NCG GUIDELINES 2020

PAEDIATRIC HEMATOLYMPHOID AND SOLID TUMOURS

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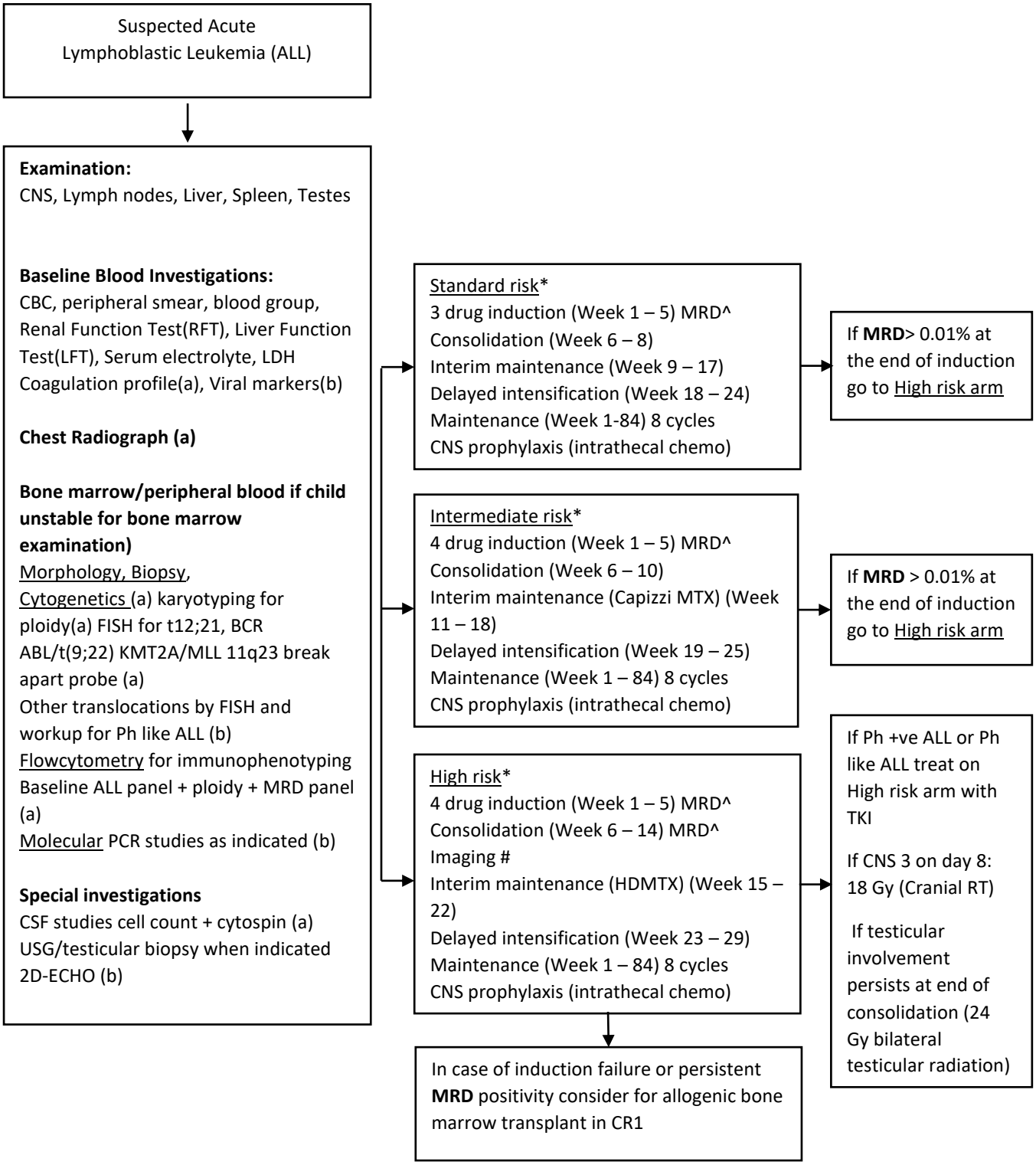


^ MRD = Minimal residual disease by flow cytometry or PCR to assess response to treatment. Risk stratification depends upon MRD assessment. To be done at centers with expertise in flowcytometry and/PCR MRD detection. # Imaging like CXR for patients with T-ALL or LBL with mediastinal mass at the end of consolidation at the end of consolidation to assess response to treatment.

