KASTURBA MEDICAL COLLEGE
MANGALORE
(A constituent unit of MAHE, Manipal)

KMC Hospital Attavar Oncology Centre

51st ICRO PG Teaching Program

Radiation Therapy for Wilm's Tumor

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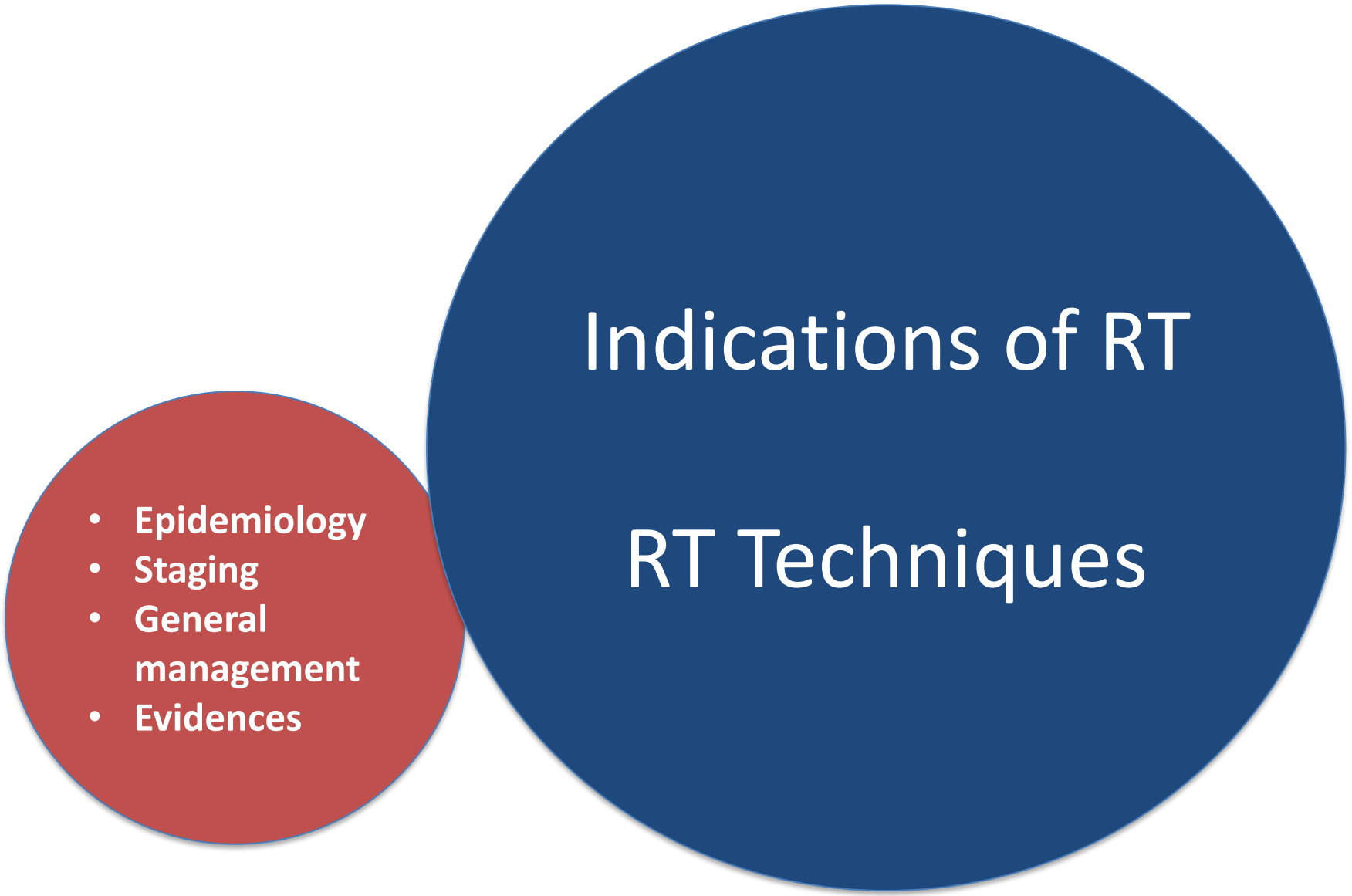
1 Disease

2 Guidelines

3 Risks Classification

5 Stages

Outline


Indications of RT
RT Techniques
Epidemiology
Staging
General management
Evidences

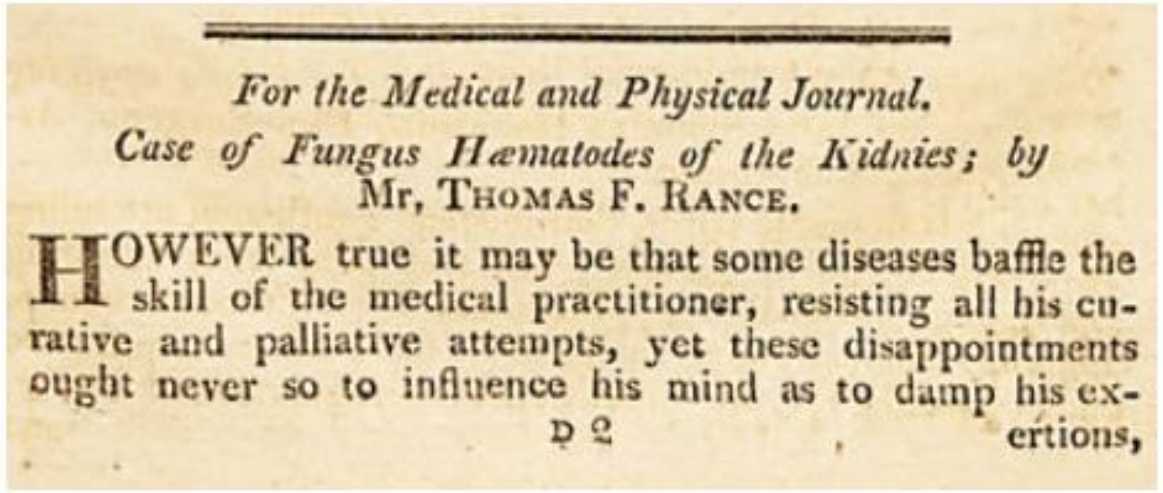
HISTORY

- 1st detailed description of pediatric nephroblastoma- **Thomas Rance.**

- In 1814, - 17-month-old girl infant with left renal mass .

- At that time neither the name “Wilms’ tumor” nor the term “nephroblastoma” had been coined.

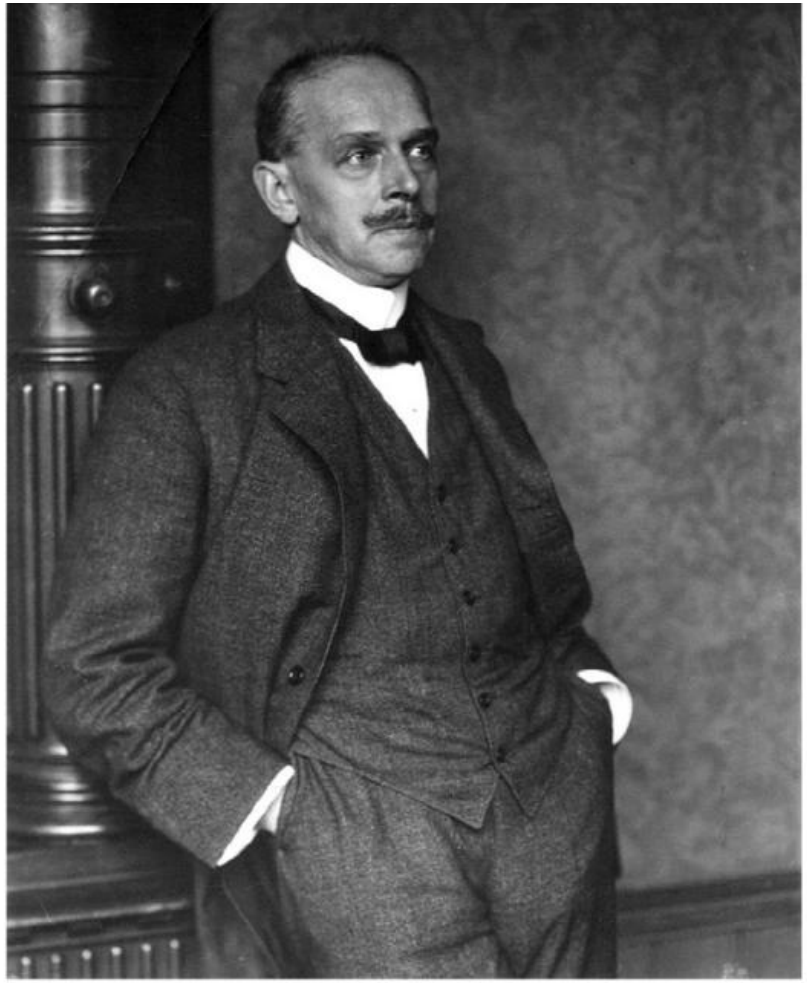
- Rance called this tumor as “*fungus haematodes of the kidnies*”



For the Medical and Physical Journal.

Case of Fungus Hæmatodes of the Kidnies; by Mr, THOMAS F. RANCE.

HOWEVER true it may be that some diseases baffle the skill of the medical practitioner, resisting all his curative and palliative attempts, yet these disappointments ought never so to influence his mind as to damp his exertions,



XIV.

Beiträge zur pathologischen Anatomie der Nierengeschwülste.

Aus dem pathologischen Institut der Universität Leipzig.

Hierzu Tafel VI und VII.

I.

Sarkomatöse Drüsengeschwulst der Niere im Kindesalter (Embryonales Adenosarkom).

Von

Professor Dr. F. V. Birch-Hirschfeld.

Die primären, nach ihrem klinischen Verlauf bösartigen Nierengeschwülste bilden keine einheitliche Gruppe im onkologischen System. Auch mit der Gegenüberstellung des aus dem Drüsenepithel hergeleiteten Carcinoms einerseits und des auf Wucherung der Zellen des bindegewebigen Stromas zurückgeführten Sarkoms andrerseits ist keineswegs eine brauchbare Grundlinie für die klare Unterscheidung der Hauptgruppen maligner Nierentumoren gegeben. Die Hauptschwierigkeit ergiebt sich aus der Thatsache, dass ein Theil der hier zu berücksichtigenden Neubildungen zwar innerhalb der Niere sich entwickelt, aber dabei aus einem Gewebe hervorgeht, das von vornherein in Anordnung und Form seiner Elemente fremdartig gegen die normale Nierenstructur absticht. Das gilt bekanntlich in erster Linie für die Neubildungen, die nach dem Vorgange von Grawitz (1) auf geschwulstförmige Weiterentwicklung von versprengten in das Nierengewebe eingeschlossenen Theilen der Nebenniere zurückgeführt werden. Unzweifelhaft sind hierhergehörige primäre Nierengeschwülste in der Casuistik theils als Carcinome, theils als Sarkome aufgeführt worden. Auch jetzt noch ist über

DIE MISCHGESCHWÜLSTE

Von

Dr. M. WILMS

HEFT 1:

DIE MISCHGESCHWÜLSTE DER NIERE

527152_1_En_1_Fig4_HTML

LEIPZIG
VERLAG VON ARTHUR GEORGI
1899.

Carolus Maximilianus Wilhelmus Wilms

20th Century

MORTALITY

90%

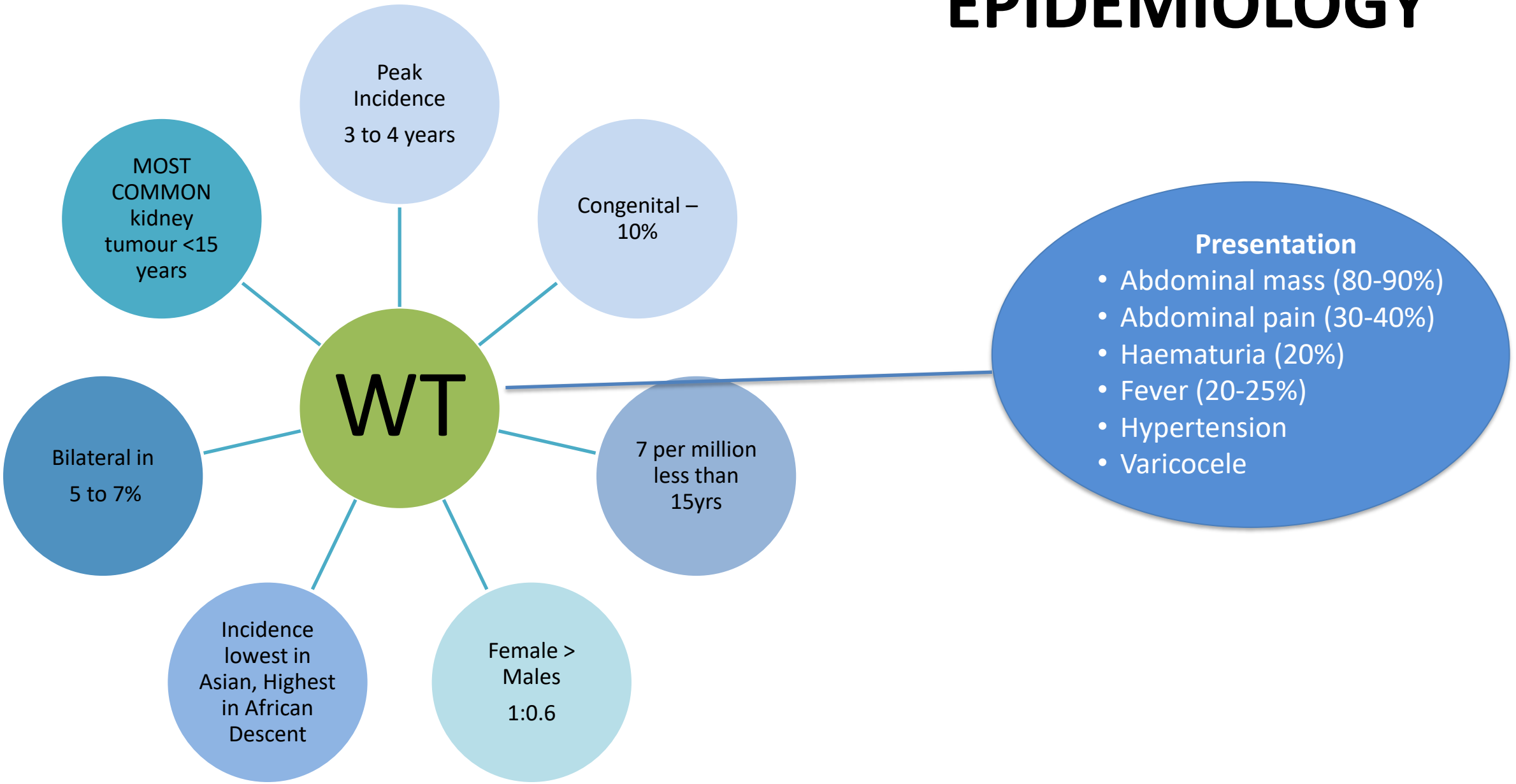
SURVIVAL

21st Century

Attributed to

- National Wilms' Tumor Study **(NWTS)**
- Societe Internationale D'oncologie Pediatrique **(SIOP)** / International Society for Paediatric Oncology

