Case Presentation

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Case Presentation

- History
  - brought to pediatrician with a right-sided abdominal mass
  - On visit, mass was appreciated by PMD who immediately obtained a KUB and abdominal US which revealed a large (12cm) cystic lesion involving right kidney.
  - Sent to Hospital for admission and further work-up.

Case Presentation

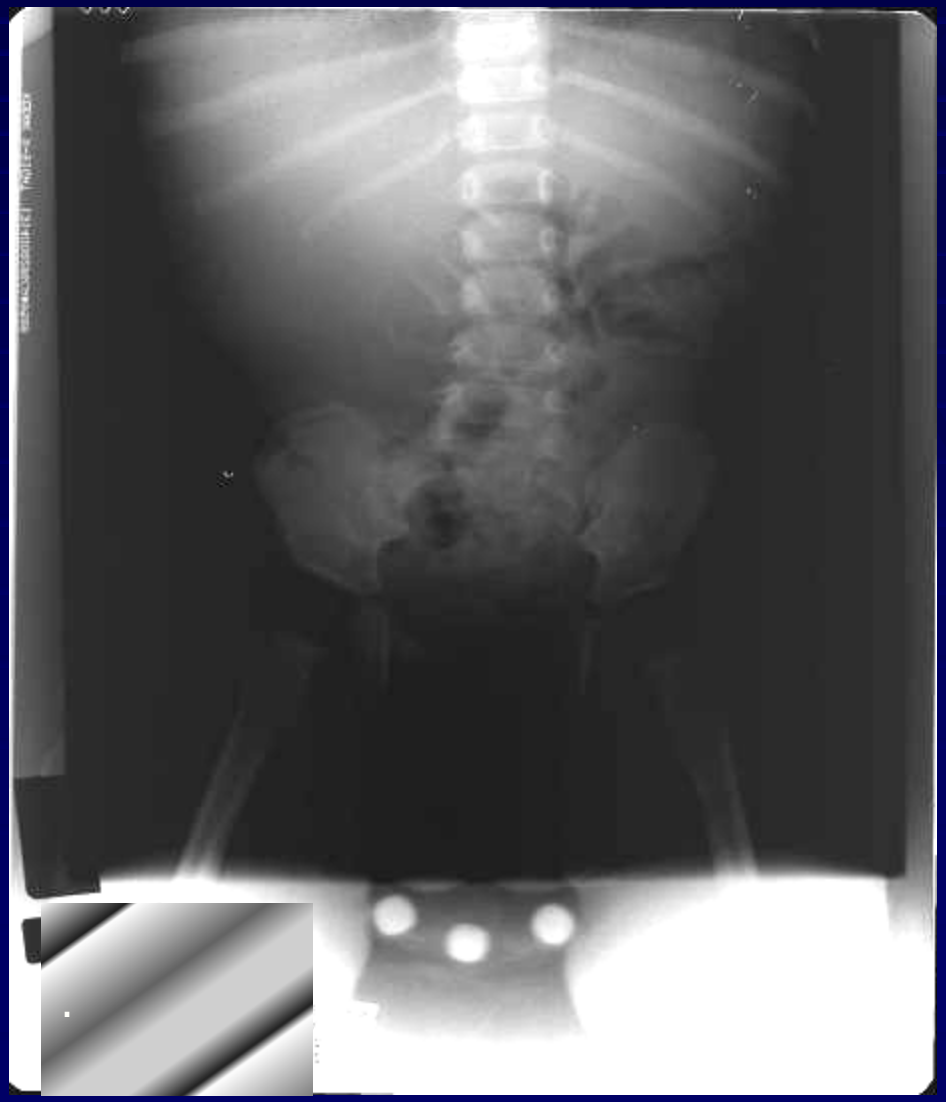
- History
  - No PMHx/PSHx. Immunizations UTD.
  - ROS: Unremarkable. No abdominal pain, vomiting, diarrhea or change in appetite. 5 WD/day, no hematuria. No recent illnesses.
  - NeoHx: 6lb 6oz, 36wk GA (emergent C-section for placenta previa w/ bleeding).
  - FamHx
    - No hx of malignancy or renal disease.
    - Mother: xx y/o, no PMHx.
    - Father: xx y/o, PMHx: HTN.
    - Siblings: xx y/o, no PMHx.

Case Presentation

- Physical Exam
  - T 97.8° / BP 108/62 / HR 150 / Wt 8.7kg (10-25 %ile)
  - WN, WD AA female infant in NAD.
  - NC/AT. PERRLA, no aniridia, no LA. CTAB, S1,S2 RRR.
  - Abd: ND, +BS, NT, firm, non-mobile right-sided abd mass. No GU abnormalities.
  - Labs
    - CBC: WBC 13.2, H/H 11/34, Plt 479
    - Chem7: BUN/Creat 12/0.3, Ca 10.2
    - LFTs: AST 39/ALT 29/ALP 228/TB 0.1
    - Coags: PT / PTT 12.2 / 47.2
    - UA: negative.

