EVIDENCE BASED MANAGEMENT OF WILMS TUMOR – RADIATION ONCOLOGY PERSPECTIVE

DR. AHITAGNI BISWAS MD(AIIMS), DNB, ECMO, FRCR(UK)

ASSOCIATE PROFESSOR

DEPARTMENT OF RADIOTHERAPY & ONCOLOGY

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, NEW DELHI

33RD AROI-ICRO TEACHING COURSE, LUCKNOW, 12-13TH OCT 2019

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

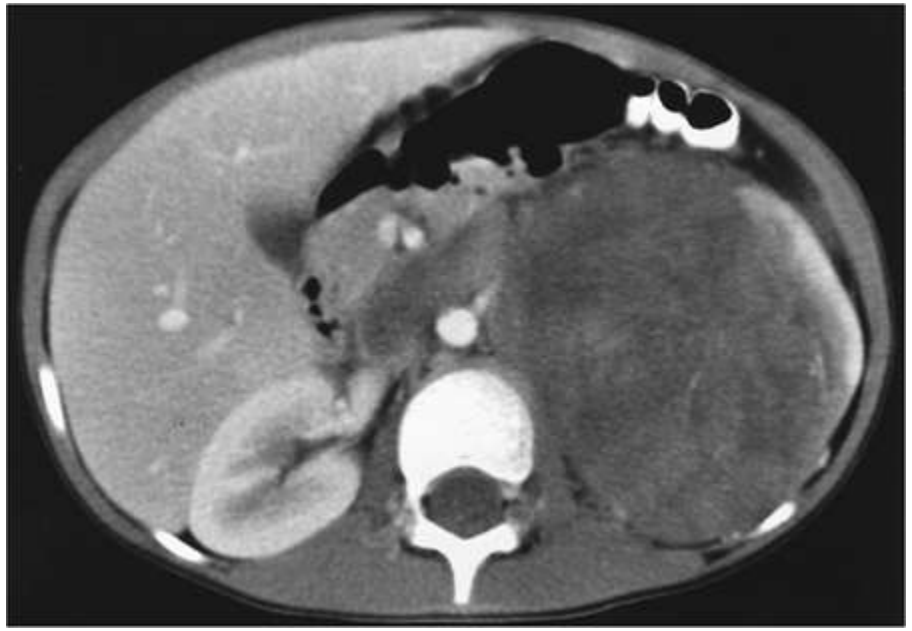
Gene	Function	Locus	Syndromic association	Frequency of genetic aberration
WT1	Tumour suppressor gene Role in glomerular & gonadal development	11p13	WAGR (WT, aniridia, genito-urinary malformation, mental retardation) Denys-Drash syndrome (pseudohermaphroditism, mesangial sclerosis, renal failure, WT)	Germline mutation: 82% in pts with renal failure/ GU anomalies 10-20% of sporadic WT 4% of familial WT
WT2	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 of IGF2 in~ 40% of sporadic WT
WTX	Tumour suppressor gene	Xq11.1	-	WTX inactivation in~30% of sporadic WT
CTNNB1	Encodes β-catenin Role in WNT pathway	3p21	-	Gain of function mutation in~ 10% of sporadic WT

CLINICAL PRESENTATION

- Abdominal mass (80-90%)
- Abdominal pain (30-40%)
- Haematuria (20-25%)
- Fever (20-25%)
- Hypertension
- Varicocele
- Metastatic symptoms-rare

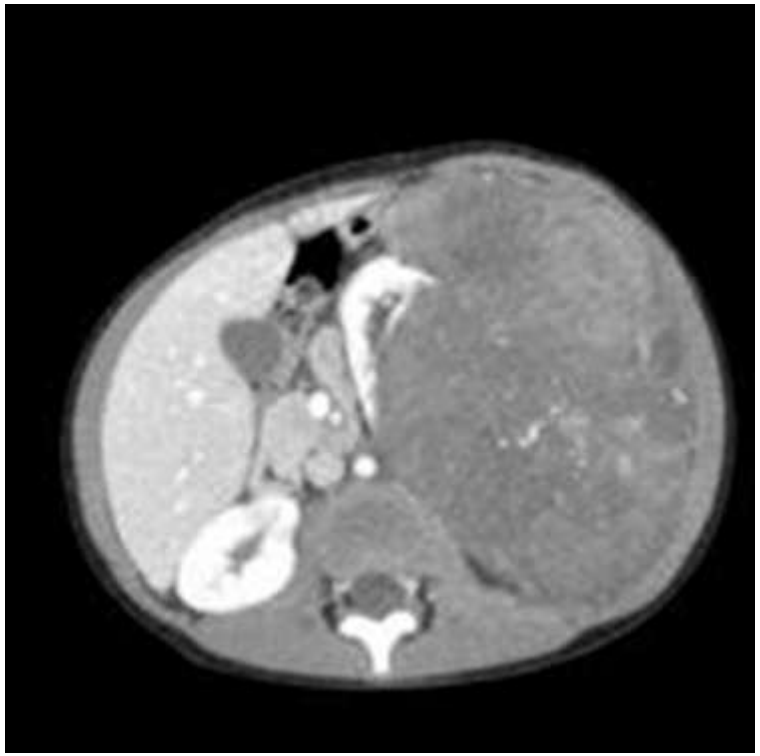
DIAGNOSTIC WORK-UP

History	Record pre-existing conditions, family history of cancer, or congenital defects
Physical examination	Blood pressure, weight, height, presence of abdominal masses, congenital anomalies particularly genitourinary, hemihypertrophy, and aniridia
Laboratory	Hemoglobin, white cell, and differential counts, platelets, urinalysis, serum blood urea nitrogen, creatinine, protein, alanine, and aspartate aminotransferases, alkaline phosphatase, bilirubin
Radiology	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)

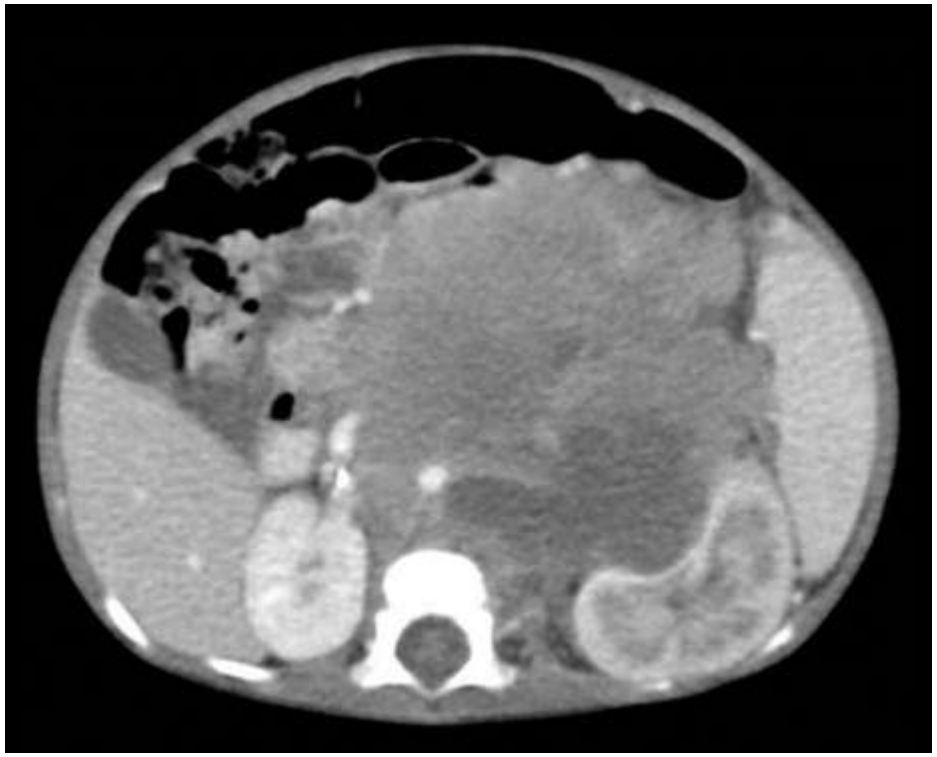


DIFFERENTIAL DIAGNOSIS

Nephroblastoma



Neuroblastoma



DD: Neuroblasoma, Mesoblastic nephroma, Hydronephrosis, PCKD

STAGING

Stage I: 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.

Stage II: 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.

