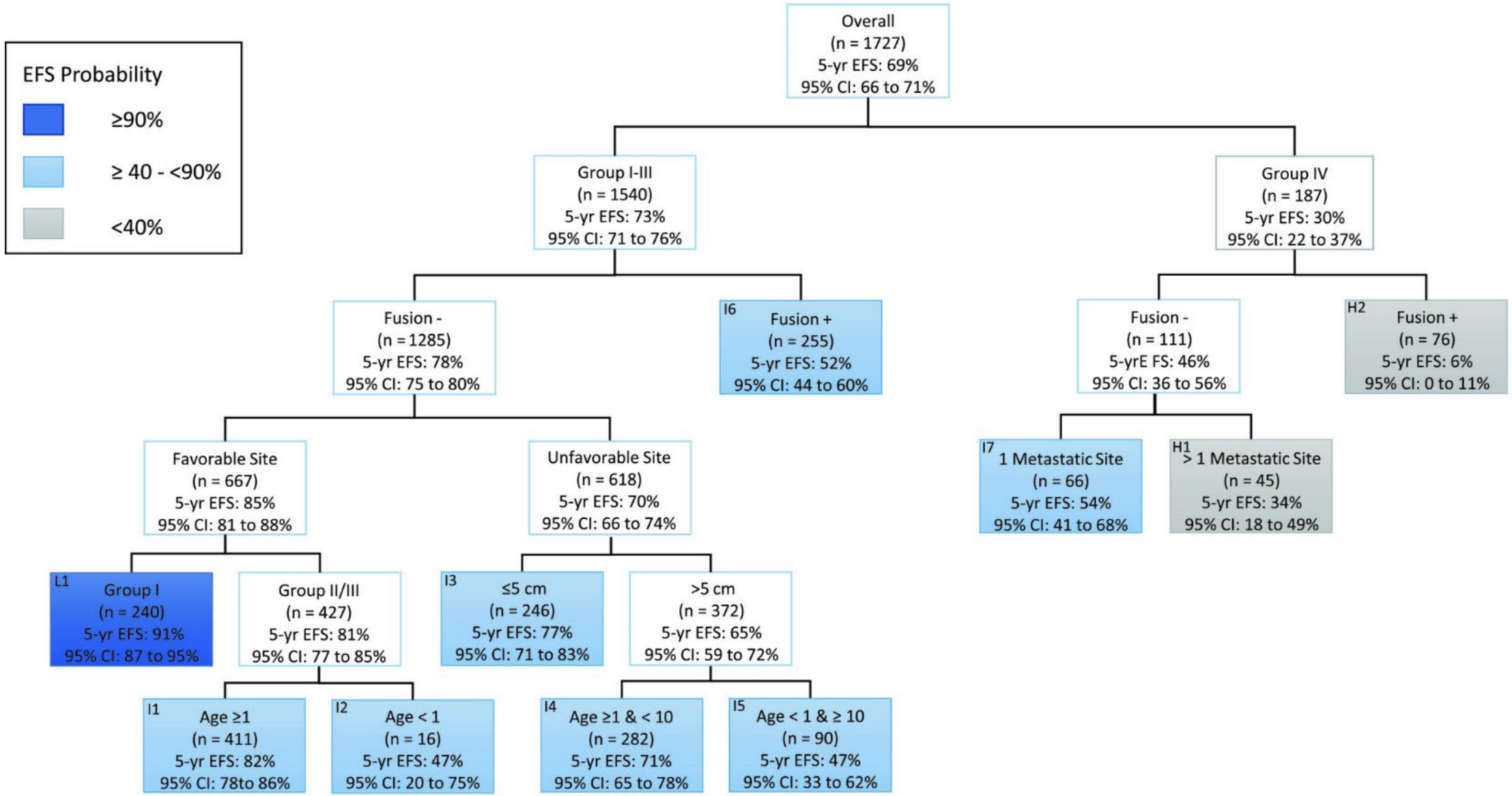
Abbreviations: CI, confidence interval; NA, not applicable; OS, overall survival.

Site (Favorable vs Unfavorable)
Size, regional nodes (Stage 2 vs 3)
Post-operative status (Group I/II vs III)
Distant Metastases (Group IV/Stage 4)
Histology (Embryonal vs. Alveolar)



Hibbits et. al., Cancer Medicine, 2019

Risk Stratification is complicated!



Treatment

Based on Risk Stratification

“Organ Sparing” Treatment: Pediatric cooperative groups

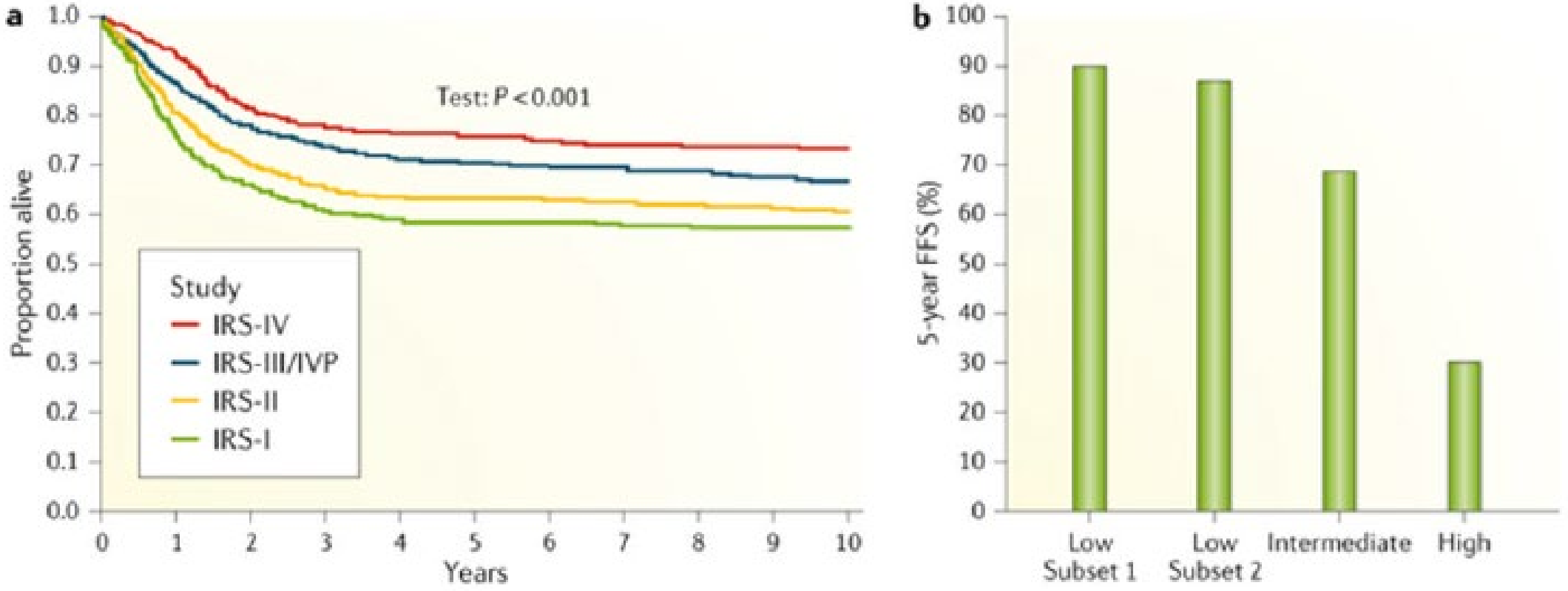
SIOP

- Initial chemo and chemo intensification
- Local control: Surgery as initial modality followed by XRT in select case
- Overall survival endpoint

COG

- Initial chemotherapy
- Local control XRT
- Event Free Survival is endpoint rather than OS to avoid salvage therapy which is more toxic

Risk stratification matters!



Nat Rev Dis Primers. 2020 August 30.

The name of the game is “LOCAL CONTROL” and “Organ sparing”

Role of Surgery……everyone agrees to a game plan…onc, radiation, surgeon, pathologists and family

RMS Treatment Strategy

- Chemotherapy and radiotherapy sensitive

  Surgery only: 25% 5 yr survival

  Chemo, XRT, surgery: 70% 5 yr survival

- Standard chemotherapy includes intensive use of:
  - Vincristine
  - Actinomycin-D
  - Cyclophosphamide
  - Irinotecan

What is the role of surgery?

- Biopsy techniques, role of LN sampling
- Pre-treatment re-excision
- Delayed Primary Excision
- Radiation considerations
- RMS in very young children
- Diversion after surgical extirpation

Surgery: Biopsy

- Tumors of the bladder, prostate and vagina may be amenable to endoscopic biopsy.

- Image-guided core needle biopsy may also be considered in the diagnostic workup of both primary and metastatic disease.
  - Given the generally smaller samples of tissue obtained, this technique garners concern for inadequate tissue sampling for molecular biology studies and an increased risk of sampling error.
  - If image-guided percutaneous core needle biopsy is chosen, a generous number of large caliber cores verified by real-time involvement of the pathologist to ensure adequate viable tissue for complete assessment of biologic markers is highly encouraged.

Surgery: Biopsy

- **If open biopsy needed, LN sampling performed to improve staging and grouping**

Surgery: Primary resection

Primary upfront resection should be performed if the location and size of the tumor allow a complete resection without compromising function or form.

- Resection should only be attempted if it is anticipated that all gross tumor can be resected, **as leaving gross residual disease has no better outcome than biopsy alone.**
- If intraoperatively it is determined that **unresectable gross or suspected microscopic disease remains**, *titanium clips* should be placed strategically to guide radiotherapy or a subsequent repeat resection
- A **margin** of 0.5 cm is considered adequate although there is minimal objective data to support this recommendation.
- All margins should be marked and oriented at the operative field with direct communication with the pathologist to ensure precise margin assessment.

Surgery: Pre-treatment re-excision

Pretreatment re-excision (PRE) is a complete wide local resection of a biopsied or incompletely excised tumor or tumor bed prior to the initiation of chemotherapy.

- This should be considered in cases where **only a biopsy was performed, residual gross or microscopic disease is present, a non-oncologic operation was initially performed, or the status of margins are unclear.**
- **PRE should be offered only if resection of the entire tumor or bed with a margin can be performed without loss of form or function.**
- **Clinical group is assigned based on resection status after PRE** and patients undergoing PRE with negative margins achieve favorable outcomes similar to other group I patients who underwent initial complete primary excision

Surgery: Delayed primary excision

Delayed primary excision (DPE) is resection of residual tumor after induction chemotherapy.

- For patients with initially unresectable tumors, DPE can be considered if a grossly complete resection is anticipated without unacceptable loss of function or form.

- A complete (R0) or microscopic residual (R1) resection can allow for reduction in RT dosing.

- **Debulking surgery leaving gross disease behind has not been shown to improve outcomes over biopsy alone at any time point and therefore is not recommended for any site**

“Second look” Surgery for residual masses after chemo/XRT

- For unresected lesions, a residual mass at the end of all planned therapy may be present.

- Second look info is challenging:
  - **Well-differentiated/mature rhabdomyoblasts can be found on pathology and easily confused for active disease on frozen section.**

- Cystoscopy, abdominal exploration, biopsy, partial cystectomy, or radical cystoprostatectomy

Surgery for Local Control for Bladder and Prostate RMS in infants

- Children with RMS receive multimodal therapy including alkylator- and anthracycline-based chemotherapy, RT, and surgery, and long-term effects can be devastating.

- A role for individualized therapy for infants and young children

- Shared decision making for the “least bad option”

XRT as Local control in very young children

XRT late effects can be devastating……

XRT dosing for BP RMS range 30 and >60 Gy

- For example, Effects on growing skeleton significant
  - Years after treatment
  - Permanent
  - Limb length discrepancies
  - Younger have greater potential for growth loss

Diversion after surgical extirpation

- Perform incontinent urinary diversion
- Not the time to “push the envelope”
- Intraop frozen sections to determine urethral margin status has a high rate of false negativity

Surgery: Lessons learned

1. Prognosis is related to group

- Group I patients have the best prognosis
- Group IV patients have the worst prognosis
- Try to remove all visible tumors if feasible without excess morbidity

2. Wide local excision is indicated for tumors to achieve negative margins, if feasible functionally and cosmetically

3. Organ function should try to be preserved (bladder, vagina)

- Primary chemotherapy followed by XRT is indicated for these sites, after initial biopsy
- Delayed excision (complete response) may improve prognosis after allowing chemotherapy ± XRT to achieve a partial response (makes the tumor resectable)

XRT: Lessons learned

1. For group I embryonal RMS there is no evidence to give XRT

- Complete surgical resection is all that is needed for local control
- Patients with group IV disease however receive XRT to the primary site, regional LNs if involved and sites of metastasis

2. Patients with group II disease have better outcome with intensified therapy

3. Local failure for group III patients is 19% for all GU sites

4. For group III patients, daily XRT up to 50.4 Gy is standard (not twice daily)

Chemotherapy: Lessons learned

1. VAC chemotherapy is standard for patients with groups III and IV disease

• No evidence that adding doxorubicin or doxorubicin and cisplatin ± etoposide improves outcomes in patients with advanced disease

2. VAC is equally effective as VAI and VIE

3. Increased dosing of cyclophosphamide has improved survival for patients with embryonal histology, but not alveolar or undifferentiated histologies

4. Toptecan can be given with VAC in patients with metastatic disease

Pathology/biology: Lessons learned

1. Alveolar histology has worse prognosis than embryonal

• With treatment intensification in subsequent studies, survival was improved

2. For bladder RMS patients, maturing rhabdomyoblasts in sequential biopsies after chemotherapy and XRT does not necessarily signify the presence of malignant cells

• When this occurs, continue chemotherapy and follow with imaging studies, to allow bladder preservation

3. 2 translocations in alveolar RMS have been identified that affect prognosis

• t(2;13) occurs in older patients and is associated with a worse prognosis

• t(1;13) occurs in younger patients and is associated with a better prognosis than t(2;13)

• No translocations have been consistently identified in embryonal RMS

Pathology/biology: Lessons learned

4. Tumors should be sent fresh to pathology for analysis, without preservatives

• This will allow for more molecular studies to be performed on these tumors

5. All patients with RMS should be followed long-term due to the risk of second malignancies

• Risk is highest in those receiving XRT and alkylating agents (cyclophosphamide, ifosfamide)

Recommended readings

Nat Rev Dis Primers. ; 5(1): 1. doi:10.1038/s41572-018-0051-2.

Rhabdomyosarcoma

Stephen X. Skapek[1,2], Andrea Ferrari[3], Abha Gupta[4], Philip J. Lupo[5], Erin Butler[1], Janet Shipley[6], Frederic G. Barr[7], Douglas S. Hawkins[8]

APSA
American Pediatric Surgical Association
Saving Lifetimes™

Handbook for Children with Rhabdomyosarcoma

Current Urology Reports (2018) 19: 11
https://doi.org/10.1007/s11934-018-0761-8

PEDIATRIC UROLOGY (D WEISS, SECTION EDITOR)

Current Treatment of Pediatric Bladder and Prostate Rhabdomyosarcoma

Amanda F. Saltzman[1] · Nicholas G. Cost[1]

ELSEVIER

CrossMark

Urologic Oncology: Seminars and Original Investigations 34 (2016) 93–102

UROLOGIC ONCOLOGY

Seminar article

Current standards of care in bladder and prostate rhabdomyosarcoma

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Clinical Scenarios in Bladder and Prostate Tumors

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Cases contributed and panelists:

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Rodrigo Romao, MD

Jonathan Ross, MD

Jonathan Routh, MD

Amanda Saltzman, MD

Case

30 mo girl with exophytic vaginal mass

Rodrigo Romao, MD, Msc

Case

- Female patient
- 30 months old
- Exophytic vaginal mass

- Vaginoscopy with biopsy
- Embryonal RMS, botryoid variant
- Negative metastatic work-up

Table 4. Soft Tissue Sarcoma Committee of the Children's Oncology Group: Rhabdomyosarcoma Risk Group Classification

Risk Group	Histology	Stage	Group
Low risk	Embryonal	1	I, II, III
	Embryonal	2, 3	I, II
Intermediate risk	Embryonal	2, 3	III
	Alveolar	1, 2, 3	I, II, III
High risk	Embryonal or Alveolar	4	IV

Proposed treatment – VAC chemotherapy with re-evaluation at week 12

Discussion about local control

Re-evaluation at 12 weeks

- Vaginoscopy
- Small clusters of superficial mucosa abnormalities – anterior and posterior wall

- Biopsy - rhabdomyoblasts

Local control in patients with low-risk group III vaginal RMS

- Important to achieve long-term remission

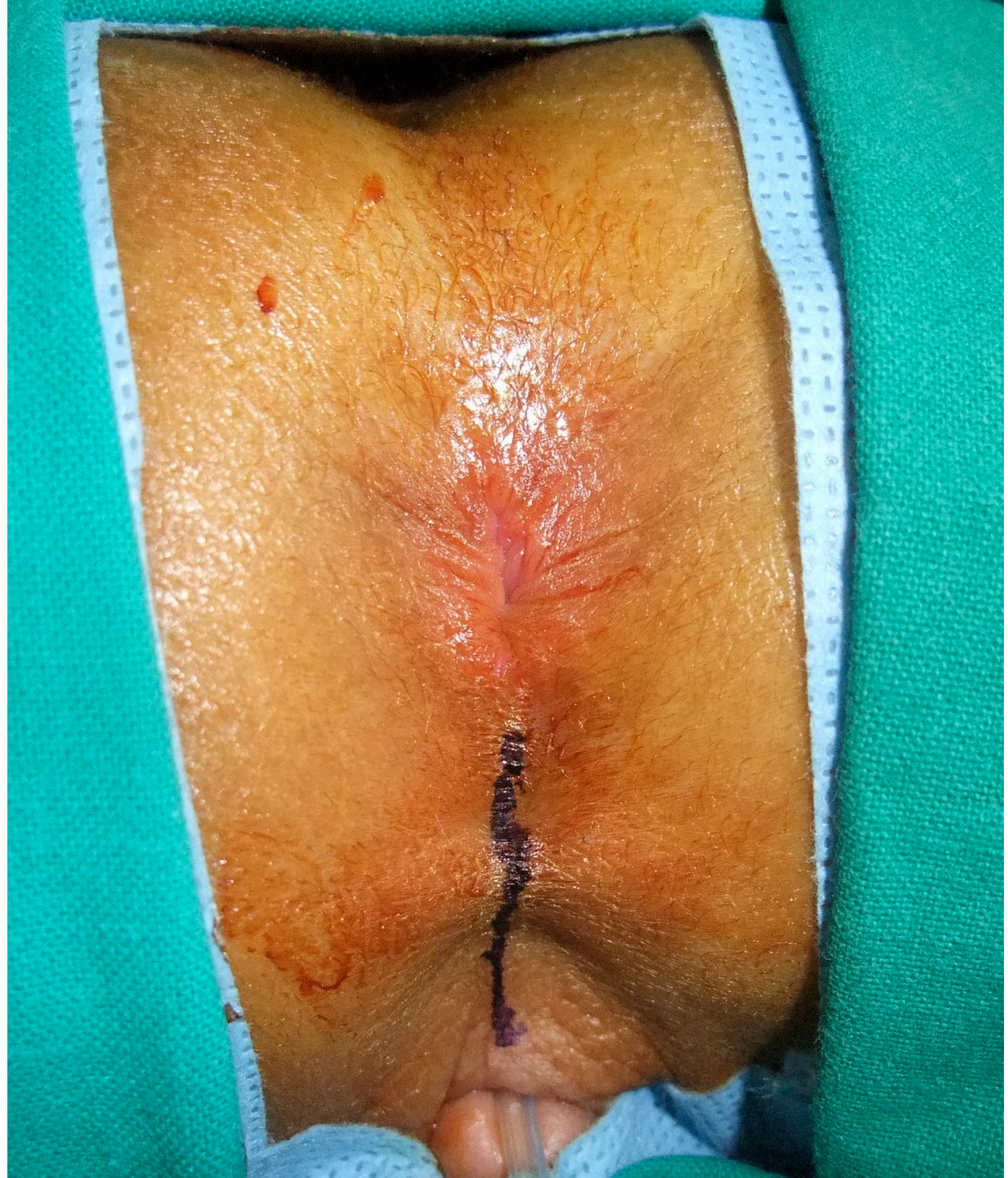
- Salvage radiation therapy after initial omission is effective and expected survival excellent

