Wilms Tumor (Nephroblastoma)

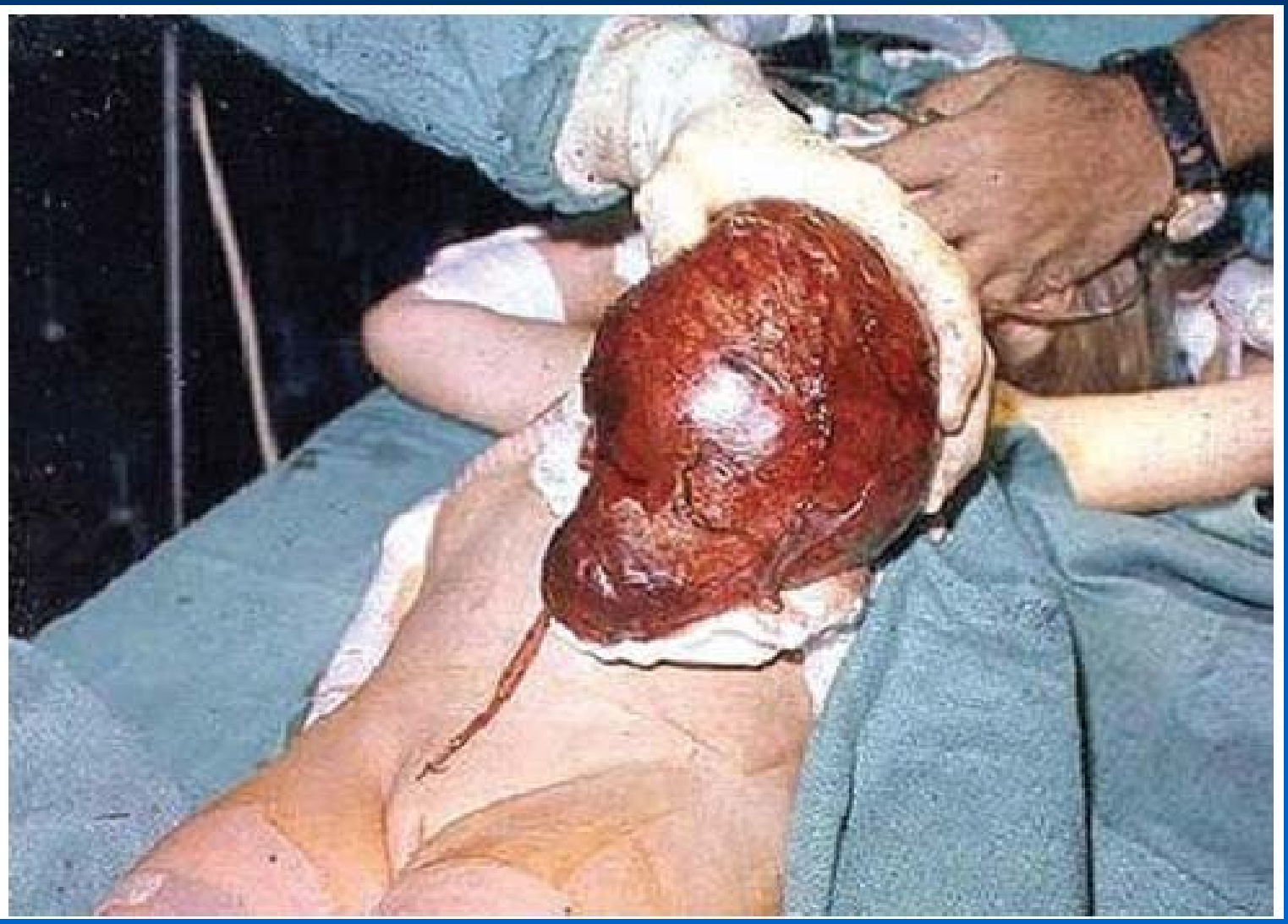
John A. Kalapurakal MD, FACR

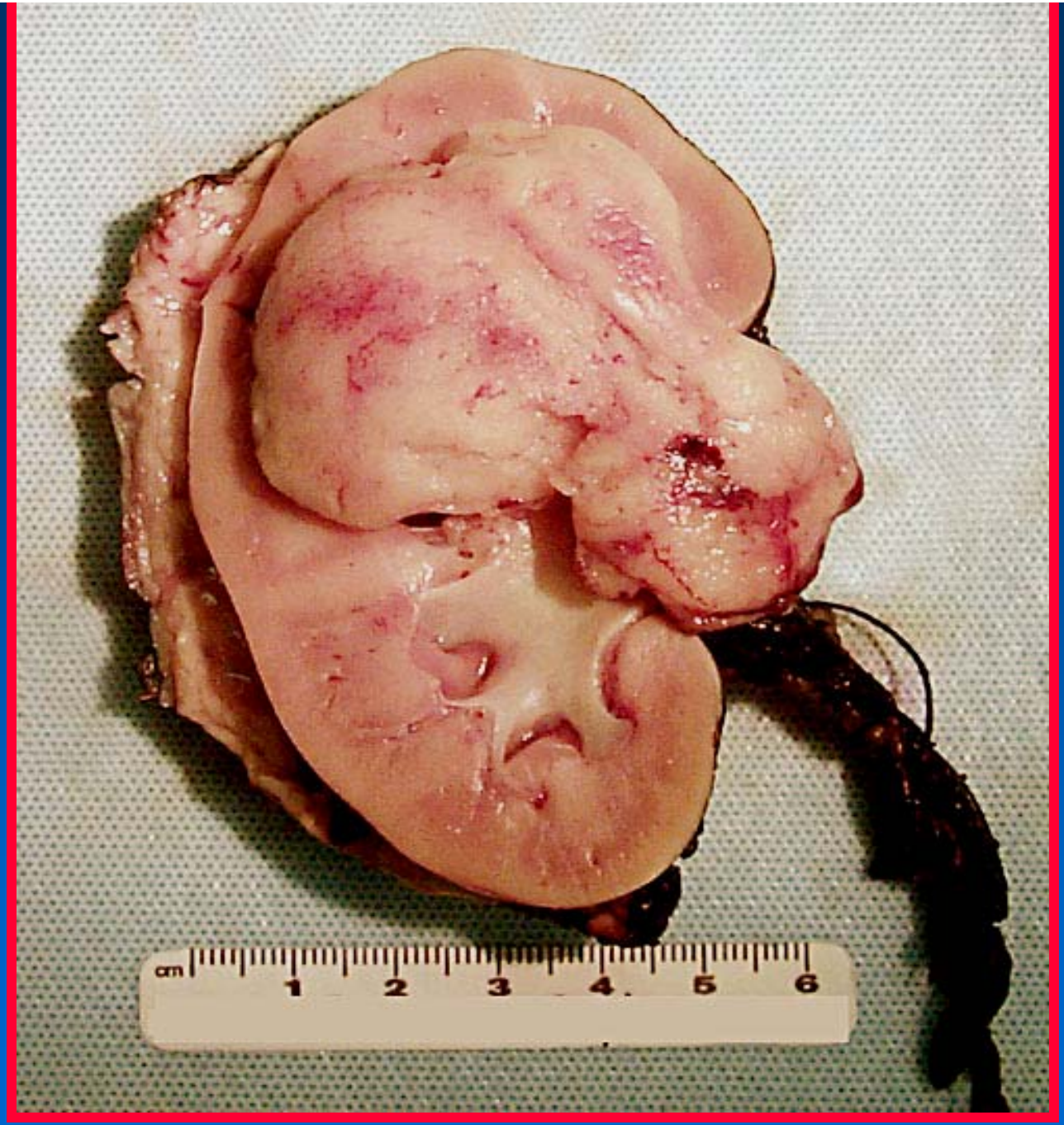
Wilms Tumor

- 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)

WT-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)

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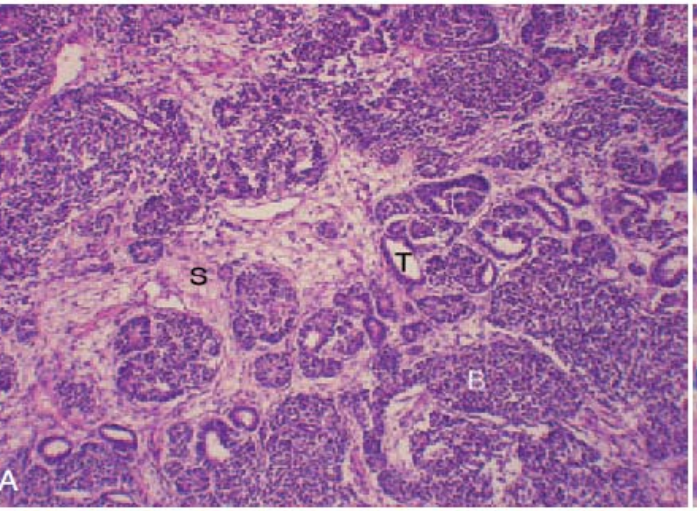
WT-Pathology

- Classic WT is triphasic with 3 cell types: blastemal, stromal and epithelial, ~90% FH subtype
- 3 entities under UH subtypes (NWTS): Anaplasia, CCSK, Rhabdoid tumor of kidney (RTK)
- Anaplasia (5%): large nuclei, hyperchromasia, mitoses
- Anaplasia may be focal or diffuse
- CCSK and RTK are not considered WT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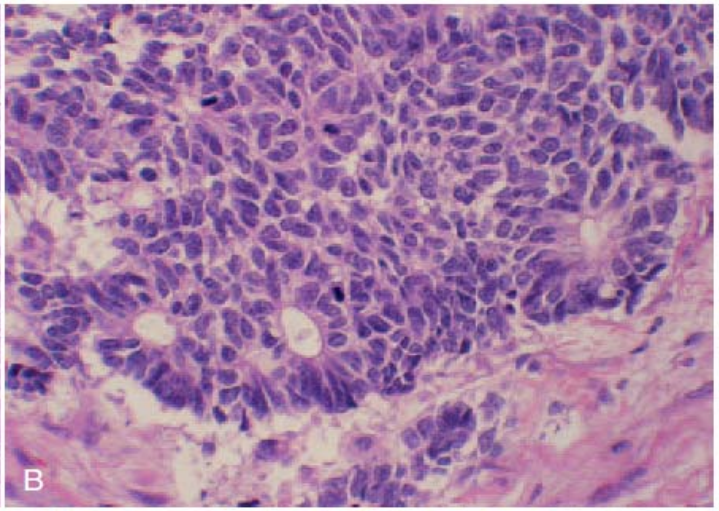
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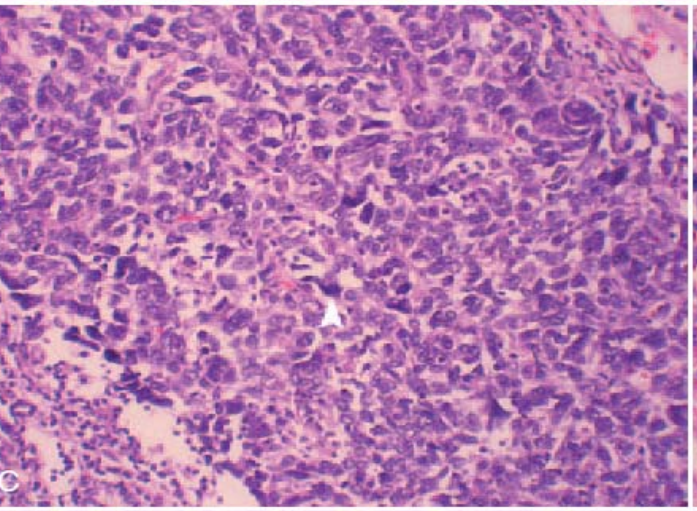
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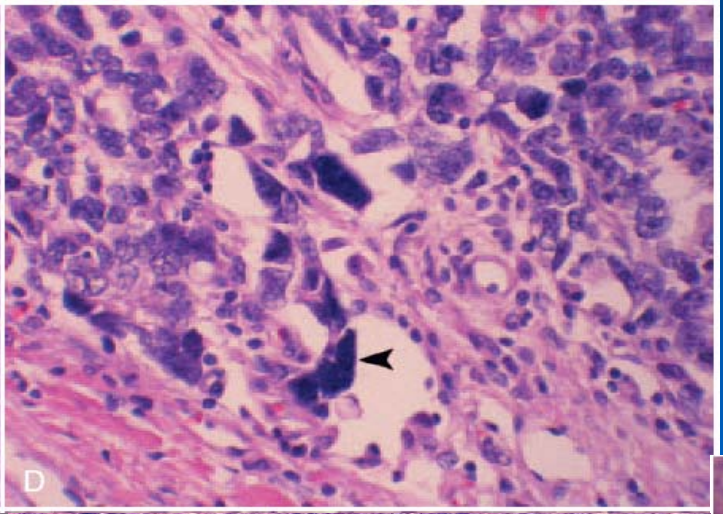
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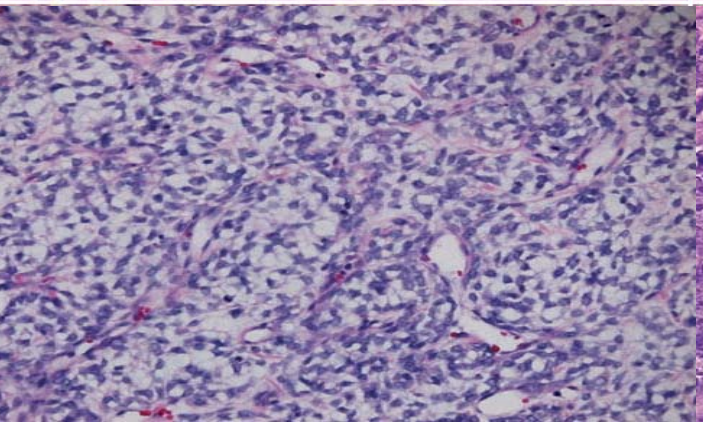