EPIDEMIOLOGY



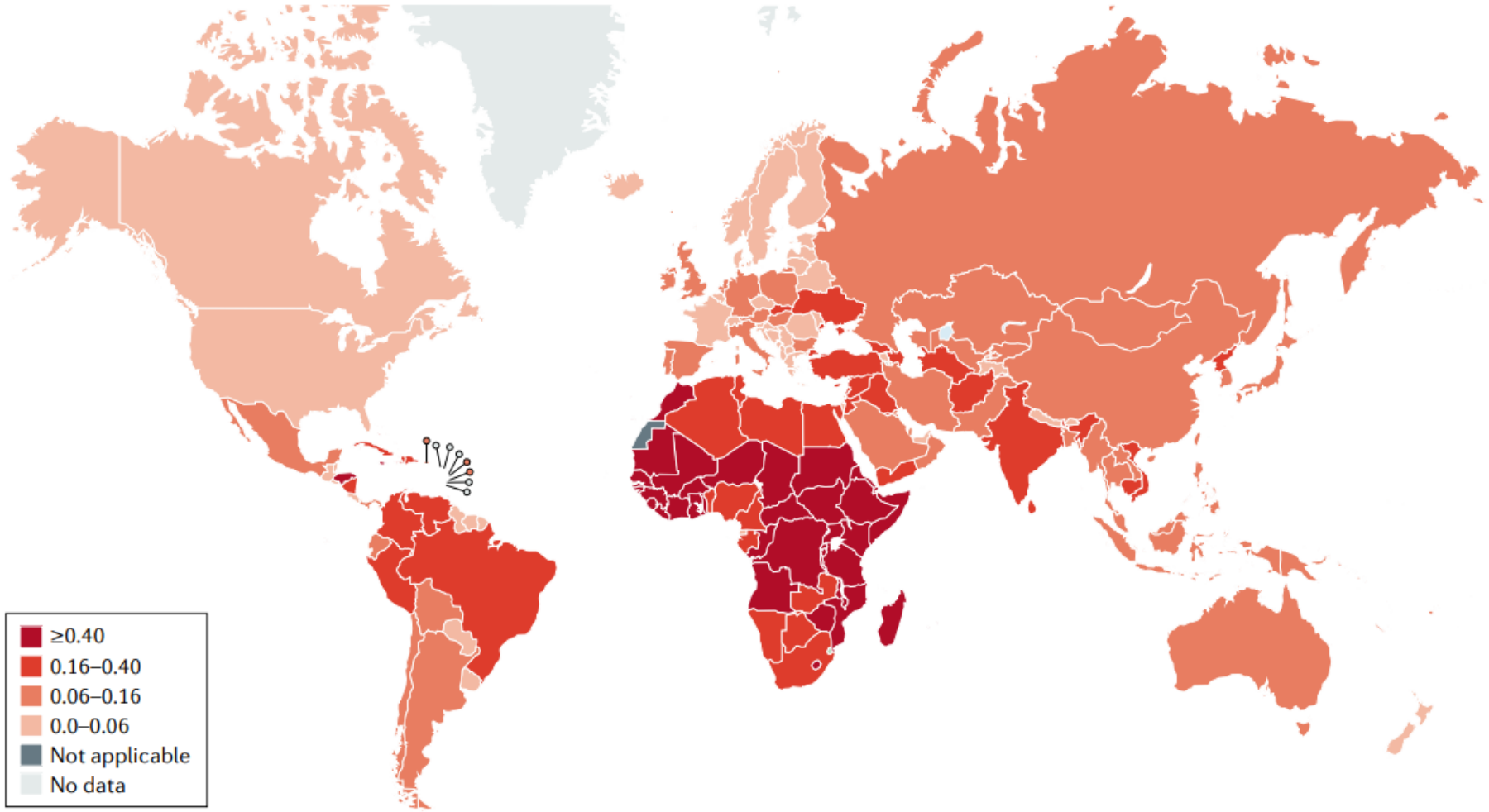
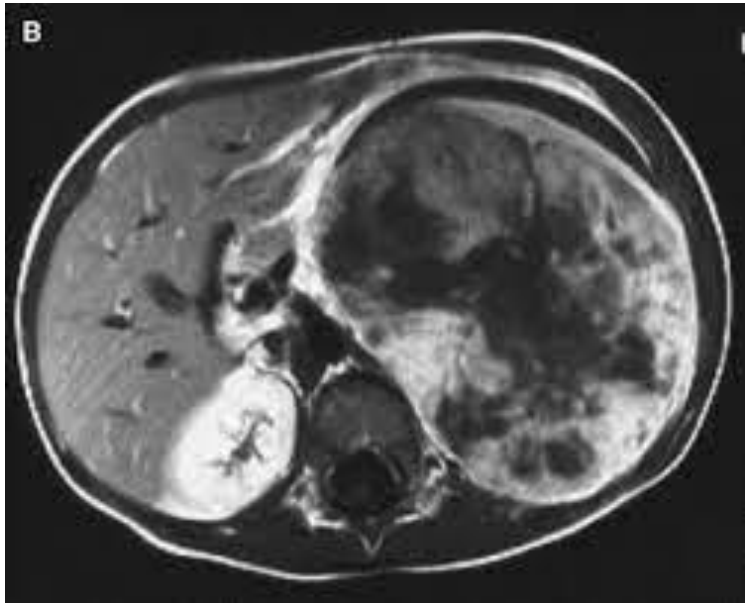
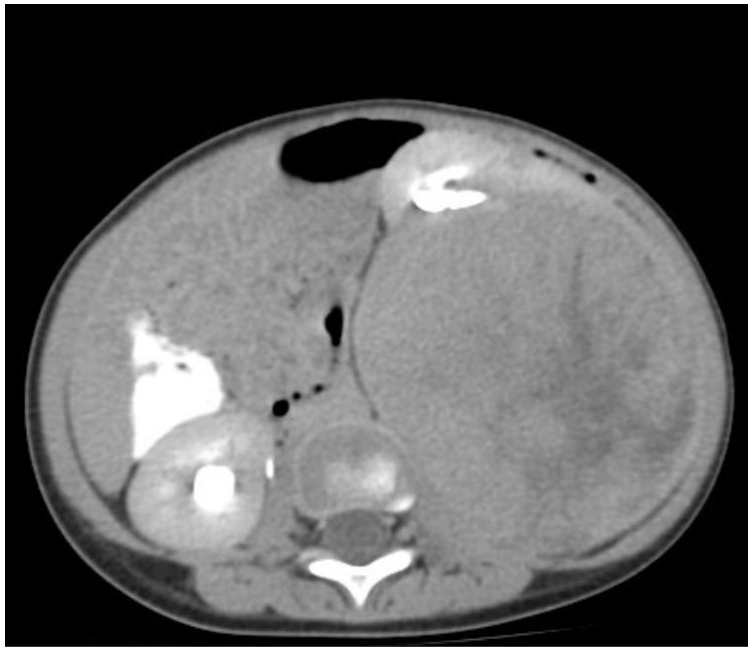


Fig. 2 | **The estimated mortality for kidney cancers according to geographical area.** Estimated age-standardized mortality rates in 2020 for kidney cancers in children aged 0–14 years in the world[234]. Reprinted from GLOBOCAN 2020,

Spreafico, F., Fernandez, C.V., Brok, J. *et al.* Wilms tumour. *Nat Rev Dis Primers* **7**, 75 (2021). https://doi.org/10.1038/s41572-021-00308-8


B

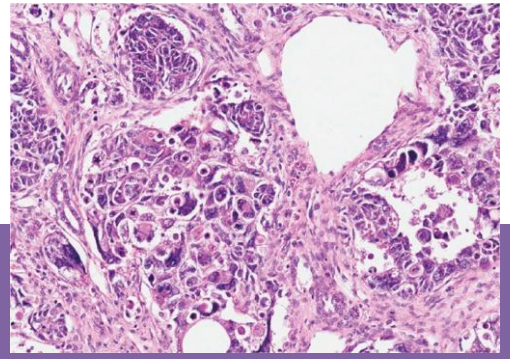



R
L
F

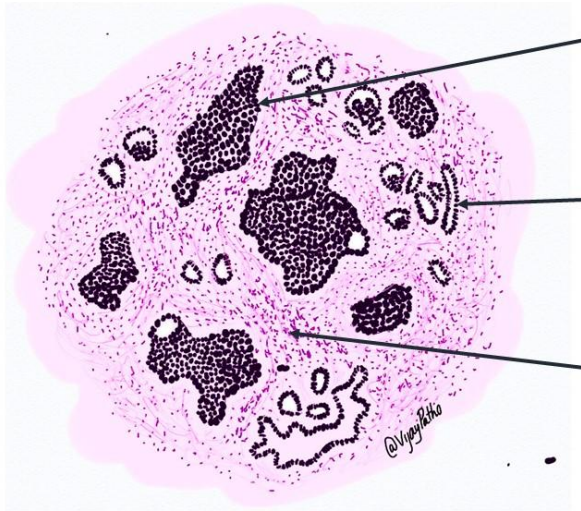
PATHOLOGY

- 87-90 % - Favourable

- 10% - Unfavourable (Anaplasia)



WILMS TUMOR (Nephroblastoma)



BLASTEMAL COMPONENT
Sheets of small blue round cells

EPITHELIAL COMPONENT
epithelial differentiation in the form of abortive tubules and abortive glomeruli.

MESENCHYMAL COMPONENT
fibroblastic

PATHOLOGY – RISK STRATIFICATION

COG

	NWTSG/COG
Low risk	Mesoblastic
Intermediate risk	Favorable histology
High risk	Anaplastic
	Clear cell sarcoma
	Rhabdoid

Gleason JM, Lorenzo AJ, Bowlin PR, Koyle MA. Innovations in the management of Wilms' tumor. *Ther Adv Urol*. 2014;6(4):165-176. doi:10.1177/1756287214528023

SIOP

	Pretreated Cases
Low risk	*Mesoblastic nephroma* *Cystic partially differentiated nephroblastoma* Completely necrotic nephroblastoma
Intermediate risk	Nephroblastoma - epithelial type Nephroblastoma - stromal type Nephroblastoma - mixed type Nephroblastoma - regressive type Nephroblastoma - focal anaplasia
High risk	Nephroblastoma - **blastemal type** Nephroblastoma - diffuse anaplasia *Clear cell sarcoma of the kidney* *Rhabdoid tumour of the kidney*

Van Den Heuvel-eibrink, Marry M., et al. "Rationale for the treatment of Wilms tumour in the UMBRELLA SIOP–RTSG 2016 protocol." *Nature Reviews Urology* 14.12 (2017): 743-752.

MOLECULAR INSIGHTS

Molecular Defect	Syndrome / Association	Risk / Frequency
WT1 mutation / deletion	**WAGR syndrome** = **W**ilms tumour, **A**niridia, **G**enitourinary anomalies, **R**etardation (developmental delay)	~50% develop Wilms
	Denys–Drash syndrome = nephropathy (early nephrotic syndrome), male pseudohermaphroditism, high Wilms risk	~75-90% develop Wilms
	Frasier syndrome = gonadal dysgenesis, progressive nephropathy, gonadoblastoma risk ± Wilms	Lower penetrance
11p15 imprinting / IGF2 dysregulation WT2	**Beckwith–Wiedemann syndrome** = macrosomia, macroglossia, visceromegaly, omphalocele, hemihyperplasia	~5% develop Wilms
CTNNB1 activating mutation	Sporadic Wilms; often co-occurs with WT1 mutations (seen in nephrogenic rests)	~15% of cases
WTX (AMER1) inactivation	Sporadic Wilms (X-linked; males more affected)	~30% of cases
LOH 1p and 16q	Marker of aggressive biology	~5% new cases; relapse risk ↑ 2.5–3×
1q gain	Poor prognostic factor	~30% of Wilms
TP53 mutation / 17p loss	Diffuse anaplastic Wilms (chemoresistant subtype)	~50–60% of anaplastic Wilms
SIX1 / SIX2, DROSHA / DGCR8 mutations	High-risk blastemal type; RNA processing pathway defects	Subset only (variable)
FBXW7 mutation, MYCN gain	Subtype-specific sporadic Wilms	<5–10% of cases
11p15 methylation (LOH)	Very-low-risk Wilms (<2 yrs, <550 g tumour weight)	Associated with increased relapse

STAGING - COG

TABLE 89.2 CHILDREN'S ONCOLOGY GROUP STAGING OF WILMS TUMOR, RHABDOID TUMOR, AND CLEAR CELL SARCOMA OF THE KIDNEY

Stage I: Tumor limited to the 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 the 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 the 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 abdominal–pelvic region are present (the presence of tumor within the adrenal gland is not interpreted as metastasis and staging depend 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

STAGING - SIOP

Stage I

- a) The tumour is limited to the kidney.
- b) Tumour is present in the perirenal fat but is surrounded by a fibrous (pseudo)capsule.
- The (pseudo)capsule may be infiltrated by viable tumour which does not reach the outer surface.
- c) Tumour may show botryoid / protruding growth into the renal pelvis or the ureter, but does not infiltrate their walls.
- d) The vessels or the soft tissues of the renal sinus are not involved by tumour.
- e) Intrarenal vessel involvement may be present.

Stage II

- a) Viable tumour is present in the perirenal fat and is *not covered* by a (pseudo)capsule, but is completely resected (resection margins 'clear').
- b) Viable tumour infiltrates the soft tissues of the renal sinus.
- c) Viable tumour infiltrates blood and/or lymphatic vessels of the renal sinus or of the perirenal tissue, but it is completely resected.
- d) Viable tumour infiltrates the wall of the renal pelvis or of the ureter.
- e) Viable tumour infiltrates the vena cava or adjacent organs (except the adrenal gland, but is completely resected.