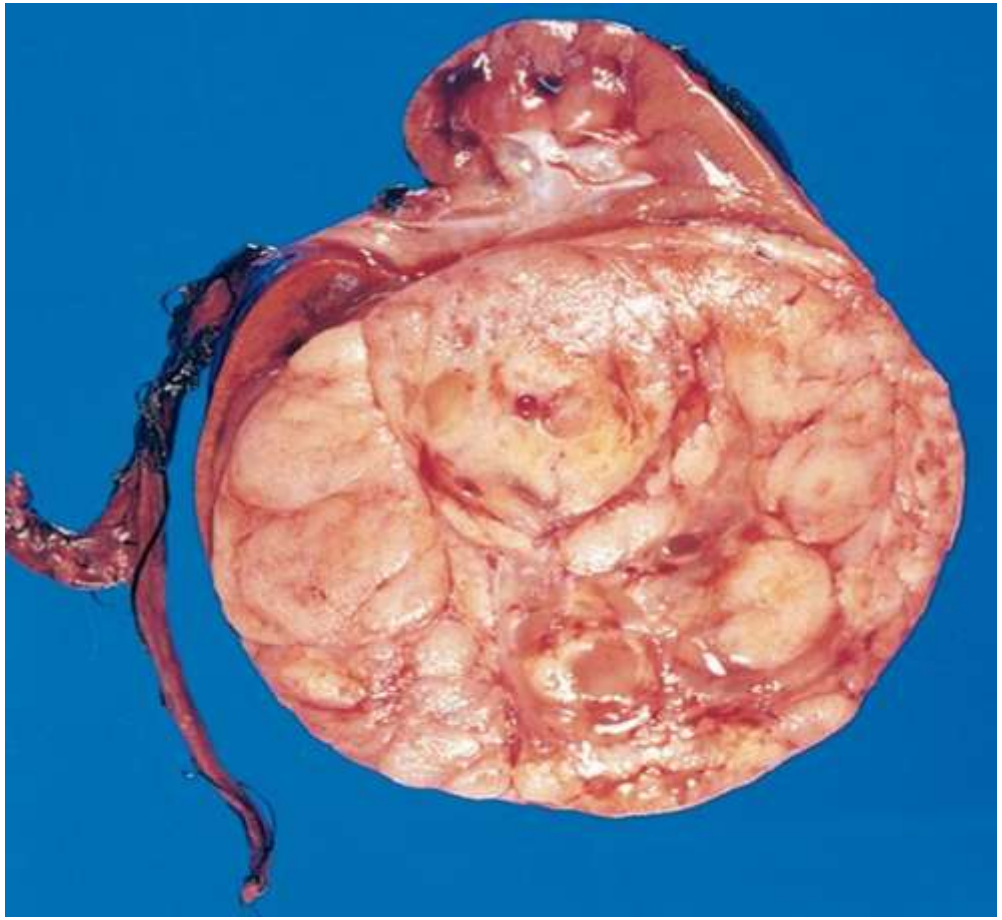
Stage III: Residual nonhematogenous tumor present following surgery and confined to abdomen. Any one of the following may occur:

- Lymph nodes within the abdomen or pelvis are involved by tumor. (Lymph node involvement in the thorax or other extra-abdominal sites 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., tumor cells are found at the margin of surgical resection on microscopic examination)
- The tumor is not completely resectable because of local infiltration into vital structures
- Tumor spillage occurring either before or during surgery
- The tumor was biopsied (whether tru-cut, open, or fine-needle aspiration) before removal
- Tumor is removed in more than one piece (e.g., tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen)

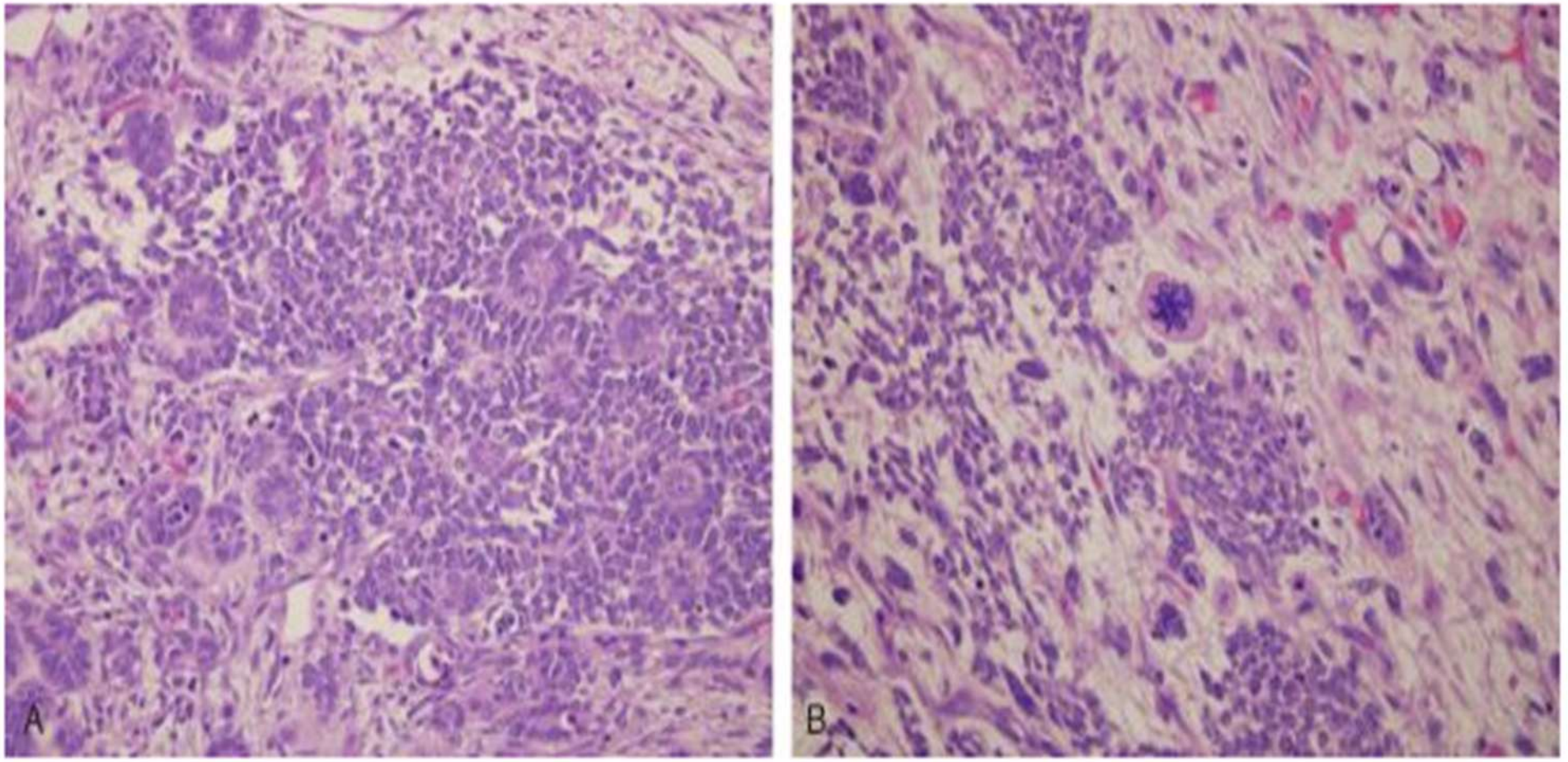
Stage IV: Hematogenous metastases (i.e., lung, liver, bone, brain) or lymph node metastases outside the abdominopelvic region are present. (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present.)

