Renal tumors in children; case presentations and overview of the current management of Wilms tumor

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IWK Health

DALHOUSIE UNIVERSITY

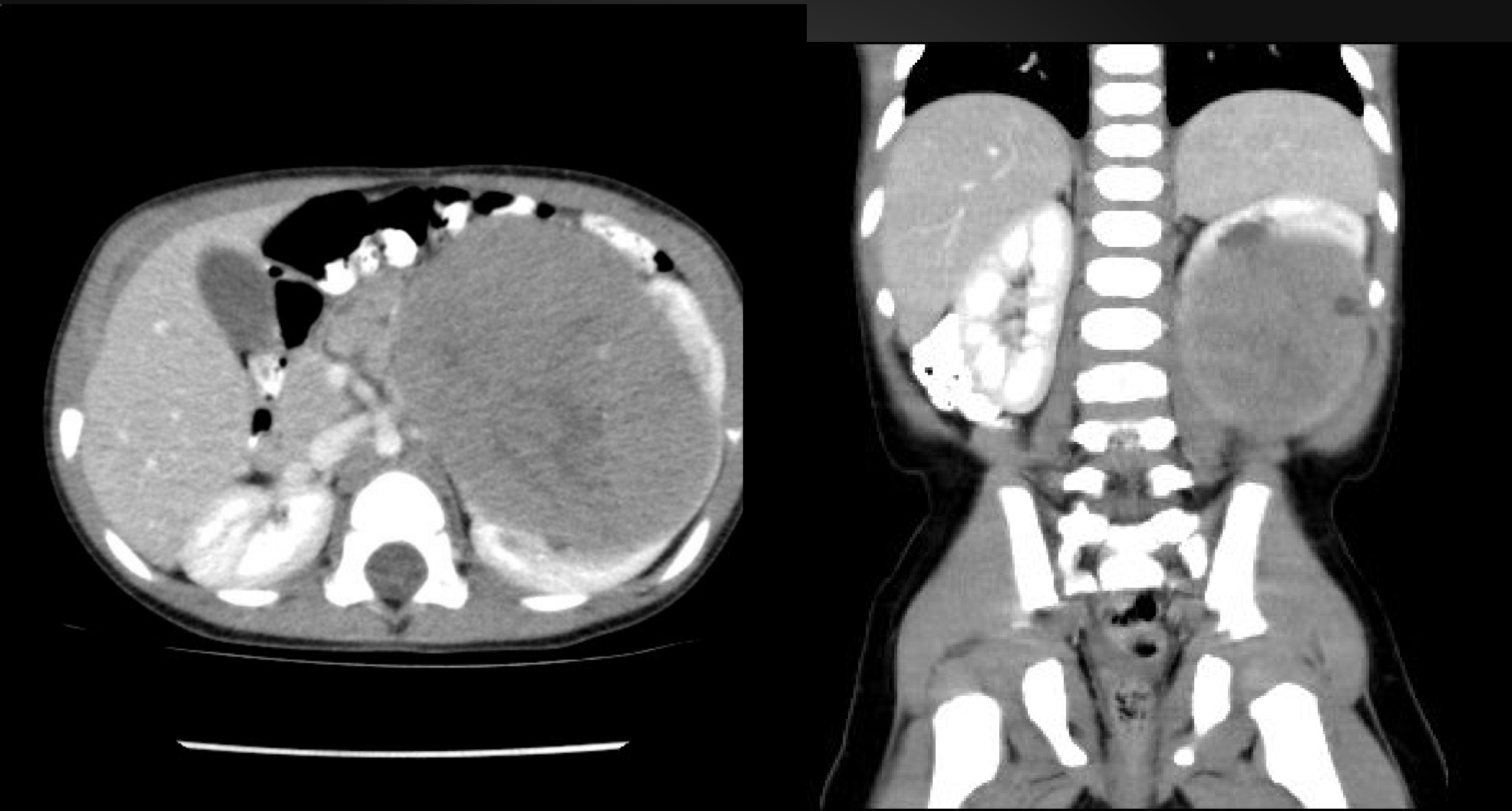
Disclosure

I have no financial disclosures.

I am a member of the Children's Oncology Group (COG) Renal Tumor Committee, but views expressed here are my own and I am NOT speaking on behalf of the committee or COG.

Outline

- Case presentations with audience participation
- Overview of the staging, risk stratification and treatment for Wilms tumor
- Focus on surgical aspects of care
- Differences between North America and Europe
- Review same cases at the end for correct answers and discussion



1-year old boy with palpable mass in the flank noticed by caregiver. No other symptoms.

Based on the imaging provided, choose the alternative that reflects the best treatment approach for this patient:

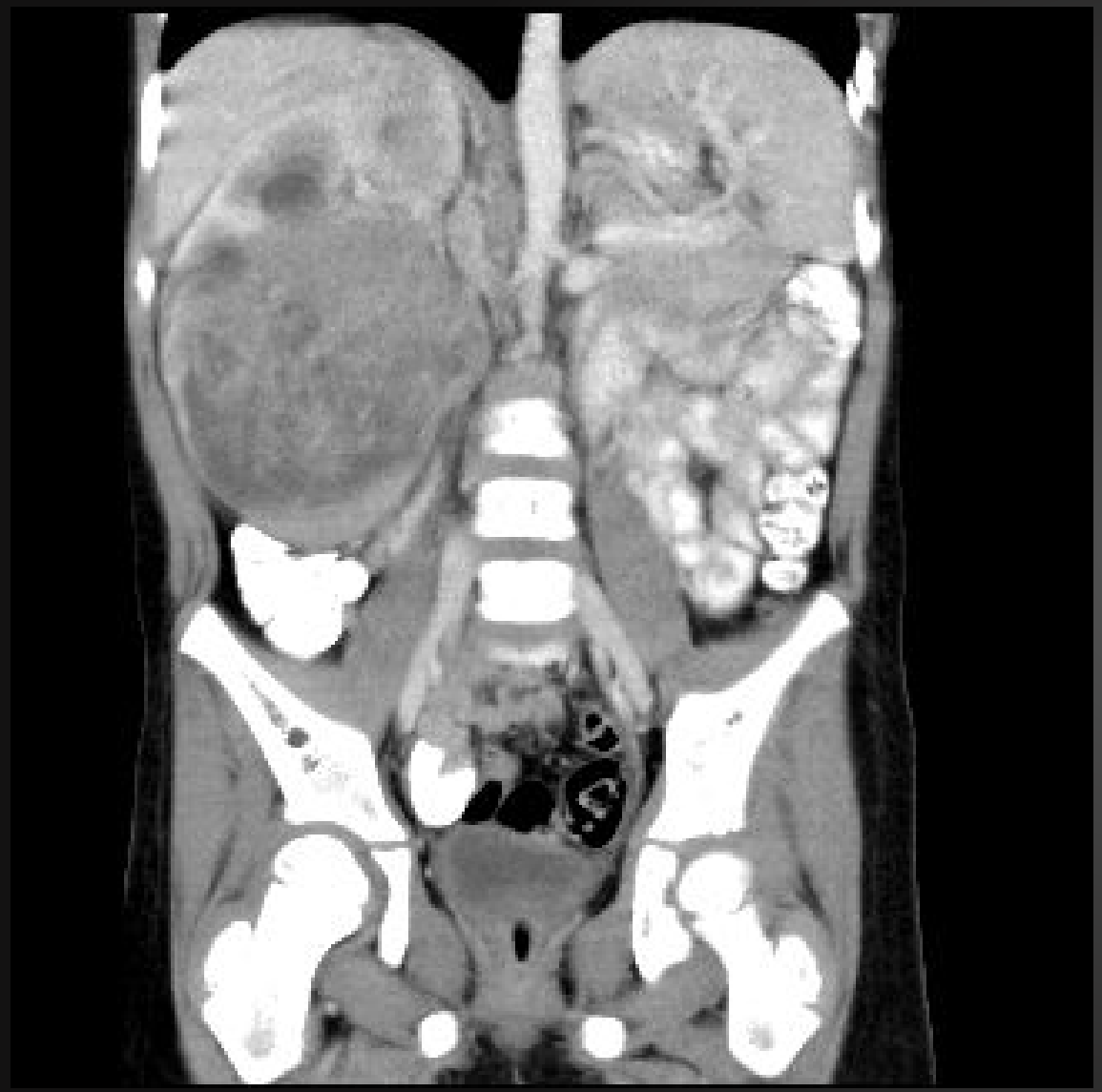
a) Neoadjuvant chemotherapy followed by nephrectomy with lymph node sampling

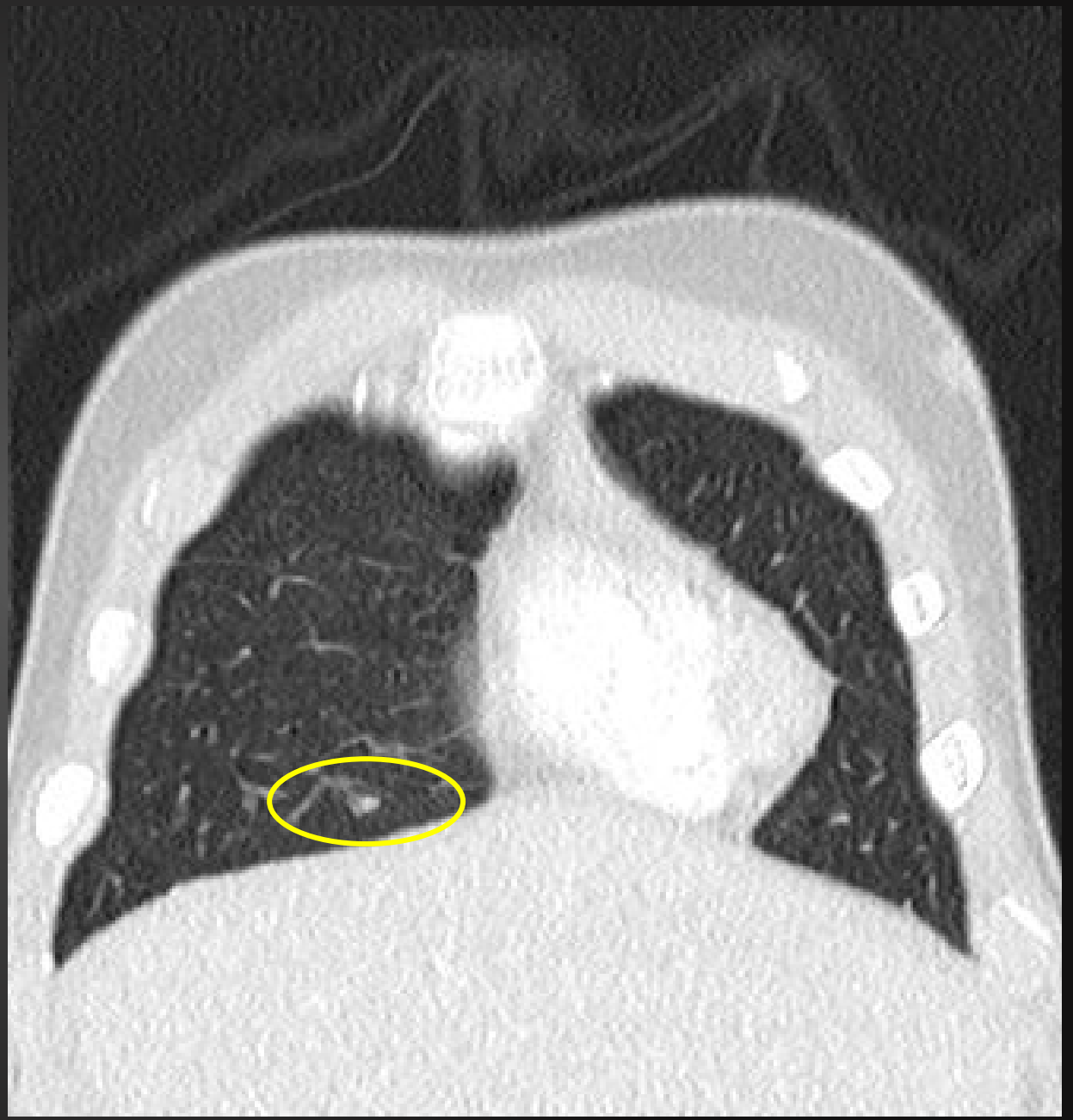
b) Upfront nephrectomy followed by adjuvant chemotherapy and radiation

c) Upfront nephrectomy + lymph node sampling as long as there is no evidence of a predisposition syndrome

d) Upfront nephrectomy with node sampling only if nodes are abnormal on imaging or intraoperatively

e) Neoadjuvant chemotherapy followed by nephrectomy and radiation





4-year old boy presents to the ED for gross hematuria. There is a palpable right-sided abdominal mass. US confirms the presence of a renal tumor; CT abdomen and chest performed. Radiology reports a single lung nodule compatible with metastatic disease. Primary tumor is restricted to the kidney with no evidence of vascular thrombus. Select the best approach for this patient:

a) Open biopsy of the renal mass, neoadjuvant chemotherapy followed by delayed nephrectomy

b) Percutaneous biopsy of the renal mass, neoadjuvant chemotherapy followed by delayed nephrectomy

c) Thoracoscopic biopsy of lung nodule, neoadjuvant chemotherapy, delayed nephrectomy

d) Upfront nephrectomy with lymph node sampling, adjuvant chemotherapy adjusted based on risk stratification and lung response to therapy

e) Percutaneous biopsy of the renal mass, thoracoscopic biopsy of the lung lesions, neoadjuvant chemotherapy, delayed nephrectomy and radiation

You perform a radical nephrectomy and lymph node sampling for a 10 cm left renal mass in a 3-year old girl. Pathology confirms a completely resected favorable histology Wilms tumor with LOH 1p and 16q with 4/10 positive nodes.