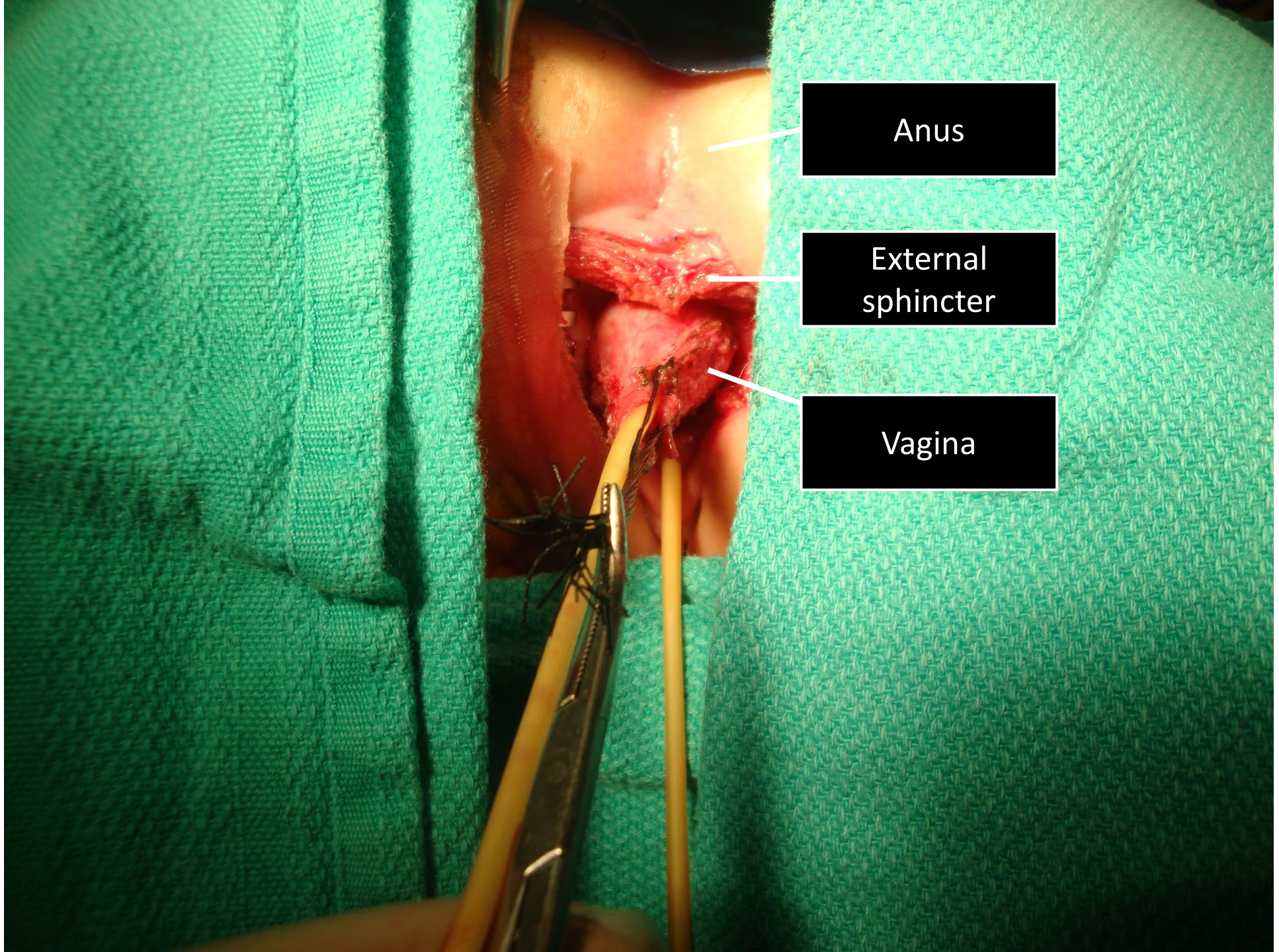
Is there a surgical local control strategy that can replace radiation with its undesirable side effects to the young pelvis?

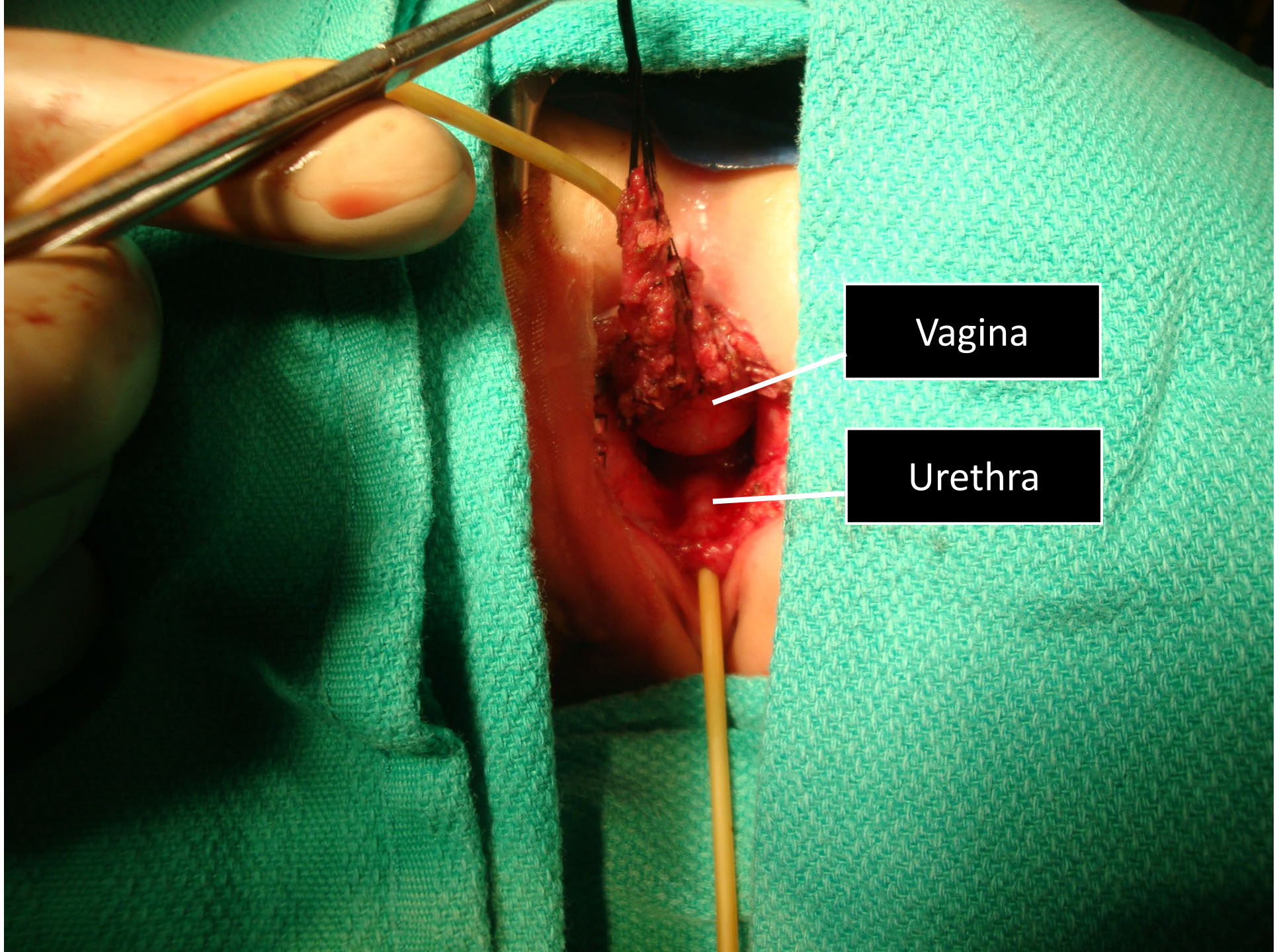
Technique

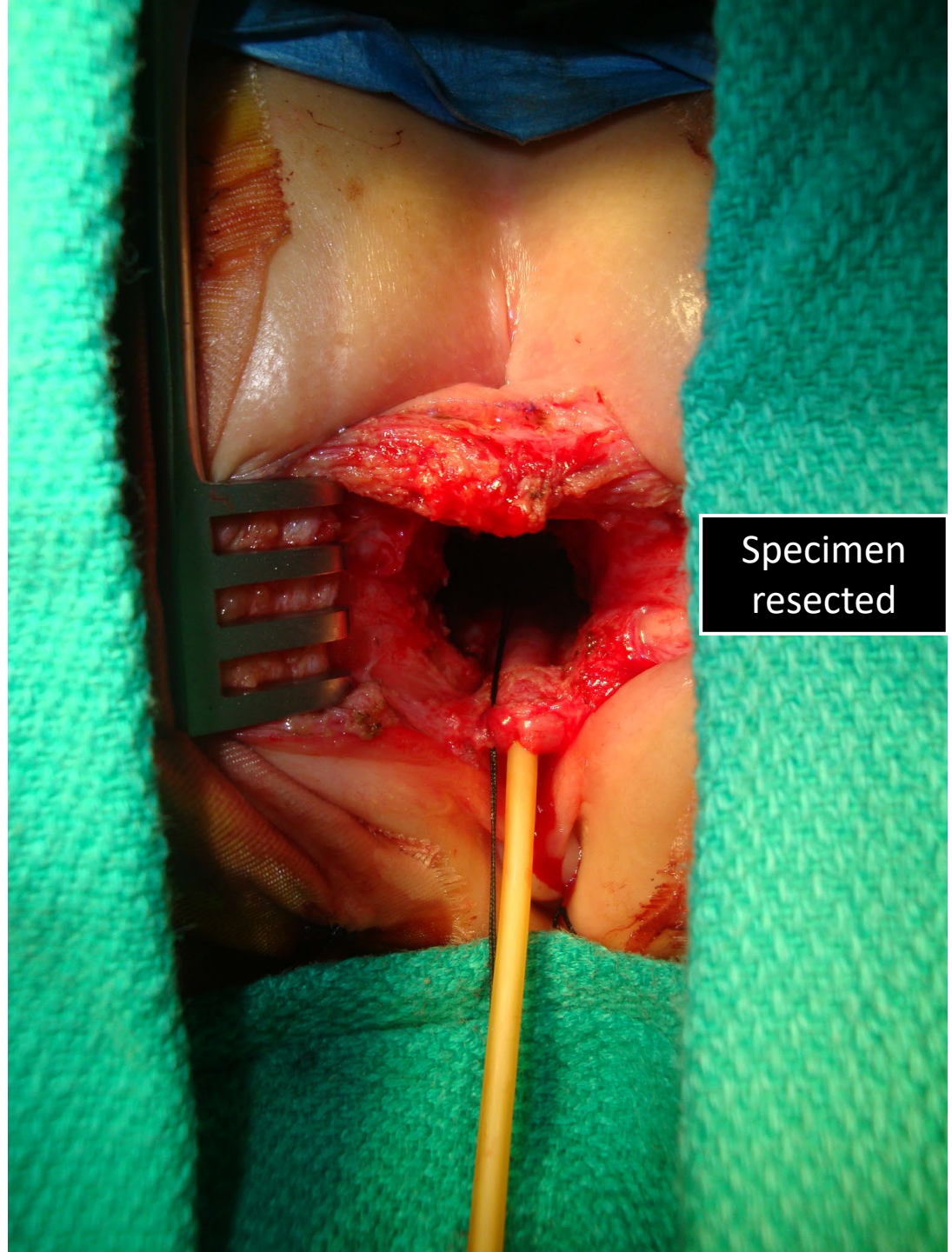
- Bilateral buccal mucosa grafts harvested from the cheeks
- Prone / jackknife position (ASTRA)
- Circumferential dissection of the vagina separating it from rectum and urethra
- Subtotal vaginectomy
- Buccal mucosa vaginoplasty