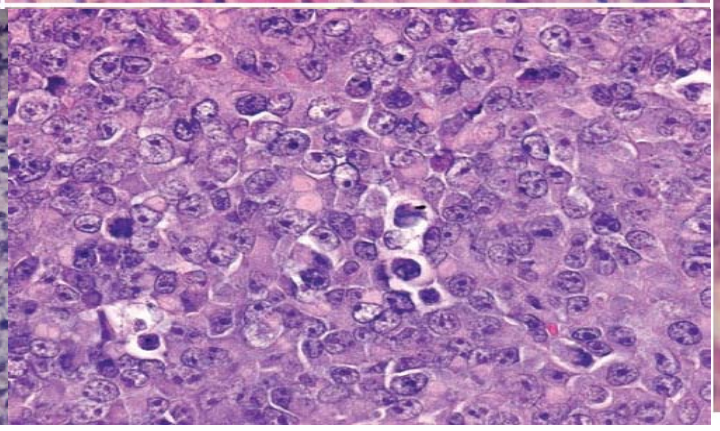

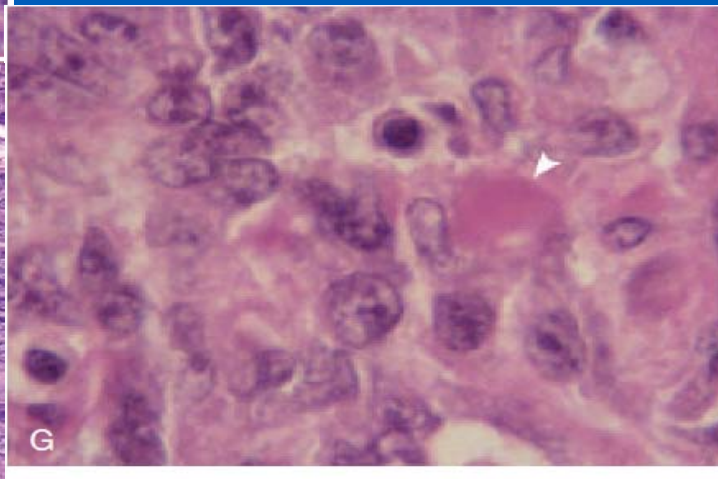
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WT-Biology

- 2-4% WT occur as part of syndromes
- *WT1 mutation* -11p13: *WAGR* and *DD* syndromes
- *WT2 mutation* -11p15.5: *BWS*
- *WTX mutation* -X chromosome*: 30% of WT (Rivera MN Science 2007)*
- *Familial WT genes 1-2%*

Clinical Presentation

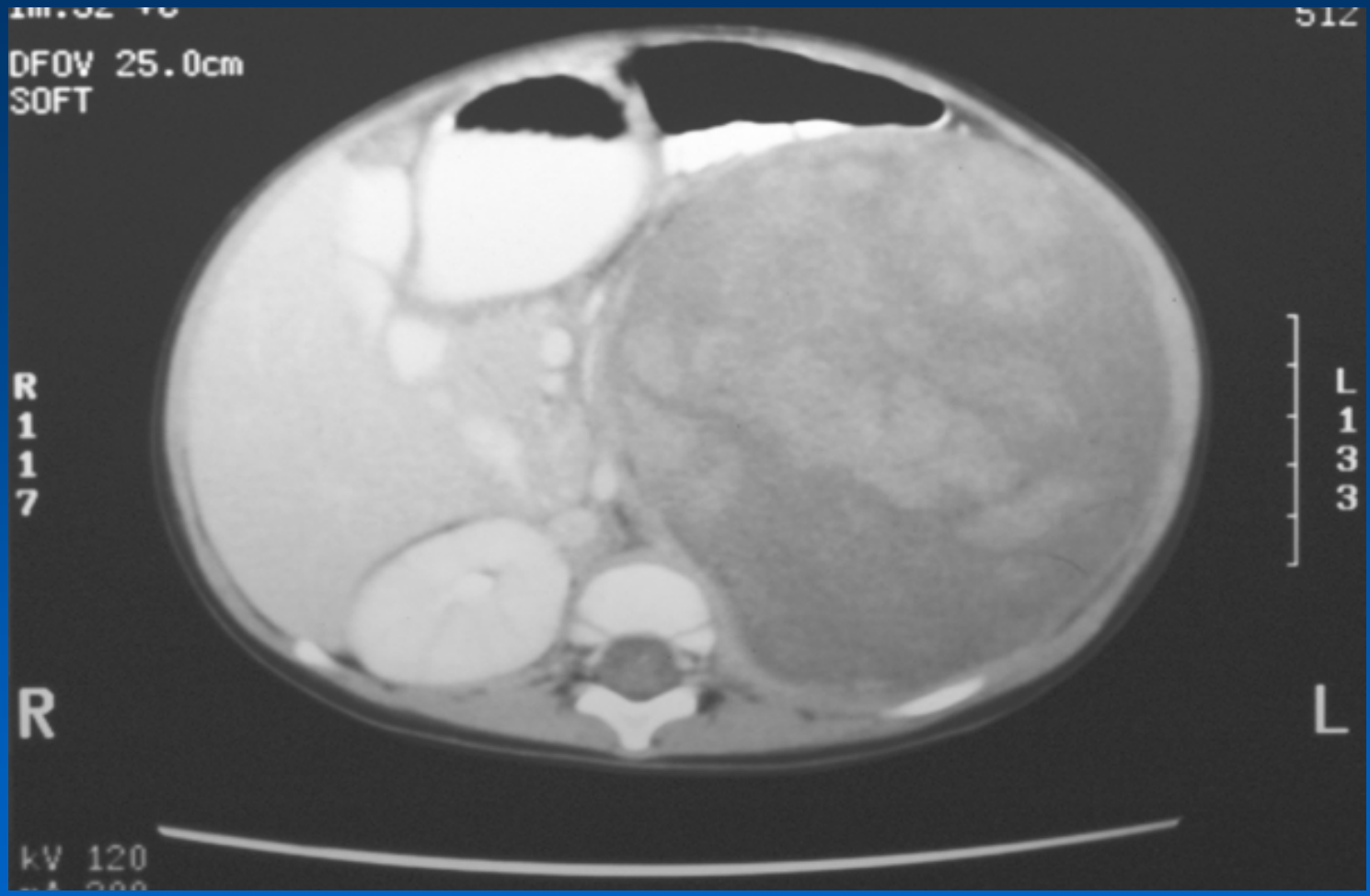
- Most present with abdominal swelling
- Pain, hematuria and fever may be present
- Hypertension (↑renin) in 25%
- Signs of Wilms tumor associated syndromes: aniridia, hemihypertrophy, GU abnormalities- hypospadias, cryptorchidism and pseudohermaphroditism

Natural History

- WT often localized at diagnosis, as surgery and RT curative in 50%
- Local spread into the renal sinus or the intrarenal blood and lymphatic vessels
- Spread to peritoneal cavity may occur, > after pre or intraoperative rupture
- Common sites of metastases - lungs (80%), lymph nodes, and liver, rarely brain

Work Up

- H&P
- Blood and Urine
- Imaging: Ultrasound, CT scan, MRI, Bone scan (CCSK), MRI brain (CCSK,RTK)
- Intrarenal SOL, presence of thrombus in IVC, LN, bilateral tumors, distant metastases
- RTK second primary ATRT posterior fossa (10-15%)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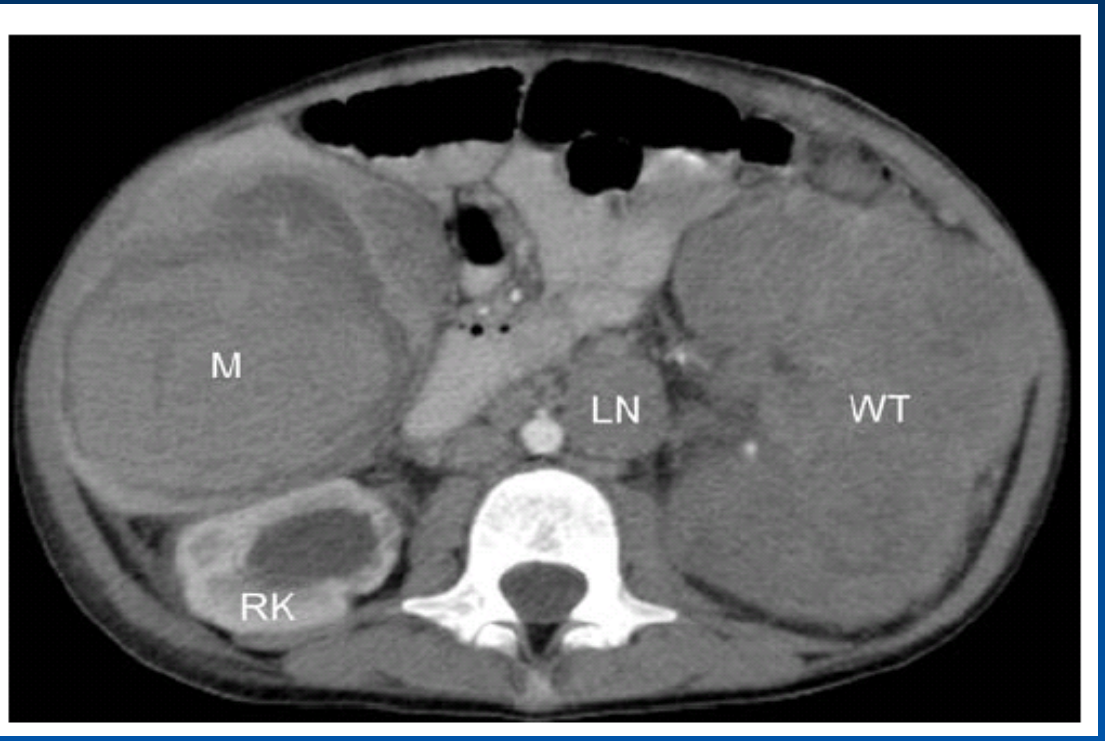
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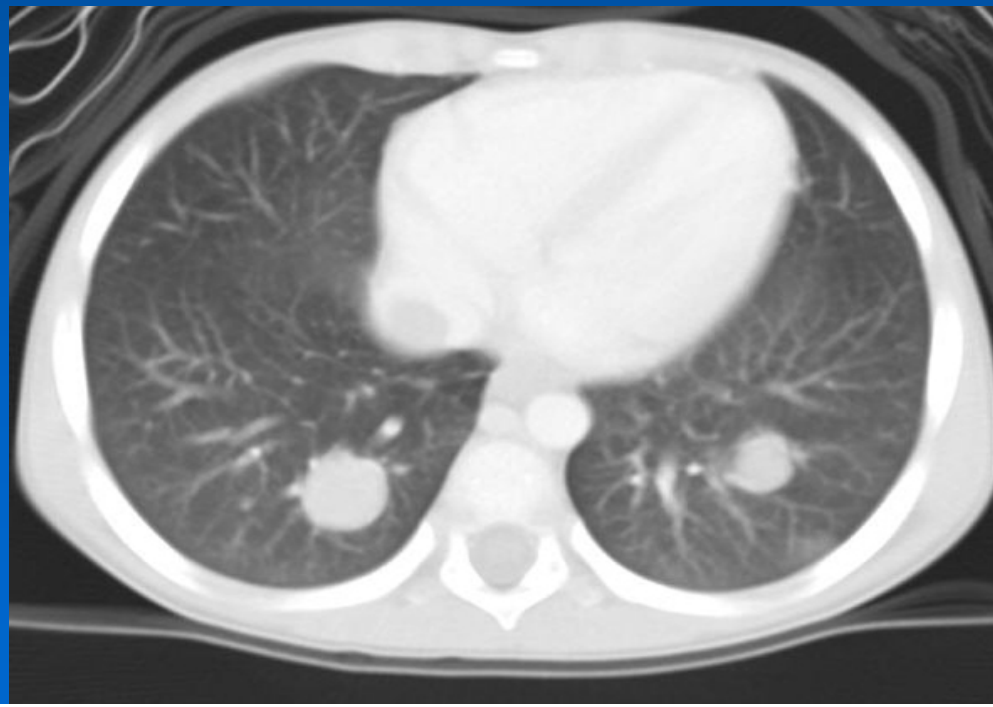


COG Staging – Surgical Staging

- I Tumor limited to kidney and completely excised. No penetration of capsule or involvement of renal sinus vessels
- II Tumor extends beyond kidney but is completely excised. There is penetration of capsule or involvement of renal sinus vessels
- III Residual tumor remains after surgery: lymph nodes involved, local spillage or needle biopsy, diffuse peritoneal contamination, peritoneal implants found, surgical margins positive-either microscopically or grossly, transected tumor thrombus, piecemeal resection, unresectable tumor
- IV Hematogenous metastases to lung, liver, bone, brain or lymph node metastasis outside the abdomen
- V Bilateral Wilms tumor

Prognostic Factors

- Tumor Stage
- Tumor Histology
- Age: Children < 24 months
- Molecular markers: LOH at 1p and 16q
- Telomerase expression

LOH at 1 p and 16q

Grundy PE, JCO 2005

- NWTS-5 prospectively analyzed prognostic value
- RR for relapse for LOH at *both* regions - significantly higher in stage I/II and stage III/IV FH (vs. no or either LOH)
- RR for death for LOH at *both* regions- significantly higher in stage I/II and stage III/IV FH (vs. no or either LOH)

Wilms molecular profiling: New targets, biostratification

- RTK - loss of *SMARCB1/INI-1* gene, repression of neural crest development and transcription, loss of cyclin dependent kinase inhibition (Gadd S Lab Invest 2010)
- Anaplastic tumors changes on 17p (TP53 deletion) and specific genomic loss on 4q and 14q and focal gain of *MYCN* (Williams RD Genes Chrom Cancer 2011)
- Very low risk WT treated surgery alone, *WT1* mutation and 11p15 loss, prospectively validated to be important predictor of relapse (Perlman EJ. JCO 2010)

WT-Surgery

- Initial treatment for most children in the US
- 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

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**

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 yrs was 89% compared to 77% (+RT) and 58% (-RT) in NWTS-1
- Also the duration of chemotherapy (6 months or 15 months) did not influence survival