Select the option that contains the correct stage and adjuvant therapy:

a) Stage II / Chemotherapy – vincristine, actinomycin D, doxorubicin
b) Stage III / Chemotherapy – vincristine, actinomycin D, doxorubicin, cyclophosphamide and etoposide
c) Stage II / Radiation therapy only
d) Stage II / 3-drug chemotherapy + abdominal radiation
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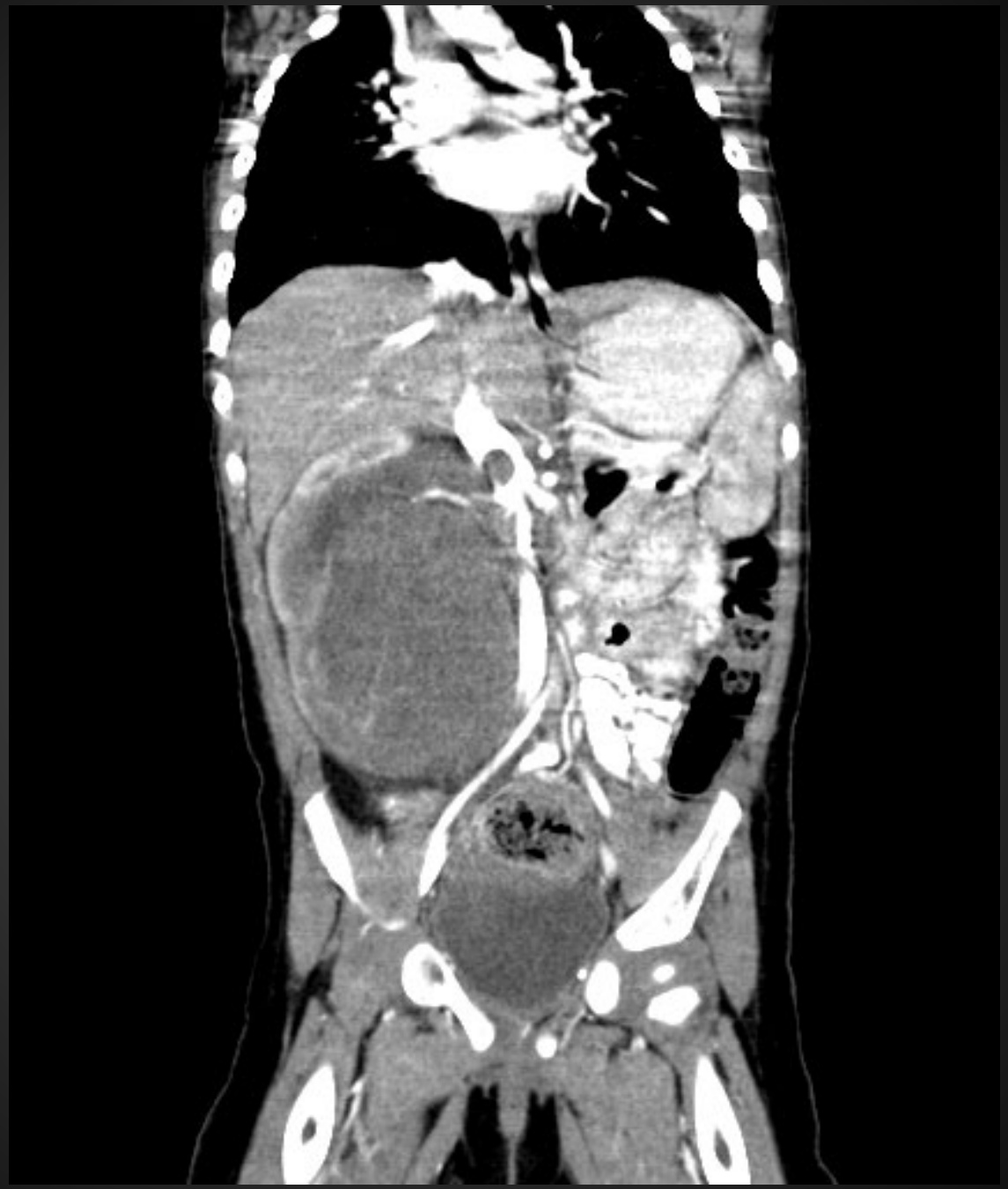


Select the best approach for this 2.5-year old girl with a renal mass and evidence of tumor thrombus extending into the IVC:

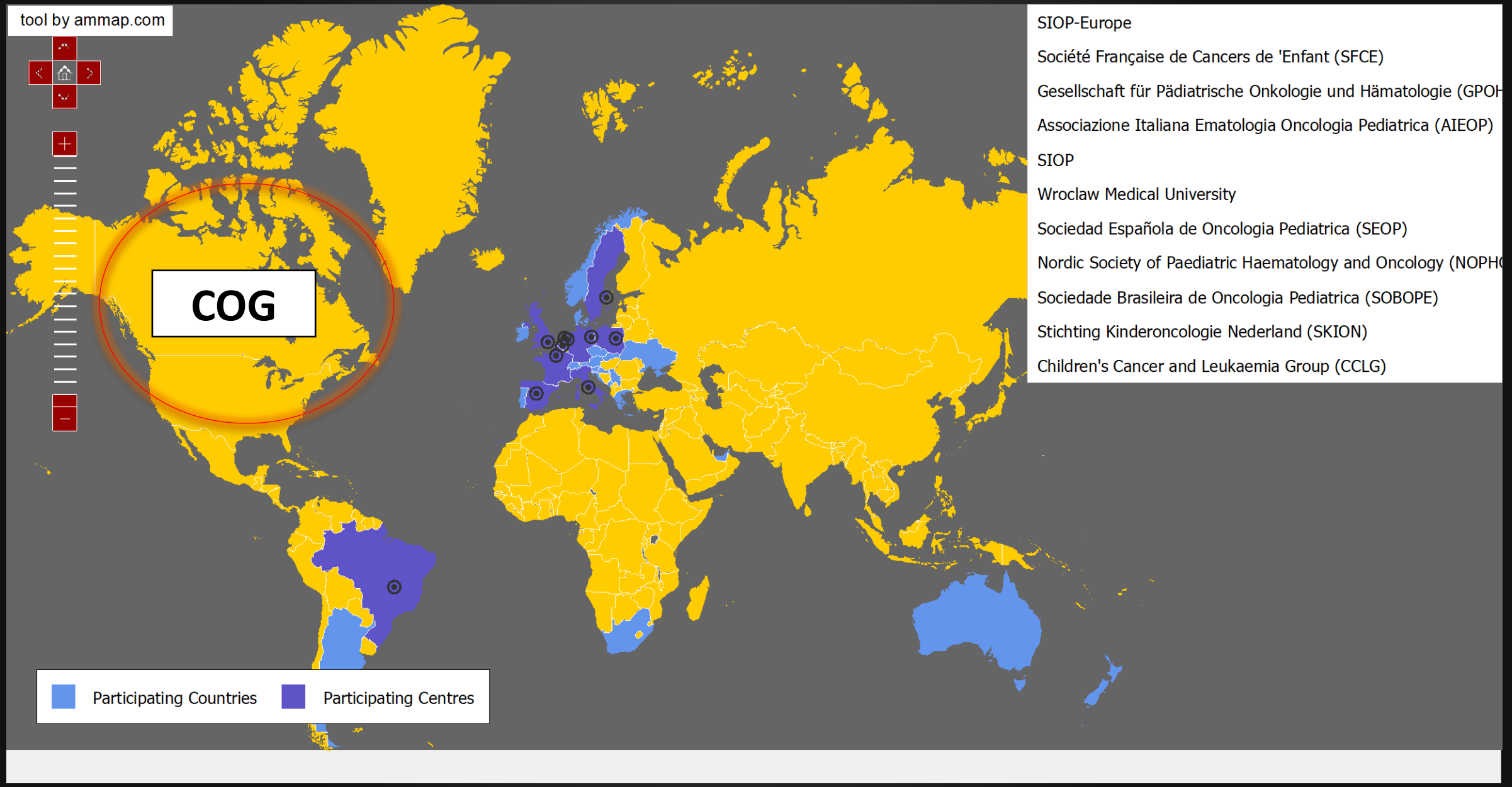
a) Percutaneous biopsy, neoadjuvant chemotherapy, delayed nephrectomy at 12 weeks with IVC exploration if residual tumor thrombus and lymph node sampling, adjuvant chemotherapy and radiation if necessary.
b) Upfront radical nephrectomy and lymph node sampling, tumor thrombectomy separate from nephrectomy specimen followed by adjuvant chemotherapy and radiation if necessary.
c) Neoadjuvant chemotherapy without biopsy, delayed nephrectomy at 12 weeks with IVC exploration if residual tumor thrombus.
d) Upfront nephrectomy and *en bloc* tumor thrombectomy, lymph node sampling, adjuvant chemotherapy and radiation if necessary.
e) Upfront nephrectomy with IVC exploration on cardiopulmonary bypass, lymph node sampling, adjuvant chemotherapy and radiation if necessary.

Epidemiology – Wilms tumor or nephroblastoma

- 1/10,000 children younger than 15 years of age
- 5-6% of all childhood cancers
- 500 new cases in the US per year
- Median age at diagnosis – between 3 and 4 years, rare in neonates (congenital mesoblastic nephroma - CMN)
- 75% diagnosed before age 5
- Main DD – neuroblastoma
- 10% - predisposition syndromes

Clinical presentation

- Palpable mass
- Significant proportion completely asymptomatic
- Trauma / bleeding
- Hematuria (20%)


tool by ammap.com
COG
SIOP-Europe
Société Française de Cancers de 'Enfant (SFCE)
Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH
Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP)
SIOP
Wroclaw Medical University
Sociedad Española de Oncologia Pediatrica (SEOP)
Nordic Society of Paediatric Haematology and Oncology (NOPH
Sociedade Brasileira de Oncologia Pediatrica (SOBOPE)
Stichting Kinderoncologie Nederland (SKION)
Children's Cancer and Leukaemia Group (CCLG)
Participating Countries
Participating Centres

Unilateral, non-syndromic WT

COG

- Upfront nephrectomy + lymph node sampling
- Adjuvant chemotherapy based on risk stratification
  - *Vincristine*
  - *Actinomycin D*
  - *(Doxorubicin)*
  - Cyclophosphamide
  - Etoposide
- Radiation

SIOP

- 6 months to 10 years
- Neoadjuvant chemotherapy without biopsy
- Delayed nephrectomy + LN sampling at 6 or 12 weeks
- Therapy adjusted based on histology after nephrectomy
  - Necrotic
  - Intermediate
  - Blastema-predominant
- Radiation

Table 2 Wilms' Tumor Staging System

I. Tumor limited to kidney and completely excised. The surface of the renal capsule is intact. Tumor was not ruptured before or during removal. There is no residual tumor apparent beyond the margins of excision.

