Wilms Tumor (Nephroblastoma)

Samir Patel, MD, FRCPC
Arnold C. Paulino, MD, FACR, FASTRO
John A. Kalapurakal, MD, FACR, FASTRO

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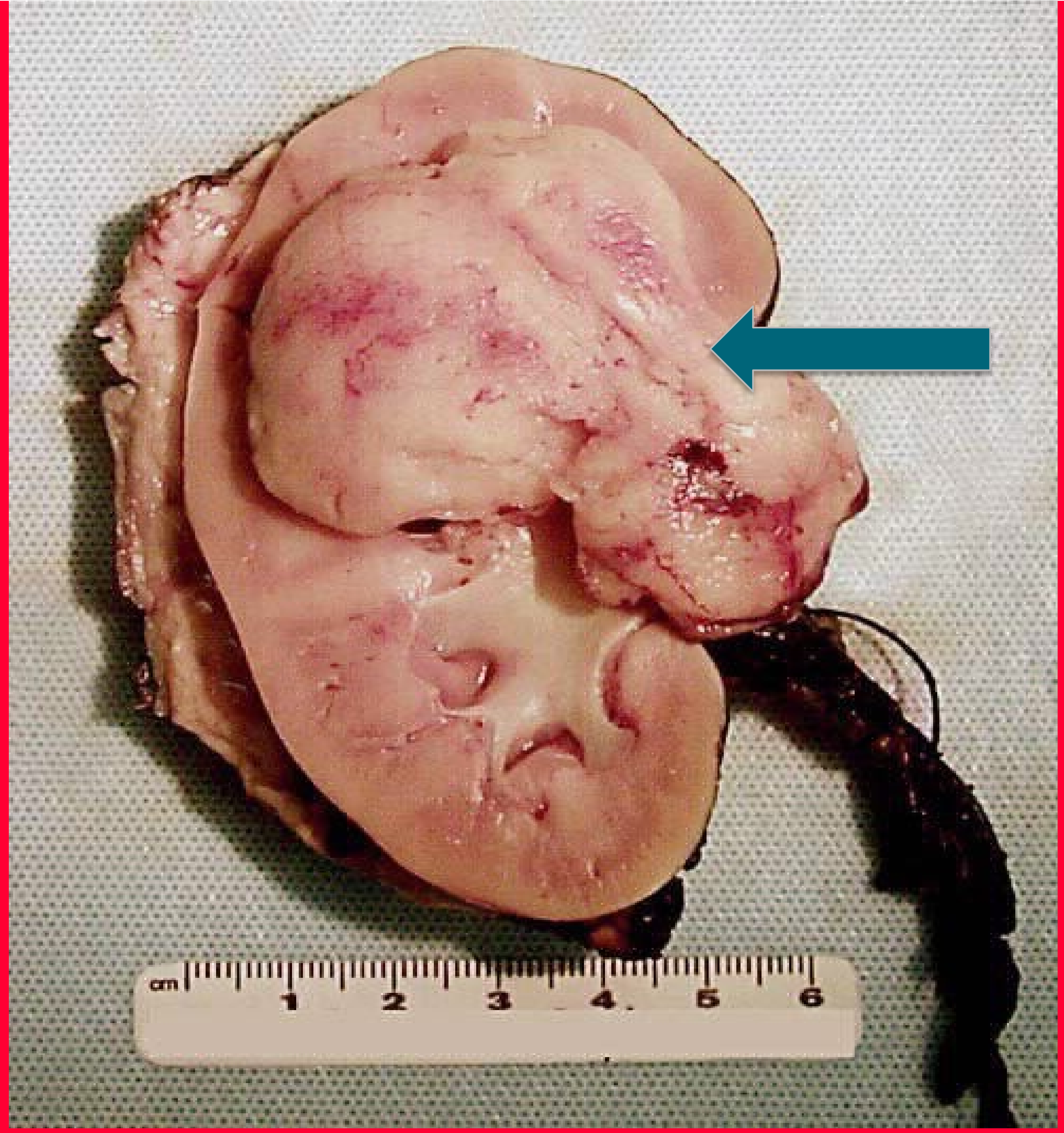
Wilms Tumor (WT)

- Most common malignant renal tumor of childhood
- Approximately 500 cases annually in the US
- Peak incidence between 3 and 4 years
- In few children occurs as part of a congenital malformation syndrome (WAGR, Denys-Drash, Beckwith-Wiedemann)

Pathology

- Most are solitary lesions; 12% may be multifocal; 7% may involve both kidneys
- Gross appearance: WT has uniform pale gray color with hemorrhage and necrosis
- Soft and friable and can be easily ruptured (spontaneous or iatrogenic)

Gross nephrectomy specimen showing Wilms tumor (arrow)



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Pathology

- Classic WT is triphasic with 3 cell types: blastemal, stromal and epithelial
- About 90% are favorable histology (FH)
- Three entities under unfavorable histology (UH) subtypes in the National Wilms Tumor Study (NWTS) include anaplasia, clear cell sarcoma of kidney (CCSK), rhabdoid tumor of the kidney (RTK)
- Anaplasia (5%): large nuclei, hyperchromasia, mitoses
- Anaplasia may be focal or diffuse
- Clear cell sarcoma of kidney (CCSK) and RTK are not considered WT

Clinical Presentation

- Most present with abdominal swelling or abdominal mass
- Pain, hematuria and fever may be present
- Hypertension (↑renin) in 25%
- Signs of Wilms tumor associated syndromes: aniridia, hemihypertrophy, genitourinary abnormalities (hypospadias, cryptorchidism, double collecting system, horseshoe kidney) and pseudohermaphroditism

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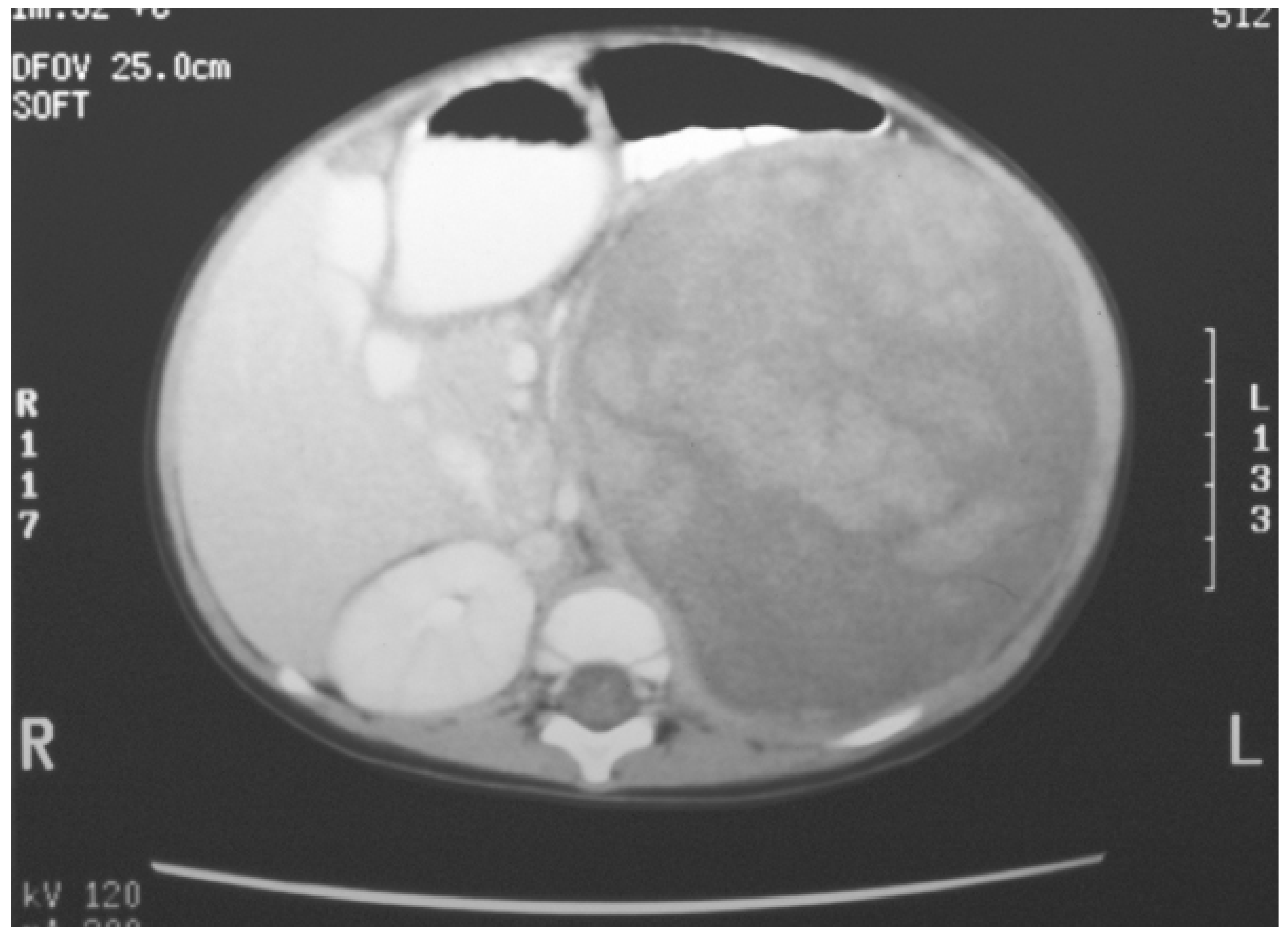
Natural History

- WT is often localized at initial diagnosis with about 15 to 20% presenting with metastatic disease
- Local spread into the renal sinus or the intrarenal blood and lymphatic vessels
- Spread to peritoneal cavity may occur, ↑after preoperative rupture or intraoperative spillage
- Common sites of metastases – lungs (> 80%), lymph nodes, and liver, rarely brain and bone

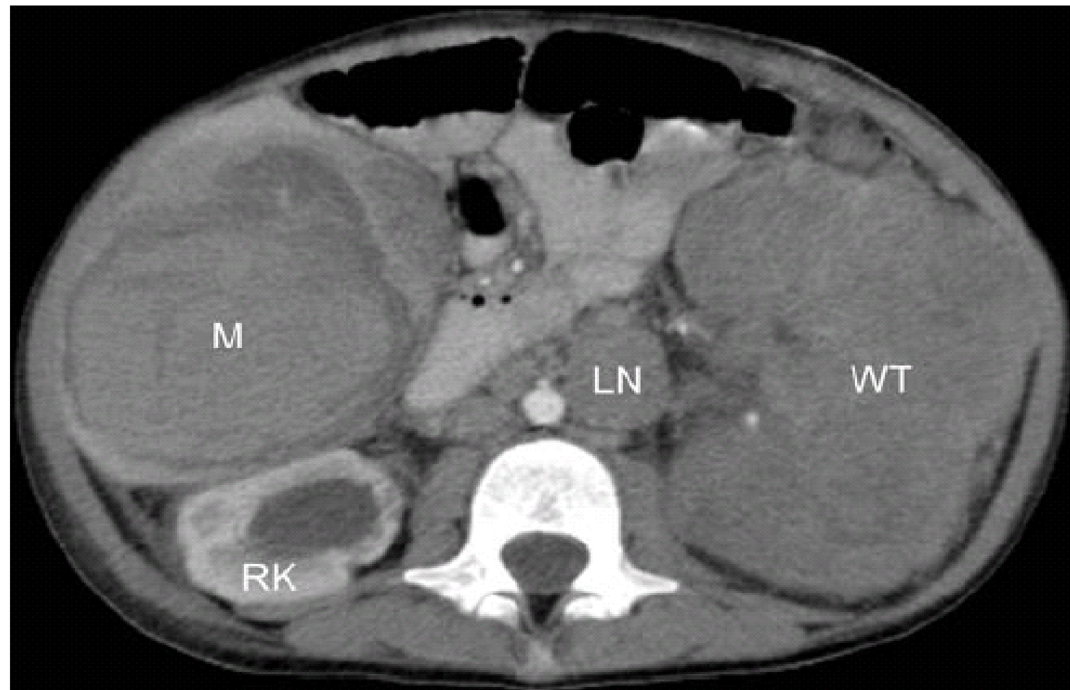
Work-up

- History and physical examination
- CBC, creatinine, BUN
- Imaging: ultrasound, CT scan, MRI, Bone scan (CCSK), MRI brain (CCSK, RTK)
- Things to look for include the renal solitary lesion, presence of thrombus in inferior vena cava (IVC), lymph node involvement, presence of tumors in both kidneys, distant metastases
- For RTK, second primary atypical teratoid rhabdoid tumor (ATRT) in the brain can occur (10-15%)

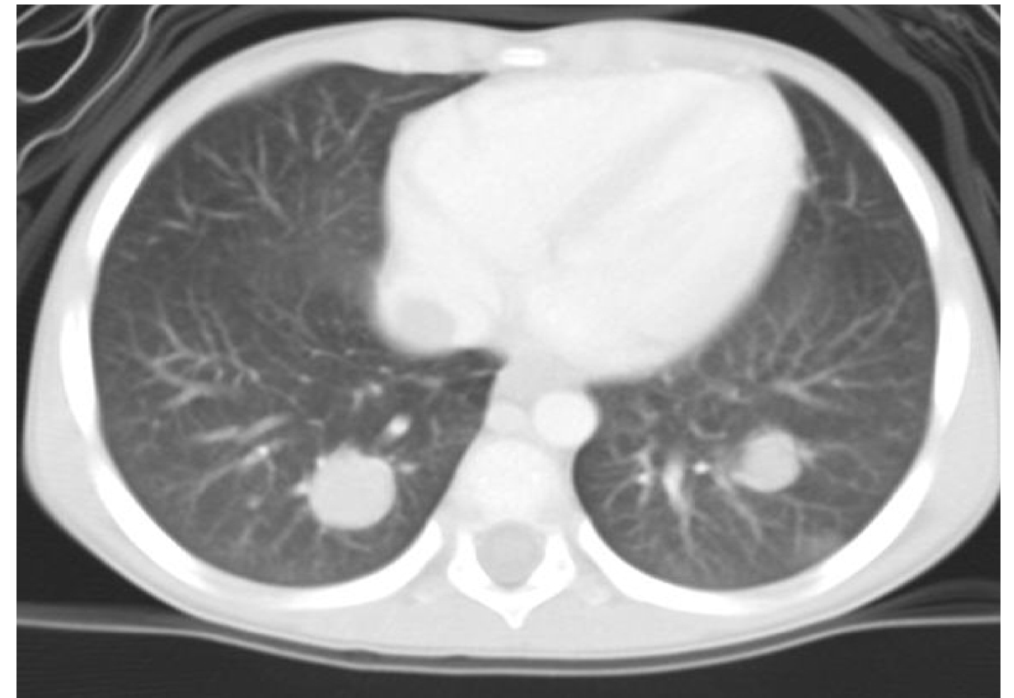
CT scan of abdomen showing left renal mass



Lymph node involvement (LN), Liver metastasis (M), Primary tumor WT



Lung metastases



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COG Staging

Stage	Criteria
I	Tumor is limited to the kidney and is completely resected with no tumor at or beyond the negative margins Renal capsule is intact No involvement of the renal sinus No tumor at or beyond the resection margins All lymph nodes sampled are negative, no hematogenous metastases Tumor is not ruptured or biopsied before removal
II	Tumor is completed resected with no tumor at or beyond the resection margins All lymph nodes sampled are negative, no hematogenous metastases Tumor extends beyond the kidney with one of the following: • Penetration of the renal capsule • Extensive invasion of the soft tissue of the renal sinus • Blood vessels outside of the renal parenchyma (including the renal sinus) contain tumor cells • Vascular extension of the tumor completely removed en bloc with the nephrectomy specimen
Benedetti et al., Nat Rev Urol 2025	

COG Staging

Stage	Criteria
III	Residual, non-hematogenous tumor confined to the abdomen, including: • Gross residual tumor (e.g., any biopsy of a renal tumor or non-renal tumor, incomplete resection) • Biopsy performed before tumor removal • Microscopic residual tumor (e.g., tumor at the surgical resection margin) • Lymph nodes in the abdomen or pelvis involved by the tumor • Tumor implants on the peritoneal surface or tumor penetration through the peritoneal surface • Tumor rupture before surgery • Intraoperative tumor spillage • Tumor removed in more than one piece (including vascular extension removed separately from the nephrectomy specimen) No hematogenous metastases
IV	Hematogenous metastases (e.g., lung, liver, bone, brain) Lymph nodes outside the abdomen or pelvis involved by the tumor
V	Bilateral renal tumors, and tumor on each side should be substaged separately using above criteria
Benedetti et al., Nat Rev Urol 2025	

Prognostic Factors

Era	Risk Stratification Factors
NTWS-1, NTWS-2	Stage
NWTS-3, NTWS-4	Histology
NWTS-5	Age <2 years Tumor weight ≥550g
COG, 1st generation	Lung nodule response Extrapulmonary metastases Bilateral/predisposition Combined LOH 1p and 16q
COG, current generation	(Tumor weight removed) Isolated LOH 1p or 16q, LOH 11p15, 1q gain Lymph node involvement Post-chemotherapy histology (in patients with predisposition) Epithelial histology

Benedetti et al., Nat Rev Urol 2025

LOH at 1p and 16q in NTWS-5

- NTWS-5 prospectively analyzed prognostic value of LOH 1p and/or 16q

LOH Status	4-year RFS (%)	4-year OS (%)
Stage I/II FH		
No LOH	91.1	98.4
LOH 1p only	80.4 (P=0.02)	91.2 (P=0.02
LOH 16q only	82.5 (P=0.01)	98.1 (P=0.6)
LOH 1p and 16q	74.9 (P=0.001)	90.5 (P=0.01)
Stage III/IV FH		
No LOH	83.0	91.9
LOH 1p only	89.0 (P=0.37)	97.6 (P=0.36)
LOH 16q only	85.3 (P=0.67)	92.0 (P=0.76)
LOH 1p and 16q	65.9 (P=0.01)	77.5 (P=0.04)

Grundy PE et al., JCO 2005

Surgery

- Initial treatment for most children in North America
- Transperitoneal approach, abdominal exploration, LN sampling, radical nephrectomy
- WT are large and compress adjacent organs without invasion
- Radical en-bloc resections of adjacent organs not recommended
- Precautions to avoid tumor spillage