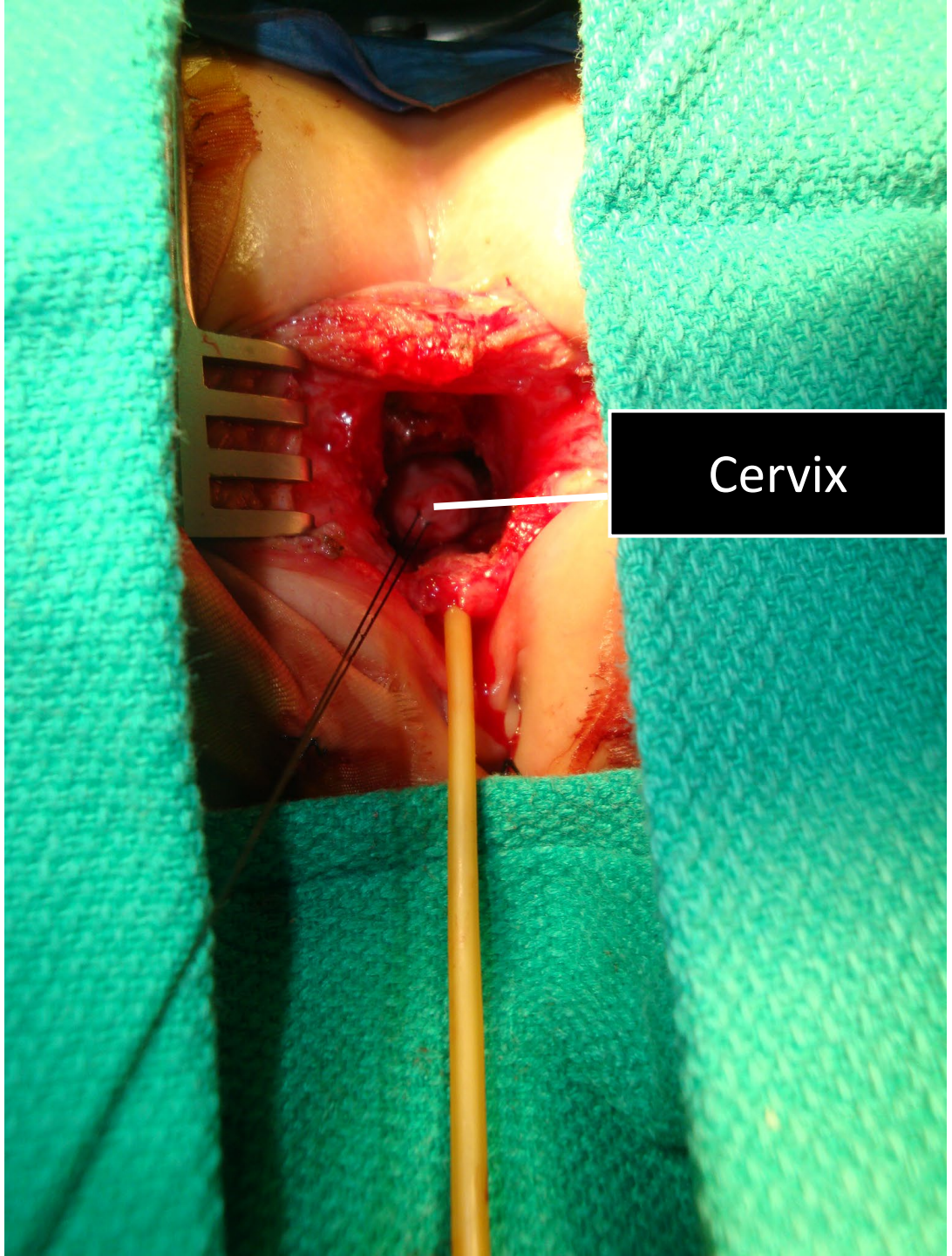
Ohmeda

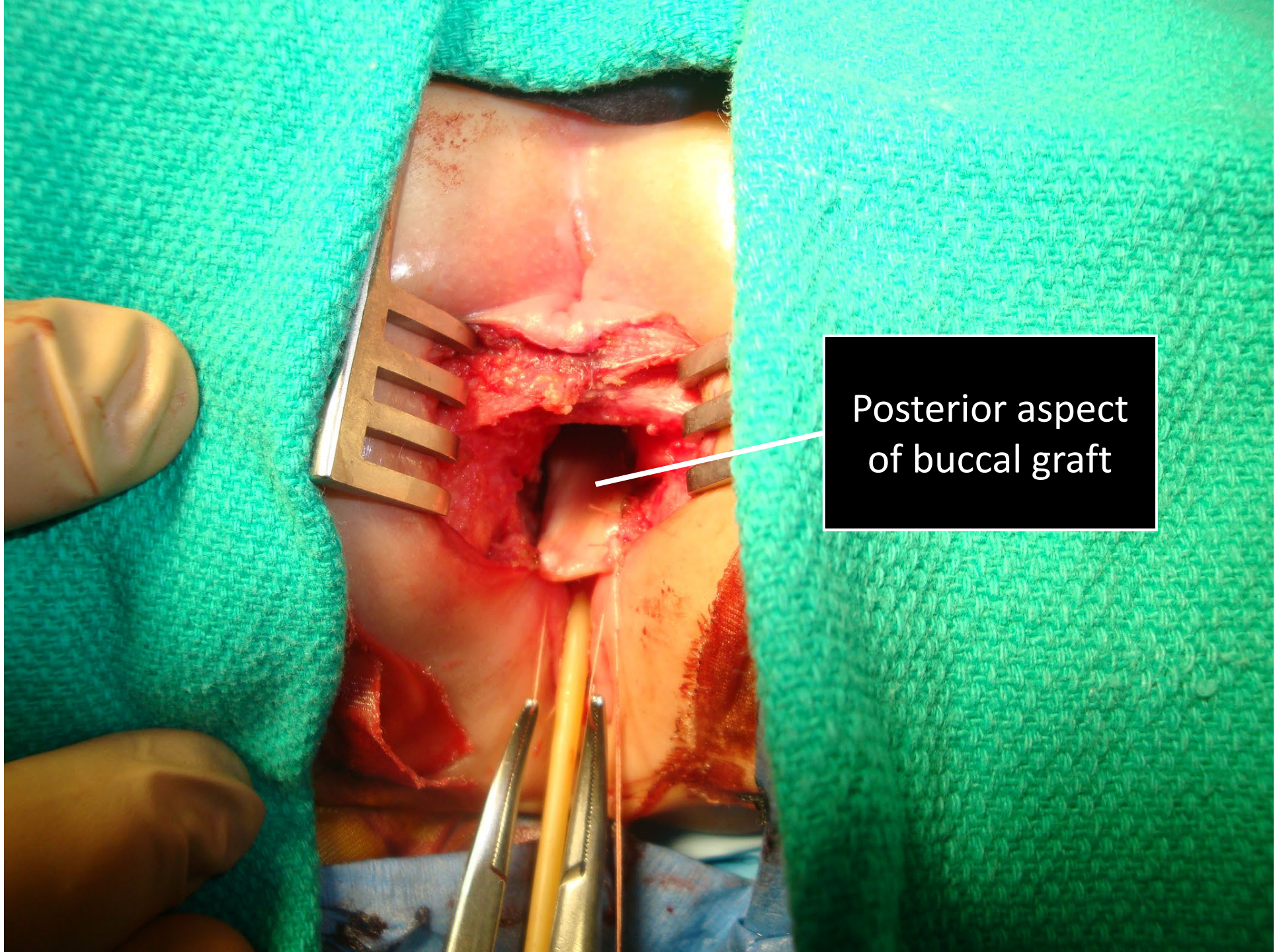


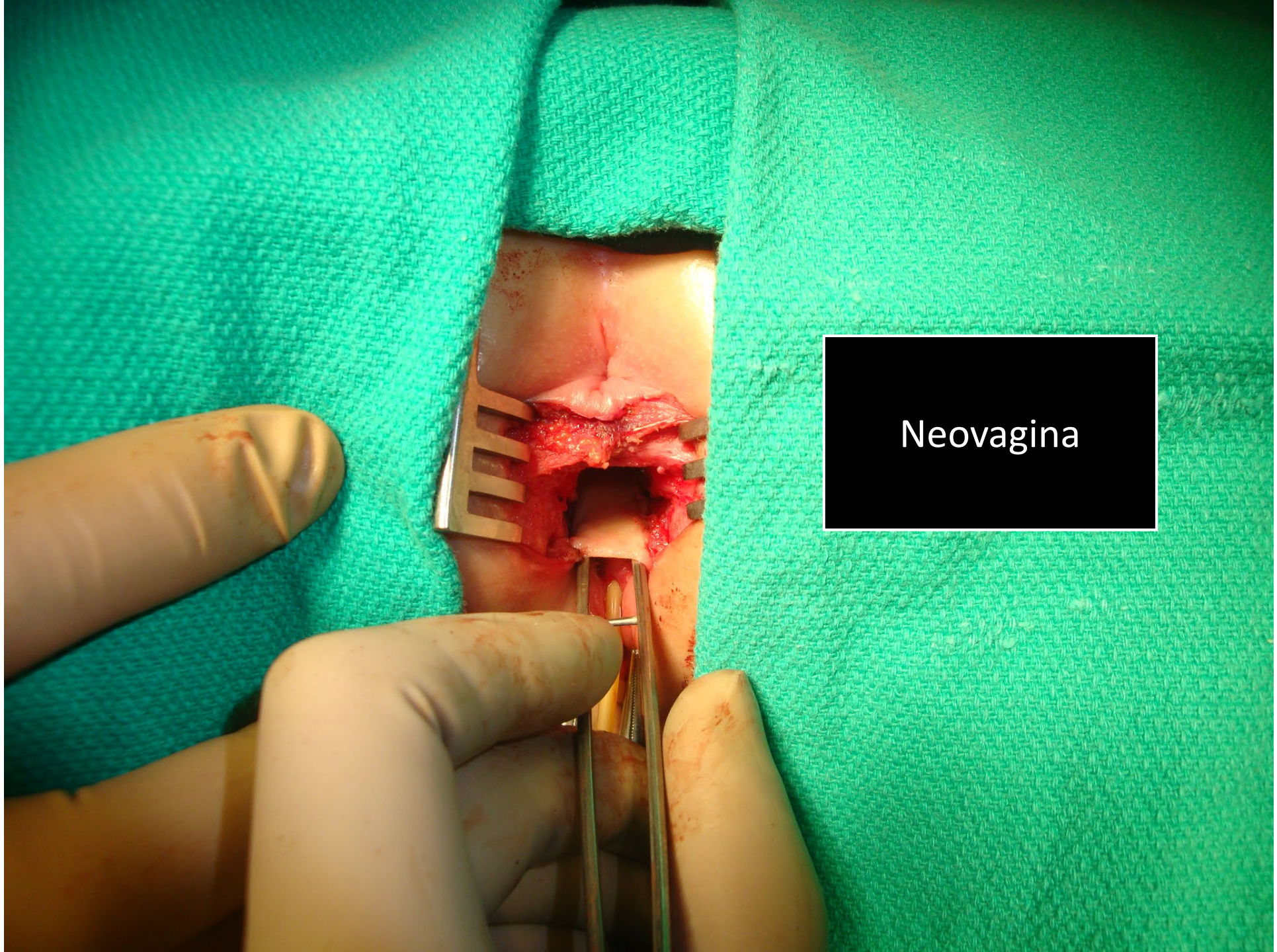

Anus
External sphincter
Vagina


Vagina
Urethra


Specimen
resected


Cervix

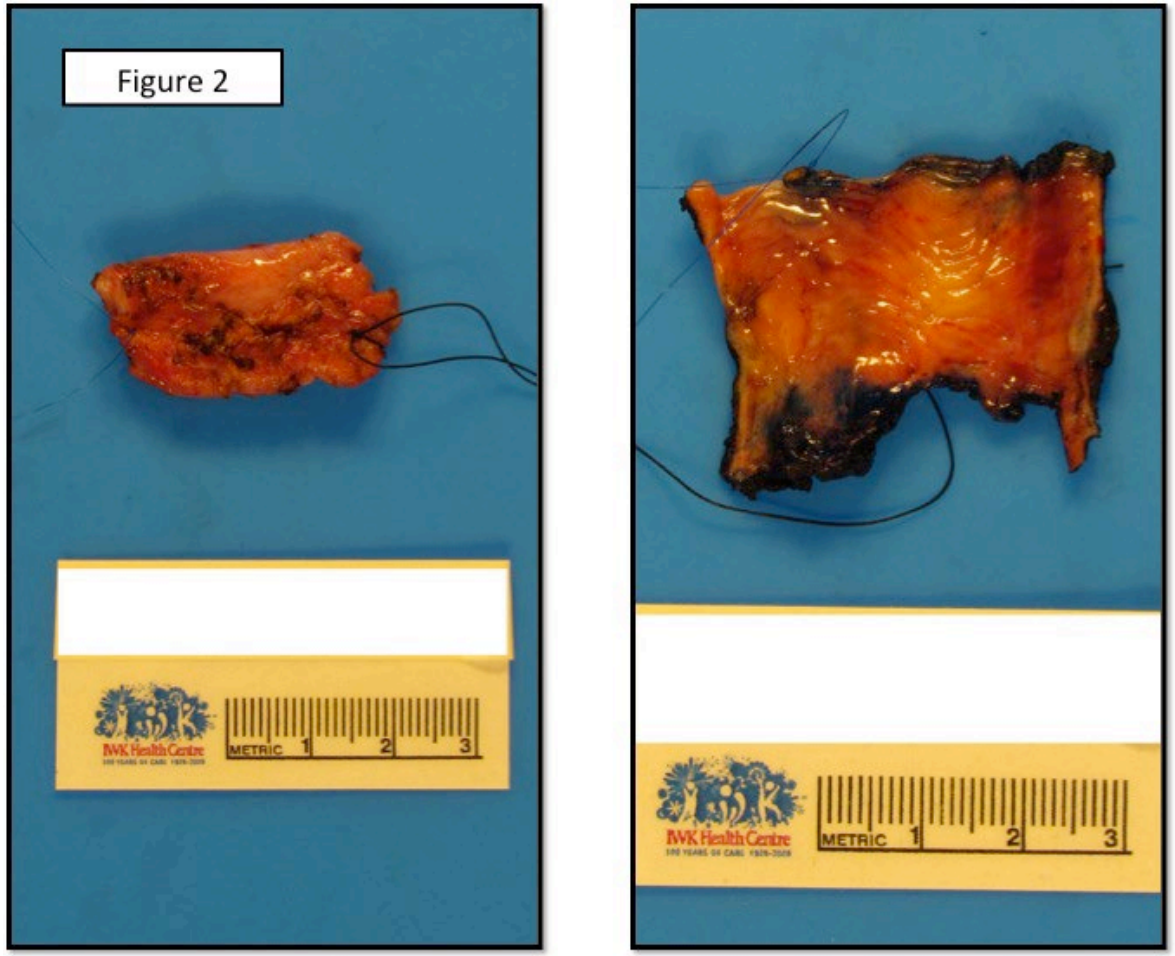

Posterior aspect
of buccal graft


Neovagina

Postoperative course

- 20 Fr. chest tube left as mold / stent
- Smooth postoperative recovery
- POD 3 – discharged
- POD 10 – stent removed
- POD 15 – superficial perineal dehiscence after a large bowel movement
  - Healing by secondary intention with no issues

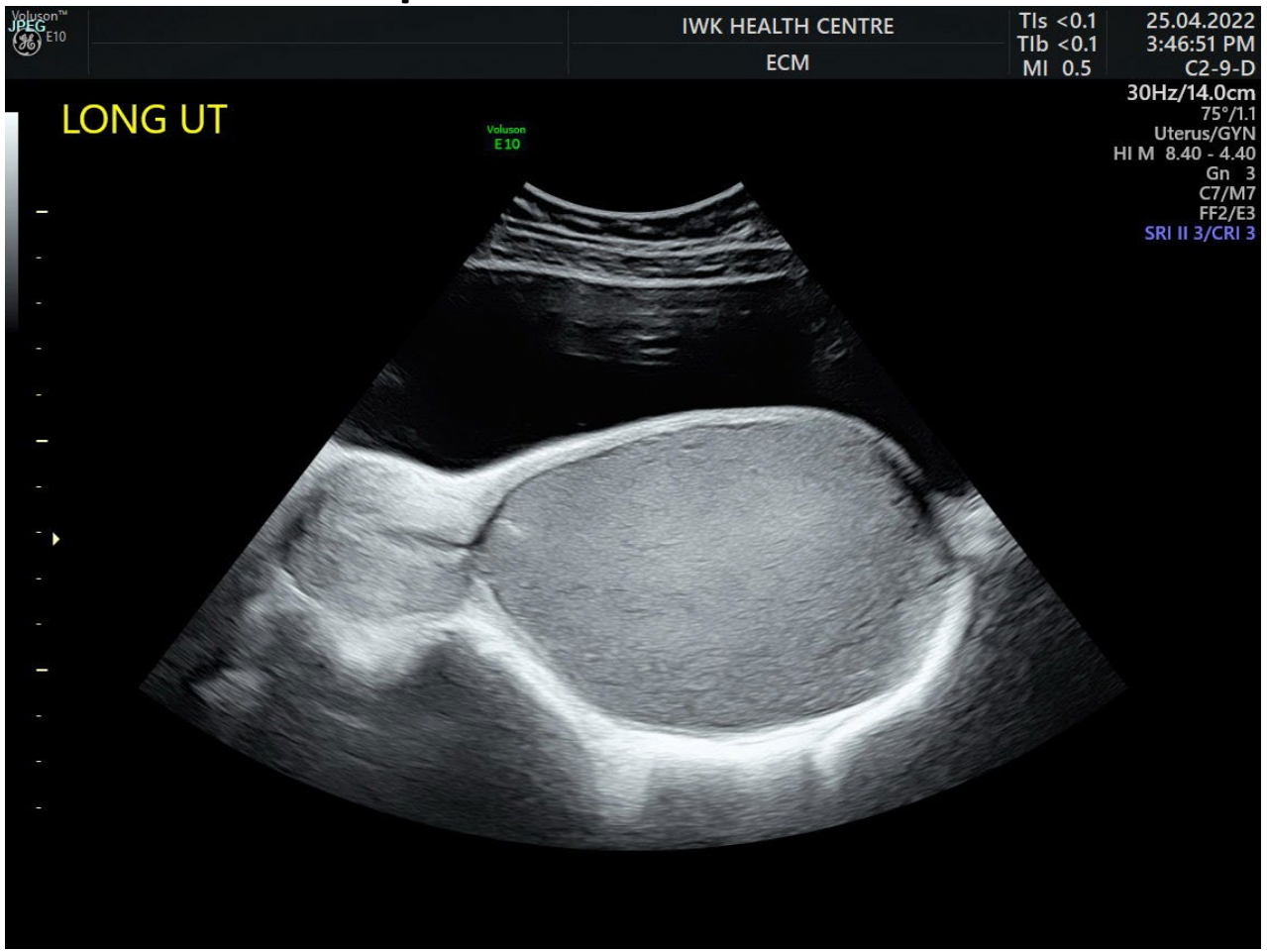
Focal residual rhabdomyoblasts with negative margins

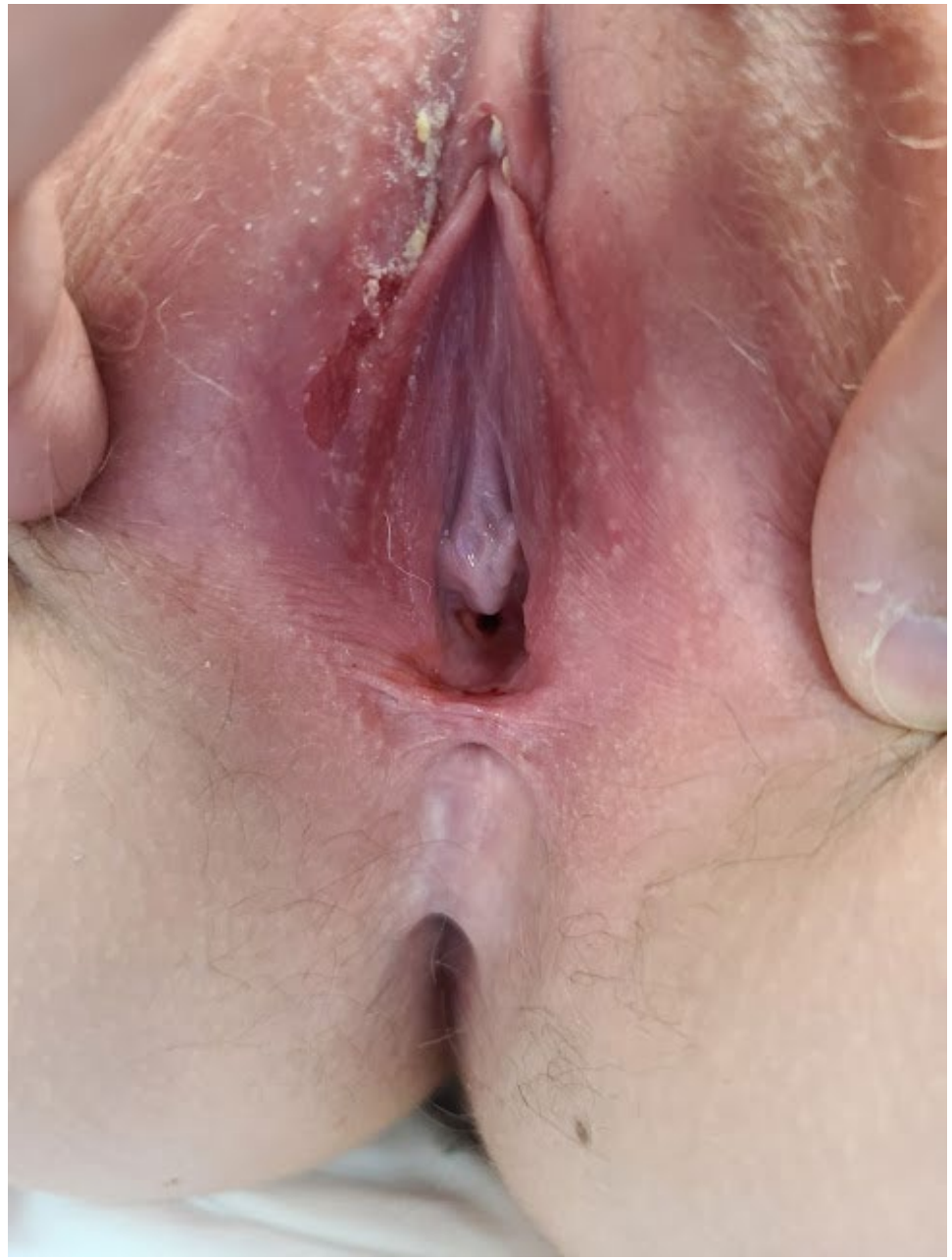


Postoperative course

- Completed chemotherapy
- Vaginoscopy at the end of treatment
  - Patent neovagina
  - No evidence of recurrence
- Follow-up with MRI and EUA
  - No evidence of recurrence at 7 years

11 years old
Lower abdominal pain





Case

Amanda Saltzman, MD

Presentation

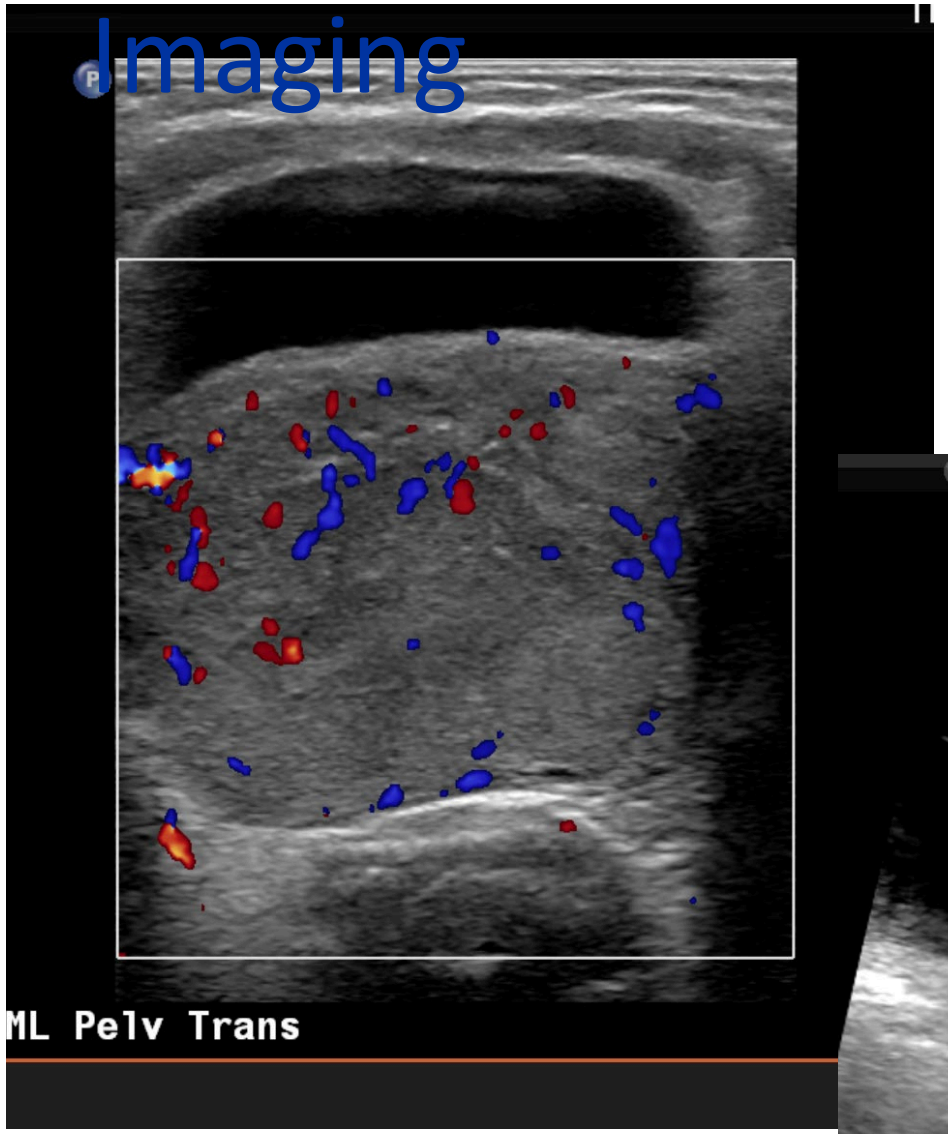
- CC: low po intake, no UOP

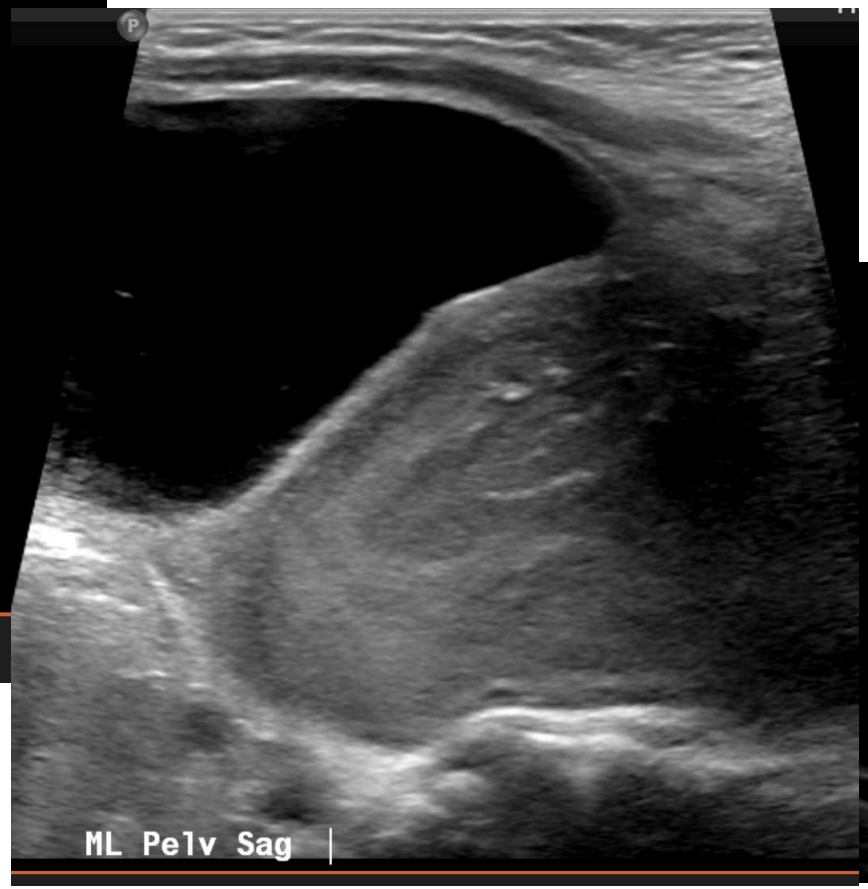
- HPI: 4mo M d male with poor PO intake, emesis, >24h since last wet diaper.
  - No hematuria
  - Never had a UTI
  - No significant history, born at term

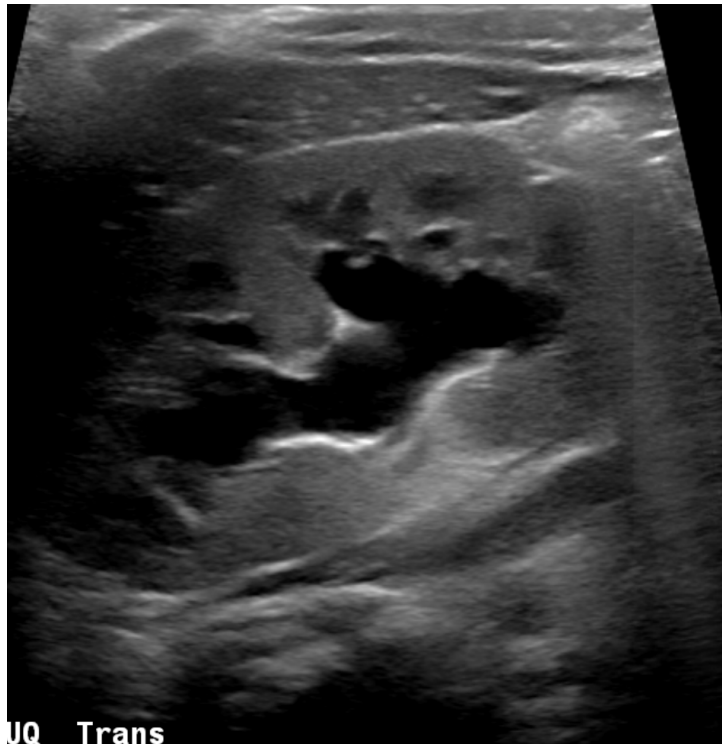
  - Distended abdomen with mass anterior to rectum on DRE

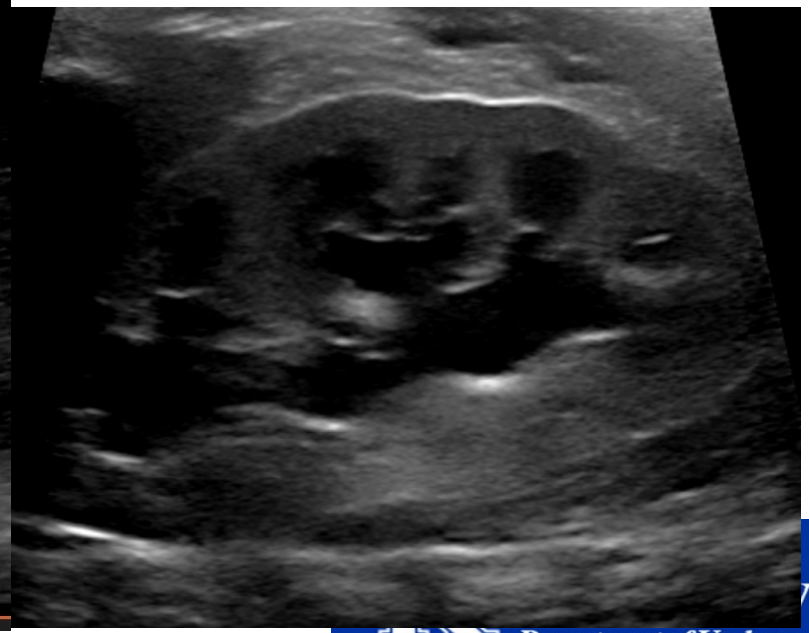
  - Abnormal imaging and Cr 0.8 in ER

Imaging









Imaging

- 5 cm pelvic mass
- Distended bladder
- B hydronephrosis

- Placed foley → 45 mL clear yellow urine
  - Cr normalized in 48h

Next Steps

- Imaging?