Risk Stratification

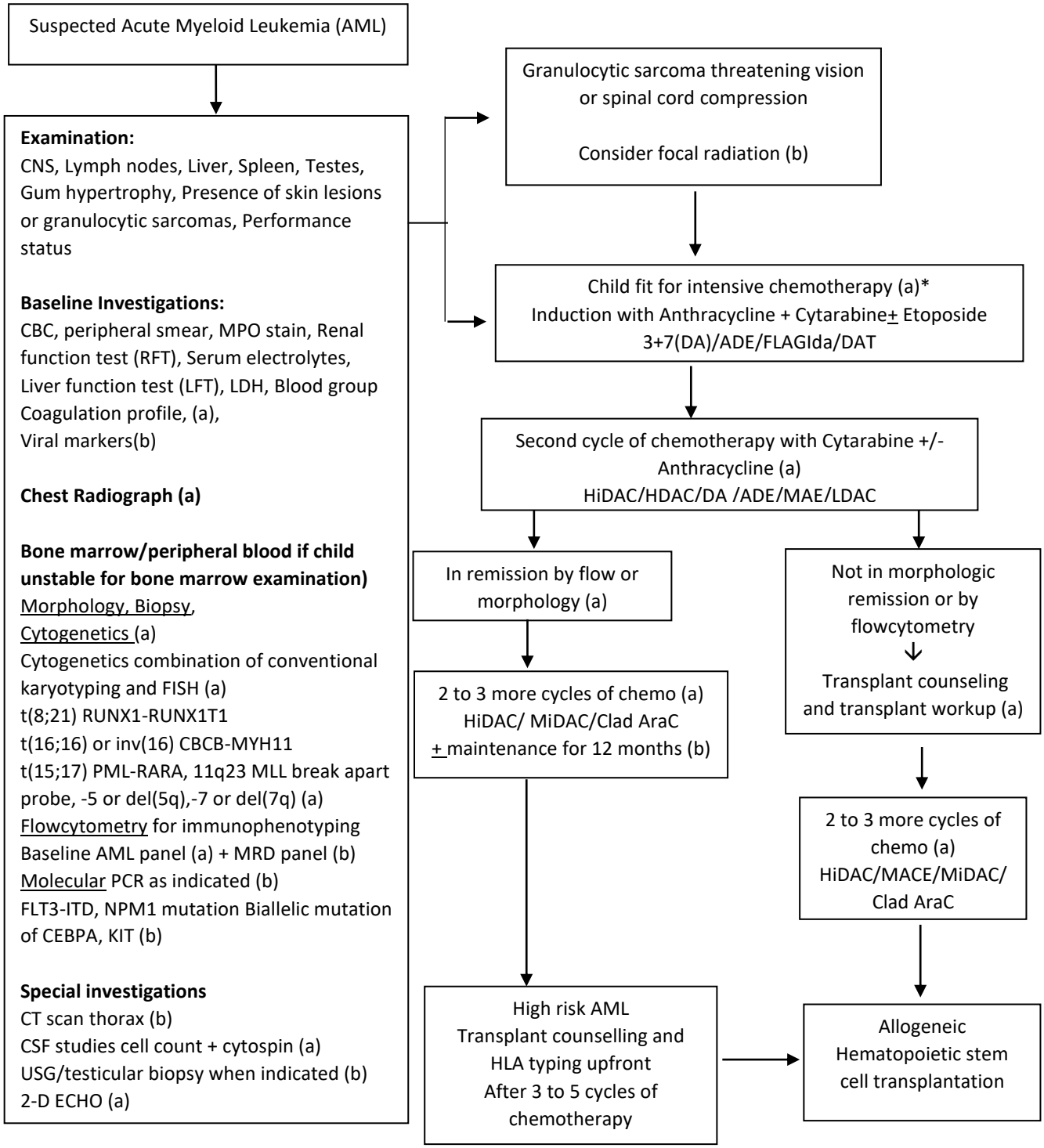
Standard Risk	Intermediate risk	High risk
B lineage ALL **and** Age > 1 and <10 years **and** WBC <50,000/mm3 **and** Prednisolone good responder **and** No testicular or bulky disease **and** No high-risk cytogenetics **and** MRD $<10^{-4}$ at week 5	B lineage ALL **and** Age ≥ 10 years **or** Presenting WBC ≥ 50,000/mm3 **or** testicular/bulky disease **and** Prednisolone good response **and** No high-risk cytogenetics **and** MRD $<10^{-4}$ at week 5	T lineage ALL **or** B lineage ALL **and** High risk cytogenetics BCR-ABL, iAMP21, MLL rearranged, t(17;19), Hypodiploidy (< 45 chromosomes or DNA index <0.81) **or** Prednisolone poor response **or** MRD positive ($>10^{-4}$) at week 5 **or** No CR at the end of induction **or** CNS disease

Protocol options:

- ICICLE-2014
- BFM 90
- BFM 95 (ALL)
- UK ALL protocols
- COG protocols
- MCP 841
- Any others with similar backbone

PEDIATRIC ACUTE MYELOID LEUKEMIA

Newly diagnosed AML



* In case patient has active infection or malnourished and child is not fit for intensive chemotherapy, may consider metronomic chemotherapy for 1 to 3 months

3+7(DA) Daunorubicin + Cyatarabine/AraC	HiDAC High dose AraC
DAE Daunorubicin AraC Etoposide	LDAC Low dose AraC
FLAG Ida Fludarabine AraC GCSF Idarubicin	MAE MItoxantrone AraC Etoposide
	Clad AraC Cladarabine AraC

Treatment Algorithm: Newly diagnosed AML

Newly diagnosed AML (AML-1)

