MANAGEMENT OF WILMS TUMOUR- ROLE OF RADIOTHERAPY

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EPIDEMIOLOGY

Wilms tumour (nephroblastoma)-embryonic kidney tumor

Most common abdominal tumour in children- 6% of childhood cancer

Incidence rate in children younger than 15 years is 7 per million population

-Birch et al. Hematol Oncol Clin North Am 1995;9:1157–1178.

470 to 500 new cases in the US per year

>75% patients present before 5 years of age

Children present with more advanced disease in less developed nations

MOLECULAR BIOLOGY

	Function	Locus	Syndromic association	Frequency of gene aberration
	Tumour suppressor gene Role in glomerular & gonadal development	11p13	WAGR (WT, aniridia, genito-urinary malformation, mental retardation) Denys-Drash syndrome (pseudohermaphroditism, mesangial sclerosis, renal failure, WT)	Germline mutation 82% in pts with ren failure/ GU anomal 10-20% of sporadic 4% of familial WT
	Effect on IGF2, the H19 tumor suppressor gene, and the P57 cell cycle regulator	11p15.5	Beckwith- Wiedemann syndrome (somatic gigantism, omphalocele, macroglossia, genitourinary abnormalities, ear creases, hypoglycemia, hemihypertrophy)	LOH 11p15.5 in~30 Loss of imprinting o IGF2 in~ 40% of spo WT
	Tumour suppressor gene	Xq11.1	-	WTX inactivation in of sporadic WT
1	Encodes β-catenin Role in WNT pathway	3p21	-	Gain of function mutation in~ 10% o sporadic WT

CLINICAL PRESENTATION

Abdominal mass (80-90%)

Abdominal pain (30-40%)

Haematuria (20-25%)

Fever (20-25%)

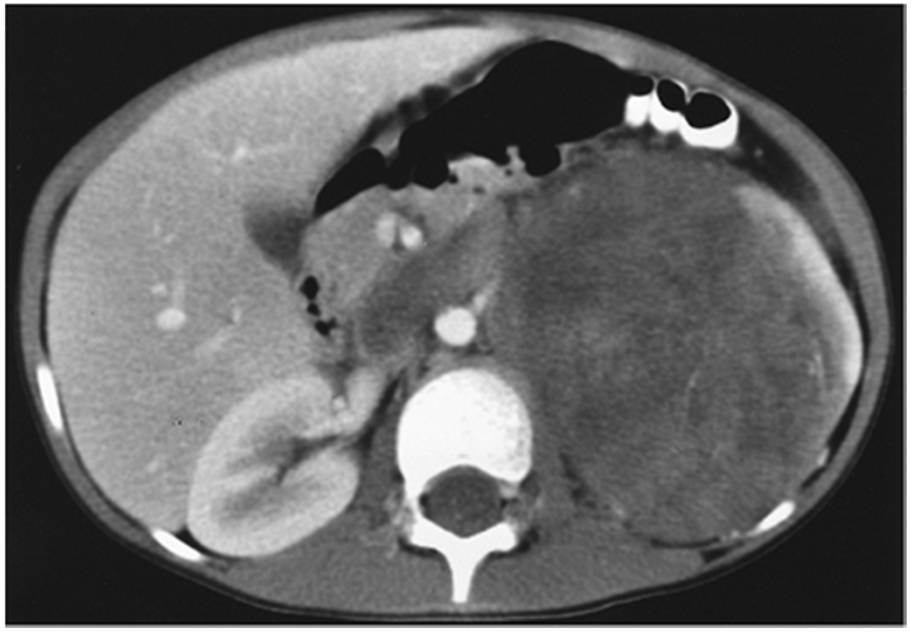
Hypertension

Varicocele

Metastatic symptoms-rare

DIAGNOSTIC WORK-UP

	Record pre-existing conditions, family history of cancer, or congenital defects
amination	Blood pressure, weight, height, presence of abdominal masses, congenital anomalies particularly genitourinary, hemihypertrophy, and aniridia
	Hemoglobin, white cell, and differential counts, platelets, urinalysis, serum blood urea nitrogen, creatinine, protein, alanine, and aspartate aminotransferases, alkaline phosphatase, bilirubin
	CT or MRI scan of the abdomen and pelvis, abdominal ultrasonography, chest CT scan, chest x-ray
	Bone scan and MRI of the brain (CCSK, RTK, and renal cell carcinoma)



STAGING

Tumor limited to kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection. *Note:* For a tumor to qualify for certain therapeutic protocols as stage I, regional lymph nodes must be examined microscopically.

The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond kidney, as is evidenced by any one of the following criteria[a]:

- There is regional extension of the tumor (i.e., penetration of the renal capsule or extensive invasion of the soft tissue of the renal sinus)
- Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor.

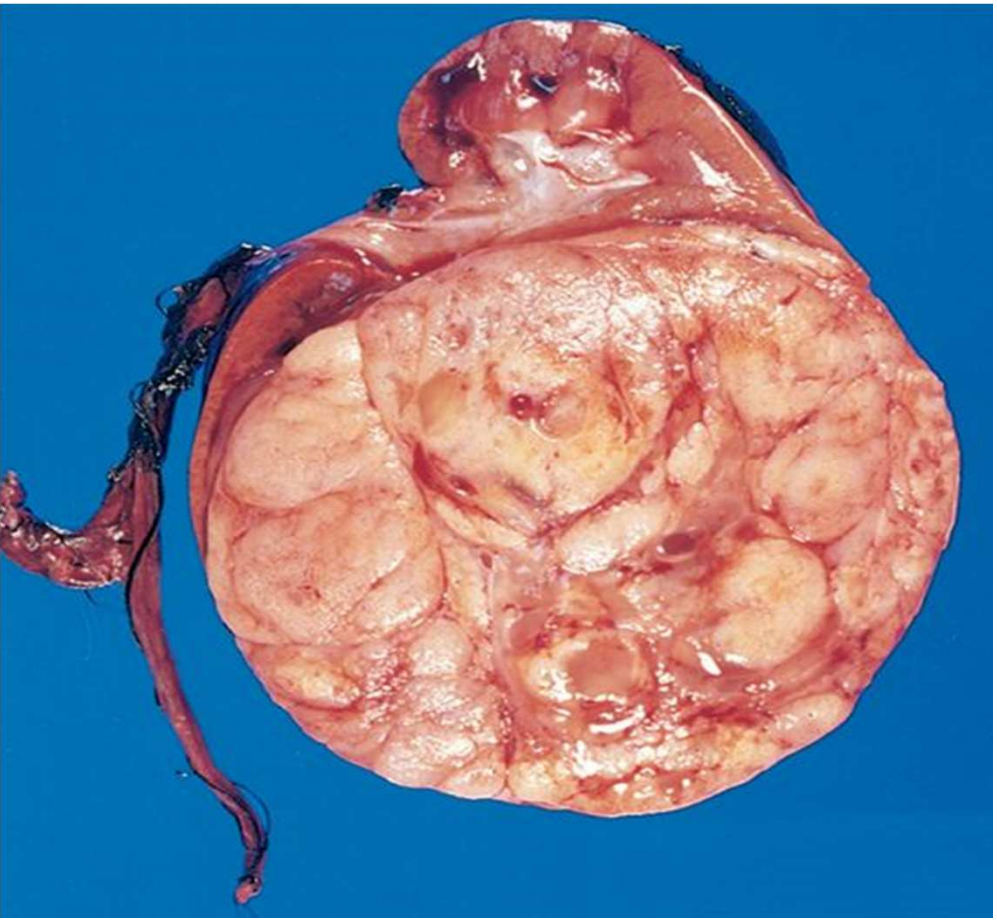
Stage III: Residual nonhematogenous tumor present following surgery an confined to abdomen. Any one of the following may occur:

- Lymph nodes within the abdomen or pelvis are involved by tu (Lymph node involvement in the thorax or other extra-abdom is a criterion for stage IV.)
- The tumor has penetrated through the peritoneal surface
- Tumor implants are found on the peritoneal surface
- Gross or microscopic tumor remains postoperatively (e.g., tumo found at the margin of surgical resection on microscopic exami
- The tumor is not completely resectable because of local infiltra vital structures
- Tumor spillage occurring either before or during surgery
- The tumor was biopsied (whether tru-cut, open, or fine-needl tion) before removal
- Tumor is removed in more than one piece (e.g., tumor cells a in a separately excised adrenal gland; a tumor thrombus withi renal vein is removed separately from the nephrectomy speci