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

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 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

WLI in stage IV WT

Nicolin G IJROBP 2008

- 102 pts in UKW2 and UKW3, 71% had WLI
- Median follow-up 9.3 yrs
- EFS WLI vs. no WLI: 79%/53% SS
- OS WLI vs. no WLI: 85%/73% NS
- Lung relapse WLI vs. no WLI: 8%/23% SS
- 3 fold increase in lung relapse if no WLI

CT-only lung metastases in FH WT-NWTS 4,5

Grundy P et al

- 186 pts, 50% treated as stage IV others per investigator discretion (2/3 drugs ± WLI)
- 5yr EFS 2/3drugs (±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

Effect of chemotherapy on outcomes for patients diagnosed to have lung metastasis by CT only

Chemotherapy	# pts	Event-free survival % at (95% CI)		p-value	Overall survival % at(95% CI)		p-value
		2 yrs	5 yrs		2 yrs	5 yrs	
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)

Effect of lung RT on outcomes for patients with lung metastasis by CT only

Lung RT	# pts	Event-free survival% at (95% CI)		p-value	Overall survival% at (95% CI)		p-value
		2 yrs	5 yrs		2 yrs	5 yrs	
No	105	75.0	70.1		94.3	83.7	
Yes	77	84.8	81.0	0.11	91.9	90.0	0.73

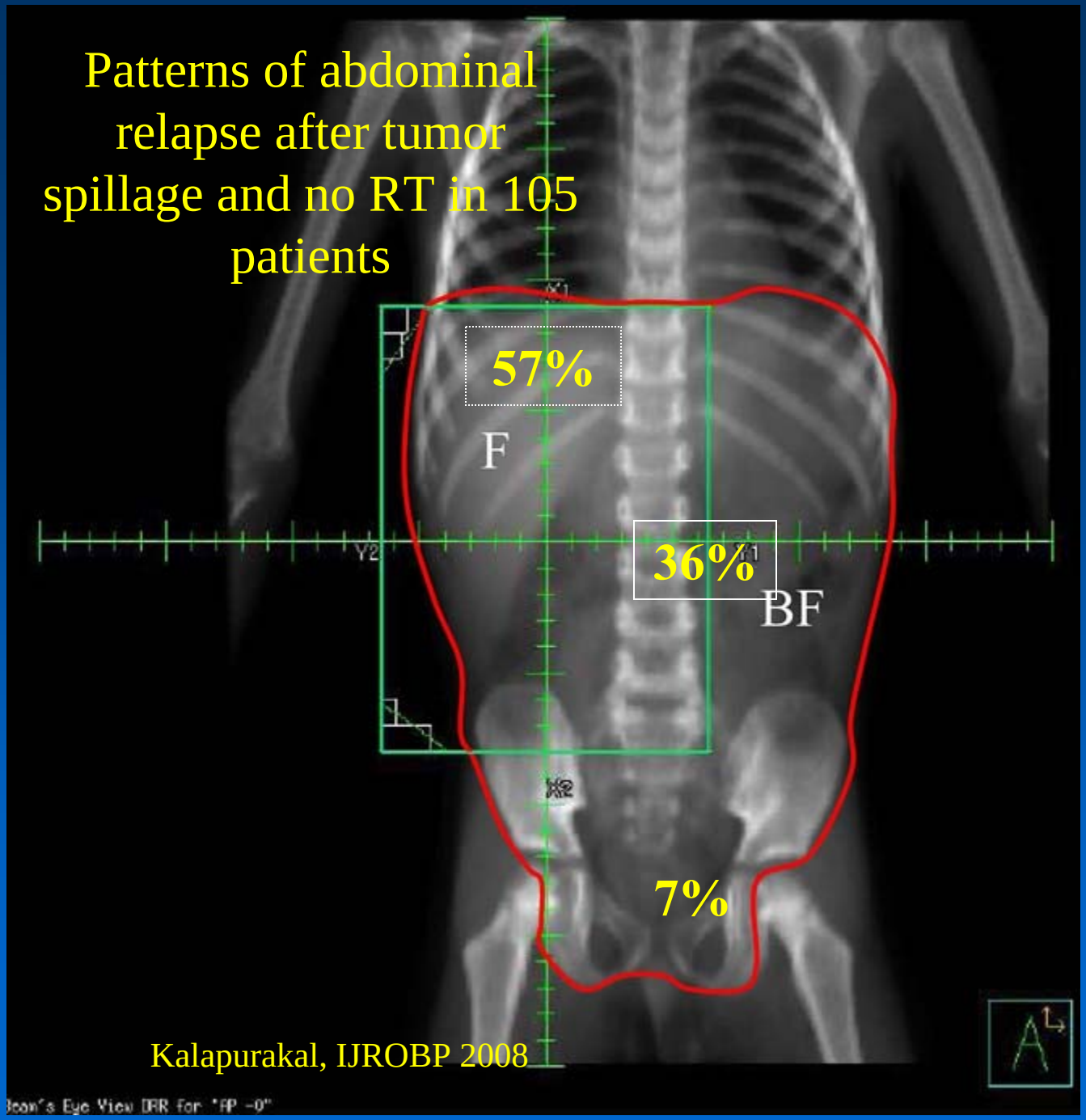
There was a non-significant trend towards improved 5-yr EFS for patients treated with lung radiation, but this trend disappeared when the analysis was adjusted for the chemotherapy regimen delivered (p=0.52). No difference in OS with WLI

Survival Outcomes in NWTS-5 (unpublished)

Stage/histology	4yr RFS (%)	4yr 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**

NWTS-3, 4 tumor spillage

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


Patterns of abdominal relapse after tumor spillage and no RT in 105 patients
57%
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36%
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7%
Kalapurakal, IJROBP 2008

Anaplastic Wilms Tumor

Dome JS JCO 2006

- 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

Current Clinical Treatment Guidelines

- 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

COG Risk Group Classification: FH WT

Age	Tumor Weight	Stage	LOH (both 1p and 16q)	Rapid Response#	Risk Group	COG Study	Regimen
< 2 yrs	< 550 g	I	Any	N/A	Very Low	AREN0532	Surgery only
Any	≥ 550 g	I	None	N/A	Low	AREN0532	EE4A
≥2yrs	Any	I	None	N/A	Low	AREN0532	EE4A
Any	Any	II	None	N/A	Low	AREN0532	EE4A
≥ 2yrs	Any	I	Yes	N/A	Standard	AREN0532	DD4A
Any	≥ 550 g	I	Yes	N/A	Standard	AREN0532	DD4A
Any	Any	II	Yes	N/A	Standard	AREN0532	DD4A
Any	Any	III	None	Any	Standard	AREN0532	DD4A
Any	Any	III	Yes	Any	Higher	AREN0533	M
Any	Any	IV	Yes	Any	Higher	AREN0533	M
Any	Any	IV	None	Yes	Standard	AREN0533	DD4A
Any	Any	IV	None	No	Higher	AREN0533	M

Children's Oncology Group (COG) Renal Protocols

Tumor Risk Classification	Multimodality treatment
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**

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
Stage I-III CCSK	Surgery, RT, Regimen I

Chemotherapy Regimens

- *Regimen EE4A* - VCR/AMD
- *Regimen DD 4A* - VCR/AMD/ADR
- *Regimen M* - VCR/AMD/ADR; CY/ETOP
- *Regimen I* - VCR/DOX/CY; CY/ETOP
- *Regimen UH1* - CY/CARBO/ETOP; VCR/DOX/CY

COG protocol- RT guidelines

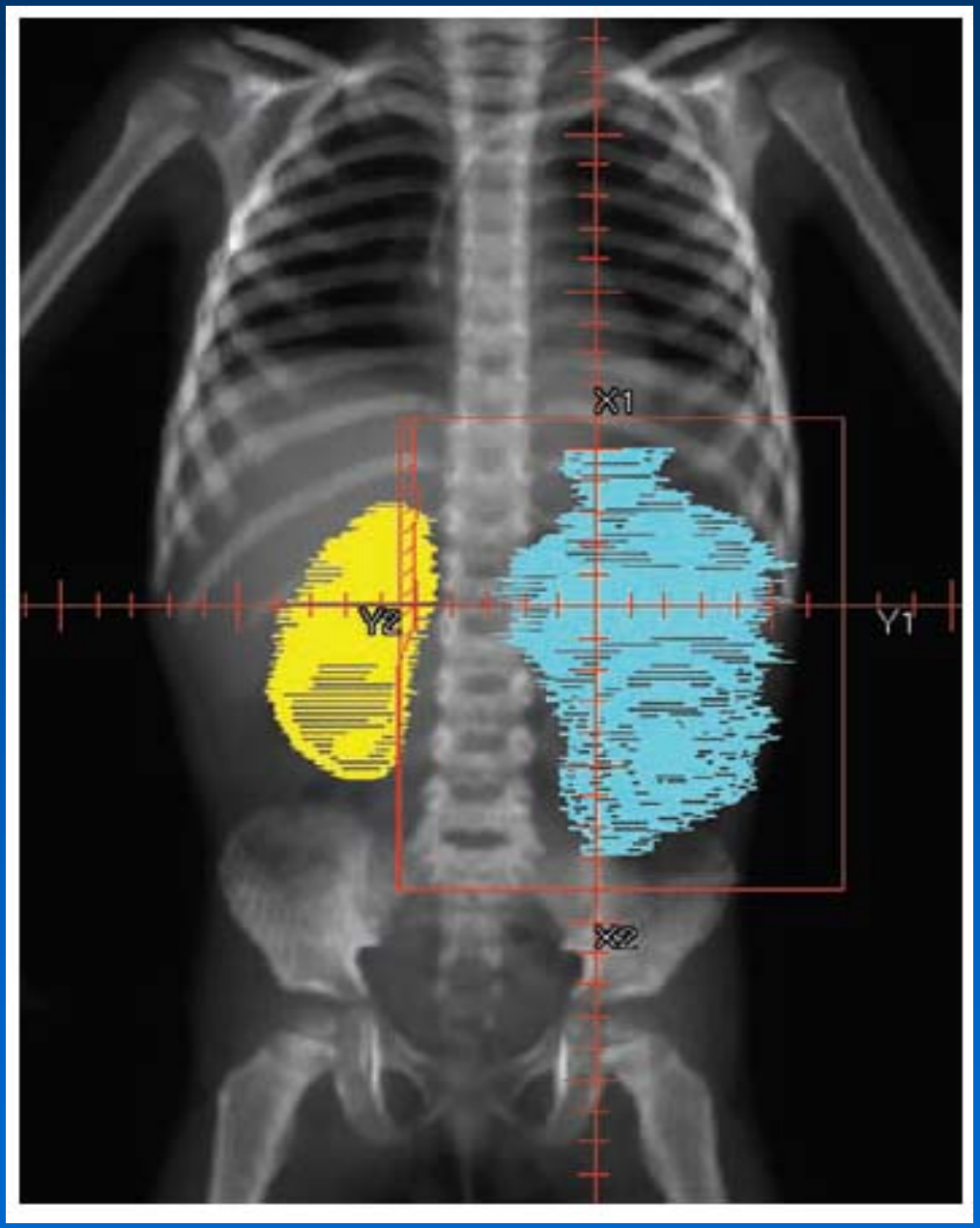
Tumor Stage/histology	**RT dose (Gy) and fields**
Stage I/II FH	No RT
Stage III FH Stage I-III FA Stage I-II DA Stage I*-III CCSK	10.8 Gy Flank* RT
Stage III DA Stage I-III RTK	**19.8 Gy** (Infants 10.8 Gy) Flank* RT

Stage IV (Lung, FH)	12 Gy WLI if no CR at week 6 of DD4A
Stage IV (lung, UH)	12 Gy WLI
Stage IV (Brain)	25.2 Gy (Whole brain) + 10 Gy (local boost)
Stage IV (Bone)	25.2 Gy (Tumor + 3 cm margin)
Unresected LN metastases	19.8 Gy
Relapsed WT (Flank/Abdomen)	12.6 -18 Gy (< 12 months of age) 21.6 Gy in older children 9 Gy boost to gross residual tumor

