Guidelines for Paediatric Solid Tumours

Vol XV

(Part B)

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Dedicated to
all our patients at
The Tata Memorial Centre

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Preface

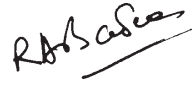
The Evidence Based Management (EBM) meetings at Tata Memorial Centre are planned to promote high quality data through hierarchy of evidence which can impact patient management in Indian scenario. In 2018, the 16th EBM meeting focuses on three distinct aspects of Cancer Care: Cancer Immunotherapy, Head and Neck Tumours and Pediatric Solid Tumours. Pediatric Solid Tumours constitute a small proportion of all cancer cases, but they form a very important demography as majority of them are curable, if treated optimally. These children have the potential of a long productive societal contribution deserving the best chance of cure.

Pediatric Solid Tumours are a mixture of heterogenous entities. Neuroblastoma, the most common extra-cranial pediatric solid tumour, is perhaps also one of the most enigmatic malignancies known. In some, it may involute by itself without any treatment and yet in others, it may not respond to

the entire known armamentarium of anti-cancer therapies. Even when metastatic, majority of Germ Cell Tumours and Wilms tumours patients can still be cured. Retinoblastoma management has improved substantially to not only save life, but also the globe and the vision of the child. These spectacular successes have been made possible as much by technological breakthroughs as by the increased understanding of their biology. The risk stratifications have evolved rapidly over last few years necessitating integration of molecular tests in routine clinical practice. This has led to augmentation of treatments for patients with prognostic factors which portend poor outcomes. Also, this has led to de-escalation of treatment for many children, saving them from serious long term side effects, without compromising on their cancer outcomes. It is indeed commendable that overcoming the inherent disadvantage of comparative rarity of these tumours, most of the accepted clinical practices in this group of patients are backed by high level of evidence. This has been made possible through the pioneering concept of formation of large multicentre multinational co-operative groups.

Part B of the XVth Volume of the EBM Guidelines from Tata Memorial Centre is an attempt to clearly and concisely document the current evidence based approach to Pediatric Solid Tumours in Indian context. The purpose of this book is to act as a ready

reference in the clinic. It is also equally important to document the lacunae in evidence and plan future research so as to advance service and science, which would make this endeavor a true success.



R A Badwe
Director,
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February 2018
Mumbai,

Neuroblastoma

Investigations

Diagnostic investigations

- 24 hours urinary vanillyl mandelic acid (VMA)
- Serum Lactate dehydrogenase (LDH) & Serum Ferritin

Imaging

- Computerized Tomography (CT) / Magnetic Resonance Imaging (MRI)

Pathology

- Biopsy
  - Histopathology
  - Molecular pathology
- N-MYC
- Chromosomal aberrations

Staging

- Metaiodobenzylguanidine (MIBG) scan (Level 1) / Positron Emission Tomography (PET) scan / Bone scan (optional)– PET scan if MIBG non-avid
- Bilateral bone marrow aspiration and biopsy
- * Presence of unequivocal Tumour cells (adequate for histopathology and molecular pathology) in bone marrow biopsy with increased levels of urinary catecholamines is adequate for diagnosis

Histology:

International Neuroblastoma Pathological Classification (INPC)

Favorable	Unfavorable
• Poorly differentiated neuroblastoma in <1.5 yrs with low or intermediate MKI • Differentiating neuroblastoma with intermediate / low MKI <1.5 yrs • Ganglioneuroblastoma intermixed • Ganglioneuroblastoma nodular with nodules showing FH • Ganglioneuroma	• Any Undifferentiated neuroblastoma • Any high MKI neuroblastoma • Poorly differentiated neuroblastoma (any MKI) in age >1.5 years • Differentiating neuroblastoma with intermediate MKI > 1.5 years • Ganglioneuroblastoma nodular with nodule showing UH histology

INRG Classification

Image defined risk factors (IDRF) (absence or presence of IDRF makes local disease as L1 or L2 respectively) (Level II)

Anatomic region	Description of IDRF
Multiple body Compartments	Ipsilateral tumour extension within two body compartments (i.e., neck and chest, chest and abdomen, or abdomen and pelvis)
Neck	Tumour encasing carotid artery, vertebral artery, and/or internal jugular vein Tumour extending to skull base Tumour compressing trachea
Cervico-thoracic junction	Tumour encasing brachial plexus roots Tumour encasing subclavian vessels, vertebral artery, and/or carotid artery Tumour compressing trachea
Thorax	Tumour encasing aorta and/or major branches Tumour compressing trachea and/or principal bronchi Lower mediastinal tumour infiltrating costovertebral junction between T9 and T12 vertebral levels (because of risk of injury to anterior spinal artery)
Thoraco-abdominal	Tumour encasing aorta and/or vena cava
Abdomen and pelvis	Tumour infiltrating portahepatis and/or hepatoduodenal ligament Tumour encasing branches of superior mesenteric artery at mesenteric root Tumour encasing origin of celiac axis and/or origin of superior mesenteric artery Tumour invading one or both renal pedicles Tumour encasing aorta and/or vena cava Tumour encasing iliac vessels Pelvic Tumour crossing sciatic notch

Intraspinaltumour	Intraspinal tumour extension (whatever the extension location) provided that more than one-third of spinal canal in axial plane is invaded, the perimedullary leptomeningeal spaces are not visible, or the spinal cord signal intensity is abnormal
Infiltration of adjacentorgans and structures	Pericardium, diaphragm, kidney, liver, duodenopancreatic block, and mesentery

Definitions of L1, L2, M and MS (INRG)

Stage	Description
L1	Localized Tumour not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional Tumour with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

