



DEPARTMENT OF
Human Oncology
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

ARROCase: Wilms Tumor

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Clinical Presentation

- 3 year old boy, normal developmental/birth history, No PMH.
- Presentation:
 - Overall malaise, emesis x 1, diarrhea, low grade fever and colicky abdominal pain x 3 days
 - Normal activity, appetite, energy
- Physical examination:
 - Awake, alert, oriented and interactive
 - General examination: No abn. findings
 - Abd: soft, nontender. Large palpable mass in the RUQ and RLQ ~7 cm in dimension. No splenomegaly noted. No abdominal ascites.

Clinical Syndromes

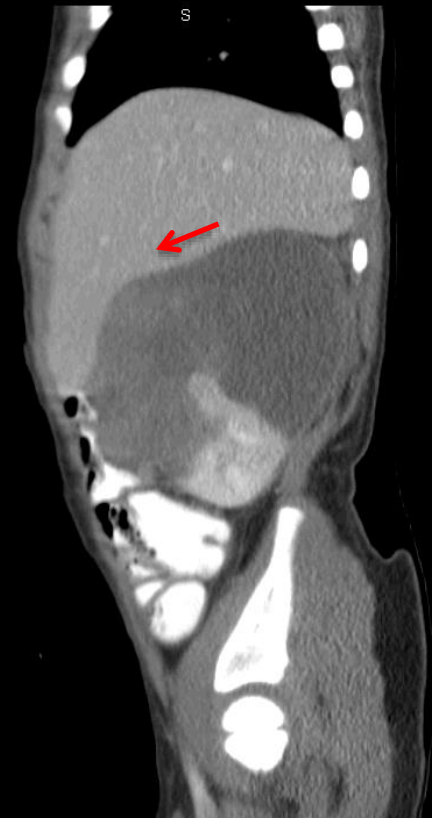
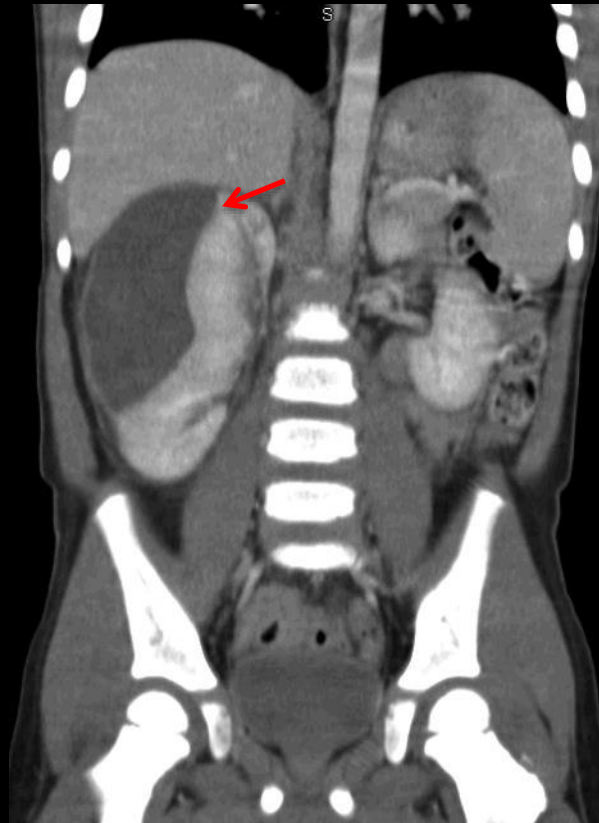
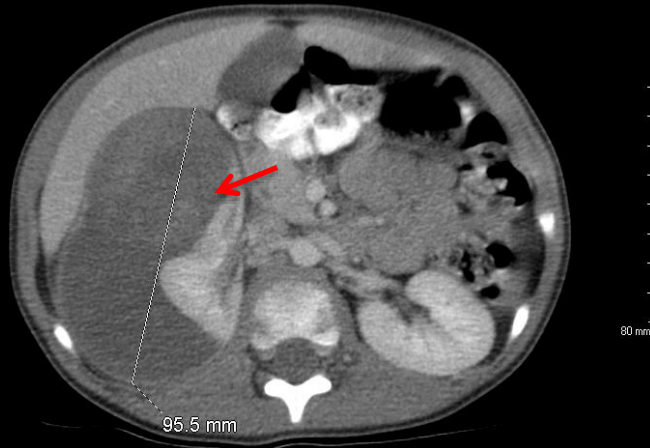
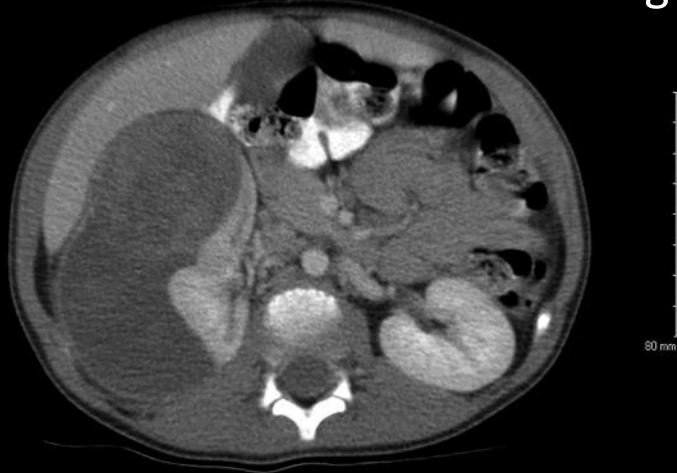
- WAGR: Wilms, Aniridia, GU abnormalities, Retardation;
 - WT1 deletion on 11p13,
 - 30% risk of developing Wilms.
- Denys Drash syndrome: Wilms, Nephritis Syndrome, Male Pseudohermaphroditism;
 - WT1 missense mutation;
 - 90% risk of developing Wilms
- Beckwith-Wiedemann syndrome: Hemi-hypertrophy, macroglossia, GU abnormalities, abdominal wall defects;
 - WT2 gene, 11p15; associated with IGF-2 gene, hypoglycemia
 - 5-10% risk of developing Wilms