II. Tumor extends beyond the kidney, but is completely excised. There is regional extension of the tumor; i.e., penetration through the outer surface of the renal capsule into perirenal soft tissues. Vessels outside the kidney substance are infiltrated or contain tumor thrombus. The tumor may have been biopsied or there has been local spillage of tumor contained to the flank. There is no residual tumor apparent at or beyond the margins of excision.

III. Residual nonhematogenous tumor confined to abdomen. Any one or more of the following occur:
   1. Lymph nodes on biopsy are found to be involved in the hilus, the periaortic chains or beyond.
   2. There has been diffuse peritoneal contamination by tumor such as by spillage of tumor beyond the flank before or during surgery, or by tumor growth that has penetrated through the peritoneal surface.
   3. Implants are found on the peritoneal surfaces.
   4. The tumor extends beyond the surgical margins either microscopically or grossly.
   5. The tumor is not completely resectable because of local infiltration into vital structures.

IV. Hematogenous metastases. Deposits beyond Stage III; i.e., lung, liver, bone, and brain.

V. Bilateral renal involvement at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of extent of disease prior to biopsy.


© Cartoonbank.com
TRUTH

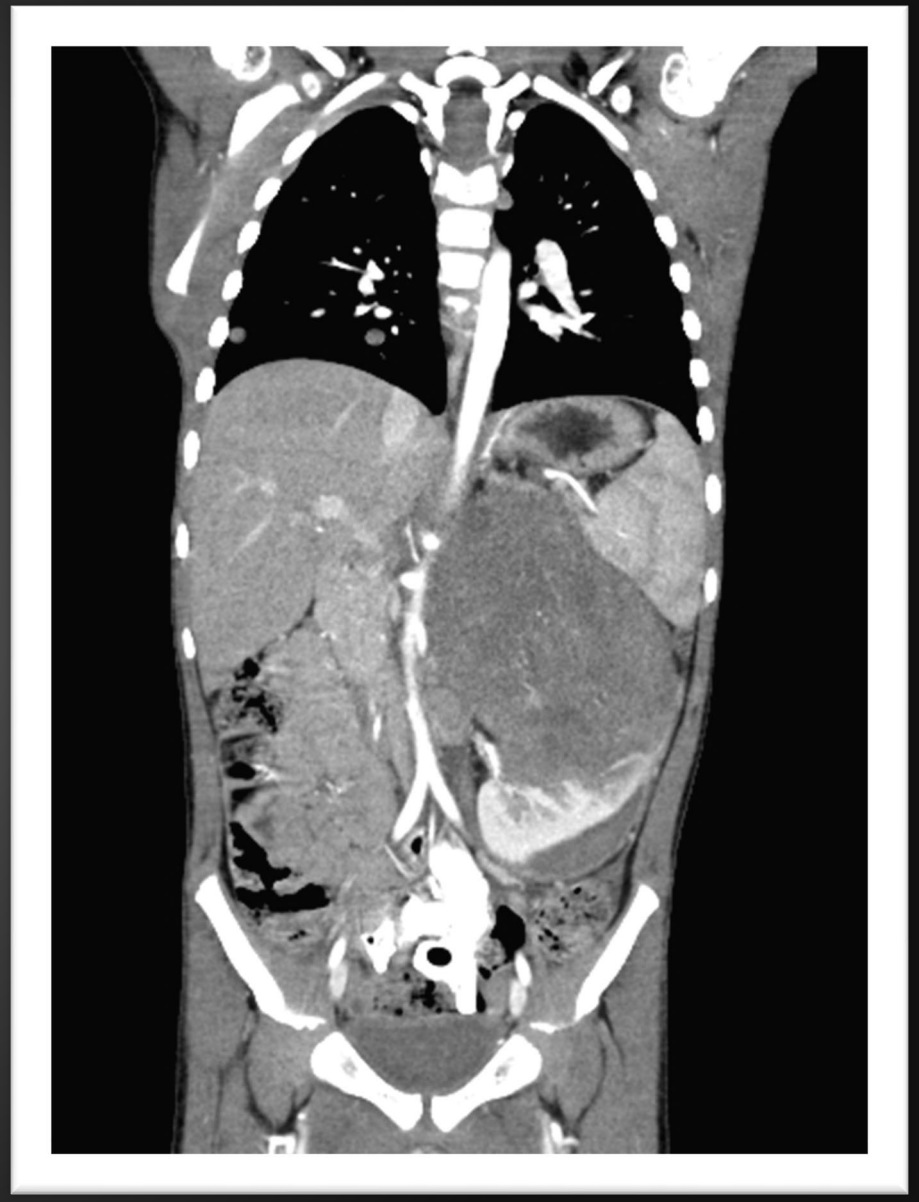
Lesion in 1 kidney, normal contralateral kidney

No known predisposition syndrome

No IVC thrombus above the hepatic veins

No pulmonary compromise due to extensive pulmonary mets

Surgeon’s judgement that nephrectomy would lead to tumor spill, mortality, excessive morbidity, residual tumor



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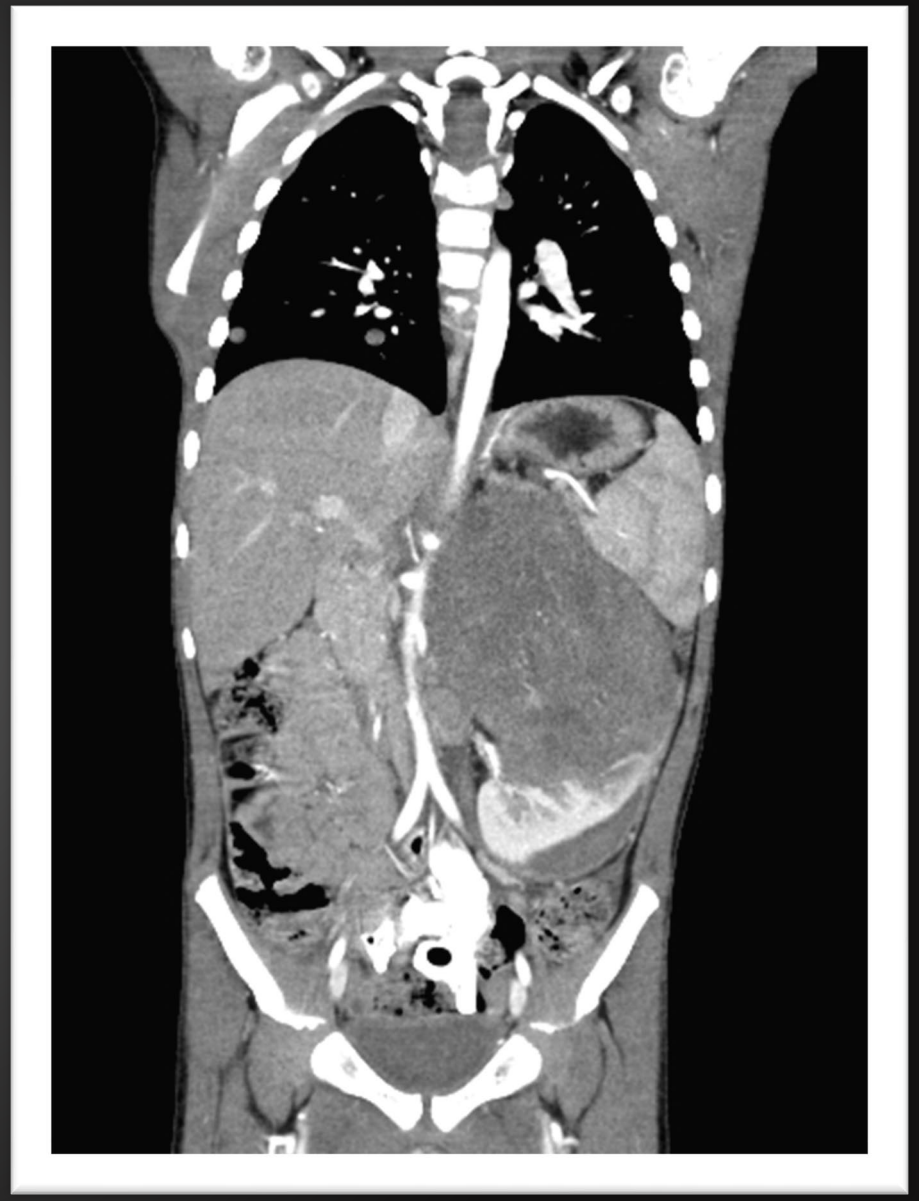


Why upfront nephrectomy?

Staging

Imaging
- Metastatic disease (lungs)

Surgical
- **Rupture / spill**
- **Vascular extension – renal vein, IVC**
- **LN sampling**
- **Biopsy**

Pathology
- Histology
  - Favorable
  - Anaplastic
- Capsule, renal sinus, vessels, margins
- Lymph node status

Risk stratification

Overall Stage (I-V)

+

Surgical stage (I-III)

+

Adverse biology features

LOH 1p

LOH 16q

1q gain

Stage I / II

Stage III / IV

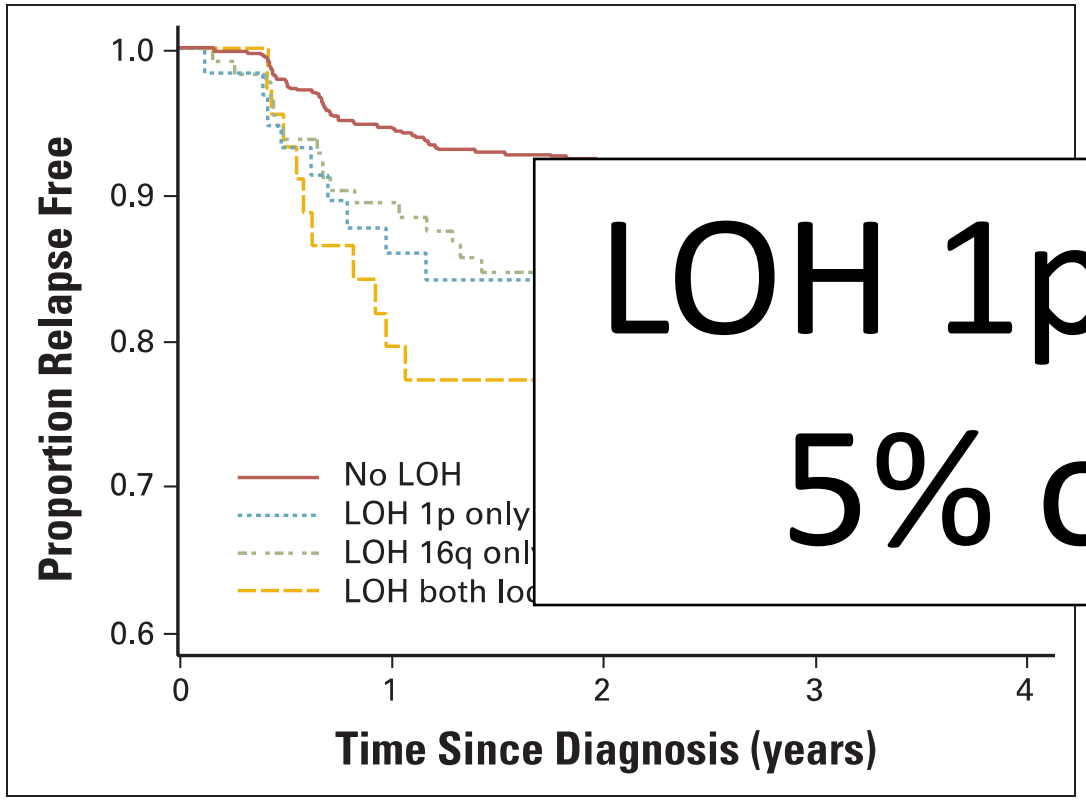
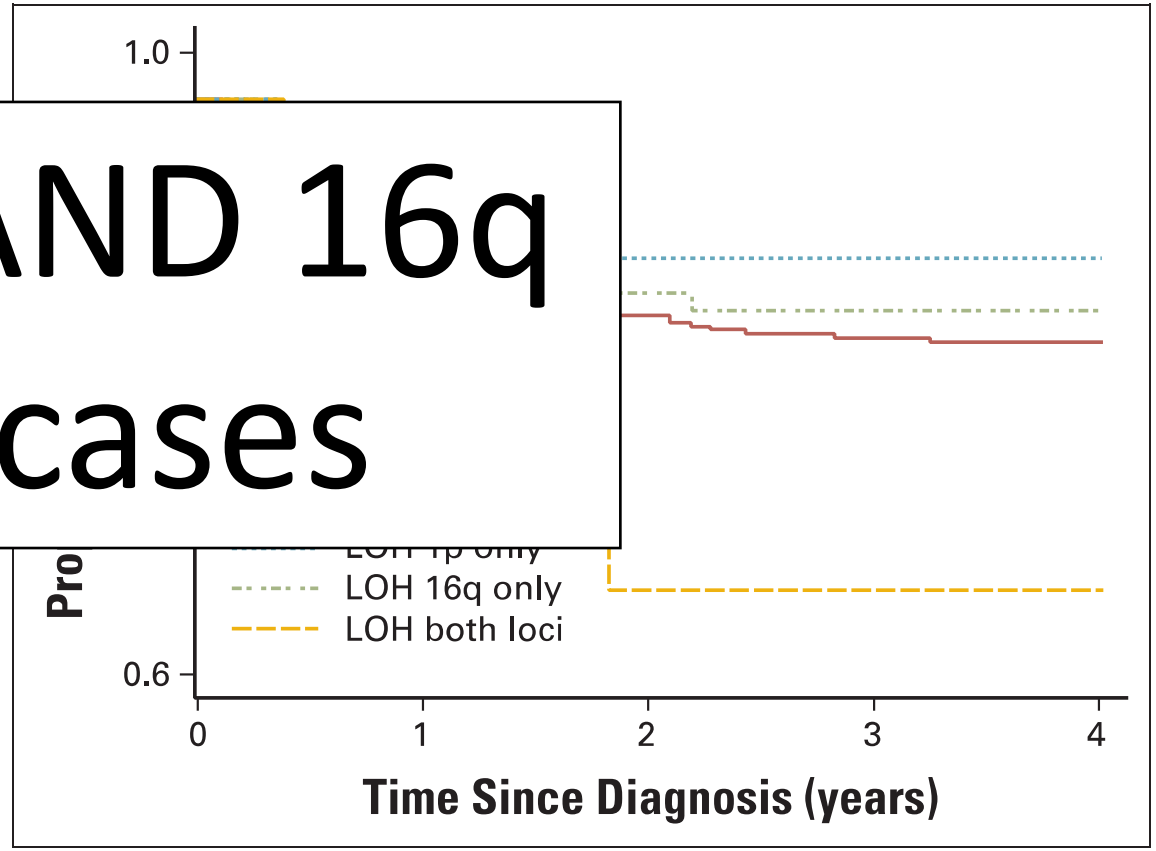