INRG Risk Stratification

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	MYCN	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing ror GNB intermixed		NA			B Very low
				Amp			K High
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	> 18	GNB nodular; neuroblastoma			No		E Low
			Differentiating	NA	Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	< 18			NA		Hyperdiploid	F Low
	< 12			NA		Diploid	I Intermediate
	12 to < 18			NA		Diploid	J Intermediate
	< 18			Amp			O High P High
MS	< 18				No		C Verylow
				NA	Yes		Q High
				Amp			R High

Neuroblastoma risk Stratification (Modified)

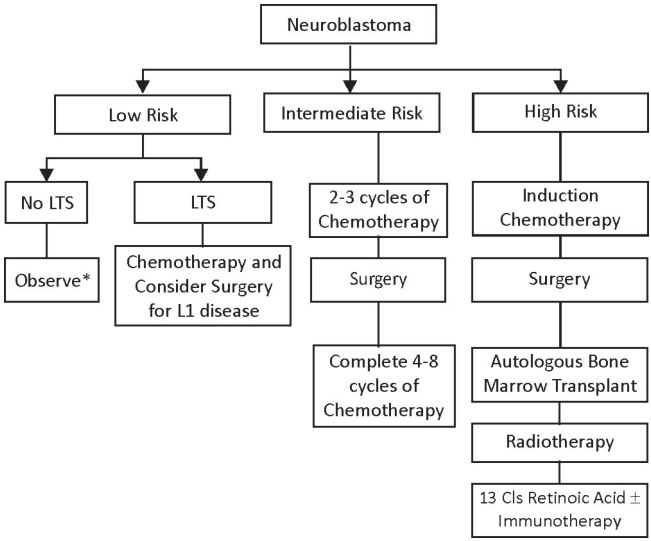
Risk	Age	INRG	MYCN status	SCA	Histology
Low	Any	L1	Non-Amp	Any	Any
	<547 days	L2/MS	Non-Amp	No	Any
	>547 days	L2	Non-Amp	No	FH
Intermediate	<547 days	L2	Non-Amp	Yes	Any
	<547 days	M	Non-Amp	Any	Any
	>547 days	L2	Non-Amp	Yes	FH
	>547 days	L2	Non-Amp	Any	UH
High	Any	Any	Amp	Any	Any
	Any	MS	Non-Amp	Yes	Any
	>547 days	M	Any	Any	Any

- Ploidy required only in N-MYC non-amplified stage M in less than 18 months of age
- SCA – are 1p, 11q and 17q aberrations

Life Threatening Symptoms (LTS)

- Pain requiring opiate treatment
- Gastrointestinal (feeding difficulty, not gaining weight)
- Respiratory distress
- Cardiovascular System (Hypertension, Inferior vena cava obstruction leading to pedal edema)
- Renal – impaired renal function, hydronephrosis
- Hepatic dysfunction
- Bladder/Bowel dysfunction
- Neurological complications

Neuroblastoma Treatment Algorithm (Level Ib, IIa)



* Infants less than 3 months (MS) are best treated rather than observed as they have a high risk of progression

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Germ Cell Tumours (GCTs)

Investigations

Diagnostic Investigations

- Serum Alpha Feto Protein (AFP) and Beta-Human Chorionic Gonadotrophin (β-HCG)

Imaging

- CT/MRI of the primary site

Pathology

- Biopsy is not mandatory except when tumour markers are normal and/or clinico-radiological non-correlation

Staging

- CT Chest and Abdomen

Staging of Malignant GCTs

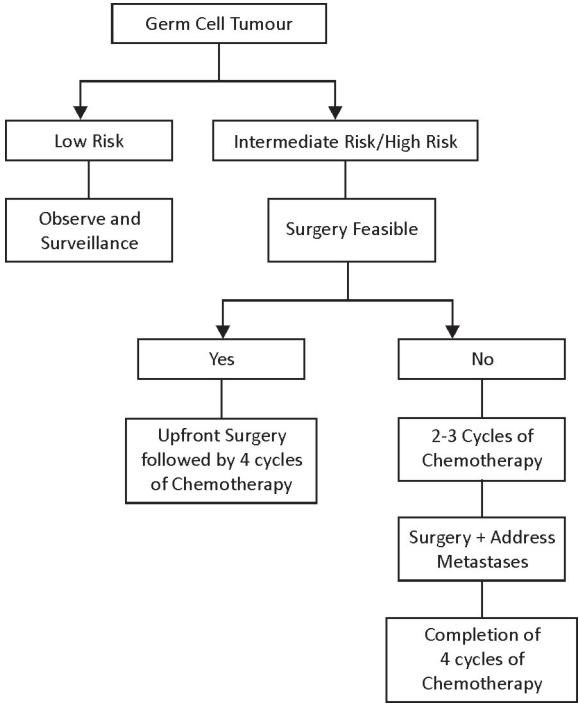
Testicular	
I	● Limited to testis, completely resected by high inguinal orchiectomy AND ● Tumour markers normal after appropriate half-life decline
II	● Transcrotal orchiectomy OR ● Microscopic disease in scrotum or high in spermatic cord (< 5 cm from proximal end) OR ● Retroperitoneal lymph node involvement (< 2 cm) and/or increased Tumour markers after appropriate half-life decline
III	● Tumour-positive retroperitoneal lymph node(s) > 2 cm diameter
IV	● Distant metastases that may include liver
Ovarian	
I	● Limited to ovary, completely resected AND ● Peritoneal washings negative for malignant cells AND ● Tumour markers negative after appropriate half-life decline
II	● Microscopic residual or positive lymph nodes (< 2 cm) AND ● Peritoneal washings negative for malignant cells ● Tumour markers positive or negative
III	● Gross residual or biopsy only OR ● Tumour-positive lymph nodes(s) >2cm diameter OR ● Contiguous visceral involvement (omentum, intestine, bladder) OR ● Peritoneal washings positive for malignant cells
IV	● Distant metastases that may include liver