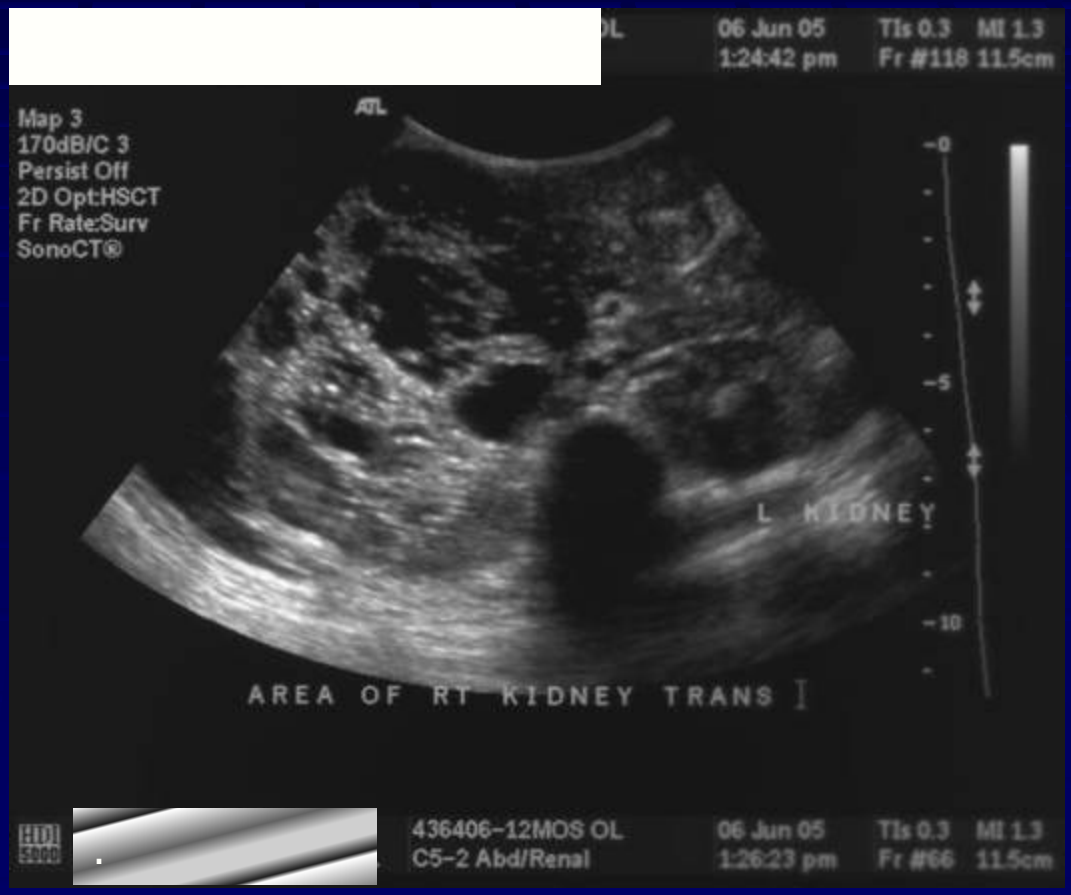
Case Presentation

- Imaging
  - KUB: *"Absence of bowel gas pattern over right abdomen. Otherwise unremarkable study."*



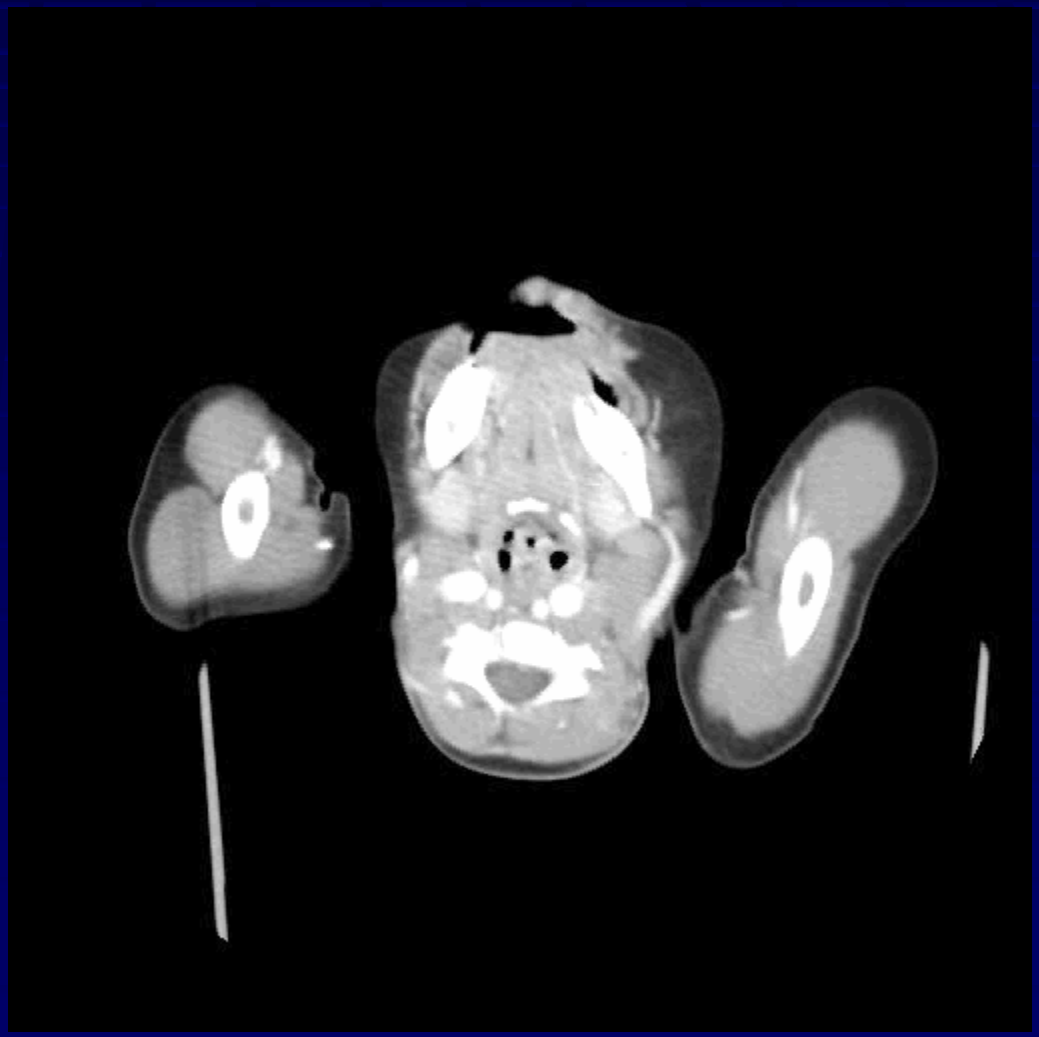
Case Presentation

- Imaging
  - US: *“Large right cystic lesion approx 10x12cm involving right kidney. No evidence of thrombus in renal vein or IVC.”*