Fig 2. Relapse-free survival by joint loss of heterozygosity at chromosomes 1p and 16q for stage I/II favorable-histology Wilms tumor patients. LOH, loss of heterozygosity.

LOH 1p AND 16q
5% of cases



Grundy et al. *JCO* 2005

VOLUME 34 · NUMBER 26 · SEPTEMBER 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Association of Chromosome 1q Gain With Inferior Survival in Favorable-Histology Wilms Tumor: A Report From the Children's Oncology Group

Eric J. Gratias, Jeffrey S. Dome, Lawrence J. Jennings, Yueh-Yun Chi, Jing Tian, James Anderson, Paul Grundy, Elizabeth A. Mullen, James I. Geller, Conrad V. Fernandez, and Elizabeth J. Perlman

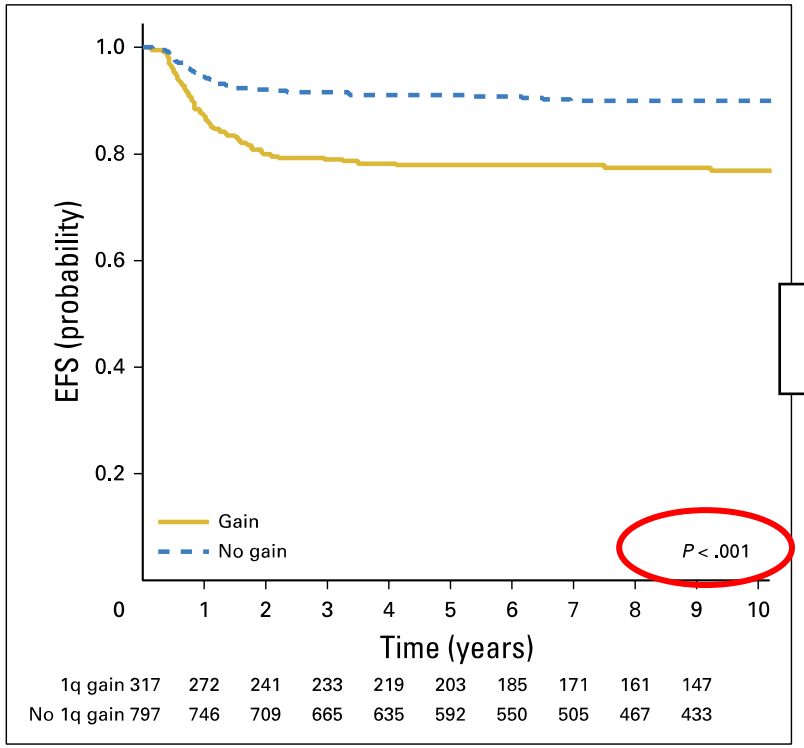


Fig 1. Event-free survival (EFS) stratified for 1q gain.

1q gain

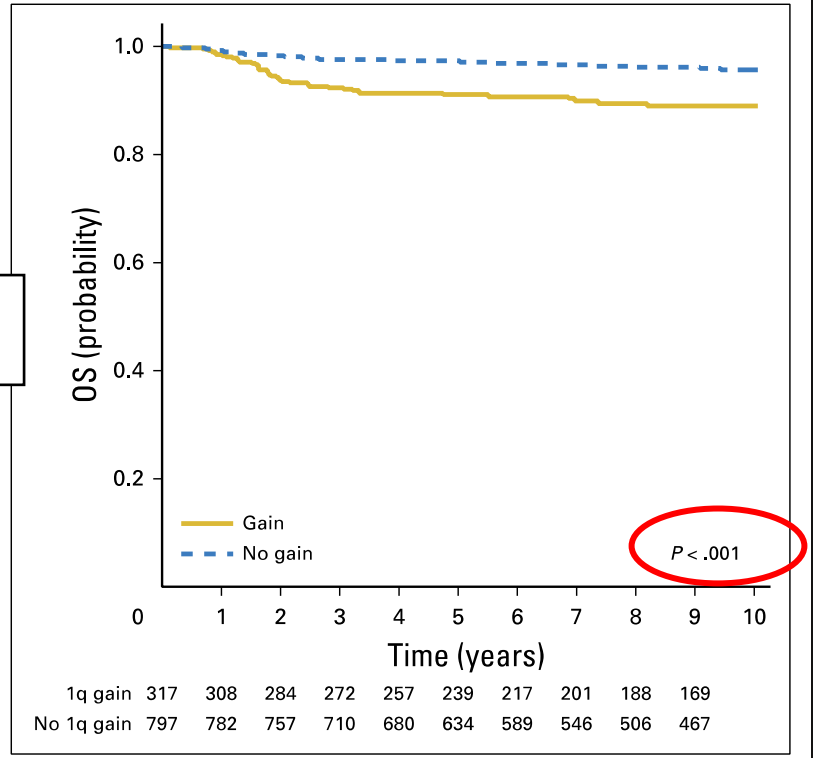


Fig 2. Overall survival (OS) stratified for 1q gain.

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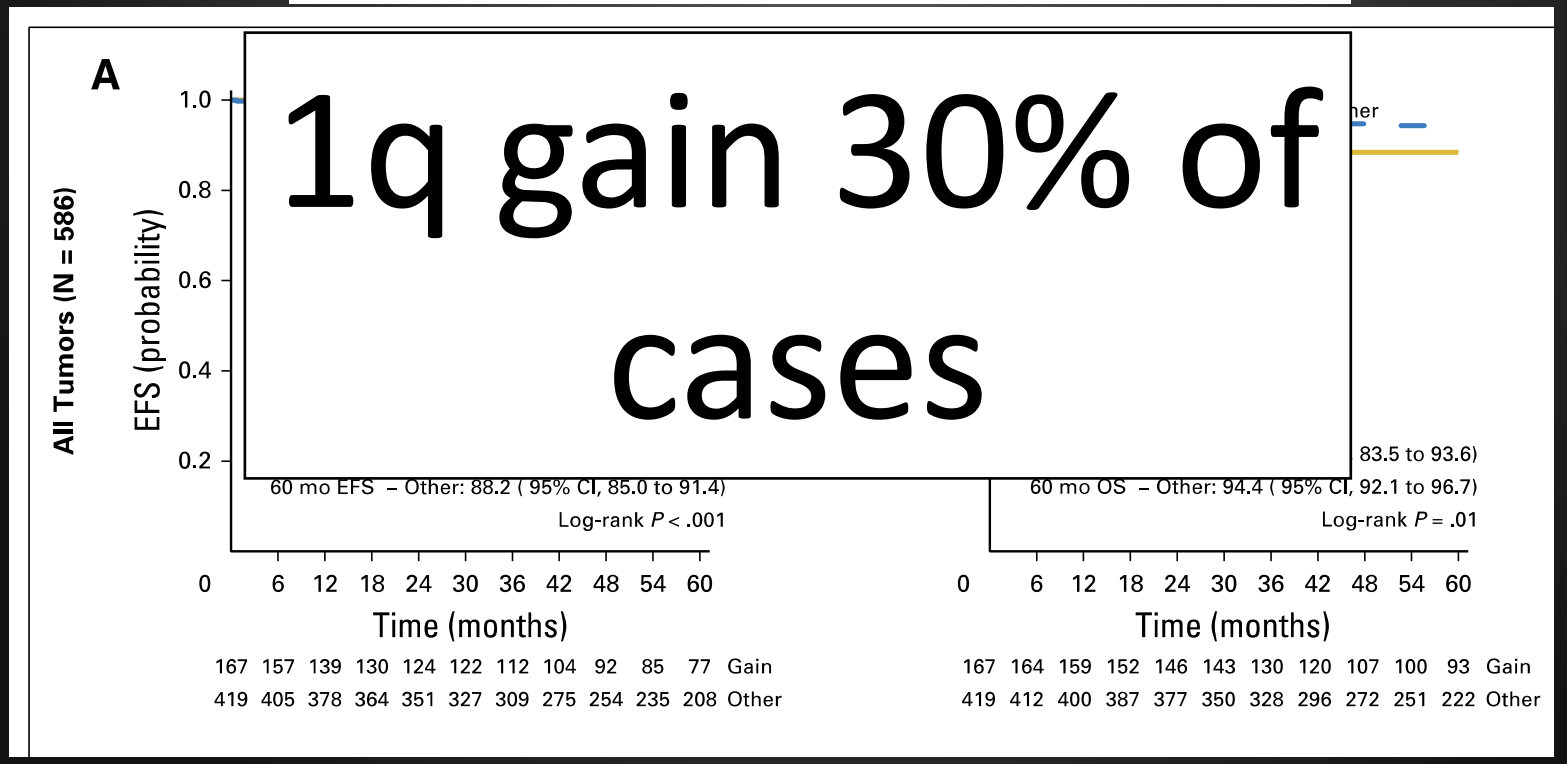
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Gain of 1q As a Prognostic Biomarker in Wilms Tumors (WTs) Treated With Preoperative Chemotherapy in the International Society of Paediatric Oncology (SIOP) WT 2001 Trial: A SIOP Renal Tumours Biology Consortium Study

Tasnim Chagtai, Christina Zill, Linda Dainese, Jenny Wegert, Suvi Savola, Sergey Popov, William Mifsud, Gordan Vujanić, Neil Sebire, Yves Le Bouc, Peter F. Ambros, Leo Kager, Maureen J. O'Sullivan, Annick Blaise, Christophe Bergeron, Linda Holmquist Mengelbier, David Gisselsson, Marcel Kool, Godelieve A.M. Tytgat, Marry M. van den Heuvel-Eibrink, Norbert Graf, Harm van Tinteren, Aurore Coulomb, Manfred Gessler, Richard Dafydd Williams, and Kathy Pritchard-Jones



1q gain 30% of cases

original reports

Circulating Tumor DNA as a Biomarker in Patients With Stage III and IV Wilms Tumor: Analysis From a Children's Oncology Group Trial, AREN0533

Laura M. Madanat-Harjuoja, MD, PhD[1]; Lindsay A. Renfro, PhD[2]; Kelly Klega, MS[1]; Brett Tornwall, PhD[3]; Aaron R. Thorner, PhD[4]; Anwesha Nag, PhD[4]; David Dix, MD[5]; Jeffrey S. Dome, MD, PhD[6]; Lisa R. Diller, MD[1]; Conrad V. Fernandez, MD[7]; Elizabeth A. Mullen, MD[1]; and Brian D. Crompton, MD[1,8]

JCO 2022

CONCLUSION ctDNA demonstrates promise as an easily accessible prognostic biomarker with potential to detect tumor heterogeneity. The observed trend toward more favorable outcome in patients with undetectable ctDNA requires validation. ctDNA profiling should be further explored as a noninvasive diagnostic and prognostic tool in the risk-adapted treatment of patients with WT.