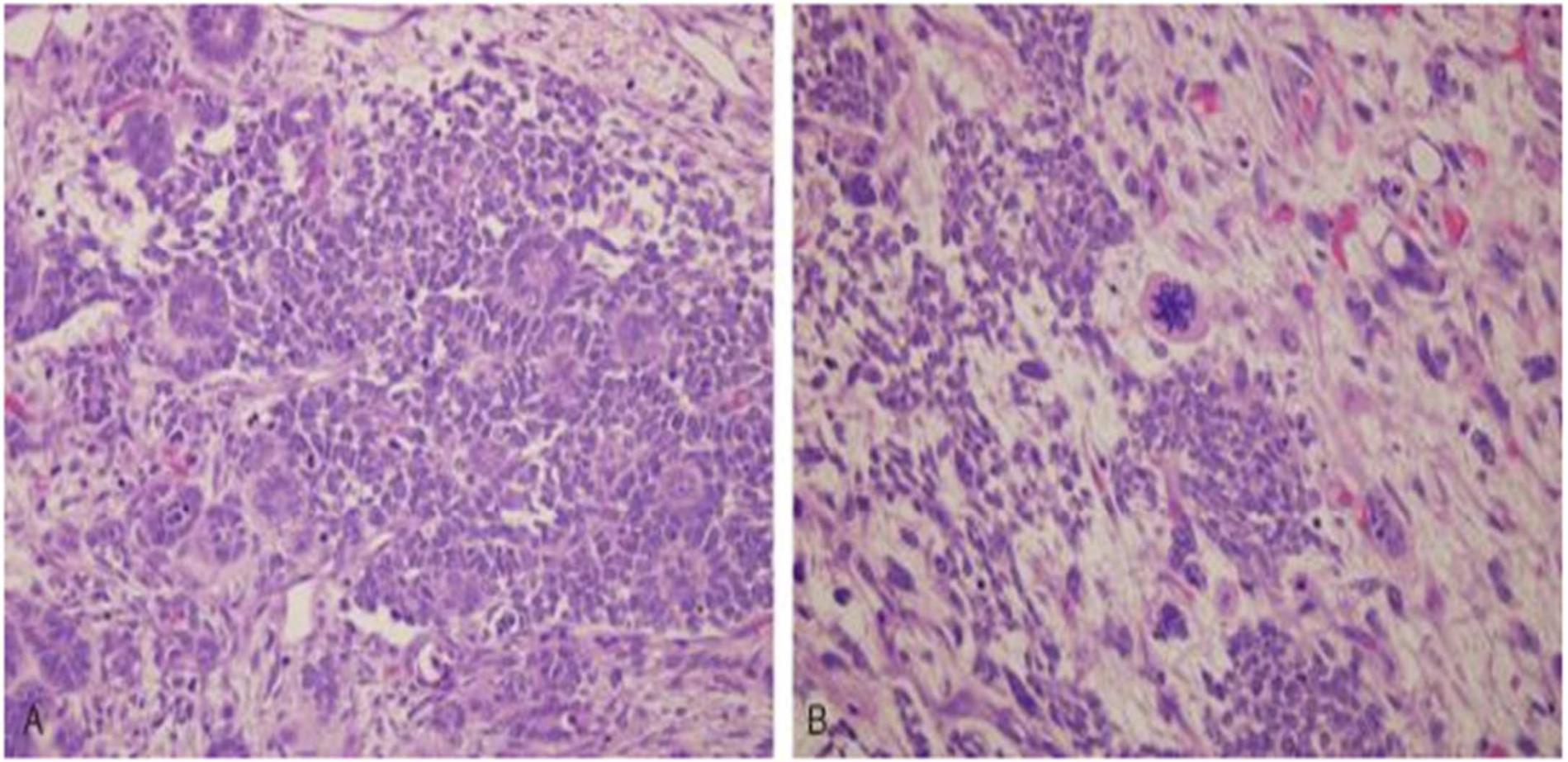
Stage IV: Hematogenous metastases (i.e., lung, liver, bone, brain) or lymph node metastases outside the abdominopelvic region are present. (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present.)

Stage V: Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the criteria here on the basis of the extent of disease.

PATHOLOGY



- Soft, homogeneous, tan to grey in colour with occasional foci of haemorrhage & necrosis
- Well circumscribed margin
- Enclosed by renal capsule/fibrous pseudo-capsule
- Bilateral-7% & multifocal -12% of cases
- Tumor can contain a mixture of cells:
  - blastemal cells
  - stromal cells
  - epithelial cells
- High degree of anaplasia associated with poor outcomes



(A) WT with tightly packed blue cells consistent with blastemal component & interspersed primitive tubules, representing the epithelial component. Although multiple mitotic figures are seen, none are atypical in this field; (B) Focal anaplasia present in other areas characterised by cells with hyperchromatic, pleomorphic nuclei & abnormal mitoses

TREATMENT OPTIONS: NWTS VERSUS SIOP

NWTS

Treatment principle: Nephrectomy→ adjuvant chemo ±RT

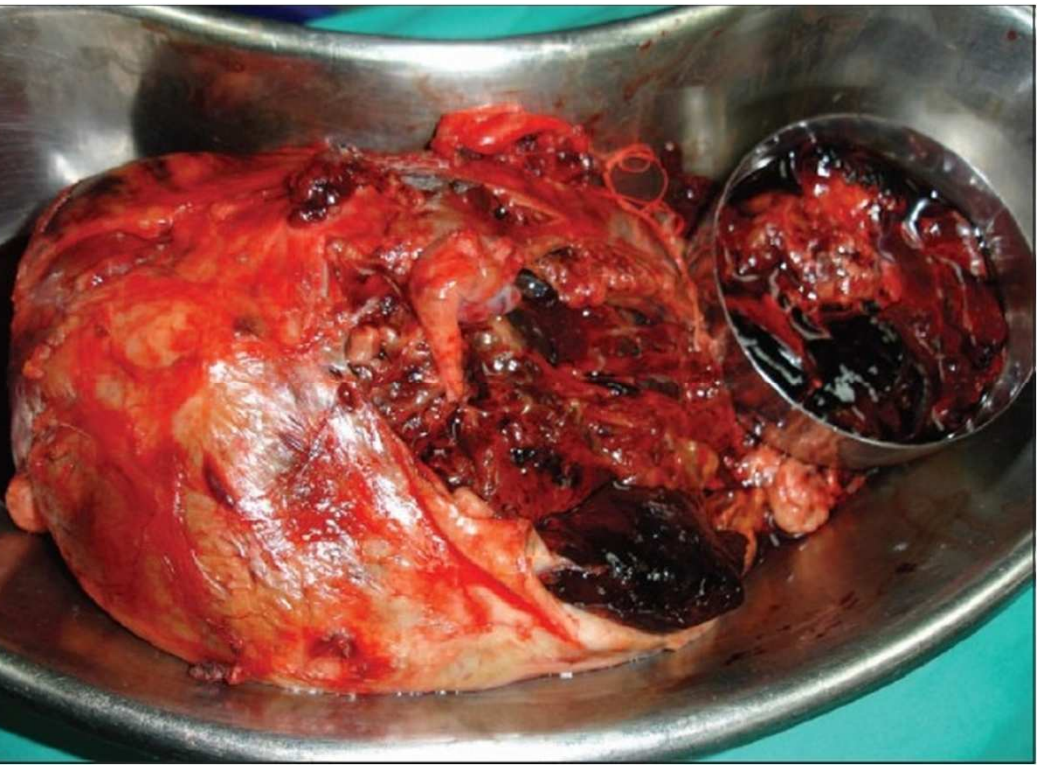
Advantages: Avoidance of

- ➢ Administration of chemo to a patient with benign disease
- ➢ Administration of chemo to a patient with a different histological type of malignant tumour
- ➢ Modification of tumour histology
- ➢ Loss of staging information

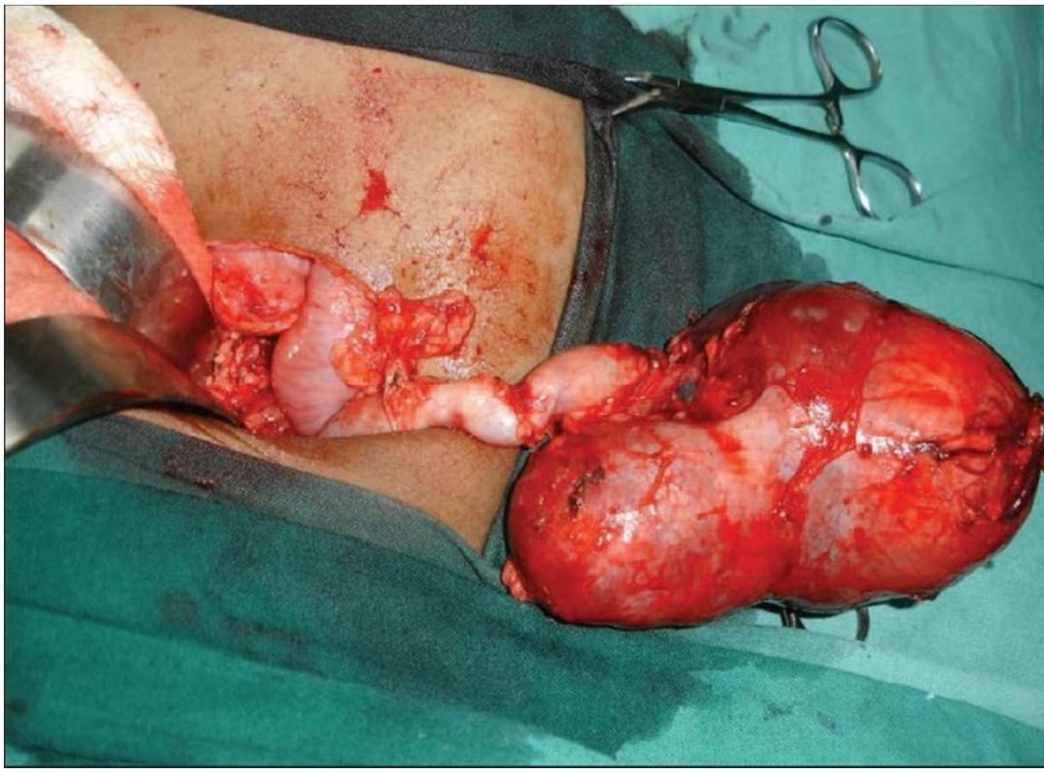
SIOP

- Treatment Principle: Pre-op chemo→ Nephrectomy→ adjuvant chemo ±RT
- Advantages:
  - ➢ Tumour downsizing thereby making surgery simpler and ↓ing intra-op tumor rupture & intra-abd recurrence
  - ➢ Makes nephron sparing surgery possible

Intra-op tumour spillage in NWTS protocol



Tumour downsizing with pre-op chemo in SIOP protocol



NWTS 1-4 SCHEMA

NWTSG study	Disease stage[a]	Treatment protocols[b]	
		RT	Chemotherapy
1	I	RT vs no RT	A
	II, III	RT	A vs V vs A + V
	IV	RT	A + V
2	I	no RT	A + V
	II, III, IV	RT	A + V vs A + V + D
3	I	no RT	A + V
	II	no RT vs 20 Gy	A + V vs A + V + D
	III	10 Gy vs 20 Gy	A + V vs A + V + D
	IV	RT	A + V + D vs A + V + D + C
4	I	no RT	A + V
	II	no RT	A + V
	III, IV	RT	A + V + D

NWTS-1 (1969 – 1974)

- Is post-op RT necessary in group I disease?
- Is single agent chemo with vincristine (VCR) or actinomycin D (AMD) equivalent to combining these drugs for group II and III disease?
- Is preoperative VCR of value in group IV disease?
- Radiation doses adjusted for age
  - Birth – 18 mo: 18 to 24 Gy
  - 18 – 30 mo: 24 to 30 Gy
  - 31- 40 mo: 30 to 35 Gy
  - 41 mo or older: 35 – 40 Gy

-D'Angio et al. Cancer 1976;38:633–646.