Case Presentation

- Imaging
  - CT: *“11x12cm cystic, fluid filled structure originating from anterior right kidney. No evidence of metastatic disease.”*



Case Presentation

- Differential Diagnoses
  - Wilms Tumor
  - Multilocular Cystic Nephroma / Cystic Partially Differentiated Nephroblastoma (CPDN)
  - Multilobular renal cyst
  - Multilocular Cystic Renal Cell Carcinoma
  - Polycystic Kidney Disease

Case Presentation

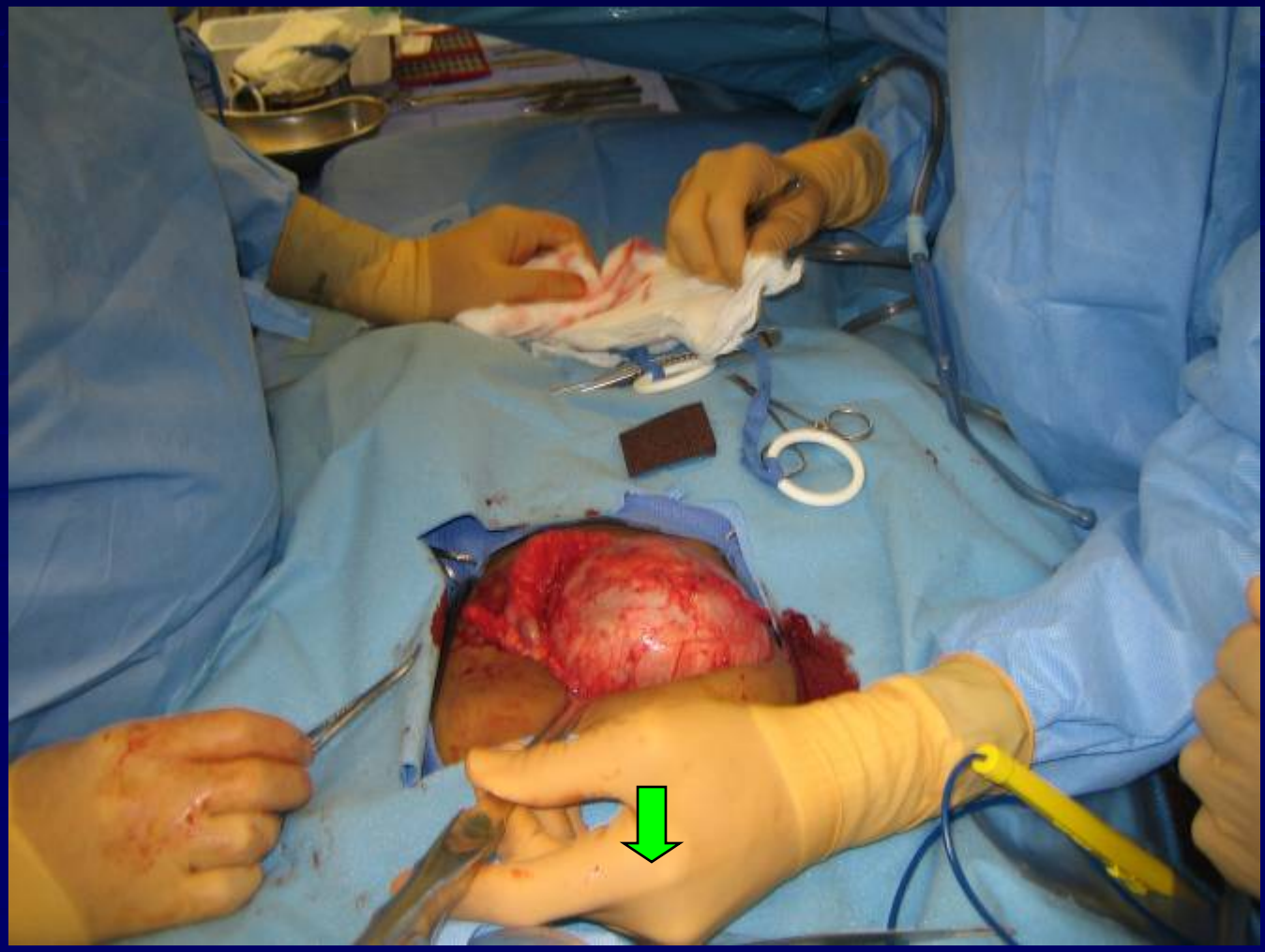
- Plan
  - Peds Oncology consult:
    - No preoperative adjuvant therapy.
    - Biopsy NOT recommended.
  - Peds Nephrology consult:
    - Likely Wilms Tumor or CPDN.
    - Biopsy NOT recommended.
  - Peds Surgery consult:
    - Exploratory laparotomy with right nephrectomy.