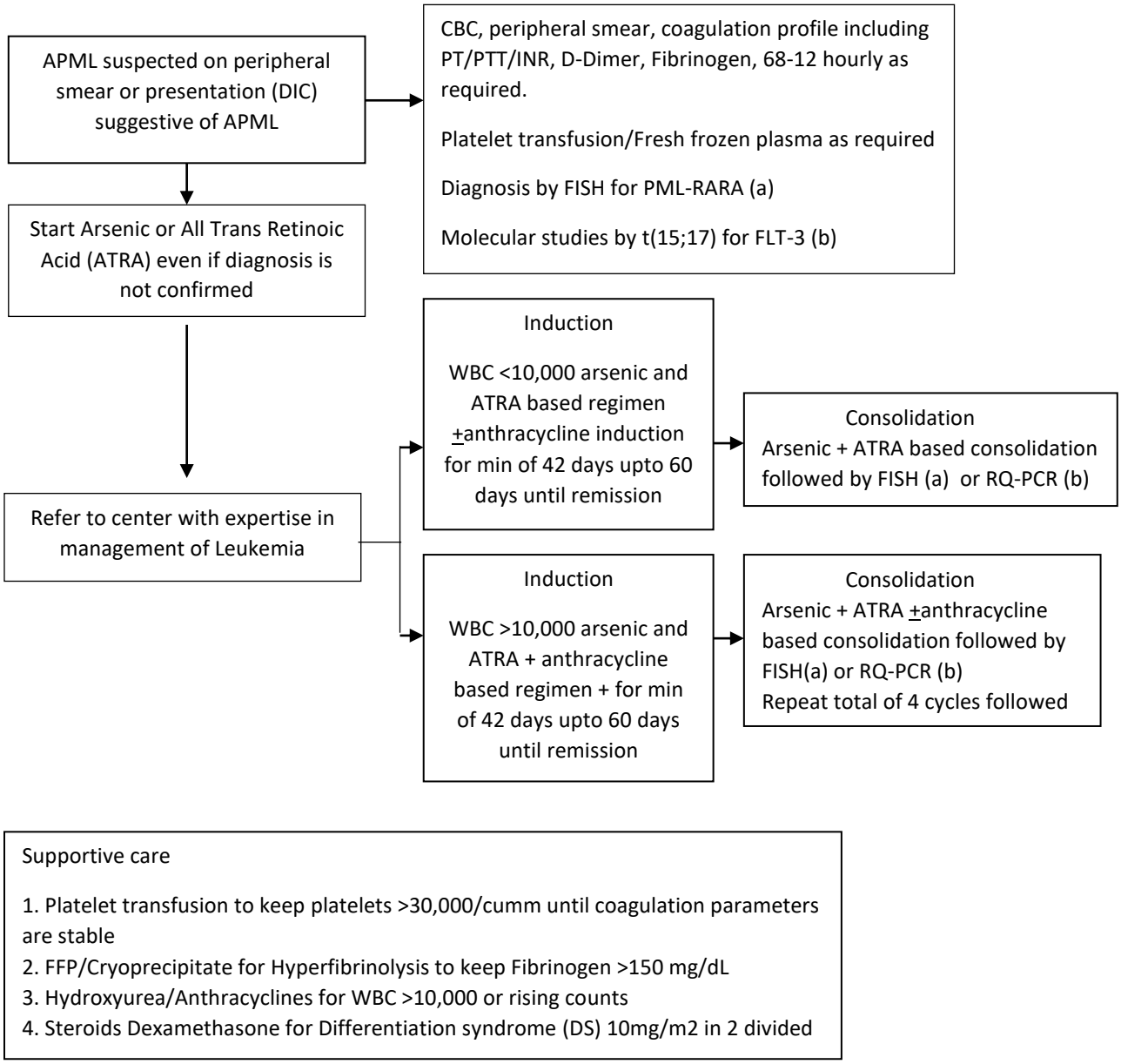
1	Standard risk	Based on cytogenetics and M1 marrow or MRD (if available) negative at end of induction II	t(8;21) RUNX1-RUNX1T1 t(16;16) or inv(16) CBCB-MYH11
2	Intermediate risk		If not satisfying criteria for high risk or standard risk
3	High risk	Based on cytogenetics and positive MRD or >5% blasts on morphology in the bone marrow at end of Chemotherapy cycle II	Complex karyotype -5 or del(5q) -7 FLT3 ITD with allelic ratio > 0.4

Protocol options

UK MRC series of protocols including Myechild-1 protocol
St Jude AML 08
BFM AML protocol
Any Anthracycline and Cytarabine based protocol

PEDIATRIC ACUTE PROMYELOCYTIC LEUKEMIA (APML)

Treatment Algorithm: Newly diagnosed APML (start from AML pathway)