Extragonadal	
I	● Complete resection at any site
II	● Microscopic residual AND ● lymph nodes negative
III	● Gross residual or biopsy only ● Regional lymph nodes negative or positive
IV	● Distant metastases that may include liver

Risk stratification

Low Risk	Stage I Testicular Stage I Ovarian
Intermediate risk	Stage II- IV Testicular Stage II-III Ovarian Stage I-II Extragonadal
High risk	Stage IV ovary Stage III-IV Extragonadal

Germ Cell Tumour Treatment Algorithm (Level Ib, IIa)



Treatment of mature and immature teratoma primarily consists of surgical excision (Level IIb)

Metastatectomy – either with the excision of primary or at end of treatment

Extragonadal sacrococcygeal teratoma surgery includes excision of the coccyx

Chemotherapy Doses (Level Ib)

Cisplatin	33.3 mg/m2/dose	Day 1, 2 and Day 3
Etoposide	167 mg/m2/dose	Day 1, 2 and Day 3
Bleomycin	15 units/m2/dose	Day 1 only

Recommendations for surgical excision of ovarian tumours

1. Collect ascites or peritoneal washing for cytology
2. Examine peritoneal surface and liver and excise suspicious lesion
3. Unilateral oophorectomy
4. Examine contralateral ovary and biopsy if suspicious lesion
5. Examine omentum and remove if adherent or involved
6. Inspection of retroperitoneal lymphnodes / biopsy of enlarged nodes

Role of Radiotherapy -To be considered only in surgically inoperable, relapsed or refractory setting

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Wilms Tumour

Investigations

Imaging

- Computerized Tomography (CT) / Magnetic Resonance Imaging (MRI) Abdomen and Pelvis

Pathology

- To consider doing biopsy if upfront surgery is not feasible

Biopsy Recommendations

- Retroperitoneal approach
- Radiology guided, whenever possible
- Adequate Trucut Biopsy cores

Staging

- CT Chest

Pathology

COG classification (Upfront surgery)

Type	Histopathology features
Favourable	No Anaplasia
Unfavourable	Focal Anaplasia Diffuse Anaplasia

SIOP Classification (upfront chemotherapy)

Risk	Histopathology features
Low	Complete Necrosis
Intermediate	Regressive (>66% Necrosis) Epithelial Stromal Mixed Focal Anaplasia
High	Blastemal Predominant Diffuse Anaplasia

Staging

Childrens Oncology Group (COG/NWTS) Staging

Stage	Criteria
I	• Limited to kidney (without sinus vessel/capsule involvement) and completely resected AND • No Tumour rupture AND • No prior biopsy
II	• Extension beyond kidney but completely resected OR • Penetration of renal capsule OR • Invasion of renal sinus vessels

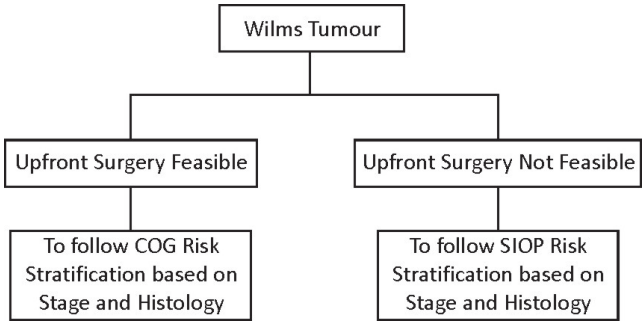
Stage	Criteria
III	• Gross or microscopic residual tumour OR • Tumour spillage OR • Regional lymphnode metastases OR • Positive peritoneal cytology OR • Transected tumour thrombus OR • Tumour rupture OR • Prior wedge biopsy
IV	• Haematogeneous metastases (lung, liver, bone, brain, etc.) OR • Lymph node metastases outside the abdomino-pelvic region
V	• Bilateral renal tumours at diagnosis

SIOP Staging

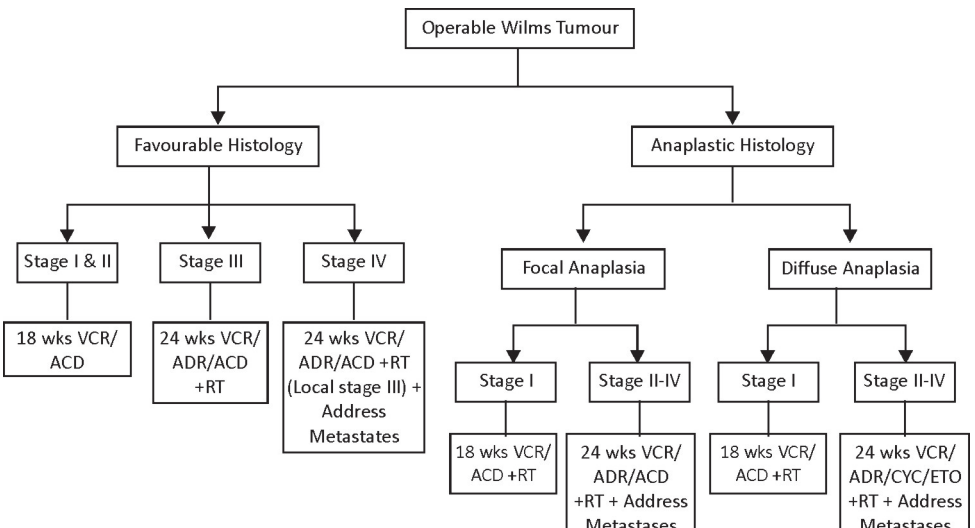
Stage	Criteria
I	• Limited to kidney (without sinus vessel/capsule involvement) and completely resected AND • No Tumour rupture
II	• Extension beyond kidney but completely resected OR • Penetration of renal capsule OR • Invasion of renal sinus vessels/ vena cava but completely excised OR • Prior biopsy (Wedge/ percutaneous/ FNAC)