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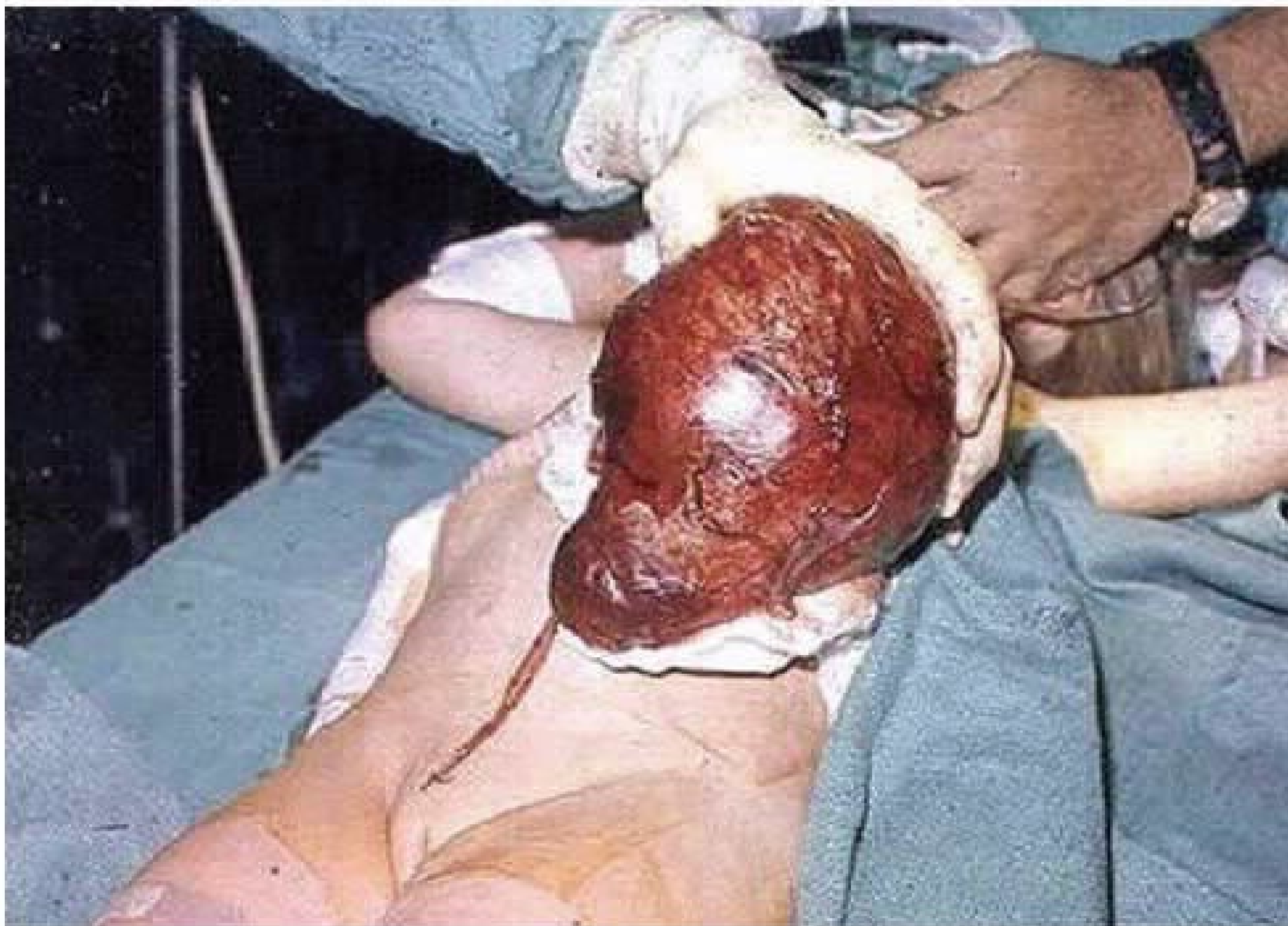

Surgeons carefully remove large tumor to avoid rupturing tumor and creating a spill in the abdomen

Results of the National Wilms Tumor Studies (NWTS)

NWTS-1 and 2

- Age adjusted dose schedule was employed for flank RT
  - <18 months of age: 18-24 Gy
  - 19-30 months: 24-30 Gy
  - 31-40 months: 30-35 Gy
  - > 40 months: 35-40 Gy
- Toxicity data that we see today are from the era of these higher doses

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NWTS-1 (1969-1974)

- Role of RT in group I WT patients?
- Postoperative RT was not necessary for children < 2 years of age with group I tumors receiving AMD, however the abdominal recurrence rates were higher without RT in older children
- RFS with AMD + VCR for irradiated group II, III children was better than that with either agent alone

NWTS-2 (1974-1979)

- Could the addition of VCR to AMD eliminate the need for RT in group I patients?
- RT not required for group I tumors
- Age did not influence outcome, RFS in children >2 years was 89% vs. 77% (+RT) and 58% (-RT) in NWTS-1
- The duration of chemotherapy (6 months or 15 months) did not influence survival

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NWTS-2 (1974-1979)

- Group II-IV tumors had superior RFS with the addition of ADR to AMD+VCR
- Children with LN positive disease had significantly lower RFS
- Histology: As in NWTS-1 children with UH had poorer outcomes compared to FH

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NWTS-3 (1979-1985)

- Children stratified according to histology and stage
- Staging system was altered with LN involvement upstaged from group II to stage III and ‘local’ tumor spillage down staged from group III to stage II
- Do stage II FH patients need RT?
- What is the dose of RT required for stage III FH?

NWTS-3 (1979-1985)

- Children with stage II FH tumors do not need RT or ADR in addition to VCR + AMD
- Children with stage III FH tumors who received 10 Gy + ADR, AMD, VCR had similar survival as those who received 20 Gy with 2 drugs
- Thus RT and ADR was eliminated in >60% of children
- Flank RT dose was reduced from 40 Gy to 10 Gy

NWTS 1-5

- RT delay of 10 or more days was associated with poor outcome
- Flank RT volume: Medial border must cross the midline to include the vertebrae
- The superior-inferior (S-I) borders of the field were defined initially by IVP, but later CT volume was considered
- NWTS 3-5: superior border need not extend up to the dome of the diaphragm

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Tumor Spill in NWTS-3 and -4

- Tumor spillage 23%
- 8-year RFS for stage II spill/no spill treated with no RT/RT: 79%/87% (P=0.07)
- 8-year OS for stage II spill/no spill treated with no RT/RT: 90%/95% (P=0.04)
- Flank and beyond-flank relapse no RT, 10 Gy and 20 Gy: 12%, 3%, 0% and 6%, 3%, 3%
- COG: stage II spills 10Gy flank + ADR to VCR, AMD

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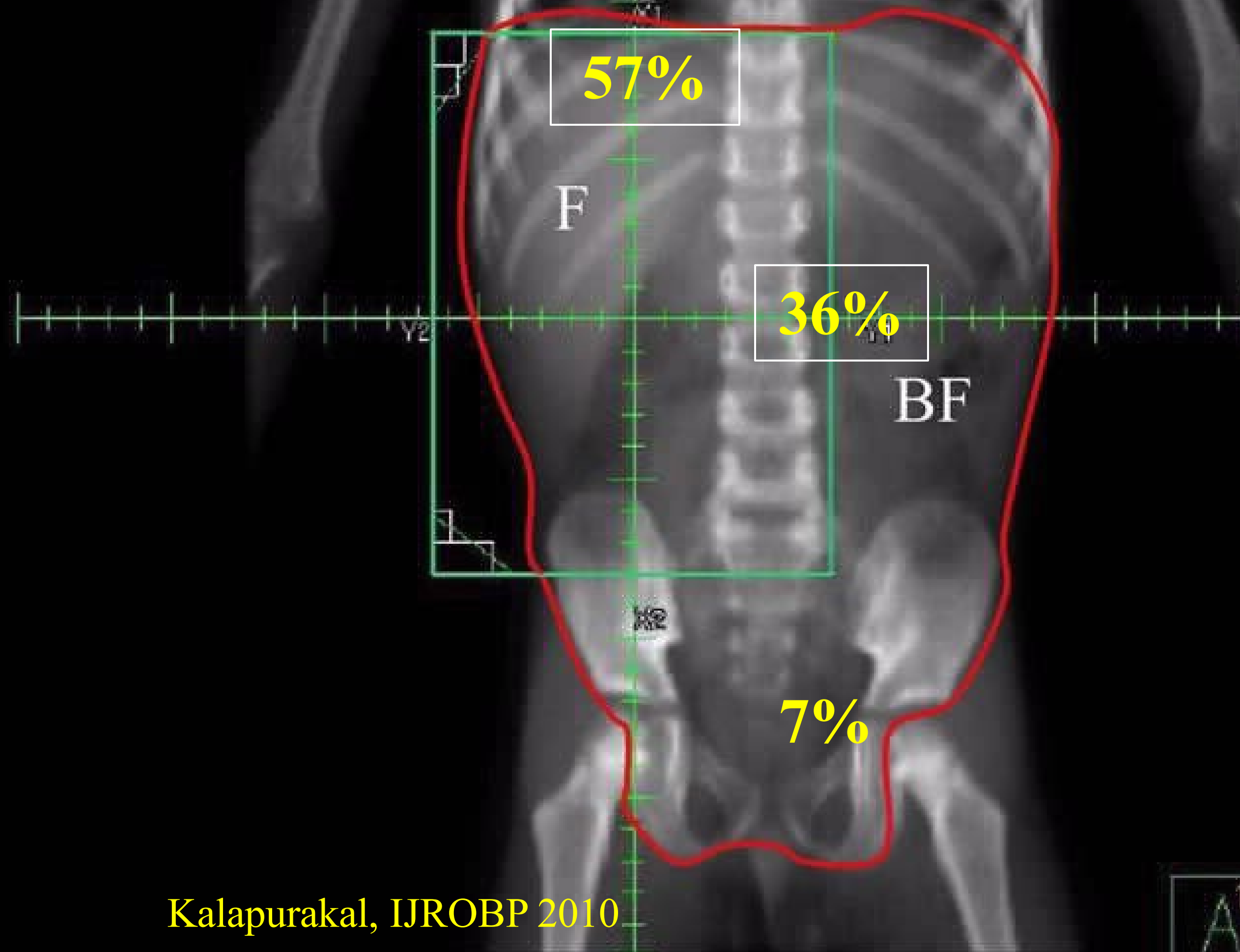

F= Flank
BF = Beyond Flank

Most common site of abdominal recurrence was flank alone followed by flank and beyond flank. Beyond flank alone was the least common pattern of abdominal failure.

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CT-only Lung Metastases in FHWT in NWTS-4 and -5

- 186 patients, 50% treated as stage IV others per investigator discretion (2/3 drugs + WLI)
- 5yr EFS 2/3 drugs (±WLI): 56%/80% SS
- WLI did not affect relapse or survival with 3 drug chemotherapy
- CT-only lesions should be treated with 3 drug chemotherapy but no WLI

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Grundy P et al., Pediatr Blood Cancer 2012

CT-only Lung Metastases in FHWT in NWTS-4 and -5

Chemotherapy regimen	n	EFS (%)			OS (%)		
		2 years	5 years	P	2 years	5 years	P
2 drugs	37	59.8	56.0		91.3	86.0	
3 drugs	145	84.2	79.7	0.0039	94.0	87.0	0.91

- When adjusted for use of lung irradiation, the EFS difference remained (P=0.03).

Grundy P et al., Pediatr Blood Cancer 2012

CT-only Lung Metastases in FHWT in NWTS-4 and -5

Lung RT	n	EFS (%)			OS (%)		
		2 years	5 years	P	2 years	5 years	P
No	105	75.0	70.1		94.3	83.7	
Yes	77	84.8	81.0	0.11	91.9	90.0	0.73

- There was a non-significant trend towards improved 5-year EFS for patients treated with lung radiation, but this trend disappeared when the analysis was adjusted for the chemotherapy regimen delivered (P=0.52). No difference in OS with WLI.

Grundy P et al., Pediatr Blood Cancer 2012

Survival Outcomes in NWTS-5 (unpublished)

Stage/Histology	4-year RFS (%)	4-year OS (%)
Stage I FH	91.5	97
Stage II FH	**81.4**	**97.6**
Stage III FH	88.7	94.8
Stage IV FH	**74.6**	**86.3**
Stage V FH	**58.4**	**79.1**
Stage I DA	**68.4**	**78.9**
Stage II DA	82.6	81.5
Stage III Anaplasia	**68.3**	**72**
Stage IV Anaplasia	**33.3**	**33.3**
Stage I FA	**67.5**	**88.9**

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Anaplastic WT in NTWS-5

- NWTS-5: 281 of 2596 patients (11%)
- 4-year RFS and OS for stage I (VCR, AMD alone): 70% and 83%
- 4-year RFS for stages II, III and IV tumors were 83%, 65% and 33%
- COG study: augment therapy for stage I, III and IV tumors

Dome J et al., JCO 2006

Bilateral Wilms Tumor in NWTS-4 – Inferior Outcomes

- 188 patients (5.6%) BWT, 87 patients had initial resection
- Anaplasia (14%) – 390 (44-1925 days)
- Core needle biopsy did not diagnose anaplasia in a single child (Hamilton et al., JPS 2006)
- End stage renal failure 23 patients (12%)
- 12% had <50% nephron sparing surgery
- *Earlier resection required for non-responsive tumors*

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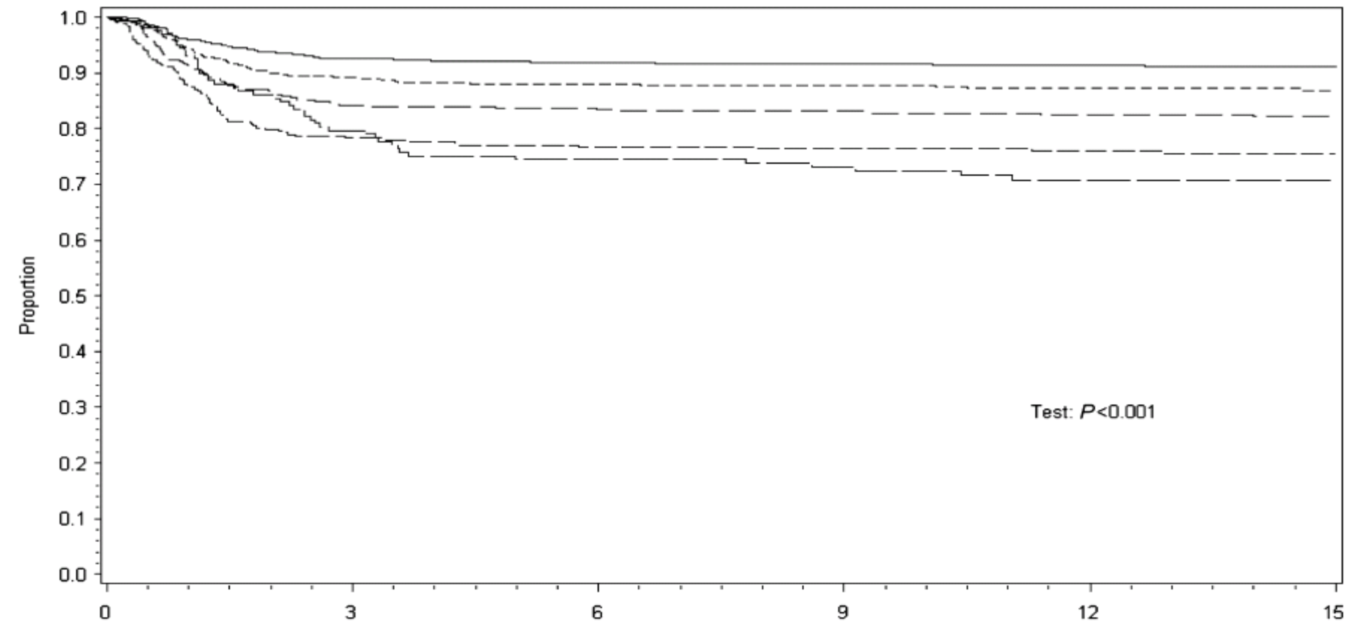
Green DM et al., Pediatr Blood Cancer 2007

- Under staging
- Under treatment
- Delay in local control
- Delay in diagnosing anaplasia (14%)



Stage	No. of Cases	8-year EFS (95% Confidence Interval)
I	918	91% (89%, 93%)
II	617	81% (77%, 84%)
III	594	84% (81%, 87%)
IV	334	71% (66%, 75%)
V	159	70% (63%, 76%)

Favorable Histology	
8-year EFS (95% Confidence Interval)	8-year OAS (95% Confidence Interval)
92% (90%, 93%)	97% (95%, 98%)
83% (80%, 86%)	94% (92%, 95%)
88% (85%, 90%)	93% (90%, 94%)
76% (71%, 81%)	82% (78%, 86%)
74% (66%, 80%)	89% (84%, 93%)

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Relapsed Wilms Tumor in NTWS 5

- 72 FH children who relapsed after VCR, AMD only (stages I, II) treated stratum on B
- Surgery, RT (~20Gy), chemotherapy (regimen I)
- 4 yr EFS/OS were 71% and 82% respectively
- Lung metastases only: 4 yr EFS/OS – 68%/81%

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Green DM et al., Pediatr Blood Cancer 2007

Relapsed Wilms Tumor in NTWS 5

- 103 FH children who relapsed after VAD/RT (stage III) treated stratum on C
- Surgery, RT (~20Gy), chemotherapy (regimen I)
- 4 yr EFS/OS were 42% and 48% respectively
- Lung mets only: 4 yr EFS/OS – 49%/53%

Malogolowkin M et al., Pediatr Blood Cancer 2008

Results of the First Generation of COG Renal Tumor Protocols

The First Generation of COG Renal Tumor Protocols

- COG protocols used LOH at both 1p and 16q in addition to tumor stage and pathology for tumor-risk groups stratification
- Tumor spillage upstaged to stage III
- Goal: reduce treatment-related toxicity in low-risk tumors and increase treatment intensity of high-risk tumors

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Dome JS et al., JNCCN 2021.

COG Risk Group Stratification

Stage	Histology	Age	Tumor weight	LOH (both 1p and 16q)	Lung nodule response	Extrapulmonary mets	Risk group	Study
I	FH	<2 years	≥550 g	No	N/A	N/A	Low risk	None
I	FH	≥2 years	Any	No	N/A	N/A	Low risk	
II	FH	Any	Any	No	N/A	N/A	Low risk	
I	FH	<2 years	<550 g	Any	N/A	N/A	Very low risk	AREN0532
I/II	FH	Any	Any	Yes	N/A	N/A	Standard risk	
III	FH	Any	Any	No	N/A	N/A	Standard risk	
IV	FH	Any	Any	No	RCR	No	Standard risk	AREN0533
III/IV	FH	Any	Any	Yes	N/A	N/A	High risk	
IV	FH	Any	Any	Any	SIR	No	High risk	
IV	FH	Any	Any	Any	Any	Yes	High risk	
I	DA/FA	Any	Any	Any	N/A	N/A	High risk	AREN0321
II-III	FA	Any	Any	Any	N/A	N/A	High risk	
II-III	DA	Any	Any	Any	Any	N/A	High risk	
IV	DA/FA	Any	Any	Any	Any	Any	High risk	
V	Any	Any	Any	Any	Any	Any	Bi/multi/pred	AREN0534

Dome JS et al., JNCCN 2021; Benedetti et al., Nat Rev Urol 2025

Treatment by Risk Group Stratification

Risk Group	Multimodality Therapy
Very Low Risk FH WT < 2 years, stage I FH, <550 g	Surgery, **NO** therapy if **central pathology review and LN sampling**
Low Risk FH WT ≥2 years, Stage I FH, ≥ 550g Stage II FH **without LOH**	Surgery, No RT, Regimen EE4A
Standard Risk FH WT Stage I and II FH **with LOH** Stage III FH **without LOH**	Surgery, Regimen **DD4A** Surgery, RT, Regimen **DD4A**

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Risk Group	Multimodality Therapy
High Risk FH WT Stage III/IV FH **with LOH** Stage IV FH **slow/incomplete responders** Stage IV FH: **CR of lung metastases at week 6/DD4A (rapid early responders)**	Surgery, RT, Regimen **M**, WLI Surgery, RT, Regimen DD4A. **No WLI**
Stages I-III FA Stage I DA	Surgery, RT, Regimen DD 4A
Stage IV FA Stage II-IV DA Stage IV CCSK Stage I-IV RTK	Surgery, RT, Regimen UH1

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COG Chemotherapy Regimens

Regimen	Agents (cumulative doses/m^2)	Length
EE-4A	Vincristine, d-actinomycin	19 weeks
DD-4A	Vincristine, d-actinomycin, doxorubicin (150mg)	25 weeks
VAD	Vincristine, d-actinomycin, doxorubicin (35mg/cycle)	6-12 weeks
Regimen M	Vincristine, doxorubicin (195mg), cyclophosphamide (8.8g), etoposide (2000mg)	31 weeks
Regimen I	Vincristine, doxorubicin (225mg), cyclophosphamide (14.0g), etoposide (2000mg)	25 weeks
Revised regimen UH1	Vincristine, doxorubicin (225 mg), cyclophosphamide (14.8g); cyclophosphamide, carboplatin, etoposide (2000mg)	28 weeks
Revised regimen UH2	Vincristine, doxorubicin (225 mg), cyclophosphamide (14.8g); cyclophosphamide, carboplatin, etoposide (2000mg); vincristine, irinotecan (800mg)	42 weeks
Regimen UH3	Vincristine, doxorubicin (225 mg), cyclophosphamide (14.8g); cyclophosphamide, carboplatin, etoposide (2000mg); vincristine, irinotecan (1000mg)	42 weeks
Benedetti et al., Nat Rev Urol 2025; Daw NC et al., JCO 2020; COG AREN1921		

COG RT Dose Guidelines

Stage	FHWT	Focal anaplasia WT	DAWT
I	N/A	10.8 Gy in 6 fractions	10.8 Gy in 6 fractions
II	N/A	10.8 Gy in 6 fractions	10.8 Gy in 6 fractions
III (flank)	10.8 Gy in 6 fractions	10.8 Gy in 6 fractions	19.8 Gy in 11 fractions
III (WAI)	10.5 Gy in 7 fractions	10.5 Gy in 7 fractions	10.5 Gy in 7 fractions (WAI) + boost 9 Gy in 5 fractions if age >12 months; Diffuse peritoneal implants, age>12 months: 21 Gy in 14 fractions (WAI, limit kidney to <14.4 Gy)
IV (WLI)	Age <12 months: 10.5 Gy in 7 fractions Age ≥12 months: 12 Gy in 8 fractions		
IV (liver)	19.8 Gy in 11 fractions (focal if 1 met, whole liver if diffuse metastases)		
IV (brain)	<5 lesions, age ≥3 years: 21.6 Gy in 12 fractions (WBRT) + boost 10.8 Gy in 6 fractions >5 lesions, age ≥3 years: 30.6 Gy in 17 fractions (WBRT) Age <3 years: 30.6 Gy in 17 fractions (focal only)		

COG RT Dose Guidelines (continued)

Stage	FHWT	Focal anaplasia WT	DAWT
IV (bone or soft tissue)	Age <16 years: 25.2 Gy in 14 fractions Age ≥16 years: 30.6 Gy in 17 fractions		
Lymph node	10.8 Gy in 6 fractions (resected); 19.8 Gy in 11 fractions (unresected)		
Relapsed WT	Flank, age <12 months: 14.4 Gy in 8 fractions Flank, age ≥12 months: 21.6 Gy in 12 fractions WAI, age <12 months: 10.5 Gy in 7 fractions + flank boost 3.6 Gy in 2 fractions (limit kidney dose <10.8 Gy) WAI, age ≥12 months: 21 Gy in 14 fractions (limit kidney dose <14.4 Gy) Diffuse peritoneal implants, age <12 months: 10.5 Gy in 7 fractions + boost 9 Gy in 6 fractions (limit kidney dose <10.8 Gy) Diffuse peritoneal implants, age ≥12 months: 21 Gy in 14 fractions (limit kidney dose <14.4 Gy)		
McAleer MF et al., Pediatr Blood Cancer 2022; COG AREN1921; COG AREN2231.			