COG-RT Fields

- **Timing of RT**

- FH cases preferably by day 9 but no later than day 14
- UH patients RT should start no later than day 9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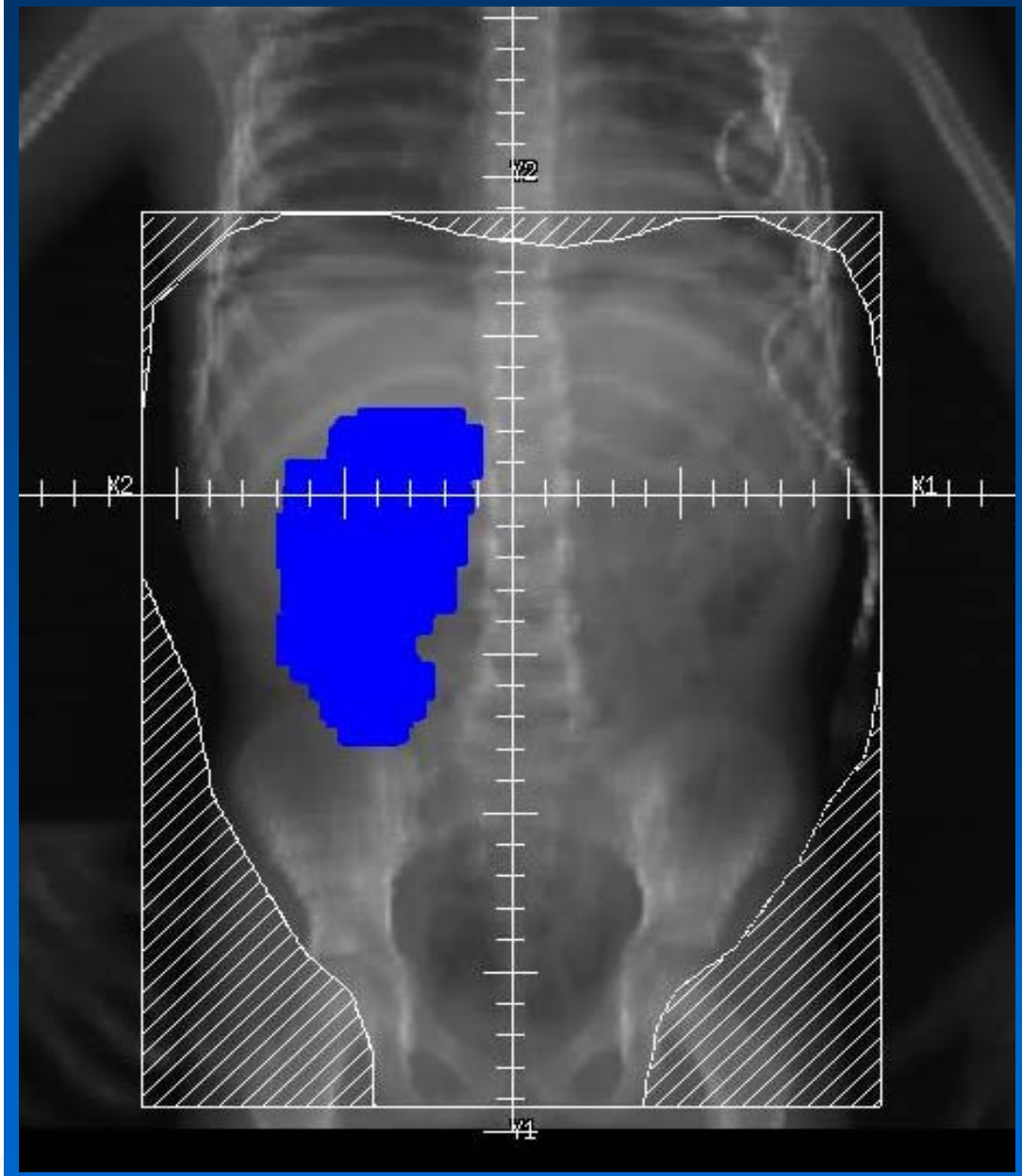
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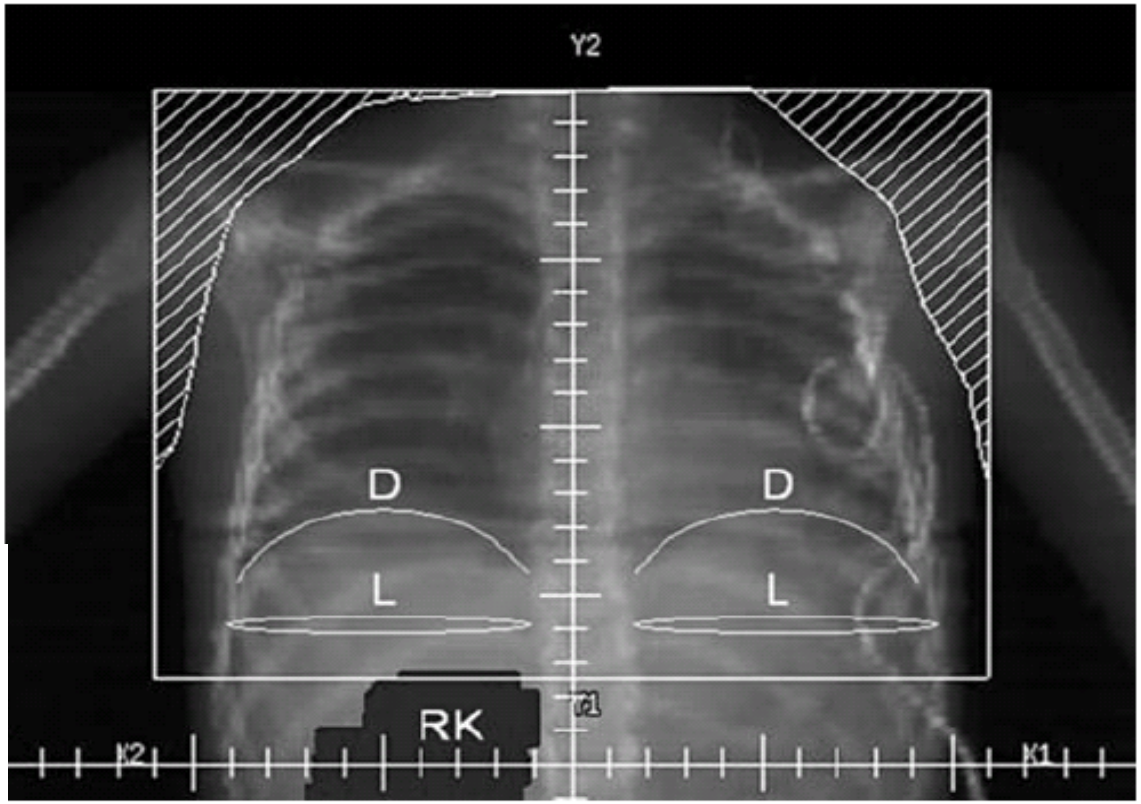
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Bilateral Wilms Tumor (BWT) NWTS-4 – Inferior Outcomes (Hamilton T et al Ann Surg 2011)

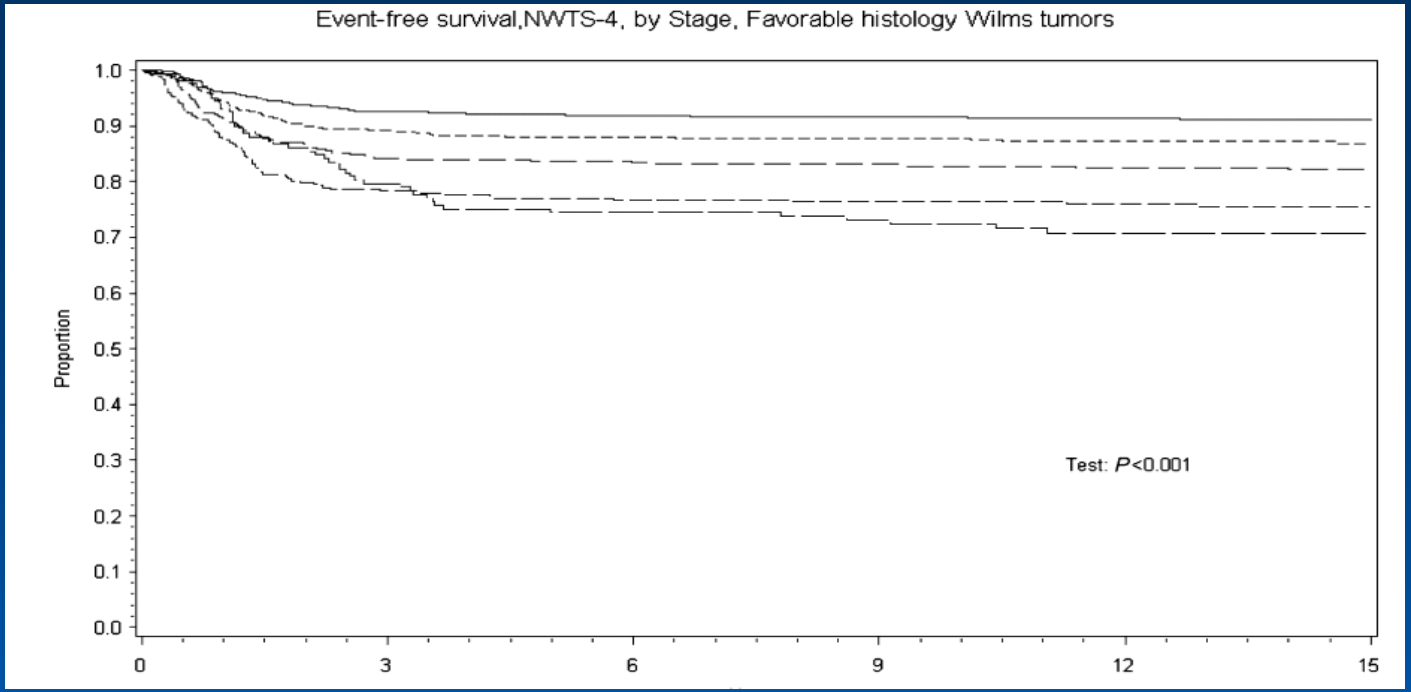
- 188pts (5.6%) BWT, 87 pts had initial resection
- Anaplasia (14%)– 390 (44-1925days)
- Core needle biopsy did not diagnose anaplasia in a single child (Hamilton JPS 2006)
- End stage renal failure 23 pts (12%)
- 12% had <50% nephron sparing surgery
- *Earlier resection required for non- responsive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

Under staging

Under treatment

Delay in local control

Delay in diagnosing anaplasia (14%)



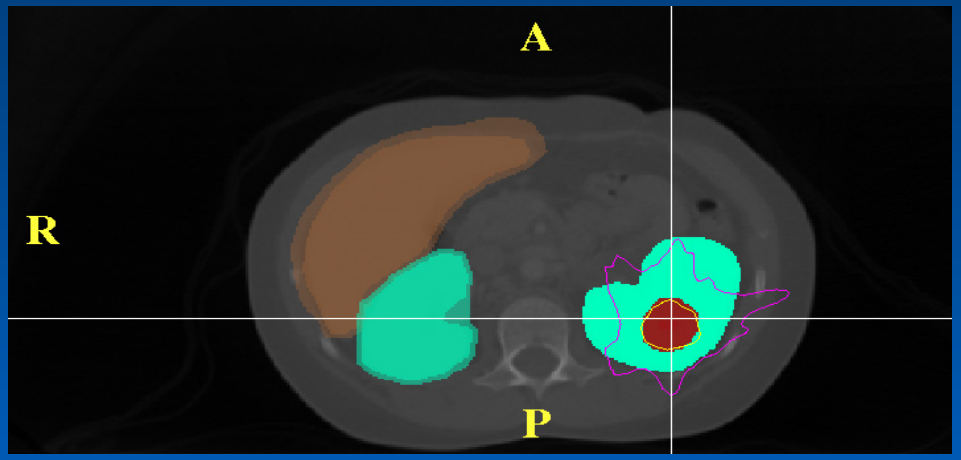
Stage	No. of Cases	8-year EFS (95% Confidence Interval)
I	918	91% (89%, 93%)
II	617	81% (77%, 84%)
III	594	84% (81%, 87%)
IV	334	71% (66%, 75%)
V	159	70% (63%, 76%)

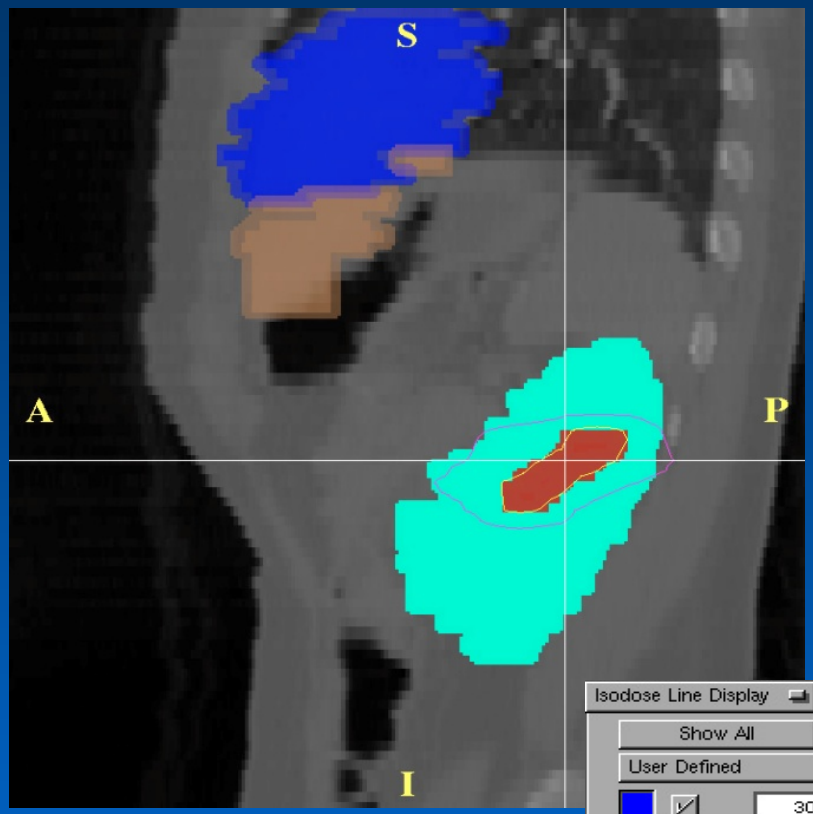
Favorable Histology	
8-year EFS (95% Confidence Interval)	8-year OAS (95% Confidence Interval)
92% (90%, 93%)	97% (95%, 98%)
83% (80%, 86%)	94% (92%, 95%)
88% (85%, 90%)	93% (90%, 94%)
76% (71%, 81%)	82% (78%, 86%)
74% (66%, 80%)	89% (84%, 93%)

BWT-AREN0534

- To improve 4 year EFS to 73% for BWT
- To prevent complete removal of at least one kidney in 50% pts by prenephrectomy 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 (21.6Gy) for selected tumors meeting all criteria: FH, hilar or polar location, unresectable or multiple positive margins after renal conserving surgery in a solitary kidney, responsive to chemotherapy

BWT-AREN0534





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☑ Color 3D surfaces by dose

Dose Normalization

Normalize to: ☑ Maximum Dose ☐ Delivered Dose

Maximum accumulated dose is 35.23 Gy

Relapsed Wilms tumor – NWTS 5

Green DM PBC 2007

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

Relapsed Wilms tumor – NWTS 5

Malogolowkin M PBC 2008

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

Results of the first generation of COG Renal Tumor Protocols

COG Renal Tumor Protocols

- AREN03B2 (Renal Tumors Classification, Biology, and Banking Study), active
- AREN0532 (Very Low Risk and Standard Risk Favorable Histology Wilms Tumor), closed 10/15/2013
- AREN0533 (Higher Risk Favorable Histology Wilms Tumor), closed 5/24/2013
- AREN0321 (High Risk Renal Tumors), closed 11/27/13
- AREN0534 (Bilateral, Multicentric, or Bilaterally-Predisposed Unilateral Wilms Tumor), closed 6/2/15