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

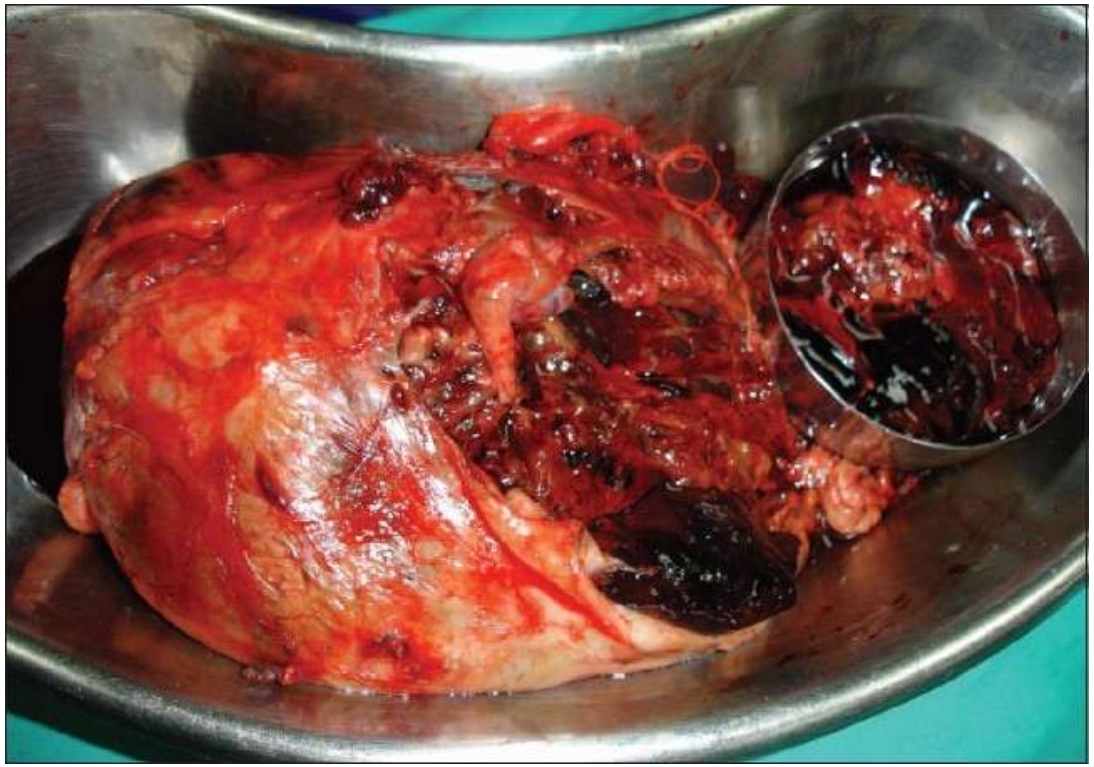
NWTS

- 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

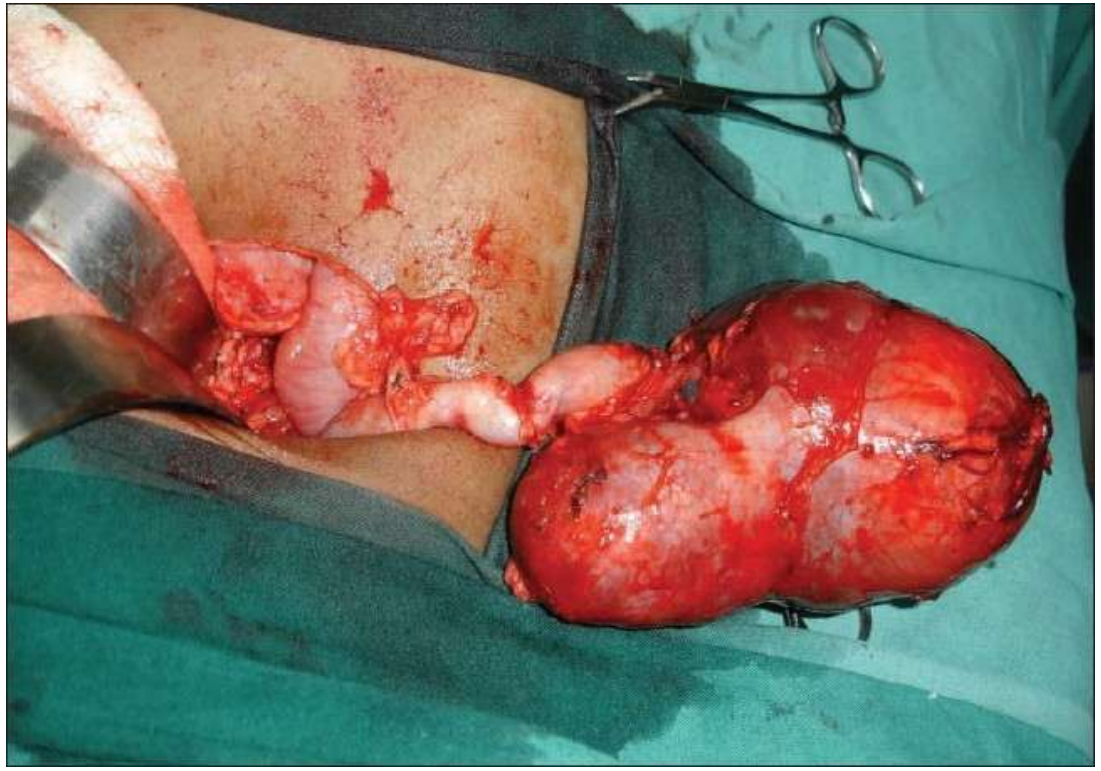
SIOP

- 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



-*Bhatnagar et al. J Indian Assoc Pediatr Surg 2009;14:6-14.*

NWTS 1-4 SCHEMA

		Treatment protocols[b]	
NWTSG study	Disease stage[a]	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: 18-24 Gy
  - 18 – 30 mo: 24-30 Gy
  - 31- 40 mo: 30-35 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

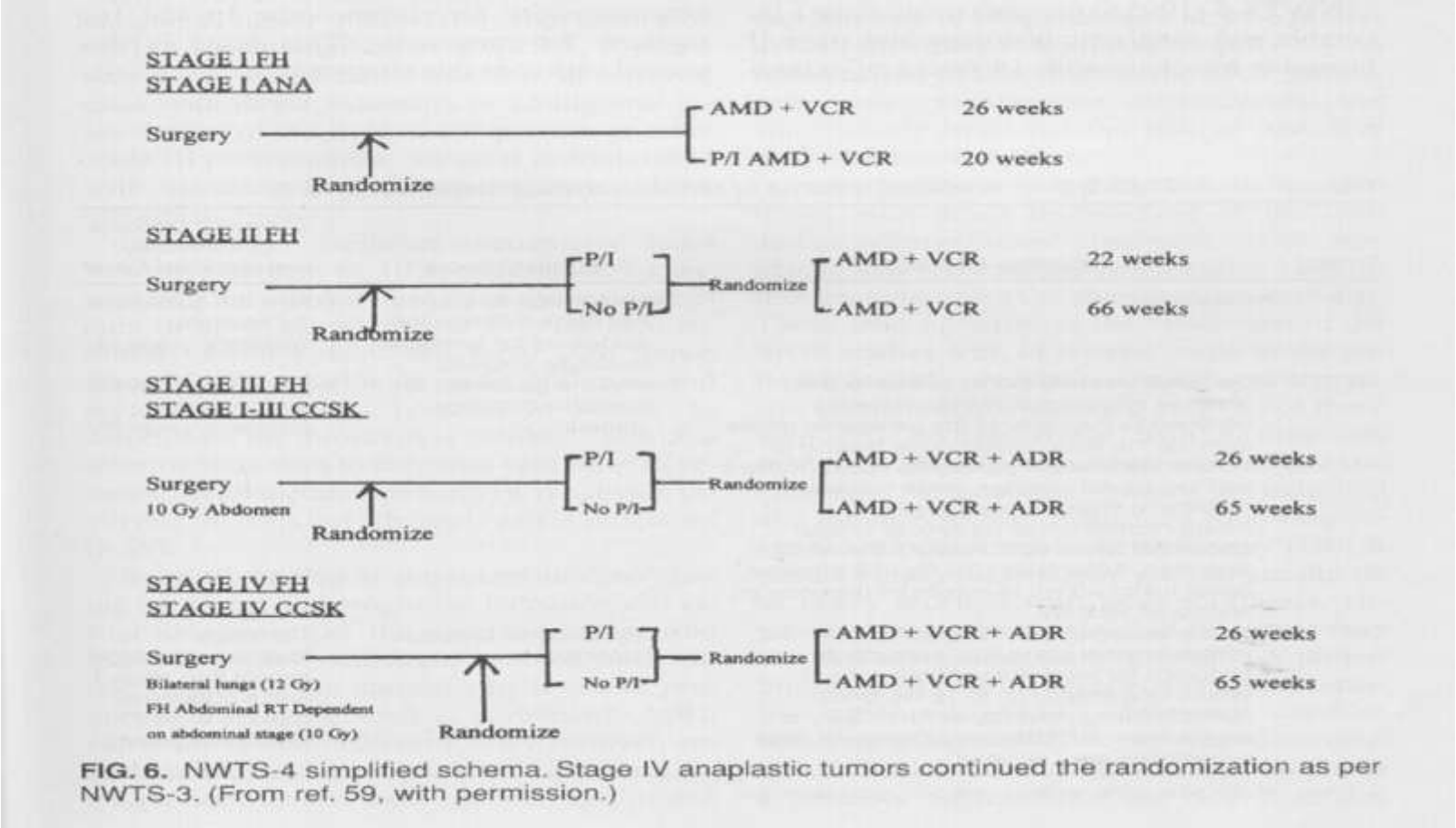


FIG. 6. NWTS-4 simplified schema. Stage IV anaplastic tumors continued the randomization as per NWTS-3. (From ref. 59, with permission.)