Stage III

- a) Viable tumour present at a resection margin. Non-viable tumour or chemotherapy yinduced changes present at a resection margin is not regarded as stage III.
- b) Abdominal lymph nodes involvement by either viable or non-viable tumour.
- c) Pre- or intra-operative tumour rupture, if confirmed by microscopic examination (= viable tumour at the surface of the specimen in the area of the rupture).
- d) Viable or non-viable tumour thrombus is present at resection margins of ureter, renal vein or vena cava inferior (always discuss resection margins with the surgeon).
- e) Viable or non-viable tumour thrombus which is attached to the IVC wall is removed piecemeal by surgeon.
- f) Wedge/open tumour biopsy prior to pre-operative chemotherapy or surgery.
- g) Tumour implants (viable or non-viable) are found anywhere in the abdomen.
- h) Tumour (viable or non-viable) has penetrated through the peritoneal surface

Stage IV

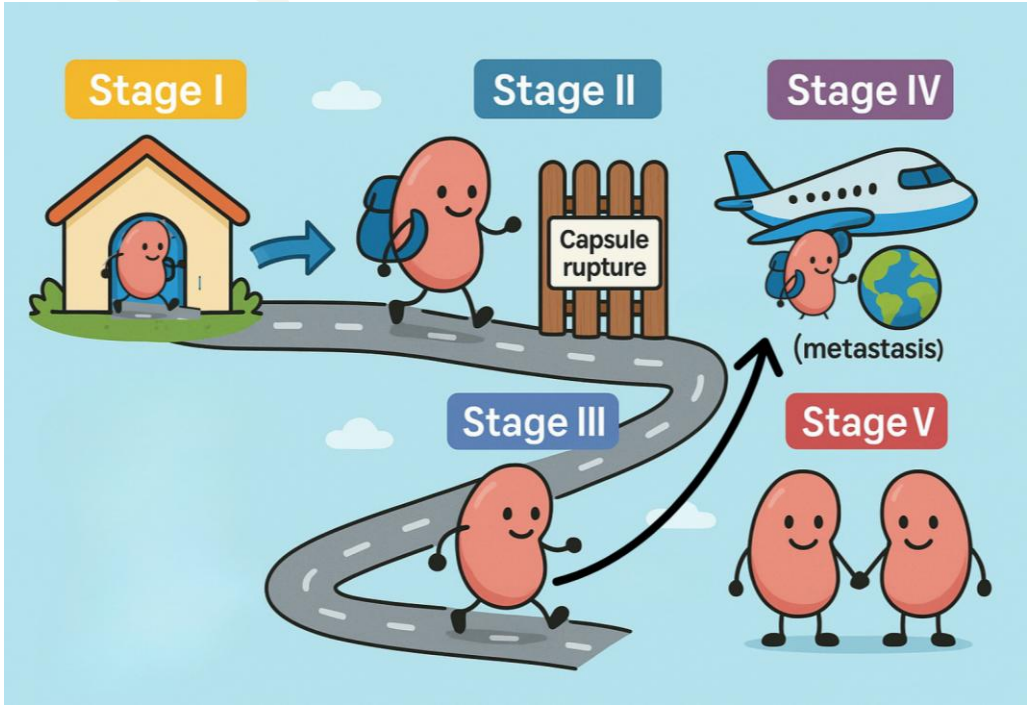
- Haematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdomino-pelvic region.

Stage V

- Bilateral renal tumours at diagnosis. Each side should be sub-staged according to the above criteria.

Brief points COG and SIOP Staging

	COG / NWTS (Upfront Surgery)	SIOP (Post-Chemo Surgery)
I	• Limited to kidney, completely resected • No sinus vessel/capsule involvement • No rupture • No prior biopsy	• Limited to kidney, completely resected • No rupture • After pre-op chemo, only intrarenal disease remains
II	• Extends beyond kidney but completely resected • Penetration of capsule • Invasion of sinus vessels	• Extension beyond kidney but fully resected • Penetration of capsule or invasion of sinus/vena cava, but excised
III	• Gross/microscopic residual • Tumour spillage (intra- or post-op) • Regional LN +ve • Positive peritoneal cytology • Transected thrombus • Prior biopsy	• Gross/microscopic residual post-surgery • Tumour rupture before/during surgery Regional LN involvement • Incomplete excision of thrombus
IV	• Hematogenous mets (lung, liver, bone, brain) • LN mets outside abdomen/pelvis	• Hematogenous mets (lung, liver, bone, brain) • Extra-abdominal LN involvement
V	• Bilateral renal tumours at diagnosis	• Bilateral renal tumours at diagnosis (treated with neoadj. chemo → staged individually per side)



General Management

COG // SIOP

Program / Trial	Year	Key Findings	RT
NWTS-1	1969–74	Established multimodality care: nephrectomy + **VCR+Act-D**; standardized staging/path.	RT standard for ≥Stage II/III; baseline for later de-escalation.
NWTS-2	1974–81	**Doxorubicin** improves outcomes in higher stage/UH.	Narrow RT to higher stage/adverse features.
NWTS-3	late ’70s–’80s	De-escalation: **Stage II FH → omit RT**; **Stage III FH: 10 Gy ≈ 20 Gy**.	Safely **omit RT** (Stage II FH); **reduce dose to 10 Gy** (Stage III FH).
NWTS-4	’80s–’90s	Optimized chemo scheduling/shorter duration; no loss of control.	Maintain **reduced RT** where indicated; no dose escalation needed.
NWTS-5	’90s–2002	Biology risk added (**LOH 1p/16q**); defined **Very-Low-Risk** (<2 yr, <550 g).	**Avoid RT** in very-low/low risk; focus RT on Stage III/UH or adverse biology.
COG AREN03B2	2006	Central imaging/path/biology backbone for risk assignment.	Ensures **consistent RT indications** after verification (stage, histology, biomarkers).
COG AREN0532	2006–2013	Confirms **surgery-only** for **Very-Low-Risk**; refines Stage I–II FH.	Many **Stage I FH** avoid RT; **Stage II FH** usually **no RT** unless adverse factors.
COG AREN0533	2007–2013	**Response-adapted** lung strategy for Stage IV FH.	**WLRT not automatic**—omit/reduce in rapid responders; coordinate with flank RT.
COG AREN0321	2007–2019	Intensified therapy improves outcomes in **diffuse anaplasia**.	**Prompt flank/abdomen RT** integral; careful field/dose selection.
SIOP-93-01	1993–2001	Standardized **pre-op chemo (~4 wks)** → surgery; lowers rupture.	RT guided by **post-chemo stage/histology** (not upfront findings).
SIOP-2001	2001–2011	Risk-adapted adjuvant; **blastemal-type = high risk (intensify)**; selected IR can de-escalate.	**Escalate RT** for blastemal/high risk; **limit/omit** in low/IR groups.
SIOP-RTSG UMBRELLA 2016	2016	Harmonizes surgery/RT/chemo; integrates **1q gain**, blastemal volume, etc.	**Personalized RT** (who/where/how much) aiming to reduce late effects.

Table 1 | First-generation Children's Oncology Group favourable-histology Wilms tumour risk stratification

Stage	Age	Tumour weight	Molecular features	Lung nodule response	EPM	Risk group[a]
I	<2 years	<550 g	Any	NA	NA	Very low risk
I	<2 years	>550 g	Normal	NA	NA	Low risk
I	>2 years	Any	Normal	NA	NA	Low risk
II	Any	Any	Normal	NA	NA	Low risk
I	Any	Any	Combined LOH	NA	NA	Standard risk
II	Any	Any	Combined LOH	NA	NA	Standard risk
III	Any	Any	Normal	NA	NA	Standard risk
IV	Any	Any	Normal	RCR	No	Standard risk
III	Any	Any	Combined LOH	NA	NA	Higher risk
IV	Any	Any	Combined LOH	Any	No	Higher risk
IV	Any	Any	Any	SIR	No	Higher risk
IV	Any	Any	Any	Any	Yes	Higher risk

Combined LOH, LOH of both 1p and 16q; EPM, extrapulmonary metastases; LOH, loss of heterozygosity; NA, not applicable; Normal, absence of combined LOH; RCR, rapid complete response; SIR, slow incomplete response. [a]Risk group assignment does not necessarily indicate the optimal treatment. Treatment changes in AREN0532 or AREN0533 did not improve outcomes for all patients, yet these risk group categories still represent relative differences in outcomes for these groups of patients. Adapted with permission from ref. 16, Wiley.

Table 2 | Evolution of prognostic factors in Wilms tumour studies in the NWTS Group and the COG

Study	Prognostic factors included												Refs.
NWTS-1	Stage	–	–	–	–	–	–	–	–	–	–	–	17,41
NWTS-2	Stage	–	–	–	–	–	–	–	–	–	–		18,115
NWTS-3	Stage	Histology	–	–	–	–	–	–	–	–	–	–	19,51
NWTS-4	Stage	Histology	–	–	–	–	–	–	–	–	–	–	20,28, 116
NWTS-5	Stage	Histology	Age	Tumour nephrectomy weight	–	–	–	–	–	–	–	–	5,14,21, 42,65
COG first-generation studies (AREN0321, 0532, 0533, 0534)	Stage	Histology	Age	Tumour nephrectomy weight	LOH of 1p and 16q	Lung metastatic response	Extrapulmonary metastases	Bilateral/ predisposition	Post-chemotherapy histology (bilateral/ predisposed only)	–	–	–	7–9,11, 27,47
COG second-generation studies (AREN2231, to be decided)	Stage	Histology[a]	Age[b]	–	LOH of 1p and/or 16q	Lung metastatic response	Extrapulmonary metastases	Bilateral/ predisposition	Post-chemotherapy histology (all)	LOH 11p15[c]	1q gain	Lymph node involvement	–

COG, Children's Oncology Group; LOH, loss of heterozygosity; NWTS, National Wilms Tumor Study. [a]New histological groups incorporated. [b]Age cut-off changed from 2 to 4 years. [c]Loss of imprinting of 11p15 also prognostic but not incorporated into AREN2231 as current testing technologies are not routinely available and do not return results fast enough to be used in upfront clinical decisions at this time.

	Pretreated Cases	Primary nephrectomy cases
Low risk	*Mesoblastic nephroma* *Cystic partially differentiated nephroblastoma* Completely necrotic nephroblastoma	*Mesoblastic nephroma* *Cystic partially differentiated nephroblastoma*
Intermediate risk	Nephroblastoma - epithelial type Nephroblastoma - stromal type Nephroblastoma - mixed type Nephroblastoma - regressive type Nephroblastoma - focal anaplasia	**Non-anaplastic nephroblastoma and its variants** Nephroblastoma - focal anaplasia
High risk	Nephroblastoma - **blastemal type** Nephroblastoma - diffuse anaplasia *Clear cell sarcoma of the kidney* *Rhabdoid tumour of the kidney*	Nephroblastoma – diffuse anaplasia *Clear cell sarcoma of the kidney* *Rhabdoid tumour of the kidney*

		Tumour volume after preoperative chemotherapy	Stage I	Stage II	Stage III
Low Risk (only CN)		All	No further treatment	AV2	AV2
Intermediate Risk		≤ 500 ml	AV1	AV2	AV2 + RT
Intermediate Risk*		> 500 ml	AV1	AVD	AVD + RT
High Risk	**BT**	All	AVD	HR-1	HR-1 + RT
	DA	All	AVD	HR-1 + flank RT	HR-1 + RT

General Management

COG // SIOP

Aspect	COG (NWTS/AREN, USA)	SIOP (Europe, Umbrella)
Initial approach	**Primary surgery first** (radical nephrectomy + LN sampling). No biopsy unless tumour unresectable.	**Pre-operative chemotherapy** for all patients → surgery after 4–6 weeks. Biopsy not routine.
Staging basis	Based on **pathology at initial nephrectomy**.	Based on **post-chemo surgical specimen**.
Biopsy	Not performed if tumour is resectable; biopsy/upfront chemo only for inoperable, solitary kidney, bilateral, caval thrombus above liver, or contiguous organ involvement.	Not required; diagnosis made clinically/radiologically, pre-op chemo given to all.
Lymph node sampling	LN sampling recommended at nephrectomy; omission risks under-staging.	LN sampling mandatory; at least 7 nodes recommended for accurate staging.
Nephron-sparing surgery	Rare; reserved for solitary kidney, bilateral predisposition, horseshoe kidney, infants with syndromes (Denys–Drash, Frasier).	Allowed in unilateral non-syndromic WT if tumour <300 mL and sufficient renal function preservation expected.

Aspect	COG (NWTS/AREN, USA)	SIOP (Europe, Umbrella)
Pre-operative chemotherapy	Given **only if**: unresectable, bilateral, solitary kidney, caval thrombus above liver, contiguous organ invasion, extensive pulmonary mets.	Given to **all patients** (standard 4 weeks for unilateral; up to 12 weeks for bilateral) except infants <6months - Recommend primary nephrectomy (unless not suitable).
Post-operative chemotherapy	All except very-low-risk (Stage I FH <2 yrs, <550 g, sampled negative nodes).	All except Stage I low-risk.
Radiotherapy indications	Tumour bed RT for **all Stage III**. WLRT for mets not in CR after chemo.	WART for rupture, spillage, peritoneal deposits. WLRT only if lung mets not in CR, or high-risk histology.
Stage V (bilateral disease)	Pre-op chemo + bilateral renal-sparing surgery; transplant delayed 1–2 yrs post-treatment.	Same, but chemo limited to ≤12 weeks, with 6-week reassessments.
Recurrence strategy	Risk groups: standard, high, very high → chemo ± surgery, RT, HSCT for very high-risk.	Groups AA/BB/CC → escalating regimens, including high-dose chemo + stem cell rescue in BB/CC.
Overall philosophy	**Histology-driven, pathology upfront.** More children exposed to surgery/RT early.	**Downstaging with chemo.** Fewer children receive RT/anthracycline; focus on reducing toxicity.

Both approaches work well — they just get there differently.

CHEMOTHERAPY REGIMENS

Group	Regimen	Drugs	Typical Duration	Used in
COG	**EE-4A**	Vincristine + Actinomycin D	~18 weeks	Stage I–II FH (standard risk)
	DD-4A	Vincristine + Actinomycin D + Doxorubicin	~24 weeks	Stage III–IV FH, higher risk
	Regimen M	Vincristine + Actinomycin D + Doxorubicin + Cyclophosphamide + Etoposide	~24–30 weeks	High risk / diffuse anaplasia / relapse
	Regimen UH-1	Vincristine + Doxorubicin + Cyclophosphamide + Etoposide ± Carboplatin	~30 weeks	Ultra high risk (very adverse histology, relapse)
SIOP	**AV-1**	Actinomycin D + Vincristine	~4–6 weeks pre-op (short course)	Standard risk, pre-op chemo backbone
	AV-2	Actinomycin D + Vincristine + Doxorubicin	~4–6 weeks pre-op	Intermediate risk, more advanced stage
	AVD	Actinomycin D + Vincristine + Doxorubicin	~25–27 weeks total	Higher risk, post-op continuation
	HR-1	Vincristine + Doxorubicin + Cyclophosphamide + Etoposide (± Carboplatin)	~25–34 weeks	High risk histology (blastemal, diffuse anaplasia, poor response)

- COG : Post nephrectomy, the chemotherapy regimen is decided as per the risk stratification - first dose of VCR given within 5–7 days of surgery, after assuring adequate bowel peristalsis, and no significant postoperative complications.

- SIOP: Two-drug (VCR+ACD) for nonmetastatic and three-drug (VCR+ACD+ADR) chemotherapy for metastatic WT patients are started soon after diagnosis. 4 weeks in case of nonmetastatic and 6 weeks in metastatic patients.