NWTS-1 RESULTS

Post-op RT not needed for group I <2 yrs

VA better than either agent alone for group II and III

Pre-op VCR not useful in group IV

4 yr RFS for group I pts >2 yrs treated with AMD +RT- 76%

4 yr RFS for group II/III pts treated with VA + RT- 79%

NWTS-1 RESULTS

2-year RFS:
- Favorable histology- 89%
- Unfavorable histology- 29%

Poor prognostic factors
- Large tumor size
- Lymph node involvement
- Age >2 years

No RT dose response between 10-40 Gy

Delays of ≤ 10 days for post-op RT found acceptable

WAI not necessary for tumor spills confined to the flank

NWTS-2 (1974-79)

Can VA substitute for RT in older children with Group I disease?

Is protracted period of adjuvant VA helpful for Groups II – IV disease?

Is addition of Doxo to VA of value in Groups II – IV disease?

-D'Angio et al. Cancer 1981;47:2302–2311.

NWTS-2 RESULTS

VA can substitute for RT in Group I disease

VA x 6 months = VA x 15 months for Group I disease

Addition of Doxo to VA+RT for Group II-IV disease provided benefit

Worse 2-year survival for LN + disease (54% vs 82%) and patients with unfavorable histology (54% vs 90%)

NWTS-3 (1979-85)

Patients stratified by stage instead of group

FH & UH incorporated in the treatment algorithm

Five questions

- Can duration of chemotherapy be shortened for Stage I FH?
- Can RT be eliminated for Stage II FH?
- What is the minimum effective RT dose for Stage III FH?
- Is Doxo clearly beneficial and necessary for Stage II & III FH?
- Will addition of CTX improve survival in Stage I – IV UH and Stage IV FH?

-*Green et al. Pediatr Clin North Am 1991;38:475-488.*

NWTS-3

- Stage I FH: VA (no RT) 24 vs 10 weeks
- Stage II FH: 3 vs. 2 drugs (VA±D) ± RT 20 Gy
- Stage III FH: 3 vs. 2 drugs (VA±D) + RT 10 vs. 20 Gy
- Stage IV FH and all UH: RT + 3 drugs ± CTX

NWTS-3 RESULTS

Stage I: VA x 10 wks vs. VA x 24 wks equivalent

- 4-year RFS 89% & OS 96%

Stage II: no difference between 2 or 3 drugs with or without RT

- 4-year RFS 87% & OS 91%

Stage III: No stat sig difference in abdominal relapse between 10 and 20 Gy of RT; trend favored use of Doxo or 20 Gy of RT

- 4-year RFS 82% & OS 91%

NWTS-3 RESULTS

Stage IV FH: 4 drugs equal to 3 drugs (both included flank RT/WAI + WLI)

- 4-year RFS 79% & OS 80%

Anaplasia

- ➢4 drugs better than 3 drugs for stage II-IV
- ➢Trend toward improved outcome with 4 drug regimen for CCSK
- ➢4 yr OS -25% for RTK in both arms

NWTS-4 (1986 – 1994)

Addressed issues of minimization of therapy and customization by stage & histology

Evaluate the role of pulse dosed intensive chemotherapy

-*Green et al. J Clin Oncol* 1998;16:237–245.

NWTS-4 SCHEMA

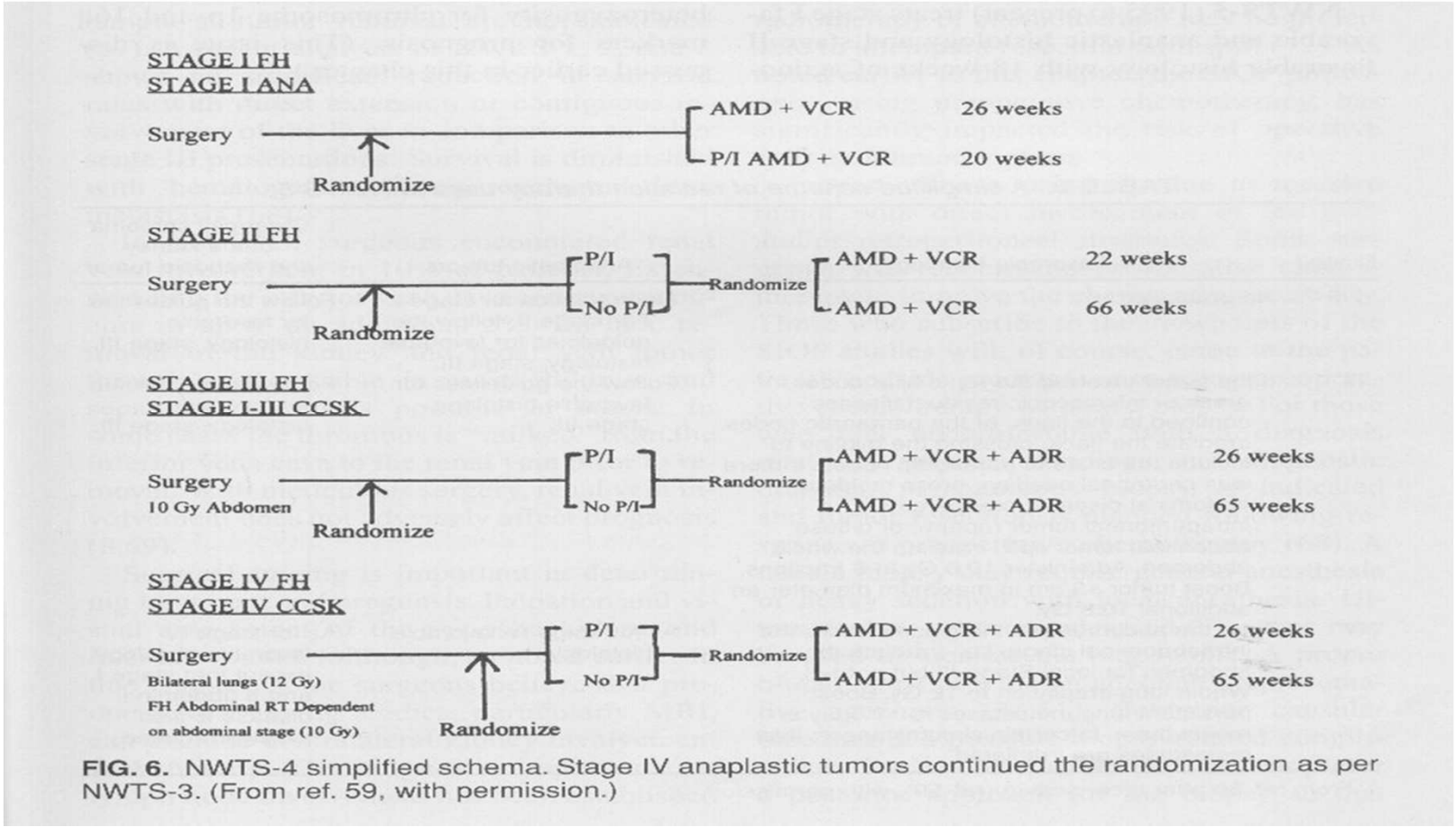


FIG. 6. NWTS-4 simplified schema. Stage IV anaplastic tumors continued the randomization as per NWTS-3. (From ref. 59, with permission.)