Next Steps

- Imaging?
  - MRI pelvis suspicious for prostatic mass
  - No LAD or other suspicious findings

- Initial surgical plan?

Next Steps

- Imaging?
  - MRI pelvis suspicious for prostatic mass
  - No LAD or other suspicious findings

- Initial surgical plan?
  - Cysto bx

Uh Oh…

- On cystoscopy, nothing to biopsy, no obvious mass in prostate or bladder

- What now?

Uh Oh…

- On cystoscopy, nothing to biopsy, no obvious mass in prostate or bladder

- What now?
  - Laparoscopic biopsy
  - Open biopsy

- Bladder management?

Uh Oh…

- On cystoscopy, nothing to biopsy, no obvious mass in prostate or bladder
- What now?
  - Laparoscopic biopsy
  - Open biopsy
- Bladder management?
- LN sampling?

Surgery/Pathology

- Open biopsy with BPLN sampling
- Left foley in place

- Ectomesenchymoma, 0/6 LNs
  - Similar to embryonal RMS but with neural component

- Group IIIa, (T1bN0M0) stage 3 BP embryonal RMS → intermed risk
- Treated per ARST 1431 → VAC/VI x 12 weeks

- Local control discussion?

Local Control

- Discussed surgery and XRT → surgery as DPE chosen
- Referred to larger center to discuss proton beam

- Had surgery at larger center
  - Radical prostatectomy
  - SP tube and foley
  - + margin…

- Full dose XRT

Age 3.5y…

- Returned to me 1y postop

- Mom noted weak stream, large PVR
- Cysto → BNC/stitch at anastomosis → stream improved
  - No permanent stitch used per op note

- Not yet potty-trained

Case

12 month old boy presented to the ED after days of increased fussiness and decreased urinary frequency of wet diapers.

Nick Cost, MD

Case Presentation

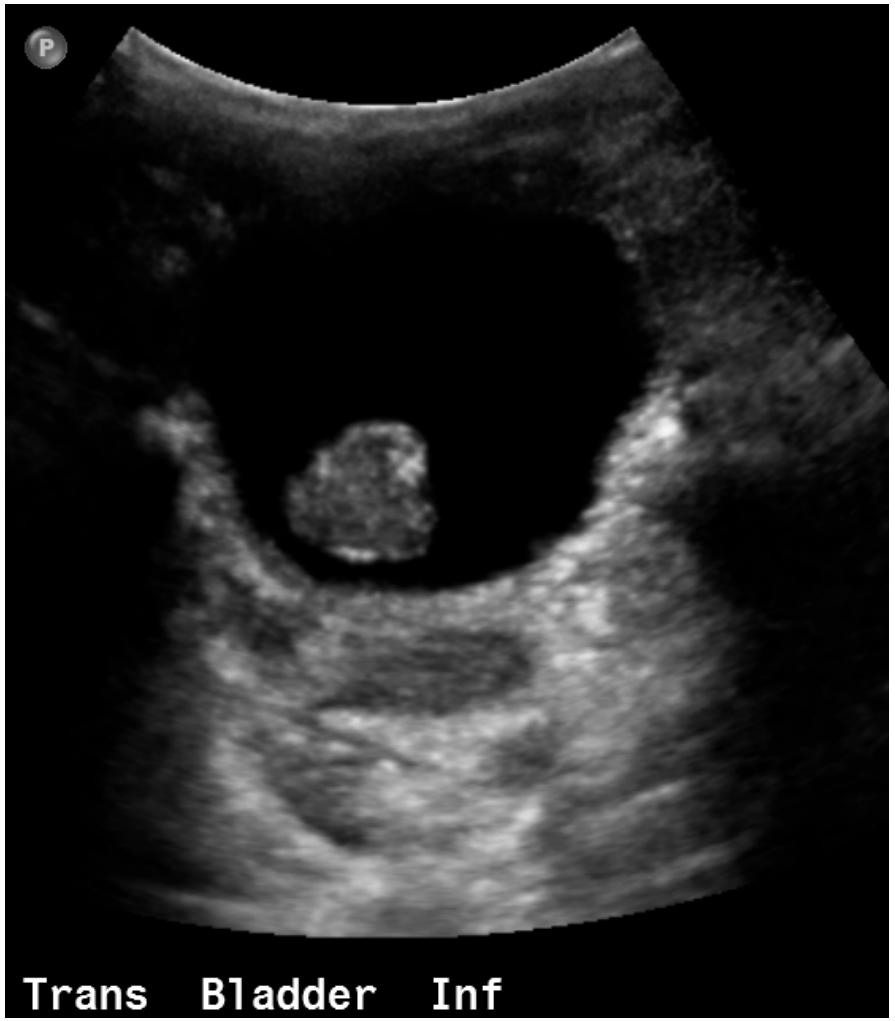
- 12 month old boy presented to the ED after days of increased fussiness and decreased urinary frequency of wet diapers. Also with a few loose bowel movements. PCP sent to ED for GI work-up.
  - Unremarkable prenatal history (prenatal u/s normal)
  - PSH: hypospadias repair and chordee repair
  - Unknown Family History

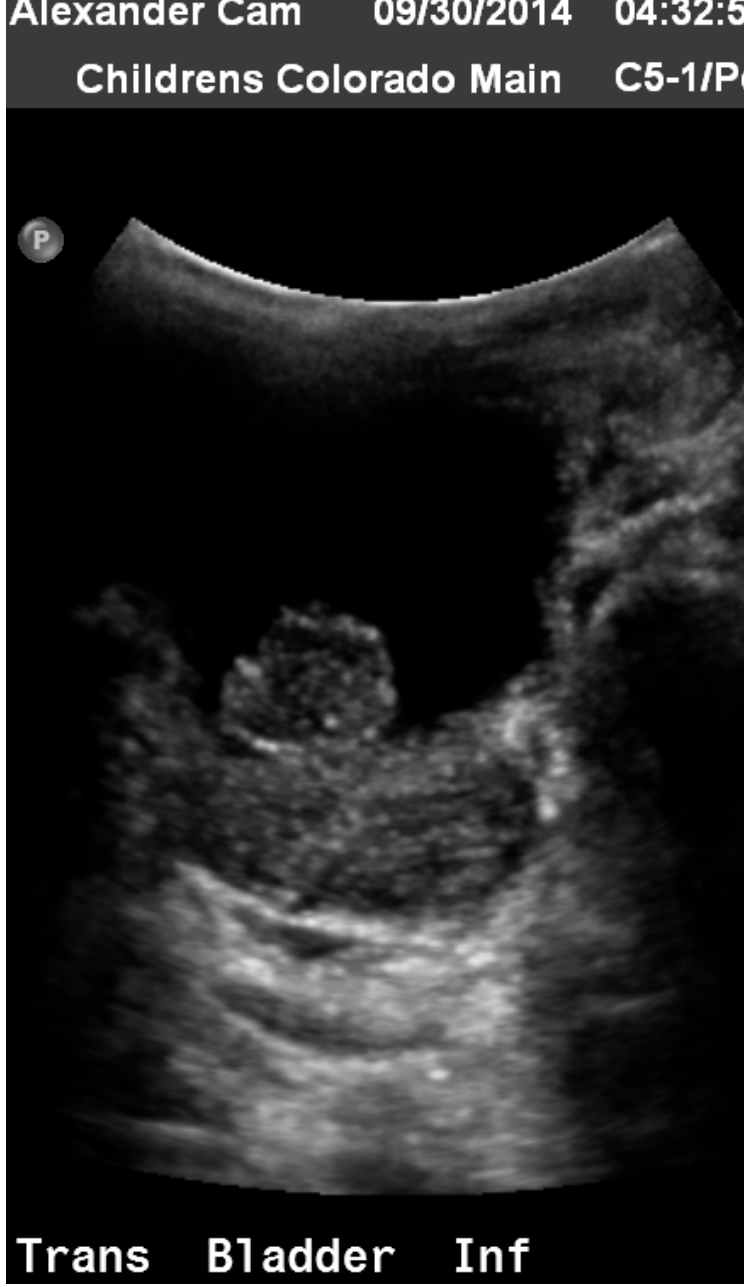
ED

- Vitals WNL
- PE: unremarkable: Circumcised with orthotopic meatus; bilateral descended testicles
- Workup: Labs unremarkable (normal Cr), US

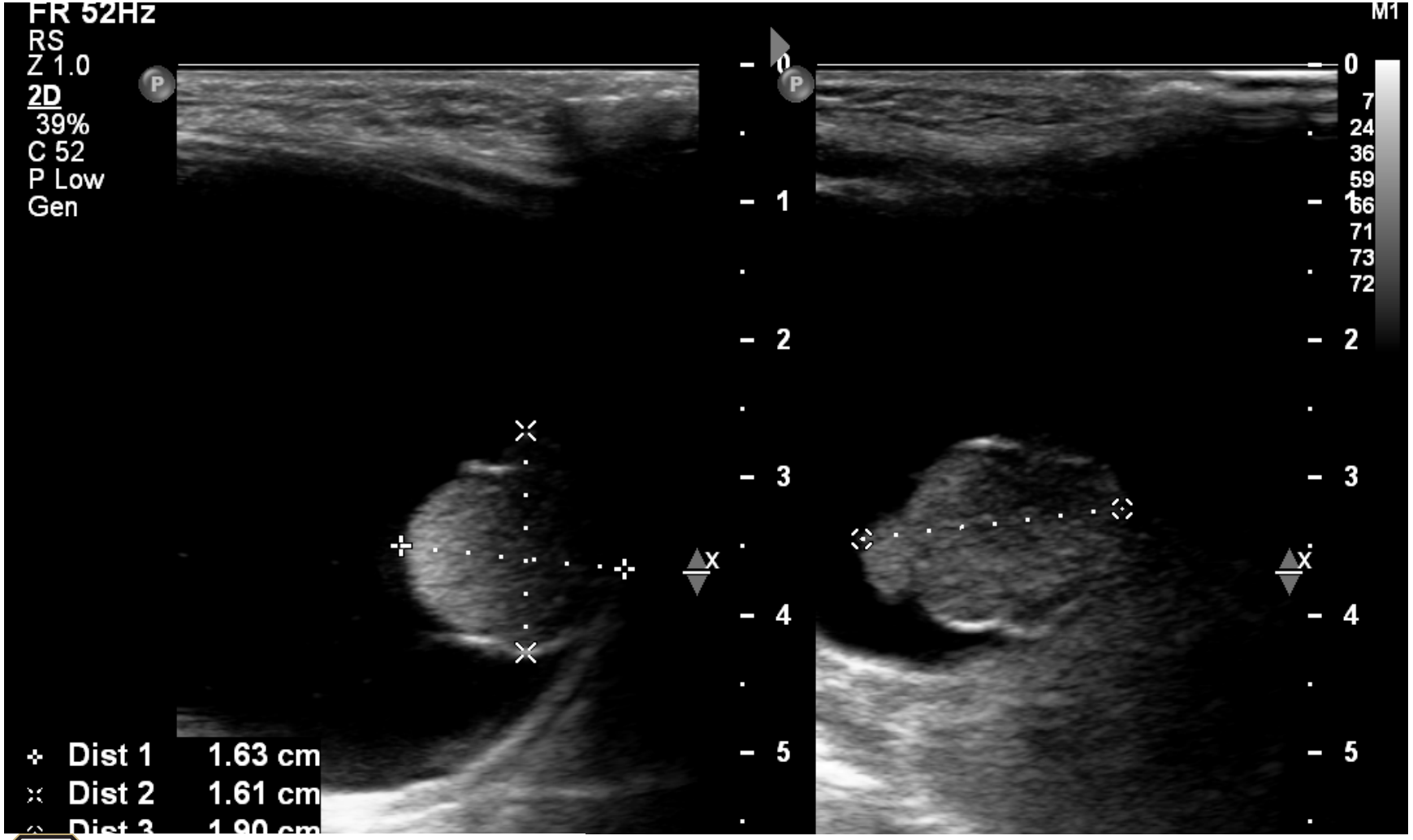
ED US

- Bladder mass





ED US



University of Colorado
Cancer Center

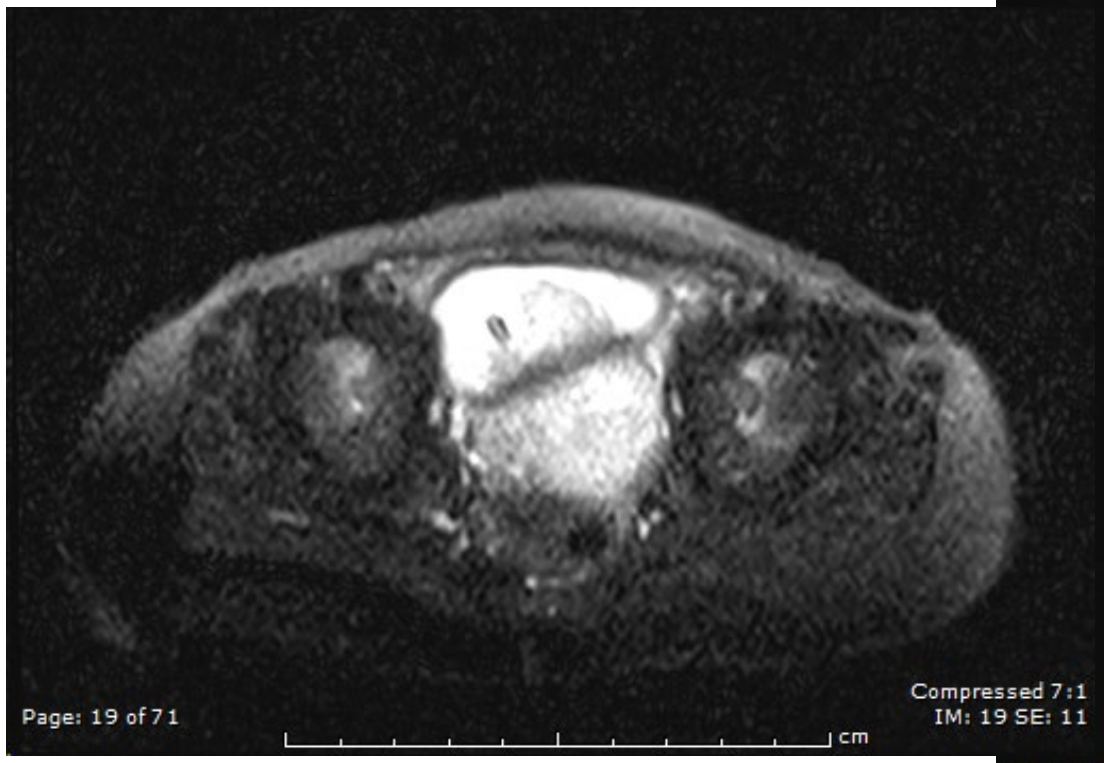
Outlet Obstruction

- Mild to moderate hydronephrosis on ultrasound with distended bladder.

- Foley catheter placed without resistance.
  - Over 100 cc of clear yellow returned. Patient with marked improvement in discomfort

- Plan for MRI and Cysto with Biopsy

MRI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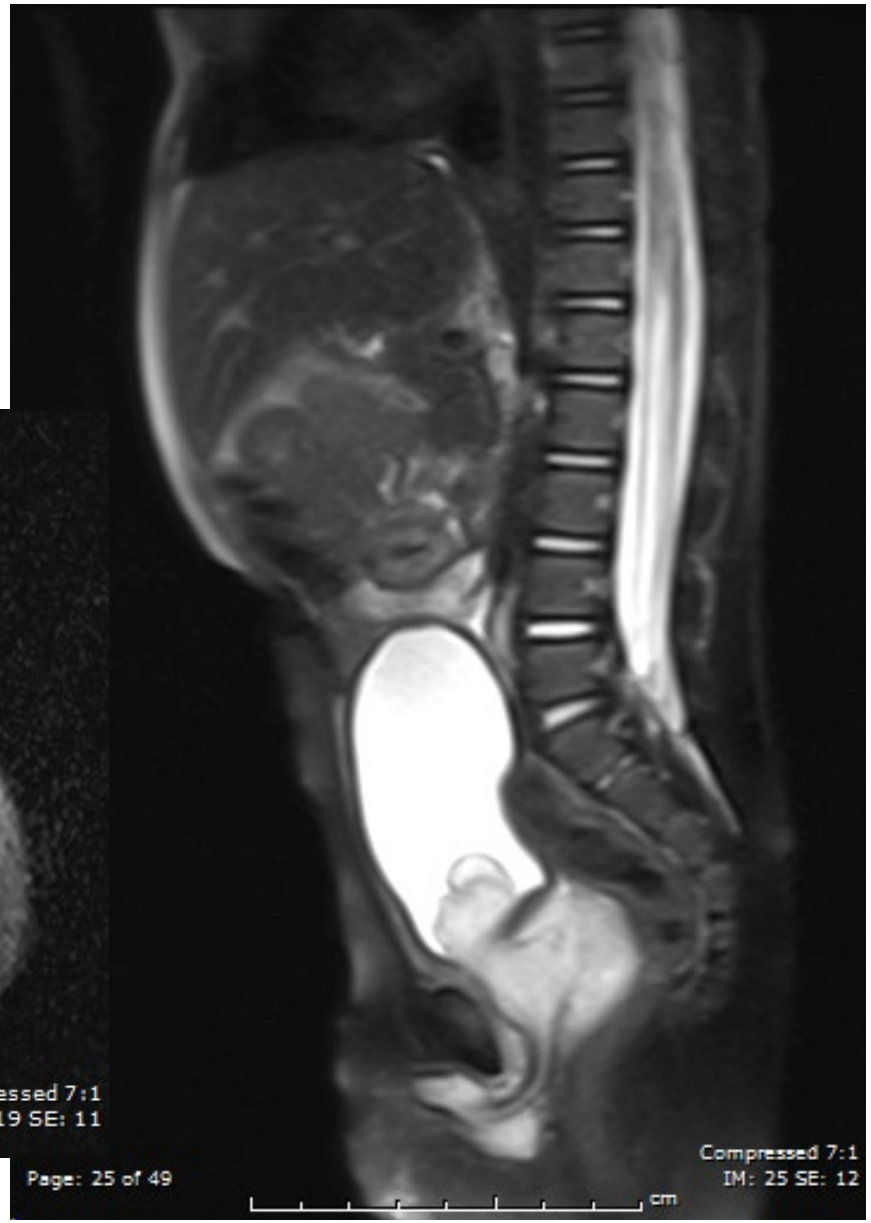
Compressed 7:1
IM: 19 SE: 11
cm


Page: 25 of 49
Compressed 7:1
IM: 25 SE: 12
cm

Cysto

- Left bladder neck mass arising from prostate, UOs spared

- Biopsy
  - DIAGNOSIS:
    PART A. BLADDER/PROSTATE MASS, BIOPSY:
    - EMBRYONAL RHABDOMYOSARCOMA.

- Mediport placed

Metastatic Workup

- PET CT:
  - Mild FDG avidity of the primary mass located at the bladder base. No evidence of metastatic disease.