Histology

Favorable (90%)

Triphasic
- blastemal
- epithelial
- stromal

Absence of anaplasia

Anaplastic

Clear cell sarcoma of the kidney (CCSK)

Rhabdoid tumor of the kidney (RTK)

Renal cell carcinoma (RCC)

Excellent oncological outcomes vs. long-term treatment related morbidity

Relapse – substantial drop in survival (90% to as low as 50%)

Current standards in the treatment of unilateral WT

- Favorable histology — 90%
  - Very low risk (AREN0532)
  - Standard risk (AREN0532)
  - Higher risk (AREN0533)
    - Stage III with LOH 1p and16q
    - Stage IV disease
- High risk (AREN0321) — 10%

Intensive treatment aimed at improving survival

The role of the pediatric urologist / surgeon

- Nephrectomy without causing spillage
- LN sampling
- Renal vein / IVC thrombus

Open radical nephrectomy for Wilms' tumor

Generous transabdominal, transperitoneal or thoracoabdominal incision to allow a complete exploration of the abdomen

Radical nephrectomy is performed with the ureter divided as distally as possible

Adrenal gland may be spared if upper pole not involved

Renal hilar, pericaval / periaortic, interaortocaval lymph node ***sampling***

Avoid tumor spill

Risk factors for intraoperative spill

> 1,000 patients enrolled on COG studies (AREN03B2)

10% spill rate

Diameter > 12cm

Right-sided tumors (16% vs. 11% - p=0.04)

Gow et al. *JPS , 2013*

Lymph Nodes

Lack of LN sampling – most common protocol violation in patients with WT

10-18% rates of no sampling!!

Ehrlich et al., 2005 and 2016
Saltzman et al. 2020

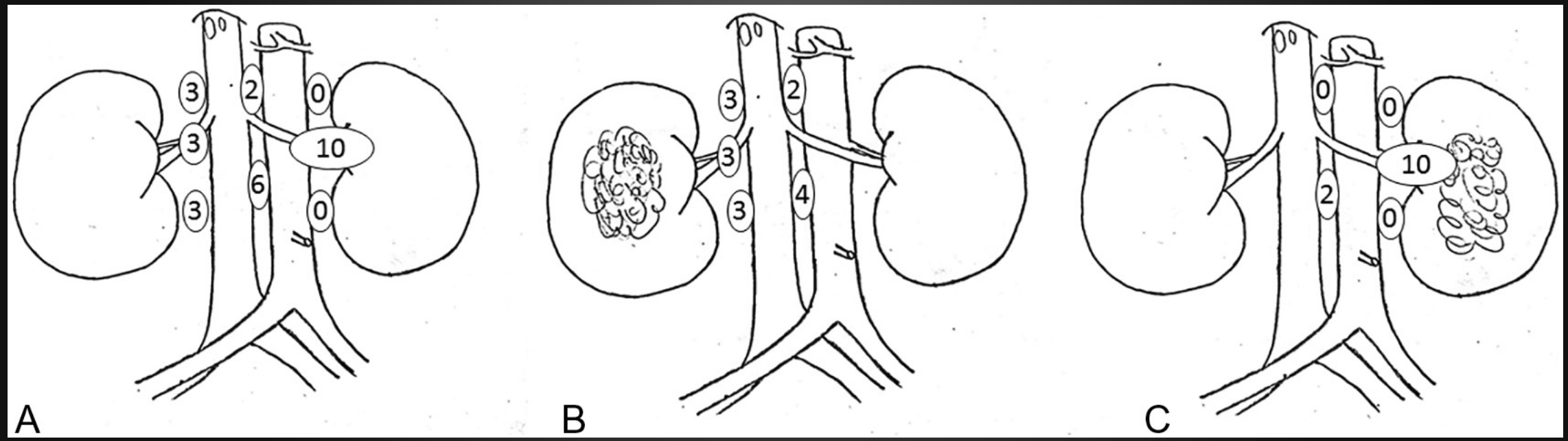
Standardizing lymph nodal sampling for Wilms tumor: A feasibility study with outcomes☆

Sajid S Qureshi [a,b,*], Monica Bhagat [a,b], Mufaddal Kazi [a,b], Seema A Kembhavi [b,c], Subhash Yadav [b,d], Badira C Parambil [b,e], Vasundhara Smriti [b,c], Akshay Baheti [b,c], Maya Prasad [b,e], Nehal Khanna [b,f], Siddharth Laskar [b,f], Tushar Vora [b,e], Girish Chinnaswamy [b,e], Nayana Amin [b,g], Mukta Ramadwar [b,d], Sanjay Talole [b,h]

JPS 2020

113 patients

Median= 8 nodes

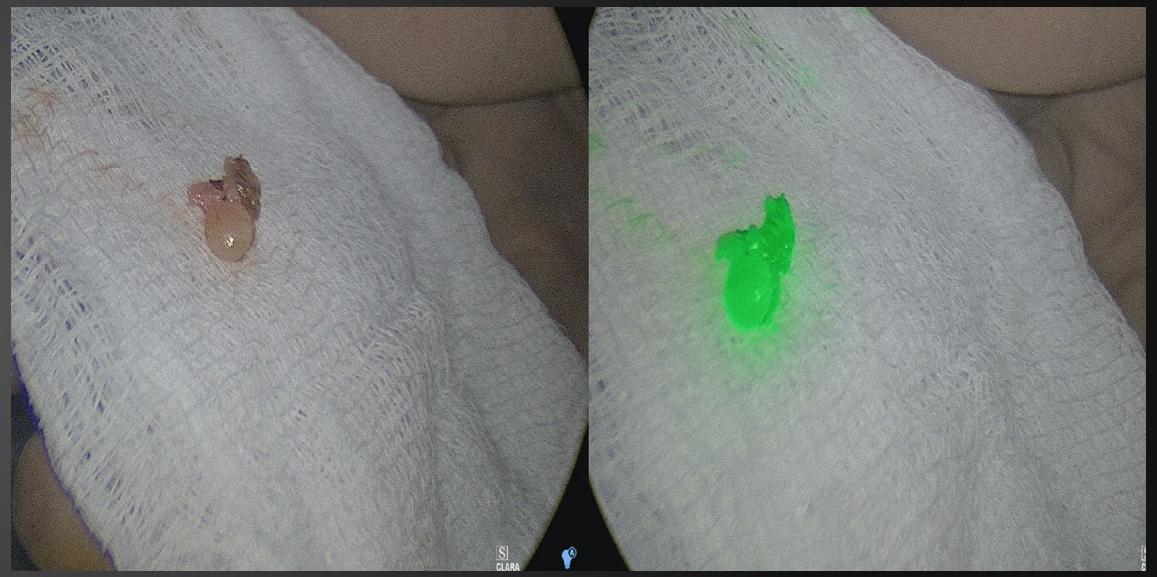


Crispen et al, Capitano et al, 2011
Kuusk et al, 2018

Fluorescent Guided Lymph Node Harvest in Laparoscopic Wilms Nephroureterectomy

Max J. Pachl

Urology 2021



NUMBER
????

NWTS4 and NWTS5 (> 3000 patients)

Median number of LN sampled in patients with at least 1 positive LN – 5

Median number of LN sampled in patients with no positive LNs – 3

Likelihood of finding a positive node based on LNY:
1-2 LNs sampled – 12%
3-6 LNs – 18%
>= 7 LNs – 28%

Kieran et al. *JPS*, 2012

Lymph node density

$$LND = \frac{\#\ \text{involved LNs}}{LNY}$$

NCD (> 2,000 patients)

Used median as LN threshold (0.38)

LND ≤0.38 → OS 94%

LND >0.38 → OS 85%

SEER (n=231)

Used log rank as LN threshold (0.4)