Work Up

- Abdominal Ultrasound
 - Poorly defined complex heterogeneous mass occupying the right renal bed measuring 6 x 8 x 11 cm. Left kidney is unremarkable.
- Labs:
 - CBC – slightly anemic with hemoglobin at 10.3, otherwise within normal limits.
 - CMP, magnesium, phosphate – within normal limits
 - Evaluate neuroblastoma panel if imaging uncertain
- UA
 - Within normal limits.
- Other work up considerations (once pathology is available):
 - For rhabdoid & clear cell – brain MRI & bone scan

CT C/A/P

- Large, heterogeneous mass lesion involving near entire right kidney with complex cystic and solid component. No evidence of vascular narrowing or thrombus. There are multiple retroperitoneal and aortocaval lymph nodes with the largest measuring 11 mm in short axis.
- Chest CT to evaluate for lung mets, which is the most common site of metastatic dz



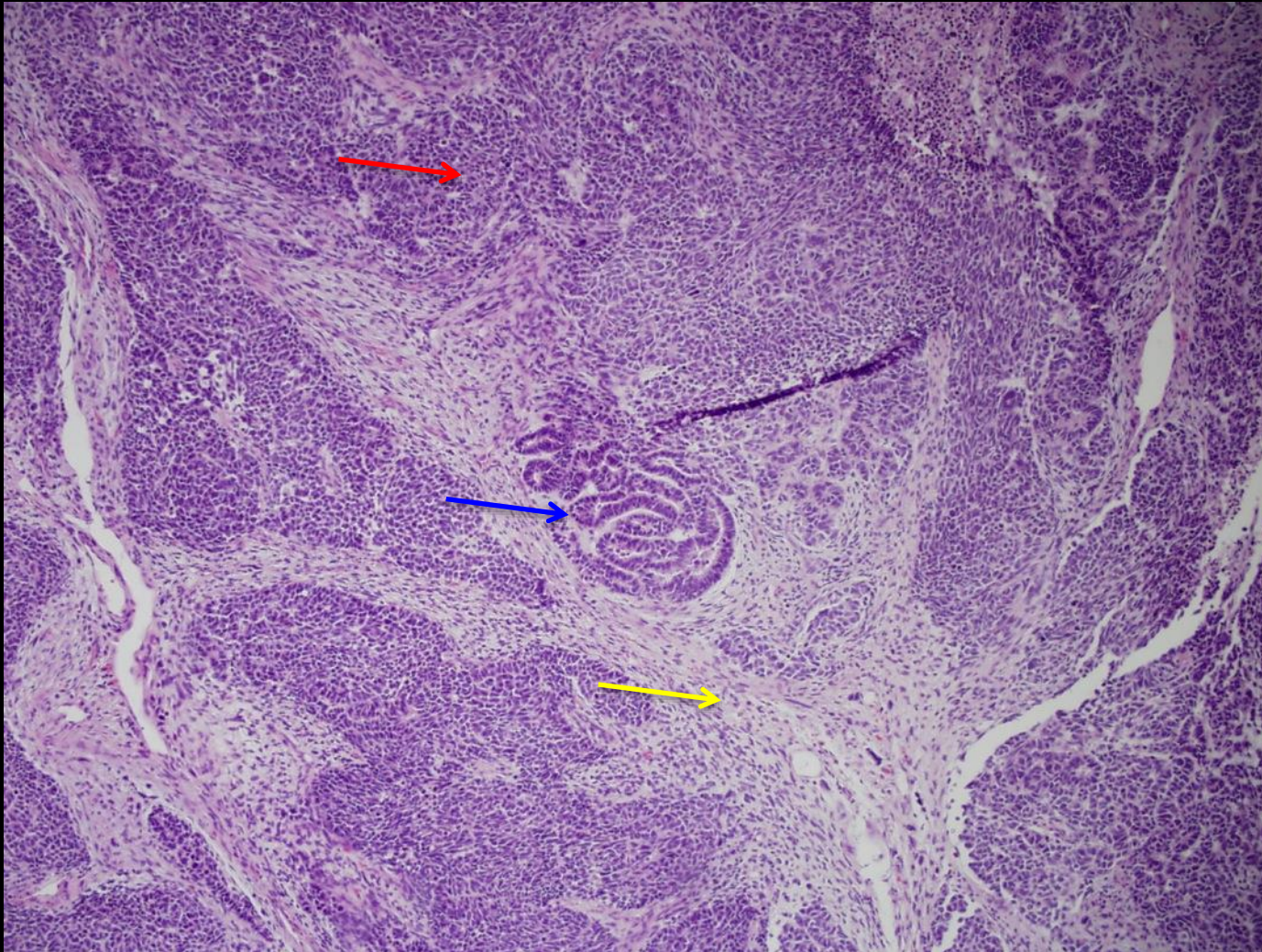
Treatment Decision Point

- Patient admitted to pediatric oncology. Surgical oncology and radiation oncology consulted.
- Treatment plan:
 - No biopsy as imaging is suggestive for Wilms.
 - NOTE: biopsy of un-ruptured tumor automatically upgrades to **stage III** and postoperative radiation is recommended due to concerns of intraperitoneal tumor seeding.
 - Nephrectomy with lymph node dissection planned.
- Review operative report and discuss with surgeon regarding evidence of peritoneal implants, tumor rupture, other abnormal findings or difficulties with resection.