RT: COG/SIOP
• FLANK RT
• WHOLE ABDOMINAL RT
• WHOLE LUNG IRRADIATION
• LIVER RT
• BRAIN RT
• RT TO METASTATIC SITES

TABLE 89.4 OUTLINE OF CHILDREN'S ONCOLOGY GROUP RENAL TUMOR STUDY

Tumor Risk Classification	Multimodality Treatment
Very Low-Risk FH Wilms Tumor	
<2 y, stage I, tumor weight <550 g	Nephrectomy without adjuvant therapy, if node sampling and central pathology review have been performed
Low-Risk FH Wilms Tumor	
≥2 y, 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	
Stage I–IV focal anaplasia	Nephrectomy, RT, regimen DD4A
Stage I diffuse anaplasia	Nephrectomy, RT, regimen DD4A
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

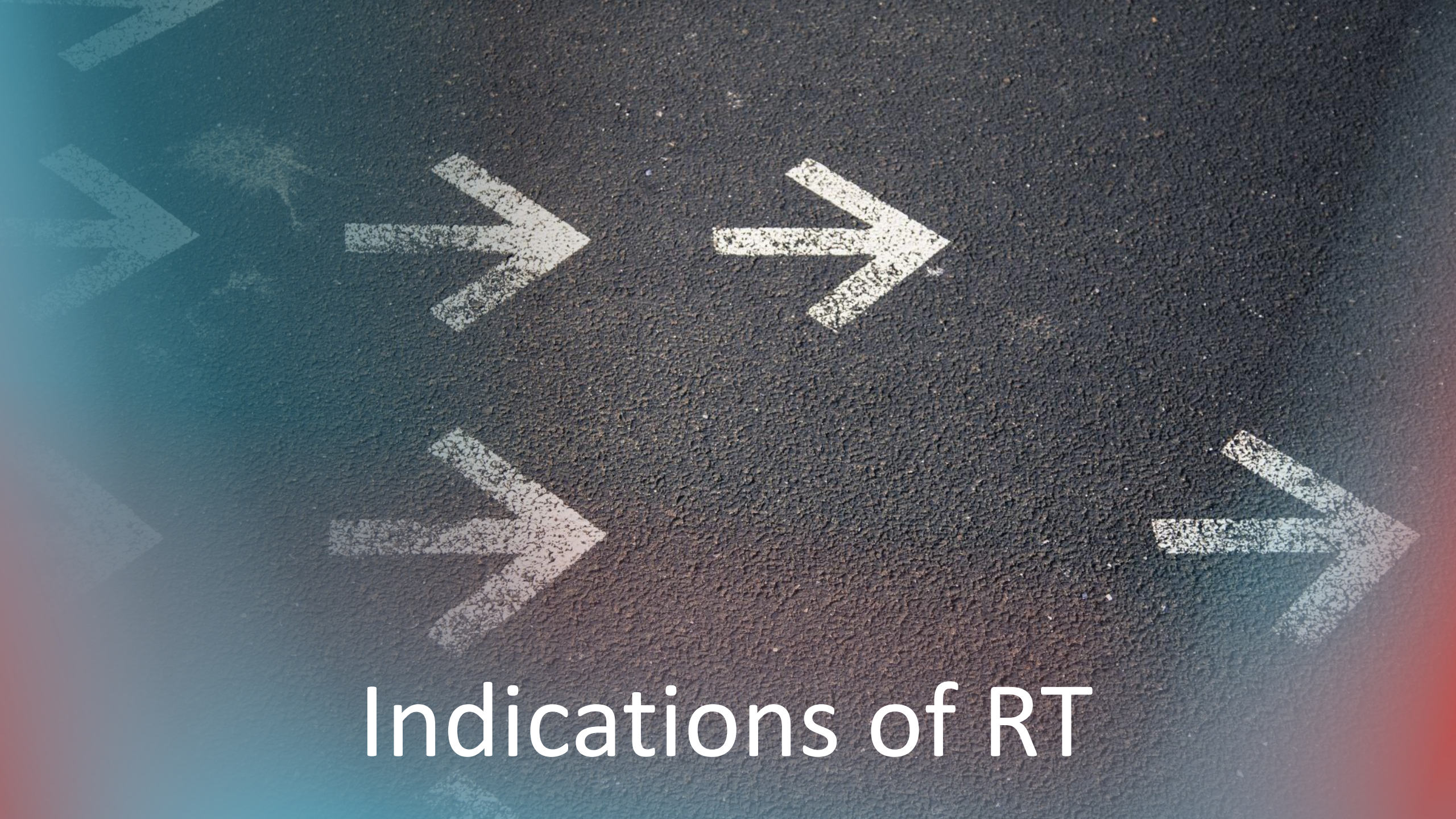
CCSK, clear cell sarcoma of the kidney; FH, favorable histology; LOH, loss of heterozygosity at 1p and 16q; regimen DD4A (V [vincristine], A [dactinomycin], D [doxorubicin]); regimen EE4A (VA); regimen M (VAD/Cy [cyclophosphamide], E [etoposide]); RT, flank or abdominal irradiation;

COG

SIOP

	Pretreated Cases
Low risk	*Mesoblastic nephroma* *Cystic partially differentiated nephroblastoma* Completely necrotic nephroblastoma
Intermediate risk	Nephroblastoma - epithelial type Nephroblastoma - stromal type Nephroblastoma - mixed type Nephroblastoma - regressive type Nephroblastoma - focal anaplasia
High risk	Nephroblastoma - **blastemal type** Nephroblastoma - diffuse anaplasia *Clear cell sarcoma of the kidney* *Rhabdoid tumour of the kidney*

		Tumour volume after preoperative chemotherapy	Stage I	Stage II	Stage III
Low Risk (only CN)		All	No further treatment	AV2	AV2
Intermediate Risk		≤ 500 ml	AV1	AV2	AV2 + RT
Intermediate Risk*		> 500 ml	AV1	AVD	AVD + RT
High Risk	**BT**	All	AVD	HR-1	HR-1 + RT
	DA	All	AVD	HR-1 + flank RT	HR-1 + RT



Indications of RT

- Radiotherapy should be started within 14 days , ideally within 9 days of surgery unless there is a contraindication.

- Newer irradiation techniques like IMRT and IGRT may be used as long as they contribute to a dose reduction in normal tissue at risk

PATHOLOGY – RISK STRATIFICATION

COG

	NWTSG/COG
Low risk	Mesoblastic
Intermediate risk	Favorable histology
High risk	Anaplastic
	Clear cell sarcoma
	Rhabdoid

Gleason JM, Lorenzo AJ, Bowlin PR, Koyle MA. Innovations in the management of Wilms' tumor. *Ther Adv Urol*. 2014;6(4):165-176. doi:10.1177/1756287214528023

SIOP

	Pretreated Cases
Low risk	*Mesoblastic nephroma* *Cystic partially differentiated nephroblastoma* Completely necrotic nephroblastoma
Intermediate risk	Nephroblastoma - epithelial type Nephroblastoma - stromal type Nephroblastoma - mixed type Nephroblastoma - regressive type Nephroblastoma - focal anaplasia
High risk	Nephroblastoma - **blastemal type** Nephroblastoma - diffuse anaplasia *Clear cell sarcoma of the kidney* *Rhabdoid tumour of the kidney*

Van Den Heuvel-eibrink, Marry M., et al. "Rationale for the treatment of Wilms tumour in the UMBRELLA SIOP–RTSG 2016 protocol." *Nature Reviews Urology* 14.12 (2017): 743-752.

Stage	COG – Favorable Histology	COG – Unfavourable Histology	SIOP – Low Risk	SIOP – Intermediate Risk	SIOP – High Risk (Blastemal)	SIOP – High Risk (Diffuse Anaplasia)
I	No RT	**10.8 Gy to flank**	No RT	No RT	No RT	No RT
II	No RT	**10.8 Gy to flank**	No RT	No RT	No RT	**25.2 Gy to flank**
III (except major rupture)	**10.8 Gy to flank** **Tumour spillage: – Localised: 10.8 Gy flank**	**Clear Cell- 10.8 Gy** **Rest: 19.8 Gy to flank** **Tumour spillage: – 19.8 Gy to whole abdomen**	No RT	**14.4 Gy to flank**	**25.2 Gy to flank**	**25.2 Gy to flank**
III (major rupture / diffuse spill)	**10.8 Gy whole abdomen**	**19.8 Gy whole abdomen**	**–**	**15 Gy whole abdomen**	**19.5 Gy whole abdomen**	**19.5 Gy whole abdomen**

Residual Disease +/- 10.8 Gy boost

- **SIOP gives RT only for higher-risk histologies and residual/ruptured disease**.

- **Doses are higher (25.2 Gy)** compared to **COG flank 10.8 Gy**, reflecting the philosophy of giving RT to fewer patients but at higher dose intensity.

- **Whole abdomen RT** is reserved for **major rupture/spillage**.

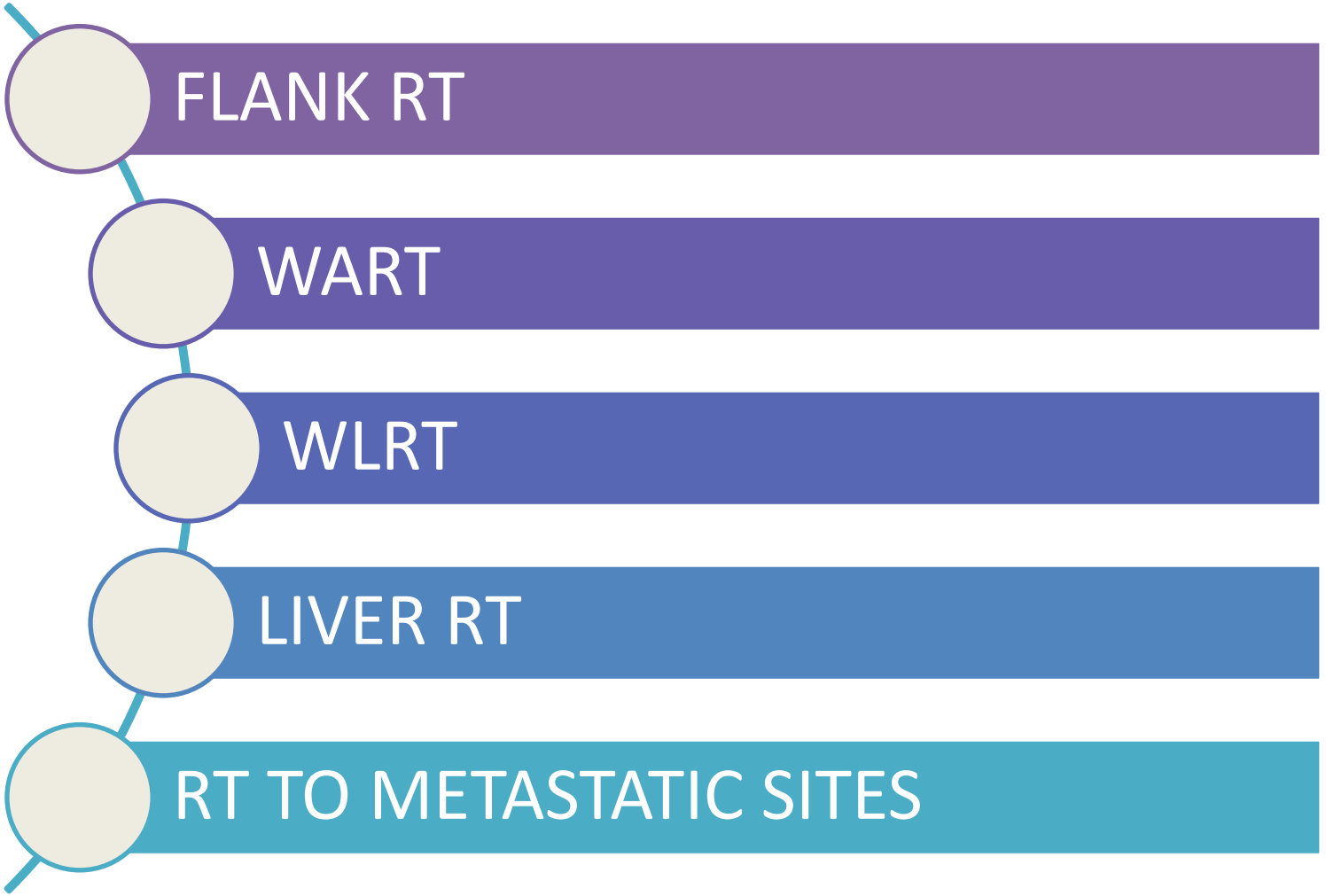
Metastatic Site	COG (NWTS/AREN)	SIOP – Intermediate Risk	SIOP – High Risk
Lung	12 Gy Whole Lung Irradiation (WLI) in 8 fx Boost 9 Gy to gross residual	12 Gy WLI in 8 fx	15 Gy WLI in 10 fx
Brain metastases	30.6 Gy Whole Brain / 17 fx OR 21.6 Gy WBRT + 10.8 Gy boost (IMRT/stereotactic)	15 Gy WBRT in 10 fx ± 10.5 Gy boost	25.2 Gy WBRT in 14 fx ± 10.5 Gy boost
Liver metastases	19.8 Gy Whole Liver in 11 fx	14.4 Gy in 8 fx (boost 10.8 Gy if residual)	20–25.2 Gy in 11–14 fx (boost 16.2 Gy if residual)
Bone metastases	25.2 Gy local RT to lesion + 3 cm margin	30.6 Gy in 17 fx OR 30 Gy in 10 fx (local field)	30.6 Gy in 17 fx OR 30 Gy in 10 fx (local field)
Unresected LN metastases	19.8 Gy	–	–

- **COG:** More prescriptive — fixed doses (WLI 12 Gy, liver 19.8 Gy, brain 21.6–30.6 Gy, bone 25.2 Gy).
- **SIOP:** Histology-based — Intermediate risk gets lower doses (lung 12 Gy, liver 14.4 Gy, brain 15 Gy), while High risk escalates (lung 15 Gy, liver up to 25.2 Gy, brain 25.2 Gy).
- **Field choice differs**: COG uses whole-organ fields more rigidly; SIOP tailors based on risk group
- In cases of recurrent disease with lung metastases without prior lung irradiation during first line treatment whole lung RT should be performed in all histology- and remission types.

Simulation & Setup

- Supine, arms up, VacLok, sedation if needed
- Planning CT ≤2-3 mm, fuse pre/post-op scans
- Include surgical clips

RT IN WILMS TUMOUR



Considerations

Imaging for planning: Use **pre-op contrast CT / T2 MRI** for tumor extent (standard of care).

Surgical markers: Clip suspicious/incompletely resected areas.

RT timing: Start day 9, not more than day 14.
- If lung RT also needed → postpone flank RT until after lung surgery.
- **High-risk (diffuse anaplasia):** Flank RT should **not be delayed**, may be given separately from lung RT.

Field considerations:
- Do **not extend into diaphragm dome** unless tumor extension.
- Avoid major heart irradiation (esp. left-sided tumors).

Nodes:
- Positive/removed nodes → irradiate entire **para-aortic chain**.
- Include nodal groups involved at presentation.
- Treat nodal areas **in continuity with primary tumor**.
- **Cranial field border:** T10–11 level (≈ celiac axis at T12 pedicle).

IMRT in Wilms' Tumour – Key Points

- **Why it matters:** Traditional whole-lung irradiation (AP/PA fields) in Wilms patients has been linked to **cardiac and pulmonary complications** (CHF, myocardial infarction, pericardial disease, restrictive lung disease). Lowering lung dose is critical for survival and quality of life.

- **Advantages of IMRT/4D-IMRT:**
  - Better **cardiac sparing** compared to AP/PA fields.
  - Allows **4D planning** to account for breathing motion.
  - Provides more **uniform dose distribution** in lungs, with fewer hotspots.
  - Avoids excessive dose to the **remaining kidney** in unilateral cases.

- **Clinical outcomes:**
  - Studies showed IMRT reduced dose to normal tissues (thyroid, heart, atria, ventricles) without compromising tumour coverage.
  - A modified **whole-lung IMRT (WL-IMRT)** approach was developed, improving sparing of thoracic structures.
  - Early trials reported **2- and 3-year progression-free survival of ~65% and 52%** in lung metastasis patients treated with WL-IMRT plus doxorubicin.