5y CSS

LND <0.4 → 90%

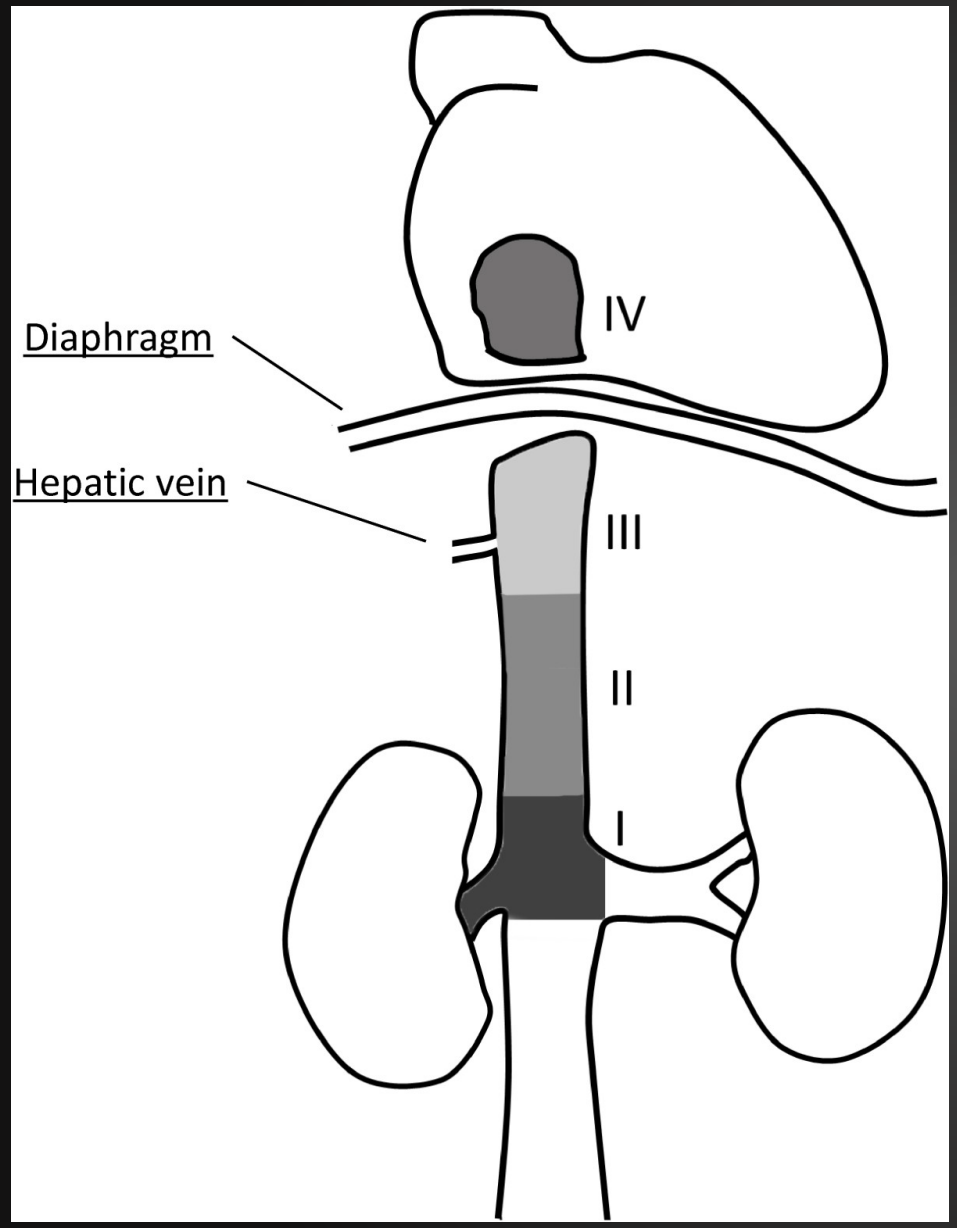
LND ≥0.4 → 79%

Saltzman et al. *JPU, 2018*

Walker et al. JPU, 2020

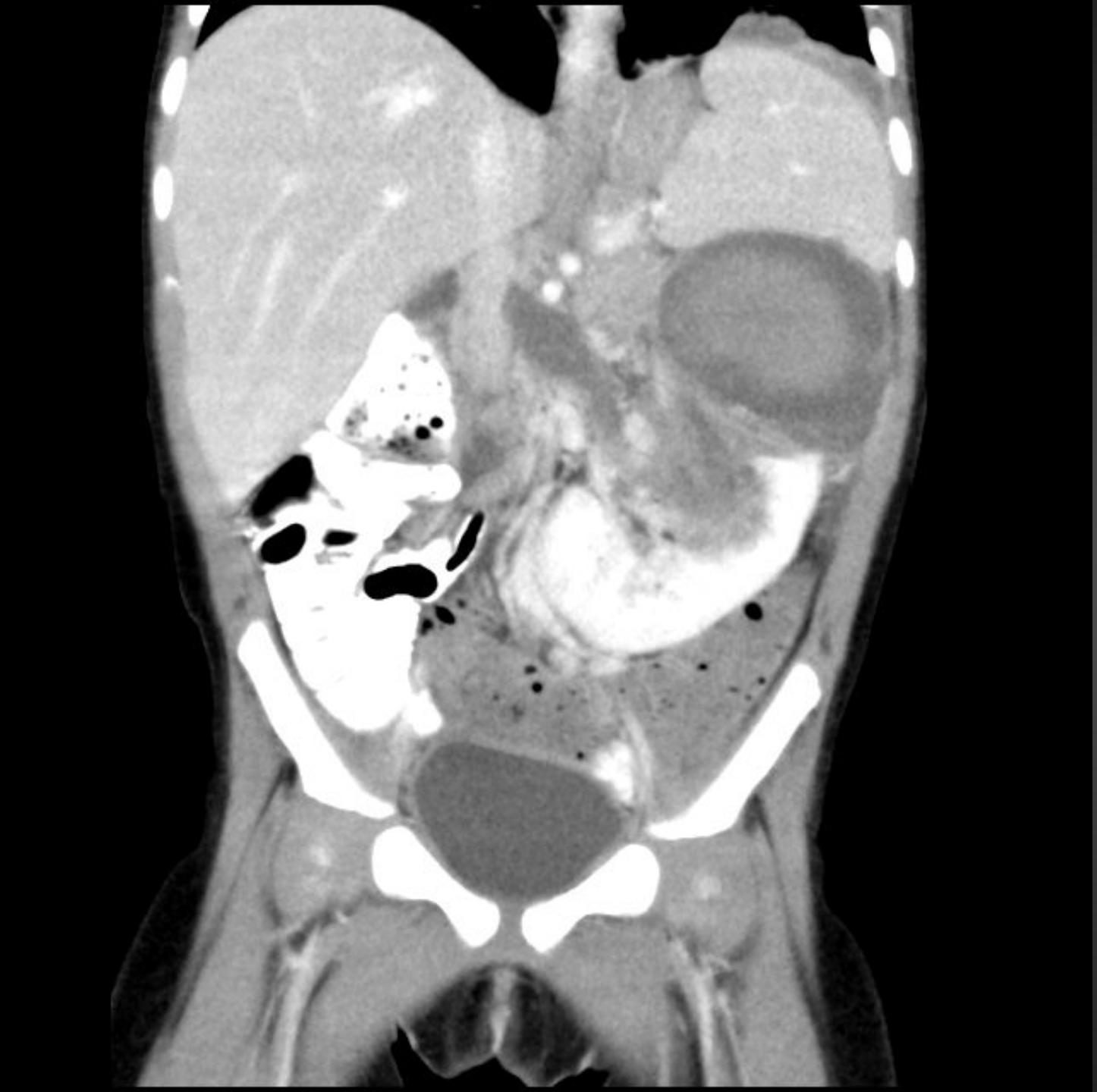
LN Yield
5-7 minimum
7-10 ideal?