NWTS-4 RESULTS

Pulse–intensive chemotherapy feasible, produce less hematologic toxicity and allow for increased drug dose-intensity

Cost analysis showed savings of $790,000 a year in the US if all Wilms patients were treated on pulse-intensive regimens

NWTS-5 SCHEMA

Stage	FH	ANAPLASTIC (UH)		CCSK	RTK
		Focal	Diffuse		
I	$(VA_{pi})_{18wk}$ No XRT	$(VA_{pi})_{18wk}$ No XRT		$(VD,VP\text{-}16,CY)_{24wk}$ 10.8 Gy flank[a] 10.8 Gy boost[b]	$(Carbo,VP\text{-}16,CY)_{24wk}$ 10.8 Gy flank[a] 10.8 Gy boost[b]
II	$(VA_{pi})_{18wk}$ No XRT	$(VAD)_{24wk}$ 10.8 Gy flank[a] 10.8 Gy boost[b]	$(VD,VP\text{-}16,CY)_{24wk}$ 10.8 Gy flank[a] 10.8 Gy boost[b]		
III	$(VAD)_{24wk}$ 10.8 Gy flank[a] 10.8 Gy boost[b]				
IV	$(VAD)_{24wk}$ 10.8 Gy flank[a] 10.8 Gy boost[b] 12 Gy lungs[c] 19.8 Gy liver 30.6 Gy brain 30.6 Gy bone	$(VD,VP\text{-}16,CY)_{24wk}$ 10.8 Gy flank[a] 10.8 Gy boost[b] 12 Gy lungs[c] 19.8 Gy liver 30.6 Gy brain 30.6 Gy bone		$(Carbo,VP\text{-}16,CY)_{24wk}$ 10.8 Gy flank[a] 10.8 Gy boost[b] 12 Gy lungs[c] 19.8 Gy liver 30.6 Gy brain 30.6 Gy bone	
Relapsed WT	12.6-18 Gy (<12 mo of age) and 21.6 Gy in older children if previous XRT is =< 10.8 Gy 9 Gy boost to residual s/p surgery 30.6 Gy max dose (<1 y of age) and 39.5 Gy max dose in older children				

FH = Favorable Histology, UH = Unfavorable Histology, V = Vincristine, A = Actinomycin-D, D = Doxorubicin, VP-16 = etoposide, CY = cyclophosphamide, Carbo = carboplatin, $_{pi}$ = pulse intensive, $_{wk}$ = weeks

[a]Whole-abdomen XRT for diffuse peritoneal implants, preoperative anterior rupture or diffuse abdominal operative spillage

[b]Boost to gross (>3cm) disease residual after surgery

[c]In patients with FH disease, if pulmonary nodules are visible on CT scans but are not detected on chest x-ray, then whole-lung irradiation is not mandatory

-Grundy et al. J Clin Oncol 2005;23:7312–7321.

NWTS-5 RESULTS-LOH 1p / 16q

	LOH	#Pts	# Relapses	% 4 yr RFS	RR relapse	p value
1p	Loss	195	37	79.9	1.56	0.01
	None	1529	198	86.2	1.0	
16q	Loss	301	58	79.9	1.49	0.01
	None	1423	177	86.7	1.0	

LOH 1p associated with significantly worse RFS in Stage II but not Stage III/IV

Suggests that adverse effects of LOH 1p can be overcome by more aggressive chemotherapy

-Grundy et al. J Clin Oncol 2005;23:7312–7321.

NWTS-5 SELECTED RESULTS - FH

Stage I FH: 4 y RFS 92% & OS 98%

Stage II FH: 4 y RFS 83% & OS 92%

Stage III FH: 4 y RFS 85.3% & OS 93.9%

Stage IV FH: 4 y EFS 74.6% (most of these patients ↓WLI)

NWTS-5 SELECTED RESULTS UH

Diffuse Anaplasia:2 yr EFS-

- Stage I- 64.3 %
- Stage II- 79.5%
- Stage III- 62.7%
- Stage IV- 33.6%

CCSK:4 yr RFS-

- Stage I –IV- 77.6%
- 6/9 Stage IV pts relapsed

- RTK
  - Stage I- 50%
  - Stage II- 33.3%
  - Stage III- 33.3%
  - Stage IV- 21.4 %
  - Stage V- 0%

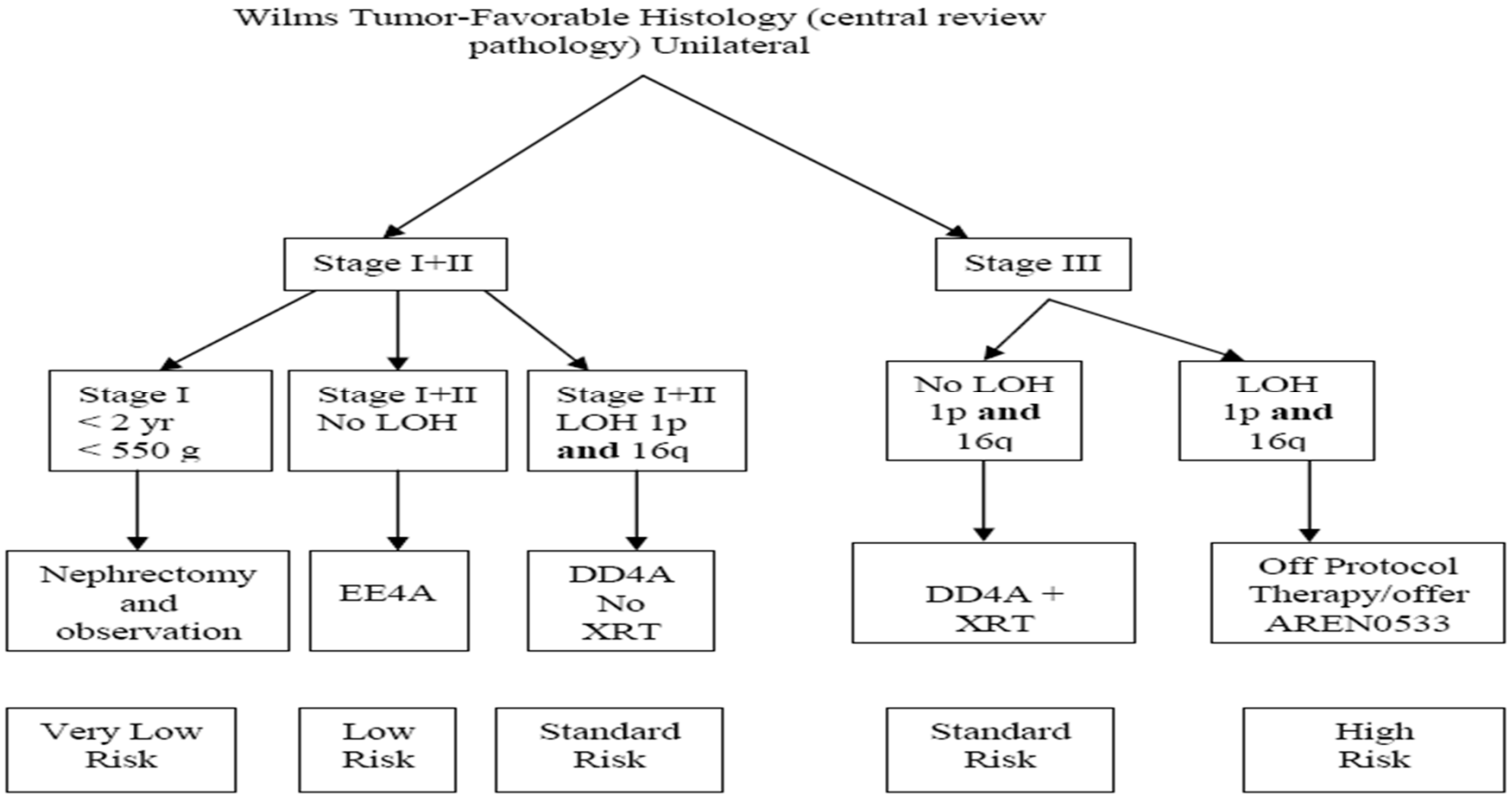
NWTS TREATMENT GUIDELINES

Stage	Treatment
Stage I FH/UH	VA x 18 wks
Stage II FH	VA x 18 wks
Stage III + IV FH	VAD x 24 wks; RT to tumour bed ± metastatic site
Stage II-IV UH	V,A,CTX,VP-16 x 24 wks; RT to tumour bed ± metastatic site