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Timing of RT

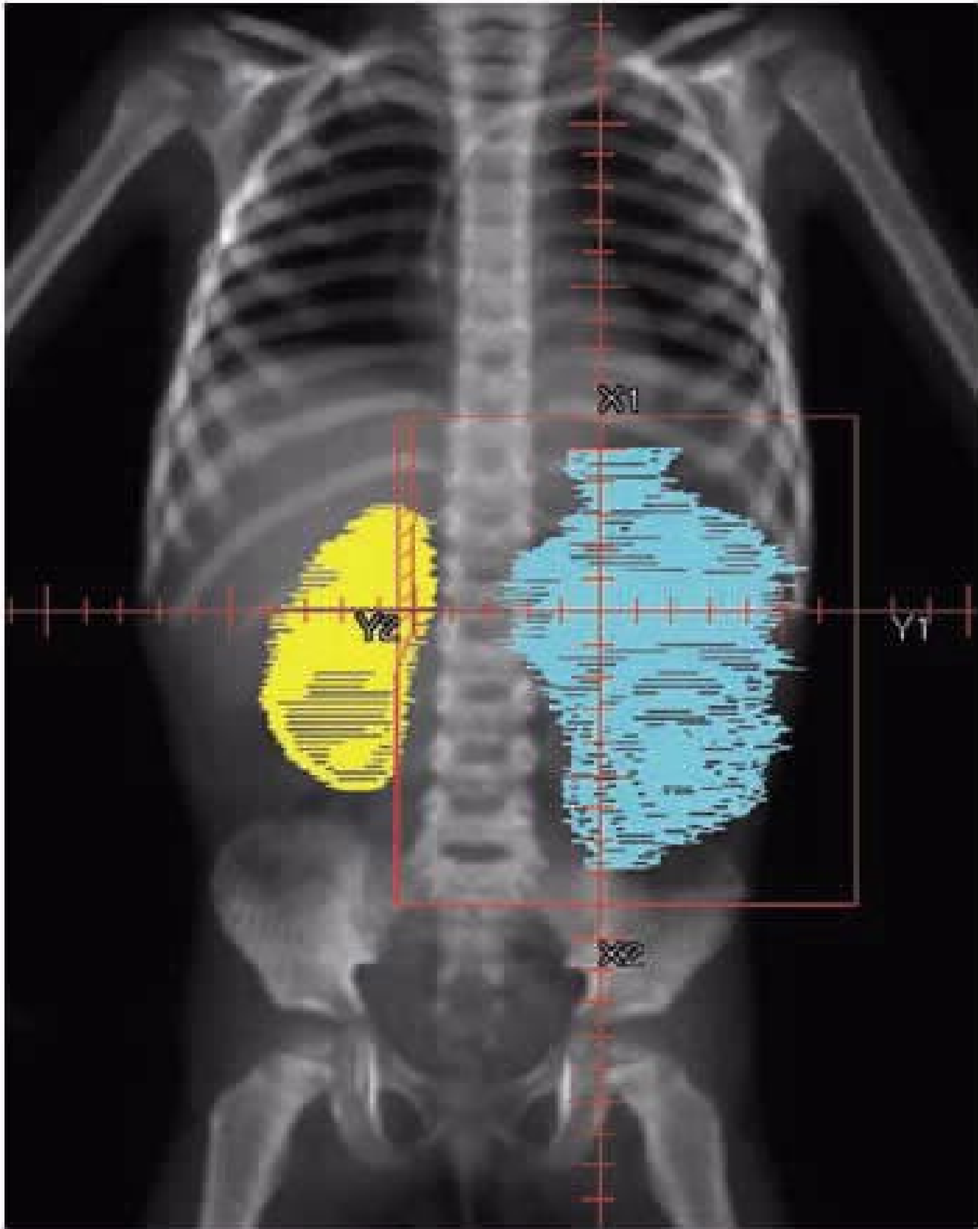
- 1226 patients with stage II-IV FH treated in NWTS-3 and NWTS-4
- RT delay was analyzed in two categories only: 0-9 days vs. ≥10 days
- Median SRI 9 days (range, 1-277 days), 8-12 days in 59% of patients
- 8-year flank recurrence for SRI 0-9 days vs. ≥10 days: 1.9 vs. 1.2% (P=0.3)
- 8-year abdominal recurrence rate for SRI 0-9 days vs. ≥10 days: 4.8% vs. 5.3% (P=0.7)
- Although RT delay ≥10 days was not associated with recurrence rates, concentration of SRI data close to 10 days did not allow for test of a meaningful difference.

Kalapurakal et al., IJROBP 2013

Timing of RT

- 1488 patients (32.1% metastatic) from NCDB database aged ≤25 years, no histology or LOH data available
- Nonmetastatic patients: SRI >14 days associated with increased mortality (adjusted HR 2.13, P=0.013); 8-year OS 87% vs. 96% (P=0.005).
  - Association significant when SRI analyzed as a continuous variable: patients 4% more likely to die for each day that RT was delayed (HR 1.04; P=0.006).
- Metastatic patients: no significant association between SRI and morality (adjusted HR 0.77, P=0.41); 8-year OS 84 vs. 85% (P=0.90).
- No difference in either nonmetastatic or metastatic patients when SRI analyzed by 9-day cut-off used in NWTS studies.

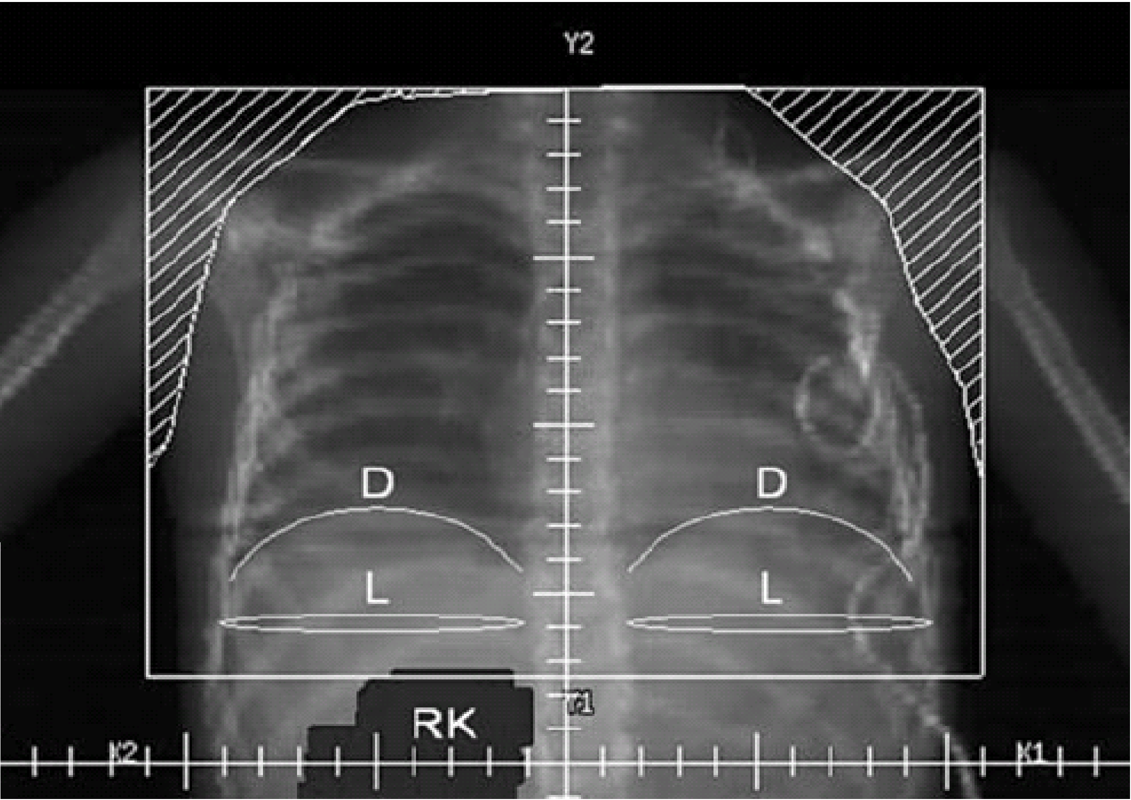
Stokes et al., IJROBP 2018

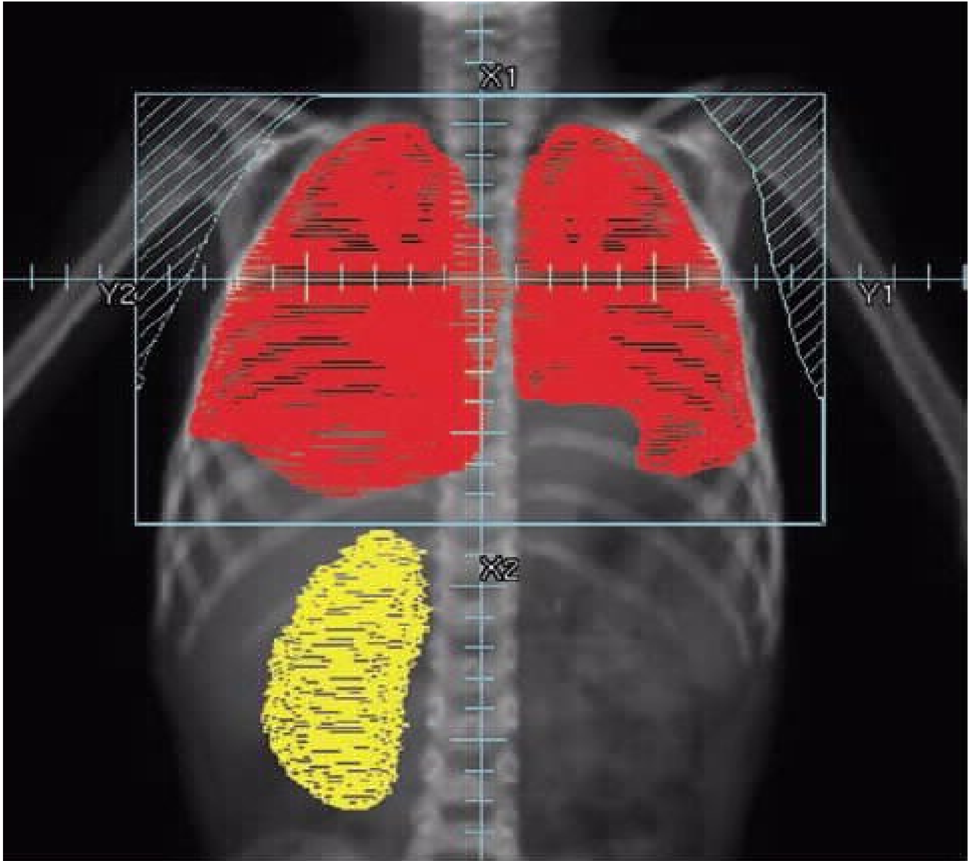


Flank Field

Whole Abdominal Field

AP/PA Whole Lung Fields





The First Generation of COG Renal Tumor Protocols

- AREN03B2 (Renal Tumors Classification, Biology, and Banking Study)
- AREN0532 (Very Low Risk and Standard Risk FHWT)
- AREN0533 (Higher Risk FHWT)
- AREN0321 (High Risk Renal Tumors)
- AREN0534 (Bilateral, Multicentric, or Bilaterally-Predisposed Unilateral WT)

AREN0532

Risk Group	Treatment	Count (%)
Very Low (Stage I, age $<$ 2 yrs, tumor wt $<$ 550 g)	Observation	116 (15.63%)
Low (Stage I, age $\geq$ 2 yrs or tumor wt $\geq$ 550 g; or Stage II, no LOH)	EE4A	51 (6.87%)
Standard (Stage I, age $\geq$ 2 yrs or tumor wt $\geq$ 550 g; or Stage II, LOH)	DD4A / no XRT	32[1] (4.31%)
Standard (Stage III, no LOH)	DD4A / XRT	543 (73.18%)

[1] One patient was treated with EE4A for 2 weeks before switching to DD4A at the confirmation of LOH being positive.

AREN0532 – Very Low Risk WT

- 116 children (<2 years) with stage I FH tumors, tumor weight <550grams, had LN sampling and central pathology review
- Nephrectomy alone no adjuvant therapy
- 4-year EFS 89.7% and 4-year OS 100%
- First site of relapse: lung (n=5), tumor bed (n=4), abdomen (n=2)
- 11p15 methylation status was associated with relapse (P=0.011): 20% relapse with LOH, 25% with LOI and 3.3% with retention of normal imprinting

Fernandez CV et al., Ann Surg 2017

AREN0532 – Stage III FHWT

- 583 eligible patients met COG Stage III criteria; 40 patients excluded from analysis secondary to combined LOH 1p and 16q
- All received DD4A chemotherapy (vincristine, dactinomycin, doxorubicin)
- Median follow-up, 42 months

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AREN0532 – Stage III FHWT

- The 4-year EFS and OS estimates were 88% and 96% respectively.
- Lymph node positive disease with either LOH 1p and 16 q has a worse EFS

		n	4-year EFS (%)	P	4-year OS (%)	P
Lymph nodes	Positive	237	95	<0.01	98	0.18
	Negative	152	83		95	
Gross residual disease	Positive	394	89	0.14	97	0.39
	Negative	134	85		93	
LOH	Neither	382	92	<0.01	97	0.55
	16q only	99	83		97	
	1 p only	56	74		93	

25TH ANNIVERSARY CHILDREN'S ONCOLOGY GROUP 2000 - 2025

Fernandez CV et al., J Clin Oncol 2018

AREN0532/AREN0533

- 4-year EFS was 91.2% without LOH and 74.9% with LOH in Stage I/II FH treated with EE4A
- 4-year EFS was 83% without LOH and 65.9% with LOH in Stage III/IV FH treated with DD4A
- Stage I/II FH patients received DD4A instead of EE4A. No RT was given
- Stage III/IV FH patients received Regimen M (VCR, DACT, DOX alternating with CPM, VP-16) instead of DD4A. RT was given

AREN0532/AREN0533 – 4-year EFS

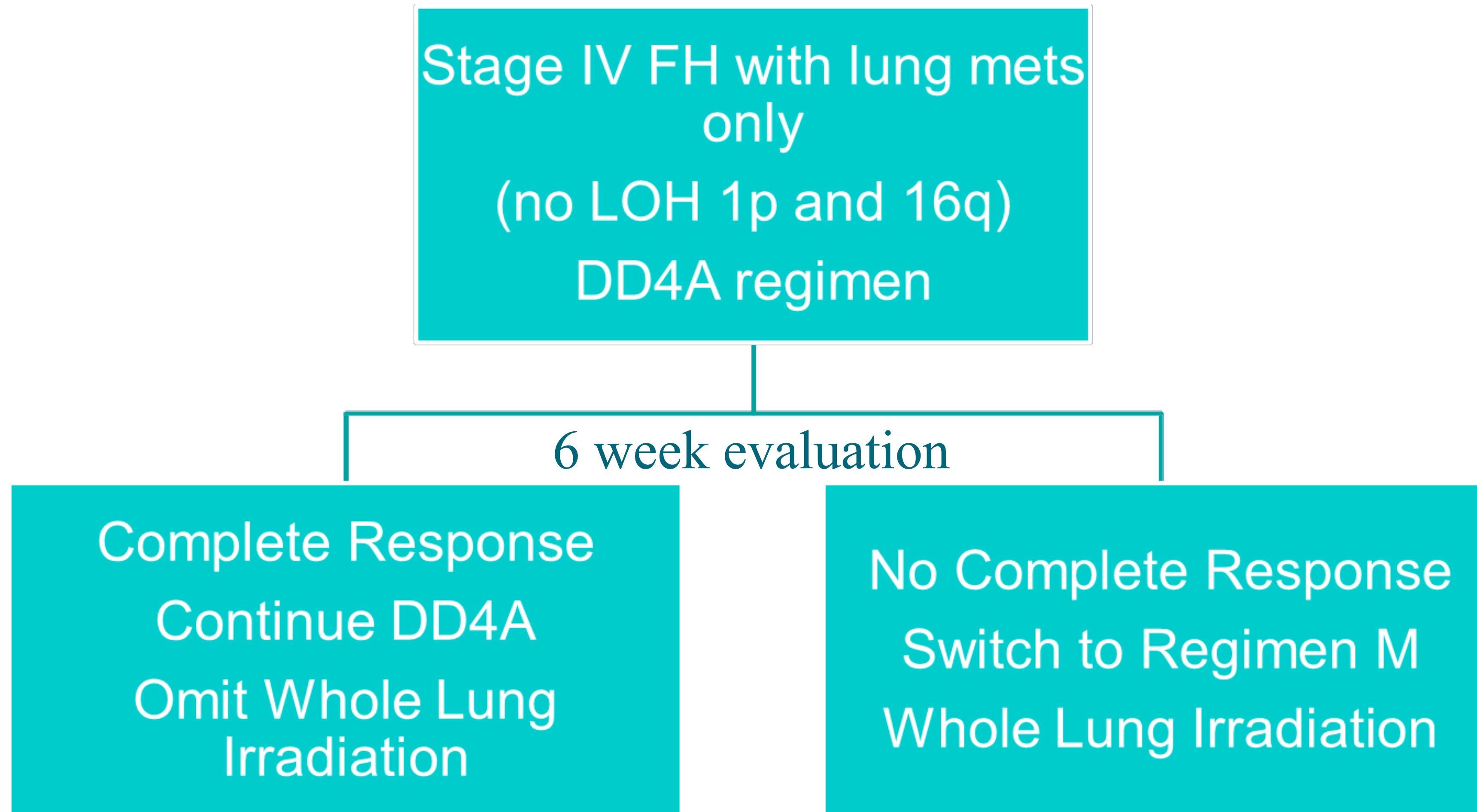
	NWTS-5	AREN0532/ AREN0533
Stage I/II LOH	74.9%	83.9%
Stage III/IV LOH	65.9%	91.5%

- Grade 3 or higher hematological toxicity seen with Regimen M in 60% of patients
- Conclusion: Regimen M therapy improved EFS for Stage III/IV FH with LOH 1p and 16q compared to historical comparison group treated with DD4A. The benefit of DD4A for Stage I/II FH LOH 1p and 16q is less clear.