- **Overall:** IMRT/4D IMRT is becoming the preferred approach for whole-lung or whole-liver RT in Wilms' tumour, offering **safer long-term toxicity profile** while maintaining efficacy

Flank RT - Conventional RT

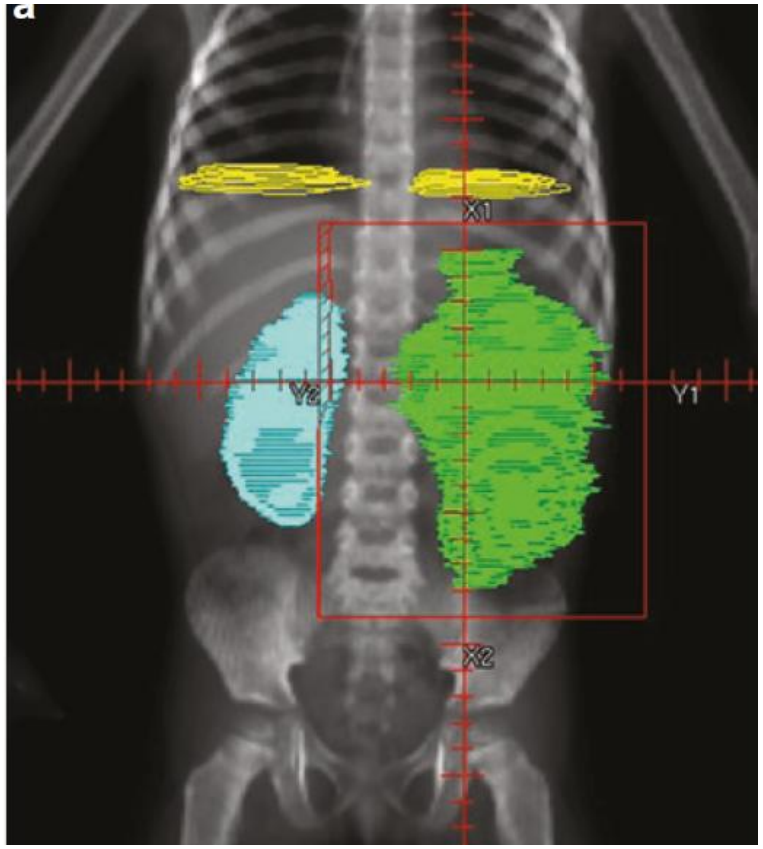
Based on imaging: CT/MR at initial presentation (before chemo)

Target volume: Kidney + tumor with **1 cm margin**

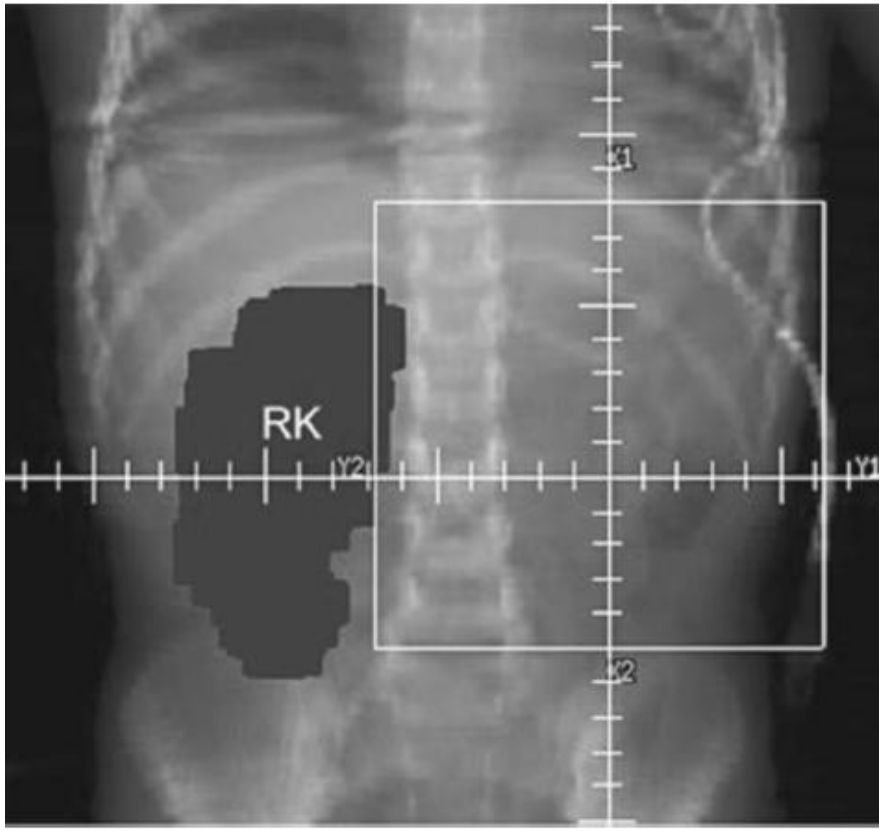
Borders:
- Superior, Inferior, Lateral → ~1 cm beyond kidney
- Medial → Extend **across midline** to include vertebral bodies + 1 cm margin

Special cases:
- **IVC thrombus:** Include whole thrombus + 1 cm margin
- **LN involvement:** Cover entire para-aortic chain (crus of diaphragm → lower border of L5)

Technique: AP-PA parallel opposed beams



Merchant TE, Kortmann RD, editors. Pediatric radiation oncology. Berlin, Heidelberg: Springer; 2018 Mar 1.



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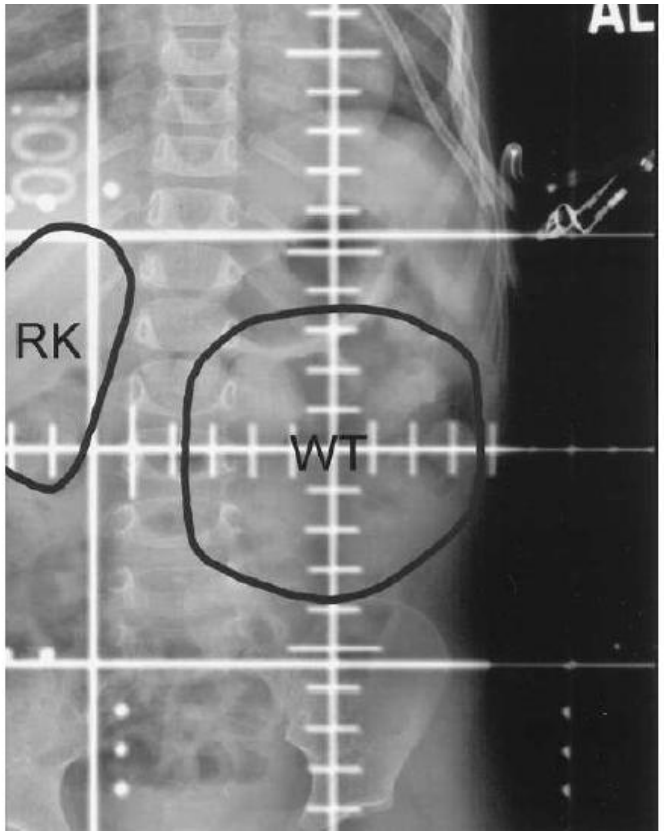
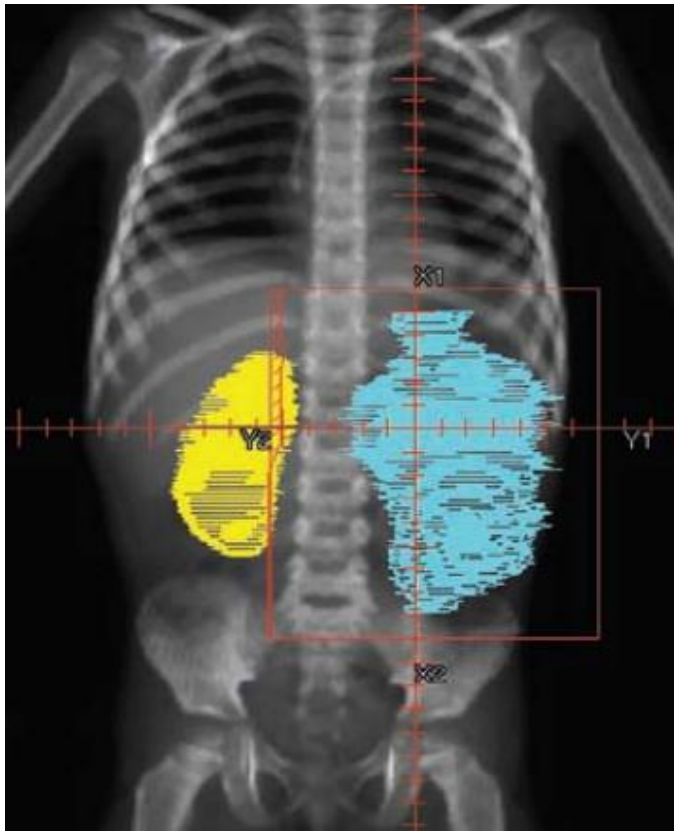


Halperin, E.C., Brady, L.W., Wazer, D.E. and Perez, C.A., 2018. *Perez & Brady's principles and practice of radiation oncology*. Lippincott Williams & Wilkins.

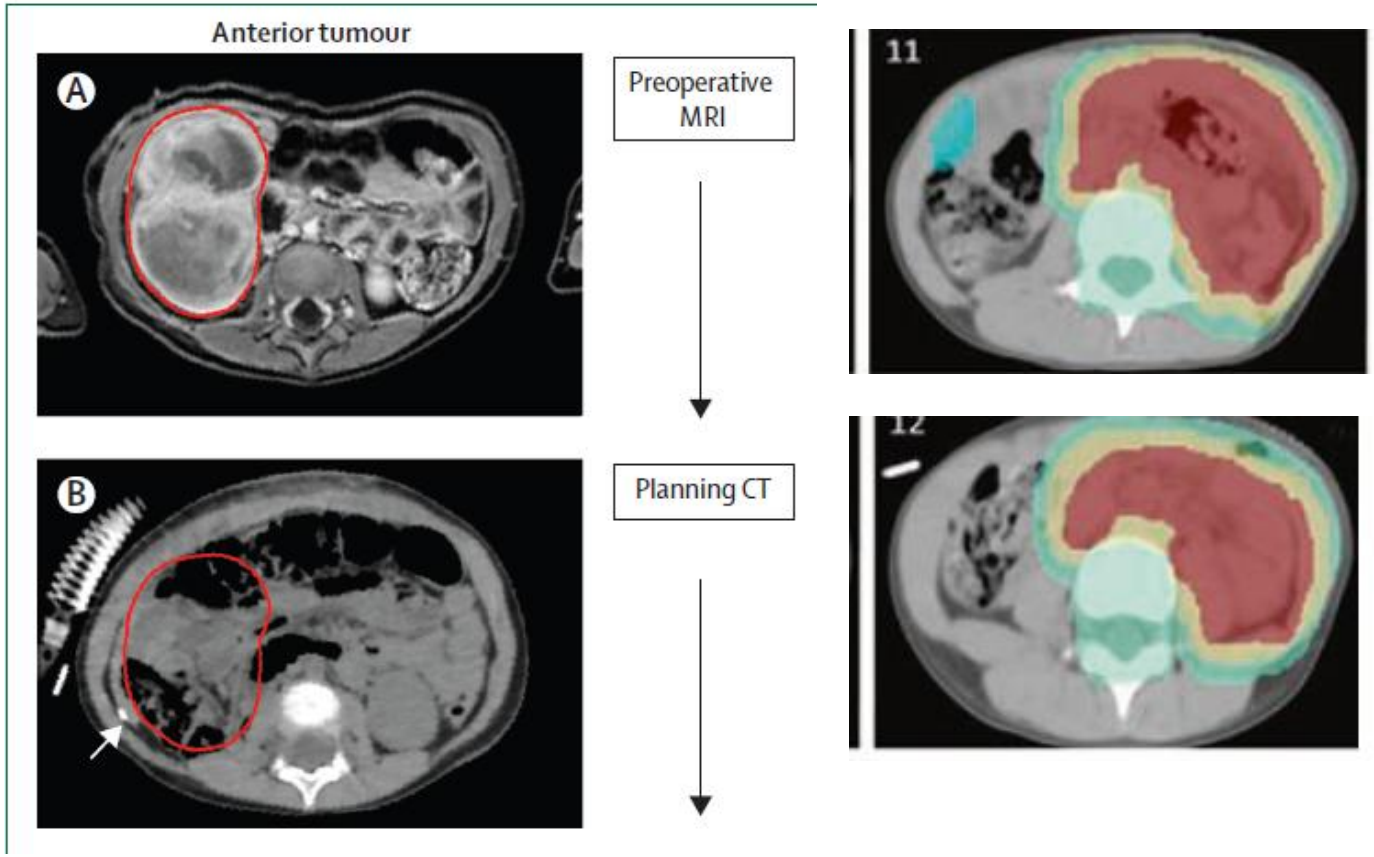


Kalapurakal JA. Wilms tumor. InPediatric Radiation Oncology 2018 Mar 2 (pp. 111-130). Cham: Springer International Publishing.