AREN0532

Risk Group	Treatment	Count (%)
Very Low (Stage I, age < 2 yrs, tumor wt < 550 g)	Observation	116 (15.63%)
Low (Stage I, age ≥ 2 yrs or tumor wt ≥ 550 g; or Stage II, no LOH)	EE4A	51 (6.87%)
Standard (Stage I, age ≥ 2 yrs or tumor wt ≥ 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 Wilms Tumor

(Fernandez CV, Annals of Surgery 2017)

- 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 overall survival 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)

AREN0532 Stage III FH Tumors

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

AREN0532- Stage III FH

The 4-year EFS and OS estimates were 88% and 96% respectively

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

Fernandez CV et al. J Clin Oncol 33 (suppl; abstr 10010)

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

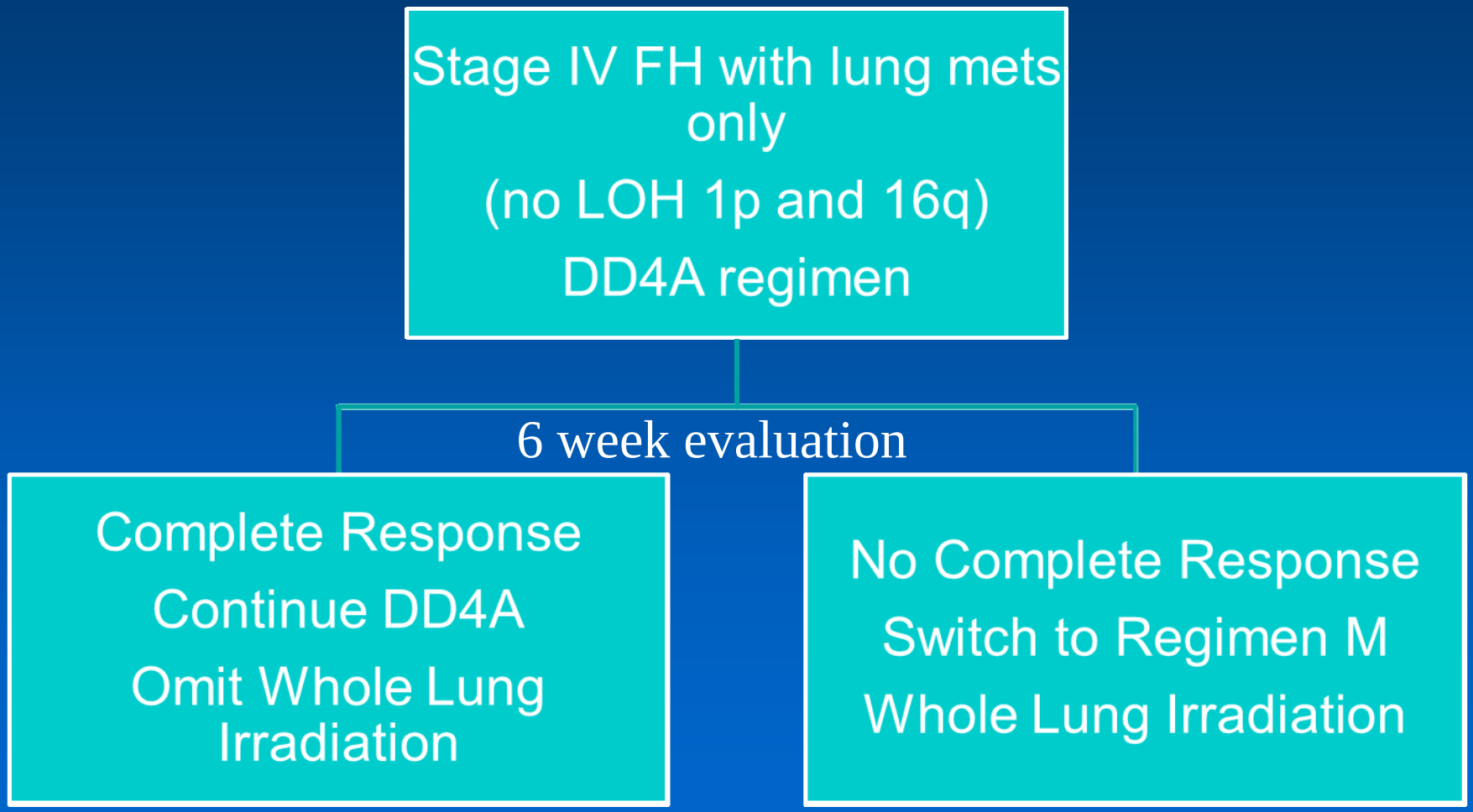
	NWTS-5	AREN0532/ AREN0533
Stage I/II LOH	74.9%	83.9%
Stage III/IV LOH	65.9%	91.5%

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.

Dix DB et al. J Clin Oncol 33, 2015 (suppl; abstr 10009)

AREN0533
Stage IV FH with lung mets



AREN0533
Stage IV FH with incomplete response

- After central radiology review at 6 weeks of chemotherapy, 163 (58.4%) out of 279 isolated lung mets had incomplete response
- The 3-year EFS and OS were 88% and 92%
- 60% of pts had Grade 3 or higher hematologic toxicity
- This showed superior EFS with the addition of cyclophosphamide and etoposide compared to historic standard (DD4A)

Dix DB et al. J Clin Oncol 32, 2014
(suppl; abstr 10001)

AREN0533
Stage IV FH with complete response

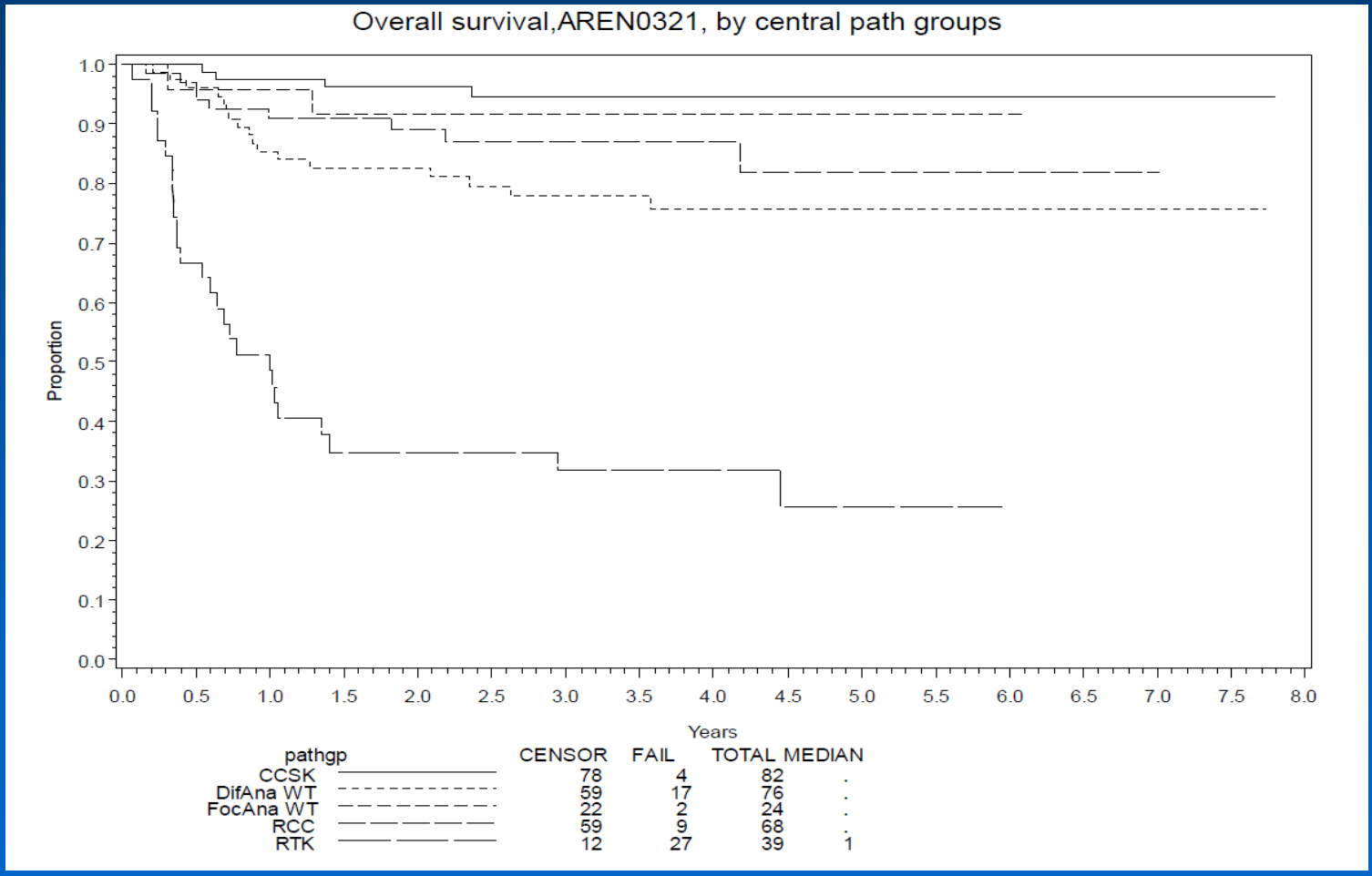
- 105 out of 391 pts had complete response (39%)
- The 4-year EFS and OS estimates were 78% and 95%
- Compared to historical standard treated with lung RT, the difference is not statistically significant. This may provide an acceptable alternative treatment approach for this patient subgroup

Dix DB et al. J Clin Oncol 33, 2015
(suppl; abstr 10011)

Stage IV, FH, Lung Mets Only

	4-year EFS	4-year OS
AREN0533	84.6%	95.2%
NWTS-5	72.4%	84.0%
	P = 0.0007	P < 0.0001

AREN0321


Overall survival,AREN0321, by central path groups
Proportion
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0
Years
pathgp CENSOR FAIL TOTAL MEDIAN
CCSK 78 4 82 .
DifAna WT 59 17 76 .
FocAna WT 22 2 24 .
RCC 59 9 68 .
RTK 12 27 39 1

Stage I Anaplastic

	4-year EFS	4-year OS
AREN0321 (DD4A + XRT)	100%	100%
NWTS-5 (EE4A, No XRT)	69.5%	82.6%

DD4A chemotherapy + XRT is now the recommended treatment

AREN0321 Stage II-IV DAWT

- In NWTS-5, 4 year EFS for diffuse anaplastic Wilms' tumor was 55% using Regimen I (VCR, DOX, CPM, VP-16) and XRT
- AREN0321 employed Regimen UH-1 (Regimen I + carboplatin) and XRT
- XRT dose for Stage III diffuse anaplastic Wilms tumor raised from 10.8 Gy to 19.8 Gy

Daw N et al. Pediatr Blood Cancer 2014: S113

AREN0321

- 66 eligible patients
- 3-year EFS for all patients: 69%
- 4-year EFS for Stage II, III and IV were 85%, 74% and 46%
- State III: Local failure rate ≈ 3% (significantly improved after 20Gy) 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 with more toxicity

Daw N et al. Pediatr Blood Cancer 2014: S113

AREN0321
Stage IV Diffuse Anaplastic

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

Daw NC et al. J Clin Oncol
32:5s, 2014 (suppl; abstr 10032)

AREN0321
Stage IV Diffuse Anaplastic

- 19 pts 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 CCSK Stage I

- 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

AREN0534 Bilateral Wilms Tumor (Ehrlich Annals of Surgery 2017 in press)

- NWTS-5, 4-year EFS (61%) and OS (80%)
- AREN0534 goal was to improve survival and preserve renal tissue by intensifying pre-operative chemotherapy (vincristine, dactinomycin, doxorubicin), complete definitive surgery by week 12
- 249 patients accrued (2009-2015); median follow up 3.75 years
- 4-year EFS (81%) and 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%)

Late Effects among Wilms Tumor Survivors

Congestive Heart Failure in Wilms survivors

(Green DM, JCO 2001)

- 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 per m2 (P< 0.001), lung RT 1.6/10Gy (P0.037), left flank RT 1.8/10Gy (P 0.013)
- New cases continue to be reported 19.9 years after diagnosis
- Long-term monitoring is required for high-risk survivors

Pregnancy Outcomes in Wilms Tumor Survivors

(Green DM, JCO 2010)

- 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:

  a) Pregnancy induced hypertension (P<0.001); b) early/threatened labor (P 0.002), c) fetal malposition (P0.04); d) Premature birth: Infants born before 37 wks gestation (10% no flank RT, 22% with > 35Gy) (P 0.001); d) Low birth weight: Infants with birth weight <2500g (9% no flank RT, 16% with >35Gy) (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

Pulmonary Disease in Wilms Tumor Survivors

(Green DM, PBC 2013)

- 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

Second Malignant Tumors in Wilms Tumor Survivors (Breslow NE, Int J Cancer 2010)

- 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 was 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 > 5years (P0.03)
- 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)

Breast Cancer in Wilms Tumor Survivors

(Lange JM, Cancer 2014)

- 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%)
- The standardized incidence ratio (SIR) for breast cancer after doxorubicin was 19.7 (P0.0002), 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 $\geq$20Gy needs to be revised

End Stage Renal Disease (ESRD) in Wilms Tumor Survivors

(Breslow NE, J Urol 2005; Lange JM, J Urol 2010)

- 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 genito-urinary anomalies (hypospadias, cryptorchidism) and 0.6% for other patients
- Cumulative incidence of ESRD at 20 years after *bilateral* Wilms tumor was 50% in children with Denys Drash syndrome, 90% in children with WAGR syndrome, 25% for genito-urinary anomalies (hypospadias, cryptorchidism) and 12% for other patients
- Children with unilateral and non-syndromic Wilms tumors have a low rate of ESRD
- Children with syndromic Wilms tumor (*WT1* mutations) should be screened *indefinitely* for renal function abnormalities and treated early for impaired renal function (proteinuria, hypertension, renal failure)