Case Presentation

- OR

Case Presentation

- OR



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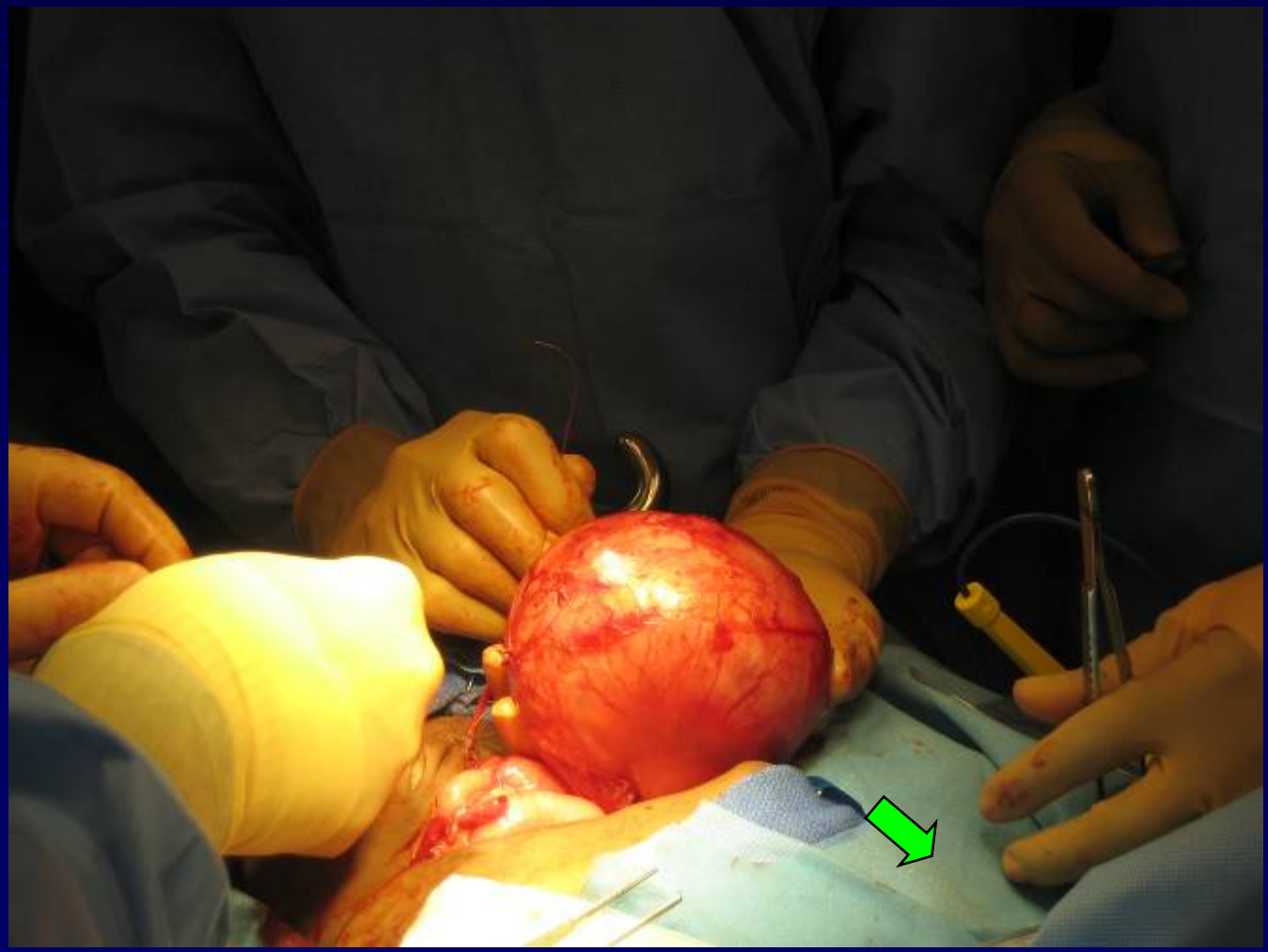

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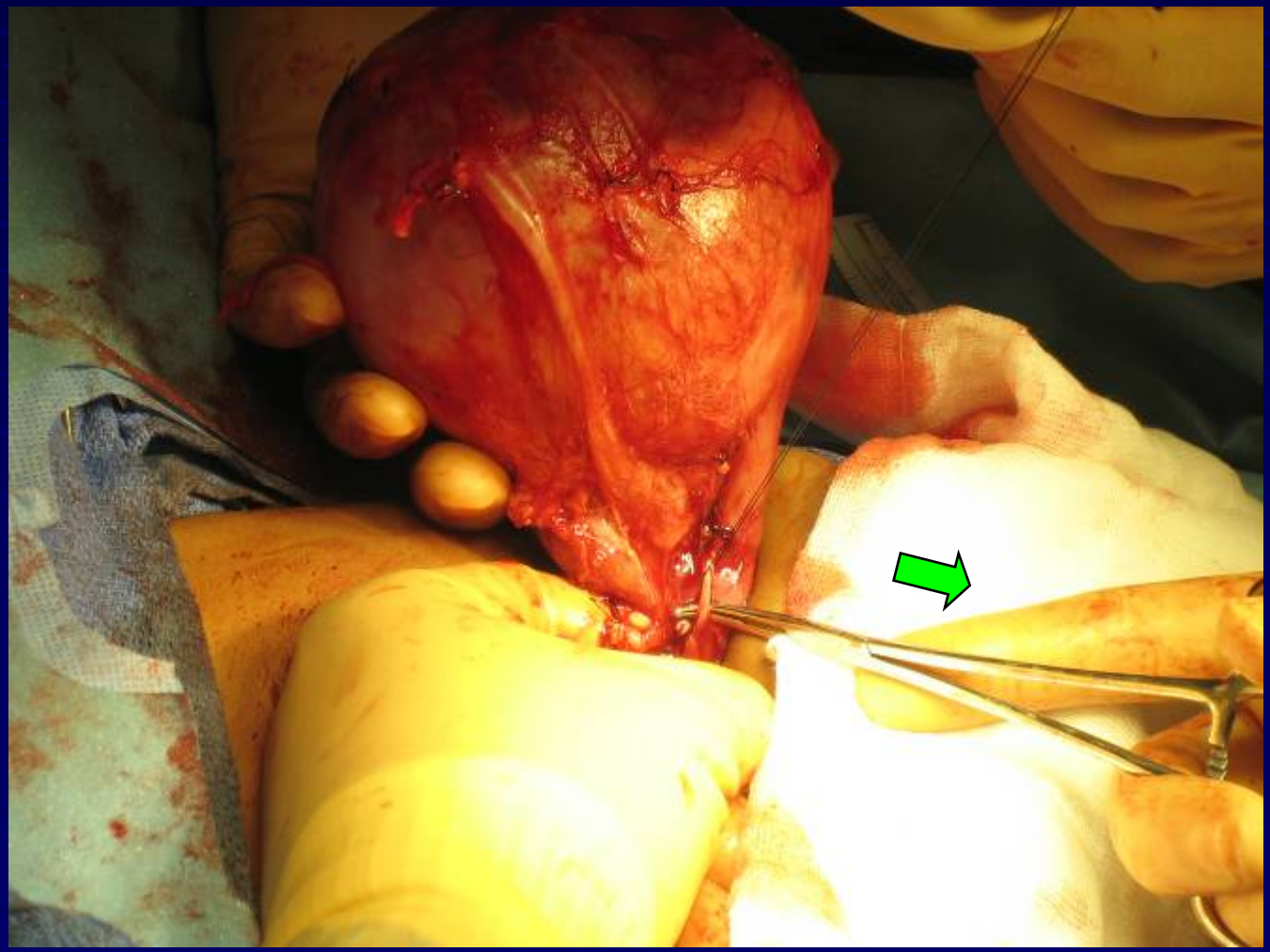