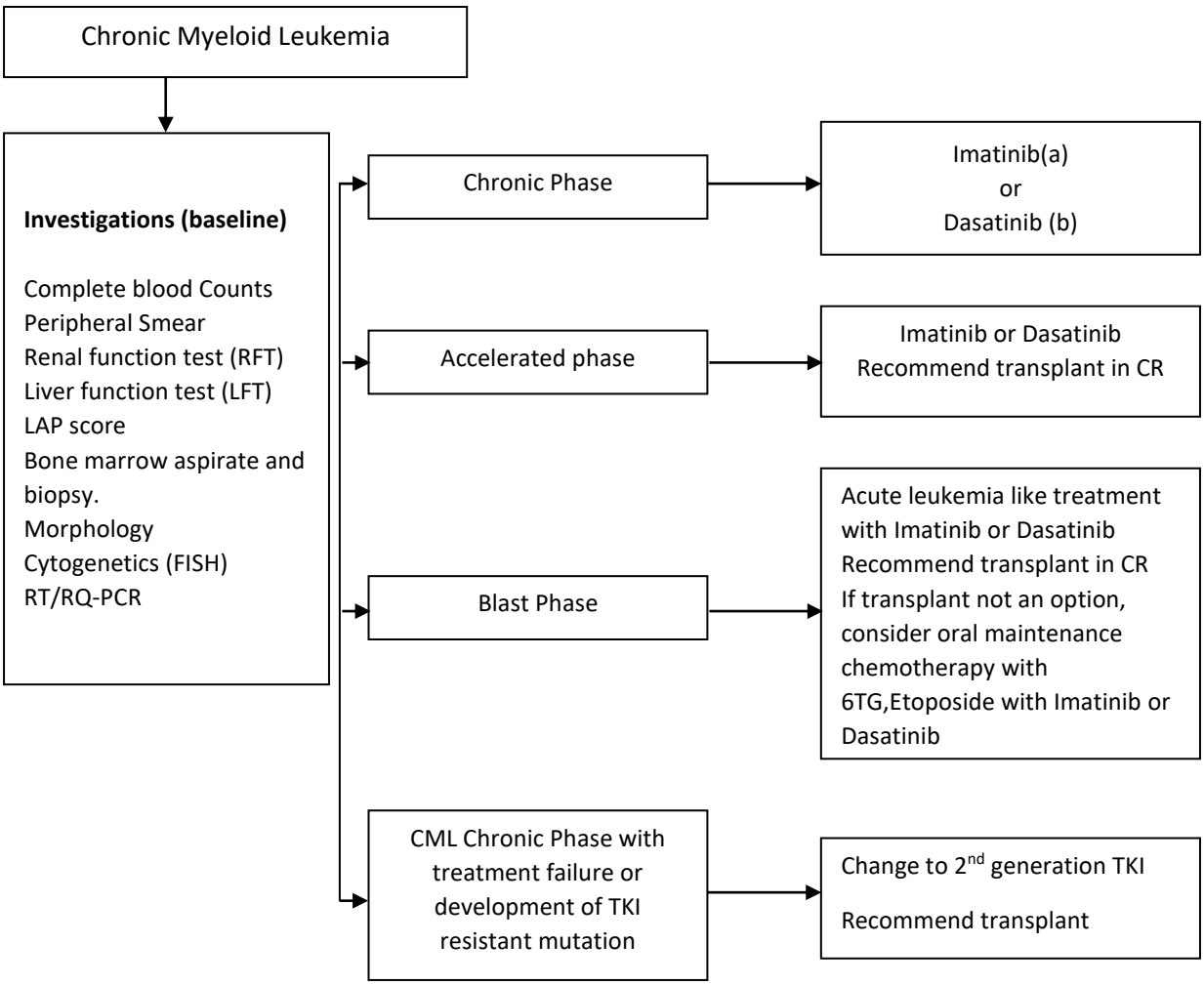


Supportive care

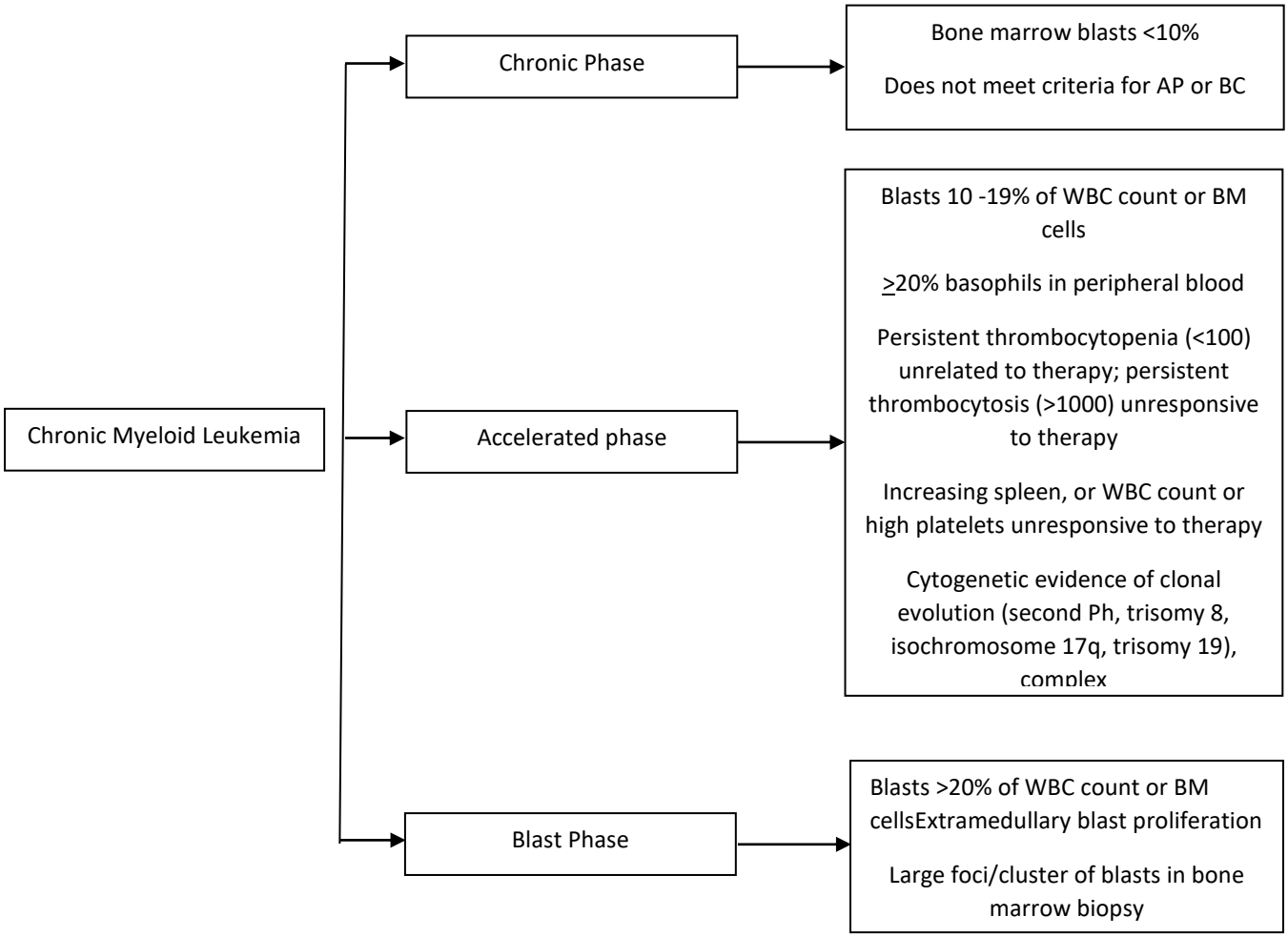
1. Platelet transfusion to keep platelets >30,000/cumm until coagulation parameters are stable
2. FFP/Cryoprecipitate for Hyperfibrinolysis to keep Fibrinogen >150 mg/dL
3. Hydroxyurea/Anthracyclines for WBC >10,000 or rising counts
4. Steroids Dexamethasone for Differentiation syndrome (DS) 10mg/m2 in 2 divided