Next Generation of COG Wilms tumor protocols

New biomarker – 1q gain

(Gratias EJ, JCO 2016)

- 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 (P0.077), III (P0.01) 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

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 (14.4Gy) underdoses liver tumor*
- Recent reports 75% survival for liver mets FH WT
- AP-PA technique: 6 WT protocols (NWTS and COG)
- 20Gy prescribed dose: at the renal tolerance of the only remaining kidney

Liver (tumor) Dose

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

- 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>14Gy)

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

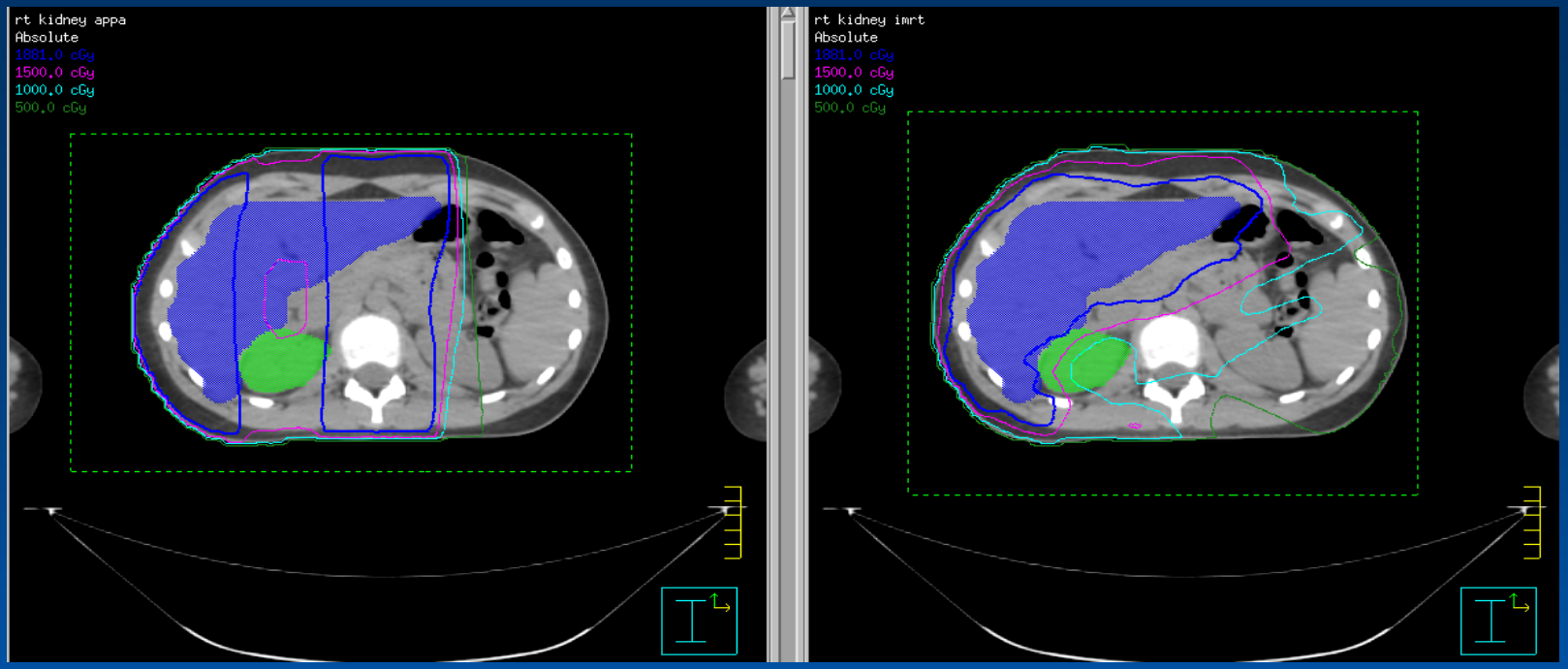
Remaining kidney Dose after Whole Liver RT *(in spite of kidney block at 14.4Gy w/AP-PA, lower liver dose w/AP-PA)*

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
1881.0 cGy
1500.0 cGy
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rt kidney imrt
Absolute
1881.0 cGy
1500.0 cGy
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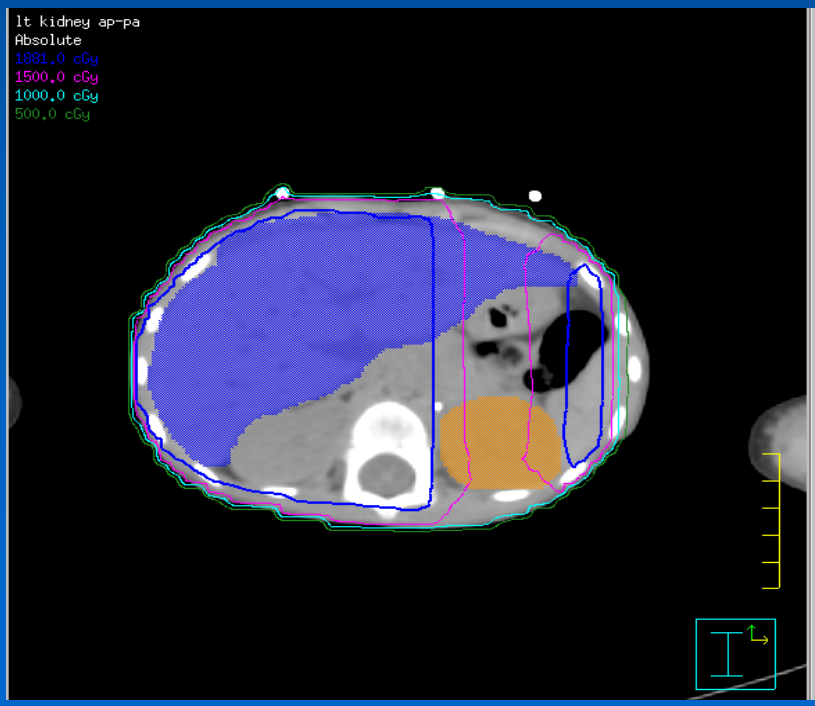
500.0 cGy


lt kidney ap-pa
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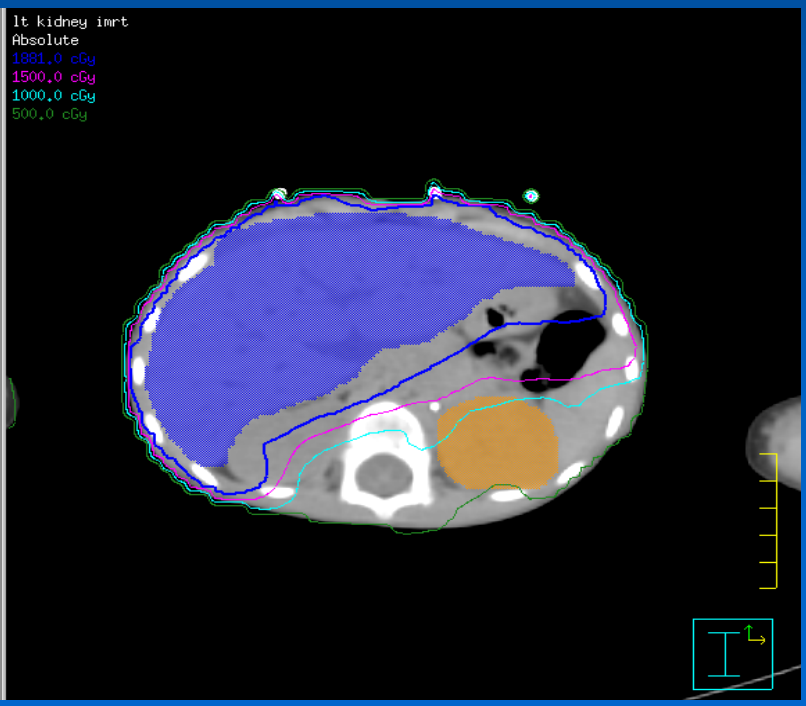
lt kidney imrt
Absolute
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1500.0 cGy
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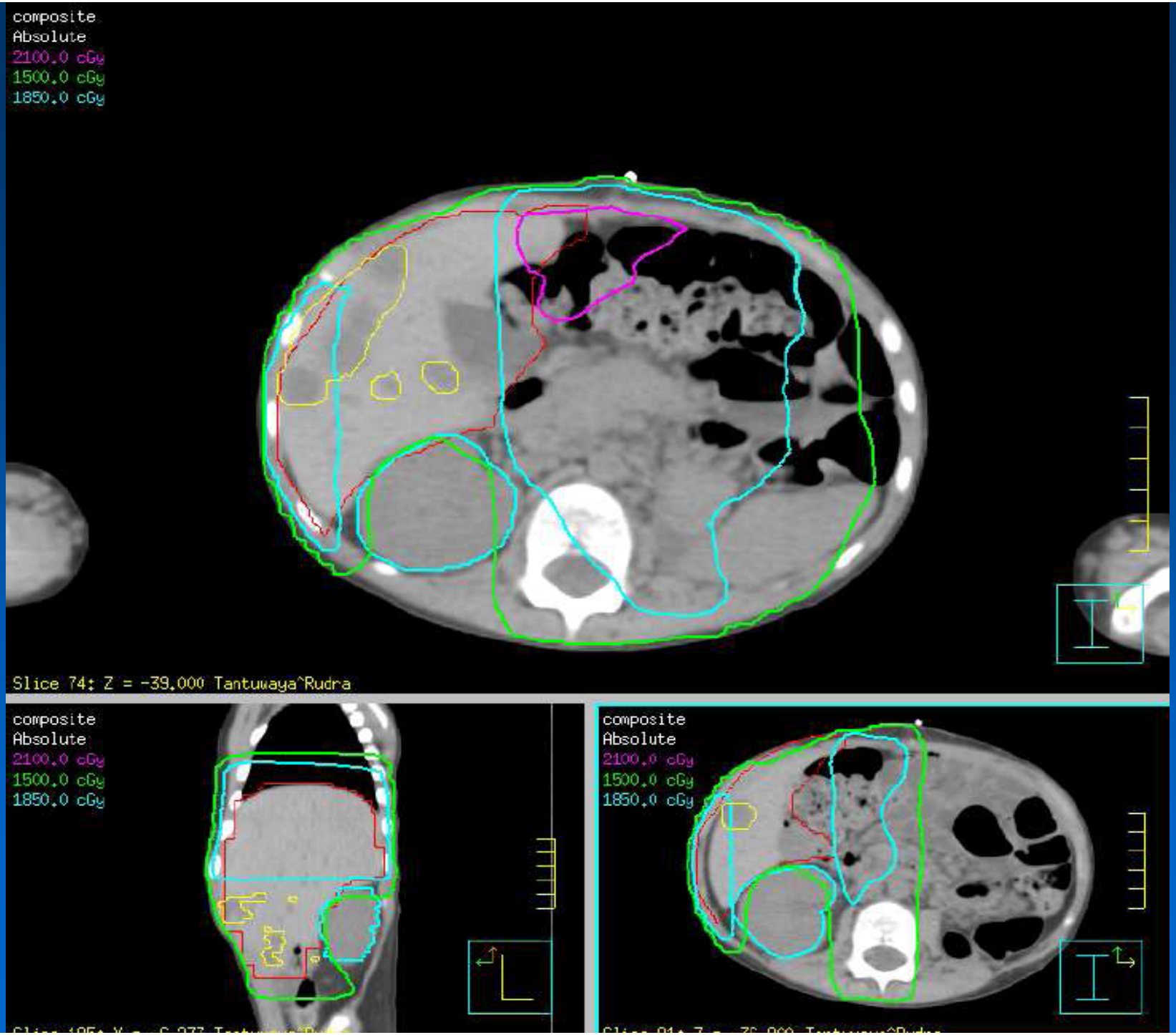
composite
Absolute
2100.0 cGy
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Slice 74: Z = -39.000 Tantuwaya^Rudra
composite
Absolute
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composite
Absolute
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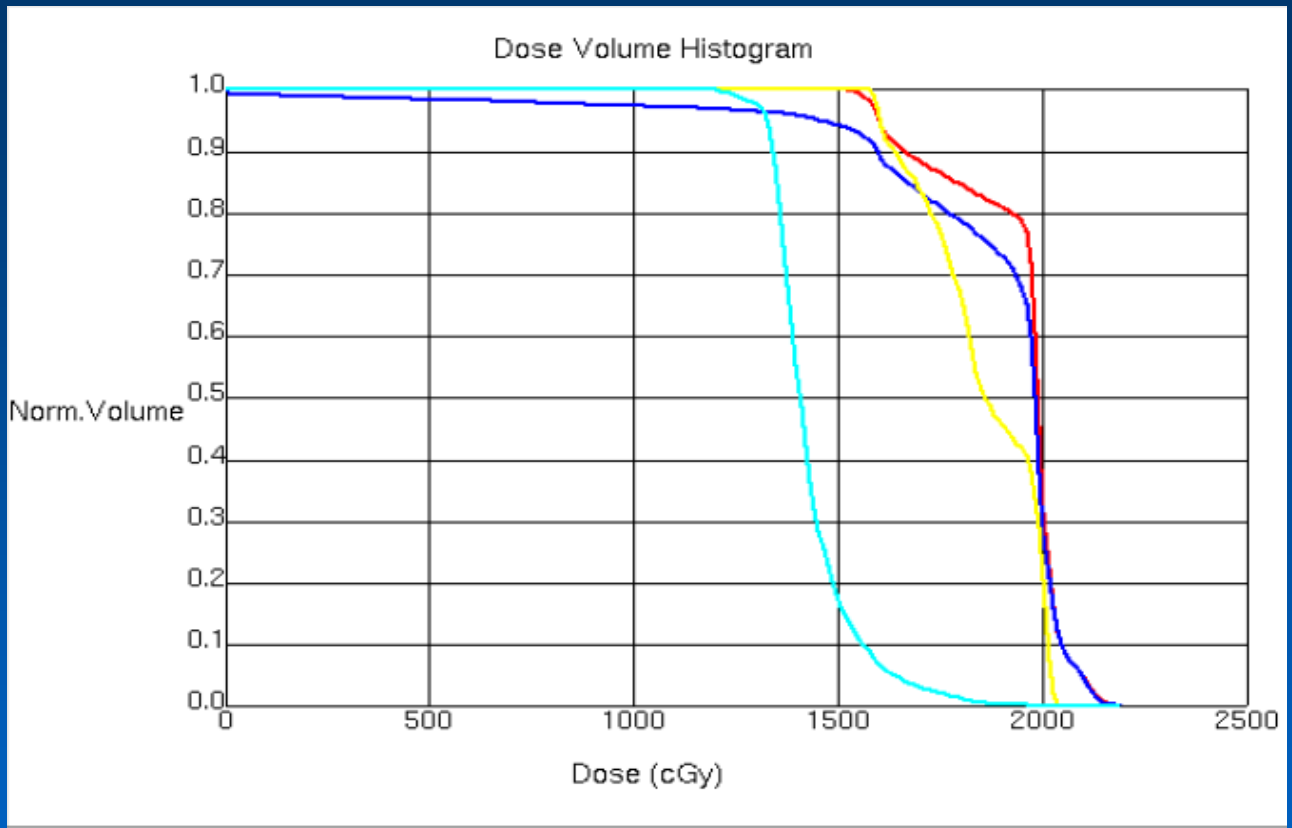
1850.0 cGy