Treatment

- Started with vincristine, dactinomycin, cyclophosphamide chemotherapy

- Discussion about primary control at week 12
  - Surgical resection
  - Proton Beam RT

Treatment

- Parents interested in surgery so at week 12 we did another EUA and Cystoscopy with planning biopsies to make sure UOs and Urethra were free of disease

Cysto

- Mass confined to prostate, UOs appeared free of disease, Urethra appeared free of disease

- Biopsy
  - DIAGNOSIS:
    PART A. URETHRAL, BIOPSY:
    - EMBRYONAL RHABDOMYOSARCOMA.

  - PART B. ADJACENT TO RIGHT URETERAL ORIFICE, BIOPSY:
    - EMBRYONAL RHABDOMYOSARCOMA.

Treatment

- Given that cystectomy likely required and not able to attain ureteral continence the parents elected for Proton Beam RT as primary disease control

Case

2 yo boy with abdominal pain

Aggressive Multimodality Therapy for a Urachal Rhabdomyosarcoma

Nick Cost, MD

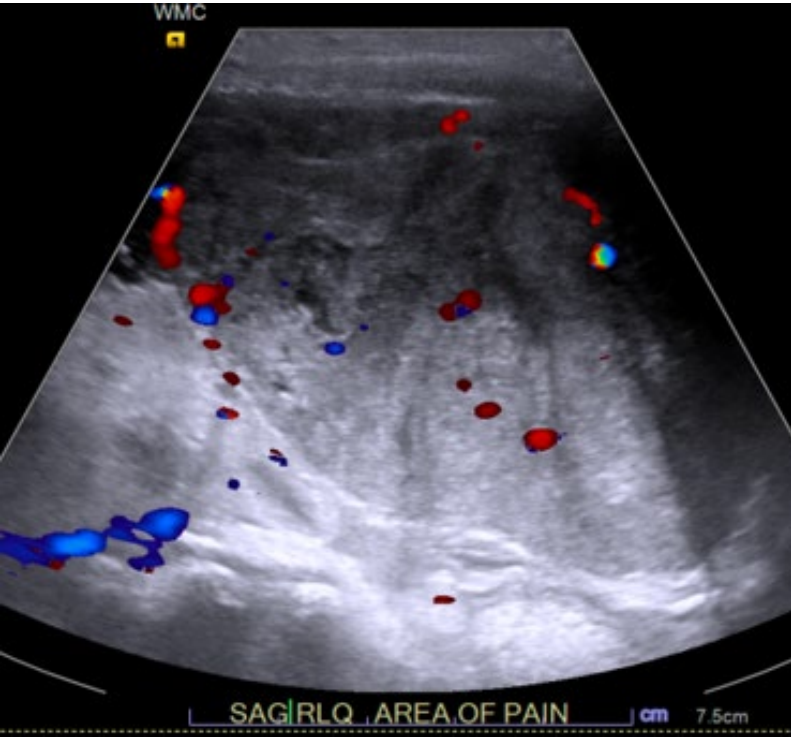
HPI

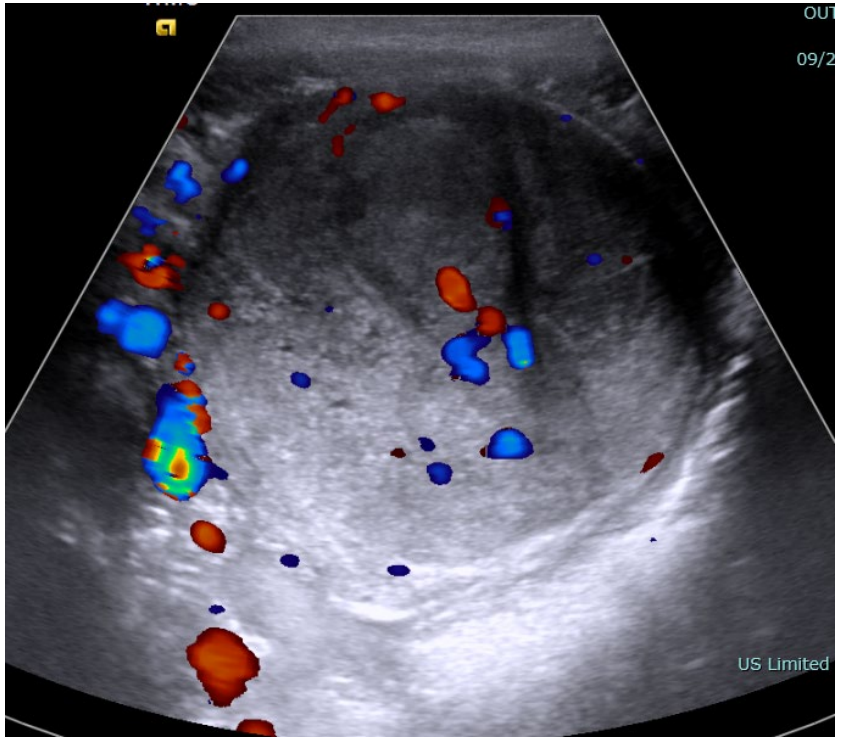
- 2 yo boy Presented to OSH with several week h/o **abdominal pain**
    - *Endorses* **(+)**: Fatigue, anorexia, urinary frequency
    - *Denies* **(-)**: Fever, weight loss, hematuria
    - Enlarged spleen palpated

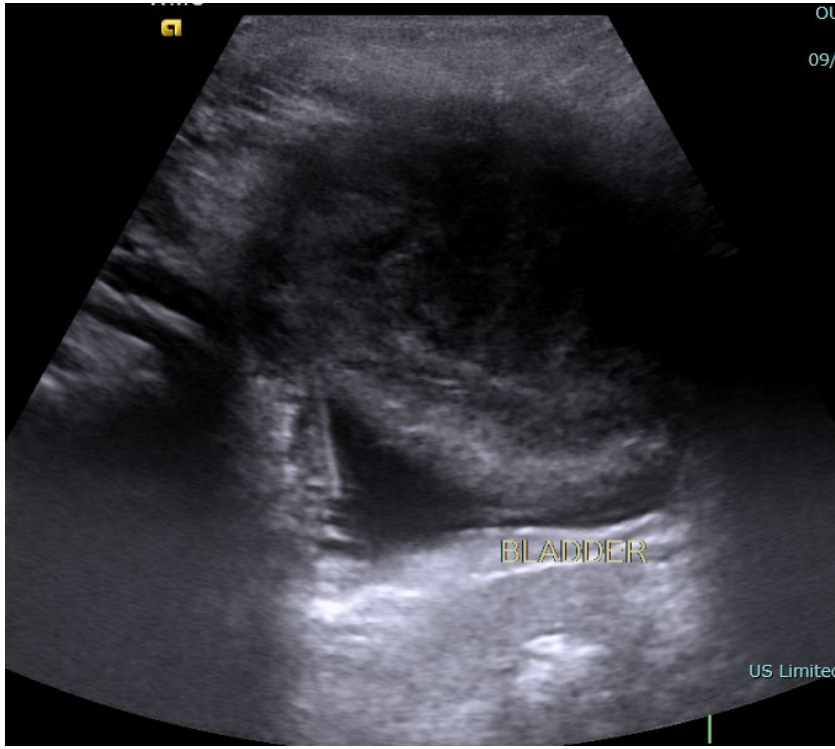
- Spiked fever on arrival. Blood cultures drawn.

- Labs:
    - WBC: 11.22
    - Uric acid: 5.7
    - UA: blood present
    - WNL: CMP, AFP, bHCG, LDH, HMA, VMA

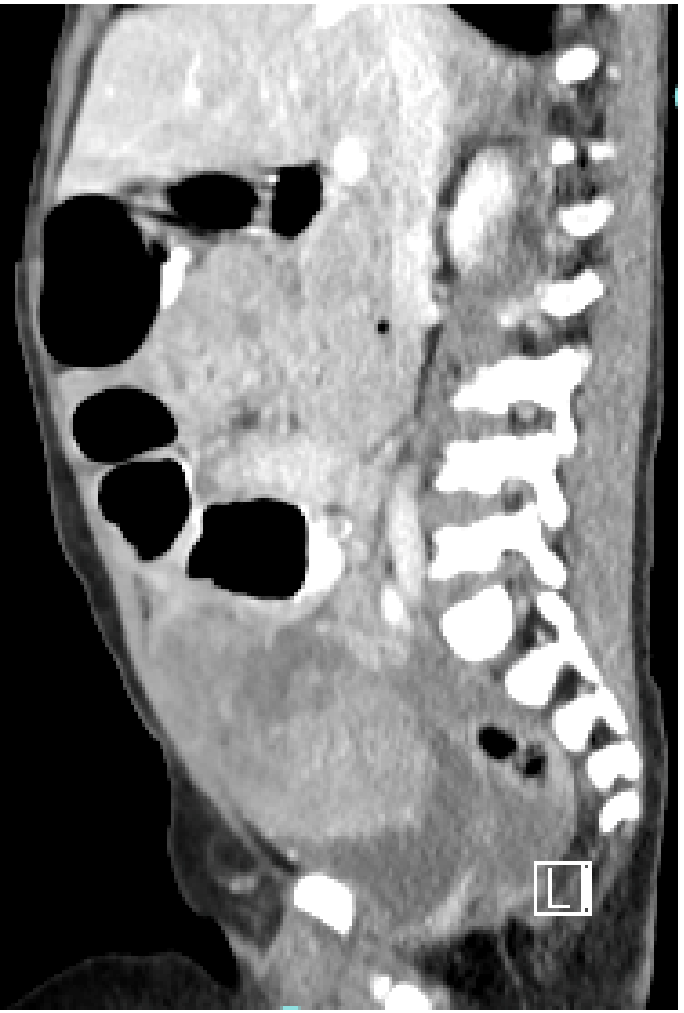
Imaging: US

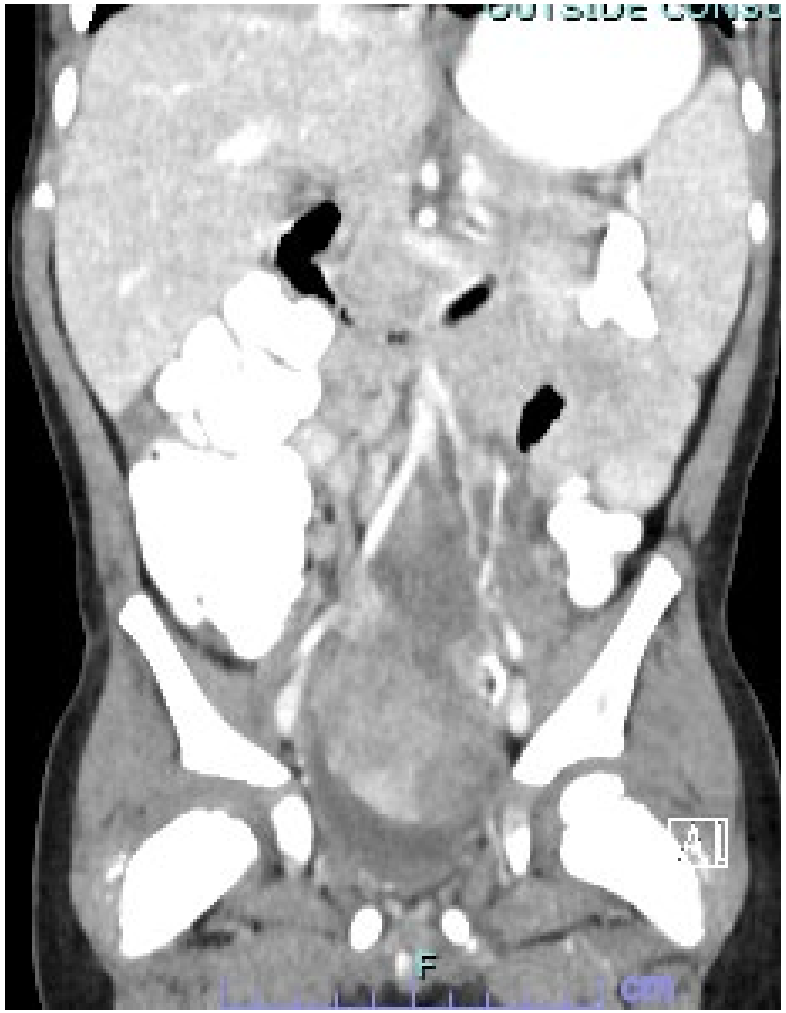

WMC
SAG RLQ AREA OF PAIN
cm
7.5cm

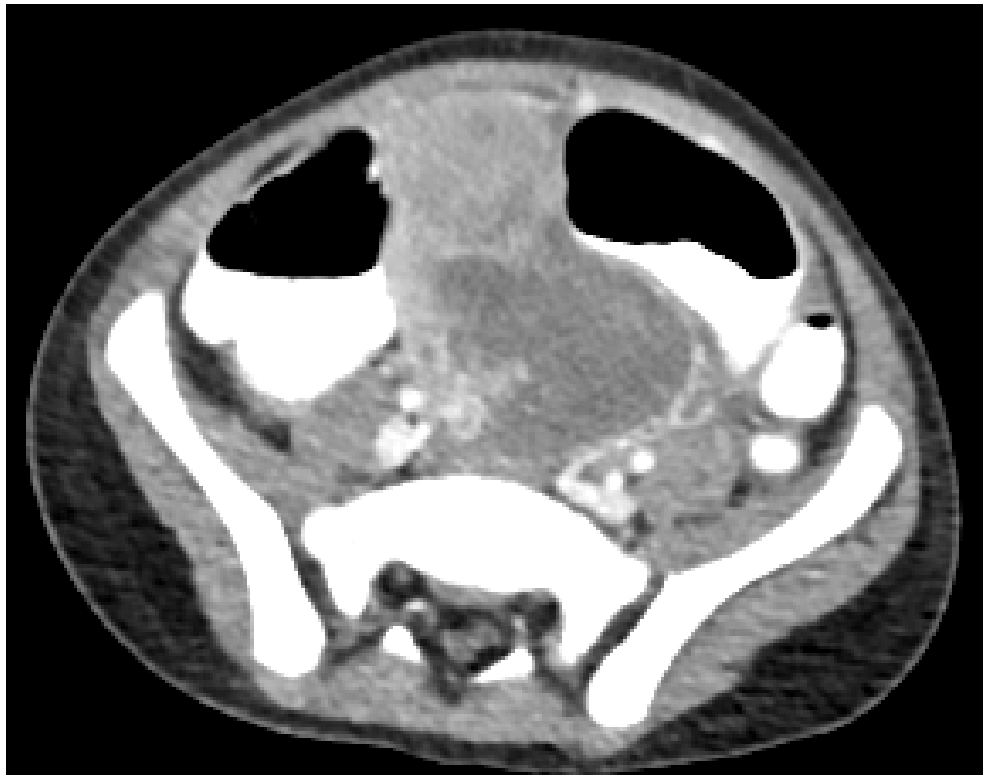

US Limited


BLADDER
US Limited

Imaging: CT







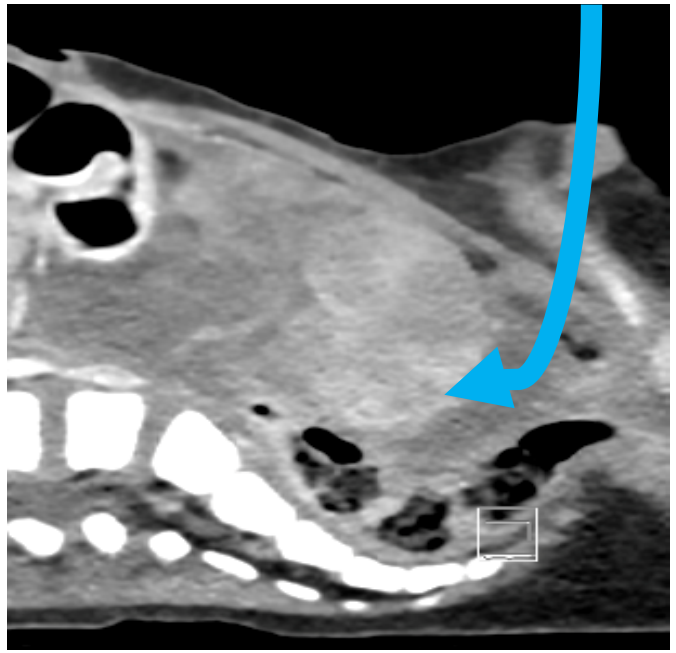
Diagnostic Biopsy

Transvesical mass biopsy

Mediport placement

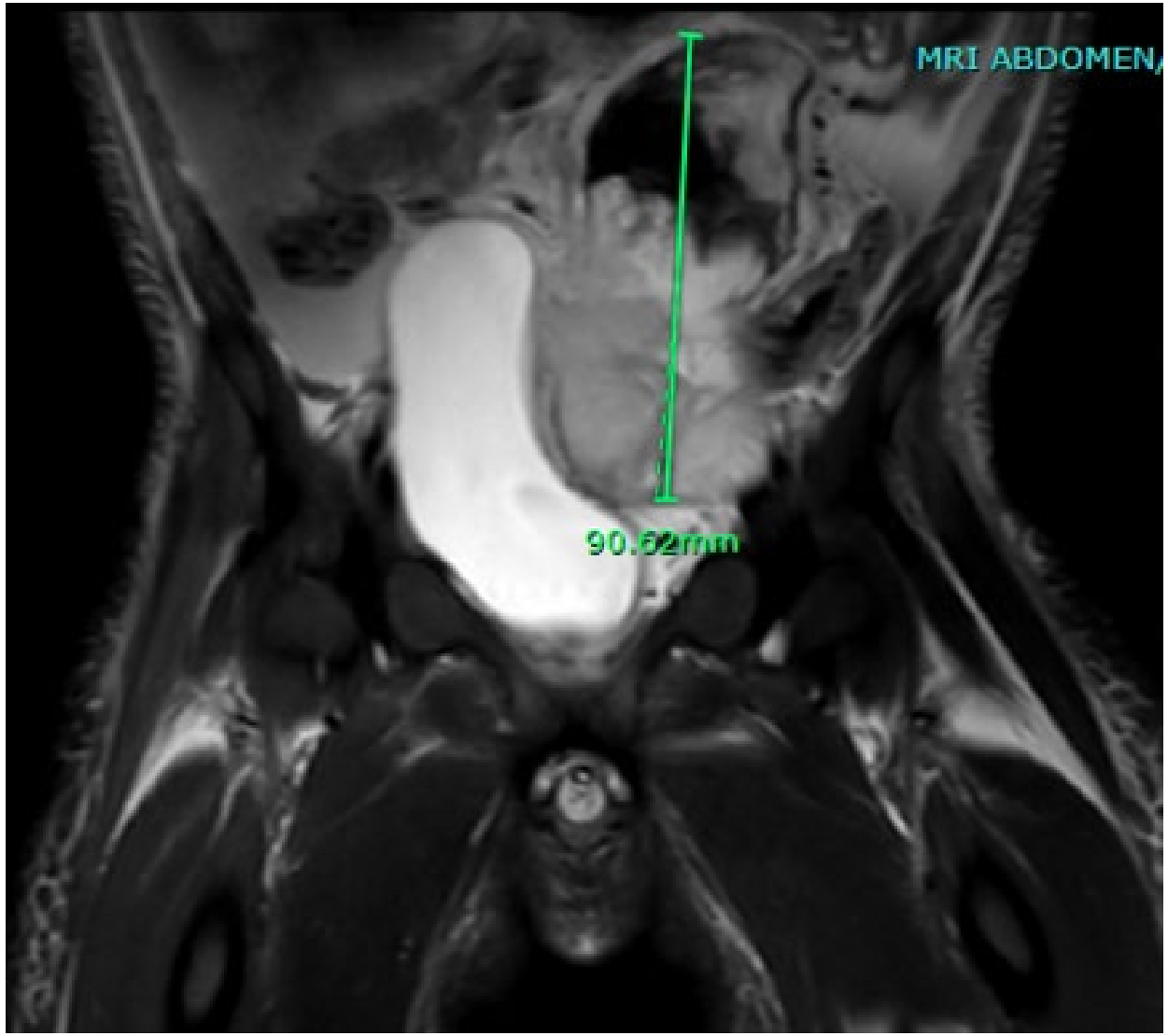
- Mass effect from tumor noted at anterior bladder wall
- Transvesical 18 gauge core needle biopsy through cystoscope working channel