Stage	Criteria
III	• Gross or microscopic residual tumour OR • Tumour spillage OR • Regional lymphnode metastases OR • Positive peritoneal cytology OR • Transected tumour thrombus OR • Tumour rupture OR • Tumour penetrating peritoneal surface/ Tumour implant on peritoneal surface OR • Ureter transected OR • Tumour removed piecemeal
IV	• Haematogeneous metastases (lung, liver, bone, brain, etc.) OR • Lymph node metastases outside the abdomino-pelvic region
V	• Bilateral renal tumours at diagnosis

Wilms Tumour Treatment Algorithm (Level Ib)

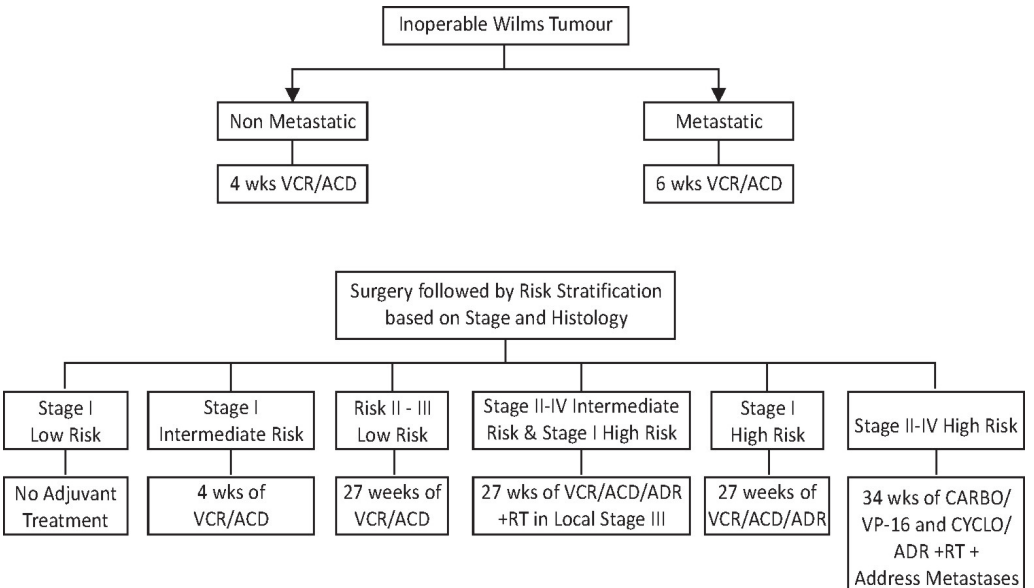


Treatment Algorithm of Operable Wilms Tumour



*In tumours with 1p AND 16q LOH – 3 drug chemotherapy for 24 weeks is recommended

Treatment Algorithm of Inoperable Wilms Tumour



Levels of evidence for chemotherapy

- Localized unilateral Wilms Tumour: Optimal duration of pre-operative chemotherapy is 4 weeks (level Ib)
- Stage I and II: Eighteen weeks of therapy with Vincristine and Actinomycin D is adequate for patients with stage I and II FH (level Ib)
- Stage I intermediate-risk and anaplastic Wilms' tumour: post-operative treatment could be shortened to only 4 weeks from the standard 18 weeks (level Ib)
- Stage III and IV FH: 6 months of therapy with Vincristine, Adriamycin and Actinomycin D is optimal (level Ib)
- Stage II- III intermediate risk histology (epithelial/ stromal): can receive 27 post-operative weeks of Vincristine, actinomycin D. The addition of Adriamycin improves EFS in large-volume (≥500 ml) stage II–III nonstromal, nonepithelial tumours(level Ib)
- Intensification of treatment for post-chemotherapy blastemal predominant Wilms Tumour improves EFS (level IIb)
- The prognosis for patients with stage III FH is best when treatment includes either 3 drug chemotherapy and 10.8 Gy of radiation therapy to the flank; or 2 drug chemotherapy and 20 Gy of radiation therapy to the flank (Level Ib)
- The outcome of patients with peritoneal implants treated with gross resection, three-drug chemotherapy, and total-abdominal radiation (10.5 Gy) is similar to that of other stage III patients (IIa)

Treatment of Pulmonary Metastases

- Patients with CT-only lung lesions may have improved EFS but not OS from the addition of doxorubicin but do not appear to benefit from pulmonary radiation. (level IIb)
- Pulmonary RT can be omitted for a majority of patients with pulmonary metastasis and a complete response after induction chemotherapy with or without surgery (level IIb)

Surgical Guidelines

- Radical nephrectomy and lymph node sampling via a transabdominal or thoracoabdominal incision is the procedure of choice (level Ib)
- Tumour removal should be complete and en bloc, and without rupture. (Level IIb)
- Sampling and histological examination of lymph nodes, even when not enlarged on clinical evaluation or radiology, is imperative for accurate staging and subsequent treatment. (level Ib)
- Renal-sparing surgery is recommended in children with bilateral WT, or those predisposed to develop bilateral Tumours (eg. Denys-Drash or Frasier syndrome) and in children with single/horseshoe kidney (level IIIb)
- It is not recommended in standard unilateral Tumours due to increased risk of tumour spill leading to recurrence and the relatively low-risk of developing end-stage renal disease.