PEDIATRIC CHRONIC MYELOID LEUKEMIA

Treatment Algorithm: Pediatric CML



Risk Stratification

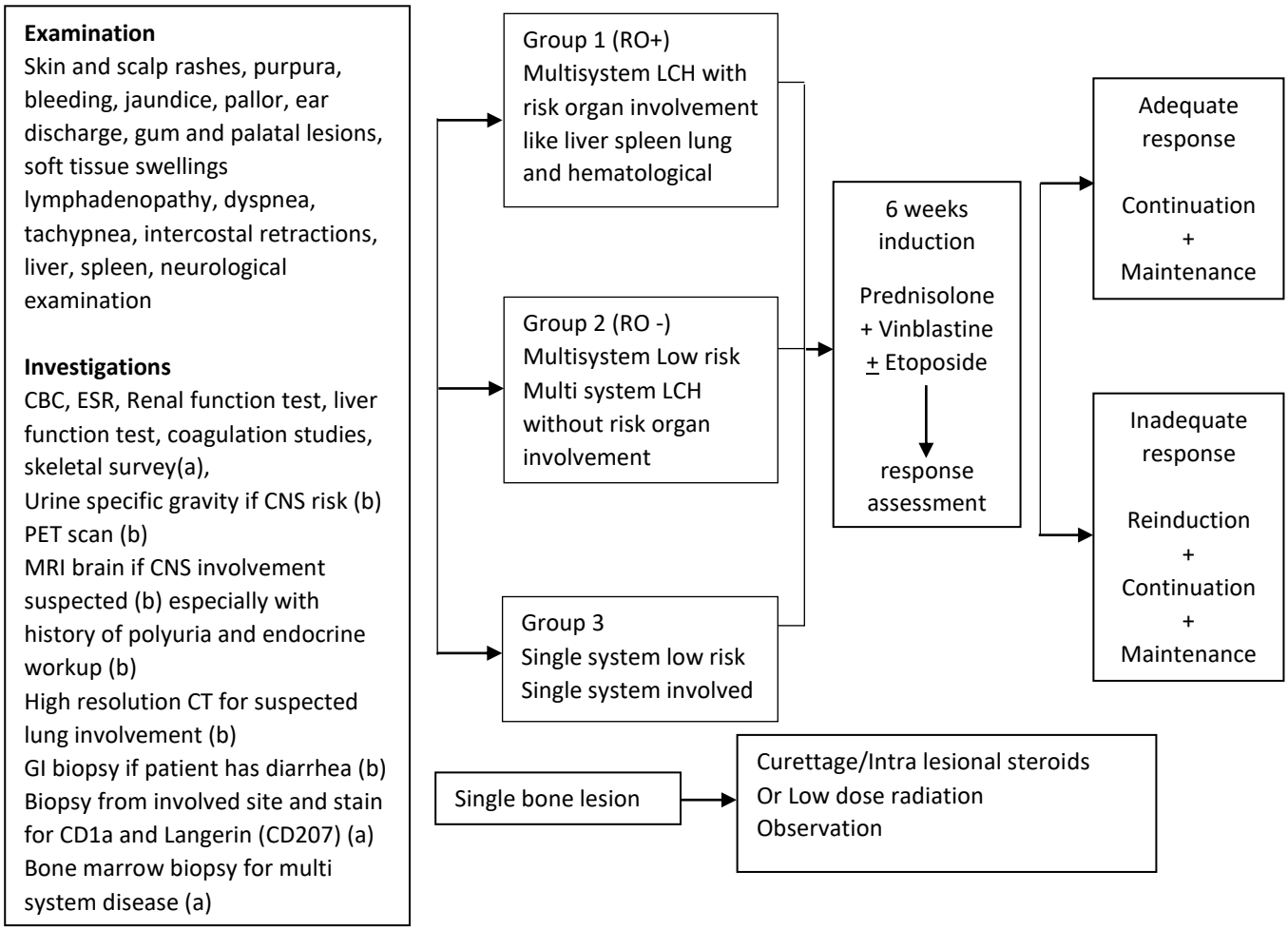


Monitoring and response guidelines in CML CP			
Time (months) {Investigation}	Failure	Warning	Optimal Response
0 {FISH+ RTPCR} (a)	NA	High risk; Additional cytogenetic abnormalities	NA
3 {FISH} (a)	No HR; stable disease or disease progression	NA	CHR PCyR; Ph+ <35% BCR-ABL< 10 % IS
6 {FISH} (a)	Less than CHR; no CyR: Ph+ >95%	NA	CCyR; Ph+ 0% BCR-ABL< 1 % IS
12 {RQPCR} (a)	Less than PCyR: Ph+ >35%	Less than MMR	MMR BCR-ABL <0.1% IS
18 {RQPCR} (a)	Less than CCyR	NA	MMR or better
After 18 months {RQPCR} (a)	Loss of CHR; loss of CCyR; TKI resistant mutation	Loss of MMR; TKI resistant mutation	

FISH **Fluorescent in-situ hybridization**