CURRENT PROTOCOLS

AREN 0532

- FH Stage I through FH Stage III Standard Risk



AREN 0533 & AREN 0321

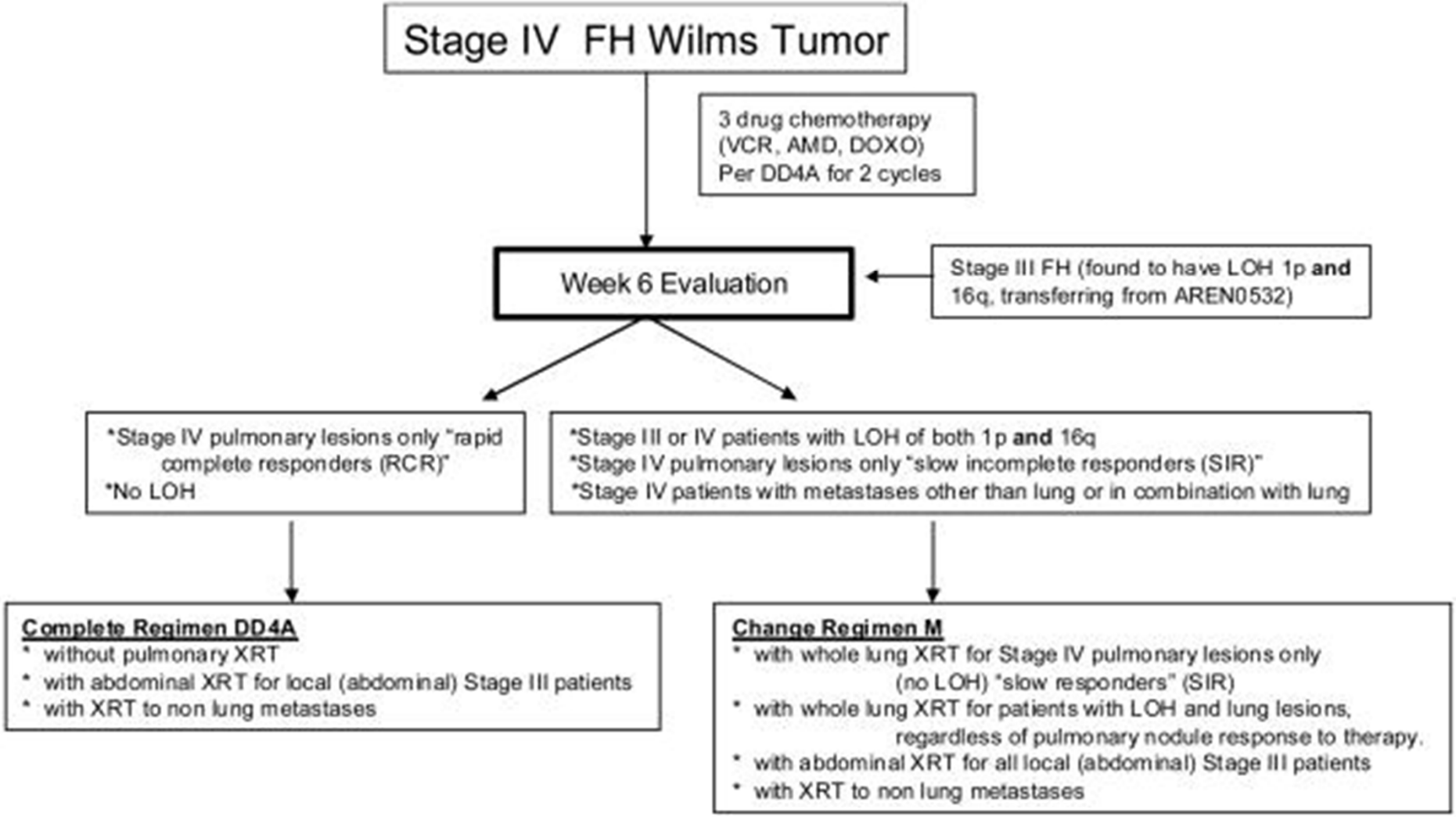
AREN 0533

- FH Stage III High Risk
- FH Stage IV

AREN 0321

- UH Wilms'
- CCSK
- RTK
- RCC

AREN 0533


Stage IV FH Wilms Tumor
3 drug chemotherapy
(VCR, AMD, DOXO)
Per DD4A for 2 cycles
Week 6 Evaluation
Stage III FH (found to have LOH 1p and 16q, transferring from AREN0532)
*Stage IV pulmonary lesions only "rapid complete responders (RCR)"
*No LOH
*Stage III or IV patients with LOH of both 1p and 16q
*Stage IV pulmonary lesions only "slow incomplete responders (SIR)"
*Stage IV patients with metastases other than lung or in combination with lung
Complete Regimen DD4A
* without pulmonary XRT
* with abdominal XRT for local (abdominal) Stage III patients
* with XRT to non lung metastases
Change Regimen M
* with whole lung XRT for Stage IV pulmonary lesions only (no LOH) "slow responders" (SIR)
* with whole lung XRT for patients with LOH and lung lesions, regardless of pulmonary nodule response to therapy.
* with abdominal XRT for all local (abdominal) Stage III patients
* with XRT to non lung metastases

COG RISK STRATIFICATION

E 85.3 CHILDREN'S ONCOLOGY GROUP RISK GROUP CLASSIFICATION FOR FAVORABLE HISTOLOGY WILMS' TUMORS

Tumor Weight	Stage	LOH	Rapid Response	Risk Group	COG Study	Treatme
<550 g	I	Any	N/A	Very Low	AREN0532	Surgery
≥550 g	I	None	N/A	Low	AREN0532	EE4A
Any	I	None	N/A	Low	AREN0532	EE4A
Any	II	None	N/A	Low	AREN0532	EE4A
Any	I	Yes	N/A	Standard	AREN0532	DD4A
≥550 g	I	Yes	N/A	Standard	AREN0532	DD4A
Any	II	Yes	N/A	Standard	AREN0532	DD4A
Any	III	None	Any	Standard	AREN0532	DD4A
Any	III	Yes	Any	Higher	AREN0533	M
Any	IV	Yes	Any	Higher	AREN0533	M
Any	IV	None	Yes	Standard	AREN0533	DD4A
Any	IV	None	No	Higher	AREN0533	M

oss of heterozygosity at both 1p and 16q; N/A, not applicable; DD4A (V [vincristine] A [dactinomycin], D [doxorubicin]); M (V
clophosphamide], E [etoposide]); EE4A (VA).

COG-RADIOTHERAPY GUIDELINES

Abdominal Tumor Stage and Histology	*RT Dose/RT Field*[a]
Stage I and II FH Wilms tumor	None
Stage III FH, stage I–III focal anaplasia	10.8 Gy to the flank[b]
Stage I–II DA, stage I–III CCSK[c]	10.8 Gy to the flank[b]
Stage III DA, stage I–III RTK	19.8 Gy flank[b] RT, infants ≤12 months 10.8 Gy
Recurrent abdominal Wilms tumor	12.6–18 Gy (<12 months)[b] 21.6 Gy (older children, previous RT ≤10.8 Gy) Boost dose of 9 Gy to gross residual tumor
Lung metastases (favorable histology)	12 Gy WLI in 8 fractions[d]
Lung metastases (unfavorable histology)	12 Gy WLI in 8 fractions
Brain metastases	30.6 Gy whole brain in 17 fractions, or 21.6 Gy whole brain + 10.8 Gy IMRT or stereotactic boost
Liver metastases	19.8 Gy whole liver in 11 fractions
Bone metastases	25.2 Gy to the lesion plus 3-cm margin
Unresected lymph node metastases	19.8 Gy

COG-TREATMENT GUIDELINES

Low-Risk FH Wilms Tumor	
stage I, tumor weight <550 g	Nephrectomy without adjuvant therapy, if node sampling and central pathology review has been performed.
Risk FH Wilms Tumor	
stage I, tumor weight 50 g, stage II without LOH	Nephrectomy, no RT, regimen EE4A
Hard-Risk FH Wilms Tumor	
I and II with LOH	Nephrectomy, no RT, regimen DD4A
III without LOH	Nephrectomy, RT, regimen DD4A
IV FH: rapid responders of g metastases at week 6 with imen DD4A, without LOH	Nephrectomy, RT, regimen DD4A; no WLI

Higher-Risk FH Wilms Tumor	
Stage III with LOH	Nephrectomy, RT, regimen M
Stage IV slow responders (lung) and nonpulmonary metastases, with LOH	Nephrectomy, RT, regimen M, WLI a RT to metastases
High-Risk UH Renal Tumors	
Stages I–IV focal anaplasia	Nephrectomy, RT, regimen DD 4A
Stage I diffuse anaplasia	Nephrectomy, RT, regimen DD 4A
Stage I–III CCSK	Nephrectomy, RT, regimen I
Stage II–IV diffuse anaplasia	Nephrectomy, RT, regimen UH1, RT metastatic sites
Stage IV CCSK	Nephrectomy, RT, regimen UH1, RT metastatic sites
Stage I–IV RTK	Nephrectomy, RT, regimen UH1, RT metastatic sites

EE4A-VA; DD4A-VAD; M-VAD/CyE; I-VDCy/CyE; UH1-VDCy/CyC(Carboplatin)E

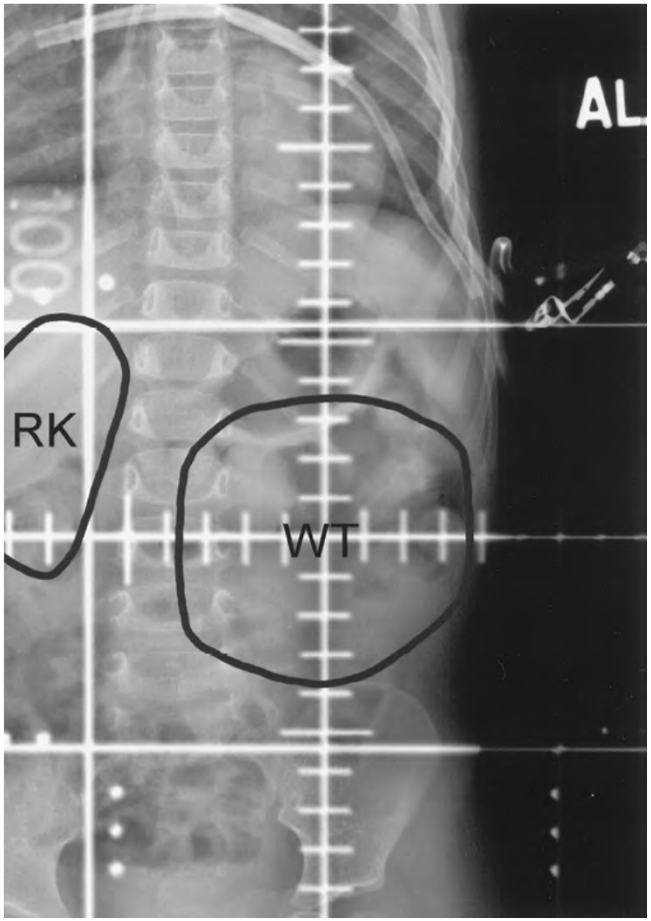
SIOP TREATMENT GUIDELINES

Risk group	Histological subtype after preoperative chemotherapy
Low	Mesoblastic nephroma*
	Cystic partially differentiated nephroblastoma
	Completely necrotic nephroblastoma
Intermediate	Nephroblastoma:
	• Mixed subtype
	• Regressive subtype
	• Epithelial subtype
	• Stromal subtype
	• Focal anaplasia
High	Diffuse anaplasia
	Blastemal-type Wilms' tumor
	Clear cell sarcoma of the kidney*
	Rhabdoid tumor of the kidney*