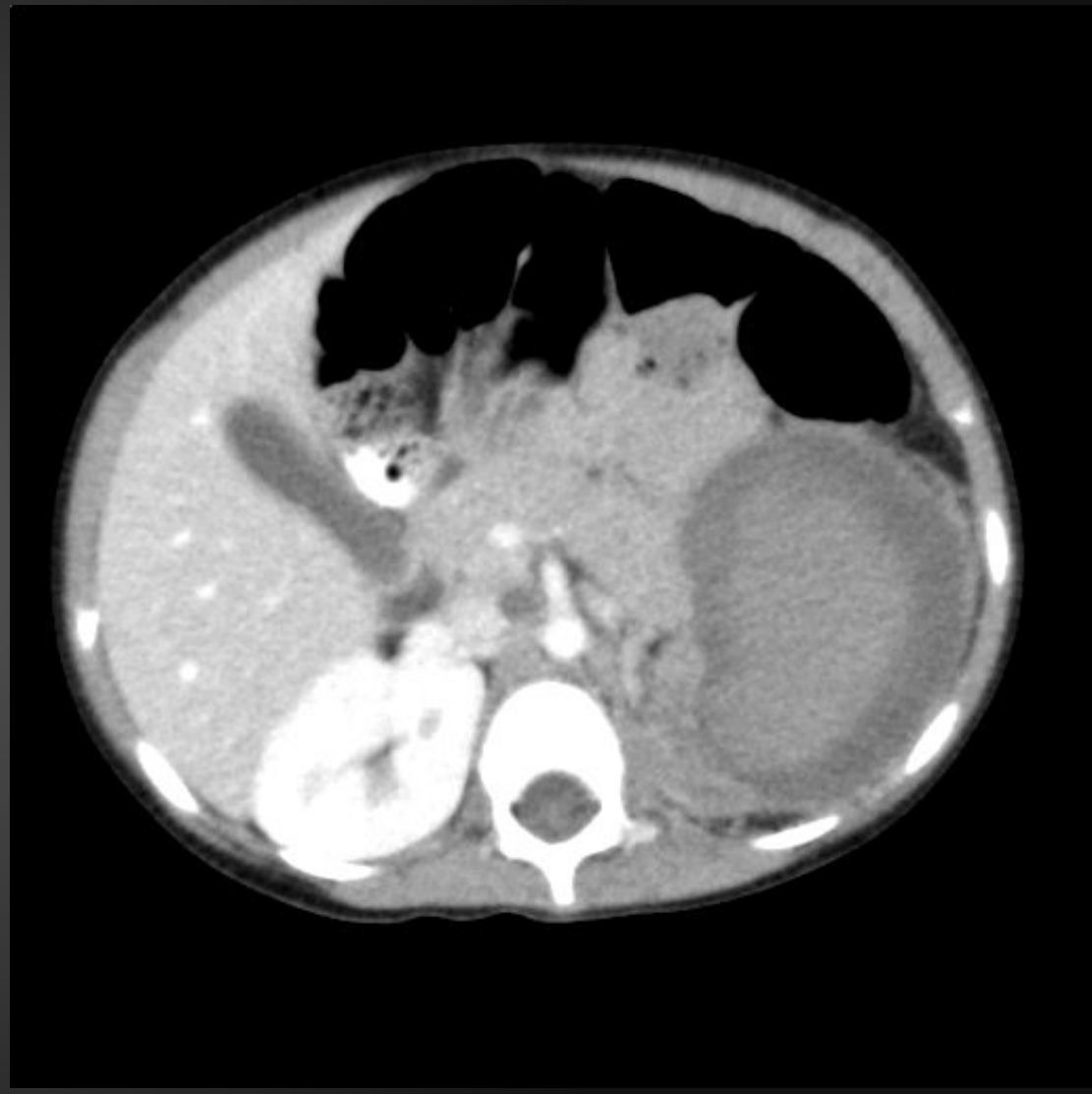
Renal Vein and IVC thrombus

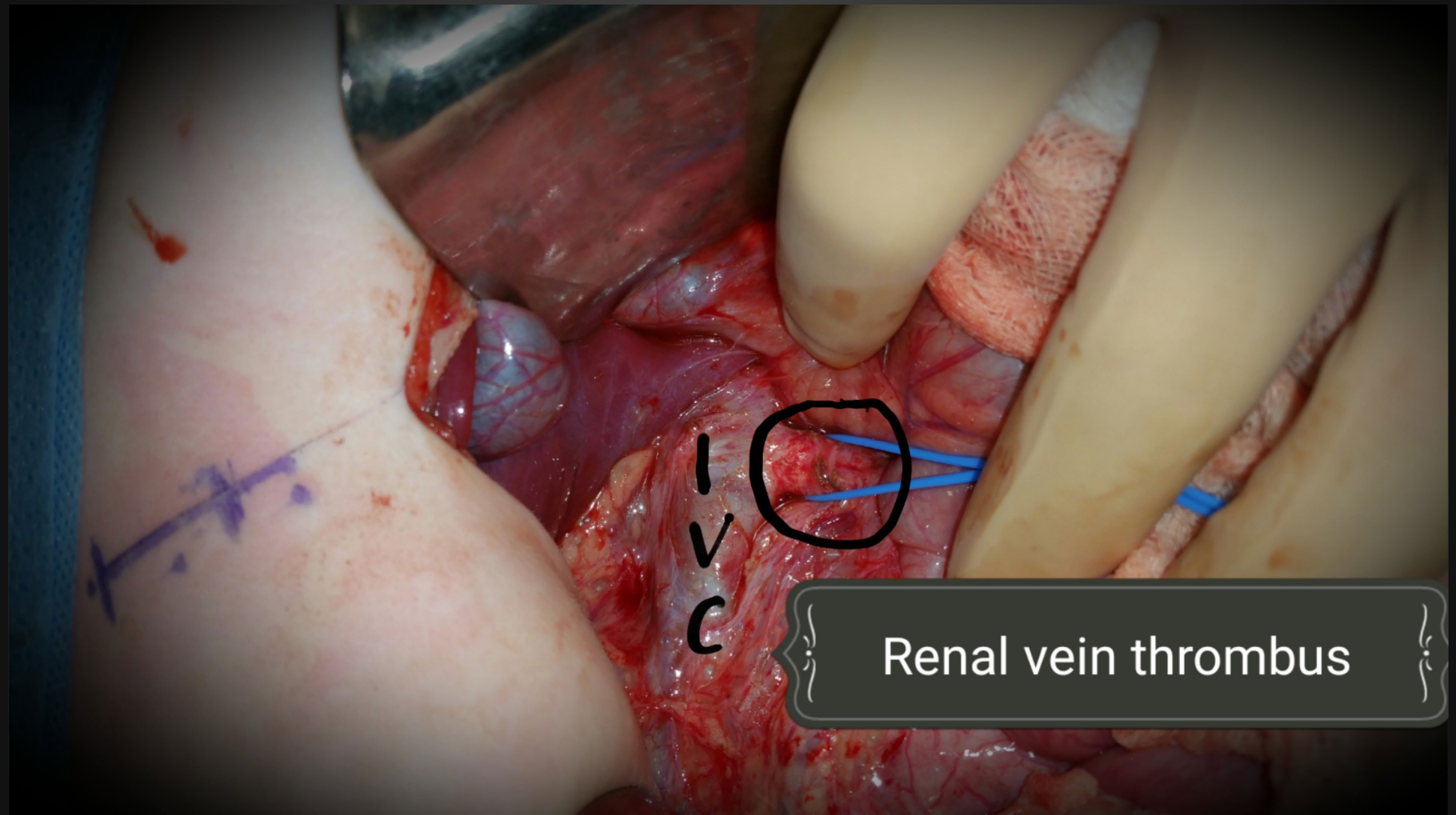


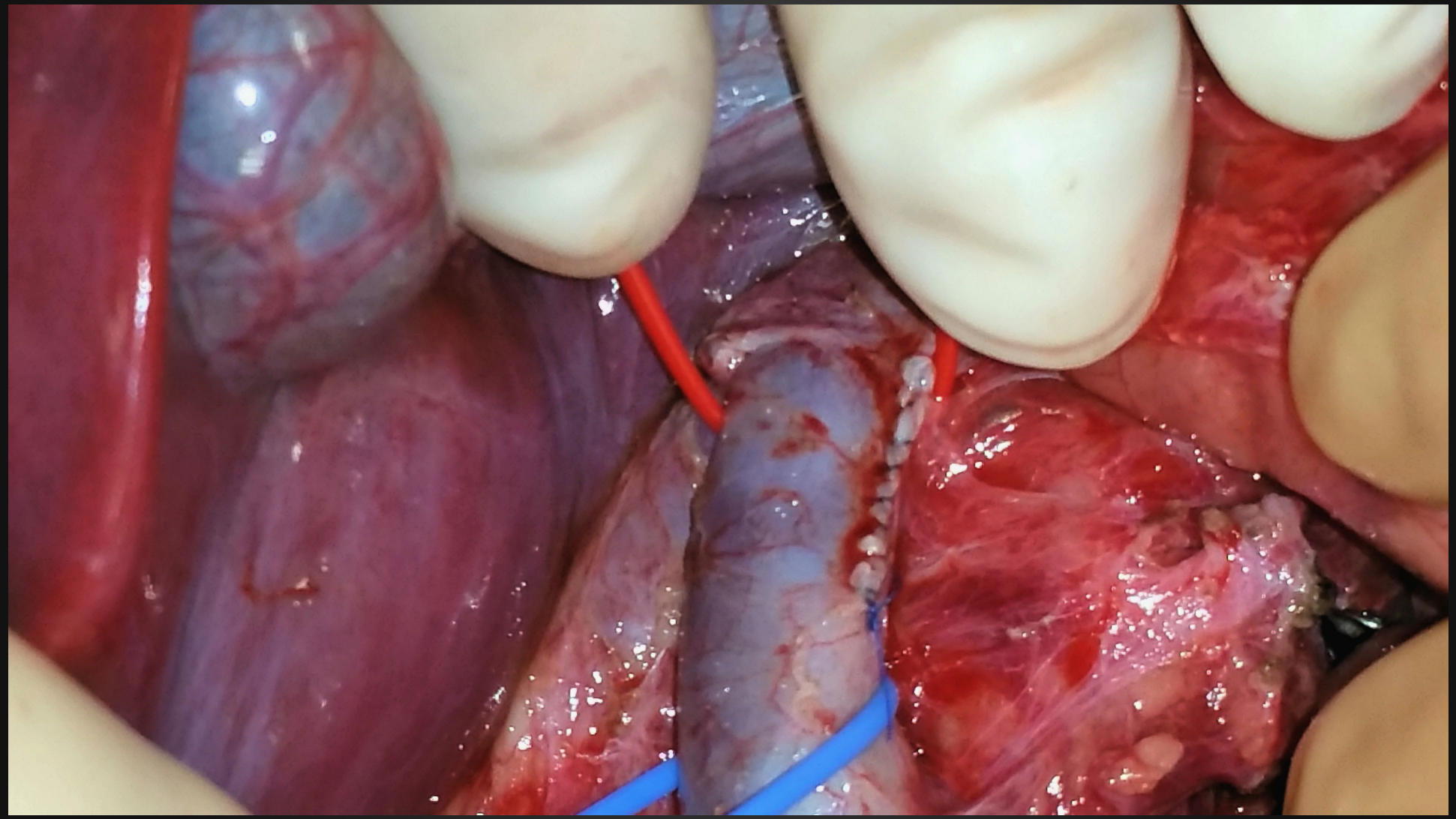
No IVC thrombus above the hepatic veins

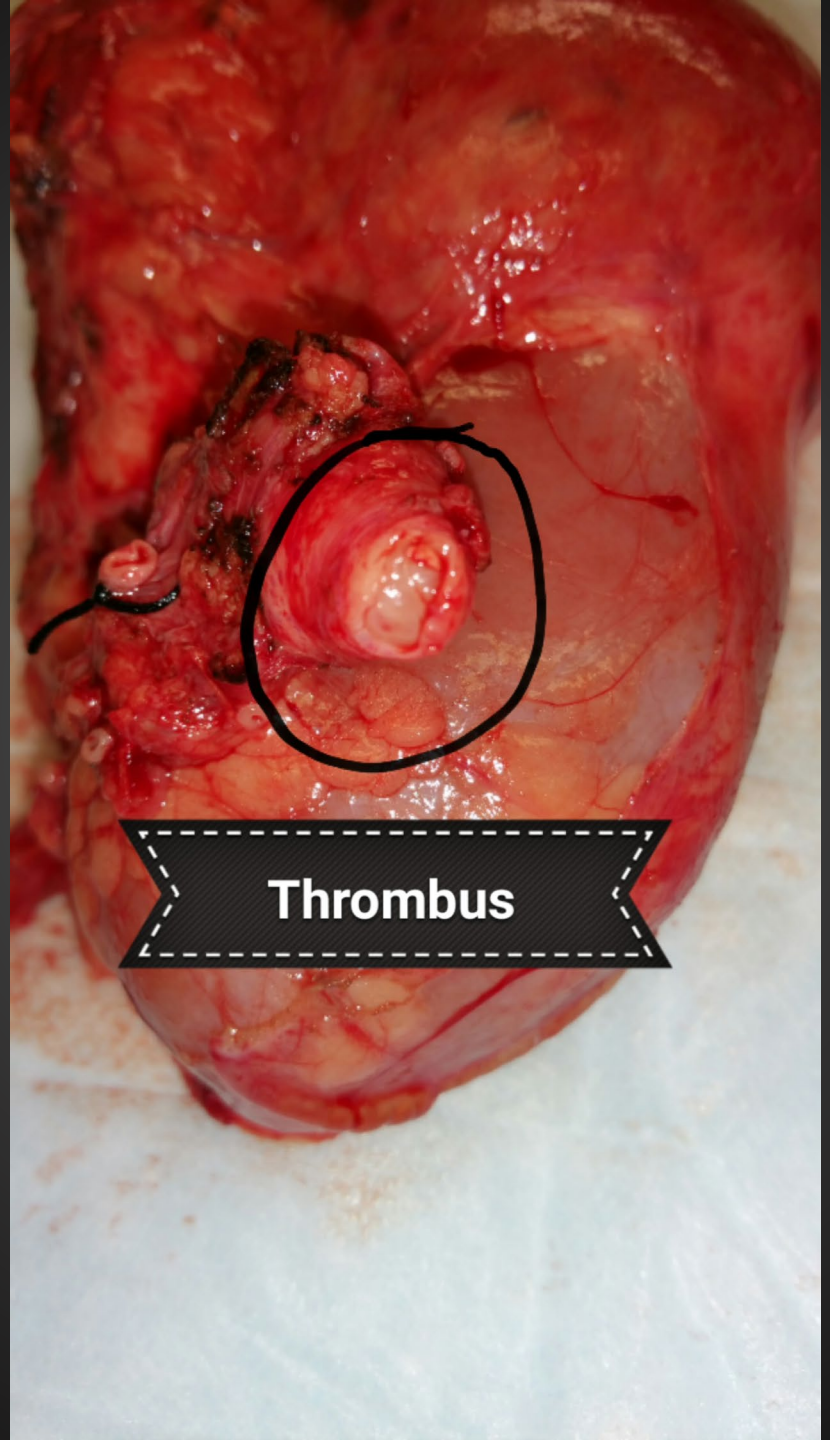
Surgeon's judgement that nephrectomy would lead to tumor spill, mortality, excessive morbidity, residual tumor






IVC
Renal vein thrombus




Thrombus

1-year old boy with palpable mass in the flank noticed by caregiver. No other symptoms. Based on the imaging

provided, choose the alternative that reflects the best treatment approach for this patient:

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b) Upfront nephrectomy followed by adjuvant chemotherapy and radiation

c) Upfront nephrectomy + lymph node sampling as long as there is no evidence of a predisposition syndrome

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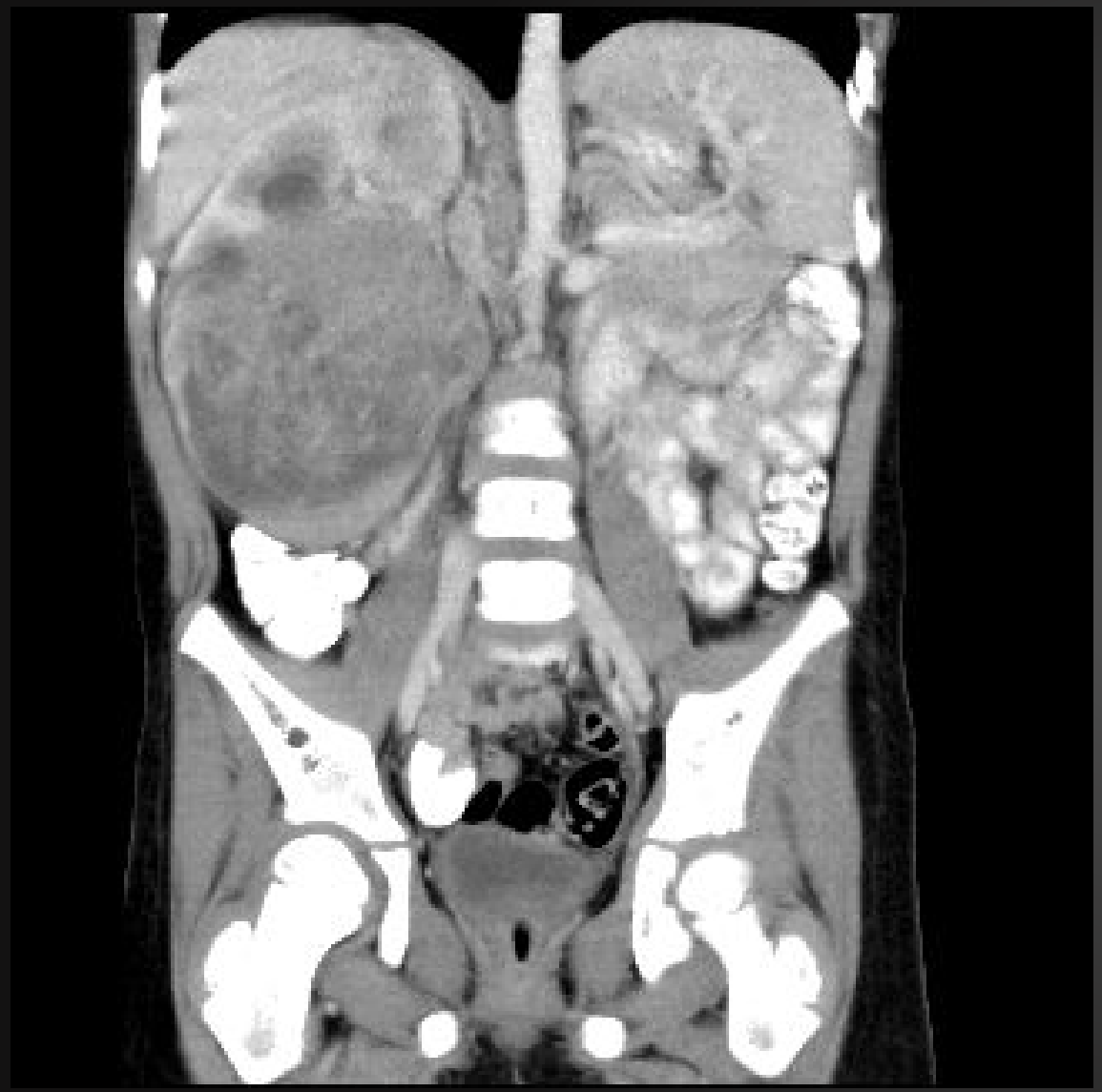
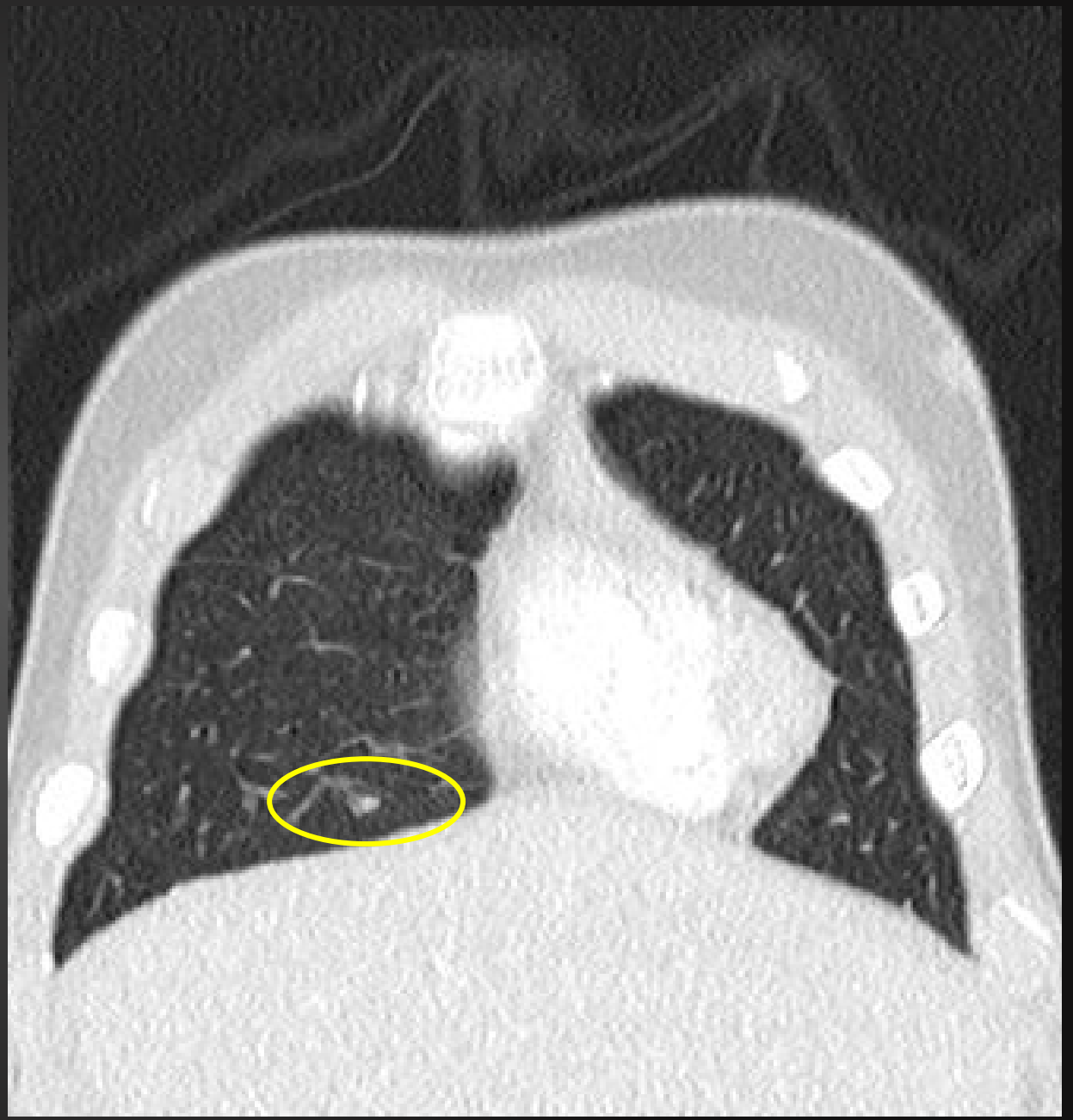
e) Neoadjuvant chemotherapy followed by nephrectomy and radiation