DVH with AP-PA technique (COG)



ROI Statistics

Line Type	ROI	Trial	Min.	Max.	Mean	Std. Dev.
	Liver	composite	919.7	2188.9	1943.3	140.3
	Liver PTV	composite	--	2188.9	1872.7	316.9
	Liver mets multiple	composite	1544.1	2037.9	1859.2	139.9
	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 12-15Gy

- Cardiac complications: NWTS 20 year CHF rate was 4.4% after initial treatment and17.4% after DOX for relapse (last event 24yrs)

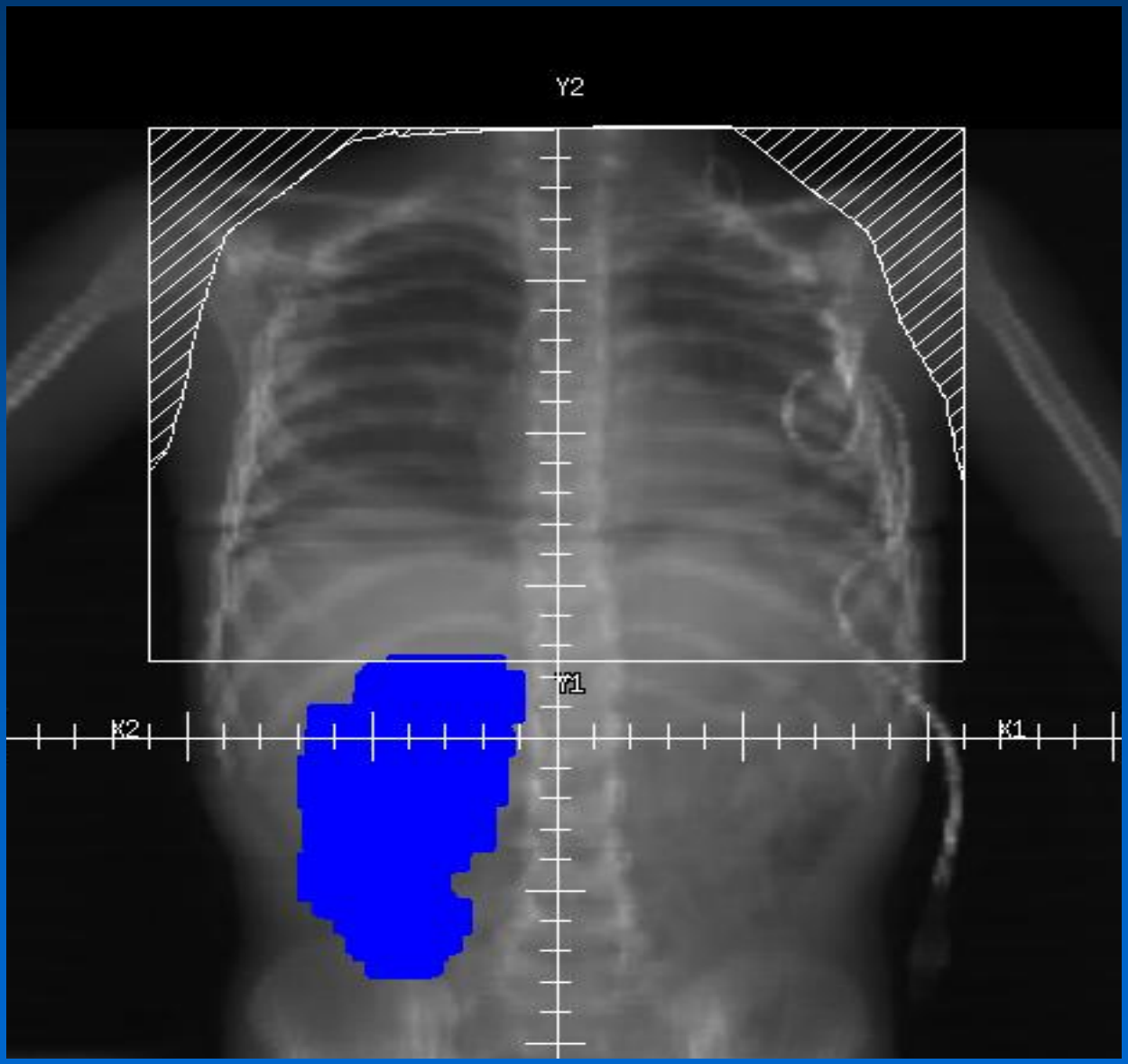
- CHF significantly higher in females RR 4.5; by DOX dose RR 3.3/100mg/m^2; lung RT RR 1.6/10Gy; left abdominal RT RR 1.8/10Gy

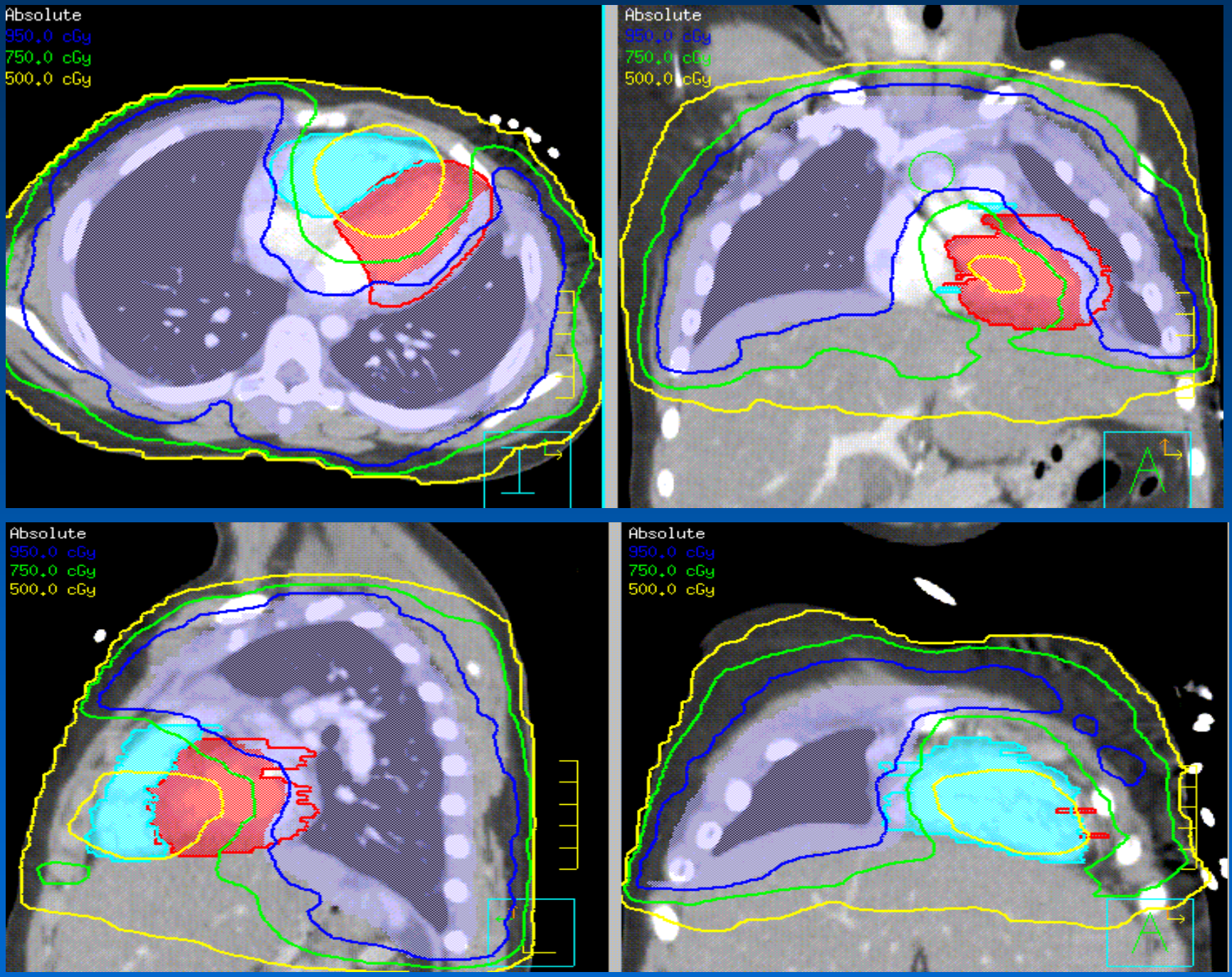
- CCSS, Gustave Roussy, French-British study – cardiac mortality RR increased after mean dose > 5Gy with anthracyclines >360mg/m^2

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

NWTS 1-5 and COG Trials




Absolute
950.0 cGy
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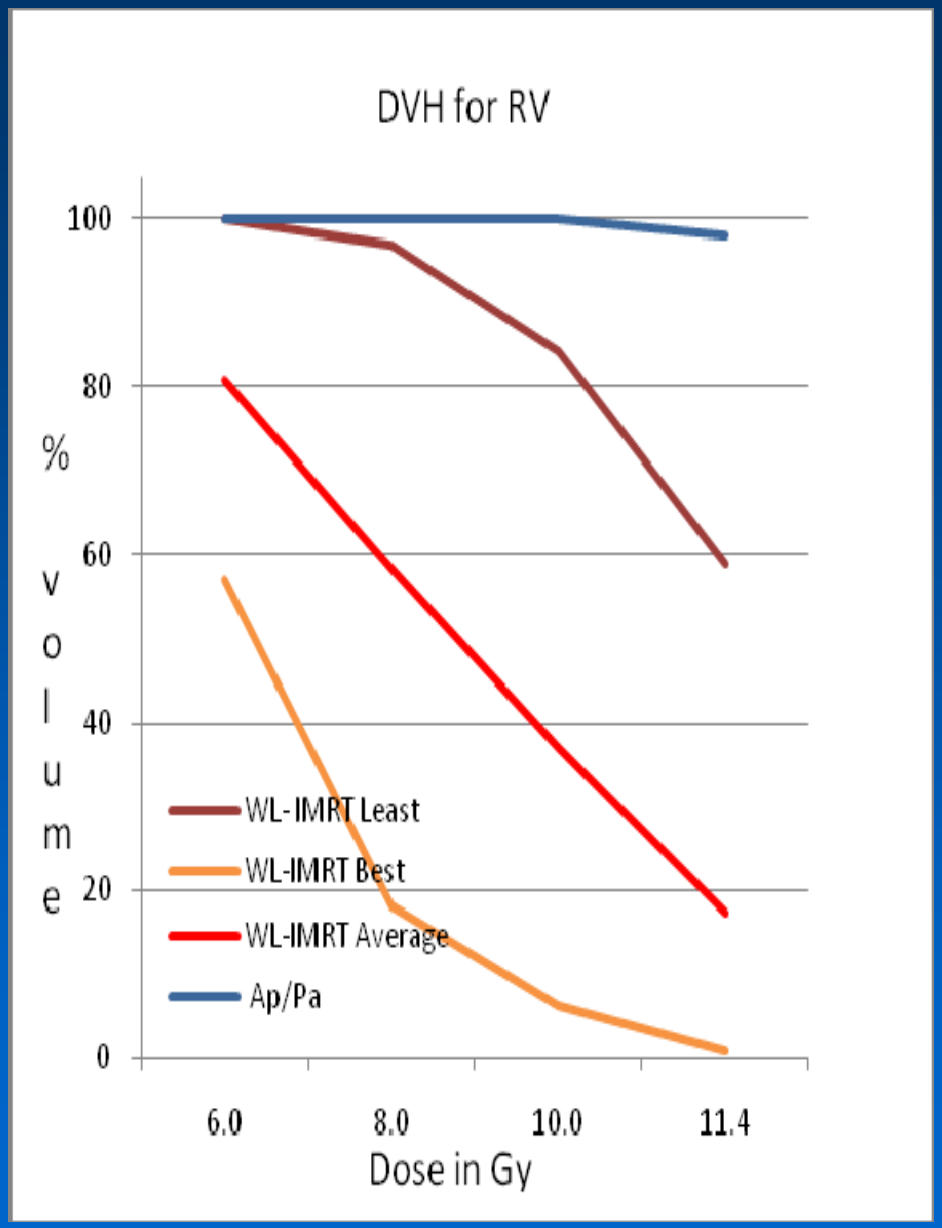
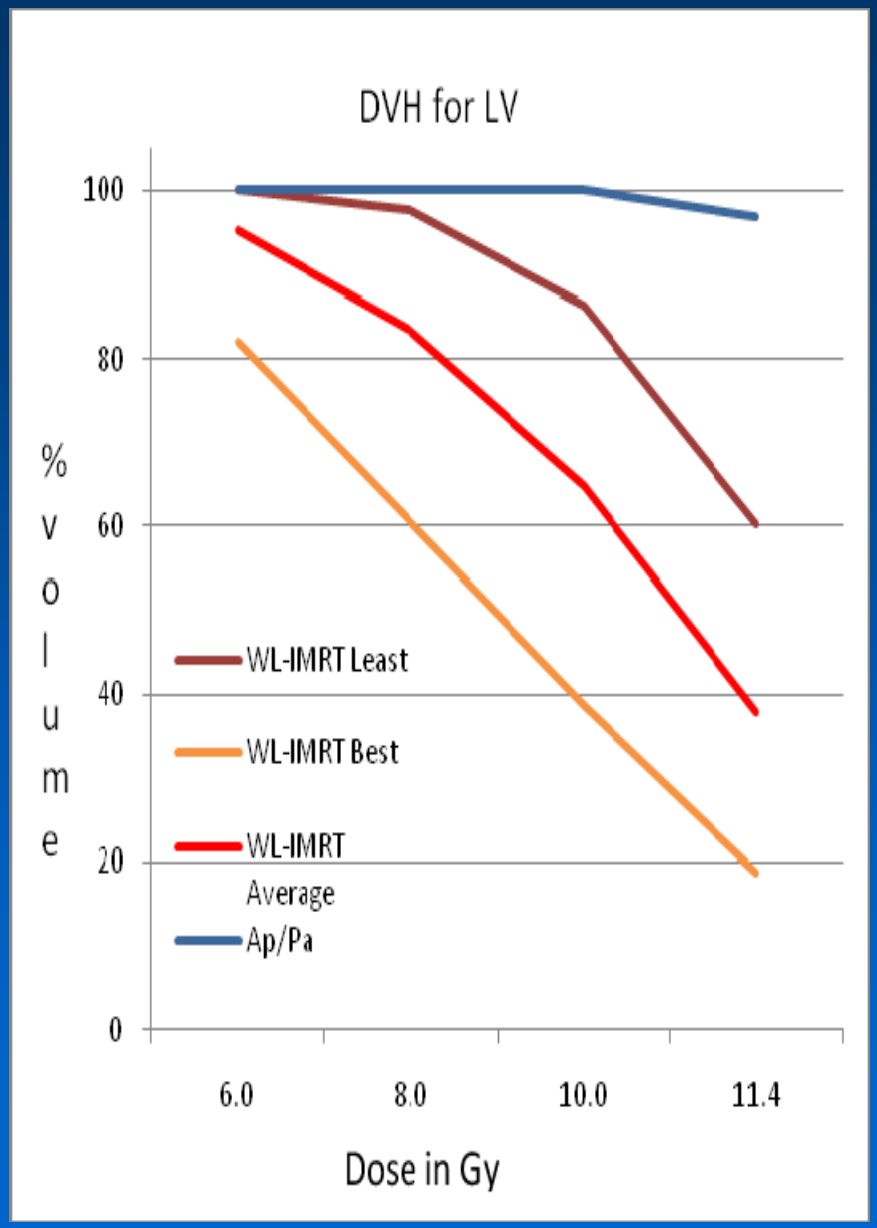