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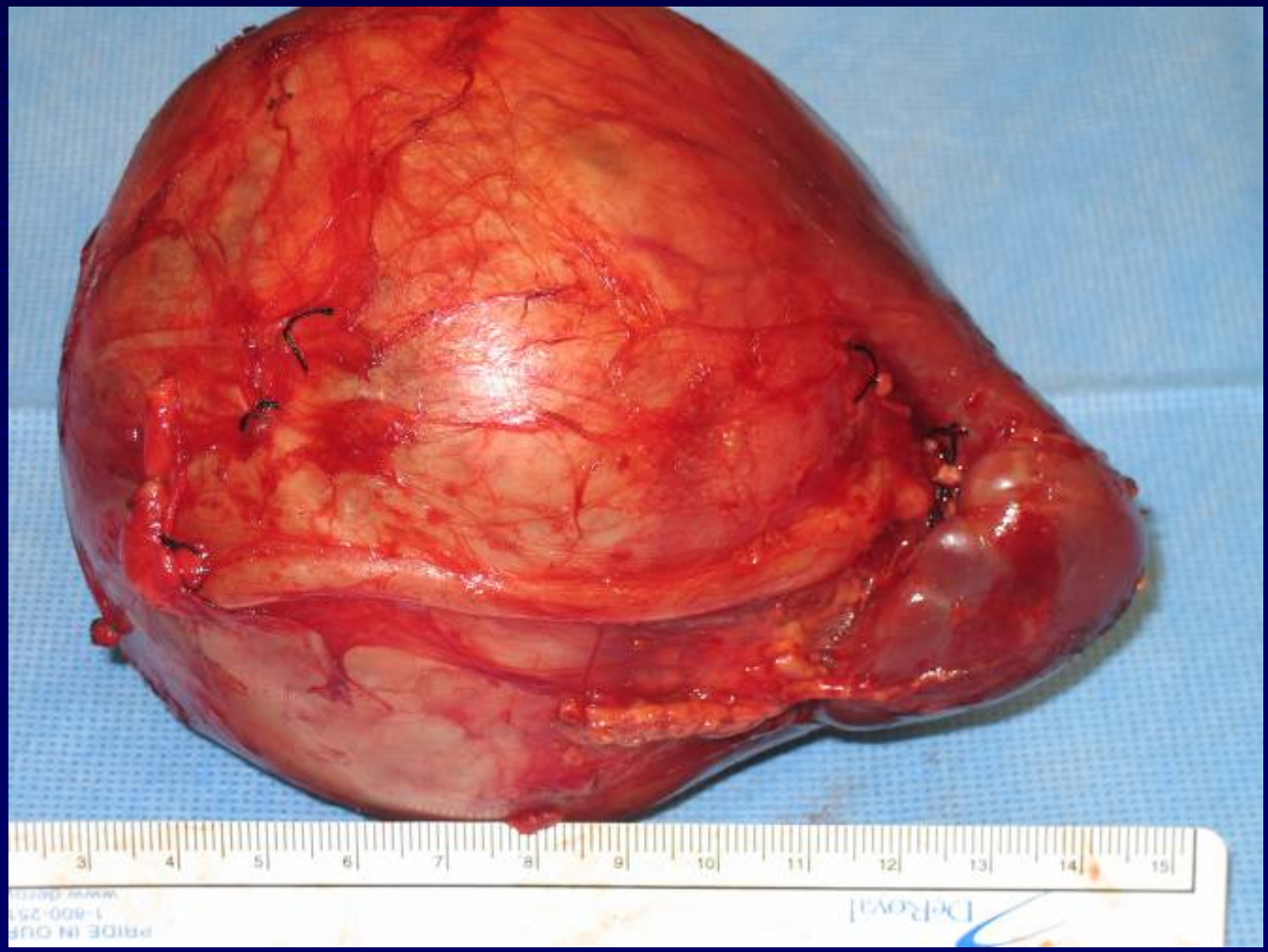