SIOP TREATMENT GUIDELINES

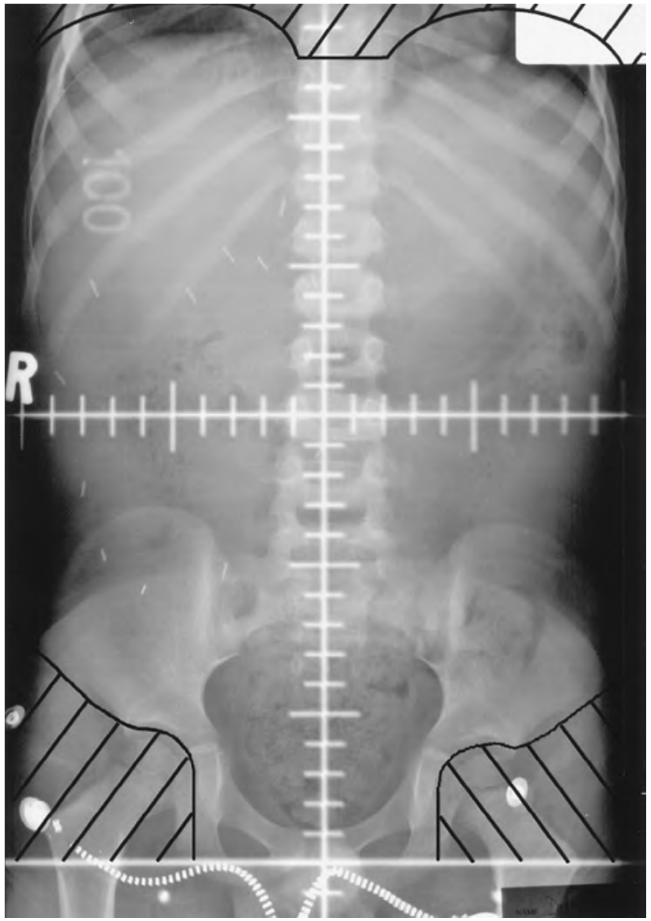
	Treatment
Pre-operative treatment	
Localised tumor	VCR + Act D ×4 wks
Metastatic tumor	VCR + Act D + Doxo ×6 wks
Post-nephrectomy treatment	
Stage I	
Low	None
Intermediate	Act D, VCR (4 wks)
High	Act D, VCR, DOX (27 wks)
Stage II	
Low	Act D, VCR (27 wks)
Intermediate	Act D, VCR, DOX** (27 wks)
High	CPM, DOX, VP16, CARBO (34 wks) + RT (anaplastic Wilms' tumor only)
Stage III	
Low	Act D, VCR (27 wks)
Intermediate	Act D, VCR, DOX** + RT (8-27 wks)
High	CPM, DOX, VP16, CARBO + RT (34 wks)
Stage IV	
Low, intermediate risk histology and good metastatic response	Act D, VCR, DOX (27 wks) without whole lung RT providing complete response of lung metastases to chemotherapy +/– surgery
High risk histology or poor metastatic response (any histology)	CPM, DOX, VP16, CARBO + RT[#] (34 wks)
Stage V	
Low and intermediate	Act D, VCR +/– DOX +/– RT[#] (duration depends on response)

FLANK RT



- RT vol to encompass the entire pre-op tumour bed
- Upper border-upper margin of tumour+1cm margin
- Lower border-lower margin of tumour+1cm margin
- Medial border-across the midline to include the entire width of the vertebral body & para-aortic LN chain
- Lateral border-abdominal wall

WHOLE ABDOMINAL IRRADIATION



- Upper border- dome of diaphragm
- Lower border-lower border of obturator foramen
- Lateral border-abdominal wall
- Femoral head & acetabulum to be shielded
- Hepatic dose <15 Gy
- Renal dose< 12-15 Gy

Appropriate shielding

CONFORMAL PLANNING

GTV→ Pre-op tumour volume using co-registered MR-CT scans

CTV→GTV+1 cm isotropic expansion

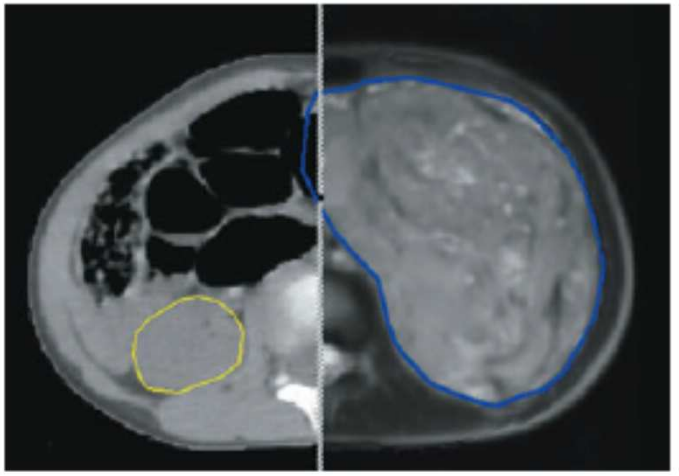
PTV→CTV+SM+IM

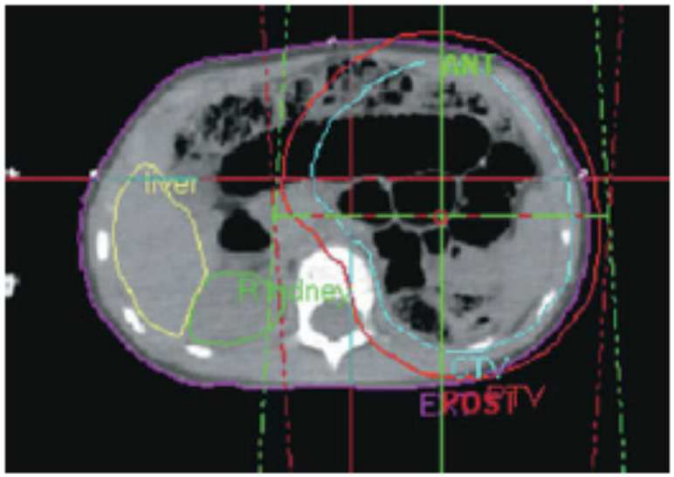
AP-PA beam arrangement with MLC shaping

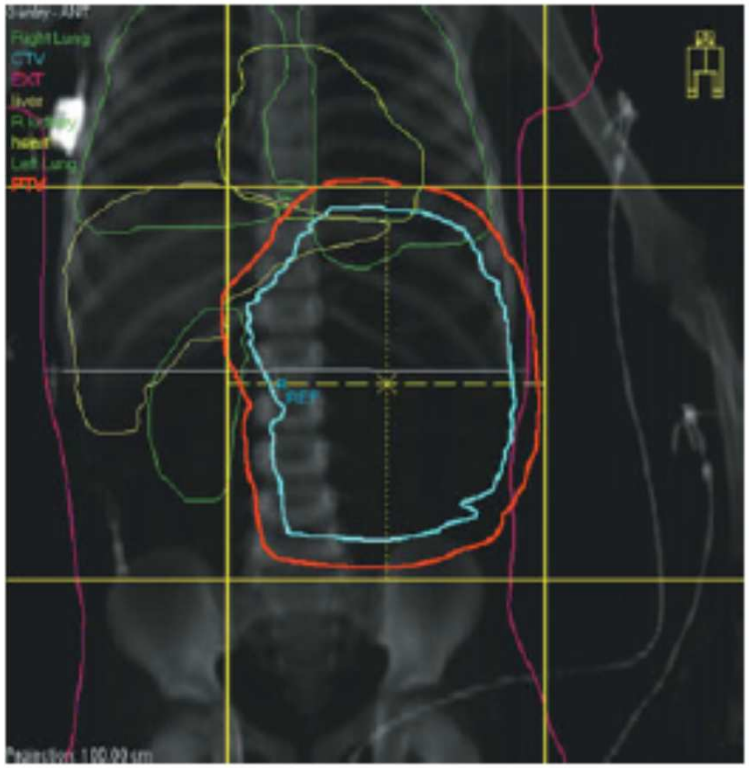
Aim→ Adequate target coverage with symmetrical irradiation of vertebrae, avoidance of contralateral kidney & minimisation of whole body dose