Pathology Review

- Intraoperative/Gross:
 - No peritoneal implants or abnormalities of liver or contralateral kidney. Several abnormal appearing lymph nodes. Nephrectomy and lymphadenectomy without any intraoperative complications, spillage/rupture of tumor. No evidence of tumor thrombus within renal artery/vein.
- Pathology review:
 - Wilms tumor (nephroblastoma) with **diffuse anaplasia**
 - Tumor with capsule intact (ie: no evidence of rupture)
 - 3/31 lymph nodes involved noted to be from the right hilum of the kidney without ECE.
 - Margins negative (closest margin posterior, 5 mm).
 - Cytology of peritoneal washing negative for malignant cells.

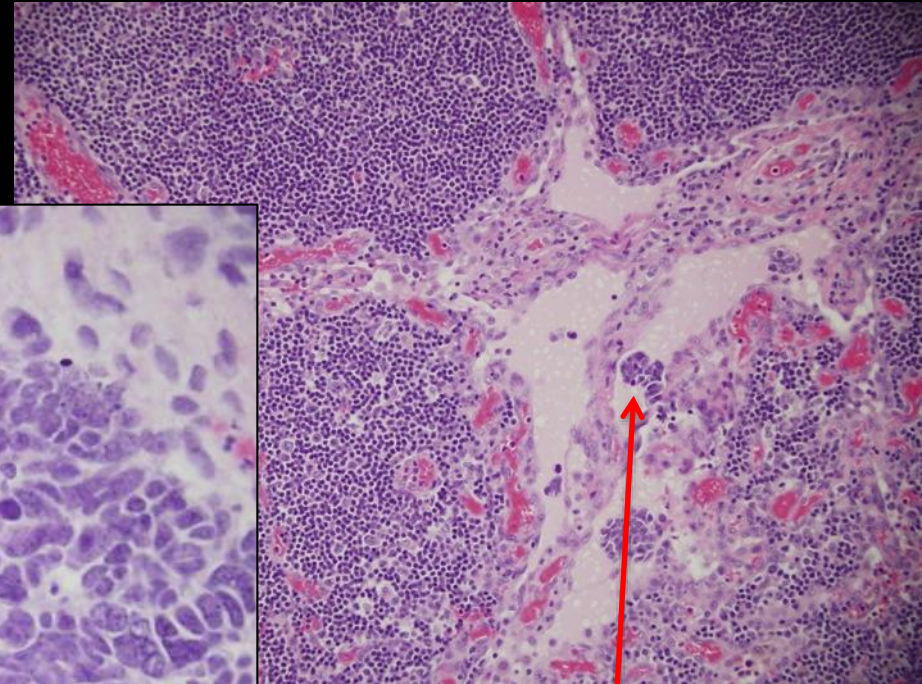
Pathology Review



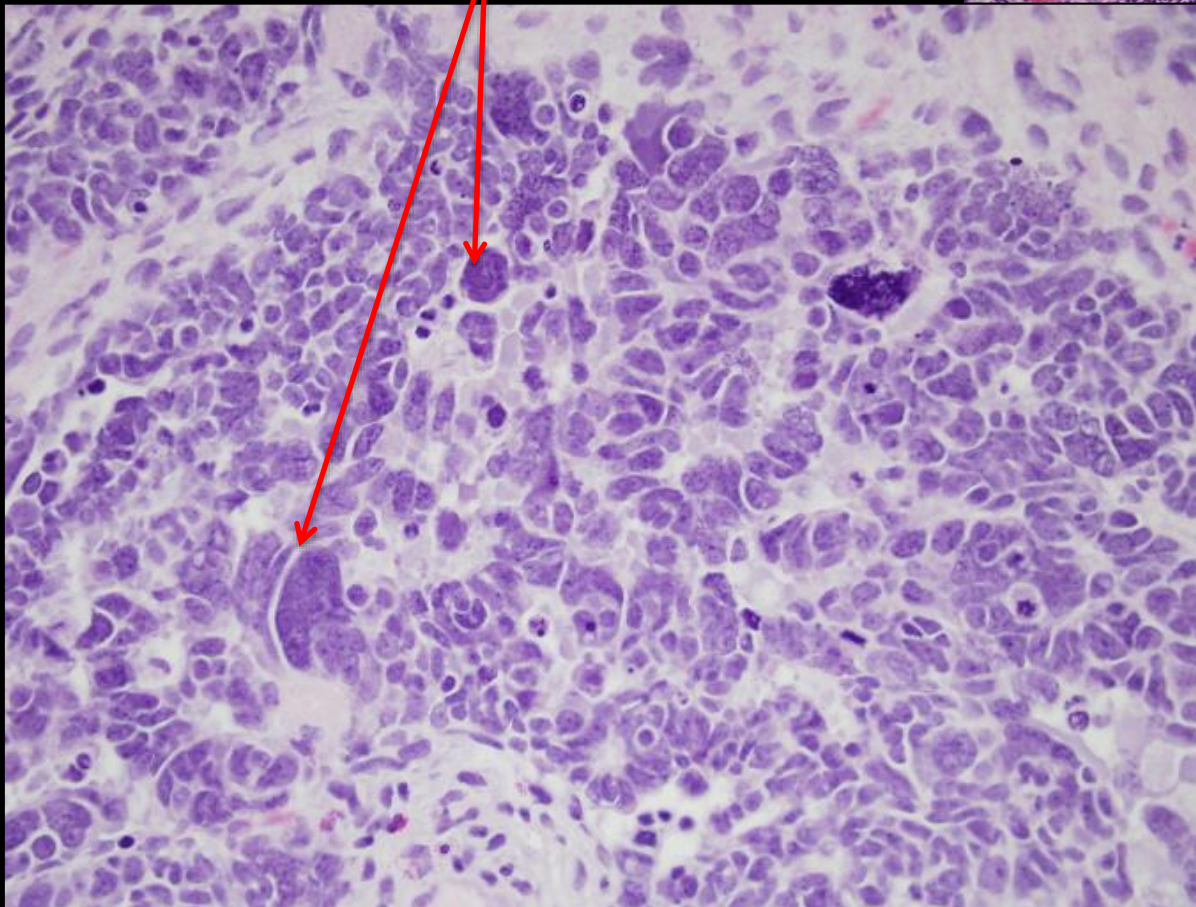
Example of three classic components of nephroblastoma:
→ = blastemal, → = epithelial, and → = stromal