25TH ANNIVERSARY CHILDREN'S ONCOLOGY GROUP 2000 - 2025

Dix DB et al., JCO 2015 (supple; abstr 10009)

AREN0533 – Stage IV FHWT with Lung Metastases



25TH ANNIVERSARY CHILDREN'S ONCOLOGY GROUP 2000 - 2025

Dix DB et al., JCO 2018

AREN0533 – Stage IV FHWT with Incomplete Response

- After central radiology review at 6 weeks of chemotherapy, 159 (54%) out of 292 isolated lung metastases had incomplete response
- The 4-year EFS and OS were 88.5% and 95.4%
- 60% of patients had grade 3 or higher hematologic toxicity
- This showed superior EFS with the addition of cyclophosphamide and etoposide compared to historic standard (DD4A)

25TH ANNIVERSARY CHILDREN'S ONCOLOGY GROUP 2000 - 2025

Dix DB et al., JCO 2018

AREN0533 – Stage IV FHWT with Complete Response

- 133 out of 292 patients had complete response (46%)
- The 4-year EFS and OS estimates were 79.5% and 96.1%
- Compared to historical standard treated with lung RT, the difference is not statistically significant. This may provide an acceptable alternative treatment approach for this patient subgroup.

Dix DB et al., JCO 2018

AREN0533 – Stage IV FHWT, Lung Metastases Only

	4-year EFS (%)	4-year OS (%)
AREN0533	84.6	92.5
NWTS-5	72.4	84.0
	P=0.0007	P<0.0001

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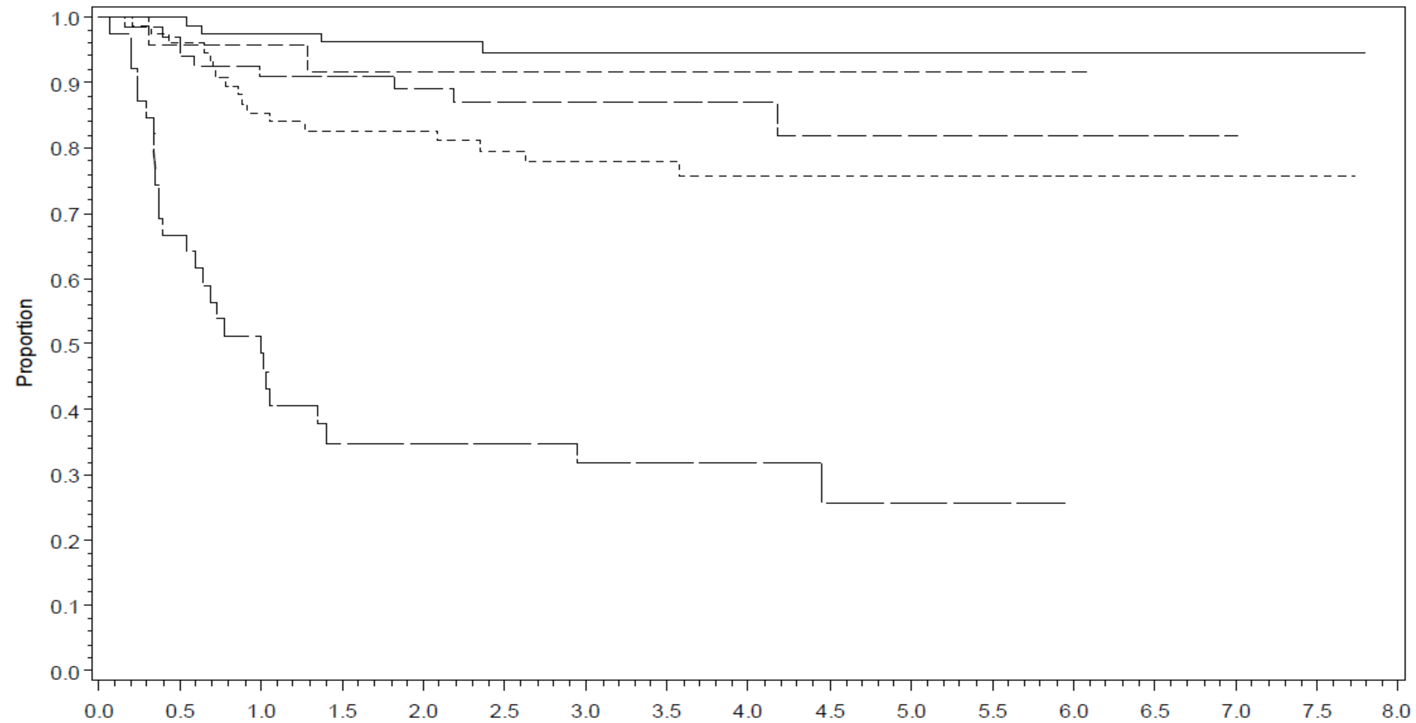
AREN0321



25TH ANNIVERSARY CHILDREN'S ONCOLOGY GROUP 2000 - 2025

AREN0321 – Stage I Anaplastic WT

	4-year EFS (%)	4-year OS (%)
AREN0321 (DD-4A + RT)	100	100
NWTS-5 (EE-4A, no RT)	69.5	82.6

- DD-4A chemotherapy + RT is now the recommended treatment.

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AREN0321 – Stage II-IV DAWT

- In NWTS-5, 4-year EFS for DAWT was 55% using Regimen I and RT
- AREN0321 employed Regimen UH-1 (Regimen I + carboplatin) and RT
- RT dose for Stage III DAWT raised from 10.8 Gy to 19.8 Gy

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AREN0321 – Stage II-IV DAWT

- 66 eligible patients
- 3-year EFS for all patients: 69%
- 4-year EFS for Stage II, III and IV were 85%, 74% and 46%
- Stage III: local failure rate ~3% (significantly improved after 20 Gy) compared to NWTS >20%
- Three patients died of toxicity (cardiomyopathy, 1; pulmonary hypertension, 1; pulmonary edema, 1)
- Compared to NWTS-5, regimen UH-1 appears to have better EFS but more toxicity

25TH ANNIVERSARY CHILDREN'S ONCOLOGY GROUP 2000 - 2025

Daw N et al., Pediatr Blood Cancer 2014: S113

AREN0321 – Stage IV DAWT

- In NWTS-5, the 4-year EFS was 33% for Stage IV DAWT
- AREN0321 evaluated the activity of VCR and Irinotecan in a phase 2 window in newly diagnosed Stage IV DAWT in patients with measurable disease
- Given two cycles if no progression. If partial response, VCR and irinotecan incorporated into regimen UH-1 plus local + lung XRT
- If stable disease, patients did not get further VCR + irinotecan

Daw N et al., JCO 2014 (suppl; abstr 10032)

AREN0321 – Stage IV DAWT

- 19 patients with measurable disease were eligible for window therapy, of which 14 elected to participate in the window.
- 11/14 (79%) had PR and 3 had progression
- Most common grade 3-4 toxicities during window were diarrhea (n = 3) and hypoxia (n = 2), elevated LFT (n =2), hypoalbuminemia (n = 2), hyperglycemia (n = 2)
- Well tolerated and produced a high response rate in Stage IV DAWT

AREN0321 – Stage I CCSK

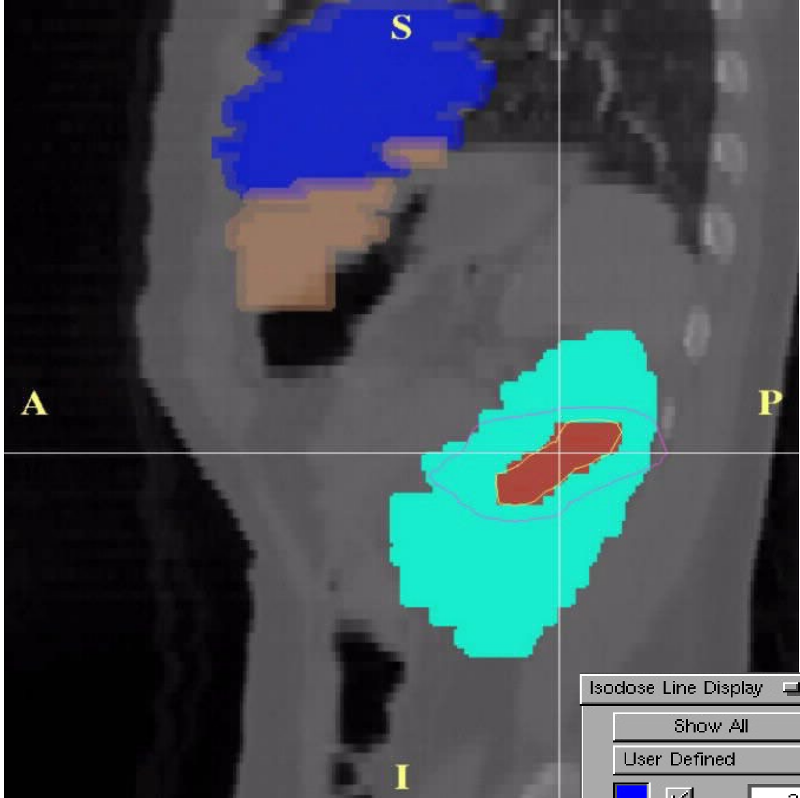
- Patients received Regimen I. No RT
- Only 8 patients
- 4-year EFS: 80%, 4-year OS: 100%
- 1 relapse in brain
- Continue with current regimen with no RT

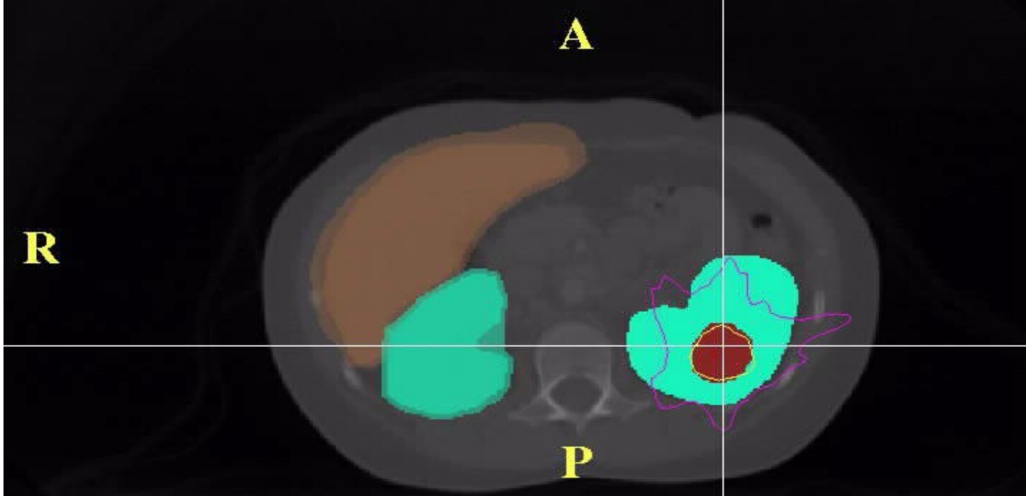
Daw N et al., JCO 2014 (suppl; abstr 10032)

Bilateral Wilms Tumor in AREN0534

- Goals:
  - To improve 4-year EFS to 73% for bilateral WT
  - To prevent complete removal of at least one kidney in 50% patients by pre-nephrectomy 3-drugs
  - To facilitate partial nephrectomy in syndromic WT with pre- nephrectomy 2-drugs (to conserve renal parenchyma and improve renal function in survivors)
- Flank RT: stage III tumors (biopsy alone not an indication for RT)
- Renal sparing IMRT/IGRT (21.6 Gy) for selected tumors meeting all criteria: FH, hilar or polar location, unresectableor multiple positive margins after renal conserving surgery in a solitary kidney, responsive to chemotherapy

Bilateral Wilms Tumor in AREN0534





25TH ANNIVERSARY CHILDREN'S ONCOLOGY GROUP 2000 - 2025

Bilateral Wilms Tumor in AREN0534

- AREN0534 goal was to improve survival and preserve renal tissue by intensifying pre-operative chemotherapy (vincristine, dactinomycin, doxorubicin), complete definitive surgery by week 12 (NWTS-5, 4-year EFS 61% and 4-year OS 80%)
- 249 patients accrued (2009-2015); median follow-up, 3.75 years
- 4-year EFS 81% and 4-year OS 94.2%
- After induction chemotherapy 163/194 (84%) underwent definitive surgical treatment in at least one kidney by 12 weeks
- 39% retained parts of both kidneys
- Surgical approaches included: unilateral total nephrectomy with contralateral partial nephrectomy (48%), bilateral partial nephrectomy (35%), unilateral total nephrectomy (10.5%), unilateral partial nephrectomy (4%) and bilateral total nephrectomies (2.5%)

Ehrlich et al., Ann Surg 2017

New biomarker – 1q gain

- 1114 patients with unilateral FH Wilms tumor on NWTS-5 were analyzed for 1q gain, 1p loss, 16q loss using multiplex ligation dependent probe amplification (MLPA)
- 317 patients (28%) displayed 1q gain
- 8-year EFS 1q gain (77%) vs. no 1q gain (90%; P<0.001)
- 8-year OS 1q gain (88%) vs. no 1q gain (96%; P<0.001)
- 1q gain was associated with inferior EFS in all stages: stage I (P=0.005), II (P=0.077), III (P=0.01) and IV (P=0.001)
- 1 q gain was associated with significantly inferior to OS in stage I (P<0.0015) and stage IV (P=0.011)
- Only 1q gain was significant on multivariate analysis
- 1q gain will be used to risk stratify patients in the next generation of COG protocols

25TH ANNIVERSARY CHILDREN'S ONCOLOGY GROUP 2000 - 2025

Gratias EJ et al., JCO 2016

New biomarker – LOH of 11p15

- 116 patients with very low risk WT enrolled on AREN0532 analyzed for 11p15
- Median follow-up, 80 months
- 1p and 16q loss, 1p gain, WT1 mutation status not associated with relapse

11p15 LOH	No relapse (%)	Relapse (%)	P
11p15 LOH = methylation changes due to chromosomal deletion and/or reduplication	32 (80%)	8 (20%)	0.011
11p15 loss of imprinting (LOI) = presence of methylation changes	6 (75%)	2 (25%)	
11p15 retention of imprinting (ROI) = absence of methylation changes	58 (97%)	2 (3%)	

- 11p15 can help select stage I FHWT patients who do not require adjuvant therapy

25TH ANNIVERSARY CHILDREN'S ONCOLOGY GROUP 2000 - 2025

Fernandez C et al., Ann Surg 2017

New biomarker – LN status and LOH 1p OR 16q

- 635 stage III FHWT DD-4A treated patients enrolled on AREN0532 or AREN03B2
- Patients without LN sampling (HR 2.12, P=0.0037), LN+ (HR 2.78, P=0.0002), LOH 1p (HR 2.18, P=0.0067), and LOH 16q (HR 1.72; P=0.042) had worse EFS.
- Patients with LN- and LOH 1p OR 16q (HR 3.05), and patients with LN+ without LOH 1p or 16q (HR 3.57) had worse EFS compared to LN- and LOH- patients.
- Patients with LN+ and LOH of 1p OR 16q had the worst EFS (HR 6.33, $P<0.0001$).
- 4-year EFS with LN+ and LOH of 1p OR 16q vs. LN- LOH-: 77% vs 91% (P=0.0016)
- 4-year OS with LN+ and LOH of 1p OR 16q vs. LN- LOH- (P=0.11)
- Findings confirm LN status as an adverse prognostic factor, in association with “isolated” LOH of 1p OR 16q.

25TH ANNIVERSARY CHILDREN'S ONCOLOGY GROUP 2000 - 2025

Evageliou N et al., Cancer 2024

Renal-sparing IMRT for Whole Liver Irradiation in Wilms tumor

(Kalapurakal JA, IJROBP 2013)

Anatomical relationship between Liver and right/left kidney: RT issues

- Right kidney >> left kidney situated very close to major portions of the liver
- *Renal blocking (14.4 Gy) underdoses liver tumor*
- Recent reports 75% survival for liver mets FH WT
- AP-PA technique: 6 WT protocols (NWTS and COG)
- 20 Gy prescribed dose: at the renal tolerance of the only remaining kidney

Liver (tumor) Dose

LEFT KIDNEY WILMS TUMOR (block on right side AP-PA >14 Gy)

- Liver (GTV) coverage: 99 ± 1% (L-IMRT) 86 ± 10% (AP-PA) ($P<0.01$)
- Liver (PTV) coverage: 97 ± 4% (L-IMRT) 83 ± 8% (AP-PA) ($P<0.01$)

RIGHT KIDNEY WILMS TUMOR (block on left side AP-PA>14 Gy)

- Liver (GTV) coverage: 100 ± 0% (L-IMRT) 96 ± 3% (APPA) ($P<0.01$)
- Liver (PTV) coverage: 99 ± 1% (L-IMRT) 94 ± 5% (AP-PA) ($P<0.01$)

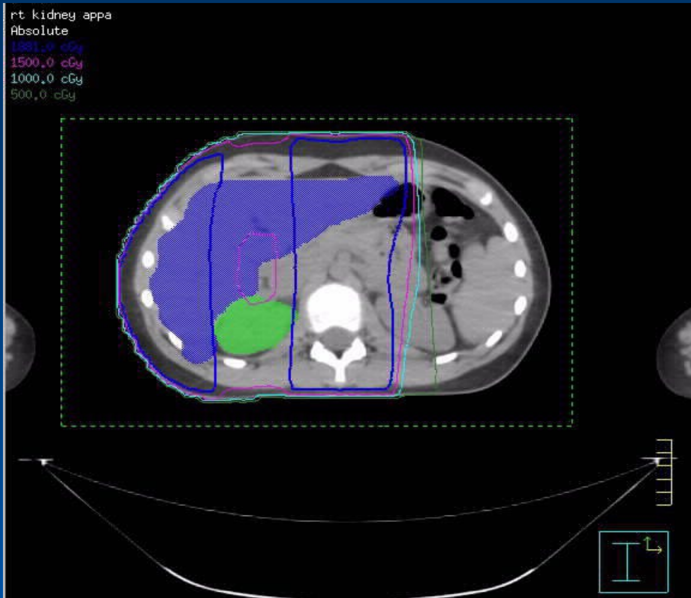
Remaining kidney Dose after Whole Liver RT *(in spite of kidney block at 14.4 Gy w/AP-PA, lower liver dose w/AP-PA)*

Right Kidney Dose *(left WT)*

- **V15Gy:** 29 ± 7% (IMRT) 61 ± 29% (AP PA) ($P<0.01$)
- **V10Gy:** 55 ± 8% (IMRT) 78 ± 25% (AP PA) ($P<0.01$)