Flank RT - Conformal RT

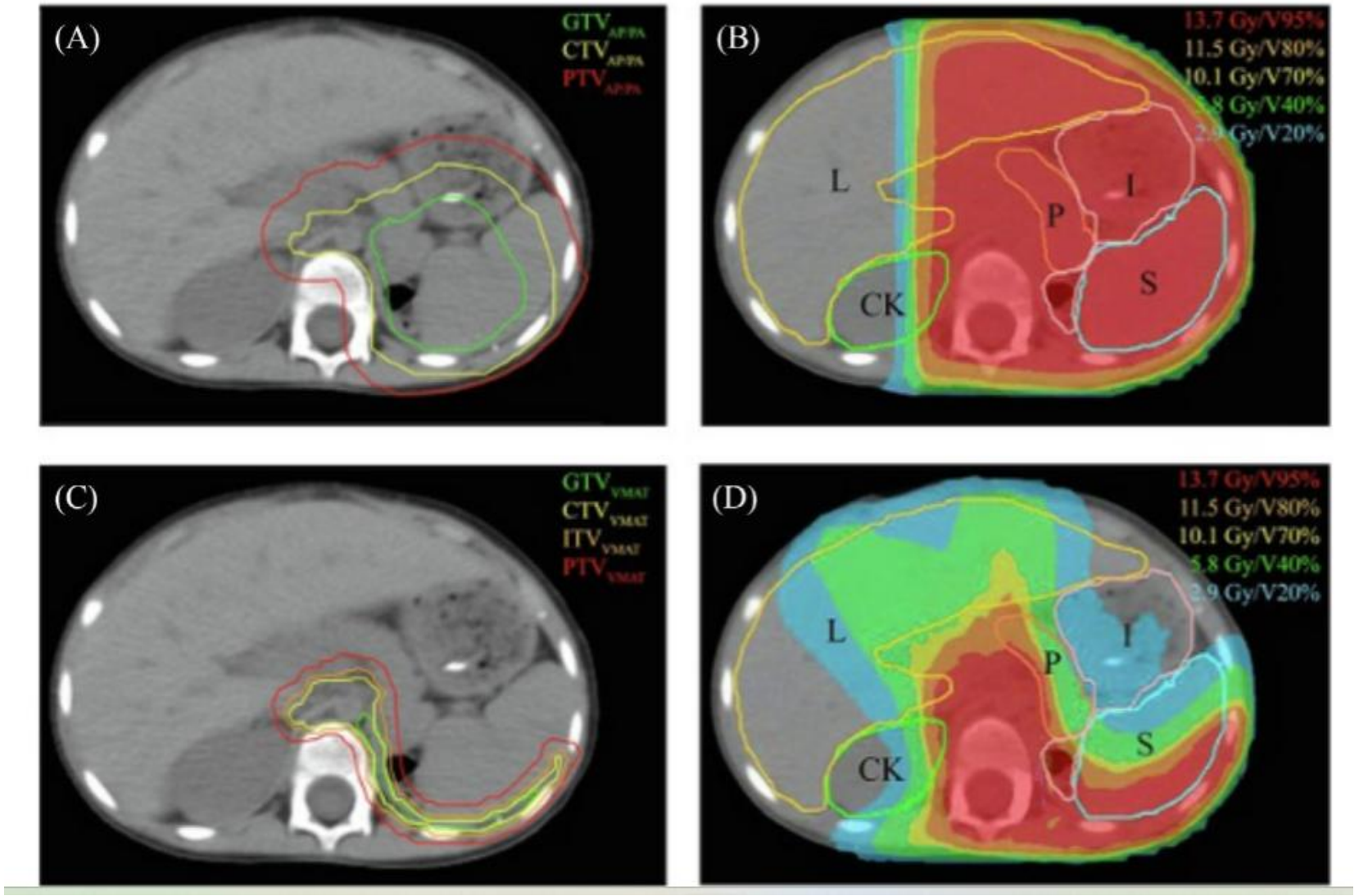
Target Volumes

- **CTV** = post chemo pre-op tumour (GTV) + kidney + 0.5-1 cm
- **PTV** = CTV + -0.5-1 cm
- Boost = macroscopic residual + 1 cm
- Contralateral Kidney – Spared as much as possible

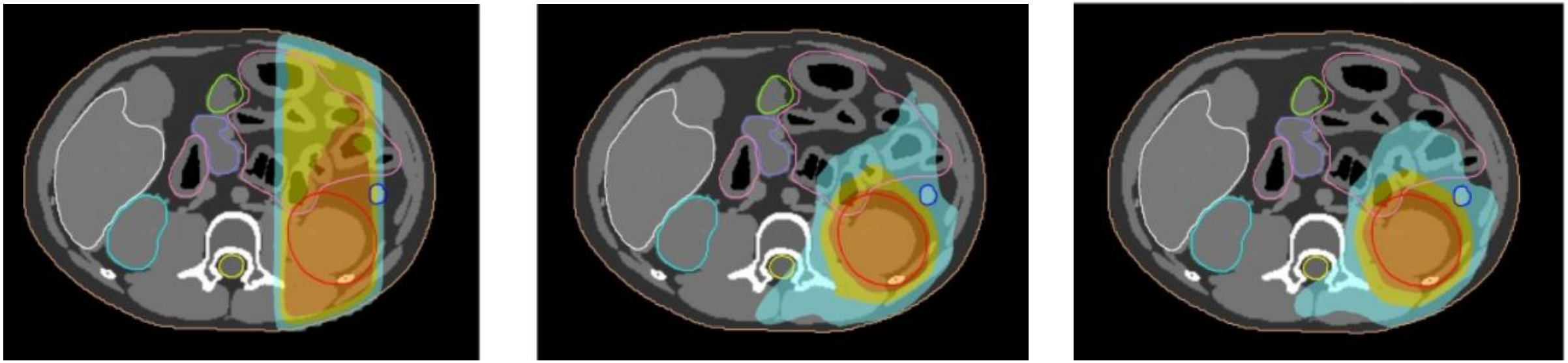


Janssens GO, Melchior P, Mul J, Saunders D, Bolle S, Cameron AL, Claude L, Gurtner K, van de Ven KP, van Grotel M, Harrabi S. The SIOP-Renal Tumour Study Group consensus statement on flank target volume delineation for highly conformal radiotherapy. The Lancet Child & Adolescent Health. 2020 Nov 1;4(11):846-52.

Anterior–posterior (AP–PA) versus VMAT flank treatment



McAleer MF, Melchior P, Parkes J, Pater L, Rübe C, Saunders D, Paulino AC, Janssens GO, Kalapurakal J. Harmonica consensus, controversies, and future directions in radiotherapy for pediatric Wilms tumors. Pediatric Blood & Cancer. 2023 May;70:e30090.



3D-CRT, IMRT and VMAT - XCAT phantoms.

Mazonakis M, Lyraraki E, Tolia M, Damilakis J. 3D-CRT, IMRT and VMAT for flank irradiation due to pediatric Wilms tumor: A comparative planning study with XCAT phantoms. Physica Medica. 2022 Nov 1;103:89-97.

Flank RT – Highly Conformal RT

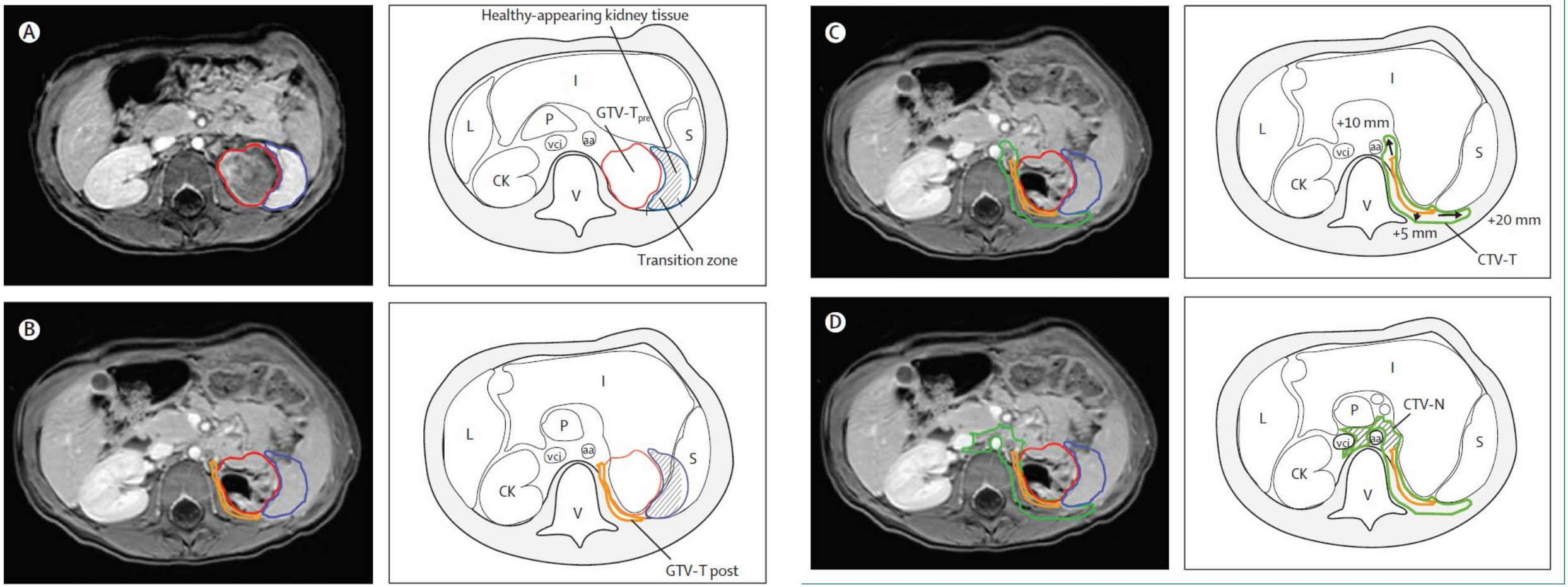
Target Volumes

	Conventional	Highly conformal
GTV-T_{pre} and GTV-N_{pre}	Preoperative macroscopic disease after chemotherapy	Preoperative macroscopic disease after chemotherapy
GTV-T_{post} and GTV-N_{post}	..	Contact zone of GTV-T_{pre} plus or minus GTV-N_{pre} with removal of all uninvolved organs at risk; lateral margin is defined by (1) lateral clip or (2) fictional line parallel with the anterior border of the vertebrae; check surgical report for adhesions or infiltration: include contact zone of the GTV-T_{pre} or GTV-N_{pre} with the involved organ
CTV-T	GTV-T_{pre} plus 10 mm; no CTV expansion inside vertebrae or outside the body	GTV-T_{post} plus 10 mm with removal of all uninvolved organs at risk (check surgical and pathology report); posterior wall: GTV-T_{post} plus 5 mm (adhesions) or plus 10 mm (invasion); healthy-appearing kidney: GTV-T_{post} plus 20 mm; involved organs at risk: GTV-T_{post} plus 5 mm (adhesions) or plus 10 mm (invasion)
CTV-N	GTV-N_{pre} plus 10 mm; lymph node area around abdominal aorta, inferior vena cava, and ipsilateral renal vessels up to the cranial border of thoracic vertebra 11 and down to aorta bifurcation	GTV-N_{post} plus 10 mm with removal of all uninvolved organs at risk; lymph node area around abdominal aorta, inferior vena cava, and ipsilateral renal vessels up to the cranial border of thoracic vertebra 11 and down to aorta bifurcation
ITV	..	With surgical (superior) clip and 4D-CT technology: individual margins; without surgical clip: fixed margin of CTV plus 5 mm
PTV	CTV plus 10 mm	ITV plus 5 mm

$GTV_{pre/post}$=gross tumour volume of the primary tumour (T) or lymph node area (N) before and after surgery, respectively. OARs=organs at risk. CTV=clinical target volume of primary tumour (T) or lymph node area (N). ITV=internal target volume. PTV=planning target volume.

Table 1: **Guideline for conventional and highly conformal flank delineation**

Janssens GO, Melchior P, Mul J, Saunders D, Bolle S, Cameron AL, Claude L, Gurtner K, van de Ven KP, van Grotel M, Harrabi S. The SIOP-Renal Tumour Study Group consensus statement on flank target volume delineation for highly conformal radiotherapy. The Lancet Child & Adolescent Health. 2020 Nov 1;4(11):846-52.



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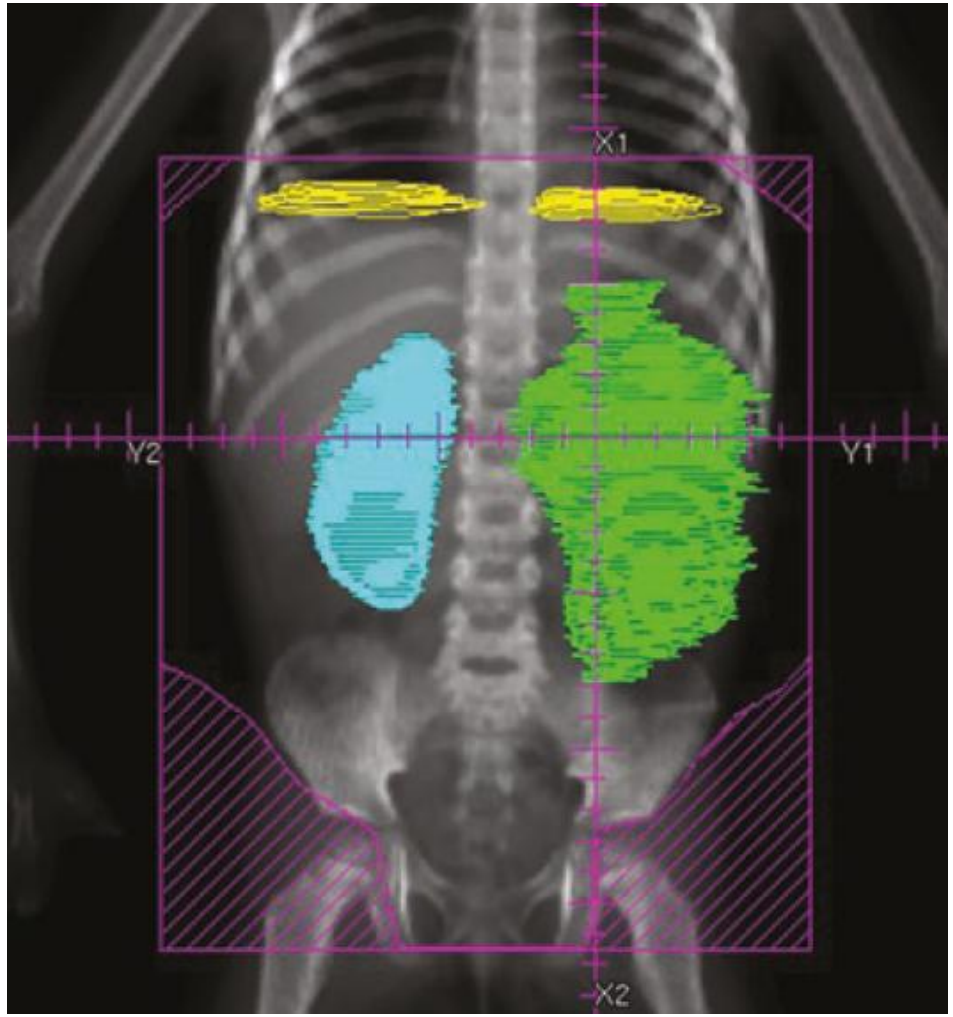
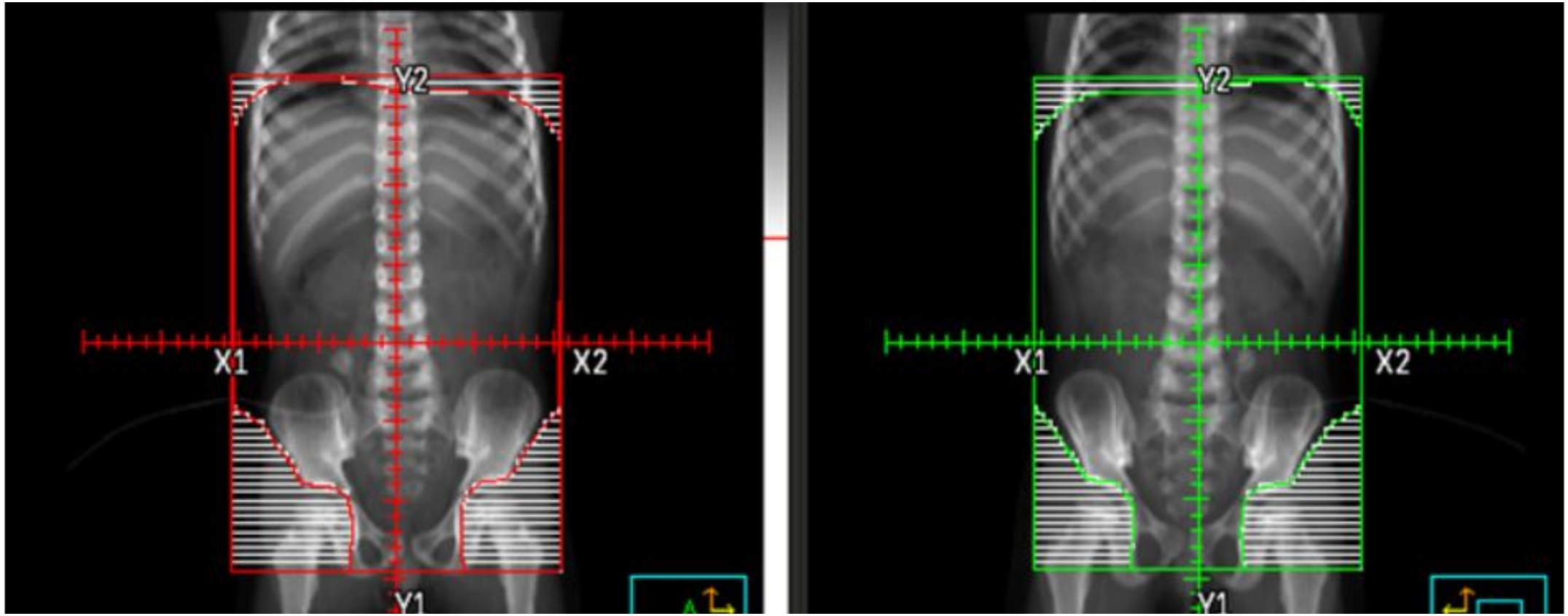
Whole Abdominal RT (WART) - Conventional