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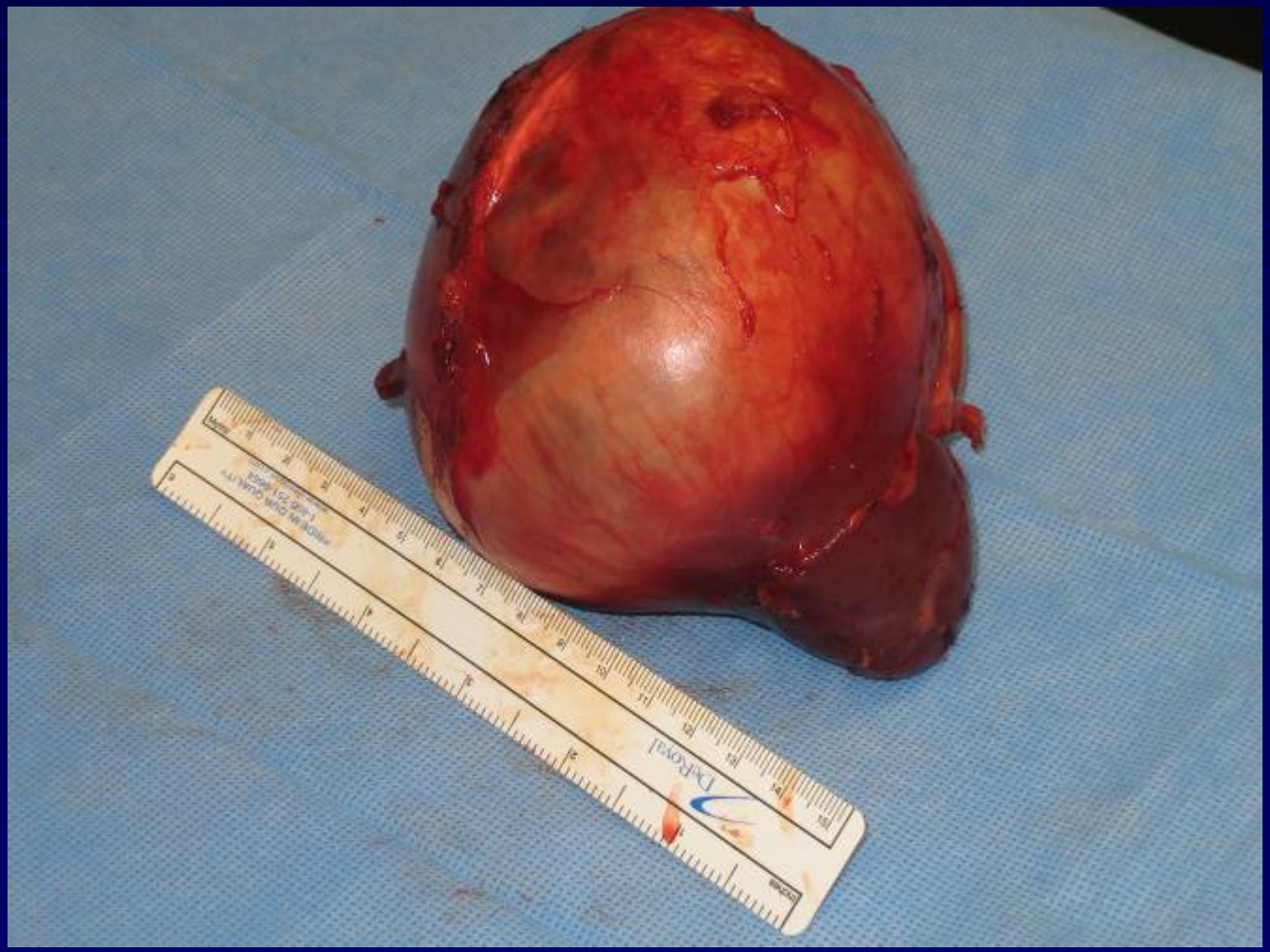

Case Presentation

- Post-Operative Course
  - Uneventful.
  - POD #1: OGT D/C'ed.
  - POD #3: +BS, started on diet, foley D/C'ed.
  - POD #7: Discharged home.

Case Presentation

- Pathology
  - Cystic Partially-Differentiated Nephroblastoma
    - Surgical margins clear.
    - Capsule not involved by tumor.
    - No tumor in renal vein or artery.
    - Lymph nodes negative for tumor.
  - No indication for chemotherapy or radiotherapy.

Nephroblastomas

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Nephroblastomas

- Overview
  - Introduction
  - History
  - Etiology
  - Molecular Genetics
  - Epidemiology
  - Evaluation and Diagnosis
  - Imaging
  - Staging
  - Histology/Precursors
  - Treatment
    - Surgical
    - Adjuvant
  - Complications
  - Prognosis

Nephroblastomas

- Introduction
  - Wilms' tumor, or nephroblastoma, is the most common primary malignant renal tumor of childhood, accounting for about 6% of all pediatric malignant disease.
  - This embryonal tumor develops from remnants of immature kidney.
  - The excellent outcome now expected for most children with this tumor is attributed to the combination of effective adjuvant chemotherapy, improved surgical and anesthetic techniques, and the radiosensitivity of the tumor.
    - Survival has improved from 30% in the 1930's to over 85% currently.
  - Current management now emphasizes reducing the morbidity of treatment for low-risk patients and reserving more intensive treatment for selected high-risk patients for whom survival remains poor.

Nephroblastomas

- History
  - Wilms tumor was named after German surgeon *Max Wilms*, who published the first comprehensive review of the disease in 1899.
  - The National Wilms Tumor Study Group (NWTSG) established in 1969.


MAX WILMS (1867 - 1918)

[*] *www.nwtsg.org.(National WIlms Tumor Study Group Official Website).*

Nephroblastomas

- Etiology
  - The etiology essentially remains unknown. The tumor may arise in 3 clinical settings, the study of which resulted in the discovery of the genetic abnormalities that lead to the disease.
  - The settings for WT are:
    - Sporadic
    - Familial
    - Association with genetic syndromes

Nephroblastomas

- Etiology
  - Most cases are not part of a genetic malformation syndrome and have no familial history.
  - Familial WT occurs in 1-2% of all cases. Analysis of families with WT has shown that the predisposition is caused by an autosomal dominant trait with incomplete penetrance*.
  - Genetic syndromes that predispose to and may include WT:
    - Beckwith-Wiedemann syndrome (macroglossia, gigantism, and umbilical hernia)
    - Hemihypertrophy
    - Congenital aniridia
    - WAGR syndrome (WT, aniridia, genitourinary malformations, and mental retardation)
    - Denys-Drash syndrome (WT, pseudohermaphroditism, and glomerulopathy)
    - Trisomy 18 mutation

* *Clericuzio CL: Clinical phenotypes and Wilms tumor. Med Pediatr Oncol 1993;21:182–187.*

Nephroblastomas

- Molecular Genetics
  - Based on the model developed originally for retinoblastoma, Knudsen and Strong proposed that WT results from 2 mutational events based on loss of function of tumor suppressor genes*.
  - The first mutation, the inactivation of the first allele of the specific tumor suppressor gene (*WT1*), involves prezygotic and postzygotic aspects.
    - Prezygotic (constitutional or germline) mutations are inherited or they result from a de novo germline mutation. This mutation is present in all body cells and predisposes the patient to familial and/or multiple WT.
    - Postzygotic mutations occur only in specific cells, and they predispose patients to single tumors and sporadic cases of WT.
  - The second mutation is inactivation of the second allele of the specific tumor suppressor gene (*WT2*).