Left Kidney Dose *(Right WT)*

- **V15Gy:** 0% (IMRT) 25 ± 19% (APPA) ($P<0.01$)
- **V10Gy:** 2 ± 3% (IMRT) 40 ± 31% (APPA) ($P<0.01$)


rt kidney appa
Absolute
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1000.0 cGy
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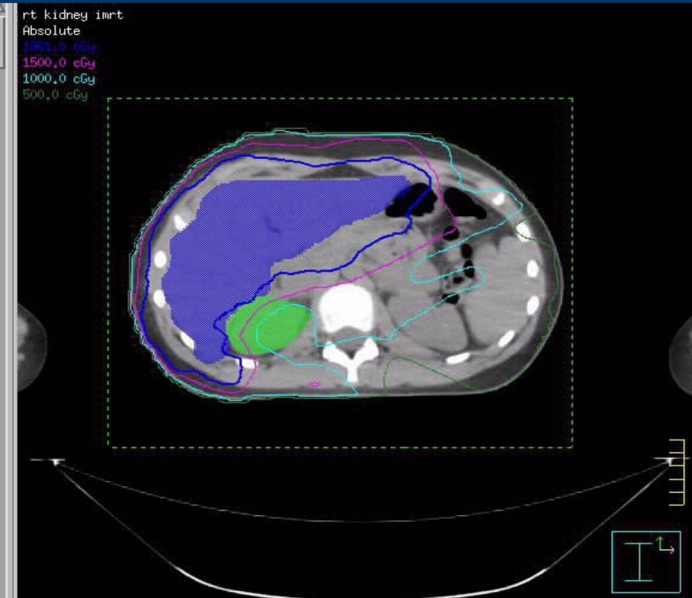
rt kidney imrt
Absolute
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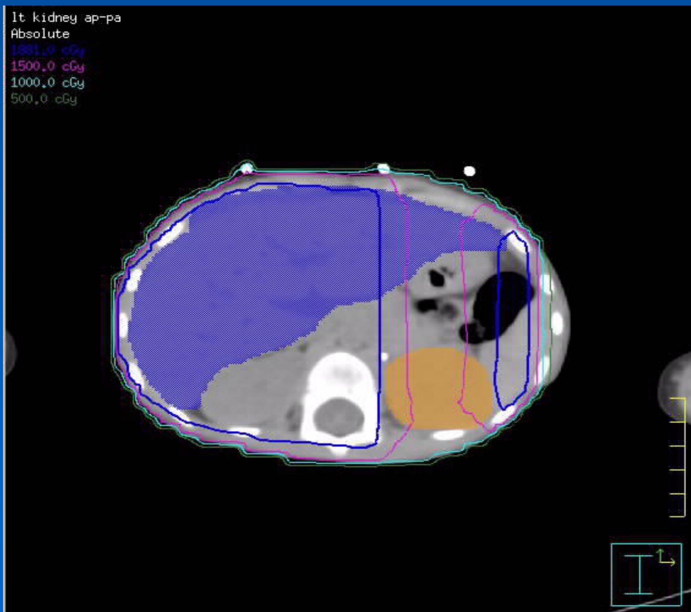
lt kidney ap-pa
Absolute
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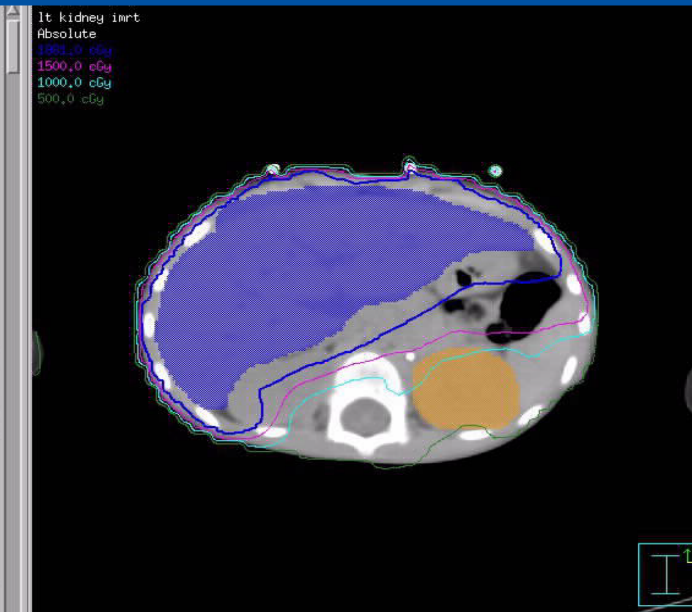
lt kidney imrt
Absolute
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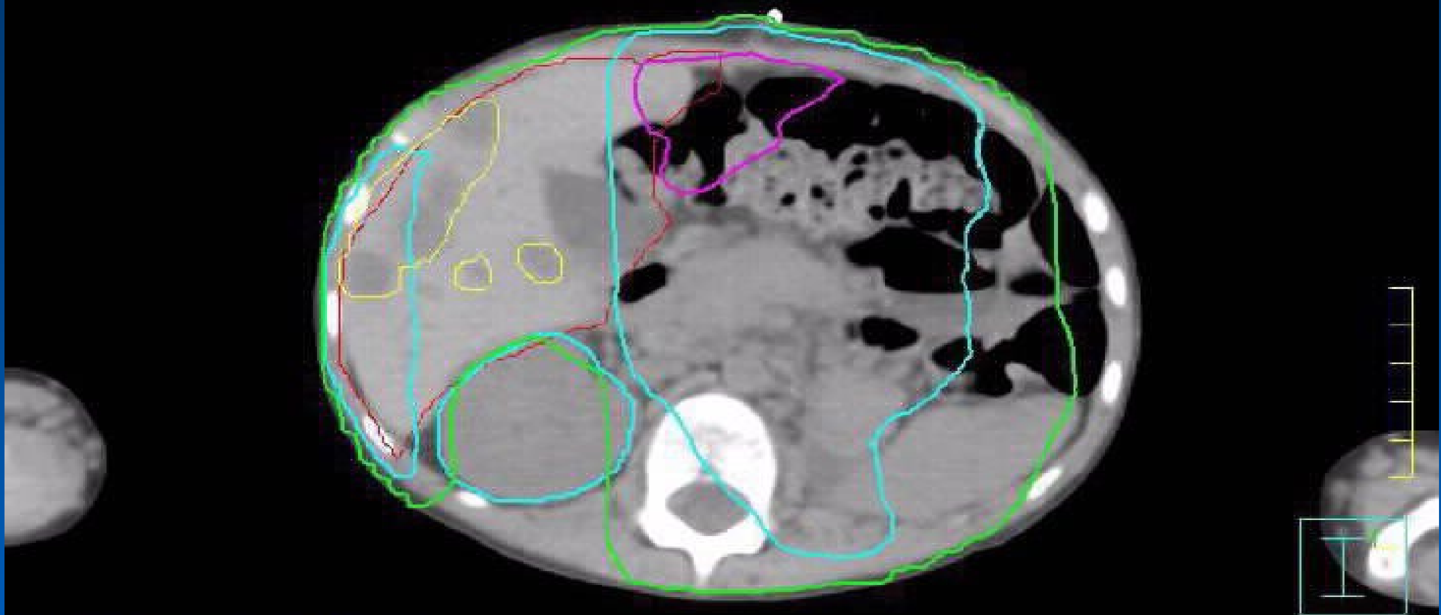
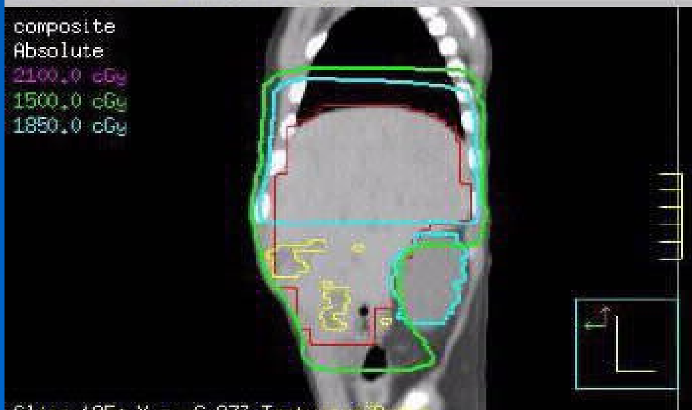
1000.0 cGy
500.0 cGy


composite
Absolute
2100.0 cGy
1500.0 cGy
1850.0 cGy
Slice 74: Z = -39.000 Tantuwaya^Rudra


composite
Absolute
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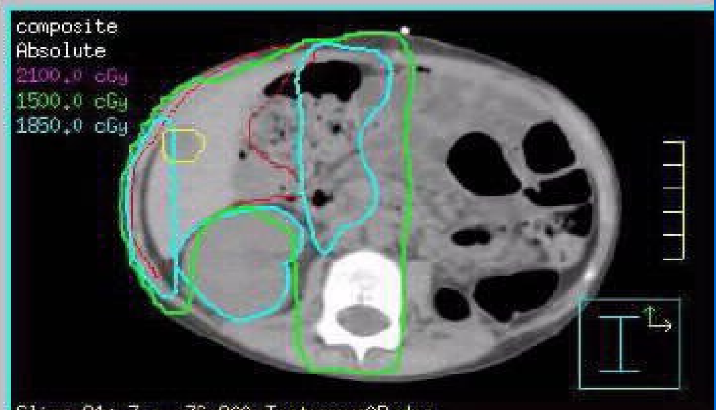
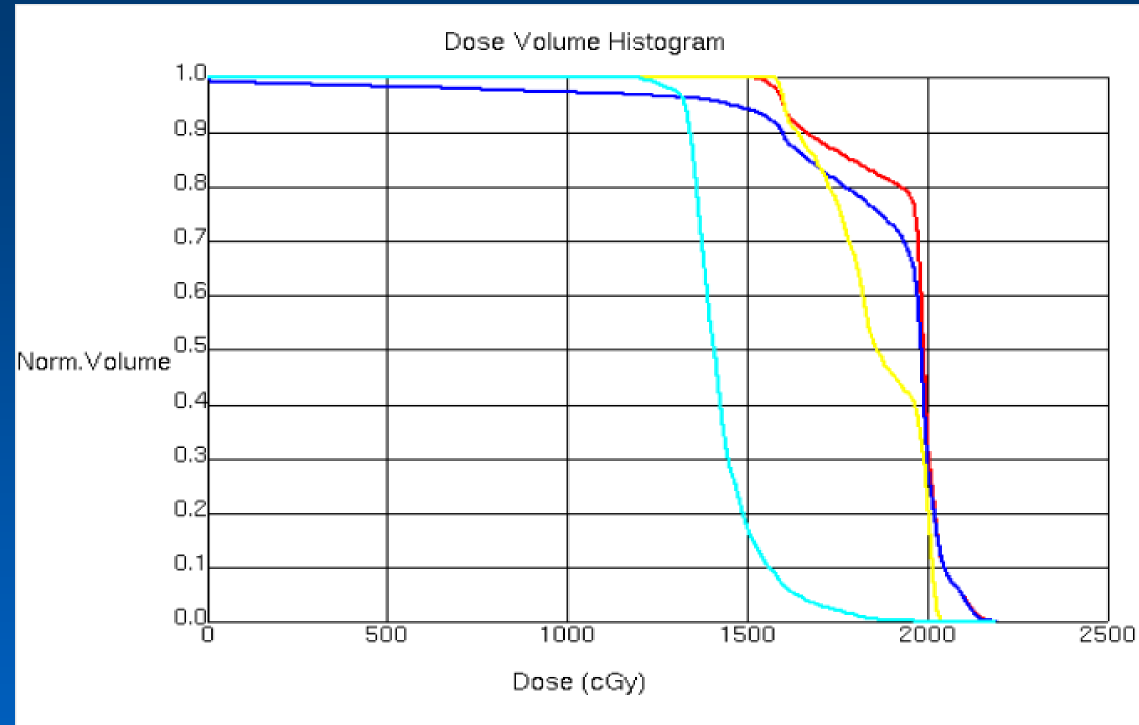
1500.0 cGy
1850.0 cGy


composite
Absolute
2100.0 cGy
1500.0 cGy
1850.0 cGy

DVH with AP-PA technique (COG)



ROI Statistics

Line Type	ROI	Trial	Min.	Max.	Mean	Std. Dev.
(red)	Liver	composite	919.7	2188.9	1943.3	140.3
(blue)	Liver PTV	composite	--	2188.9	1872.7	316.9
(yellow)	Liver mets multiple	composite	1544.1	2037.9	1859.2	139.9
(cyan)	Rt Kidney	composite	1168.1	1965.2	1429.2	101.7

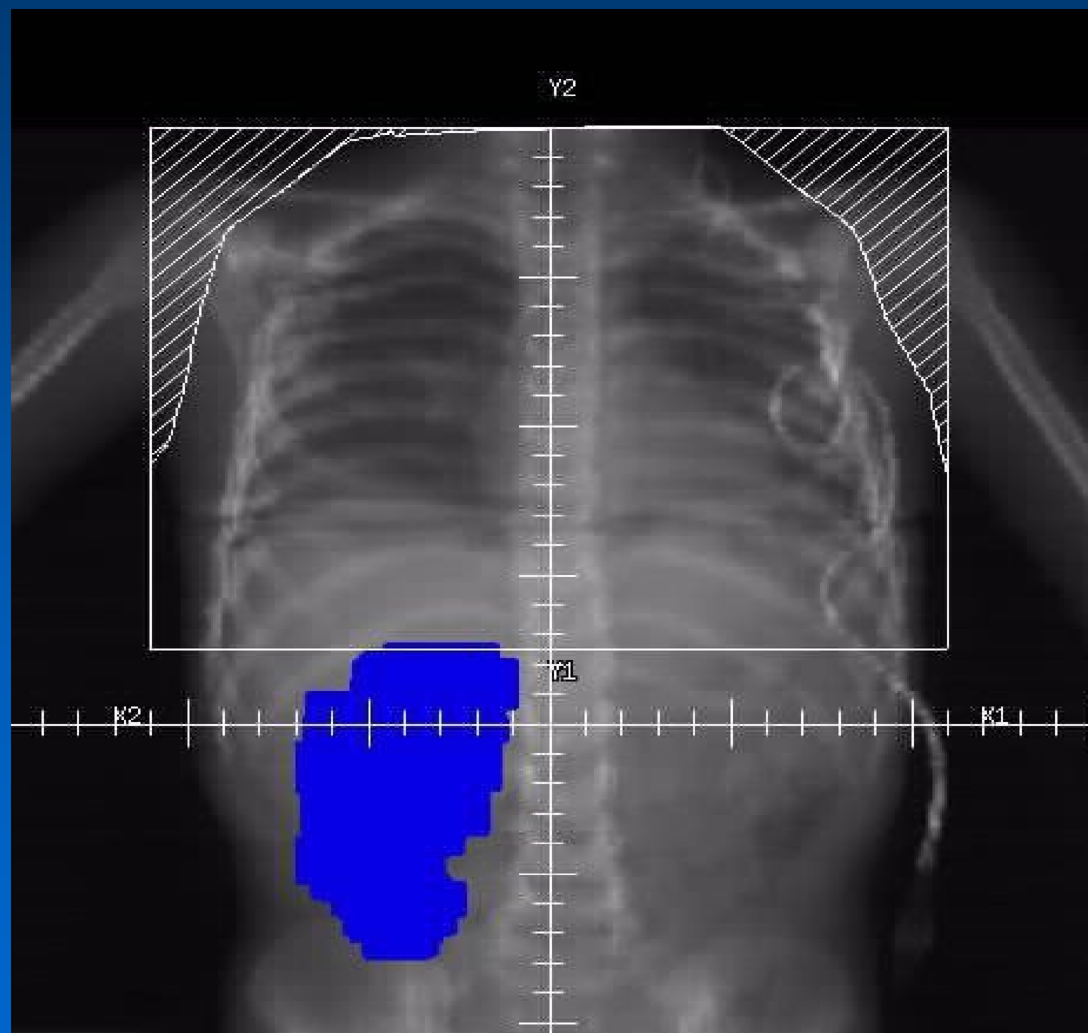
FINAL REPORT OF A PROSPECTIVE CLINICAL TRIAL OF CARDIAC SPARING WHOLE LUNG IMRT IN PATIENTS WITH METASTATIC PEDIATRIC TUMORS (Kalapurakal JA, IJROBP 2016)

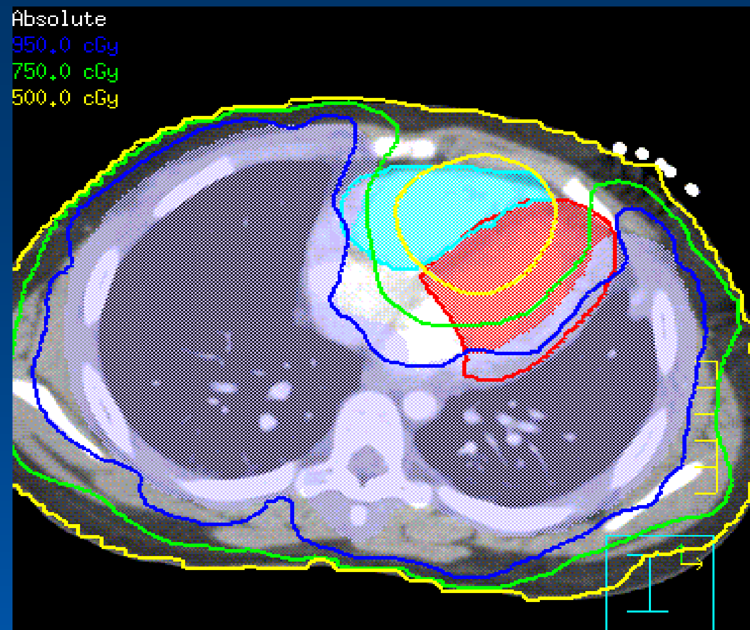
- AP-PA WLI shown to improve survival and is widely used for lung metastases from Wilms, Ewing Sarcoma and rhabdomyosarcoma
- Children's Oncology Group (COG) protocols 12-15 Gy
- Cardiac complications: NWTS 20 year CHF rate was 4.4% after initial treatment and17.4% after DOX for relapse (last event 24 years)
- CHF significantly higher in females RR 4.5; by DOX dose RR 3.3/100 mg/m^2; lung RT RR 1.6/10 Gy; left abdominal RT RR 1.8/10 Gy
- CCSS, Gustave Roussy, French-British study – cardiac mortality RR increased after mean dose > 5 Gy with anthracyclines >360 mg/m^2

Brief rationale for cardiac sparing WLI

- NWTSG: 20 yr CHF rate 4.4% after initial diagnosis and 17.4% after treatment for relapsed WT
- NWTS-1,2: 4.5%@20 years (last event 24.3 years), NWTS-3,4: 1.2%@11 (last event 15.6 years)
- CCSS: cardiac RT ≥ 15 Gy increased CHF and MI risk by 2-6 times
- Institut Gustave Roussy: 20 yr CHF rate 18% after >*3.7 Gy* to heart and 9% for lower doses
- French-British cancer survivors study: RR cardiac deaths was 12.5 after *5 -14.9 Gy* and 25.1 for > *15 Gy*
- Along with SMN, CV disease-leading cause of morbidity and mortality >20 years cancer survivors