- **Indications**
- Major rupture (intra- or retroperitoneal)
- Diffuse spill
- Peritoneal seeding / positive ascites

- **Borders**
- Superior: diaphragm domes
- Inferior: symphysis/obturator foramen
- Lateral: abdominal wall
- Shield hips/gonads

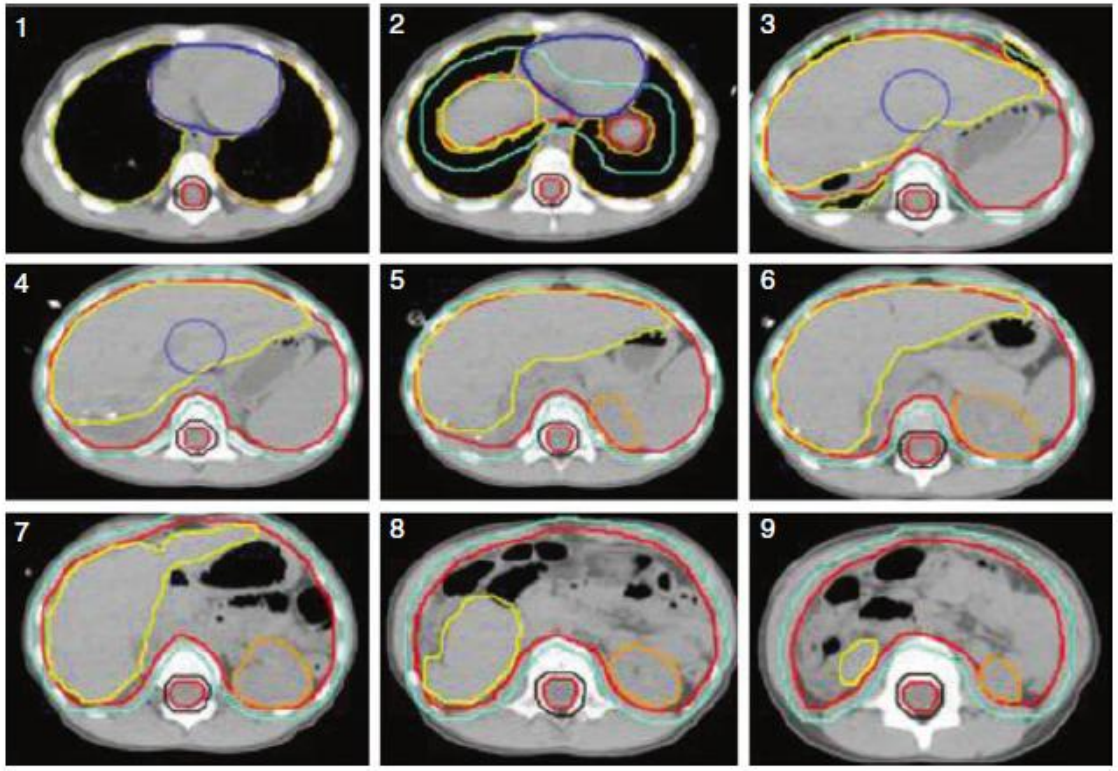


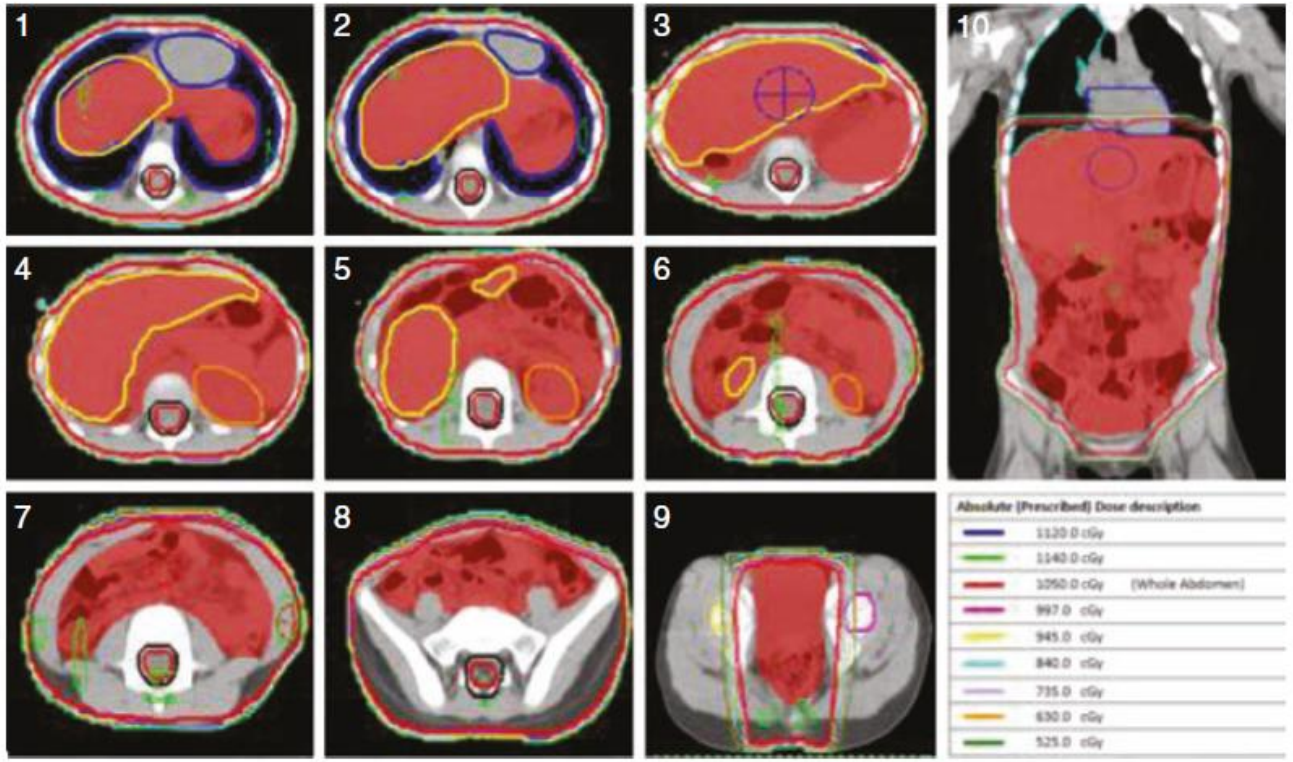
Merchant TE, Kortmann RD, editors. Pediatric radiation oncology. Berlin, Heidelberg: Springer; 2018 Mar 1.



https://pressbooks.uiowa.edu/radiationtherapy/chapter/kidney-wilms-neuroblastoma/

Whole Abdominal RT (WART) - Conformal





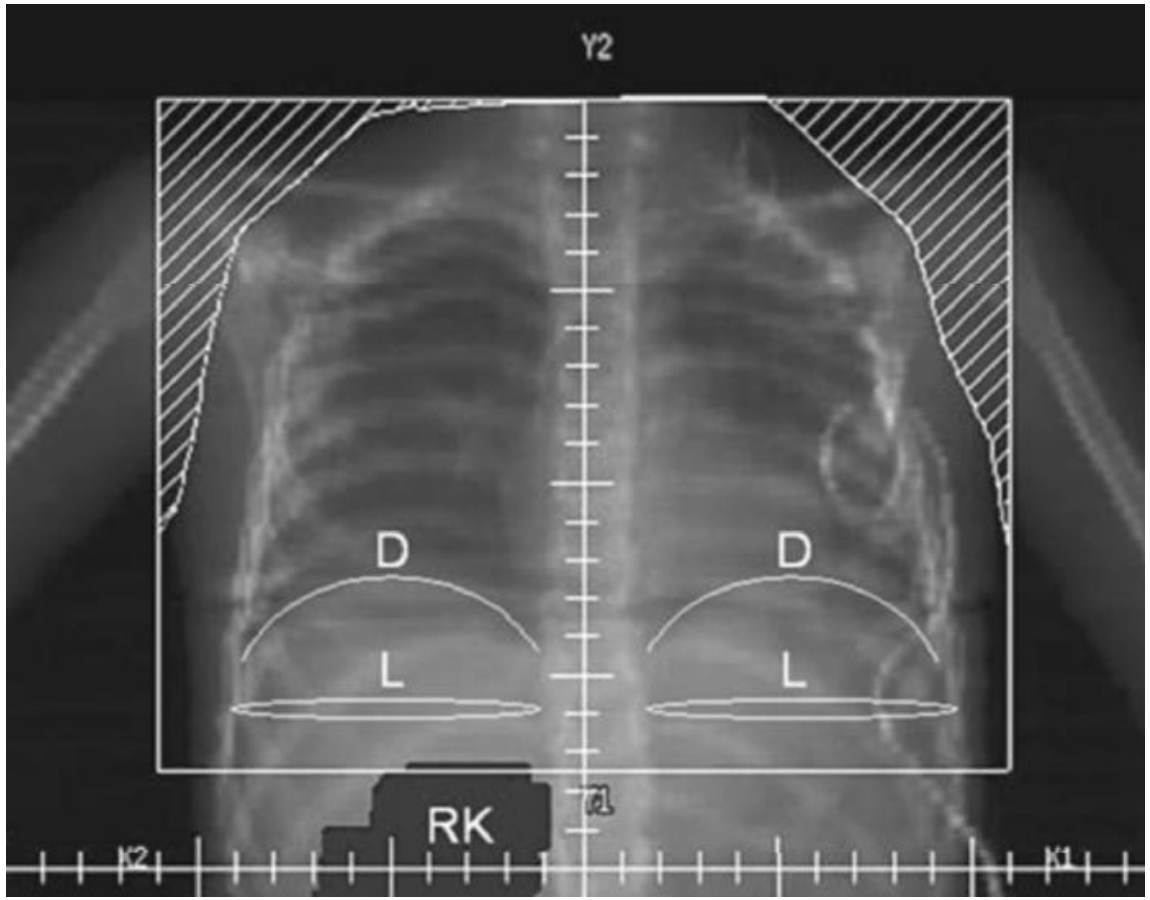
Entire Peritoneal Cavity. CTV to PTV = 0.5cm

Terezakis SA, MacDonald SM, editors. Target volume delineation for pediatric cancers. Springer International Publishing; 2019.

Whole Lung RT (WLRT) - Conventional

- **Indications**
- Stage IV lung mets not in CR post-chemo
- High-risk histology with pulmonary mets (regardless of response)

- **Borders**
- Cranial: 2–3 cm above clavicle
- Caudal: 2–4 cm below diaphragm
- Lateral: thoracic wall
- Shield shoulders



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Halperin, E.C., Brady, L.W., Wazer, D.E. and Perez, C.A., 2018. *Perez & Brady's principles and practice of radiation oncology*. Lippincott Williams & Wilkins.

Whole Lung RT (WLRT) - Conformal

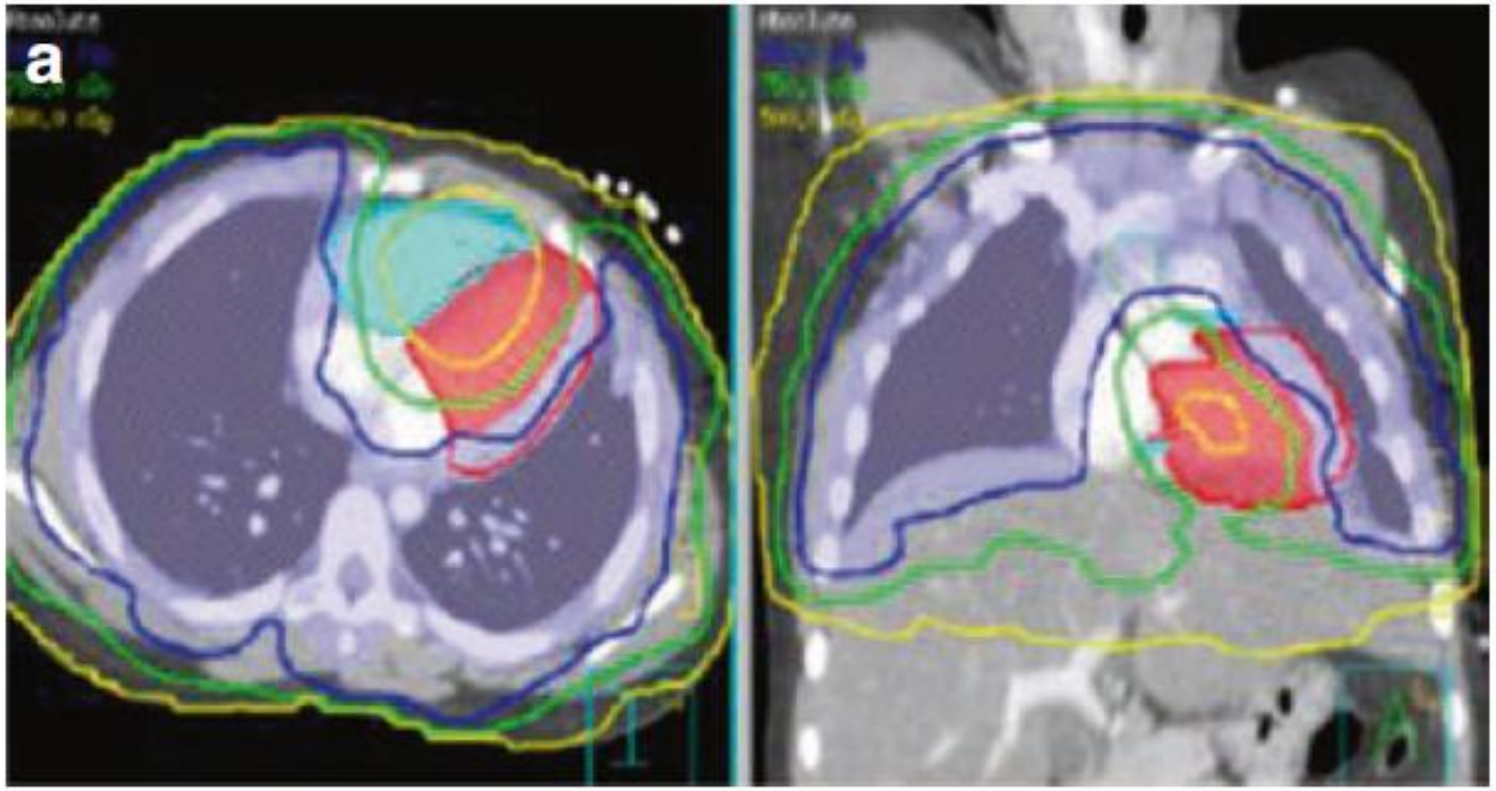
Target Volumes

- CTV = Entire lung volumes + mediastinum + pleural recesses, especially the inferior-most anterior & posterior costo-diaphragmatic recesses (per 3D/4D CT simulation).