Pathology Review

Example of anaplasia, if found in several samples of the tumor = diffuse anaplasia



Normal lymph node background with small focus of Wilms tumor cells



Other criteria to consider

- Anaplasia is an aggressive pathological feature.
- LOH of 1p & 16q is predictive for increased risk of relapse.
- Other unfavorable histologies such as clear cell and rhabdoid of the kidney were included in National Wilms Tumor Study group trials and now included in the COG high risk renal tumor trial
- Patient should start adjuvant radiation **preferably by 9 days** from surgery date but **no later than day 14**. Coordination of care is crucial.

Treatment Decision Point

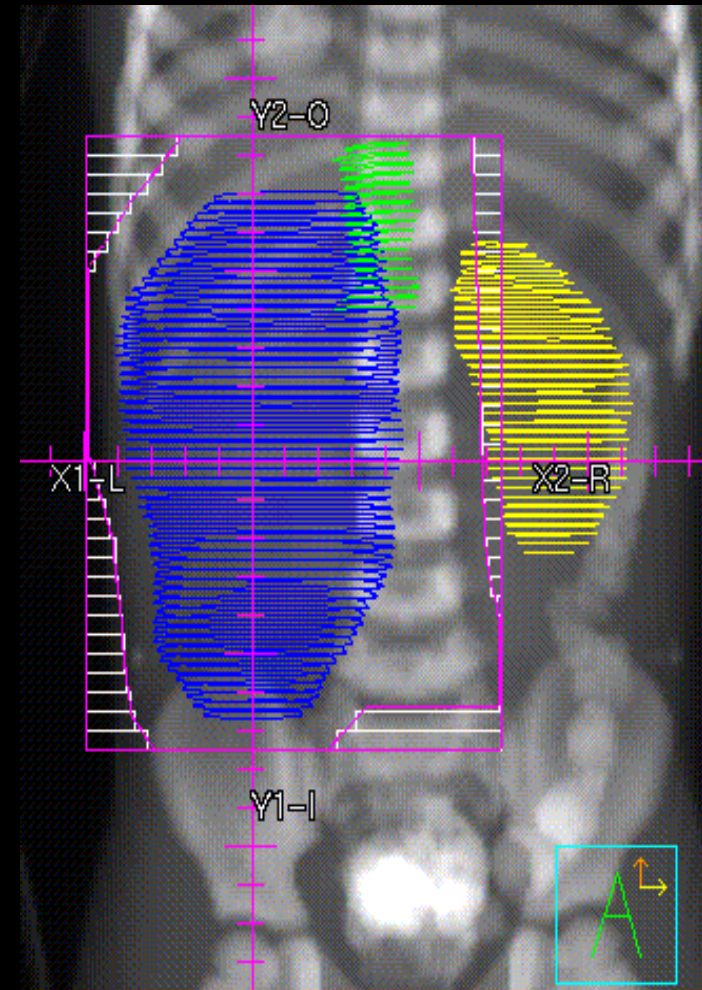
- Decisions regarding adjuvant radiation depends upon:
 - Favorable Histology: All stage III pts.
 - SLURPPP— Spillage, LN+, Unresectable, Residual tumor, Peritoneal Implants, Piecemeal resection/transected tumor, Prior Bx
 - Presence of unfavorable histology (diffuse anaplasia, clear cell, rhabdoid)
 - Metastatic disease
 - LOH of 1p and 16q (for consideration of whole lung)
- Final recommendation: treat flank only, dose prescribed to **19.8 Gy** due to evidence of diffuse anaplasia without tumor rupture.
 - NOTE: If diffuse anaplasia was not present, the dose would be reduced to **10.8 Gy** (see table in subsequent slides). If presence of tumor rupture, fields would include **whole abdomen**.