** Coppes MJ, Pritchard-Jones K. Principles of Wilms' tumor biology. Urol Clin North Am 2000;27:423-33.*

Nephroblastomas

- Molecular Genetics
  - *WT1*
    - The first WT predisposing gene (at chromosome arm 11p13), was identified as a direct result of the study of children with WT that also had WAGR syndrome.
    - The 11p13 locus was demonstrated to encompass a number of contiguous genes, including the aniridia gene and the WT tumor suppressor gene *WT1,* which was cloned in 1990.
  - *WT2*
    - A second WT predisposing gene has been identified (but is not yet cloned) at 11p15.
    - This locus has been proposed based on studies of patients with both WT and Beckwith-Wiedemann syndrome (BWS), a congenital WT predisposition syndrome linked to chromosome arm 11p15.

Nephroblastomas

- Epidemiology
  - Annual incidence rate of WT in children <15 y/o is about 7-10 cases per million.
  - Approximately 450 new cases are diagnosed each year in North America*.
  - Typically affects young children:
    - Median age of 3.5 years.
    - more than 80% of patients identified before 5 years of age.
    - Older children and sometimes even adults can be affected.
  - Male-to-female ratio was 0.92 : 1.
  - Relatively more common in blacks than in whites and is less common in East Asians.
  - Bilateral disease occurs in 5-7% of patients with WT.

** Coppes MJ, de Kraker J, van Dijken PJ, et al. Bilateral Wilms' tumor: long-term survival and some epidemiological features. J Clin Oncol 1989;7:310-5.*

Nephroblastomas

- Evaluation and Diagnosis
  - A palpable, smooth abdominal mass is present on physical examination in more than 90% of children.
  - Other presenting signs and symptoms are gross hematuria (30%), fever, and/or abdominal pain (30-40%)*.
  - PE reveals hypertension in about 25% of patients and congenital anomalies (aniridia, genitourinary malformations, hemihypertrophy, or signs of overgrowth) in 13–28% of children*.
    - Abdominal exam should be performed carefully. Concern has been raised that palpating a mass too vigorously could lead to rupture of a large tumor into the peritoneal cavity.
  - <10% have coagulopathy (acquired von Willebrand disease).

* *www.nwtsg.org.(National Wilms Tumor Study Group Official Website).*

Nephroblastomas

- Imaging Studies
  - Ultrasound
    - Initial diagnosis of a renal or abdominal mass, possible renal vein or IVC thrombus
    - Information regarding liver and other kidney
  - CT Scan
    - Differential diagnosis of a kidney tumor vs. adrenal tumor (neuroblastoma)
    - Liver metastases
    - Status of chest with respect to metastases
    - Status of opposite kidney
    - Lymph node assessment

Nephroblastomas

- Imaging Studies
  - Chest XR
    - As a baseline for pulmonary metastases (*the lung is the most common site of distant metastasis*).
  - MRI
    - The value of MRI in diagnosing this disorder has yet to be established.
    - Useful for MRV to aid in the diagnosis of thrombus of the renal vein or IVC.

Nephroblastomas

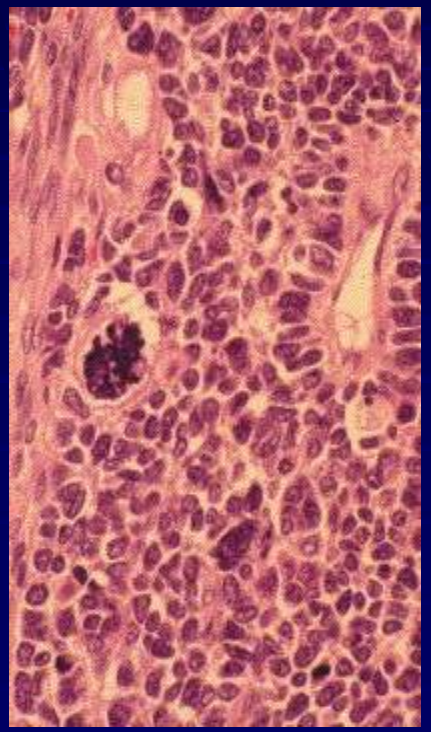
- Staging (National Wilms Tumor Study)

Stage	Description
Stage I	Tumor limited to the kidney and completely excised. The renal capsule is intact and the tumor was not ruptured before removal. There is no residual tumor.
Stage II	Tumor extends through the perirenal capsule but is completely excised. There may be local spillage of tumor confined to the flank, or the tumor may have been biopsied. Extrarenal vessels may contain tumor thrombus or be infiltrated by tumor.
Stage III	Residual nonhematogenous tumor confined to the abdomen: lymph node involvement, diffuse peritoneal spillage, peritoneal implants, tumor beyond surgical margin either grossly or microscopically, or tumor not completely removed.
Stage IV	Hematogenous metastases to lung, liver, bone, brain, or other organ.
Stage V	Bilateral renal involvement at diagnosis.

* *www.nwtsg.org.(National Wilms Tumor Study Group Official Website).*

Nephroblastomas

- Histology
  - The classic histologic pattern is composed of epithelial, blastemal, and stromal elements (triphasic).
  - Approximately 90% of all renal tumors have this so-called favorable histology (FH).
  - 3-7% of tumors are characterized by anaplastic changes and is also referred to as unfavorable histology (UH).
    - If diffusely anaplastic throughout the tumor, predicts for poor outcome.