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

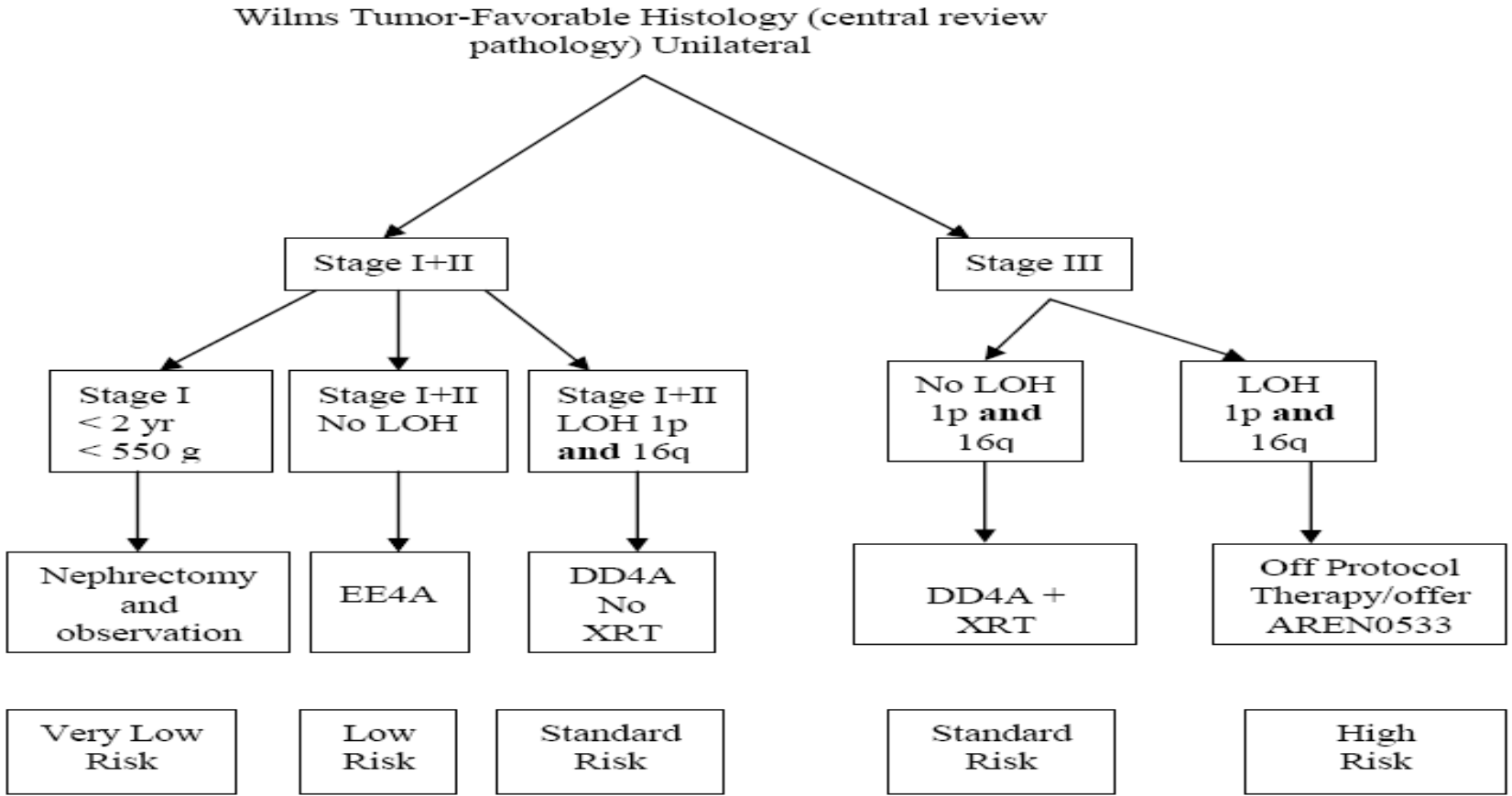
- Diffuse Anaplasia:2 yr EFS-
  - Stage I- 64.3 %
  - Stage II- 79.5%
  - Stage III- 62.7%
  - Stage IV- 33.6%
- CCSK:4 yr RFS-
  - Stage I –IV- 77.6%
  - 6/9 Stage IV pts relapsed
- RTK
  - Stage I- 50%
  - Stage II- 33.3%
  - Stage III- 33.3%
  - Stage IV- 21.4 %
  - Stage V- 0%

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,D,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



VOLUME 36 · NUMBER 3 · JANUARY 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Outcome and Prognostic Factors in Stage III Favorable-Histology Wilms Tumor: A Report From the Children's Oncology Group Study AREN0532

Conrad V. Fernandez, Elizabeth A. Mullen, Yueh-Yun Chi, Peter F. Ehrlich, Elizabeth J. Perlman, John A. Kalapurakal, Geetika Khanna, Arnold C. Paulino, Thomas E. Hamilton, Kenneth W. Gow, Zelig Tochner, Fredric A. Hoffer, Janice S. Withycombe, Robert C. Shamberger, Yeonil Kim, James I. Geller, James R. Anderson, Paul E. Grundy, and Jeffrey S. Dome

ABSTRACT

Background

The National Wilms Tumor Study (NWTS) approach to treating stage III favorable-histology Wilms tumor (FHWT) is Regimen DD4A (vincristine, dactinomycin, and doxorubicin) and radiation therapy. Further risk stratification is required to improve outcomes and reduce late effects. We evaluated clinical and biologic variables for patients with stage III FHWT without combined loss of heterozygosity (LOH) at chromosomes 1p and 16q treated in the Children's Oncology Group protocol AREN0532.

Methods

From October 2006 to August 2013, 588 prospectively treated, centrally reviewed patients with stage III FHWT were treated with Regimen DD4A and radiation therapy. Tumor LOH at 1p and 16q was determined by microsatellite analysis. Ineligible patients (n = 5) and those with combined LOH 1p/16q (n = 40) were excluded.

Results

A total of 535 patients with stage III disease were studied. Median follow-up was 5.2 years (range, 0.2 to 9.5). Four-year event-free survival (EFS) and overall survival estimates were 88% (95% CI, 85% to 91%) and 97% (95% CI, 95% to 99%), respectively. A total of 58 of 66 relapses occurred in the first 2 years, predominantly pulmonary (n = 36). Eighteen patients died, 14 secondary to disease. A better EFS was associated with negative lymph node status ($P < .01$) and absence of LOH 1p or 16q ($P < .01$), but not with gross residual disease or peritoneal implants. In contrast, the 4-year EFS was only 74% in patients with combined positive lymph node status and LOH 1p or 16q. A total of 123 patients (23%) had delayed nephrectomy. Submitted delayed nephrectomy histology showed anaplasia (n = 8; excluded from survival analysis); low risk/completely necrotic (n = 7; zero relapses), intermediate risk (n = 63; six relapses), and high-risk/blastemal type (n=7; five relapses).

Conclusion

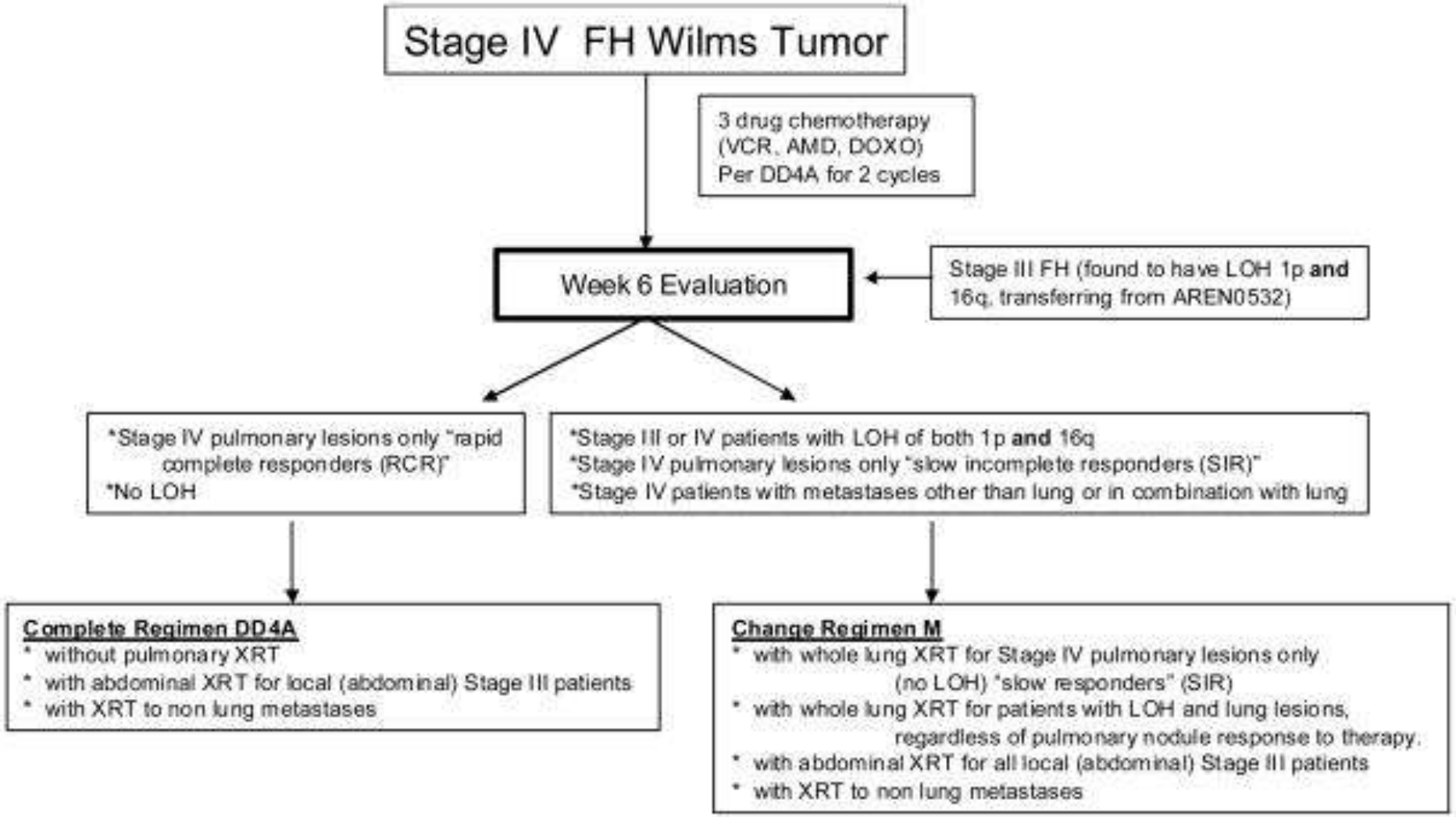
Most patients with stage III FHWT had good EFS/overall survival with DD4A and radiation therapy. Combined lymph node and LOH status was highly predictive of EFS and should be considered as a potential prognostic marker for future trials.