Radiation Planning (3D)

- Patient supine, in mold for reproducibility.
 - Special attention to removal of undergarments at pelvis (for simulation and treatments) and alignment of spine and pelvis as straight as possible.
- General anesthesia (per clinical judgment)
- Contours*:
 - GTV – Recapitulate location of tumor + entire kidney. This contour may extend into liver or spleen and bowel that was displaced preoperatively.
 - CTV & PTV – The CTV and PTV combined should be 1-1.5 cm beyond the GTV. The superior, inferior and lateral borders of the radiation therapy field should be placed at the edge of the PTV, i.e. approximately 1 cm from the GTV
 - The medial border is extended across the midline to include all of the vertebral bodies (with a margin of 1 cm) at the level concerned, but not far enough to overlap the contralateral kidney.
 - For the positive lymph nodes, the entire length of the para-aortic chain of lymph nodes is included
- OAR: contralateral kidney, liver, heart, lung

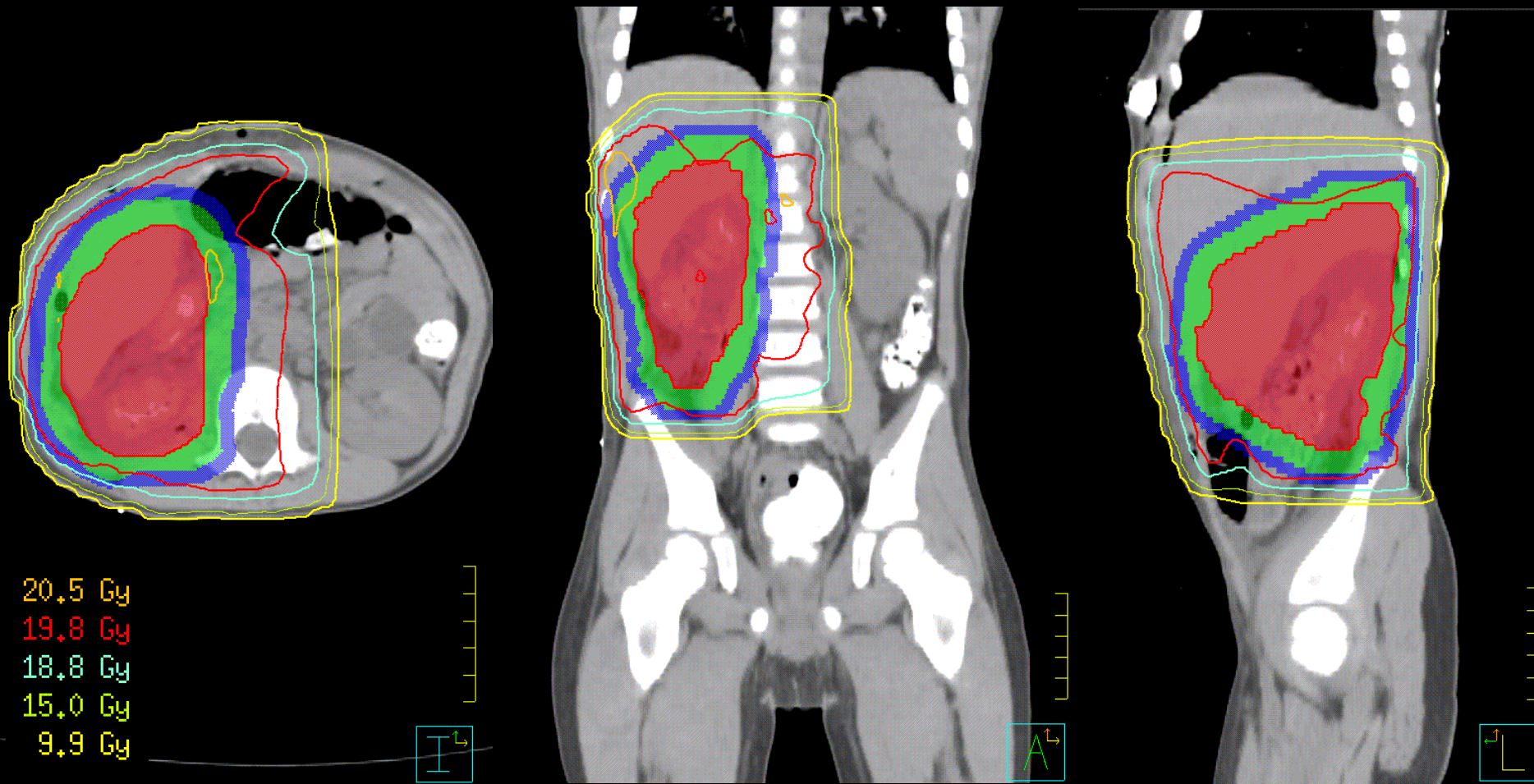
Flank only– 3D field design

- AP:PA field arrangement
- Medial border:
1 cm beyond vertebral body on the contralateral side but exclude contralateral kidney
- Lateral border:
1 cm beyond kidney/tumor
- Superior border:
1 cm beyond kidney/tumor & including entire PA LN chain if LN+
Block Heart on left side
- Inferior border:
1 cm beyond kidney/tumor and cover entire PA LN chain if LN+
- MLCs drawn at vertebral body interspaces to limit bone growth abnormalities.



PTV – blue, left kidney – yellow,
diaphragmatic crus – green

Radiation Planning (3D)