RQ-PCR **Real-time Quantitative PCR**
CHR **Complete Hematological response**
PCyR **Partial Cytogenetic response**
CCyR **Complete cytogenetic response**
MMR **Major molecular response**

LANGERHANS CELL HISTIOCYTOSIS

Treatment Algorithm: `Newly diagnosed case of Langerhans cell Histiocytosis



AD better = Active disease better with reduction In size of lesion or SUV uptake on PET/Based on CT/Xray
AD worse = Active disease worse
RO+ Risk organ involved
RO- No involvement of Risk Organs

Chemotherapy options for salvage (recurrent or refractory LCH)

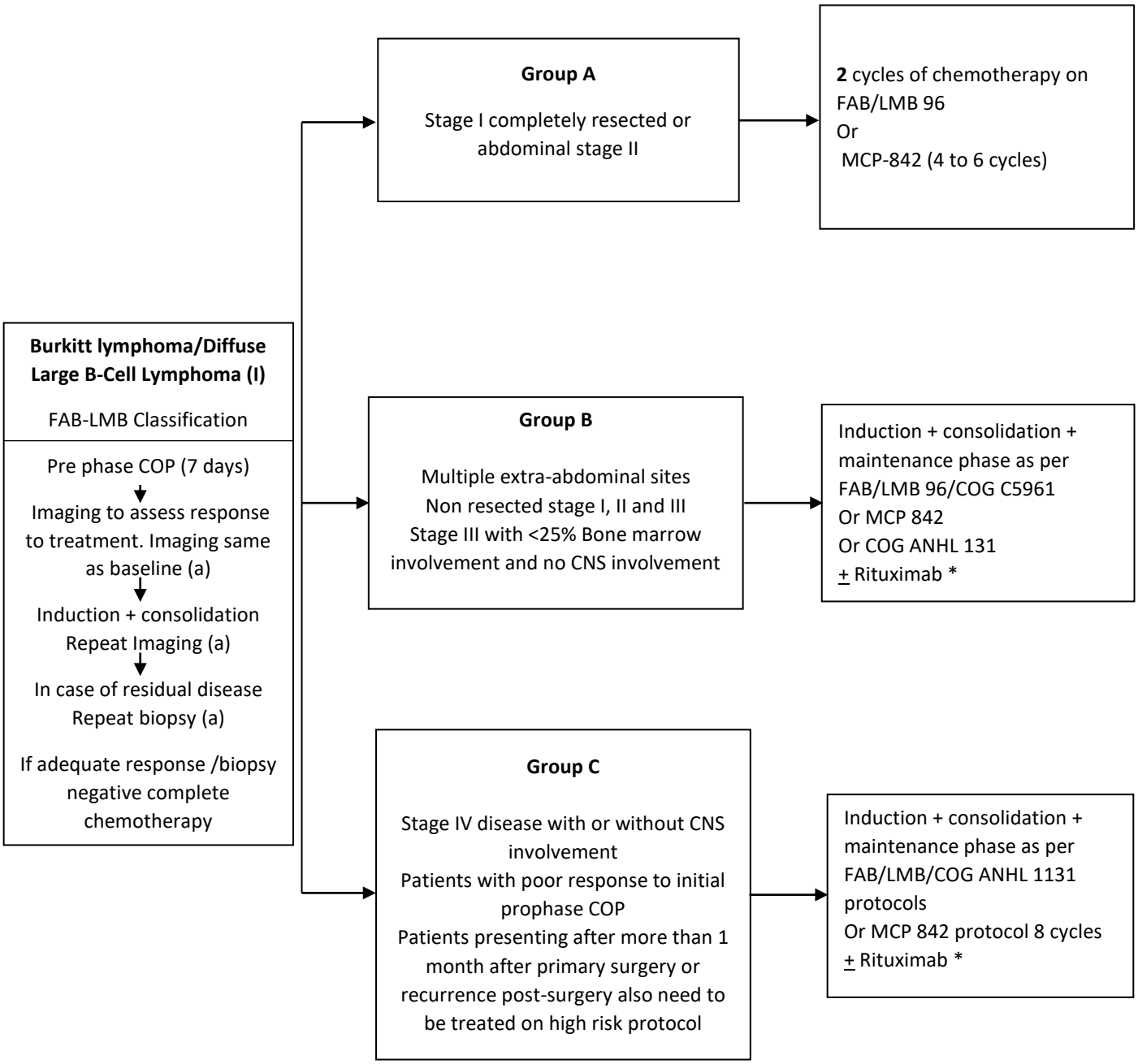
- Cladribine/Cytarabine
- Lenalidomide and Dexamethasone
- Vincristine/Cytarabine
- BRAF inhibitors (for BRAF V600E positive refractory or recurrent LCH)