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

VOLUME 36 · NUMBER 16 · JUNE 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Treatment of Stage IV Favorable Histology Wilms Tumor With Lung Metastases: A Report From the Children's Oncology Group AREN0533 Study

David B. Dix, Nita L. Seibel, Yueh-Yun Chi, Geetika Khanna, Eric Gratias, James R. Anderson, Elizabeth A. Mullen, James I. Geller, John A. Kalapurakal, Arnold C. Paulino, Elizabeth J. Perlman, Peter F. Ehrlich, Marcio Malogolowkin, Julie M. Gastier-Foster, Elizabeth Wagner, Paul E. Grundy, Conrad V. Fernandez, and Jeffrey S. Dome

ABSTRACT

Purpose

The National Wilms Tumor Study (NWTS) treatment of favorable histology Wilms tumor with lung metastases was vincristine/dactinomycin/doxorubicin (DD4A) and lung radiation therapy (RT). The AREN0533 study applied a new risk stratification and treatment strategy to improve event-free survival (EFS) while reducing exposure to lung RT.

Methods

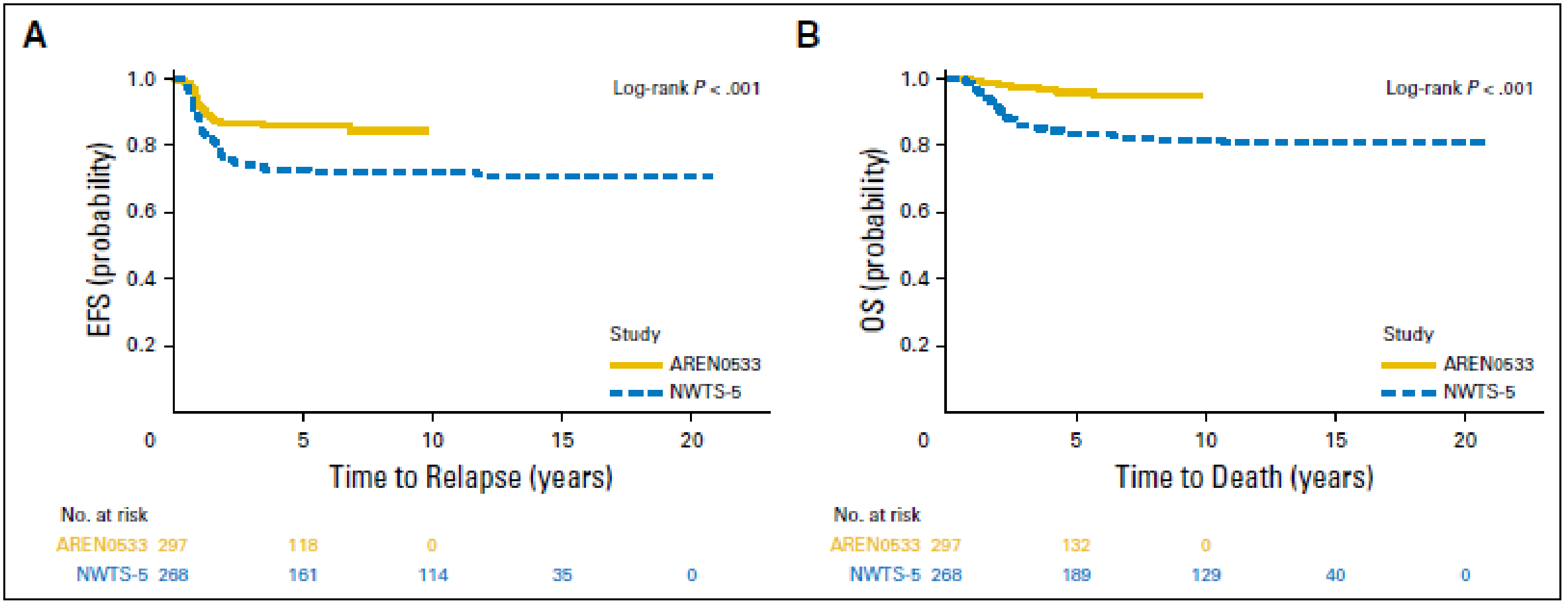
Patients with favorable histology Wilms tumor and isolated lung metastases showing complete lung nodule response (CR) after 6 weeks of DD4A continued receiving chemotherapy without lung RT. Patients with incomplete response (IR) or loss of heterozygosity at chromosomes 1p/16q received lung RT and four cycles of cyclophosphamide/etoposide in addition to DD4A drugs (Regimen M). AREN0533 was designed to preserve a 4-year EFS of 85% for lung nodule CR and improve 4-year EFS from 75% to 85% for lung nodule IR.

Results

Among 292 assessable patients, 133 had CR and 159 had IR. For patients with CR, 4-year EFS and overall survival (OS) estimates were 79.5% (95% CI, 71.2% to 87.8%) and 96.1% (95% CI, 92.1% to 100%), respectively. Expected versus observed event rates were 15% and 20.2% ($P = .052$), respectively. For patients with IR, 4-year EFS and OS estimates were 88.5% (95% CI, 81.8% to 95.3%) and 95.4% (95% CI, 90.9% to 99.8%), respectively. Expected versus observed event rates were 25% and 12.2% ($P < .001$), respectively. Overall, 4-year EFS and OS were 85.4% (95% CI, 80.5% to 90.2%) and 95.6% (95% CI, 92.8% to 98.4%) compared with 72.5% (95% CI, 66.9% to 78.1%; $P < .001$) and 84.0% (95% CI, 79.4% to 88.6%; $P < .001$), respectively, in the predecessor NWTS-5 study.

Conclusion

Excellent OS was achieved after omission of primary lung RT in patients with lung nodule CR, although there were more events than expected. EFS was significantly improved, with excellent OS, in patients with lung nodule IR using four cycles of cyclophosphamide/etoposide in addition to DD4A drugs. The overall AREN0533 treatment strategy yielded EFS and OS estimates that were superior to previous studies.


A
1.0
0.8
0.6
0.4
0.2
EFS (probability)
Log-rank P < .001
Study
ARENO533
NWTS-5
0
5
10
15
20
Time to Relapse (years)
No. at risk
ARENO533 297 118 0
NWTS-5 268 161 114 35 0
B
1.0
0.8
0.6
0.4
0.2
OS (probability)
Log-rank P < .001
Study
ARENO533
NWTS-5
0
5
10
15
20
Time to Death (years)
No. at risk
ARENO533 297 132 0
NWTS-5 268 189 129 40 0

COG RISK STRATIFICATION

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

Age	Tumor Weight	Stage	LOH	Rapid Response	Risk Group	COG Study	Treatment
<2 yr	<550 g	I	Any	N/A	Very Low	AREN0532	Surgery only
Any	≥550 g	I	None	N/A	Low	AREN0532	EE4A
≥2 yr	Any	I	None	N/A	Low	AREN0532	EE4A
Any	Any	II	None	N/A	Low	AREN0532	EE4A
≥2 yr	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

LOH, loss of heterozygosity at both 1p and 16q; N/A, not applicable; DD4A (V [vincristine] A [dactinomycin], D [doxorubicin]); M (VAD/Cy [cyclophosphamide], 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

Very Low-Risk FH Wilms Tumor	
<2 yr, stage I, tumor weight <550 g	Nephrectomy without adjuvant therapy, if node sampling and central pathology review has been performed.
Low-Risk FH Wilms Tumor	
≥2 yr, stage I, tumor weight ≥550 g, stage II without LOH	Nephrectomy, no RT, regimen EE4A
Standard-Risk FH Wilms Tumor	
Stage I and II with LOH	Nephrectomy, no RT, regimen DD4A
Stage III without LOH	Nephrectomy, RT, regimen DD4A
Stage IV FH: rapid responders of lung metastases at week 6 with regimen 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 and 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 to all metastatic sites
Stage IV CCSK	Nephrectomy, RT, regimen UH1, RT to all metastatic sites
Stage I–IV RTK	Nephrectomy, RT, regimen UH1, RT to all metastatic sites