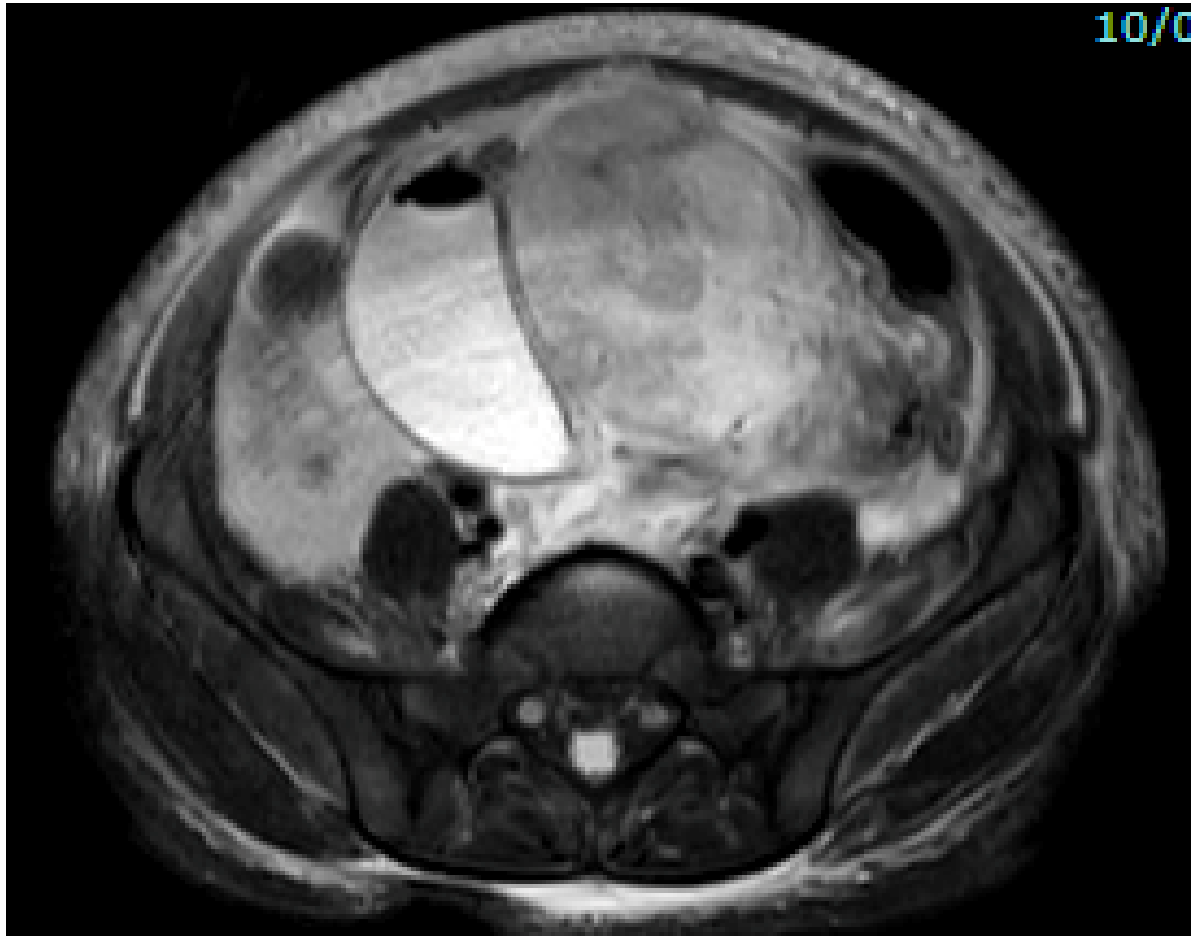
- Preliminary frozen = **rhabdomyosarcoma**
- Due to frozen, proceeded with port placement



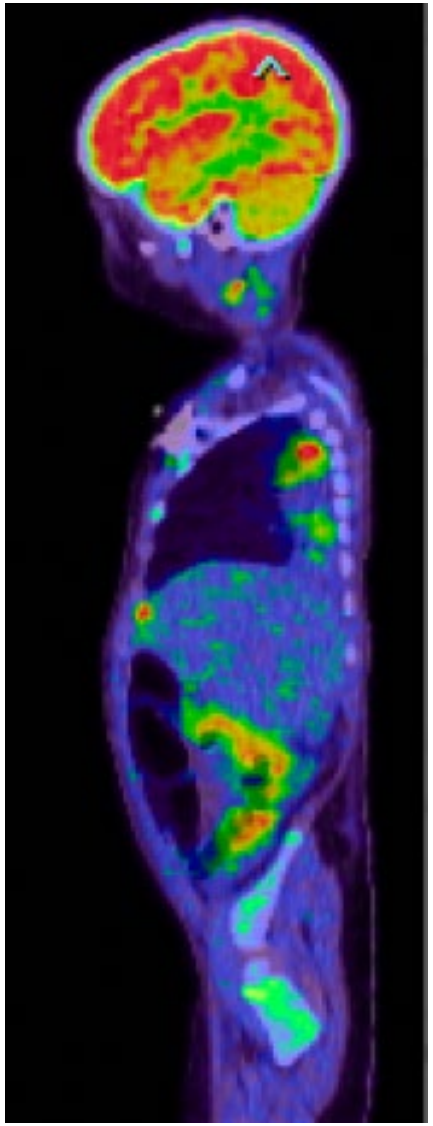
FINAL PATHOLOGY:
Embryonal rhabdomyosarcoma.
FOXO1 fusion negative.

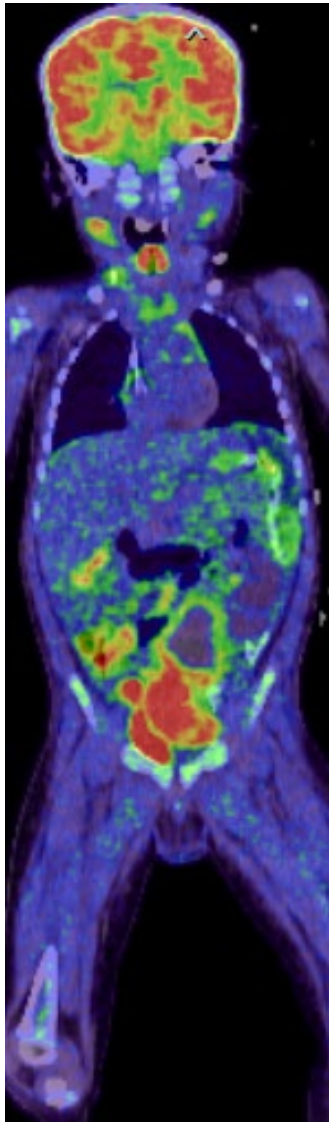
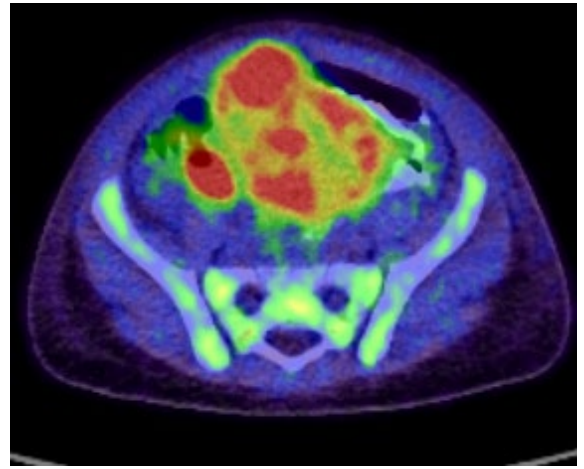
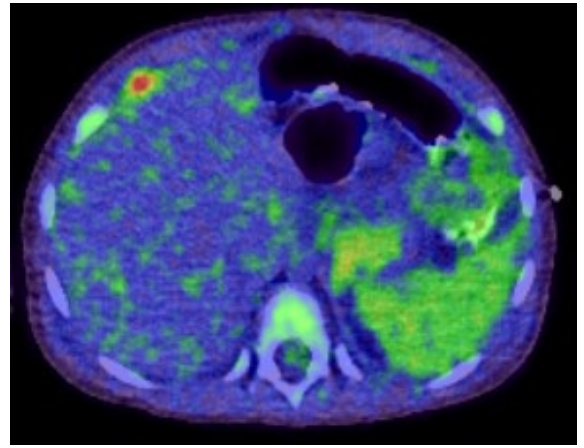
Imaging: MRI





Imaging: PET/CT



Surgical Resection

1. Cystoscopy
2. Temporary left ureteral stent placement
3. **Resection of urachal mass**
   i. Resection of mesenteric lymph node performed by pediatric surgery
   ii. Evaluated liver intra-operatively

- Cystic area of tumor ruptured preoperatively
  - Encountered **bloody ascites**

- Tumor involving **root of small bowel mesentery, sigmoid colon, and ileum**

Final Pathology

- **Stage III, group IIIb** urachal embryonal rhabdomyosarcoma.
  - Focal necrosis.
  - Fusion negative.
  - Vascular margin negative.
  - Small foci of anaplasia.
- Lymph node negative for RMS.
- Negative for Li-Fraumeni, DICER-1, TP53, NF1

Stage 3	Unfavorable	T1 or T2	< 5 cm	N1	M0
		OR	≥ 5 cm	N0, N1, NX	M0

Group III	**Gross residual disease**
Group IIIa	Localized or regional disease, Biopsy
Group IIIb	Localized or regional disease, Resection (debulking of more than 50% of tumor)

Embryonal	III	2,3	Intermediate risk

Treatment

- **COG protocol D9803**
  - 42 weeks of Vincristine, Actinomycin, Cyclophosphamide

- XRT beginning at week 12
  - 24 Gy in 16 fractions to whole abdomen/pelvis
  - Then boost to sites of unresected disease for **total of 50.4 Gy**

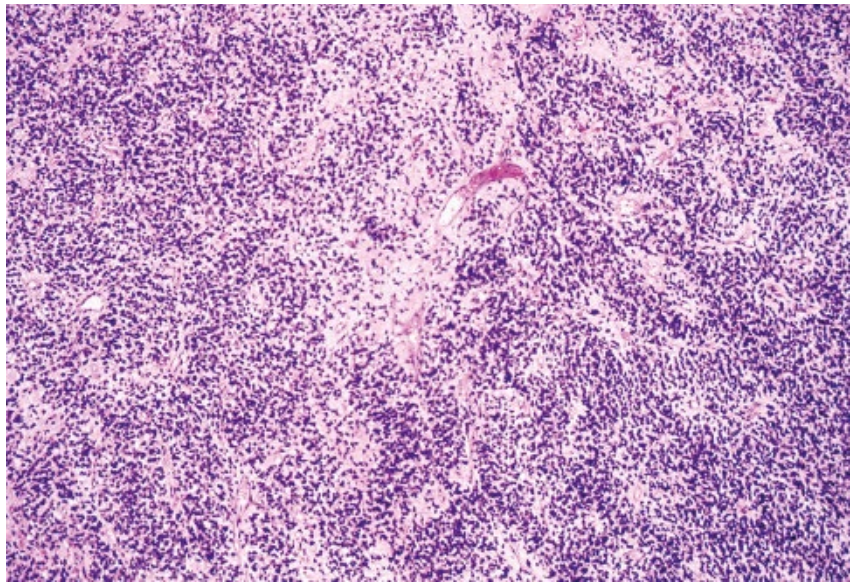
Currently: Completed chemotherapy. MediPort removed. No residual masses seen on imaging.

Wolden SL, Lyden ER, Arndt CA, et al. Local Control for Intermediate-Risk Rhabdomyosarcoma: Results From D9803 According to Histology, Group, Site, and Size: A Report From the Children's Oncology Group. *Int J Radiat Oncol Biol Phys*. 2015;93(5):1071-1076. doi:10.1016/j.ijrobp.2015.08.040

Arndt CA, Stoner JA, Hawkins DS, Rodeberg DA, Hayes-Jordan AA, Paidas CN, Parham DM, Teot LA, Wharam MD, Breneman JC, Donaldson SS, Anderson JR, Meyer WH. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: children's oncology group study D9803. J Clin Oncol. 2009 Nov 1;27(31):5182-8. doi: 10.1200/JCO.2009.22.3768. Epub 2009 Sep 21. PMID: 19770373; PMCID: PMC2773476.

Embryonal Rhabdomyosarcoma

- Epidemiology
  - 4% pediatric cancers; 60% of all rhabdomyosarcomas
  - Bimodal age distribution: 2-5 yo, 15-19 yo
  - Slight male predominance
  - A/w: Li-Fraumeni, NF1, Costello, Noonan syndrome, Beckwith-Wiedemann



- Undifferentiated mesenchymal cells
  - Resembles **developing skeletal muscle**

- Usually painless mass, unless mass effect

Embryonal Rhabdomyosarcoma

- Diagnosis:
  - Cross sectional imaging: CT/MRI
  - Biopsy

- Treatment is multimodal:
  - **Surgery**
  - **Chemotherapy (VAC)**
  - **Radiotherapy**
  - 5-year survival: 60-70% in children

Urachal RMS

- Largest series reported: 8 patients from 1984 to 2013
    - Age 1 yo – 8 yo

- Relatively **rare** entity
    - Typically embryonal (6/8)
    - **Ascites** is quite common (series showed 8/8 patients)
    - Median size: 10.3 cm
    - Typically stage III (2/8) or stage IV (6/8)

Cheikhelard A, Irtan S, Orbach D, Minard-Colin V, Rod J, Martelli H, Sarnacki S. Urachal rhabdomyosarcoma in childhood: a rare entity with a poor outcome. J Pediatr Surg. 2015 Aug;50(8):1329-33. doi: 10.1016/j.jpedsurg.2014.12.023. Epub 2015 Jan 7. PMID: 25913896.

Urachal RMS

- **Poor prognosis** a/w peritoneal metastasis

- Outcomes:
  - 7/8 in complete remission at end of treatment
  - 4/8 patients relapsed within median 25 months after treatment
  - **4/8 patients died 18-57 months after diagnosis**

Cheikhelard A, Irtan S, Orbach D, Minard-Colin V, Rod J, Martelli H, Sarnacki S. Urachal rhabdomyosarcoma in childhood: a rare entity with a poor outcome. J Pediatr Surg. 2015 Aug;50(8):1329-33. doi: 10.1016/j.jpedsurg.2014.12.023. Epub 2015 Jan 7. PMID: 25913896.

Conclusions

- **Rare** primary site for GU RMS
- **Poor prognosis** compared to other GU sites
  - Even worse than bladder/prostate RMS
- Decision made for **aggressive multimodal therapy** with resection, chemotherapy, and radiation

Case

2yo boy with rectal prolapse, distended bladder….. embryonal rhabdo

Jon Routh, MD

Case Presentation

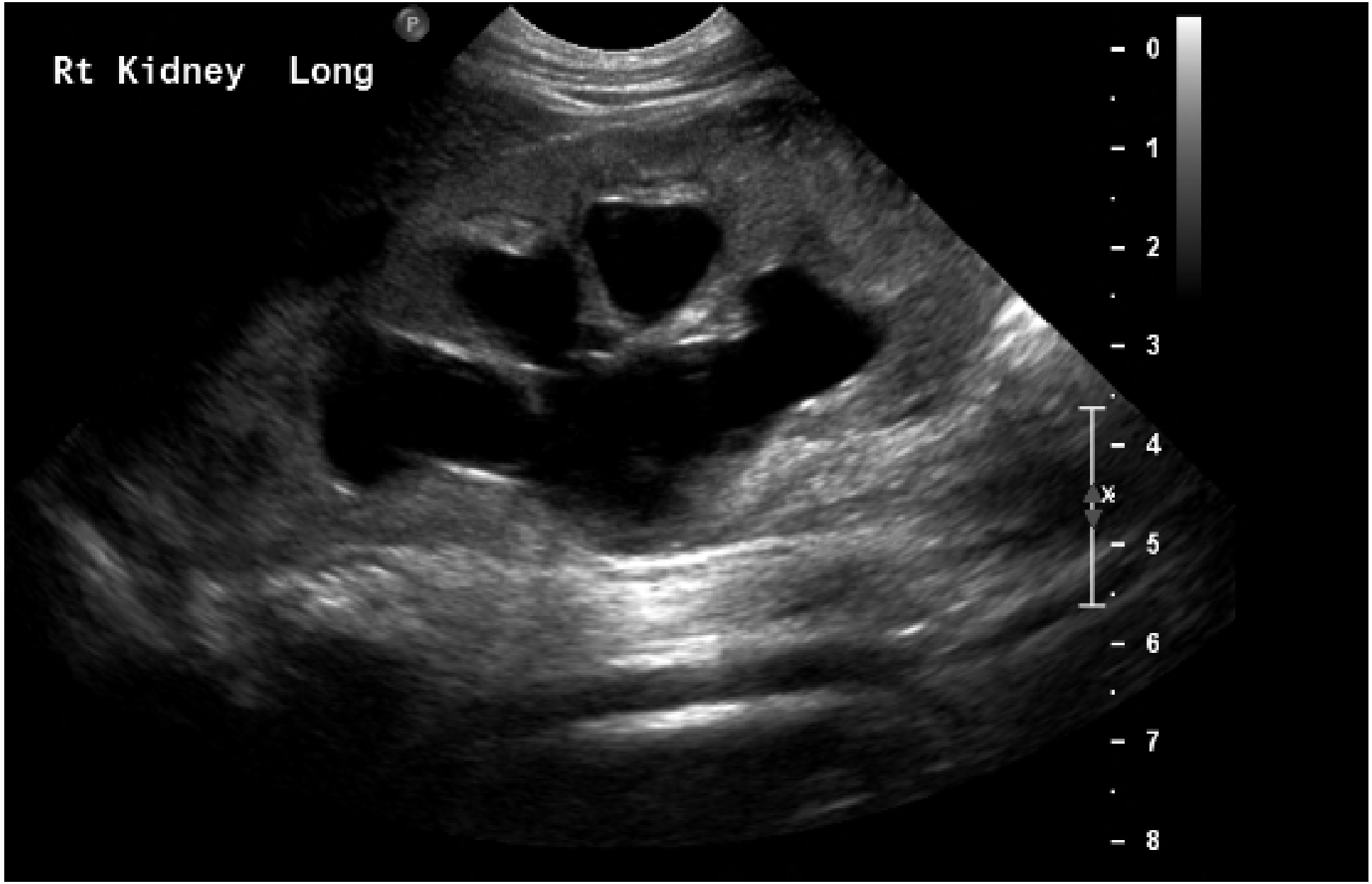
- CC: Transfer from OSH for further workup and treatment of embryonal rhabdomyosarcoma

- HPI: Pt is a 2 yo male ex 26-weeker with chromosomal abnormality and dysmorphic facies, global DD, panhypopituitarism, multiple abdominal hernias, and recent rectal prolapse with subsequent diagnosis of embryonal rhabdomyosarcoma of bladder s/p partial cystectomy who presents as transfer from OSH.
- Initially presented to OSH with non-reducible rectal prolapse secondary to straining on micturition. Exam under anesthesia revealed largely distended bladder.

Case Presentation

- Workup revealed **elevated Cr** and renal US and VCUG were significant for **severe bilateral hydronephrosis with Grade 4 VUR on R**, and **large intraluminal filling defect**. MRI revealed **polypoid bladder mass** at bladder base and left lateral wall.

- Pt subsequently underwent open partial cystectomy on 8/3/15 with pathology consistent with embryonal rhabdomyosarcoma. Pt was transferred to DUH on 8/7/15 for further management.