DVH for RV
100
80
60
40
20
0
% volume
WL-IMRT Least
WL-IMRT Best
WL-IMRT Average
Ap/Pa
6.0
8.0
10.0
11.4
Dose in Gy


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 (1cm 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

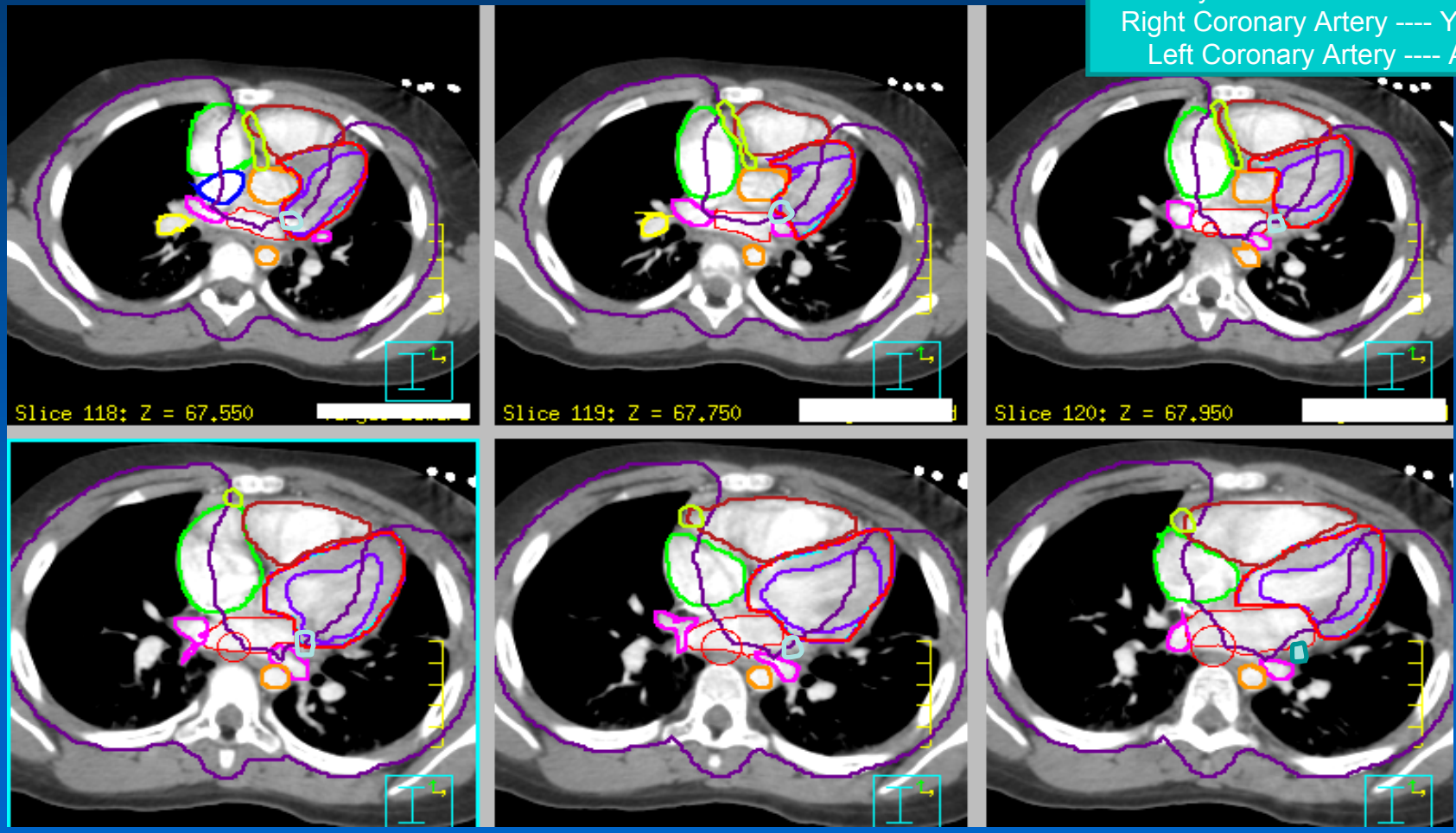
- Dose uniformity: 95% PTV should receive at least 95% of prescribed dose; ≥2% of the PTV >105%, ≥1% >110% of the prescribed dose

- 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 yrs (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 15Gy using a median of 9 field angles
- Dose: 15Gy (15pts); 12 Gy (5pts)
- Prescription isodose: median 100% (98% - 100%)

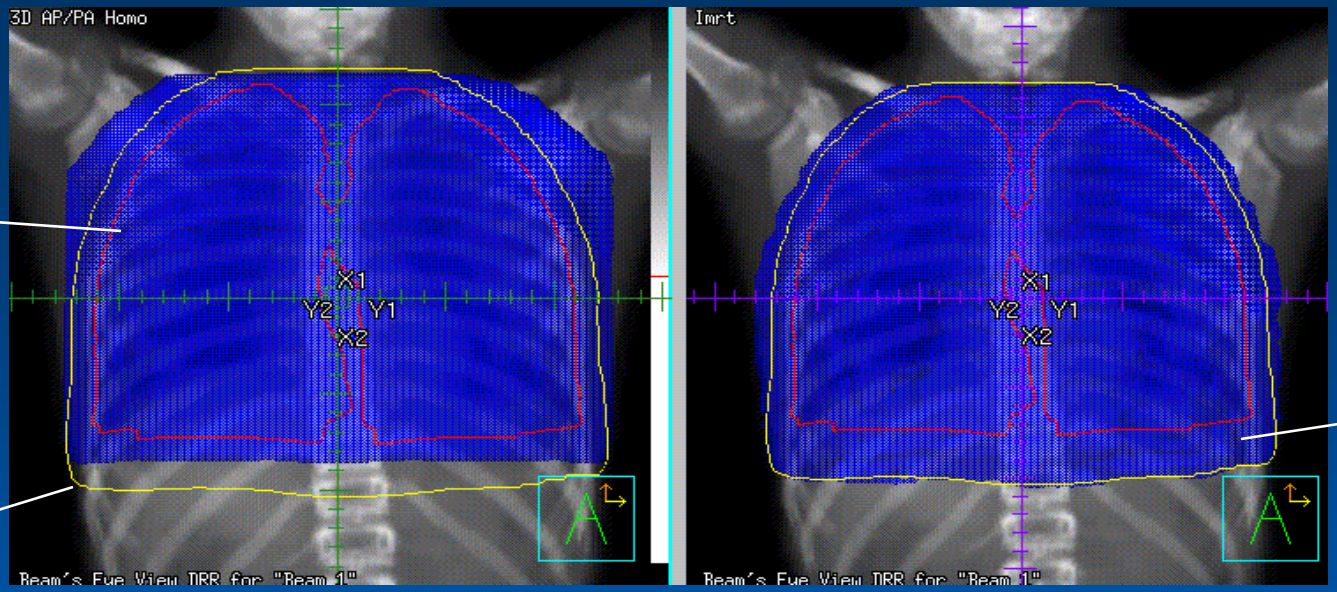
Aim # 2 Dosimetry comparison between CS-IMRT and AP-WLI

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

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

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

3D lung volume

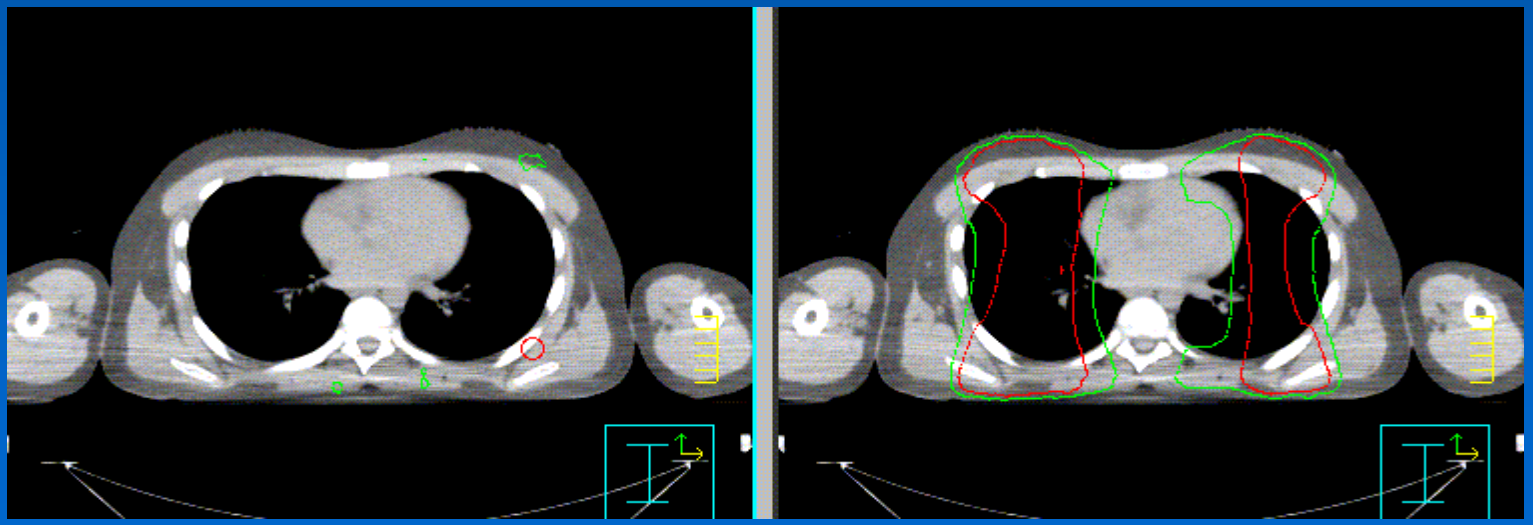


95% IDL

4D PTV

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 (14.3Gy)	97%	39%	<0.0001
V83 (12.5Gy)	99.2%	65%	<0.0001
V67 (10Gy)	99.5%	85%	<0.0001
V50 (7.5Gy)	99.7%	96%	0.0083

Mean left ventricle volume dose

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

Mean right ventricle volume dose

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

Mean Myocardium volume dose

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

Mean left coronary artery volume dose

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

Mean right coronary artery volume dose

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

FUTURE DIRECTIONS IN COG

- Use novel molecular biomarkers for COG risk stratification: 1q gain, LOH 1p and 16q for *stage I-IV* and LOH11p15 for *very low risk tumors after surgery only*
- Use IMRT for lung and liver metastasis with QARC central review
- Re-evaluate need for RT for patients after preoperative chemotherapy
- Re-evaluate need for WA RT in children with localized preoperative tumor rupture limited to the flank without ascites or peritoneal implants
- Intensify therapy for children with stage III FH and lymph node metastases who have a higher risk of tumor relapse
- To determine the value of surgical resection or focal radiation therapy boost doses to residual lung lesions after whole lung irradiation
- Reduce the dose of cyclophosphamide in regimen M to reduce gonadal toxicity