IMRT rarely needed & conformal treatment adequate

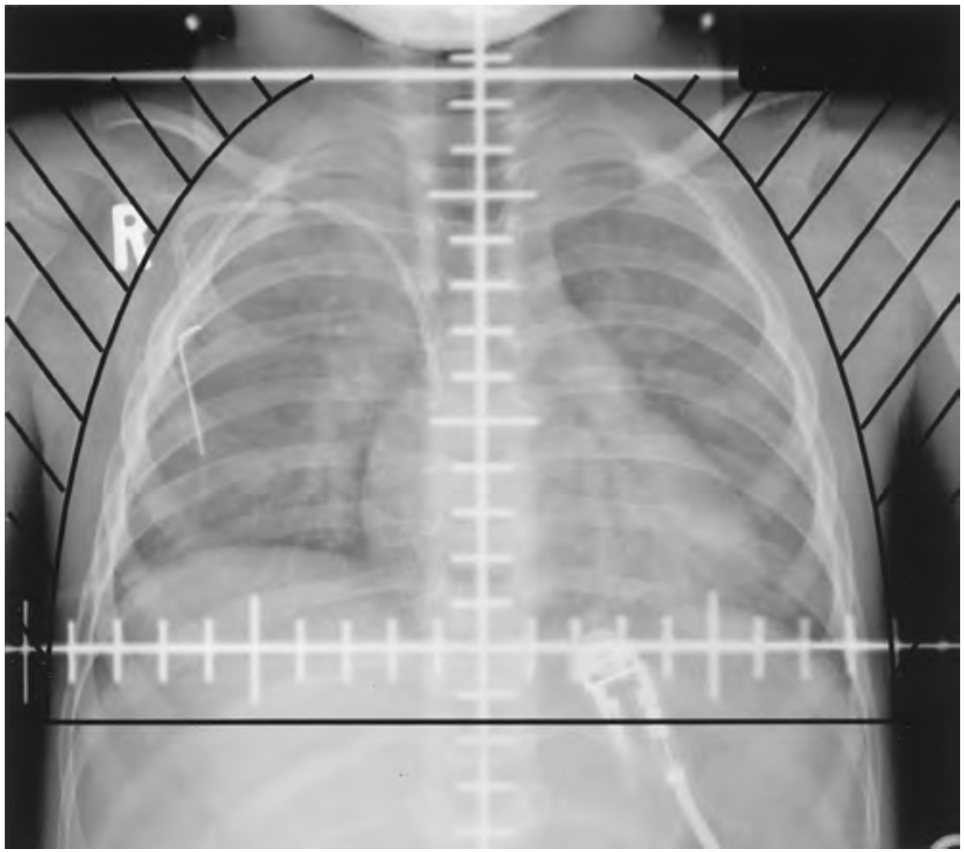
CONFORMAL PLANNING







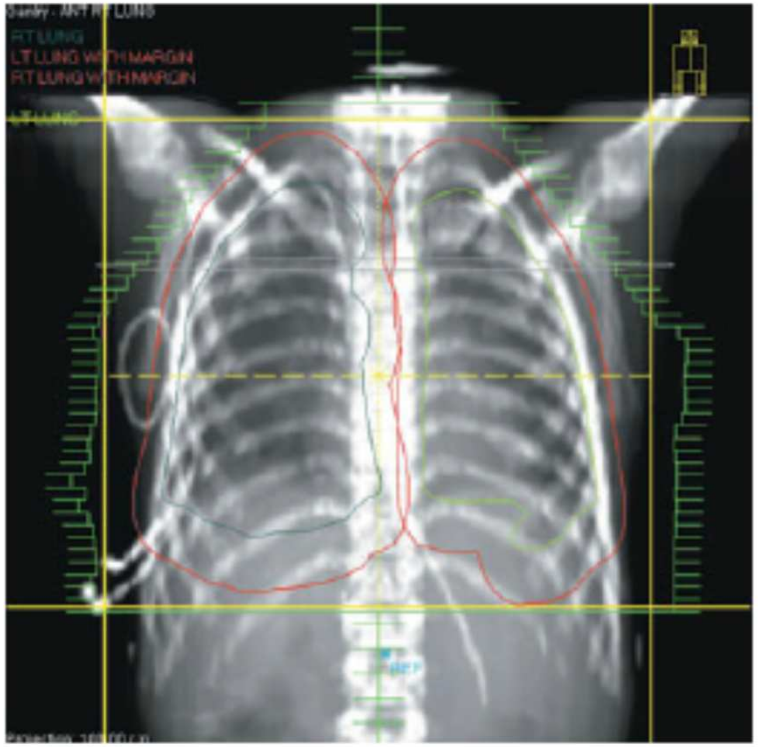
WHOLE LUNG IRRADIATION



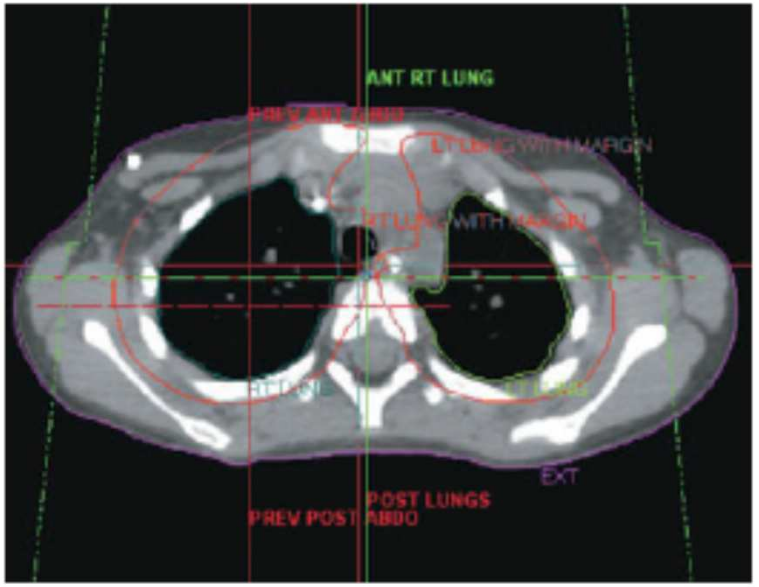
- Upper border- to include both the lung apices
- Lower border- to include the pleural reflection infero-laterally
- Lat border-chest-wall
- Humerus & shoulder joint to be shielded bilaterally