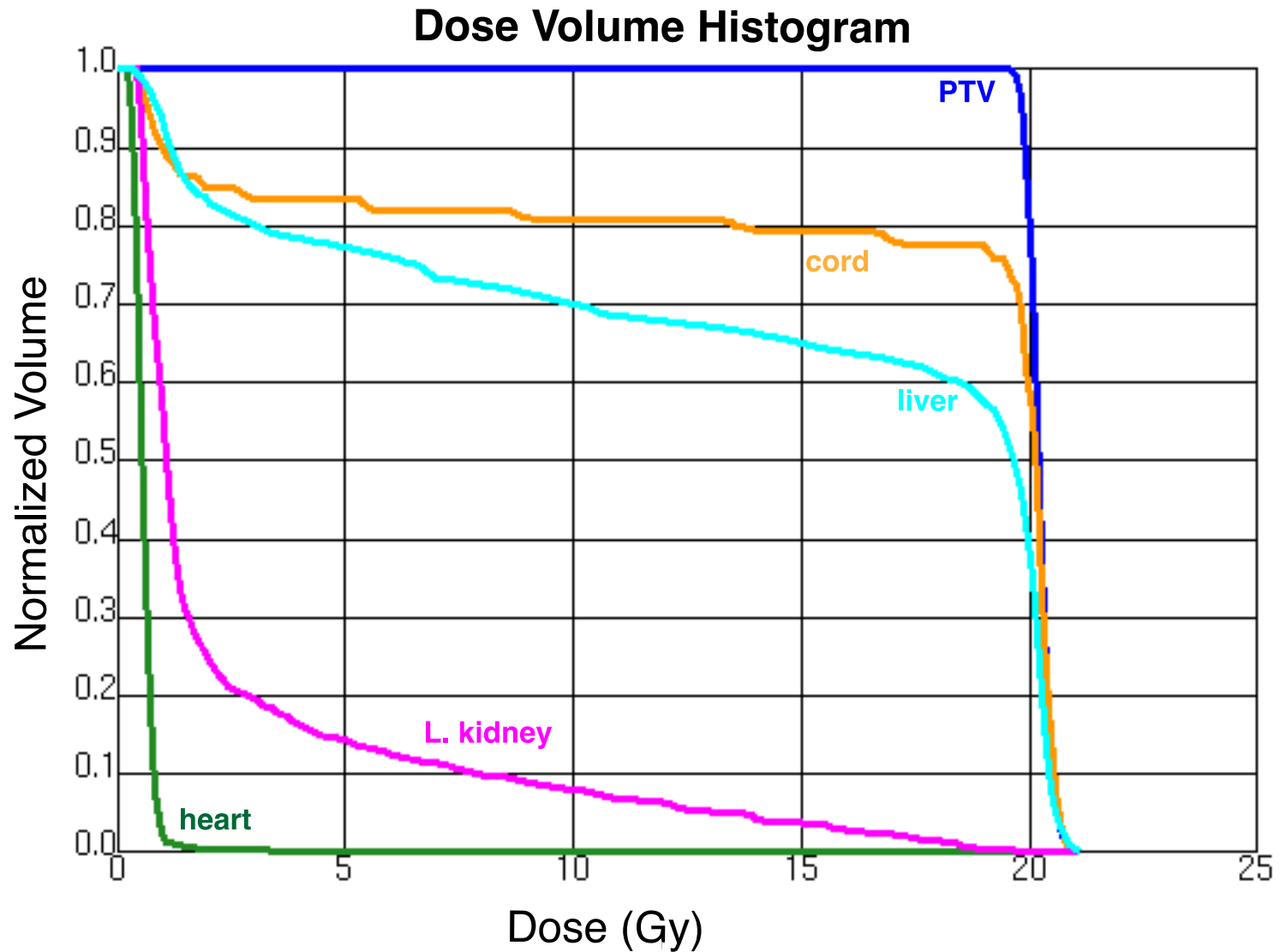


GTV – red,
CTV – green (1 cm expansion, contours adjusted off of bone/anatomic barriers),
PTV – blue (0.5 cm expansion)

Radiation Planning

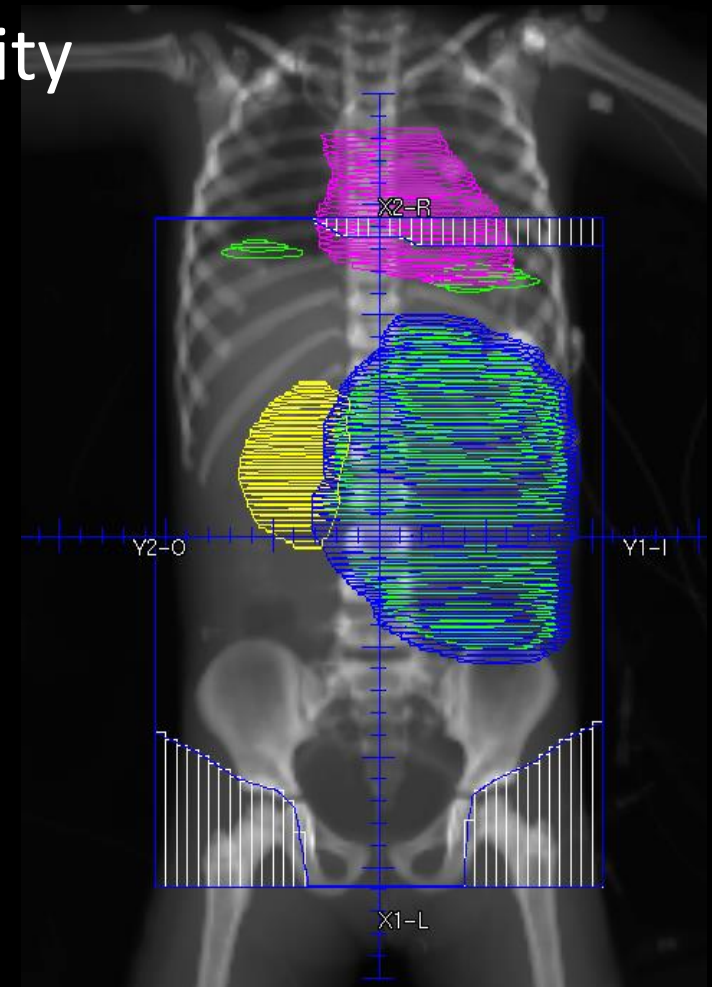
- Prescription:
 - Flank PTV prescribed to 19.8 Gy in 1.8 per fraction using 6 MV photons.
- PTV coverage goals:
 - For conventionally defined beams (i.e. AP/PA flank field), dose variations in the targeted volume should be within +7%, -5% of the prescription dose.
 - For volume-based plans, the entire PTV should be encompassed within the 95% isodose surface and no more than 10% of the PTV should receive greater than 110% of the prescription dose