NWTS 1-5 and COG Trials

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750.0 cGy
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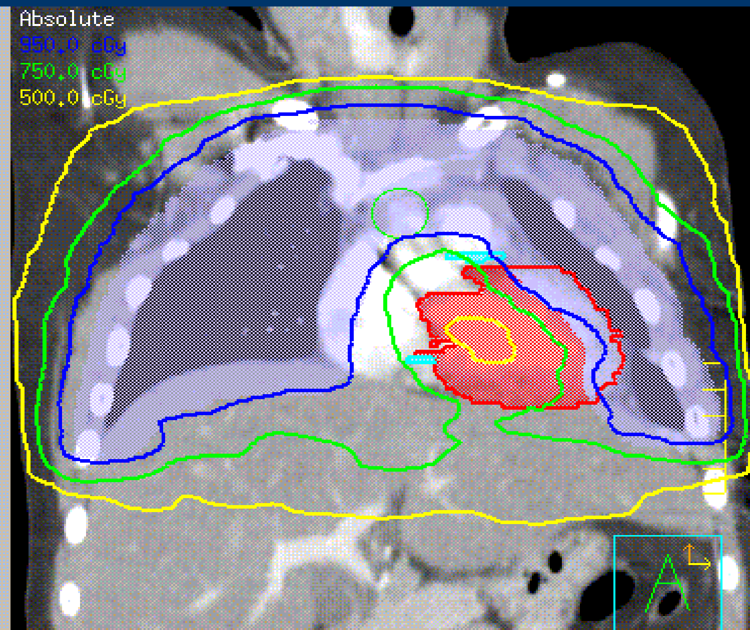
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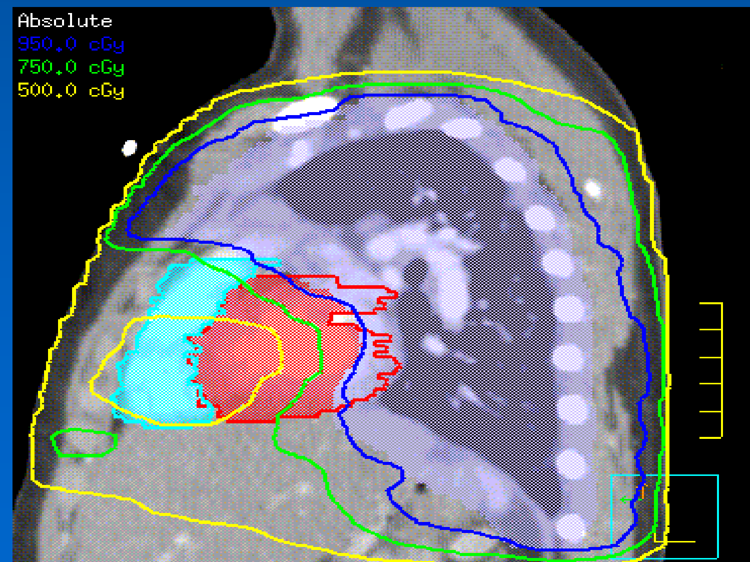
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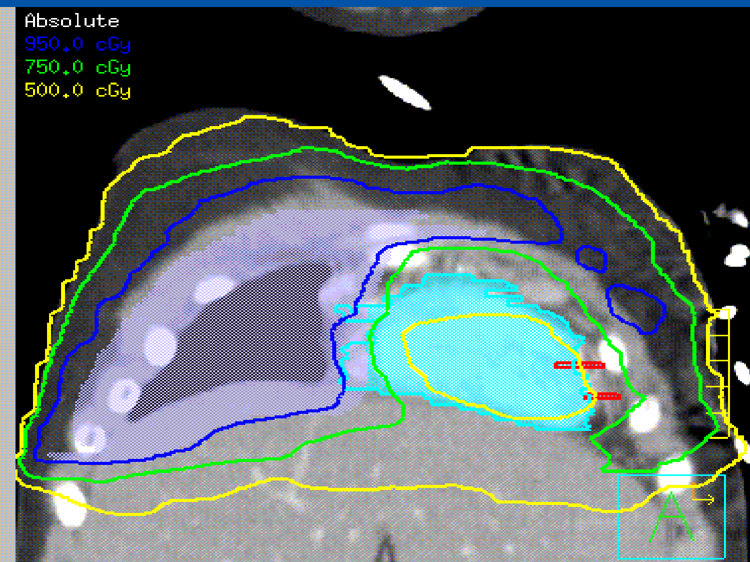
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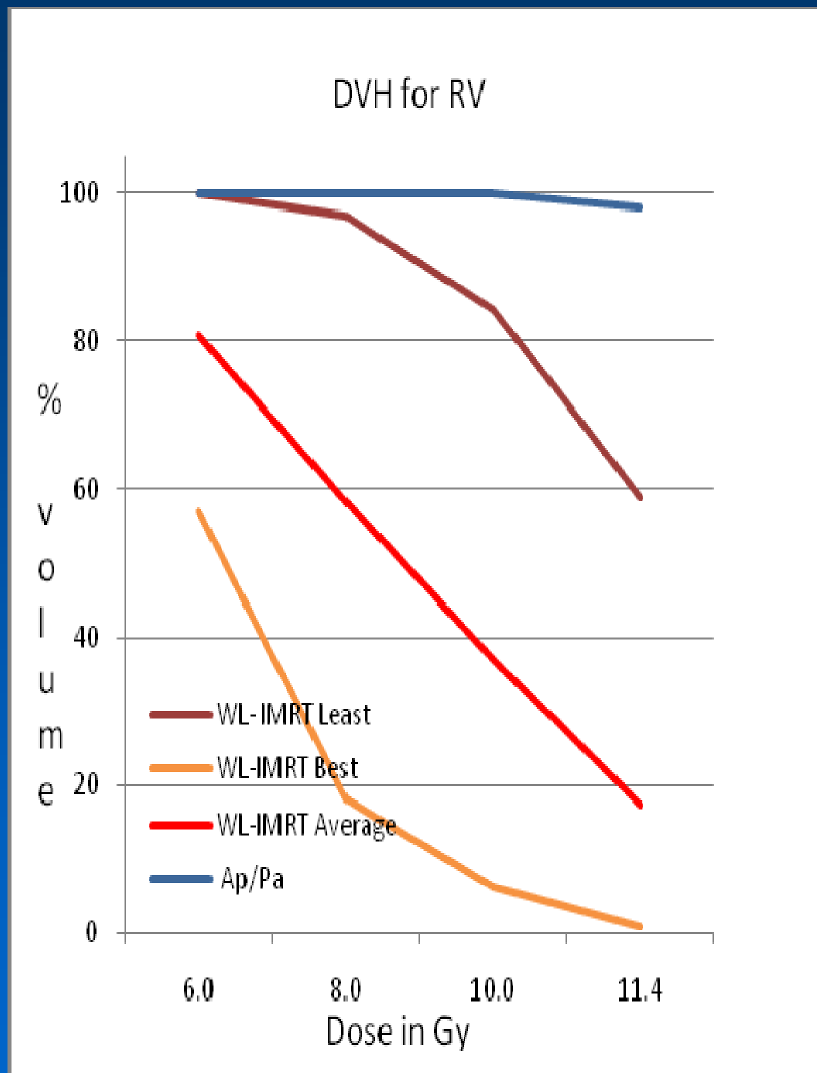
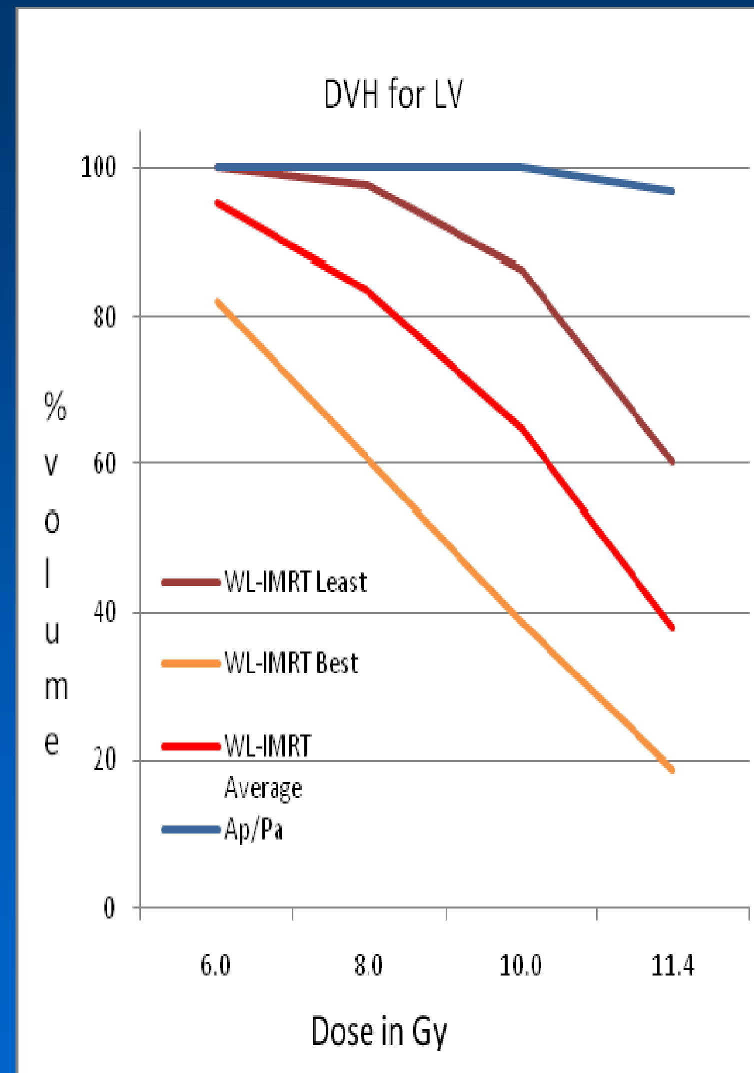

DVH for RV
100
80
60
40
20
0
% volume
WL-IMRT Least
WL-IMRT Best
WL-IMRT Average
Ap/Pa
6.0
8.0
10.0
11.4
Dose in Gy


DVH for LV
100
80
60
40
20
0
% volume
WL-IMRT Least
WL-IMRT Best
WL-IMRT Average
Ap/Pa
6.0
8.0
10.0
11.4
Dose in Gy

Purpose

- 1. To demonstrate feasibility of delivering cardiac-sparing WL-IMRT in a multi-institutional setting, with central quality control (QARC), for children and young adults with lung metastasis

- 2. To prospectively determine dosimetric advantages of WL-IMRT over AP-WLI by comparing organ (cardiac structures, lungs, liver, thyroid) dose-volume histograms in enrolled patients

- 3. ***To present the final report after the stipulated 2 year minimum follow-up of all accrued patients***

Methods and Materials

- All centers completed protocol-specific IMRT credentialing requirements (phantom irradiation and analysis IROC Houston)
- Treatment protocol was approved by all IRBs
- SIMULATION: 3D and CE- 4D gated chest CT scan using a standard gating device
- CTV was the 4D MinIP of both lungs (1 cm PTV)
- All target volumes, cardiac contours and plans *were centrally reviewed before treatment (QARC, PI, Radiology, Physics)*

Methods and Materials

- Cardiac Anatomy Definitions (contouring guidelines and planning atlas) and Heart dose-volume constraints for IMRT planning (Northwestern data www.qarc.org)

- Tissue heterogeneity: Heterogeneity corrections applied for all cases

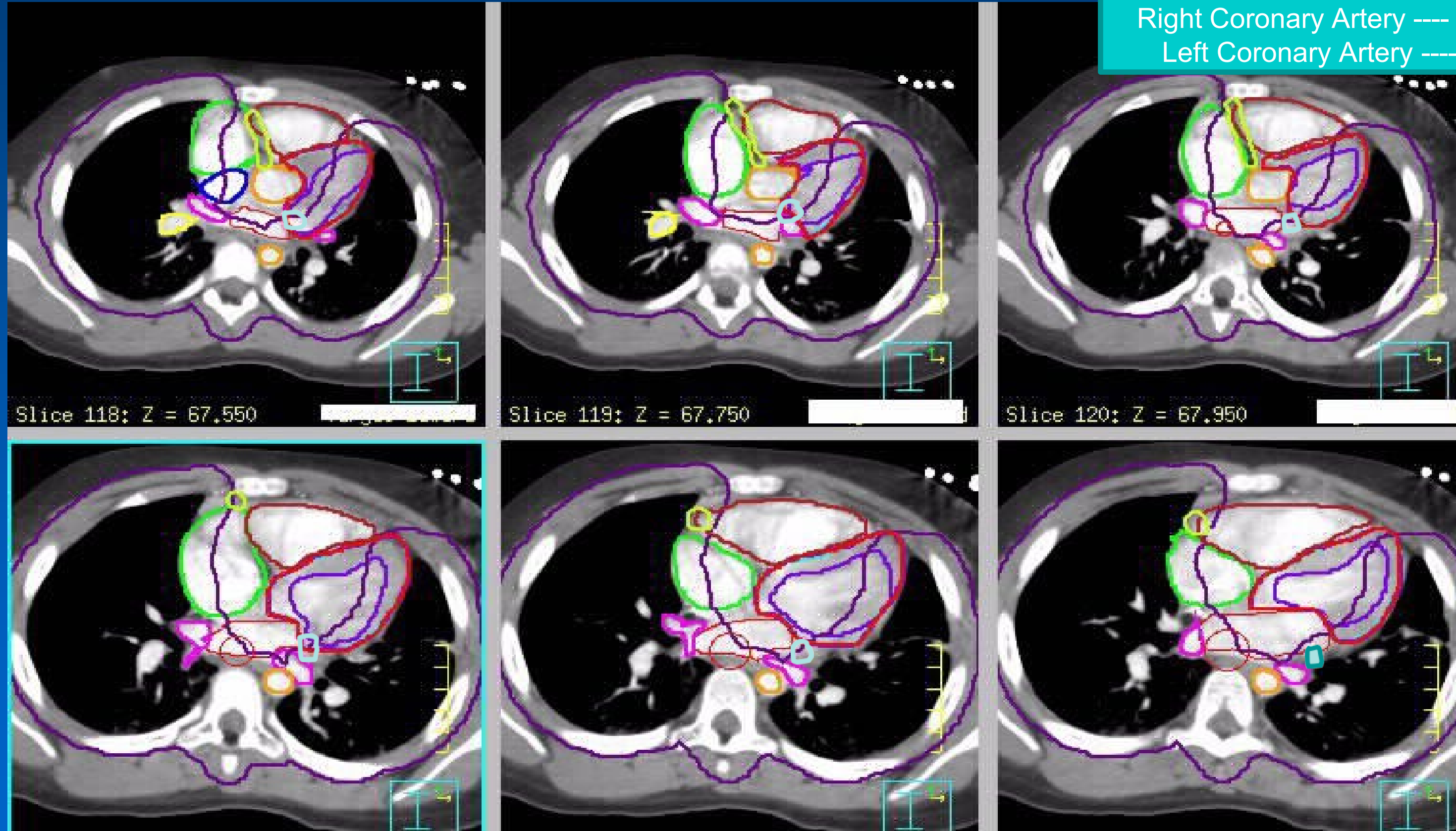
- Dose uniformity: 95% PTV should receive at least 95% of prescribed dose; ≥2% of the PTV >105%, ≥1% >110% of the prescribed dose

- Dosimetry comparison between AP-PA vs. CS-IMRT, various organ cardiac volumes (V) receiving % RT dose was estimated and compared

- All patients were followed at a minimum of 6m x 4 with a H&P, CBC, Liver enzymes, CT chest, EKG and Echocardiogram

WL-IMRT Contours

Aorta----Orange
Superior Vena Cava-----Blue
Pulmonary Artery-----Yellow
Pulmonary Vein----- Purple
Right Atrium----- Green
Left Atrium ---- Thin Red
Right Ventricle ----- Brown
Left Ventricle ---- Thick red
LV Myocardium border ---- Stale blue
Right Coronary Artery ---- Yellow green
Left Coronary Artery ---- Aqua blue



Statistics

- Feasibility was defined as an enrolled patient receiving the IMRT treatment as planned
- It was expected that the treatment will be feasible in at least 90% of patients
- If the treatment was feasible in 16 or more out of 20 patients, then the treatment would be declared feasible
- Statistical analysis for tumor and normal tissue volume dose comparisons between techniques and tumor control rates and survival

Patient characteristics

- Target 20 patients were accrued in >2 years from 5 centers
- Non-COG patients, Median age 10 years (1-25 years), 11 males
- Ewing Sarcoma 11, Rhabdomyosarcoma 2, other sarcoma 1, Wilms 5, Hepatoblastoma 1
- 15/20 received RT to primary site
- CS-IMRT was part of primary therapy in 15 vs. relapse/progressive disease therapy in 5 patients
- At time of CSIMRT, 18/20 patients' lung tumors were in remission or stable and 2 had progressive disease

Real time multidisciplinary pre-treatment central review and intervention (24-48 hrs)

- Target contour changes in 7 (35%) patients
- Re-planning in 3 (15%) patients
- Minor deviations in 2 (10%) patients
- ***No major deviations***

Aim # 1

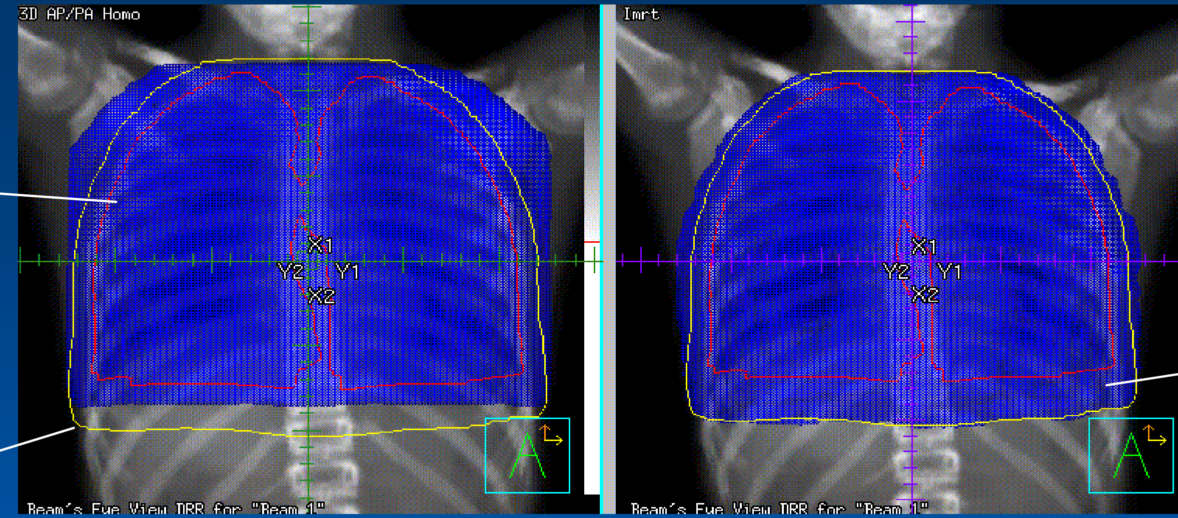
- CS-IMRT WLI technique was feasible in all 20 patients
- Median RT dose was 15 Gy using a median of 9 field angles
- Dose: 15Gy (15 patients); 12 Gy (5 patients)
- Prescription isodose: median 100% (98% - 100%)

Aim # 2 Dosimetry comparison between CS-IMRT and AP-WLI

Lung target volume coverage during WL-IMRT vs. AP-WLI

- 4D lung volumes (WL-IMRT) were significantly larger than 3D volumes (AP-WLI) (P<0.0001)

- The use of AP-WLI technique would have significantly under dosed 4D lung volumes (P=0.008)



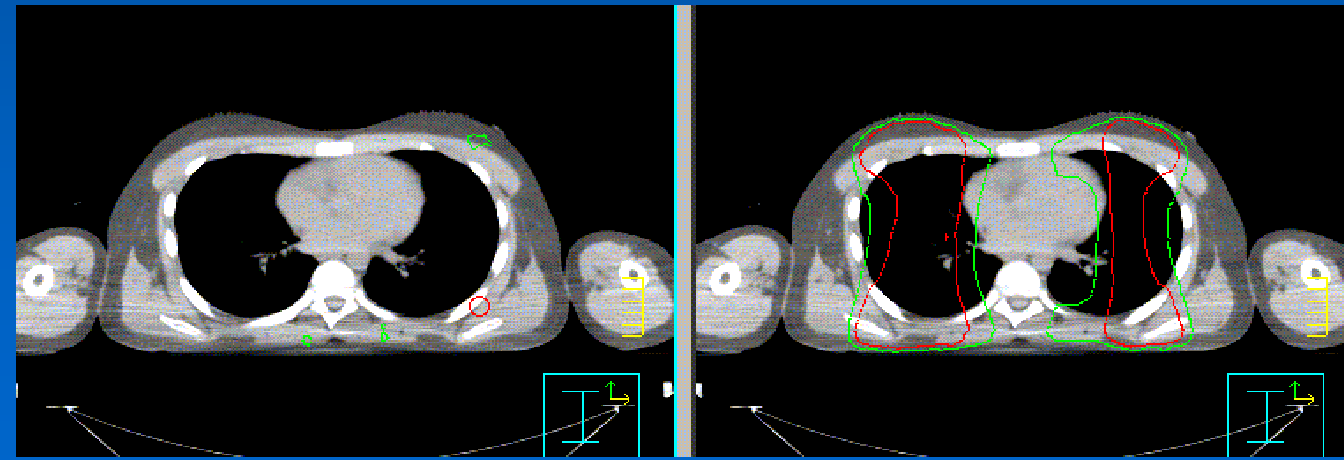
3D lung volume

4D PTV

95% IDL

3D AP-PA

WL-IMRT



WL-IMRT hot spots

3D AP-PA hot spots

Mean whole heart volume dose

Volume/%Dose Gy	Standard WLI	IMRT	P-value
V95 (14.3 Gy)	97%	39%	<0.0001
V83 (12.5 Gy)	99.2%	65%	<0.0001
V67 (10 Gy)	99.5%	85%	<0.0001
V50 (7.5 Gy)	99.7%	96%	0.0083