Indications for upfront and delayed surgery (consensus SIOP and COG)

Suitable for up-front surgery:	Consider for (biopsy plus) neoadjuvant chemotherapy followed by delayed surgery
Unilateral Non-metastatic tumour	Bilateral Wilms Tumour
Completely intra-renal location (sinus and/or pelvis but not the ureteric involvement)	Solitary/Horseshoe kidney
If bulging outside, pseudo-capsule visible or renal capsule visible on imaging.	Extension of Tumour thrombus above the level of the hepatic veins (level IIb)
Renal vein patent or renal vein thrombosis, not extending into IVC on imaging	Involvement of contiguous structures necessitating s removal of the other structure (level IIb)
Renal artery free or encased but origin from aorta free	Extensive pulmonary compromise from a massive
No enlarged retroperitoneal nodes	Tumour or widespread pulmonary disease and are high-risk surgical candidates
Children <6 months old who are more likely to have non-Wilms tumour histology	Nephrectomy likely to result in significant or unnecessary morbidity/mortality, diffuse Tumour spill, or residual tumour (level IIb)

Recommendations for Radiotherapy (COG) in Wilms Tumour

	Abdominal Tumour Stage/ Histology	RT Dose (RT Field)
1.	Stage I & II/ Favorable	No RT
2.	Stage III/ Favorable and Focal Anaplasia	10.8Gy/ 6# @ 1.8Gy/ Fraction (level Ib)
3.	Stage I – II/ Diffuse Anaplasia	10.8Gy/ 6# @ 1.8Gy/ Fraction
4.	Stage III/ Diffuse Anaplasia	19.8Gy/ 11# @ 1.8Gy/ Fraction
5.	Recurrent Abdominal Disease	10.8Gy/ 6# @ 1.8Gy/ Fraction
6.	Lung Mets (Favorable & Unfavorable) Microscopic Disease Gross Disease/ Nodules	12.6Gy/ 7# @ 1.8Gy/ Fraction + 9.0Gy/ 5# @ 1.8Gy/ Fraction (Boost)
7.	Liver Mets (Favorable & Unfavorable Histology)	10.8Gy/ 6# @ 1.8Gy/ Fraction (Whole Liver) + 9.0Gy/ 5# @ 1.8Gy/ Fraction (Boost to Gross residual disease)
8.	Skeletal Mets (Favorable & Unfavorable Histology)	25.2Gy/ 14# @ 1.8Gy/ Fraction (Lesion + 3cm)
9.	Unresected Lymph Nodal Mets (Favorable & Unfavorable Histology)	19.8Gy/ 11# @ 1.8Gy/ Fraction (Nodal Region)

Bilateral Wilms Tumour

- Three-drug preoperative chemotherapy, surgical resection (nephron sparing) within 12 weeks of diagnosis and response and histology-based post-operative (level IIa)

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10. Grundy PE, Green DM, Dirks AC, Berendt AE, Breslow NE, Anderson JR, Dome JS. Clinical significance of pulmonary nodules detected by CT and Not CXR in patients treated for favorable histology Wilms Tumour on national Wilms Tumour studies 4 and 5: A report from the Children's Oncology Group. Paediatric blood & cancer. 2012 Oct 1;59(4):631-5.

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with stage IV nephroblastoma with risk-based use of pulmonary radiotherapy. Journal of Clinical Oncology. 2012 Aug 27;30(28):3533-9.

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Hepatoblastoma

Investigations

Diagnostic Investigations

- Serum Alpha Feto Protein (AFP)

Imaging

- Triple phase Contrast Enhanced CT abdomen / MRI
- Abdominal ultrasound to evaluate the IVC and portal vein involvement (optional)

Pathology

- Histopathology confirmation may not be required if
  - Age between 6 months and 3 years AND
  - Serum AFP significantly raised AND
  - Compatible radiology
- If Biopsy is done - Minimum of 5 cores (ideally 10 cores) measuring 1x0.3 cm each from different areas of Tumour

Staging

- CT Chest

Table 1. Serum AFP values of term babies without additional factors associated with AFP elevation

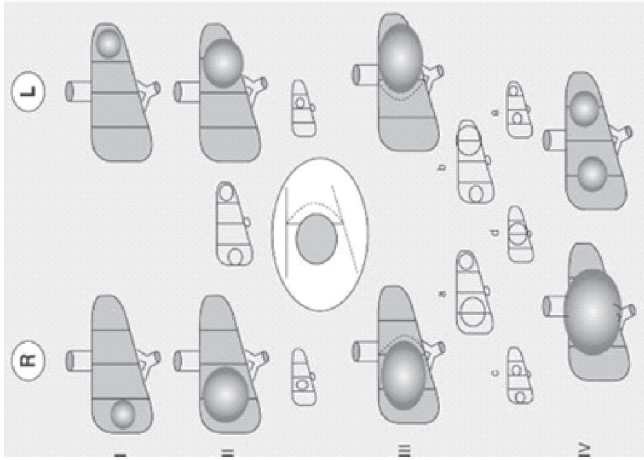
Age (days)	AFP mean (ng/ml)	AFP 95.5% interval (ng/ml)	Half-life (days)
0	41,687	9,120 - 190,546	
1	36,391	7,943 - 165,959	
2	31,769	6,950 - 144,544	
3	27,733	6,026 - 125,893	
4	24,210	5,297 - 109,648	
5	21,135	4,624 - 96,605	5.1
6	18,450	4,037 - 84,334	
7	16,107	3,524 - 73,621	
8-14	9,333	1,480 - 58,887	
15-21	3,631	575 - 22,910	
22-28	1,396	316 - 6,310	
29-45	417	30 - 5,754	14
46-60	178	16 - 1,995	
61-90	80	6 - 1,045	28
91-120	36	3 - 417	
121-150	20	2 - 216	42
151-180	13	1.25 - 129	
181-720	8	0.8 - 87	No correlation

Table 2. Serum AFP values in premature babies without additional factors associated with AFP elevation