CONFORMAL WLI

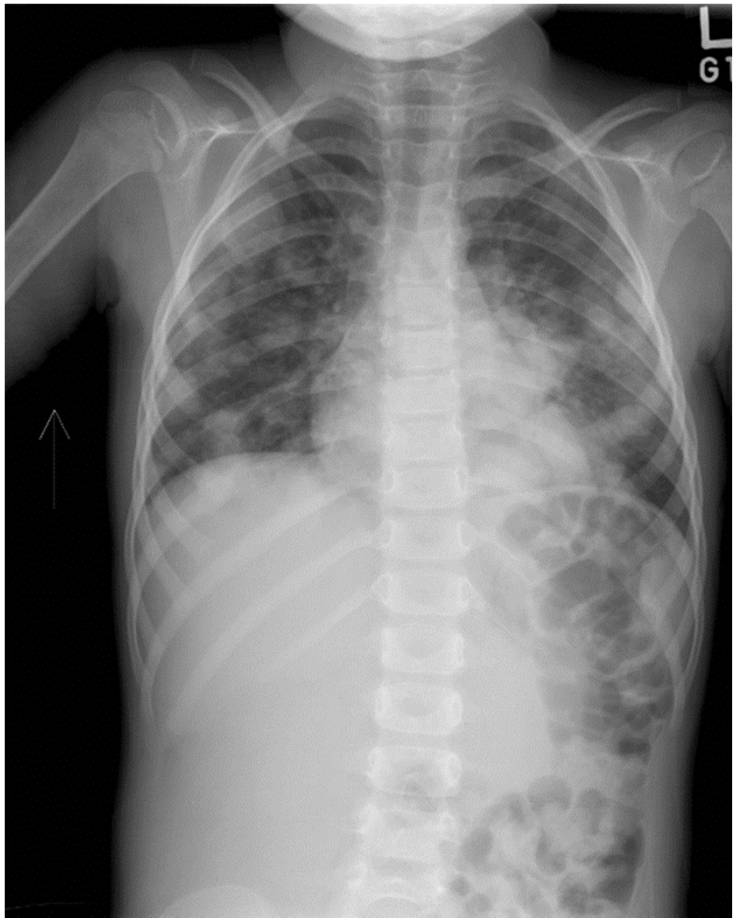
Coronal DRR

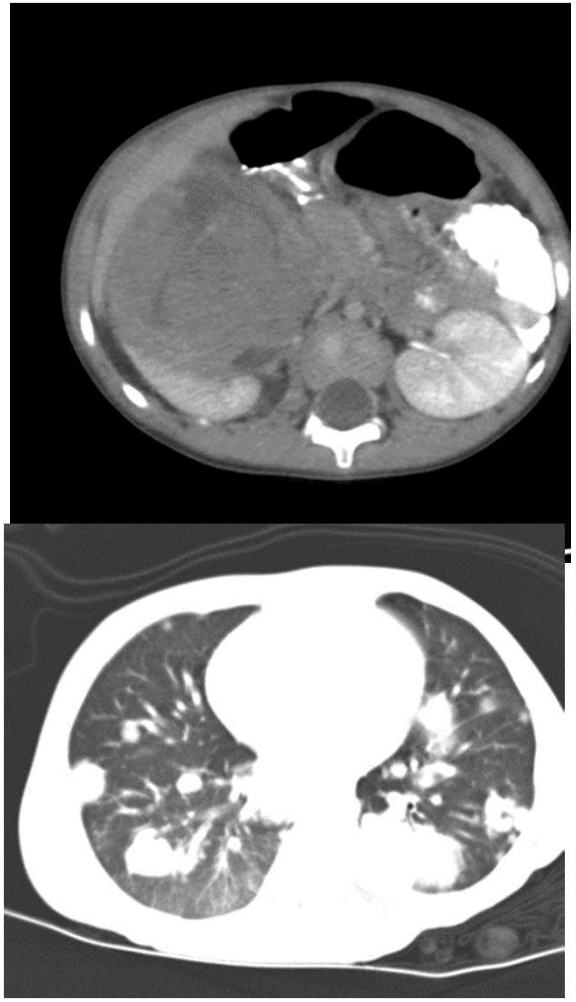


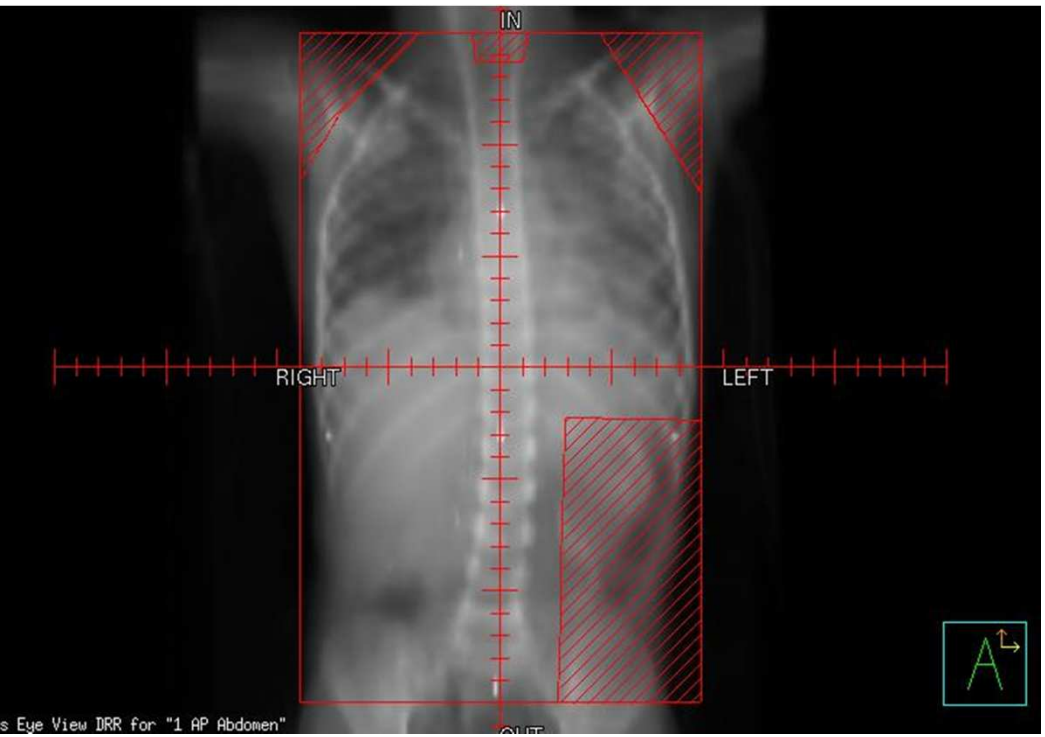
AP-PA beam arrangement

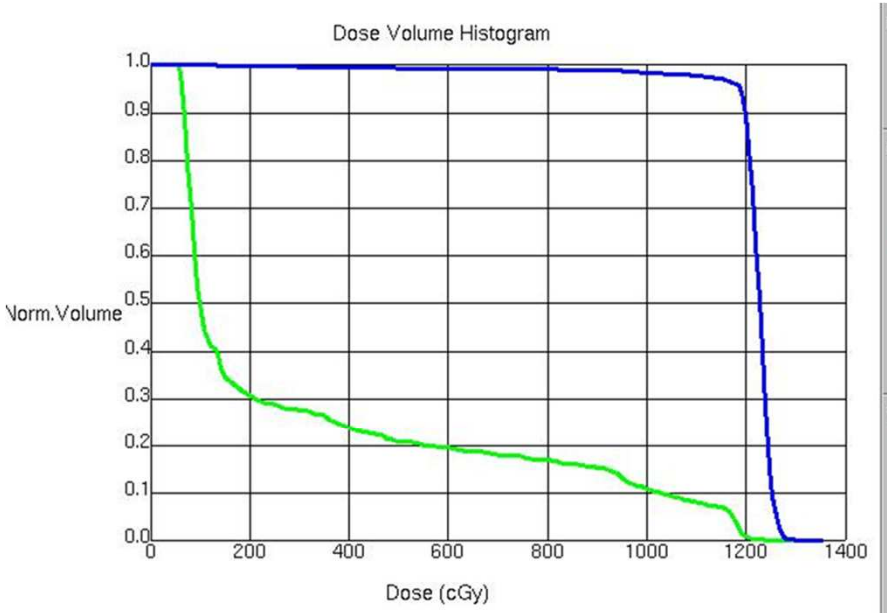


WLI + FLANK RT









ROI Statistics

Line Type	ROI	Trial	Min.	Max.	Mean	Std. Dev.	% Outside Grid	% > Max
	l kidney	AP-PA	55.7	1236.5	301.9	368.7	0.00 %	0.00 %
	liver	AP-PA	82.7	1294.7	1213.1	104.3	0.00 %	0.00 %

LONG TERM TREATMENT OUTCOME (NWTS 3 & 4)

Category	Number of Patients	10-Year RFS (%)	10-Year OS (%)
Stage I FH	1,582	91.4	96.6
Stage II FH	1,006	85.5	93.4
Stage III FH	1,038	84.2	89.5
Stage IV FH	592	75.2	80.7
Stage V FH	344	65.1	77.9
All FH	4,562	84.4	90.8
Clear cell sarcoma	170	67.1	77.1
Stage II–III anaplasia	128	43.0	49.2
Stage IV anaplasia	55	18.2	18.2
Rhabdoid tumor	88	27.3	28.4

-In Perez & Brady's Principles & Practice of Radiation Oncology, 6th edition, 20

TREATMENT OF RELAPSE

Children with relapsed FH WT can have favorable outcome based on

- Initial stage
- Time from initial diagnosis
- Site of relapse
- Previous therapy

- Adverse factors for relapsed WT
  - Prior use of Doxorubicin
  - Relapse < 12 months from initial diagnosis
  - Intra-abdominal relapse after previous abdominal RT

RESTAGING

Stage 1R – Localized disease, completely excised

Stage 2R – Gross total resection with evidence of regional spread

Stage 3R – Residual non-haematogenous tumor present and confined to abdomen

Stage 4R – Haematogenous mets present

Stage 5R – Bilateral renal involvement

RADIOTHERAPY GUIDELINES FOR RELAPSE

RT is administered at site of relapse

Dose to infradiaphragmatic sites

- CR after surgery (1R/2R) who have either received no previous RT or have received 10.8 Gy
  - Birth – 12 months – 12.6 - 18 Gy
  - 13 months or older – 21.6 Gy
- Gross residual disease after Sx
  - Should get an additional boost (9Gy)
  - Total dose including boost should not exceed 30.6 Gy

- Dose to infradiaphragmatic sites
  - Total nominal dose (including previous RT)
    - <36 months – should not exceed 30.6 Gy
    - >36 months – should not exceed 39.6 Gy
  - Total spine dose < 41.4 Gy
  - Total liver dose < 30.6 Gy
  - Total remaining kidney dose < 19.8 Gy

RADIOTHERAPY GUIDELINES FOR RELAPSE

Lung Irradiation

- Complete remission & no previous RT
  - ≤ 18 months: 9 Gy; 1.5 Gy/fraction
  - > 18 months: 12 Gy, 1.5 Gy/fraction
- Gross residual disease after surgical resection & no previous RT
  - Can boost gross disease with additional 7.5 Gy

Liver, Brain, Bone mets

- Follow guidelines from NWTS 5

CLEAR CELL SARCOMA OF KIDNEY (CCSK)

Primitive mesenchymal neoplasm of kidney

Constitutes 4% of childhood renal tumours

Cell of origin unknown

Propensity for bone mets (In NWTS 4 study incidence of bone mets 23% in CCSK versus 0.3% in other tumours)

- In NWTS 1-4 study, 351 pts of CCSK included
- OS rate-69%
- On MVA, independent prognostic factors:
  - Age
  - Tumour stage
  - Tumour necrosis
  - Use of Doxorubicin

-Argani P et al. Am J Surg Pathol 2000;24:4-18.

RHABDOID TUMOUR OF KIDNEY (RTK)

Highly malignant renal tumour

Unrelated to WT or RMS

Probably of neural crest origin

Usually detected in first 2 yrs of life

Associated with CNS lesion

- NWTS 1-5 study,142 pts of RTK included
- 4 yr OS-23%
- Prognostic factors:
  - Age
  - Tumour stage
  - Higher dose of RT (>25 Gy)

-Tomlinson et al. J Clin Oncol2005;23:7641–7645.

LATE EFFECTS OF TREATMENT

Scoliosis-54% in patients treated with a median dose of 30Gy

- Thomas et al. IJROBP 1983;9:651-57.

CHF-4.4% at 20 years (NWTS1-4)

- Green et al. JCO 2001;19:1926-34.

End stage renal disease (ESRD)-20 year cumulative incidence

- 74% in children with Denys-Drash syndrome
- 36% in children with WAGR syndrome
- 7% in children with GU abnormalities
- 0.6% in children without any syndrome/ abnormality

- Breslow NE et al. J Urol 2005;174:1972-75.

LATE EFFECTS OF TREATMENT

Second malignant neoplasm (SMN)-15 year cumulative incidence 1.6%

- Leukaemia/ lymphoma incidence 0.4% at 8 years with no case thereafter
- Solid malignancy incidence continued to rise sharply with time
- 73% of the solid malignancies arose in previous RT field
- Associated factors: higher dose of RT, use of Doxorubicin & Rx of relapse

- Breslow et al. JCO 1995;13:1851-59.

Adverse pregnancy outcome-

- Foetal malposition
- Premature labour
- LBW baby
- Congenital malformation

- Green et al. JCO 2010;28:2824-30.

FUTURE DIRECTION

Deintensification of Rx in LR pts & intensification of Rx in HR pts

Refinement of tumour risk stratification using molecular signature

IMRT- cardiac & renal sparing in whole lung & liver RT respectively

Re-evaluation of the necessity of RT in all pts receiving pre-op chemo

Re-evaluation of the current recommendation of WAI in localised pre-op tumour rupture limited to the flank

Biochemotherapy in pts of RTK & WT with DA

CONCLUSION

WT- highly curable childhood neoplasm

The prognosis of children with WT has dramatically improved from a very high mortality rate at the beginning of the 20th century to the current cure rate of >90%

The management of WT- paradigm for successful interdisciplinary treatment of solid tumours of childhood to maximize cure rates and minimize treatment-related complications


THANK YOU