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

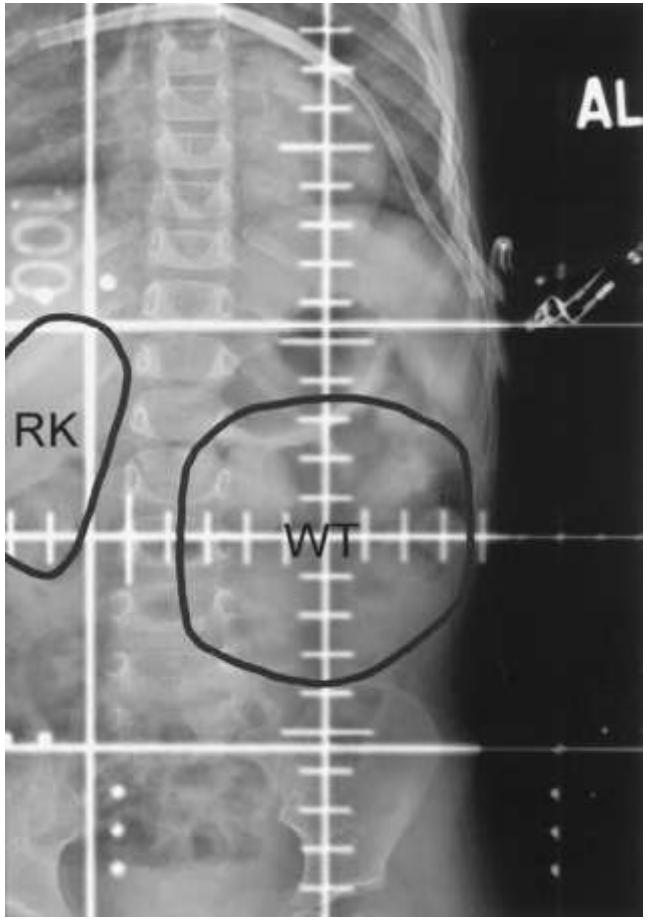
SIOP TREATMENT GUIDELINES

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

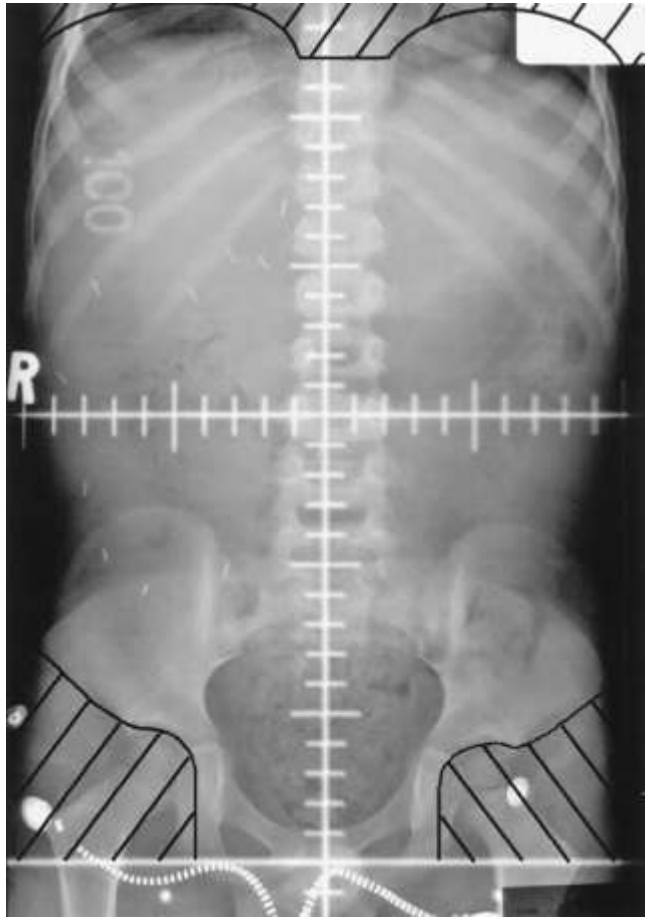
	Treatment
Pre-operative treatment	
Localised tumor	VCR + Act D ×4 wks
Metastatic tumor	VCR + Act D + Doxo ×6 wks
Post-nephrectomy treatment	
Stage I	
Low	None
Intermediate	Act D, VCR (4 wks)
High	Act D, VCR, DOX (27 wks)
Stage II	
Low	Act D, VCR (27 wks)
Intermediate	Act D, VCR, DOX** (27 wks)
High	CPM, 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



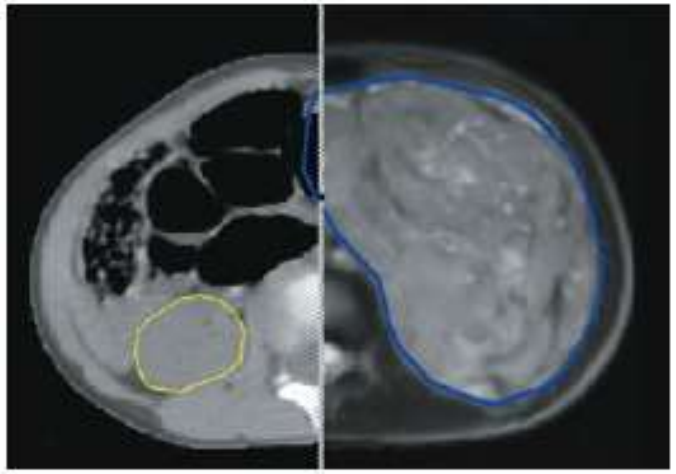
- Upper border- dome of diaphragm
- Lower border-lower border of obturator foramen
- Lateral border-abdominal wall
- Femoral head & acetabulum to be shielded
- Hepatic dose <15 Gy
- Renal dose< 12-15 Gy