Age (days)	AFP mean (ng/ml)	AFP 95.5% interval (ng/ml)	Half-life (days)
0	158,125	31,261 - 799,834	
1	140,605	27,797 - 711,214	
2	125,026	24,717 - 632,412	
3	111,173	21,979 - 562,341	
4	98,855	19,543 - 500,035	6
5	87,902	17,378 - 444,631	
6	77,625	15,346 - 392,645	
7	69,183	12,589 - 349,945	
8-14	43,401	6,039 - 311,889	
15-21	19,230	2,667 - 151,356	
22-28	12,246	1,164 - 118,850	14
29-45	5,129	389 - 79,433	
46-60	2,443	91 - 39,084	
61-90	1,047	19 - 21,878	
91-120	398	9 - 18,620	
121-150	193	4 - 8,318	
151-180	108	3 - 4,365	
181-720	47	8 - 2,630	
151-180	18	4 - 832	100
181-720	4	0 - 372	

Table 1 and 2: Alpha Feto-Protein Level at different ages in term infants and preterm infants

PRETEXT / POST-TEXT Staging (Level Ib)



Hepatoblastoma High Risk Stratification (modified) (Level 1b)

High risk: Patients with any of the following
Serum AFP<100 ¼g/l
PRETEXT IV
Small cell undifferentiated subtype
Additional PRETEXT criteria:
Extrahepatic intra-abdominal disease (E).
Distant metastases (M)
Nodal metastases (N)
Tumour extension into the main and/or both branches of the portal vein (P)
Tumour extension into the vena cava or all three hepatic veins (V)
Intraperitoneal Haemorrhage (H)
Tumour rupture (R)

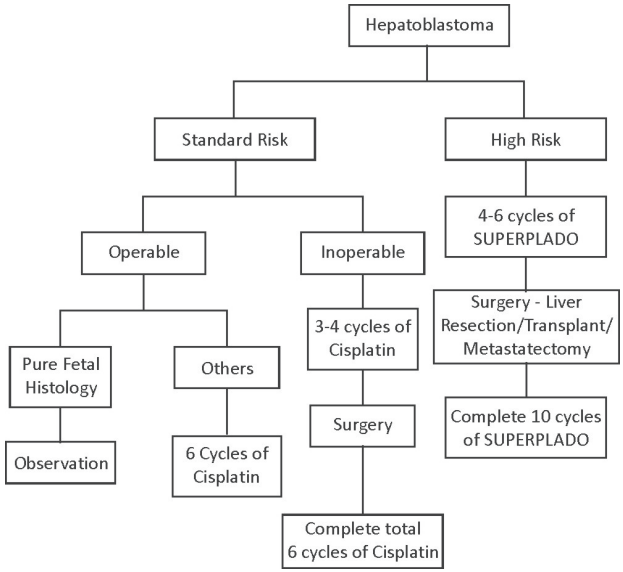
Hepatoblastoma not meeting the High Risk definition considered as Standard Risk

Chemotherapy Recommendations (Level Ib)

Cisplatin 90 mg/m2 IV per cycle every 3 weeks

Cisplatin 80 mg/m2 IV over 24 hours cycles alternating with carboplatin 500 mg/m2 and doxorubicin 60 mg/m2 over 48 hours

Hepatoblastoma Treatment Algorithm



Surgical Recommendations

- Tumours considered resectable at diagnosis includes
  - PRETEXT 1
  - PRETEXT 2 with >1 cm radiographic margin on the middle hepatic vein, the retrohepatic IVC and the portal bifurcation.
- Tumours considered resectable after Neoadjuvant Chemotherapy includes
  - Tumour with POST-TEXT 2 with > 1 cm radiographic margin on the middle hepatic vein, the retrohepatic IVC, or the portal bifurcation (Level 1)

- Metastatectomy to be considered after neo-adjuvant chemotherapy (Level 3A)
- Indications for Liver Transplant:
    - o Unifocal PRETEXT IV
    - o Multifocal PRETEXT III or IV
    - o Solitary PRETEXT IV that did not downstage to POSTTEXT III
    - o Hepatoblastoma with major venous invasion: all 3 hepatic veins/ retrohepatic vena cava/ portal vein
    - o Unifocal, centrally-located Tumours involving main hilar structures or main hepatic veins

Radiotherapy

Currently no evidence for use of radiotherapy.

Suggested Reading

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Rhabdomyosarcoma

Investigations

Imaging

- CT/MRI of the primary site (MRI is preferred in parameningeal, paraspinal, pelvic masses including bladder and prostate)

Pathology

- Biopsy (or upfront excision where feasible) of primary site
- Molecular studies for t(1:13) and t(2:13)

Staging

- CT Chest and abdomen / Bone scan / Bone marrow studies
- PET/CT with bone marrow studies can be an alternative option to conventional staging
- CSF cytology for parameningeal cases

Risk stratification depends on

1. Pretreatment TNM staging
2. Surgical Grouping
3. Age and histology (molecular).

TNM staging system:

Stage	Primary Tumour Site	T Stage Invasiveness	T Stage Size	Regional Lymph Nodes	Distant Metastasis
I	Favorable	T1 or T2	Any	N0 or N1 or NX	M0
II	Unfavorable	T1 or T2	a- 5 cm	N0 or NX	M0
III	Unfavorable	T1 or T2	a- 5 cm	N1	M0
			b- > 5 cm	N0 or N1 or NX	
IV	Any	T1 or T2	Any	N0 or N1 or NX	M1

Site information

Favorable sites - orbit, non-parameningeal head and neck, genitourinary tract (other than kidney, bladder and prostate), biliary tract

Parameningeal sites - middle ear, nasal cavity, paranasal sinuses, nasopharynx, pterygoid- infratemporal fossa.