	Induction (Vinblastine+ Prednisolone)	Reassessment PET	Post induction Treatment	Maintenance (3month/cycle)	Total duration of treatment
Group 1	High Risk (+Etoposide)	NAD/NED #	Continuation (+Etoposide)	6 cycles of maintenance (Etoposide in first 2 cycles)	24 months (in good responders)
		AD Better/Intermediate	Reinduction> Continuation		
		AD Worse	Salvage		
Group 2	Low Risk (-Etoposide)	NAD/NED	Continuation	3 cycles of maintenance (Etoposide)	15 months (in good responders)
		AD Better/Intermediate	Reinduction> Continuation		
		AD Worse	Salvage		
Group 3	Low Risk (-Etoposide)	NAD/NED	Continuation	None Stop treatment after Week 25 (End of continuation)	6 months (in good responders)
		AD Better/Intermediate	Reinduction> Continuation		
		AD Worse	Salvage		

 # AD Active disease
NAD No active disease
NED No evidence of disease

NON-HODGKIN LYMPHOMA (NHL)

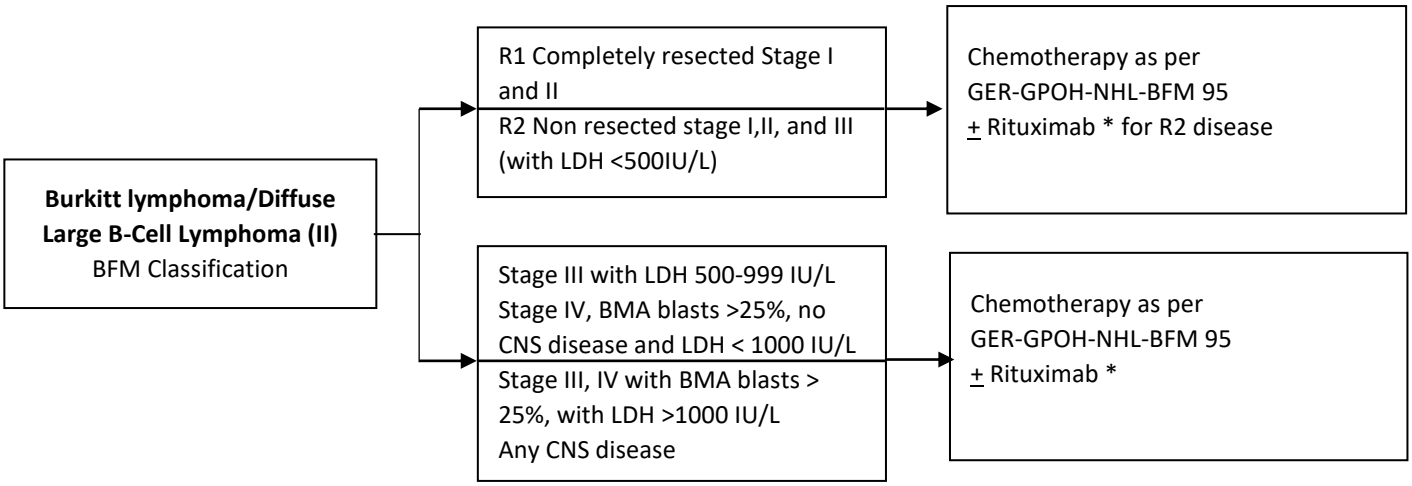
Treatment Algorithm: Newly diagnosed Non-Hodgkin lymphoma