Radiation Planning



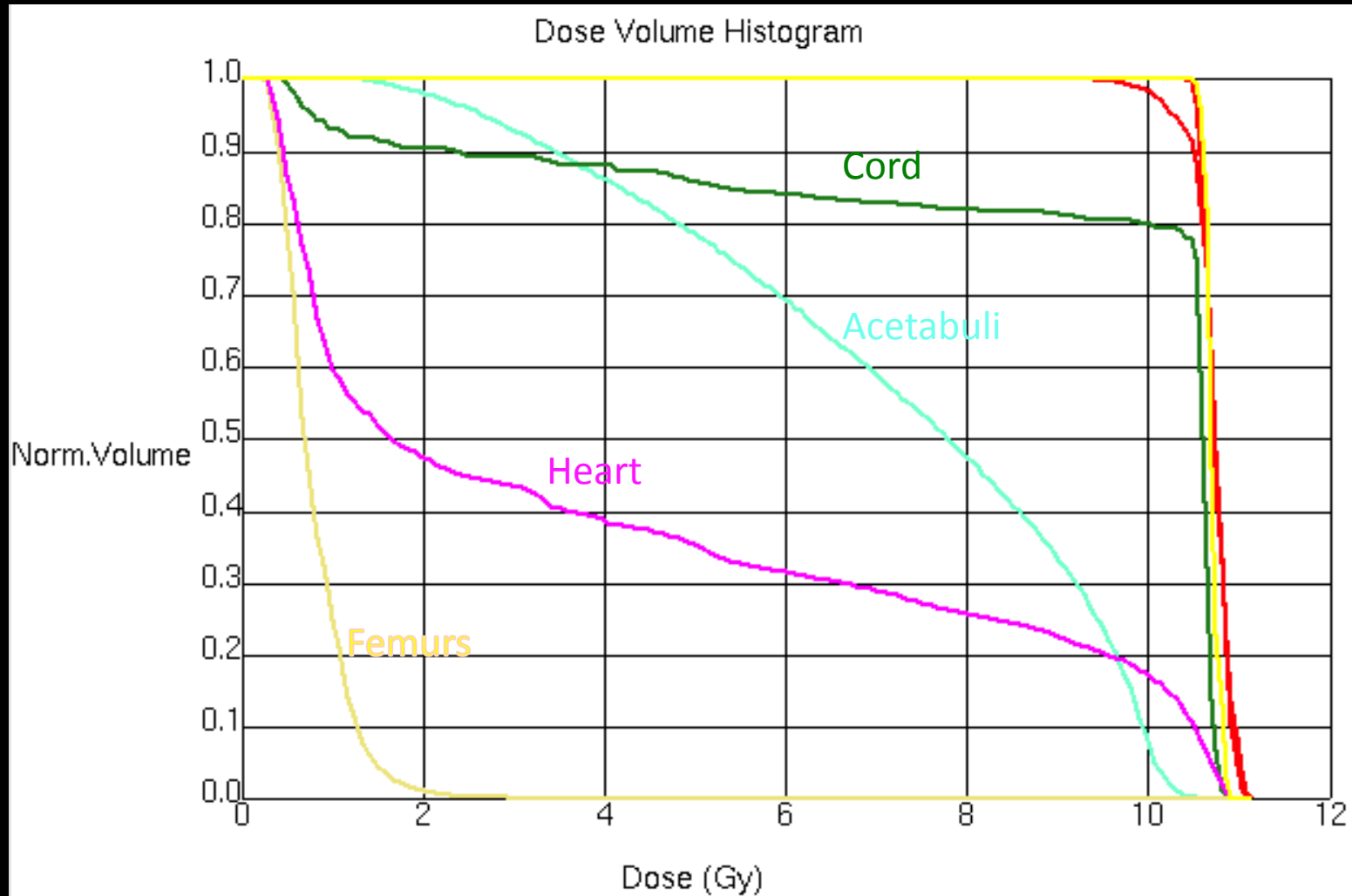
Whole Abdomen – 3D field design for comparison

- Encompass entire peritoneal cavity
- Lateral border:
1 cm beyond abdominal wall
- Superior border:
1 cm beyond top of diaphragm
Block Heart as feasible
- Inferior border:
Bottom of obturator
foramen
Draw peritoneal reflection to
guide femur block



PTV– blue, right kidney– yellow, Top of diaphragm– green, Heart– pink

Whole Abdomen DVH



Right kidney– yellow,
PTV and surgical bed– red

Side Effects of Treatment

- Acute:
 - Loose stools
 - Nausea – provide prophylactic anti-emetics
 - Fatigue
- Long term:
 - Bowel adhesions
 - Infertility (females > males) or future pregnancy complications
 - Greater in females treated with whole abdomen with both ovaries and uterus in the field.
 - Scoliosis/vertebral body foreshortening
 - Hypertension
 - Secondary to fibrosis of contralateral renal artery
 - Renal failure (low incidence if treating flank)
 - CHF – risk is ~4% in patients receiving adriamycin¹
 - Liver failure (chemotherapy associated)
 - 2nd malignancy (1.6% cumulative risk)