T information:

T1 - confined to anatomic site of origin (non-invasive)

T2a - with Tumour extension and/or fixation to surrounding tissues (invasive); Tumour less than or equal to 5 cm in maximum diameter;

T2b - Tumour extension and/or fixation to surrounding tissues (invasive); Tumour greater than 5 cm in maximum diameter.

N information

N0 - absence of nodal spread

N1 - presence of regional nodal spread beyond the primary disease

NX - Unknown nodal status.

M information

M0 - absence of metastatic spread

M1 - presence of metastatic spread beyond the primary site and regional lymph nodes

Surgical-pathologic group

Group	Definition
I	A localized Tumour that is completely removed with pathologically clear margins and no regional lymph node involvement.
II	A localized Tumour that is grossly removed with (a) microscopic disease at the margin, (b) involved, grossly removed regional lymph nodes, or (c) both (a) and (b).
III	A localized Tumour with gross residual disease after incomplete removal or biopsy only.
IV	Distant metastases are present at diagnosis.

Assignment of Risk Group

Risk Group	Histology	Stage	Group
Low risk	Embryonal	1	I, II, III
	Embryonal	2, 3	I, II
Intermediate risk	Embryonal	2, 3	III
	Alveolar	1, 2, 3	I, II, III
High risk	Embryonal or Alveolar	4	IV

Embryonal histology – absence of t(1;13) and t(2;13)

Alveolar histology – presence of t(1;13 or t(2;13)

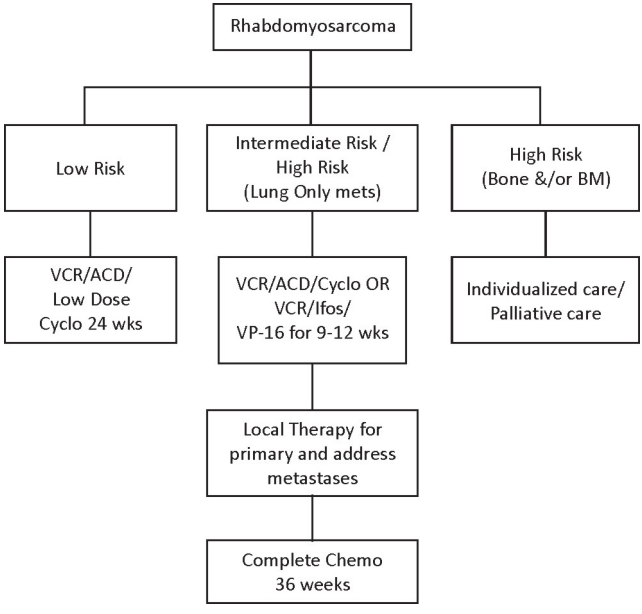
Simplified Risk Stratification

High-risk : All Metastatic (M1) diseases irrespective of histology

Intermediate-risk : Locoregional ARMS, Unresectable ERMS at unfavorable site

Low-risk : ERMS at favorable site, completely resected ERMS at unfavorable sites

Treatment algorithm for Rhabdomyosarcoma



Chemotherapy Schedules	
VCR/ACD/Cyclo	
Vincristine	1.5mg/m2, maximum 2mg
Dactinomycin	0.045mg/kg, maximum 2.5mg
Cyclophosphamide	1200mg /m2 for low risk
	2200mg /m2 for intermediate or high risk
VCR/Ifos/VP-16	
Vincristine	1.5mg/m2, maximum 2mg
Ifosphosphamide	1800mg/m2, 5days
Etoposide	100mg/m2, 5days

Radiotherapy Guidelines for Rhabdomyosarcoma

S.No.	Site / Stage / Histology	RT Field	RT Dose
1.	Group I		
	Embryonal	No RT	
	Alveolar	Pre - Chemotherapy primary site	36Gy
2.	Group II		
	N0 (microscopic residual disease after surgery)	Pre - Chemotherapy primary site	36Gy
	N1 (resected regional lymph node involvement)	Pre - Chemotherapy primary site + Nodes	41.4Gy

S.No.	Site / Stage / Histology	RT Field	RT Dose
3.	Group III		
	All	Pre - Chemotherapy primary site	50.4Gy
	Patients undergoing delayed surgical resection with negative margins	Pre-chemotherapy primary site	36Gy
4.	Group IV	Treat primary site as for other groups + all metastatic sites if technically feasible & safe	

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Retinoblastoma

Investigations

Imaging

- Ultrasound Orbit (B-scan)
- Magnetic Resonance Imaging (MRI) Orbits and screening Brain [CT Brain + Orbits done only if MRI not available or, in rare situations, to establish diagnosis of retinoblastoma]

Examination under Anaesthesia (EUA):

- Intra ocular pressure recording (mmHg)
- Anterior Segment findings
- Retinal Camera Imaging (RetCam)
- Indirect Ophthalmoscopy with Fundus Drawings of the involved eye(s)
    - Tumour – faithful depiction of number, size in DD (disc diameter), site (anterior/posterior to equator and distance in DD from disc and macula), elevation and growth pattern(Endophytic, Exophytic, Diffuse Infiltrating)

- o Retinal detachment
- o Subretinal seeds
- o Vitreous seeding

Staging

- CSF and bone marrow studies in extraocular disease / optic nerve involvement. (Level IIa)

International Retinoblastoma Staging System

Stage	Definition
0	Treated conservatively
I	Completely resected, microscopically no residue
II	Microscopic residue Transcleral invasion Positive cut end of optic nerve
III	Regional Extension Overt Orbital disease Pre auricular or cervical lymphnodes
IV	Metastatic disease Hematogenous metastases CNS extension Pre chiasmatic CNS mass Leptomeningeal and CSF disease