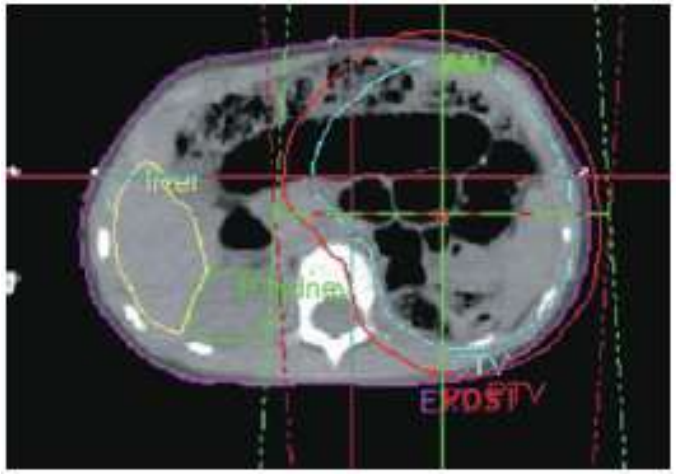
Appropriate shielding

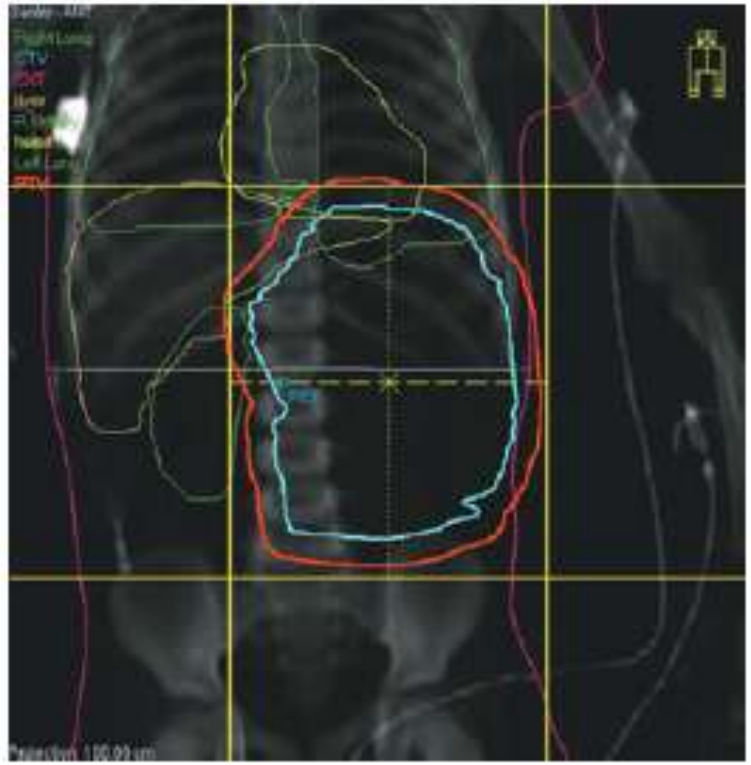
CONFORMAL PLANNING

- 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

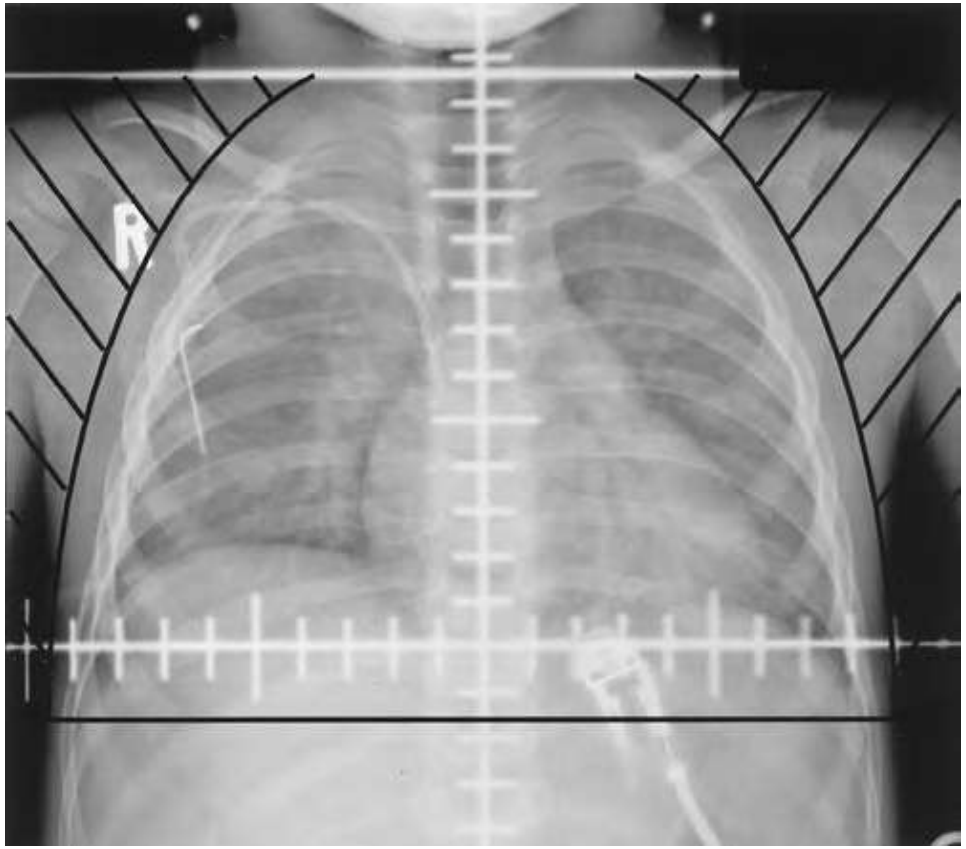
CONFORMAL PLANNING







WHOLE LUNG IRRADIATION

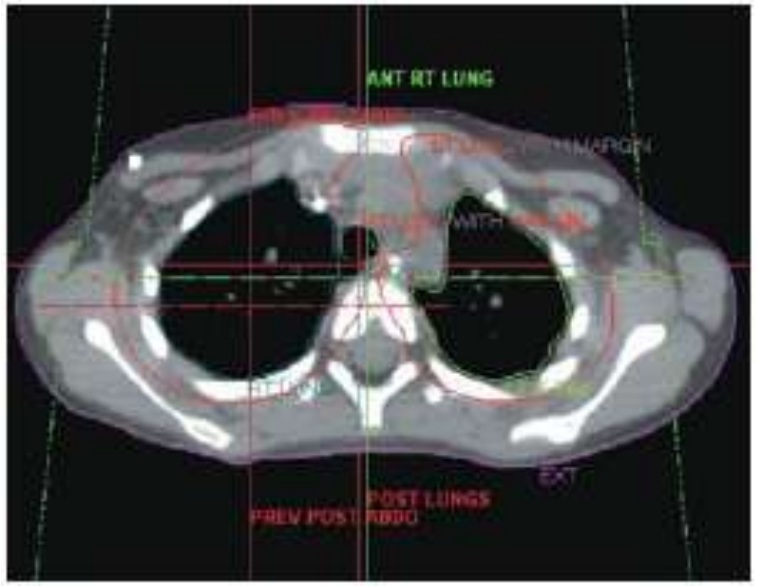


- Upper border- to include both the lung apices
- Lower border- to include the pleural reflection infero-laterally
- Lat border-chest-wall
- Humerus & shoulder joint to be shielded bilaterally