Mean left ventricle volume dose

Volume/%Dose Gy	Standard WLI	IMRT	P-value
V95 (14.3 Gy)	98.7%	33%	<0.0001
V83 (12.5 Gy)	99.8%	61%	<0.0001
V67 (10 Gy)	99.95%	82%	<0.0001
V50 (7.5 Gy)	100%	95%	0.006

Mean right ventricle volume dose

Volume/%Dose Gy	Standard WLI	IMRT	P-value
V95 (14.3 Gy)	97.2%	18%	<0.0001
V83 (12.5 Gy)	98.8%	42%	<0.0001
V67 (10 Gy)	99.2%	69%	<0.0001
V50 (7.5 Gy)	99.45%	91%	0.002

Mean Myocardium volume dose

Volume/%Dose Gy	Standard WLI	IMRT	P-value
V95 (14.3 Gy)	98.7%	32%	<0.0001
V83 (12.5 Gy)	99.8%	59%	<0.0001
V67 (10 Gy)	99.5%	80%	<0.0001
V50 (7.5 Gy)	100%	94%	0.005

Mean left coronary artery volume dose

Volume/%Dose Gy	Standard WLI	IMRT	P-value
V95 (14.3 Gy)	100%	66%	<0.0001
V83 (12.5 Gy)	100%	92%	0.0008
V67 (10 Gy)	100%	98%	0.051
V50 (7.5 Gy)	100%	99.8%	0.33

Mean right coronary artery volume dose

Volume/%Dose Gy	Standard WLI	IMRT	P-value
V95 (14.3 Gy)	96%	53%	<0.0001
V83 (12.5 Gy)	99.3%	88%	<0.0001
V67 (10 Gy)	99.7%	97.7%	0.025
V50 (7.5 Gy)	100%	100%	---

Clinical Outcomes

- CSIMRT was well tolerated, all patients had reversible chemotherapy and CSIMRT related reversible drop in blood counts
- No patient had RT pneumonitis or pulmonary symptoms despite use of chemotherapy in all patients, and pulmonary toxic/radiosensitizing therapy in relapsed patients (gemcitabine and lung reirradiation)
- Post CSIMRT CT scans revealed no evidence of lung consolidation or fibrosis
- Follow up ECHO,EKG did not reveal any new RT-related cardiac toxicity
- The 2 and 3 year overall survival was 90% and 90%
- The 2 and 3 year lung-metastasis progression-free survival was 65% and 52%

Conclusions

- This trial has demonstrated the feasibility of CS-IMRT in children and young adults with lung metastases
- We have confirmed the reported advantages of CS-IMRT : superior cardiac protection and superior dose coverage of 4D lung volumes
- Large field CS-IMRT and chemotherapy was well tolerated with no pulmonary toxicity at 2 years
- Tumor control rates and survival are comparable to other reported outcomes
- CS-IMRT targeting 4D lung volumes will be utilized in future COG and perhaps SIOP trials (QA monitoring IROC Providence RI)

Standard versus Modified WLI IMRT

- The cardiac-sparing WLI IMRT can be modified to reduce RT exposure to the thyroid gland and breast tissues by reducing the PTV around these OARs.
- 4D-CT sim with neck rest/aquaplast mask, Vac-Lok, 2-3 mm slices
- ITV = maximum lung expansion volume on minIP
- PTV = ITV + 10mm except superiorly (5 mm to facilitate thyroid sparing) – thyroid gland and breast tissues PRV (+ 3 mm) [edited to maintain ≥5 mm around lung ITV adjacent to thyroid and ≥3-5 mm adjacent to breast)
- Dosimetric study of 10 patients: modified versus standard WLI IMRT provides similar lung PTV dose coverage, superior reduction of thyroid (P=0.005) and breast (P=0.0002) doses without compromising cardiac protection. Benefits seen when modified WLI treated with flank and WAI RT.

Kalapurakal et al., Pract Radiat Oncol 2019

Kidney-sparing WAI using VMAT

- 7 patients treated with VMAT WAI with liver sparing (constrained to 14 Gy)
- VMAT planned using 1-3 arcs up to 340° (no 4D-CRT or IGRT used)
- Median follow-up, 40.8 months
- Median CrCl before RT and at last follow-up: 110.1 vs. 103.3mL/min/1.73m^2 (P=0.13).
- Compared to replanned 3D-CRT, VMAT-LS plans had lower median uninvolved kidney dose (7.7 vs. 11.3 Gy, P=0.018), similar median heart dose (7.4 Gy vs 7.1 Gy, P=0.87), lower median liver dose (14.4 Gy vs. 14.8 Gy, P=0.028), better median D95 for PTV (14.9 Gy vs. 12.0 Gy, P=0.018).

Chen MJ et al., Pediatr Blood Cancer 2020

The Next Generation of COG Renal Tumor Protocols

The Next Generation of COG Renal Tumor Protocols

- AREN1721 (Axitinib/Nivolumab vs. single agent Nivolumab for TFE/Translocation renal cell carcinoma), treatment completed
- AREN1921 (DAWT, Relapsed FHWT), active
- AREN2231 (Unilateral FHWT), active

AREN1921: Treatment of DAWT and Relapsed FHWT

- First COG WT study to allow cardiac-sparing IMRT for WLI, IMRT for liver RT
  - Exploratory Aim 1.3.6: To determine the feasibility of IMRT with central RTQA monitoring to reduce radiation induced toxicity to the heart, thyroid, breast and solitary kidney for children with lung and liver metastases.
  - A contouring and planning atlas is provided on the IROC-RI website (https://www.qarc.org/)
- First COG WT study to allow proton therapy for flank RT, WAI, and liver (NOT WLI)
- Mandatory central RTQA by IROC

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AREN1921 Timing of RT

When indicated, radiation therapy shall begin on Week 7 for patients receiving Regimen UH-3 for Stage 2-4 diffuse anaplastic Wilms tumor (DAWT) and standard-risk relapsed favorable histology Wilms tumor (SRrFHWT). All sites that require irradiation will be treated concurrently.

The timing of radiation therapy at Week 7 for Regimen UH-3 was designed to coincide with a point in the chemotherapy backbone to minimize toxicity resulting from radiation interactions with doxorubicin and carboplatin. It is **strongly recommended** that the primary tumor resection be completed upfront (when possible) or by Week 7 at the latest, prior to radiation therapy. In exceptional cases when resection by Week 7 is not feasible, radiation therapy should proceed prior to surgery. Please refer to Section 4.1 for additional details regarding the treatment plan. The feasibility and safety of pre-operative radiation therapy and chemotherapy for Wilms tumor has been demonstrated by a prospective clinical trial conducted by SIOP.[85] Note: For patients on study with relapsed FHWT, timing of local control (surgery and radiation) for sites of relapse may require timing adjustments best suited for individual patient's needs determined by the primary treating team.

AREN1921 RT Contouring Guidelines

- 4D CT sim is encouraged, Vac-Lok for immobilization, with 2-3 mm thick slices from mandible to iliac crest or mid pelvis (or upper thighs for WAI)
  - Arms up (may use wing board), neck rest with chin up (may use aquaplast mask)
  - Place marker on breasts to identify breast buds in young children
  - Before CBCT, kV images can help ascertain patient positioning to avoid large shifts after CBCT fusion
  - Contrast enhanced CT scans (or co-registration to diagnostic contrast enhanced CT scans) facilitate contouring of the atria and ventricles
  - For simulation and treatment, an empty stomach is recommended to avoid abdominal distension and nausea after treatment
- Daily cone-beam CT with 6-degree correction during treatment delivery

WLI IMRT on AREN1921 (see COG Contouring Atlas)

- Contour left and right lungs
- Co-register MinIP sim lung scan to the planning scan
- Expand left and right lung volumes to maximum lung expansion on MinIP scan (do not reduce if MinIP volumes are smaller) = left and right lung CTVs
- Combine the left and right lung CTVs = CTV_Lung, PTV_Lung = CTV_Lung + 1 cm
- Modify the PTV_Lung around:
  - (a) breast buds in girls and thyroid with 5 mm expansion instead of 1 cm,
  - (b) sternum and mediastinum to include lymph nodes up to 2 cm below carina,
  - (c) include vertebral body except in older children and adults, and
  - (d) prevertebral space: at least 1 cm margin anterior to vertebra from 2 cm below carina superiorly to inferior extent of the volume
- For the heart volume, merge 4 cardiac chambers and fill in gaps to smooth contour

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Combined WLI+WAI IMRT on AREN1921

- Contour whole abdominal cavity from domes of the diaphragm to the mid-obturator foramen = CTV (do not include full chest/abdomen thickness to omit breast buds)
- Field matching volume (FMV) = superior portion of CTV from diaphragm superiorly to about 1 cm below the last cardiac contour
- Add FMV to combined lung PTV to create final planning PTV_Lung+WAI
- WAI treated with AP/PA (photons) at the bottom of the PTV_Lung+WAI with a half-beam block (10.5 Gy in 7 fractions)
- The final 1.5 Gy fraction is delivered only to the PTV_Lung for a total of 12 Gy in 8 fractions to the PTV_Lung

Combined WLI+Flank IMRT on AREN1921

- Contour preop kidney GTV based on co-registered preop diagnostic CT or MRI scan, and modify to account for anatomic changes (diaphragm, abdominal wall)
- CTV_Kidney = GTV_Kidney + 5 mm
- Contour PA LN from T10 to L5 = CTV_PA Nodes
- CTV_Flank = CTV_Kidney + CTV_PA Nodes, PTV_Flank = CTV_Flank + 5 mm +
  - include corresponding vertebral bodies, and
  - trim PTV_Flank crossing over lateral vertebral body to avoid or minimize overlap with contralateral uninvolved kidney.
- If the superior border of PTV_Flank is inferior to the lower border of the PTV_Lung (with a gap), half-beam blocked AP/PA fields can treat the flank without an FMV.

Combined WLI+Flank IMRT on AREN1921 (continued)

- If the PTV_Flank extends up to or superior to the lower border of the PTV_Lung, a FMV is required to spare the heart and breast buds.
  - The FMV is a rectangular contour from the anterior to posterior abdominal wall, from the ipsilateral abdominal wall to the lateral margin of the vertebrae, and from 0.8-1.0 cm below the last cardiac contour superiorly for a total length of ~1 cm inferiorly. Do not include the entire thickness of the abdominal wall.
  - If the FMV covers the superior edge of PTV_Flank, merge the FMV with the PTV_Lung to create the final planning PTV_Lung+Flank.
  - If the PTV_Flank extends superior to the FMV, add that superior portion of the PTV_Flank to the FMV to create the final planning PTV_Lung+Flank.
- Flank treated with AP/PA (photons) at the bottom of the PTV_Lung+WAI with a half-beam (10.5 Gy in 7 fractions)
- The final 1.5 Gy fraction is delivered only to the PTV_Lung for a total of 12 Gy in 8 fractions to the PTV_Lung

AREN2231: Risk Adapted Treatment of Unilateral FHWT

Stage	Age (years)	LOH	LN positivity	Lung nodule response	Extrapulmonary mets	Post-chemo histology	Other	Stratum (lower to higher relapse risk)
I	Any	Normal	N/A	N/A	N/A	N/A	Epithelial histology and no predisposing condition	Surgery only
I	<4	Normal	N/A	N/A	N/A	N/A	No predisposing condition	Surgery only
I	Any	Combined LOH, 1q gain or 11p15 LOH	N/A	N/A	N/A	N/A	N/A	EE-4A
I	>4	Any	N/A	N/A	N/A	N/A	N/A	EE-4A
II	Any	Normal	N/A	N/A	N/A	N/A	N/A	EE-4A
II	Any	Isolated LOH	N/A	N/A	N/A	N/A	N/A	EE-4A
III	Any	Normal	N/A	N/A	N/A	N/A or LR or IR	N/A	EE-4A ± RT
III	Any	Isolated LOH	N/A	N/A	N/A	N/A or LR or IR	N/A	EE-4A ± RT
II	Any	Combined LOH or 1q gain	N/A	N/A	N/A	N/A	N/A	DD-4A vs. VIVA

AREN2231: Risk Adapted Treatment of Unilateral FHWT

Stage	Age (years)	LOH	LN positivity	Lung nodule response	Extrapulmonary mets	Post-chemo histology	Other	Stratum (lower to higher relapse risk)
IV	Any	Normal	Any	RCR	No	NA or LR or IR	NA	DD-4A ± RT
IV	Any	Isolated LOH	No	RCR	No	NA or LR or IR	NA	DD-4A ± RT
III	Any	Combined LOH or 1q gain	Any	N/A	N/A	NA or LR or IR	NA	Regimen M vs. MVI + RT
III	Any	Isolated LOH	Yes	N/A	N/A	NA or LR or IR	NA	Regimen M vs. MVI + RT
IV	Any	Combined LOH or 1q gain	Any	Any	No	NA or LR or IR	NA	Regimen M vs. MVI + RT
IV	Any	Isolated LOH	Yes	Any	No	NA or LR or IR	NA	Regimen M vs. MVI + RT
IV	Any	Any	Any	SIR	No	NA or LR or IR	NA	Regimen M vs. MVI + RT
IV	Any	Any	Any	Any	Yes	NA or LR or IR	NA	Regimen M vs. MVI + RT
III	Any	Any	Any	N/A	N/A	High risk	NA	Regimen UH-3 + RT
IV	Any	Any	Any	Any	Any	High risk	NA	Regimen UH-3 + RT
Benedetti DJ et al., Nat Rev Urol 2025								

AREN2231 RT Guidelines

- Flank RT/WAI, if needed, for stage IV patients after lung response assessment at week 6 to avoid overlapping RT fields (reduce lung, heart, liver dose)
  - Exploratory Aim 1.3.14: To determine the flank and abdominal tumor control rates in children with Stage IV FHWT who received abdominal RT after 2 cycles of chemotherapy in this study (delayed abdominal RT) and compare it to AREN0533 study where abdominal RT was performed within 2 weeks of nephrectomy (upfront abdominal RT).
  - Exploratory Aim 1.3.15: To compare abdominal relapse according to protocol-recommended RT fields (flank vs. whole abdominal) in the current study and compare it to the abdominal relapse according to RT fields in the AREN0532 and AREN0533 studies.
- Patients with no combined LOH of 1p and 16q, no 1q gain and if LN+ no LOH 1q OR 16q and RCR after 2 cycles of initial chemotherapy with no EPM can avoid WLI
  - In AREN0533, stage IV (lung mets) patients with combined LOH of 1p and 16q were not eligible for omission of WLI. In AREN2231, patients with 1q gain or, if LN+, isolated LOH of 1q OR 16q will also receive WLI.

Timing of Abdominal XRT in Stage IV FH Wilms (AREN2231)

- For patients with local Stage III tumors who may need lung XRT, radiotherapy to abdomen is delayed until 2 cycles of DD4A chemotherapy to assess lung response to chemotherapy. This will avoid overlap between the abdominal and whole lung fields which was seen in AREN0533 protocol when abdominal XRT was delivered within 14 days of nephrectomy.

AREN2231 RT Guidelines

- Proton therapy allowed for flank RT, WAI, and liver RT (NOT WLI) with central RTQA and pre-approval:
  - Exploratory Aim 1.3.12: To determine the feasibility of employing IMRT and proton therapy with central RTQA monitoring within the prescribed time frame.
  - Exploratory Aim 1.3.13: To determine the lung and liver tumor control rates using IMRT and/or proton therapy versus standard 3-D CRT in the current and the AREN0533 studies.

Late Effects Among Wilms Tumor Survivors

Congestive Heart Failure

- Survivors of NWTS 1-4 trials were assessed for CHF
- Cumulative incidence of CHF – 4.4% at 20 years (doxorubicin at diagnosis), 17.4% at 20 years (doxorubicin at relapse)
- Higher Relative Risk (RR): females 4.5 ($P=0.04$), doxorubicin dose
- 3.3/100mg/m^2 ($P<0.001$), lung RT 1.6/10 Gy ($P=0.037$), left flank RT 1.8/10 Gy ($P=0.013$)
- New cases continue to be reported 19.9 years after diagnosis
- Long-term monitoring is required for high-risk survivors

Green DM et al., JCO 2001

Pulmonary Disease

- 6449 Wilms tumor survivors from NWTS 1-4 were evaluated
- 64 fully evaluable and 16 partially evaluable cases of pulmonary disease were identified
- Cumulative incidence of pulmonary disease at 15 years since Wilms tumor diagnosis was <0.5% after no RT/abdomen RT
- Cumulative incidence of pulmonary disease at 15 years since Wilms tumor diagnosis was around 5% after lung RT
- Rates of pulmonary disease were higher among those who received lung RT compared to no lung RT or those who received abdomen RT (HR 30.2) (P<0.001)
- Long-term survivors should be monitored for lung functions and advised to avoid smoking

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Green DM et al., Pediatr Blood Cancer 2013

Pregnancy Outcomes

- Survivors of NWTS 1-4 were evaluated for pregnancy outcomes
- 1021 pregnancies of ≥20 weeks gestation were reported
- Flank RT dose response was noted for following:
  - Pregnancy induced hypertension (P<0.001)
  - Early/threatened labor (P=0.002)
  - Fetal malposition (P=0.04)
  - Premature birth: infants <37 weeks gestation (10% no flank RT, 22% with >35 Gy) (P=0.001)
  - Low birth weight: infants <2500g (9% no flank RT, 16% with >35 Gy) (P=0.01)
- 1/3 women after WART had premature delivery and low birth weight infants <2500g birth weight
- Obstetric management of female Wilms tumor survivors should consider these risks

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Green DM et al., JCO 2010

Second Malignant Tumors

- Combined cohort of 8884 (North America), 2893 (British), 1574 (Nordic) diagnosed before 15 years of age during 1960-2004
- After 169,641 person-years of observation, 174 solid tumors and 28 leukemias in 195 subjects
- Leukemia incidence was higher within 5 years of diagnosis while solid tumor incidence peaked at 10-19 years
- Standardized Incidence Ratio (SIR) for solid tumors and leukemia were 5.1 and 5.0
- Cumulative incidence of solid tumor SMN at age 40 years was 6.7%
- Incidence of SMN was higher if age at diagnosis was >5 years (P=0.03)
- Age-specific mortality increased 15-fold after solid tumor SMNs
- Incidence of solid tumors was lower for those diagnosed after 1980s, while leukemias were higher for those diagnosed after 1990 (P=0.003)

Breslow NE et al., Int J Cancer 2010

Breast Cancer

- 2492 female survivors of NWTS 1-4 (1969-95) were followed for *invasive* breast cancer from age 15 through 2013
- Cumulative risk at age 40 after whole lung RT: 16/369 (14.8%)
- Cumulative risk at age 40 after abdomen RT: 10/894 (3%)
- Cumulative risk at age 40 who did not get RT: 2/1229 (0.3%)
- Standardized Incidence Ratio (SIR) for breast cancer after doxorubicin was 19.7 (P=0.0002), however all who got doxorubicin also received RT thus could not separate RT/doxorubicin association
- Current COG guidelines that recommend screening (mammography/MRI) only for those who receive chest RT >20 Gy needs to be revised

Lange JM et al., Cancer 2014

End Stage Renal Disease (ESRD)

- Among 5910 patients enrolled between 1969-1994, the cumulative incidence of ESRD at 20 years after *unilateral* Wilms tumor was 74% in children with Denys-Drash syndrome, 36% in children with WAGR syndrome, 7% for GU anomalies (hypospadias, cryptorchidism) and 0.6% for other patients
- Cumulative incidence of ESRD at 20 years after bilateral WT was 50% in children with Denys-Drash syndrome, 90% in children with WAGR syndrome, 25% for GU anomalies (hypospadias, cryptorchidism) and 12% for other patients
- Children with unilateral and non-syndromic WT have a low rate of ESRD
- Children with syndromic WT (WT1 mutations) should be screened indefinitely for renal function abnormalities and treated early for impaired renal function (proteinuria, hypertension, renal failure)

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Breslow NE et al., J Urol 2005; Lange JM et al., J Urol 2010

PENTEC Comprehensive Review of Renal Toxicity

NFK grade	CTCAE v5 grade	Patient Condition (GFR, mL/min/1.73m^2)	Action
1	1	Kidney damage, normal or increased GFR (≥90)	Treat comorbid condition/slow progression
2	1	Mild decreased GFR (60-89)	Estimating progression
3	2	Moderately decreased GFR (30-59)	Evaluate and treat complications
4	3	Severely decreased GFR (15-29)	Prepare for transplant
5	4	Renal failure (<15 or dialysis)	Replacement

Poppe et al., IJROBP 2024

PENTEC Comprehensive Review of Renal Toxicity

Endpoint	Whole kidney dose in 2 Gy/fraction (95% CI) predicted to be associated with 5% risk
HTN	9.6 (9.1-10.3)
NFK ≥1	8.5 (7.1-10.2)
NFK ≥2	10.2 (9.3-11.2)
NFK ≥3	14.5 (12.2-19.0)

Technique	Predicted risk of HTN (%, 95% CI)	Predicted risk of NFK ≥1 (%, 95% CI)	Predicted risk of NFK ≥2 (%, 95% CI)	Predicted risk of NFK ≥3 (%, 95% CI)
WAI, 10.5 Gy (1.5x7)	4.9 (4.2-5.8)	7.5 (3.6-11.1)	4.2 (3.1-5.5)	1.2 (0.2-2.8)
TBI, 12 Gy (1.5x8)	7.0 (5.9-8.3)	11.9 (7.5-16.3)	6.4 (4.7-8.4)	1.8 (0.6-3.8)
TBI, 12 Gy (2x6)	8.8 (7.4-10.5)	16.1 (11.7-20.9)	8.4 (6.2-11.1)	2.5 (1.0-4.7)

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Poppe et al., IJROBP 2024

PENTEC Comprehensive Review of Renal Toxicity

Recommendations for clinical trial data reporting standards	
Patient sex, race, age	Timing and agents of nephrotoxic chemotherapy
Clinical indication for RT	Frequency of clinical follow-up for late effects
RT beam and technique	Frequency of labs and/or imaging follow-up
RT prescription dose and fractionation	n (total) and n (with toxicity)
Left and right kidney (and combined) DVH, 0.1 Gy resolution	Description of toxicity endpoints, scoring system
Min, max, mean dose to kidney	Patient-reported outcomes and symptoms (e.g. HTN, renal impairment or failure)
V10Gy, V15Gy, V20Gy, V30Gy to each kidney	Other co-morbid illnesses, concurrent medications, etc. contributing to renal disease

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Poppe et al., IJROBP 2024

Strategies to Reduce Risk of Late Effects

- 3D/4D-based treatment planning
- IMRT/VMAT and proton therapy using highly conformal target volumes
- Image-guided RT
- Standardizing vertebral body coverage
- Evaluation of lower RT doses
- Prospective RT quality assurance of volumes and doses by peer review
- Supportive therapy
- Future directions: adaptive RT, RCT of lower RT doses, biological predictors of RT response/assess need for RT dose reduction or escalation

Wens et al., Radiother Oncol 2025

Flank RT for Contained Rupture/Spill?