Rt Kidney Long
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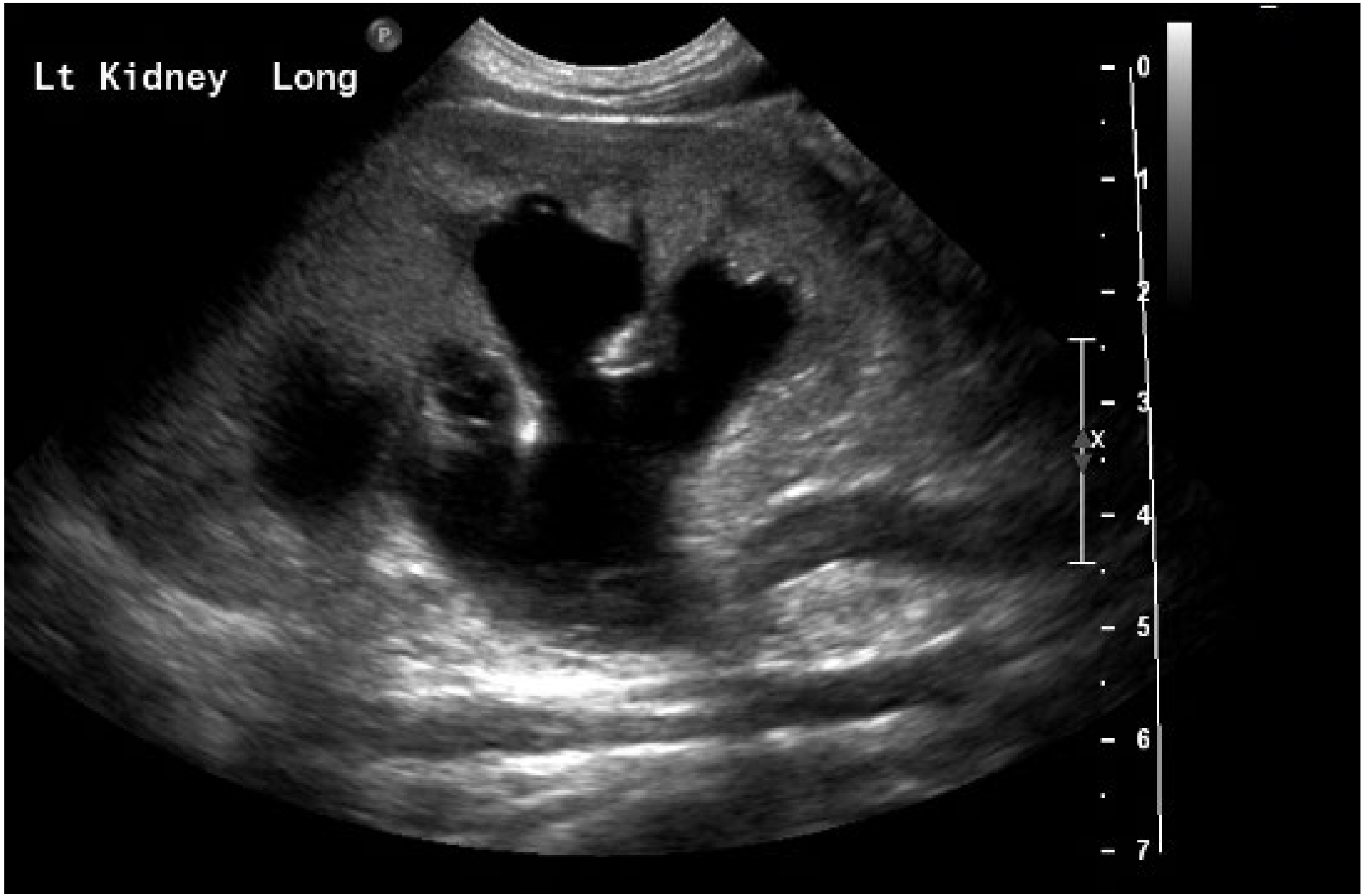
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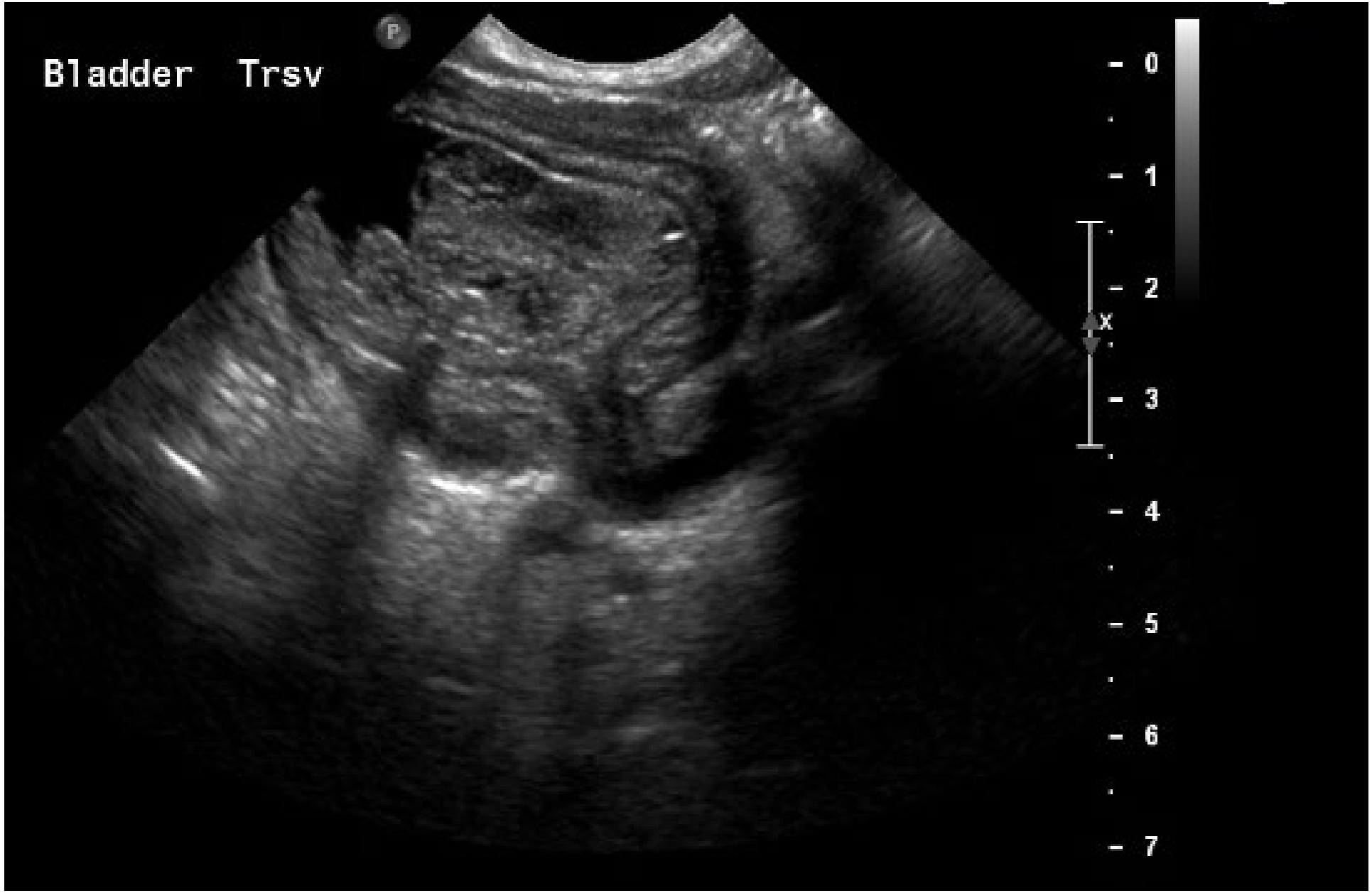
Bladder Trsv
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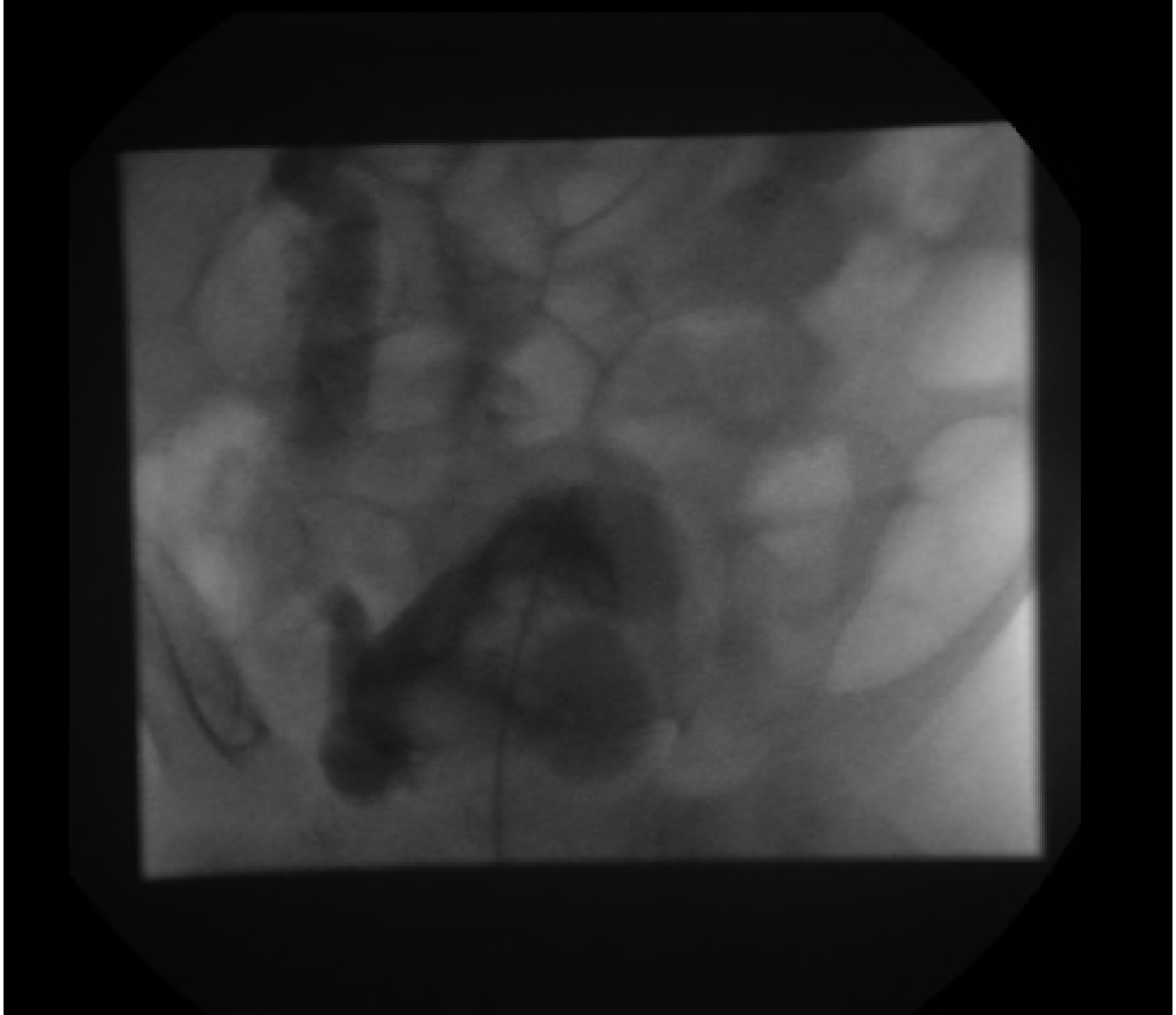

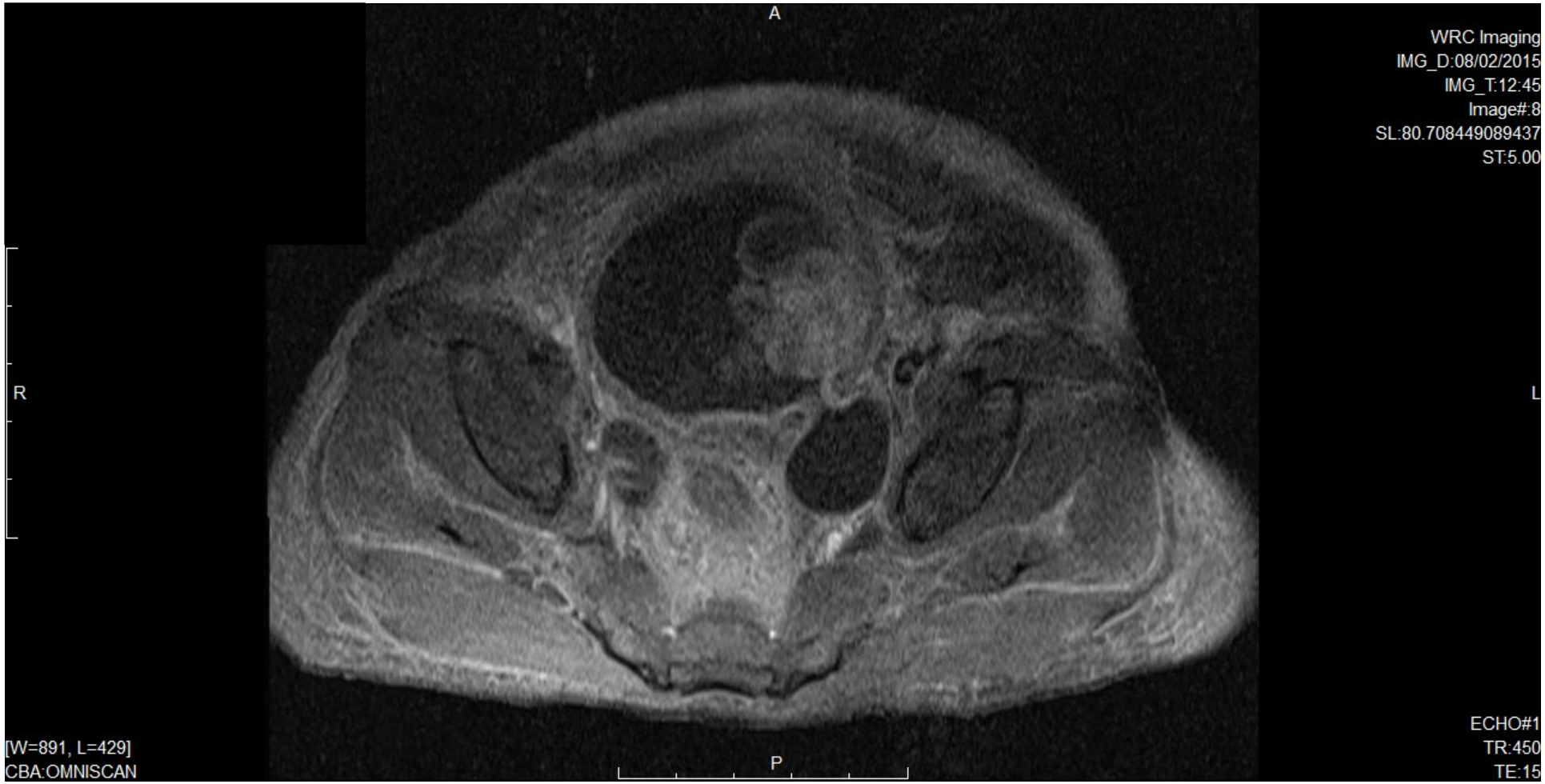
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CBA:OMNISCAN
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TE:15

Case Presentation

- **PMHx:**
- 26 wk gestation, global DD
- multiple congenital abnormalities (dysmorphic facies, laryngomalacia, periventricular leukomalacia, congenital diverticulum of bladder, PDA)
- panhypopituitarism,
- chromosomal abnormality (microarray duplications of 17 and 18)
- bilateral grade II IVH
- abnormal CF newborn screening
- retinopathy of prematurity
- bilateral inguinal hernia (s/p repair), abdominal wall hernia, umbilical hernia
- cryptorchidism, **rectal prolapse**

- **PSHx:**
- bilateral inguinal hernia repair
- laparoscopic gastrostomy and PEG tube placement
- PDA ligation
- vitreous retinal surgery
- circumcision, orchiopexy
- **partial cystectomy**

Case Presentation

- Meds: Hydrocortisone, Levothyroxine, Albuterol, Budesonide, Neomycin-Polymyxin-Dexamethasone ophthalmic ointment, Nystatin ointment

- Allergies: Latex, Medical tape/band-aids

- FHx: Unspecified genetic disorder in mother, father, maternal aunt. DM in mother, maternal grandmother. Renal failure maternal grandmother. **No known GU or soft tissue cancer history.**

- SHx: Lives with mother and father and commonly cared for by grandparents. Father and grandparents smoke outside.

Case Presentation

- PE: T 36.4 C, HR 135, RR 36, BP 124/61
  - Gen: Well appearing, alert interactive child, nonverbal occasionally fussy, dysmorphic facies, no acute distress
  - Abd: Soft, non-distended, Reducible L abdominal hernia, normoactive bowel sounds, PEG tube in place with mild surrounding erythema and crusting, Suprapubic incision clean, dry, intact with mild grimicing/crying on palpation
  - GU: Normal appearing circumcised male genitalia, Foley in place draining clear yellow urine
- Labs: WBC 6.7, H/H 10.8/33, Plt 255, **Cr 0.6** (elevated from baseline 0.2-0.3), BMP otherwise WNL
  - OSH Labs: BCx (8/4)- No growth x3d, Ucx (8/3)- No growth x1d

Workup & management

- CT Chest/Abd/Pelvis: **No evidence of pulmonary or solid organ metastatic disease**
- Bone Scan- **Negative**
- Bone Marrow Biopsy- **Negative**
- Cystoscopy with **bilateral stent placement**
- Central Line and Port Placement for chemo
- After initial VAC/VI, cystectomy and ileal conduit followed by completion of chemotherapy course and pelvic XRT
- Currently 5 years out from treatment with no recurrence and excellent functional status

Case

3-year-old boy with gross hematuria & dysuria

Jon Routh, MD

Case #2

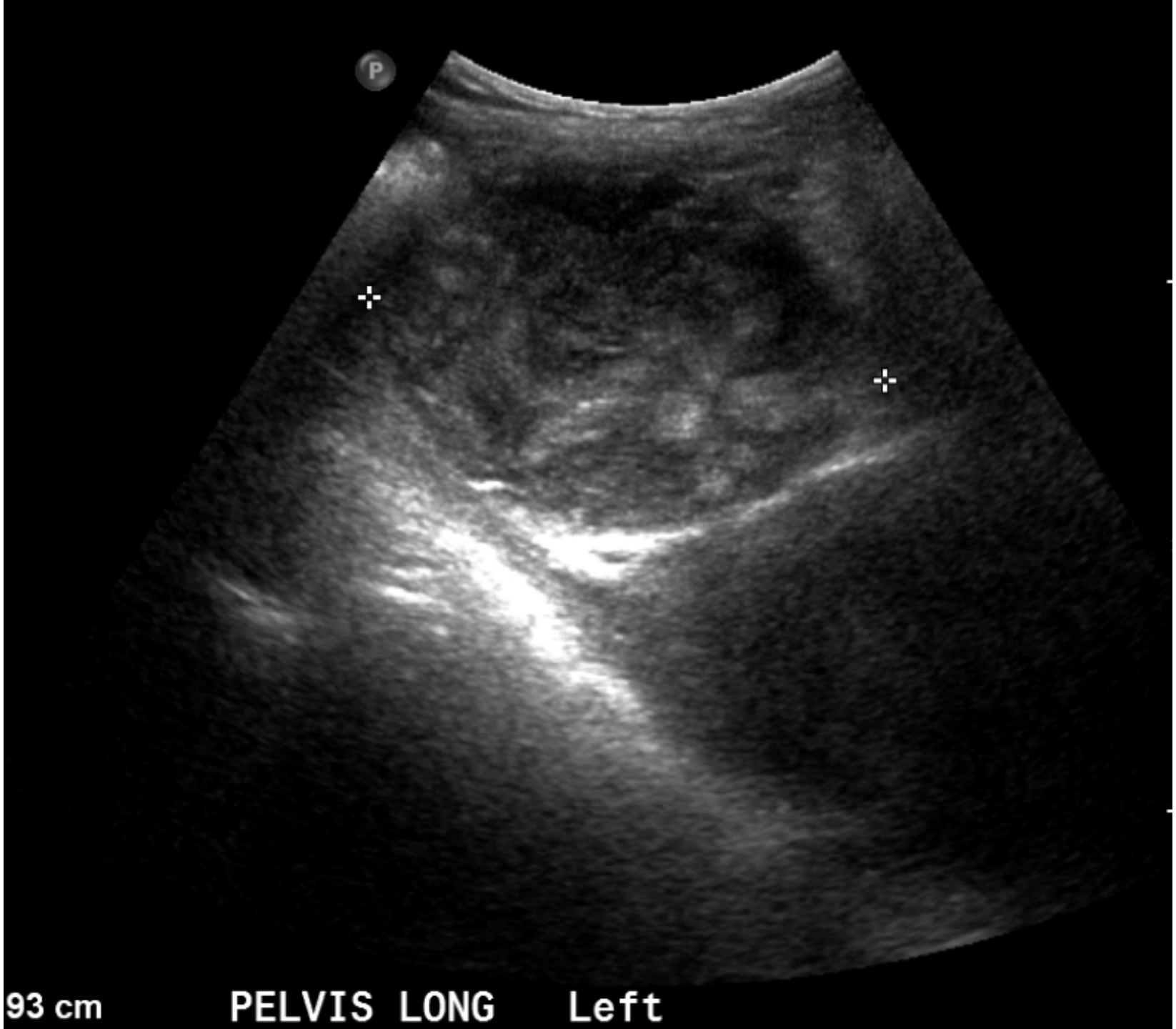
HPI: 3-year-old boy with gross hematuria & dysuria