¹ Review of National Wilms Tumor Studies (NWTs) 1-4

Staging

| | |
|-----|--|
| I | Limited to the kidney and completely excised without tumor rupture. |
| II | Extends beyond kidney but is completely excised without tumor rupture. |
| III | Residual gross disease confined to the abdomen, positive lymph nodes, positive margins, peritoneal implants, spillage of tumor, or <i>initial biopsy</i> |
| IV | Hematogenous metastatic disease (lung, liver, brain, bone) or distant metastatic lymph nodes. |
| V | Bilateral renal involvement at diagnosis. |

Teaching Points

| <u>Stage</u> | <u>Radiation Treatment</u> |
|--|--|
| Stage I-II, FH | <ul style="list-style-type: none">• NONE |
| Stage III, FH Stage I-III, focal anaplasia Stage I-III, DA | <ul style="list-style-type: none">• 10.8 to the flank |
| Stage III, DA | <ul style="list-style-type: none">• 19.8 Gy to the flank |
| Stage III (SLURPPP) | <ul style="list-style-type: none">• 10.5 Gy to whole abdomen if preop tumor rupture, +ascites, diffuse operative spill, peritoneal seeding• 21 Gy to whole abdomen if diffuse peritoneal mets noted at the time of surgery. |

FH – favorable histology, DA – diffuse anaplasia, LOH – loss of heterozygosity for 1p & 16q

SLURPPP: Spillage, LN+, Unresectable, Residual tumor, Peritoneal Implants, Piecemeal resection/transected tumor, Prior Bx

NWTS Vs SIOP approach

- NWTS (National Wilms Tumor Study Group)/ US approach:
 - Primary surgery
 - Confirms pathological diagnosis
 - Adjuvant treatment based on surgical staging
 - Additional prognostic implication of surgical pathology
- SIOP (International Society of Paediatric Oncology)/ European approach:
 - Pre-operative chemotherapy approach
 - Reduced spillage
 - Tumor downstaging and improved surgical resectability
 - Potentially avoids or reduces intensity of adjuvant therapy
- UK Children's Cancer Study Group, UKW3 randomized trial: Immediate nephrectomy vs Preoperative Chemotherapy
 - Improved stage distribution with preop. Approach
 - 20% reduced use of radiotherapy or doxorubicin
 - Similar event-free and overall survival

NWTS studies

- NWTS 1 (1969-74):
 - Post-operative RT not needed for stage I kids < 2 years age treated with AMD, but needed for older kids
 - Combined AMD and VCR better than either drug alone in stage II/ III
- NWTS 2 (1974-78):
 - ADR and VCR x 6 months may suffice for older stage I kids, thereby avoiding RT
 - Adriamycin needed for stage II or more
- NWTS 3 (1979-85):
 - 10 weeks AMD + VCR is sufficient (not 6 months) in stage I, Favorable histol. (FH)
 - No RT needed for stage II, FH
 - 10 Gy equivalent to 20 Gy for stage III, FH
- NWTS 4 (1986-94):
 - No RT randomizations in the study
 - Single dose pulse intensive chemotherapy reduces hematological toxicity and costs (compared to standard course 5 day course)
- NWTS 5 (1995-2002):
 - Identified LoH 16 q and 1p as negative prognostic factor
 - Addition of etoposide improved outcomes in stage II or more

AREN Studies

- Recently completed COG renal protocols:
 - AREN0532 - Very Low, Low & Standard Risk FH Wilms
 - AREN0533 - Higher Risk FH Wilms – st III FH w/ LOH or st IV FH
 - Key RT study question: evaluated omission of lung RT for patients with CR in lung to 6 weeks of chemo & without LOH of 1p & 16q
 - AREN0534 - Bilateral Wilms
 - AREN0321 - High Risk Renal Tumors (WT w/ anaplasia, clear cell sarcoma of kidney, malignant rhabdoid tumor, renal cell carcinoma)
- Future Direction - single, multi-strata trial for pts with FH WT
 - Will use ROI at 11p15 & gain of chromosome 1q as biomarkers for risk stratification
 - Strata 1 – st I FHWT – aim is to determine whether pts with ROI at 11p15 will have outstanding OS w/o adjuvant chemo
 - Strata 2 – st III FHWT w/o gain of 1q & w/o LOH at 1p and 16q – to determine whether doxorubicin can be eliminated from front-line therapy
 - Strata 3 – pts w/ FHWT & gain of 1q – does augmentation of therapy improve RFS (add doxo for st I/II, add cyclo/etop for st III/IV)
 - St IV pts – determine feasibility of IMRT for whole lung & liver RT

References

- NWTS 1:
<http://www.ncbi.nlm.nih.gov/pubmed/184912?dopt=Abstract>
- NWTS 2:
<http://www.ncbi.nlm.nih.gov/pubmed/6164480?dopt=Abstract>
- NWTS 3:
<http://www.ncbi.nlm.nih.gov/pubmed/2544249?dopt=Abstract>
- NWTS 4:
<http://www.ncbi.nlm.nih.gov/pubmed/9440748?dopt=Abstract>
- NWTS 5:
<http://www.ncbi.nlm.nih.gov/pubmed/16129848?dopt=Abstract>
- Additional NWTS studies:
 - Bilateral Wilms:
<http://www.ncbi.nlm.nih.gov/pubmed/1650403?dopt=Abstract>
 - Tumor spillage:
<http://www.ncbi.nlm.nih.gov/pubmed/19395185?dopt=Abstract>