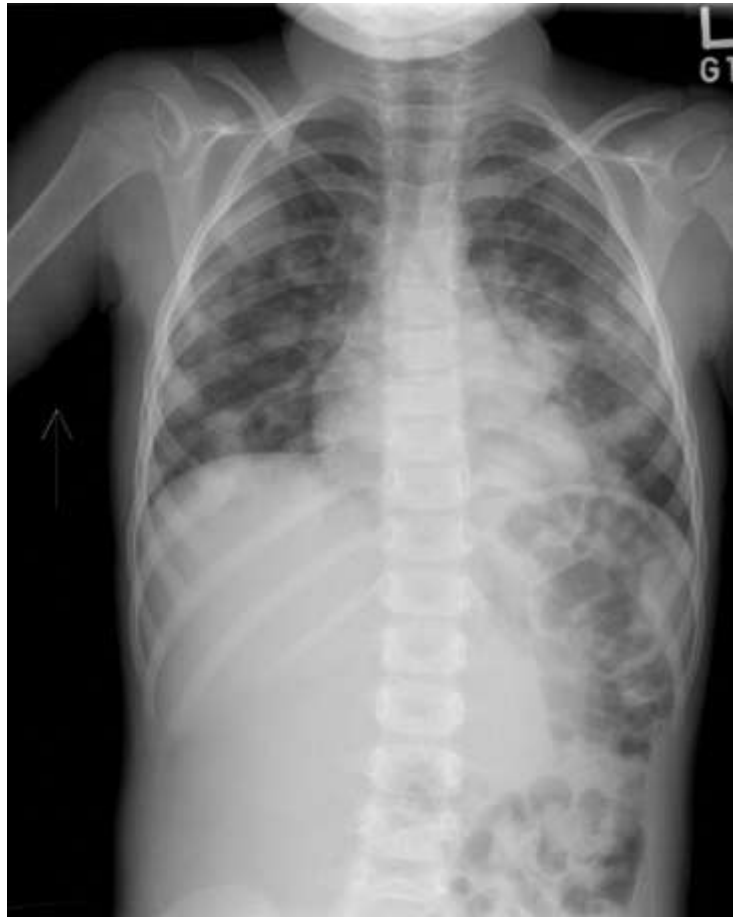
CONFORMAL WLI

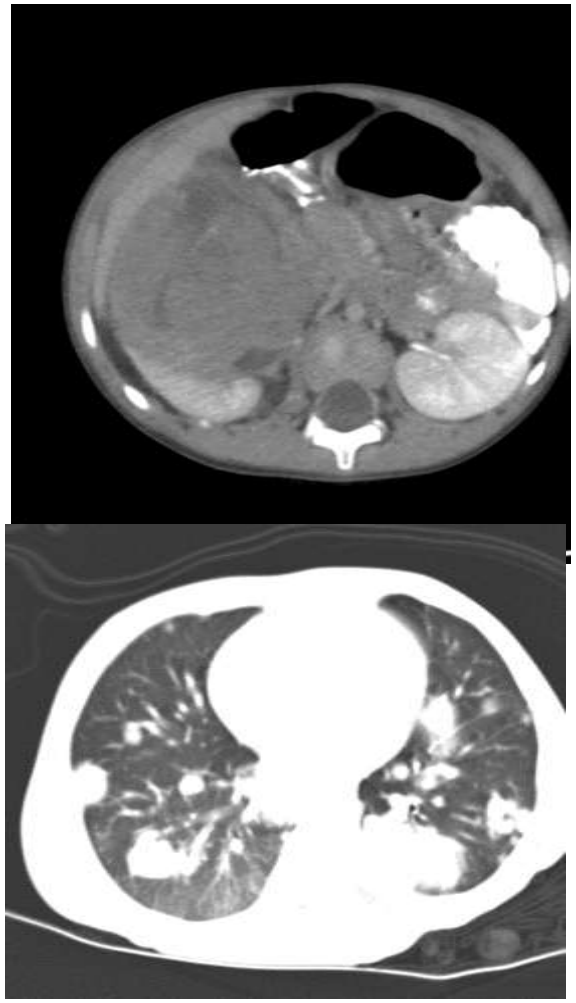
Coronal DRR

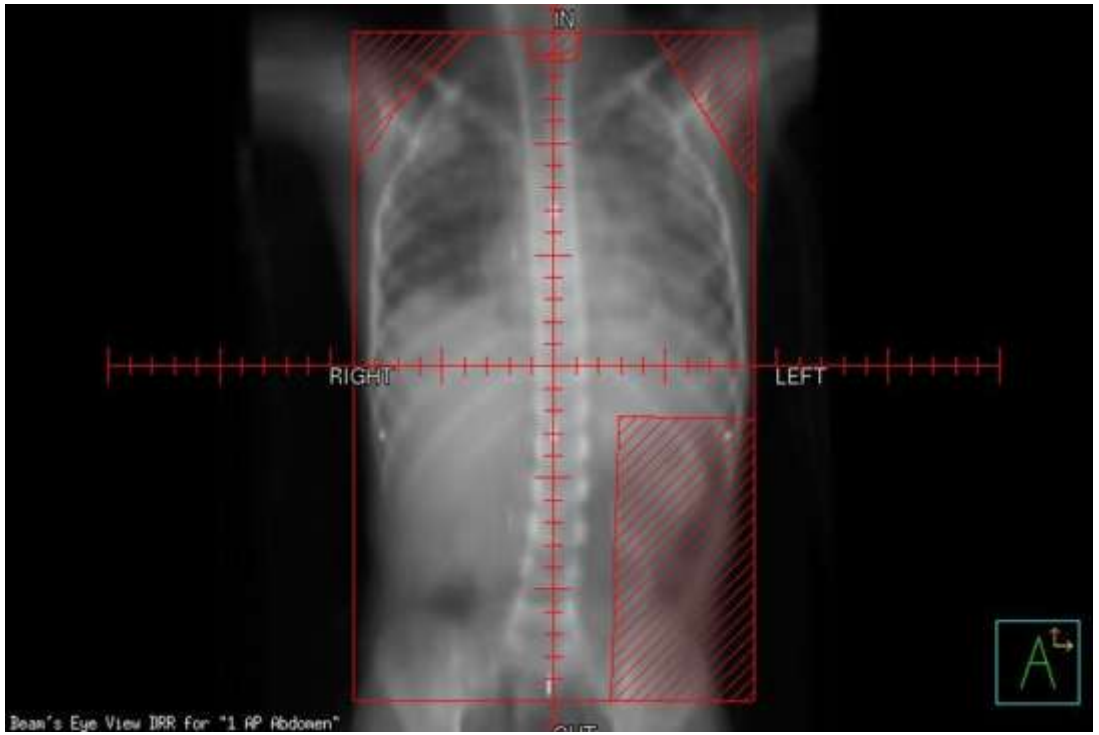
AP-PA beam arrangement

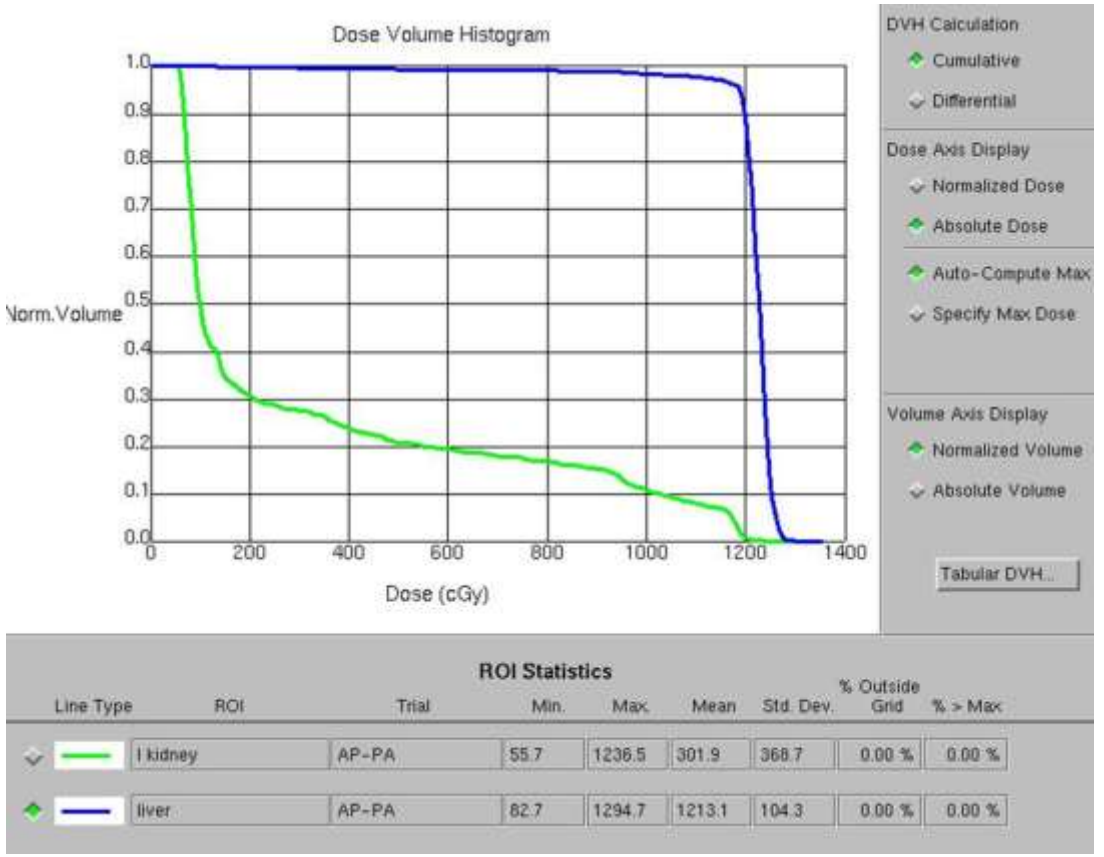


WLI + FLANK RT






IN
RIGHT
LEFT
Beam's Eye View DRR for "1 AP Abdomen"


Dose Volume Histogram
Norm.Volume
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
200
400
600
800
1000
1200
1400
Dose (cGy)
DVH Calculation
Cumulative
Differential
Dose Axis Display
Normalized Dose
Absolute Dose
Auto-Compute Max
Specify Max Dose
Volume Axis Display
Normalized Volume
Absolute Volume
Tabular DVH...
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, 2013

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 malignant 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 Oncol 2005;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

MCQ

- 1) Aniridia in WAGR syndrome is due to mutation in:
  (A) PAX 6 gene
  (B) WT1 gene
  (C) WT2 gene
  (D) WTX gene

Ans: A

MCQ

- 2) The incidence of transformation of nephrogenic rest to nephroblastoma is around:
  (A) 1-5%
  (B) 5-10%
  (C) 10-15%
  (D) 50%

Ans: A

MCQ

- 3) The incidence of calcification in Wilms tumour on X-ray abdomen is:
  (A) 5-15%
  (B) 15-20%
  (C) 20-30%
  (D) 60-70%

Ans: A

MCQ

- 4) A 20 months old girl with left sided Rhabdoid Tumour of the Kidney (RTK) with single left sided lung and left femoral metastases. She had intraoperative tumour spillage during surgery. Subsequently she is treated on AREN 0321 protocol. She has rapid complete response in the lung following chemotherapy. The COG recommendations for RT (WAI-whole abdominal irradiation; WLI- whole lung irradiation) are:

  (A) WAI-10.8 Gy + RT to femoral mets-25.2 Gy

  (B) WAI-10.8 Gy+ WLI-12 Gy+ RT to femoral mets-19.8 Gy

  (C) L flank RT- 19.8 Gy + WLI-12 Gy+ RT to femoral mets-30.6 Gy

  (D) WAI-19.8 Gy+ WLI-12 Gy+ RT to femoral mets-25.2 Gy

Ans: D

MCQ

- 5) A 3 year old girl underwent radical nephroureterectomy for a left sided renal tumour (R1 resection). Post-operative histopathology showed Clear Cell Sarcoma of Kidney (CCSK). She underwent left flank RT (10.8Gy). The COG recommendation for chemotherapy regimen(VCR-Vincristine, AMD-Actinomycin D, DOXO-Doxorubicin, CTX-Cyclophosphamide, IFOS-Ifosfamide, VP-16-Etoposide, CBDCA-Carboplatin) is :

  (A) Alternating VCR, AMD, DOXO/ CTX, VP-16

  (B) Alternating VCR, DOXO, CTX/ CTX, VP-16

  (C) Alternating VCR, DOXO, CTX/ CTX, VP-16, CBDCA

  (D) Alternating VCR, AMD, DOXO/ IFOS, VP-16

Ans: B

MCQ

- 6) A 3 years old boy with right sided stage I favourable histology (FH) Wilms' tumour (WT) was on close follow-up after right sided radical nephroureterectomy followed by 18 weeks of chemotherapy with VCR and AMD. After 1 year abdominal USG showed a 5 cm mass in right renal fossa. CECT chest and whole abdomen confirmed the same lesion with no other evidence of metastasis. He underwent complete resection of the recurrent lesion (Sage IR) and post-op histopathology report showed FH WT. He was started on chemotherapy with VCR and AMD as per NWTS 5 relapse protocol. The COG recommendation for RT is:

  (A) No RT

  (B) Right flank RT 10.8 Gy at 1.8Gy/fraction/day

  (C) Right flank RT 21.6 Gy at 1.8Gy/ fraction/day

  (D)Right flank RT 30.6 Gy at 1.8Gy/ fraction/day

Ans: C

MCQ

- 7) In patients with stage I-II, favourable histology Wilms tumour, LOH of 1p & 16q predicts higher risk of:
  (A) Relapse
  (B) Mortality
  (C) Both relapse & mortality
  (D) None of the above

Ans: C

MCQ

- 8) The common treatment related late effects which can contribute to mortality in patients of Wilms tumour include all except:
  (A) Radiation induced liver disease
  (B) Second malignant neoplasm
  (C) End stage renal disease
  (D) Congestive cardiac failure

Ans: A

THANK YOU