Nephroblastomas

- Multilocular Cystic Renal Tumors
  - Considered benign variants of WT but can only be differentied from cystic WT pathologically.
  - Anatomically Cystic Nephromas and Cystic Partially-Differentiated Nephroblastomas (CPDN) are identical.
  - They are histologically distinct:
    - In cystic nephroma, the septa consist of fibrous tissue that may contain well-differentiated renal tubules but no poorly differentiated tissues or blastemal cells.
    - CPDN has the histologic features of cystic nephroma with the addition of septal blastemal cells in any amount, with or without other embryonal stroma or epithelial cell types.
  - Treated as Stage I-FH WT (with the exception of chemotherapy).

[*] *Eble JN, Bonsib SM: Extensively cystic renal neoplasms: Cystic nephroma, cystic partially differentiated nephroblastoma, multilocular cystic renal cell carcinoma, and cystic hamartoma of renal pelvis. Semin Diagn Pathol 1998;15:2–20.*

Nephroblastomas

- Surgical Treatment
  - According to the NWTSG protocol, the first step in the treatment of WT is surgical staging followed by radical nephrectomy, if possible.
  - Thorough exploration of the abdominal cavity (through a transverse abdominal incision) is necessary to exclude local tumor extension, liver and nodal metastases, and peritoneal seeding.
  - Formal exploration of the contralateral kidney should be performed before nephrectomy:
    - If bilateral disease is diagnosed, nephrectomy is not performed but biopsy specimens are obtained.
    - If the disease is unilateral, radical nephrectomy and regional lymph node dissection or sampling are performed.

Nephroblastomas

- Surgical Treatment
  - The renal vein and IVC are palpated to exclude intravascular tumor extension before vessel ligation.
  - Selective sampling of suspicious nodes is an essential component of local tumor staging.
    - Formal retroperitoneal lymph node dissection is not recommended.
  - If the tumor is unresectable, biopsies are performed and the nephrectomy is deferred until after chemotherapy (which will shrink the tumor in most cases).

* *www.nwtsg.org.(National Wilms Tumor Study Group Official Website).*

Nephroblastomas

- Surgical Treatment
  - The other major responsibility when performing a nephrectomy for WT is complete removal of the tumor without contamination of the operative field.
  - Gentle handling of the tumor throughout the procedure is mandatory to avoid tumor spillage, which leads to a sixfold increase in local abdominal relapse*.
  - Transcutaneous biopsy is not indicated and may in fact complicate treatment.

* *Farhat W, McLorie G, Capolicchio G. Wilms' tumor. Surgical considerations and controversies. Urol Clin North Am 2000;27:455-62*

Nephroblastomas

- Pre-operative Chemotherapy
  - The NWTSG recommends preoperative chemotherapy (after initial ex-lap and biopsy) in the following cases:
    - Intracaval tumor extension
      - Occurs in 5% of cases of WT.
      - Associated with a 40% rate of surgical complications.
      - Upfront chemotherapy after staging and biopsy reduces tumor and thrombus size, which account for 25% of surgical complications.
    - Inoperable tumors
      - Large tumors that involve vital structures make resection difficult.
      - The complication rate is high, and the incidence of tumor spillage also is high.
      - Upfront chemotherapy reduces spillage by 50%.
    - Bilateral WT
      - Second-look surgery is performed after completion of the initial course of chemotherapy, usually at 8-10 weeks.
      - At the time of the second-look procedure, partial nephrectomies or wedge excisions of the tumors are performed.

Ritchey ML: The role of preoperative chemotherapy for Wilms' tumor: the NWTSG perspective. National Wilms' Tumor Study Group. Semin Urol Oncol 1999 Feb; 17(1): 21-7

Nephroblastomas

- Post-operative Chemotherapy and Radiotherapy
  - Postoperative chemotherapy and radiotherapy protocols are based on the surgical staging and follow the guidelines of the NWTSG.
    - Stage I FH and UH or stage II FH
      - Postoperative vincristine and actinomycin D (18 wk)
    - Stage II focal anaplasia or stage III FH and focal anaplasia
      - Abdominal radiation (1000 rad)
      - Vincristine, actinomycin D, and doxorubicin (24 wk)
    - Stage IV FH or focal anaplasia
      - Abdominal irradiation according to local stage
      - Bilateral pulmonary irradiation (1200 rad) with Bactrim prophylaxis for PCP
      - Chemotherapy with vincristine, actinomycin D, and doxorubicin
    - Stage II and stage IV diffuse anaplasia
      - Abdominal irradiation
      - Whole lung irradiation for stage IV
      - Chemotherapy for 24 months with vincristine, actinomycin D, doxorubicin, etoposide, and cyclophosphamide

D'Angio GJ, Breslow N, Beckwith JB, et al. Treatment of Wilms' tumor: results of the Third National Wilms' Tumor Study. Cancer 1989;64:349-60

Nephroblastomas

- Complications
  - Small bowel obstruction (7%)
  - Hemorrhage (6%)
  - Wound infection, hernia (4%)
  - Vascular complications (2%)
  - Splenic and intestinal injury (1.5%)

  - Long term complications:
    - Renal function: The rate of chronic renal failure (CRF) is 1% overall. Of these cases, 70% are children with bilateral WT.
    - Cardiac function: The overall incidence rate of some form of cardiac damage is 25% in those treated with Doxorubicin.
    - Pulmonary function: Radiation pneumonitis is encountered in 20% of the cases receiving total pulmonary radiation.
    - Hepatic function: Actinomycin D and radiation may damage the liver, with an overall incidence rate of 10%.

Nephroblastomas

- Prognosis
  - Approximately 80-90% of diagnosed children survive with current multimodality therapy.
  - Patients with FH tumors have at least an 80% overall survival rate at 4 years after initial diagnosis, even in patients with stage IV disease.
  - Synchronous bilateral cases have a 70-80% survival rate, while those with metachronous tumors have a 45-50% survival rate.
  - The prognosis for patients who relapse is poor, with only 30-40% expected to survive after retrieval therapy.

[*] *www.nwtsg.org.(National Wilms Tumor Study Group Official Website).*