- Encompass both lungs regardless of the number/location of mets.

- If WLRT is needed with flank or whole-abdomen RT, treat concurrently (same course).

- Technique: AP-PA or cardiac-sparing IMRT may be used for WLRT.



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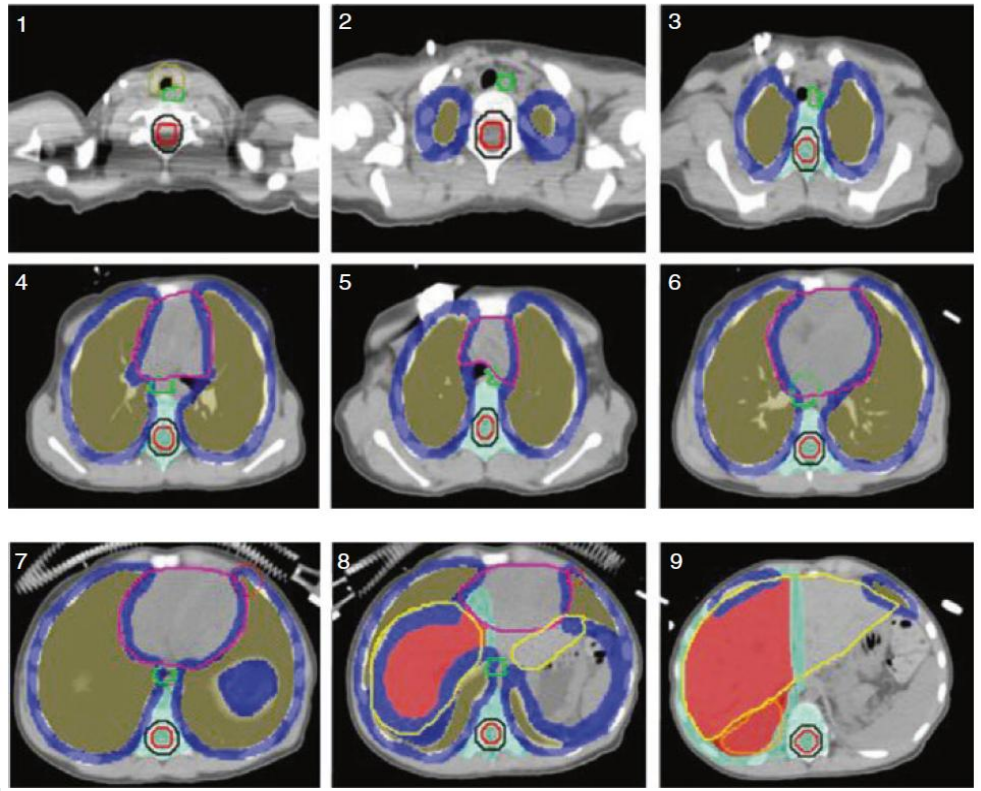

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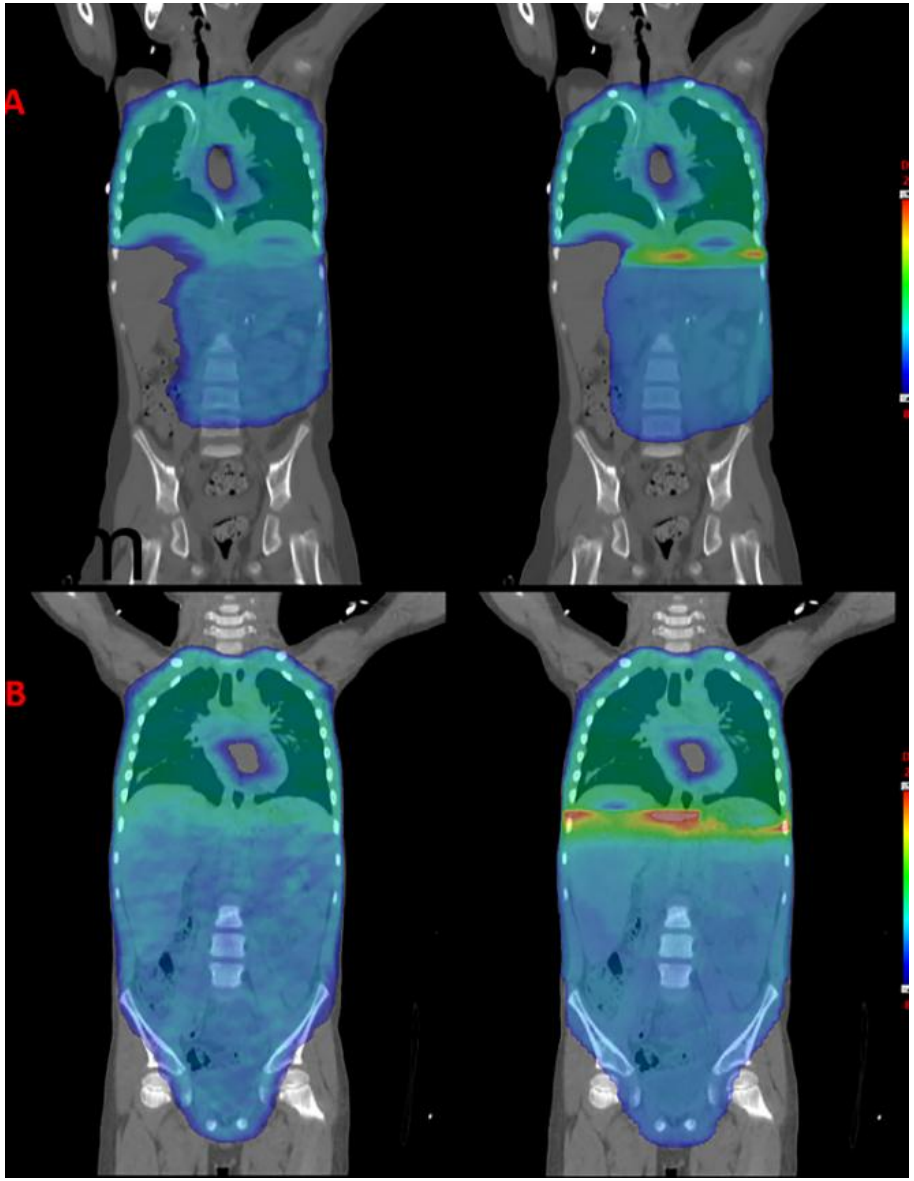


Combining Lung and Flank RT

Combining Lung and abdominal RT

Chaballout BH, McComas KN, Khattab M, Seymore GP, Martinez SK, Luo G, Kirschner A, Luo LY. Dosimetric Advantage of Combined IMRT for Whole Lung and Abdomen Irradiation for Wilms Tumor. Advances in Radiation Oncology. 2024 Aug 1;9(8):101527.

Liver RT - Conventional

Indications

- Solitary or multiple **liver metastases** not completely resected.
- **Residual disease** after surgery/chemo.
- Occasionally whole-liver RT in diffuse hepatic involvement (rare, very high risk).

Borders

- **Whole liver RT**: AP/PA fields covering diaphragm dome superiorly and inferior edge of liver inferiorly.

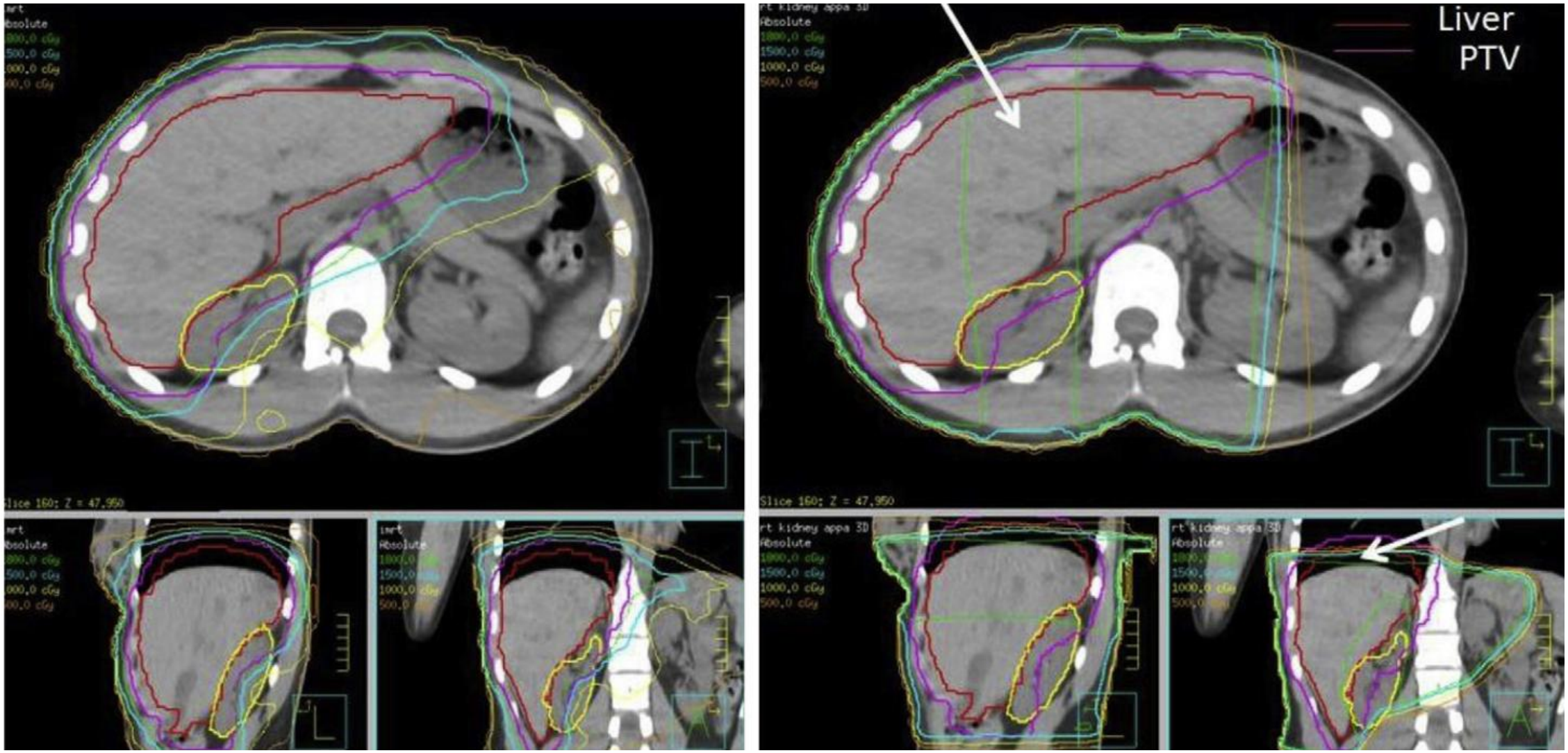
- **Focal RT**: tangential or wedged fields tailored to lesion site

Liver RT - Conformal

Target Volume Delineation

- **CTV**: whole liver if diffuse involvement; otherwise residual lesion + 2 cm margin.
- **PTV**: add margin (ideally use 4D CT).

- **Boost**: residual gross lesion to higher dose.
- OARs: spare stomach, bowel, kidney, spinal cord.



Whole LIVER RT – IMRT vs 3DCRT

Brain Metastasis RT

Indications

- Documented **CNS spread** (rare, 1–2%).
- Residual/resected brain mets.

Target Volume Delineation

- **CTV**: whole brain for leptomeningeal disease; focal GTV + 0.5–1 cm margin for isolated lesions.
- **Boost**: focal residual to 30–36 Gy.

Conventional Planning

- Whole brain RT with opposed lateral fields:
  - Superior: flash scalp.
  - Inferior: C2 vertebra/base of skull.
  - Anterior: flash frontal bone.
  - Posterior: flash occiput.

Bone Metastasis RT

Indications

- Symptomatic bony mets.
- Residual bone lesions after chemo.

Target Volume Delineation

- **CTV**: GTV = bone lesion (on CT/MRI) + 2-3 cm margin.
- **PTV**: 0.5-1cm
- Do not irradiate whole bone (to avoid growth arrest).

Conventional Planning

- Parallel opposed fields (AP/PA or lateral) over involved bone segment.
- Borders: lesion + ≥2 cm margin.
- Example: femur → local field, not entire femur.

Other Sites (rare)

- **Pulmonary nodules**: covered in WLRT; boost if persistent.
- **Mediastinum/lymph nodes**: AP/PA fields including nodal station.
- **Soft tissue mets**: GTV + 1–2 cm margin; 3DCRT/IMRT preferred.

Organs at Risk

Contralateral kidney: D100% ≤14.4 Gy

Liver:

- Uninvolved liver, D50% ≤19.8 Gy;
- With liver metastases, D75% ≤30.6 Gy

Bilateral whole lungs:

- 9 Gy (age <1.5 years) or
- 12 Gy (age >1.5 years)

Organ	Dose (Gy)
Kidney-whole	14.4 Gy
Kidney-partial (50%)	19.8 Gy
Liver-whole	23.4 Gy
Liver-partial (50%)	30.6 Gy
Lung-whole	12.0 Gy
Lung (when PTV occupies > ½ bilateral lung volume)	15.0 Gy
Lung (when PTV occupies < ½ bilateral lung volume)	18.0 Gy

CHILDREN'S ONCOLOGY GROUP AREN0532 Treatment for Very Low and Standard Risk Favorable Histology Wilms Tumor

Toxicities

Acute:

- Loose stools
- Nausea –provide prophylactic anti-emetics
- Fatigue

Long term:

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

Special Situations

- Relapse
- Bilateral Wilms
- Resected Tumour With Unknown Staging
- Wilms in Horsheshoe kidney / Single Kidney
- Resource Challenged Set up
- No response to chemotherapy
- Nephroblastomatosis
- Extra Renal Wilms

Relapse	RISK GROUPS
Bilateral Wilms	Bilateral Wilms tumour management now follows a unified COG–SIOP consensus, avoiding upfront biopsy and using preop chemotherapy with surgery within 12 weeks. Nephron-sparing approach preserves renal function and lowers relapse rates.
Resected Tumour With Unknown Staging	3 drug regimen
Wilms in Horsheshoe kidney / Single Kidney	NACT- NSS
Resource Challenged Set up	Survival less than HIC
No response to chemotherapy	Stratification
Extra Renal Wilms	0.5 to 1% of Wilms' tumor
Nephroblastomatosis	Multiple - SIOP - two-drug chemotherapy (VCR+ACD) for a total duration of 1 year. Surgery / Wedge Resection

Take-home Messages

1. RT is stage- and risk-driven, not one-size-fits-all

2. Timing and field definition matter more

3. Growth-aware planning is unique in paediatric RT

4. Survivorship and late effects are equally important

Thank you

For any queries :

abhishek.krishna@manipal.edu

G-Drive Link to all references used