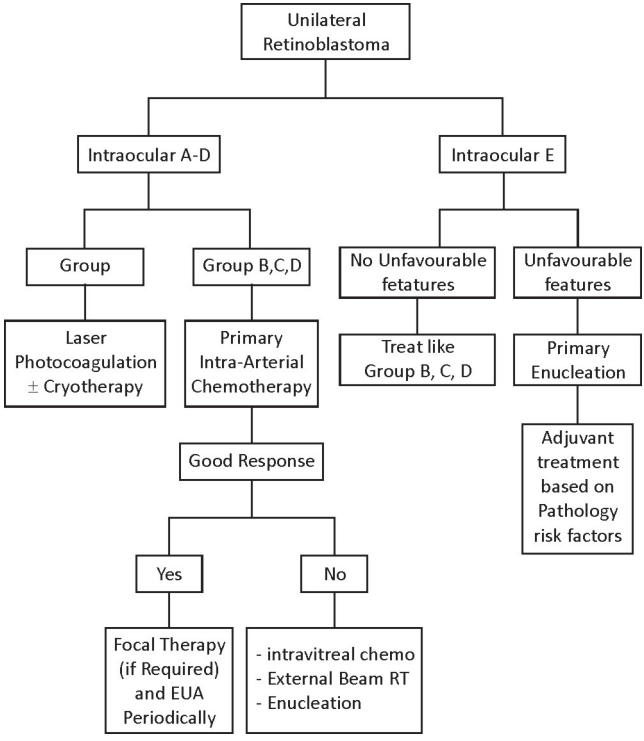
International Group Classification for Intra-Ocular Retinoblastoma

Group A	Small Tumours away from foveola and disc
	● Tumours < 3 mm, confined to the retina, and ● Located at least 3 mm from the foveola and 1.5 mm from the optic nerve.
Group B	All remaining Tumours confined to the retina ● all other Tumours confined to retina and not in Group A ● Subretinal fluid (without subretinal seeding) <3 mm from the base of the Tumour.
Group C	Local vitreous or subretinal seeding ● Subretinal fluid alone > 3mm and < 6 mm from the Tumour ● Vitreous or subretinal seeding < 3mm from the Tumour
Group D	Diffuse vitreous or subretinal seeding ● Subretinal fluid alone > 6 mm from the Tumour ● Vitreous or subretinal seeding > 3mm from the Tumour
Group E	Presence of any one or more of these poor prognosis features ● More than 2/3 of the globe filled with Tumour ● Tumour in anterior segment or anterior to vitreous ● Tumour in ciliary body ● Neovascularization of Iris (NVI) ● Neovascular glaucoma ● Opaque media from hemorrhage ● Tumour necrosis with aseptic orbital cellulitis ● Phthisis bulbi

Pathological risk factors (post enucleation)

1. Massive choroidal infiltration
2. Extra-scleral spread
3. Iris and ciliary body infiltration
4. Post-laminar optic nerve involvement (PLONI)
5. Cut-margin of optic nerve positive for Tumour

Treatment Algorithm – Unilateral Retinoblastoma



- Unfavourable Features of Group E – Neovascularization of Iris, Pthisis bulbi, Media opacity, secondary glaucoma, buphthalmos
- If Intraarterial Chemotherapy is not available – use systemic chemotherapy followed by focal therapy.

Indications for Adjuvant Radiotherapy:

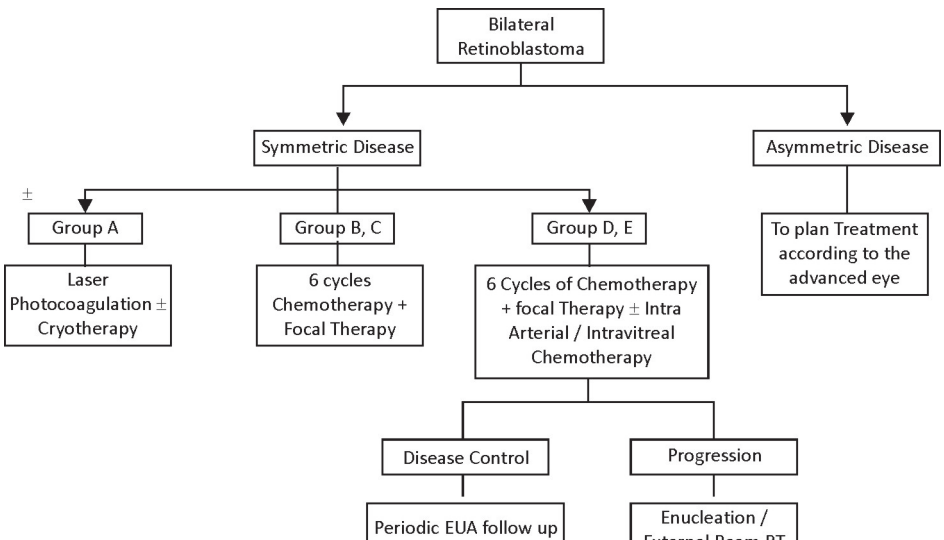
1. Extra-scleral spread on histology
2. Cut-margin of optic nerve positive for Tumour on histology
3. Definitive evidence of extra-ocular mass at presentation on MRI

Indications for Adjuvant Chemotherapy:

1. Massive choroidal infiltration
2. Post-Laminar optic nerve involvement (PLONI)
3. Extra-scleral spread
4. Cut-margin of Optic Nerve positive for Tumour
5. Definitive evidence of extra-scleral mass on presentation on MRI
6. Definitive evidence of Optic Nerve involvement at presentation on MRI
7. Iris and ciliary body infiltration

*For extrascleral spread of disease a total of 12 cycles of chemotherapy to be considered

Treatment algorithm for Bilateral Retinoblastoma



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Suggested Reading

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