- Retrospective review of 54 patients treated at a single institution
- Median age, 4.5 years. Median follow-up, 6 years
- Flank RT considered at the RO's discretion for those with rupture or spill contained to the tumor bed or flank based on preoperative imaging and surgical findings
- WAI given to all patients with diffuse rupture or spill
- 0/13 patients treated with flank for contained rupture/spill had abdominal failure
- Cumulative 5-year abdominal failure rate of 2%, 5-year distant failure rate of 10%
- Can flank RT be used for patients with contained rupture/spill to reduce late effects of WAI? Needs further study.

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Conte B et al., Am J Clin Oncol 2024

Emerging Ideas

Highly Conformal Radiation Therapy (HC-RT)

- For decades, two opposed photon beams has been conventional RT for WT.
- Centers are attempting HC-RT for flank RT by delineation of the target volumes and treatment with IMRT and IGRT for better OAR sparing.
- At time of resection, surgical clip placement is helpful:
  - Superior clip near the diaphragm for motion registration during 4D-CT simulation
  - Lateral clip to on abdominal wall close to the paracolic peritoneal reflection at the site of retroperitoneal dissection indicate lateral margin of the post-operative tumor bed GTV
  - Extra clips as needed, e.g. to indicate residual mass or adhesions
- Co-registration of CT simulation with pre-operative MRI (or CT) is recommended.
- Use of a predefined CT window/level can help standardize contours.
- SIOP-RTSG has published consensus guidelines for flank target volume delineation

Janssens GO et al., Lancet Child Adoles Health 2020

SIOP-RTSG Consensus Statement

Recommended OARs contours	+OARs for flank targets extending into the pelvis
Heart	Bladder
Lungs	Uterus
Mammary buds	Ovaries. Consider ovarian transposition, tissue cryopreservation, or both.
Contralateral kidney	Testicles
Liver	
Spleen	
Pancreas	
Stomach, small and large bowels	
Vertebrae adjacent to the PTV (Hoeben et al)	

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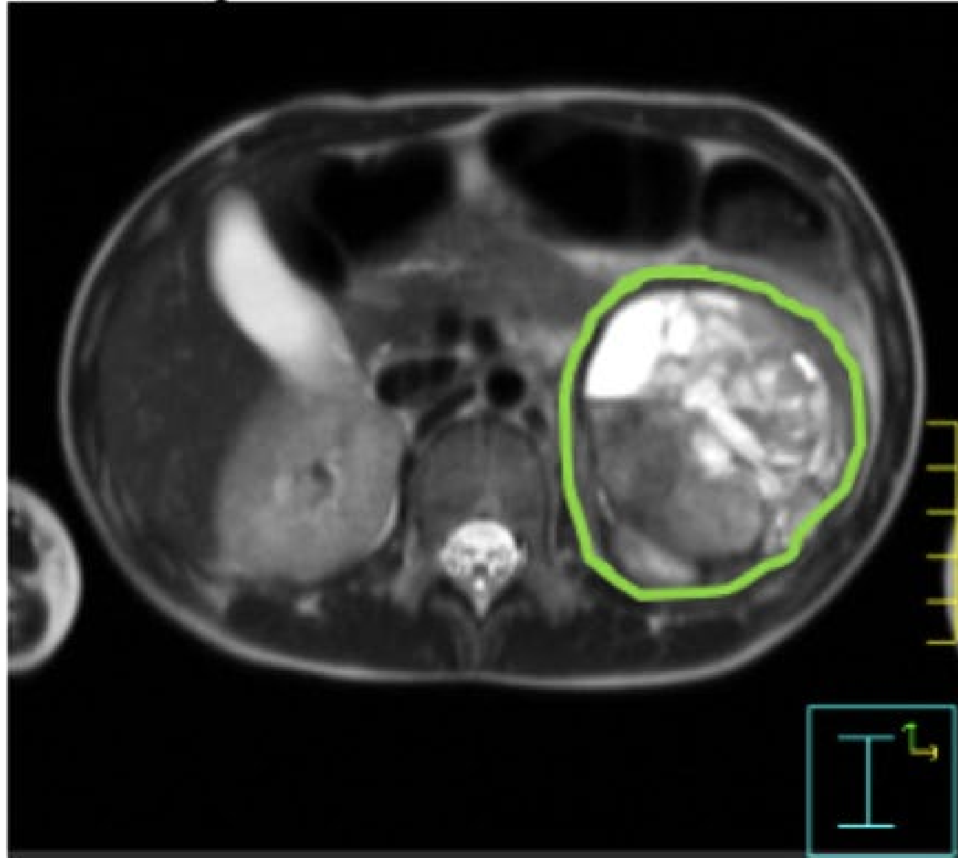
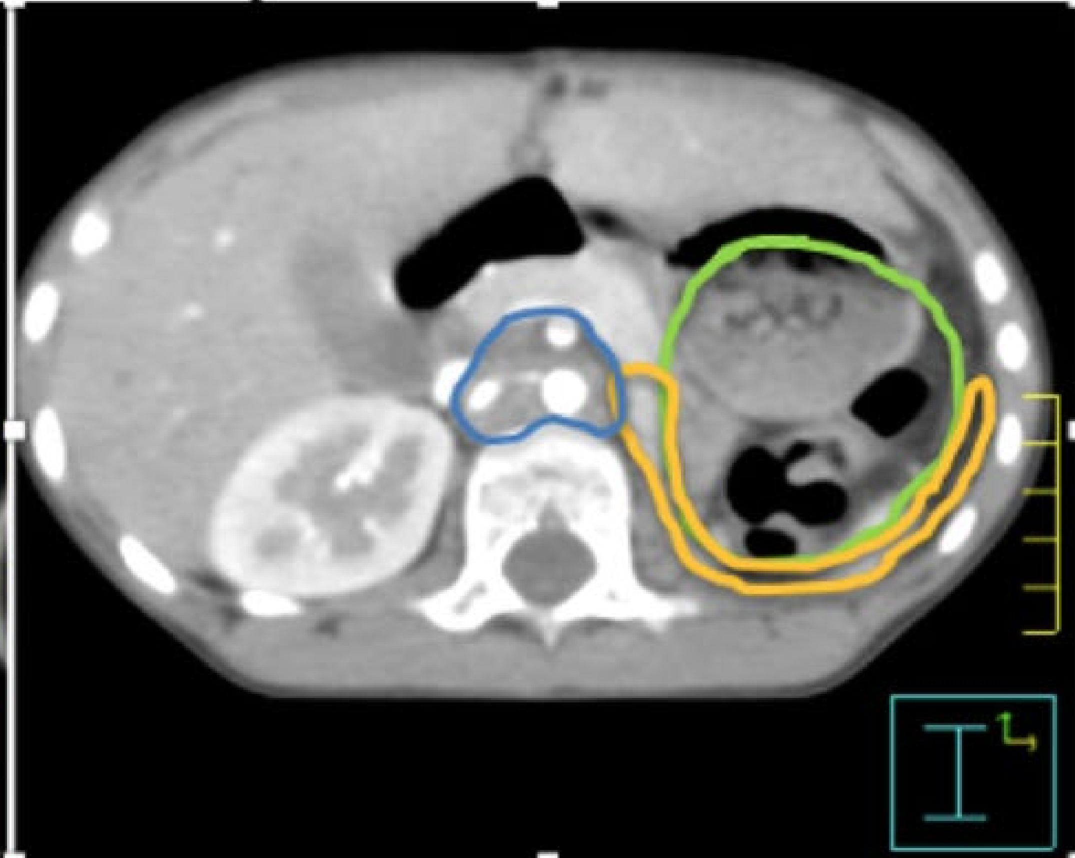
Janssens GO et al., Lancet Child Adoles Health 2020; Hoeben BA et al., Lancet Oncol 2019

SIOP-RTSG Consensus Statement





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McAleer MF et al., Pediatr Blood Cancer 2022; Janssens GO et al., Lancet Child Adoles Health 2020

SIOP-RTSG Consensus Statement

- ITV =
  - If 4D-CT simulation available and surgical clips placed, minimal ITV = resolution and slice thickness of CT since smaller intrafraction motions cannot be measured.
  - If no 4D-CT simulation available, ITV = CTV + 5 mm in all directions.
- PTV = ITV + 5 mm in all directions.

Dutch National Cohort

- 36 patients with renal tumors (32 WT, 3 RTK, 1 CCSK) treated with flank ± WLI HC-RT as per SIOP-RTSG guidelines between 01/2015 and 12/2019.
  - 4D-CT sim co-registered with pre-operative 1.5 T MRI (after pre-operative chemotherapy)
  - VMAT using full-arc 10 MV photon beams, ≥95% of prescription dose to cover ≥99% of CTV and ≥95% of PTV. Dose constraints for kidney, liver, lung, pancreas, spleen, heart.
- Median age at diagnosis, 3.1 years. Median follow-up, 3.1 years.
- 2-year locoregional control rate 94%, disease-free interval 91%, OS 94%.
- 2 patients had locoregional failure (LRF):
  - 1 stage III WT → infield (adrenal gland)/outfield (contralateral paravertebral space) failure
  - 1 stage III WT with viable IVC and right atrium tumor thrombus → marginal (IVC and contralateral retroperitoneal space) failure
- These relapses would not have been covered by conventional beams.

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Mul J et al., Radiother Oncol 2021

French Cohort of SIOP-2001

- 1259 WT patients registered in the French SIOP-2001 database from 2001-2017.
  - 58 patients had relapse: 14/316 treated with postoperative RT had abdominal relapse, 32/943 without RT had abdominal relapse, 12 had unknown relapse site
- 3/14 abdominal relapses with postoperative RT occurred in WT patients treated after flank RT ± WLI + 1 other patient had isolated hepatic failure.

Patient	Resection margin	LN status	Surgery-to-RT interval	RT dose
1, intermediate-risk	+	Not sampled	9 days	14.4 Gy 3D-CRT (DICOM-RT plan lost)
2, high-risk (DA), incomplete resection	+	+	32 days	21 Gy 3D-CRT 12 Gy boost to residual
3, high-risk (DA)	+	-	40 days	15 Gy IMRT, no boost

- LRF after flank RT for WT is rare and exclusively located in the retroperitoneum.

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Jouglar E et al., Pediatr Blood Cancer 2022

PediaRT French Registry

- 79 patients with renal tumors registered between 03/2013 to 09/2019.
  - 73 WT, 6 other histology; 2 stage I, 8 stage II, 69 stage III
  - 66 no rupture, 8 minor rupture, 3 major rupture, 2 unknown rupture)
  - All patients treated with post-op flank RT, median dose of 14.4 Gy (10.8-27.2); abdominal boost in 8/39 patients in 3D-CRT group, and 2/40 in HC-RT group (P=0.048)

	3D-CRT (n=39)	**HC-RT (n=40)**	**P**
Type of target volume			
Based on pre-operative tumor bed	26 (67%)	15 (38%)	**0.0095**
Retroperitoneal tumor bed	13 (33%)	25 (62%)	
GTV to CTV margins (mm), median (range)	10.0 (9.0-20.0)	10.0 (0.0-10.0)	0.92
CTV to PTV margins (mm), median (range)	9.0 (0.0-15.0)	6.0 (0.0-16.0)	**0.021**
PTV volume (mL), median (range)	750 (144-2449)	498 (17-1683)	**0.014**
Target volume coverage, V95 (%)			
Median (range)	96.9 (82.0-100.0)	98.0 (76.0-99.8)	**0.0067**
V95% ≥95%, n (%)	22 (69%)	35 (88%)	0.052

PediaRT French Registry

- Median age, 4.0 years. Median follow-up, 4.5 years.
- More patients achieved all dose constraints with HC-RT (P=0.014)
- Highly conformal RT offered lower Dmean for peritoneal cavity (P=0.018), Dmean <10 Gy for pancreas (P=0.038), Dmean for contralateral mammary bud (P=0.0045)
- 3 LRFs: 2/39 patients (3D-CRT) vs. 1/40 (HC-RT; P=0.62)
- 3-year locoregional control rate 94.7% (3D-CRT) vs. 97.4% (HC-RT)
- Acute toxicity 33/39 (85%; 3D-CRT) vs. 24/40 (60%; HC-RT; P=0.015), in particular diarrhea 17/39 (44%) vs. 7/40 (17%; P=0.012)

Le Quellenec G et al., Pediatr Blood Cancer 2023

Pencil Beam Scanning (PBS) Proton Therapy for HC-RT

- Dosimetric study of 11 patients treated with conventional RT replanned with flank HC-RT (the ipsilateral retroperitoneum and para-aortic nodes) using PBS protons
- Significantly lower OAR doses with PBS vs. photon AP/PA 3D-CRT plans
  - Contralateral kidney: mean dose P=0.009) and median dose to ≥50% (D50; P=0.000001)
  - Bowel: mean dose (P=0.001), D20 (P=0.04), and D50 (P=0.004)
  - Liver: mean dose (P=0.02; P=0.002 for right-sided tumors), D20 (P=0.02), and D50 (P=0.4; P=0.0001 for right-sided tumors)
  - Integral dose (P=0.05)
- PBS is feasible for flank HC-RT, and needs further study.

25TH ANNIVERSARY CHILDREN'S ONCOLOGY GROUP 2000 - 2025

Vogel J et al., Pediatr Blood Cancer 2016

Pencil Beam Scanning Proton Therapy for HC-RT

- Prospective phase II trial at the Children's Hospital of Philadelphia, planned interim analysis reported of 11 patients enrolled from 01/2018-12/2021.
  - 4D-CT simulation, pre-operative image registration, 1 cm tool used to contour retroperitoneal space, CTV = GTV + 1 cm (PALN included when involved)
  - ≥98% of CTV receiving ≥98% of planned 10.5 Gy in 5 fractions achieved for all patients (9 Gy boost for unresected PALN or margin+)
  - Planning constraints: kidney V80<10 Gy, cord max 12 Gy, heart max 11 Gy and V50<10 Gy, liver V70<20 Gy. Constraints met for all patients.
- Median follow-up 26 months.
- No patients had local recurrence.
- No patients experienced grade 2 or higher CTCAEv4.0 toxicity. Most common patient-reported outcomes: constipation (n=3), nausea (n=2), vomiting (n=1).

Hill-Kayser CE et al., IJROBP 2022 (abstr.); https://www.clinicaltrials.gov/study/NCT03810651

Inter-oncologist Contouring Variability

- 6 renal cancer cases eligible for flank RT based on SIOP-RTSG UMBRELLA 2016
  - Reference target volumes, contralateral kidney, spleen, liver, heart, lungs, and vertebrae contoured by 3 expert SIOP-RTSG board radiation oncologists (ROs) in 3 live meetings
  - 10 participant ROs from 7 countries contoured $GTV_{pre\text{-}op}$, $GTV_{post\text{-}op}$, $CTV_{TumorBed}$, CTV_{Nodes}, pancreas, bowels in 2 test phases each followed by consensus meetings and a QA phase (two cases per phase)
- 57/60 contour sets were collected within the given timeframe
  - Dice similarity coefficient (DSC) between reference and participant CTV was 0.55; no improvement after sequential cases (P for case 3-4 vs. 5-6 = 0.15)
  - For cases 5-6, ≥1 major deviation in 5/18 $GTV_{pre\text{-}op}$, 12/17 $GTV_{post\text{-}op}$, 18/18 $CTV_{TumorBed}$, and 4/9 CTV_{Nodes} contours submitted by participants
  - Unacceptable variation in CTV submitted by 7/9 participants for case 5 and 6/9 for case 6.
- Results support need for training and centralized real-time review for HC-RT.

Mul J et al. Clin Transl Radiat Oncol 2021

Deep-learning MRI-based Treatment Planning?

- MRI-based synthetic CT (sCT) has been reported for treatment planning of brain, H&N, lung, prostate, and abdomen tumors for x-ray and proton RT in adults to omit need for conventional CT (reduce registration uncertainties, radiation exposure)
- 66 children with WT (n=24) or neuroblastoma (n=42) underwent CT and MR
- Mean age, 4 years (range, 1-9 years)
- MR intensities converted to CT Hounsfield units (HUs) by use of UNet-like neural network trained to generate sCT from T1- and T2-weighted MR sequences
- Mean error -5 HU, mean absolute error 57 HU, peak signal-to-noise ratio 30.3, dise similarity coefficient 76% for bones, 92% for lungs, mean dose difference <0.5% for both VMAT and PBS, average gamma pass-rates >99% for VMAT, >96% for PBS

Florkow MC et al., Radiother Oncol 2020

Future Directions

- Use of novel biomarkers for COG risk stratification: WT predisposition, post-chemotherapy histology, 1q gain, 11p15 LOH, peritoneal and pelvic metastases
- Reevaluate need for WAI with localized preoperative rupture contained to flank without ascites or peritoneal implants
- Determine the value of focal boost RT to gross residual disease after surgery, residual lung lesions after WLI, unresected lymph nodes
- Highly-conformal flank RT vs. 3D-CRT using two parallel-opposed beams
- Partial kidney irradiation (e.g. IMRT and protons) including dose-response curves for renal injury and chemotherapy effects
- Image-guided RT, motion management to decrease uninvolved kidney dose
- Contour renal cortex and medulla separately for future toxicity analysis?

Benedetti et al., Nat Rev Urol 2025; Conte B et al., Am J Clin Oncol 2024; Poppe et al., IJROBP 2024