4-year old boy presents to the ED for gross hematuria. There is a palpable right-sided abdominal mass. US confirms the presence of a renal tumor; CT abdomen and chest performed. Radiology reports a single lung nodule compatible with metastatic disease. Primary tumor is restricted to the kidney with no evidence of vascular thrombus. Select the best approach for this patient:

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b) Percutaneous biopsy of the renal mass, neoadjuvant chemotherapy followed by delayed nephrectomy
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d) Upfront nephrectomy with lymph node sampling, adjuvant chemotherapy adjusted based on risk stratification and lung response to therapy
e) Percutaneous biopsy of the renal mass, thoracoscopic biopsy of the lung lesions, neoadjuvant chemotherapy, delayed nephrectomy and radiation

You perform a radical nephrectomy and lymph node sampling for a 10 cm left renal mass in a 3-year old girl. Pathology confirms a completely resected favorable histology Wilms tumor with LOH 1p and 16q with 4/10 positive nodes.

Select the option that contains the correct stage adjuvant approach:

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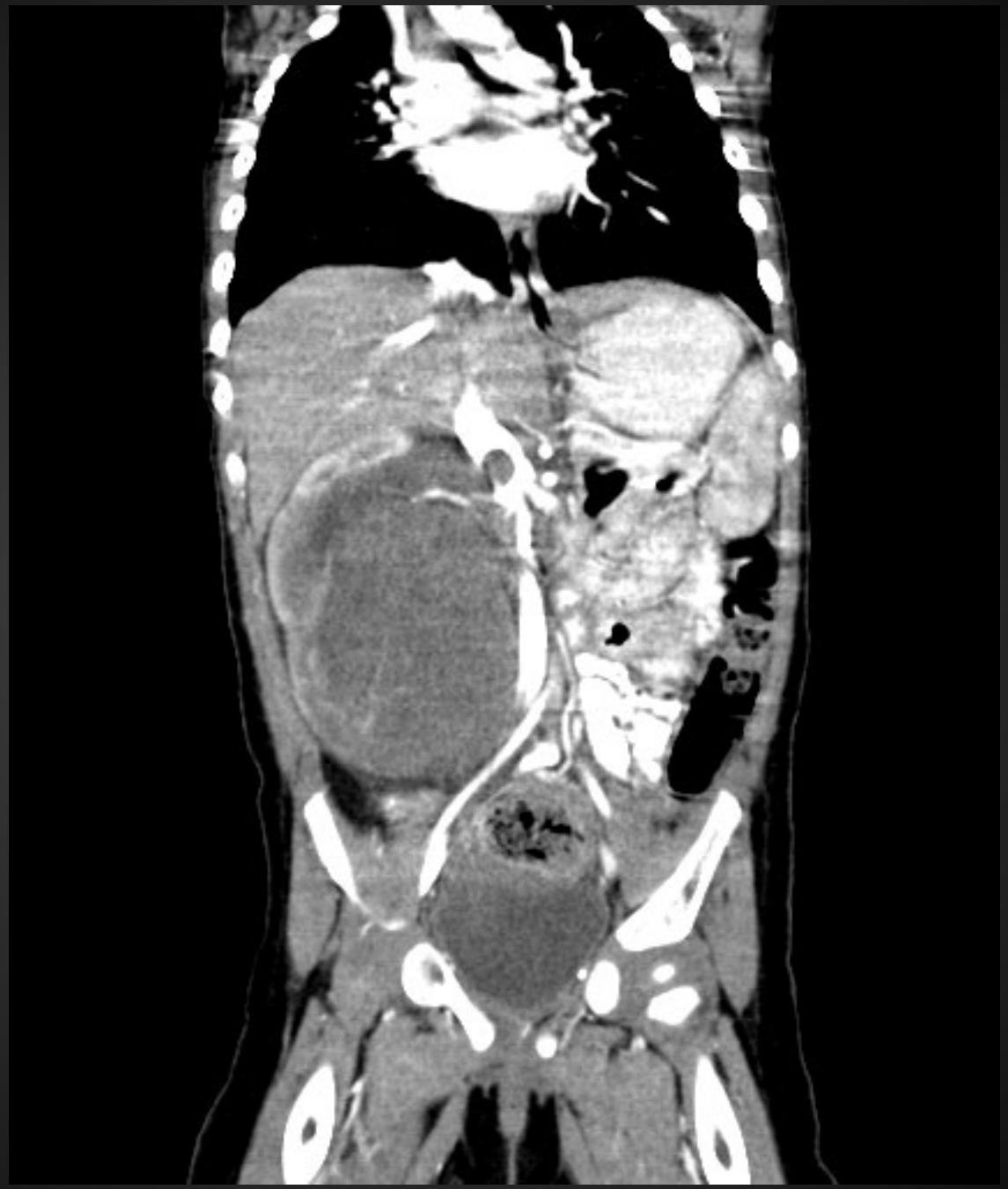

Select the best approach for this 2.5-year old girl with a renal mass and evidence of tumor thrombus in the IVC:

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b) Upfront radical nephrectomy and lymph node sampling, tumor thrombectomy separate from nephrectomy specimen followed by adjuvant chemotherapy and radiation if necessary.
c) Neoadjuvant chemotherapy without biopsy, delayed nephrectomy at 12 weeks with IVC exploration if residual tumor thrombus.
d) Upfront nephrectomy and *en bloc* tumor thrombectomy, lymph node sampling, adjuvant chemotherapy and radiation if necessary.
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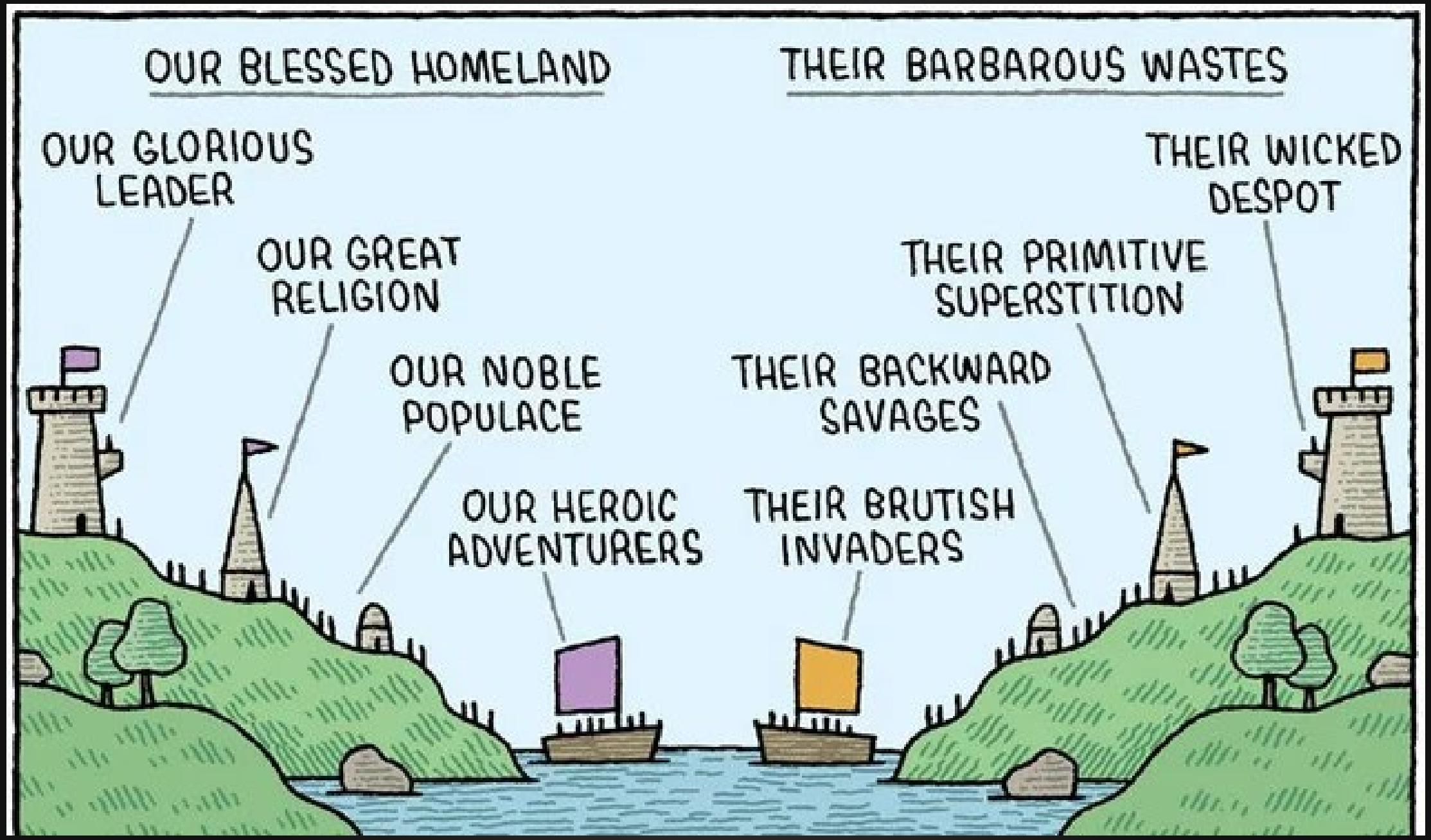
OUR BLESSED HOMELAND
THEIR BARBAROUS WASTES
OUR GLORIOUS LEADER
OUR GREAT RELIGION
OUR NOBLE POPULACE
OUR HEROIC ADVENTURERS
THEIR BRUTISH INVADERS
THEIR BACKWARD SAVAGES
THEIR PRIMITIVE SUPERSTITION
THEIR WICKED DESPOT


TEAMWORK
PARTNERSHIP
RELATIONSHIP
SUPPORT
COLLABORATION
MISSION
TEAM

Thank you!

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