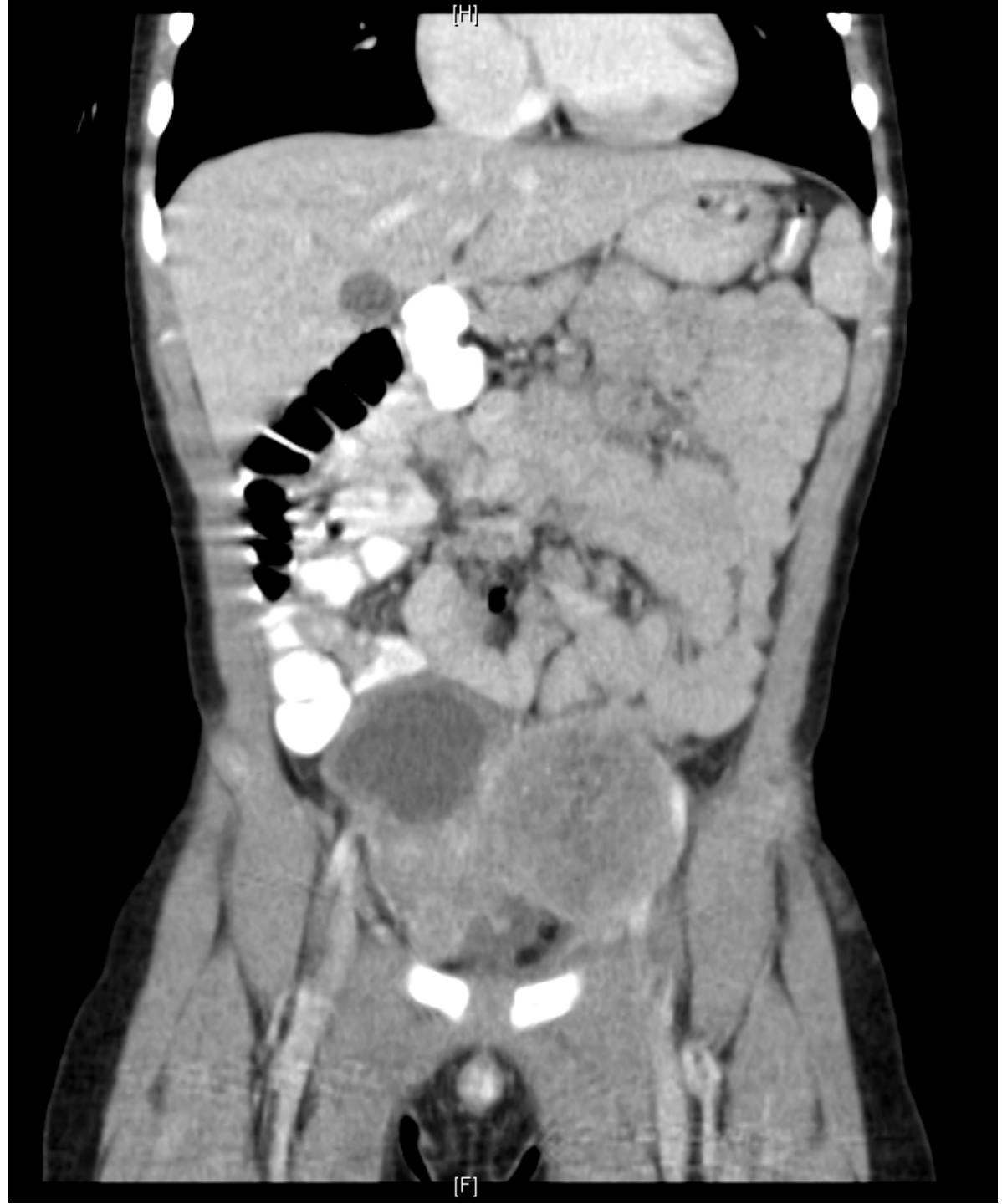
PMH: Normal pregnancy/delivery

PE: P 90 BP 90/60 RR 20

Gen: Running around clinic, happy

Abd: NTND, firm suprapubic mass


93 cm
PELVIS LONG
Left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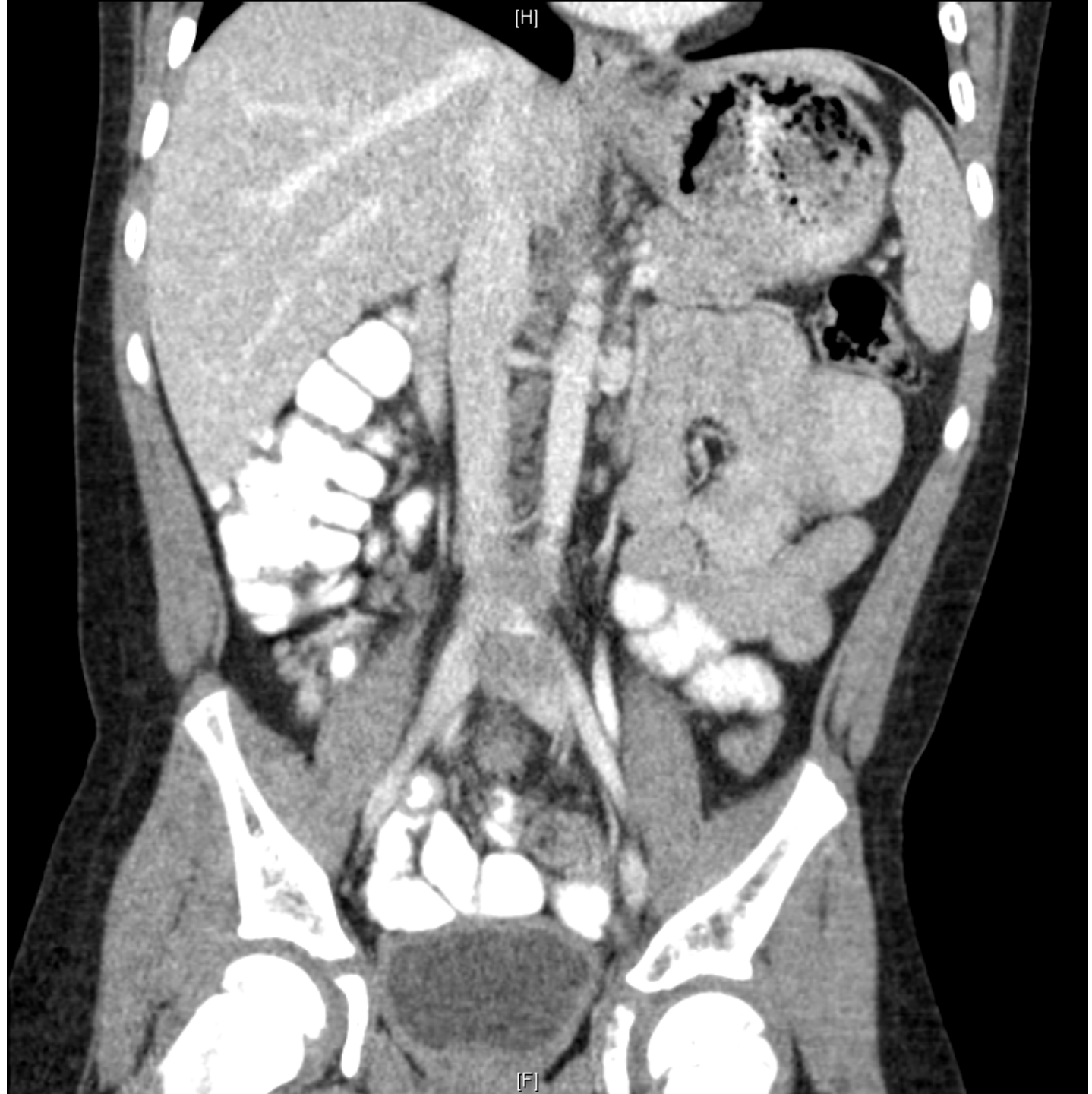
Case #2

- Management: Attempted cystoscopic biopsy followed by open biopsy, lymph node sampling, chemotherapy, radiation
- Final Diagnosis: Non-fusion (embryonal) rhabdomyosarcoma of the bladder & prostate
- Long-term: Surveillance, bladder function monitoring

8 years after diagnosis

Long-term outcomes

- 8 years after treatment, no recurrent tumor
- Frequent UTIs & severe phimosis managed by circumcision
- Overactive bladder managed by oxybutynin and timed voiding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Case

6-year-old girl with hematuria

Jon Routh, MD

Case #3

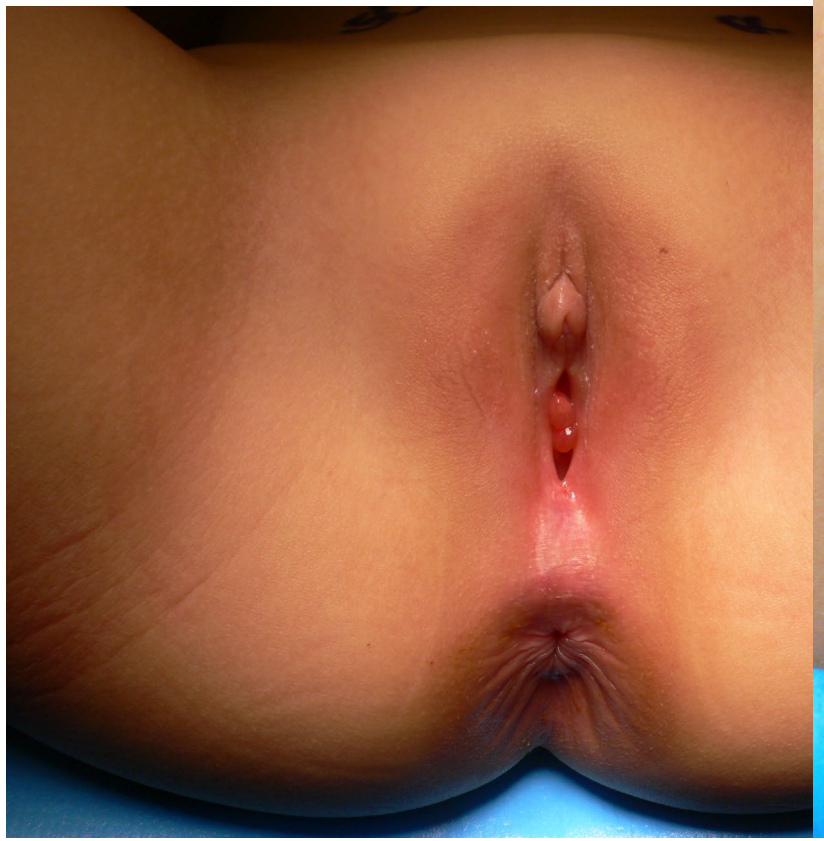
HPI: 6-year-old girl with hematuria

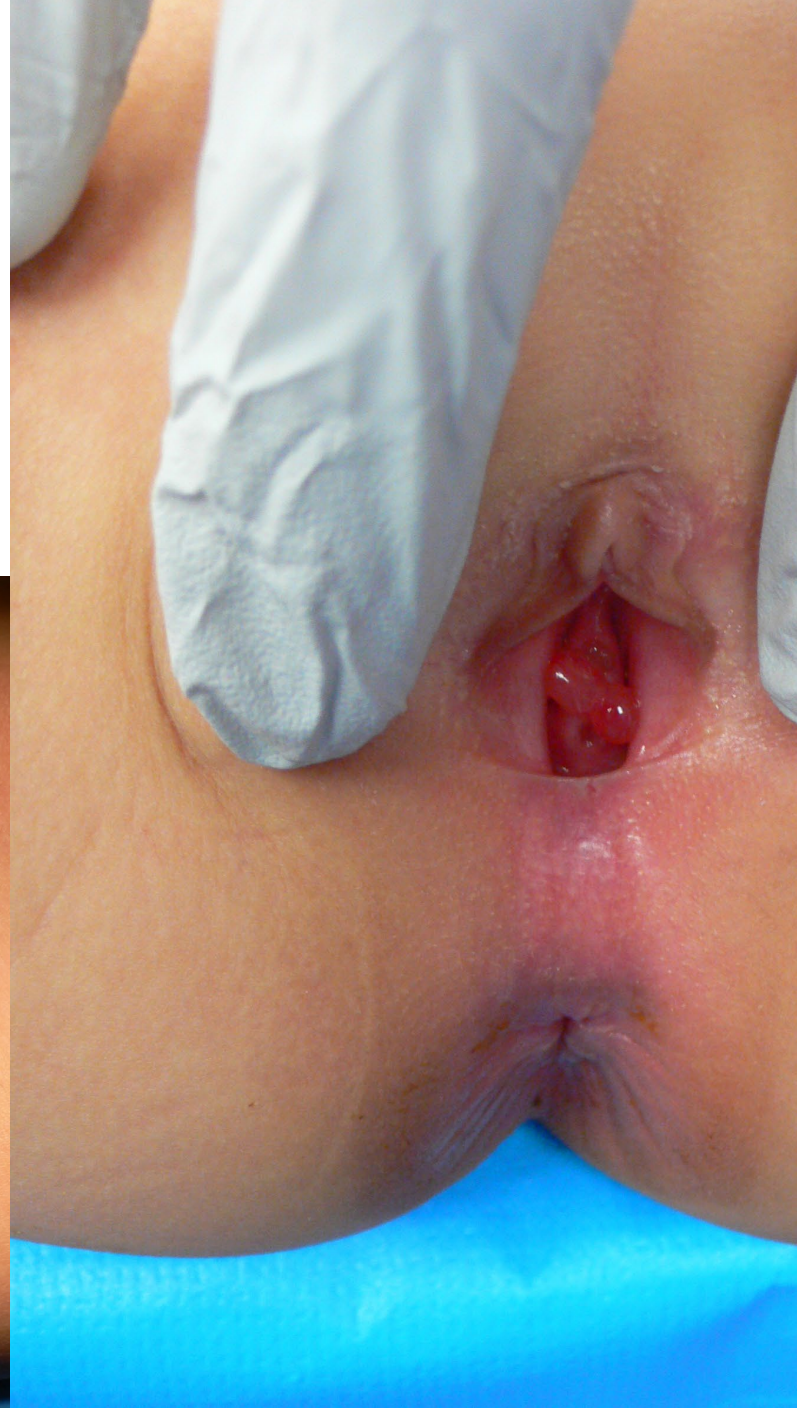
PMH: Otherwise healthy

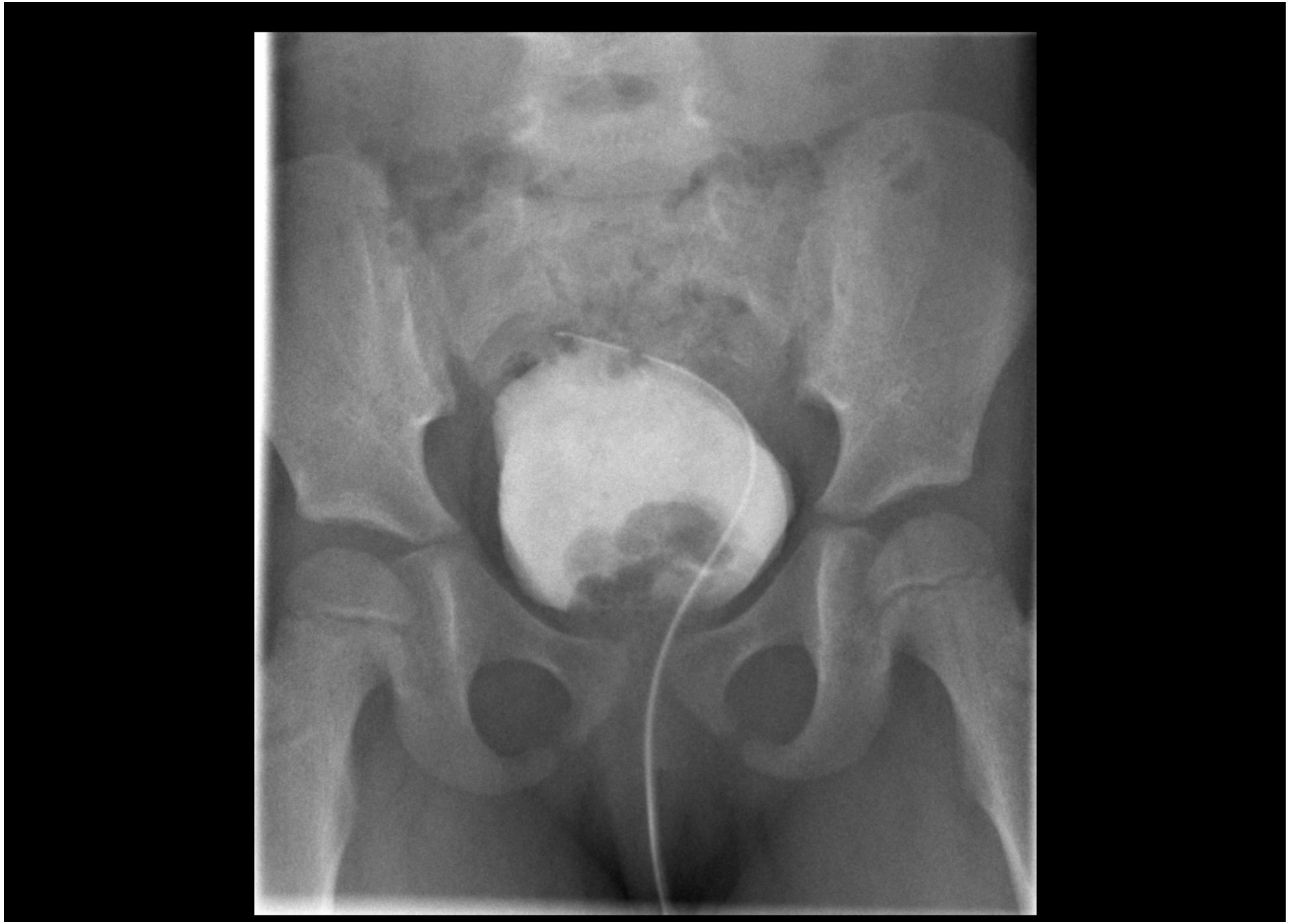
PE: P 90 BP 91/62 RR 20

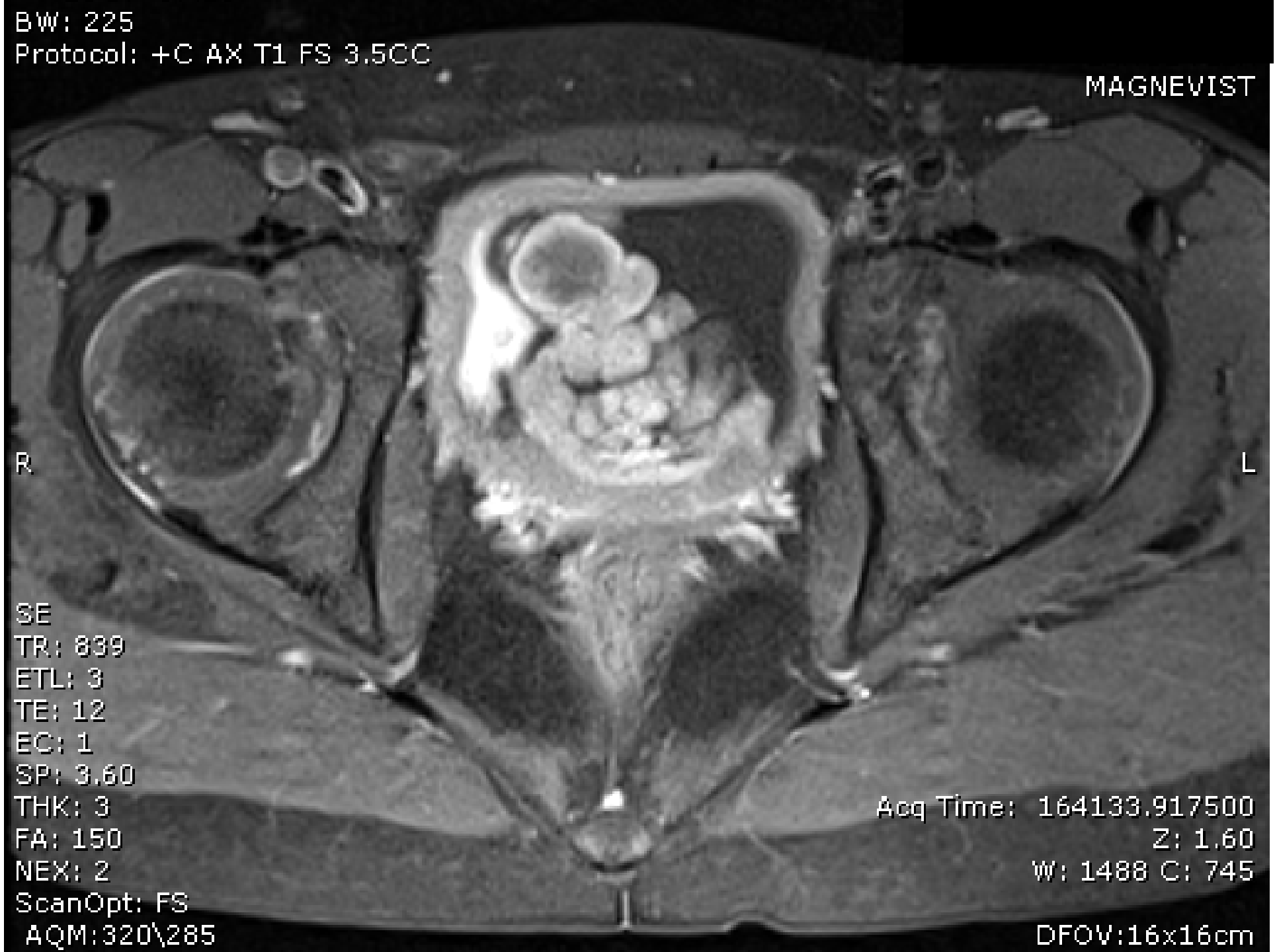
Abd: NTND

GU exam:





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THK: 3
FA: 150
NEX: 2
ScanOpt: FS
AQM:320\285
Acq Time: 164133.917500
Z: 1.60
W: 1488 C: 745
DFOV:16x16cm

Case #3:

Diagnosis:

- Embryonal rhabdomyosarcoma (non-fusion)

Management:

- Radical cystectomy (vaginal preserving)
- Ileal conduit urinary diversion
- Planned long-term continent reconstruction

Thank you to our panel!