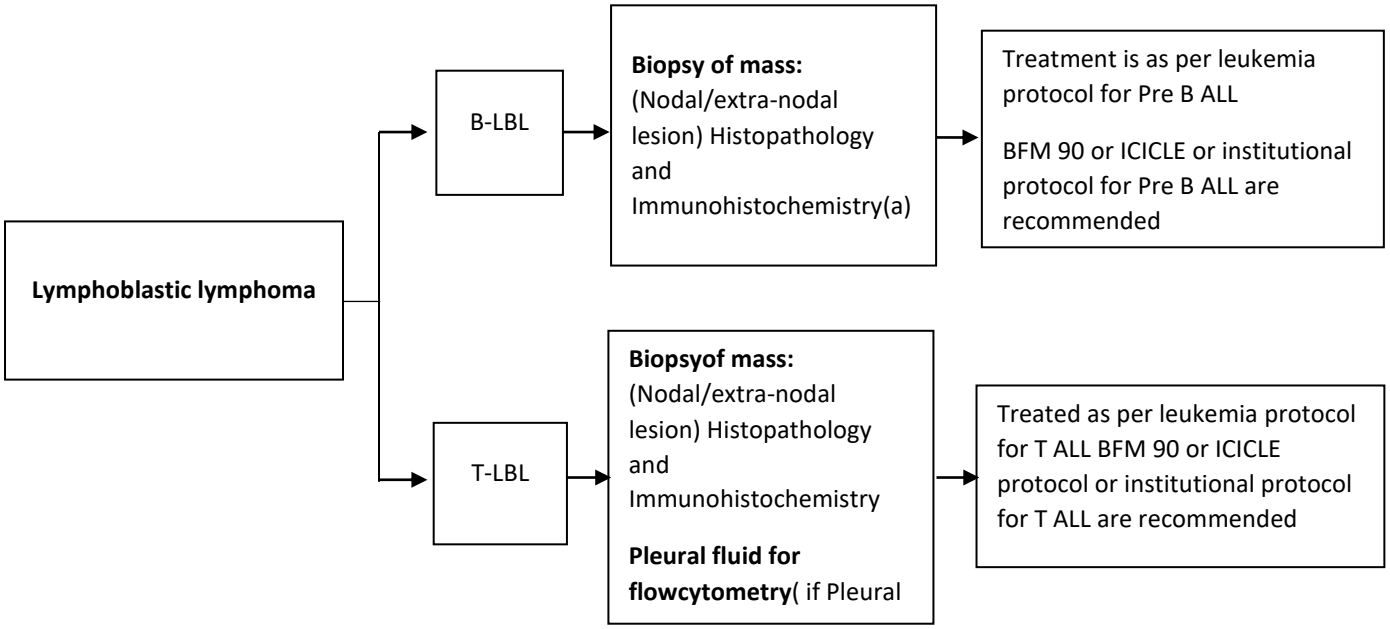


* ± Rituximab can be given in following cases (b)

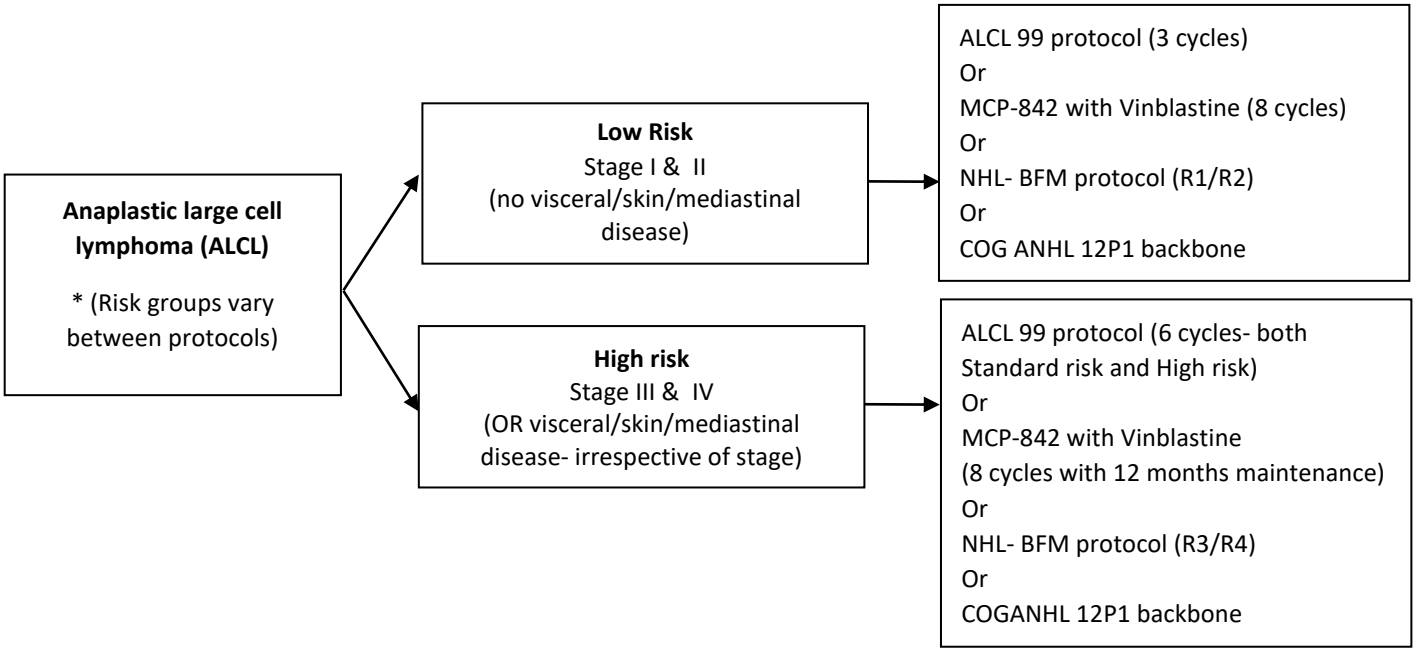
- Group B with Bone marrow involvement / Group C / inadequate initial response
- R2 disease Stage II stage IV as in the BFM classification below

Alternate Regimen option: BFM Classification and treatment





Primary Mediastinal B cell lymphoma(PMBCL) specific type of B cell lymphoma treated on DA-REPOCH (Dose adjusted R EPOCH) 6 cycles (a) Reassessment scan is done only after the 6 cycle of chemotherapy



ALCL relapse is salvageable with Vinblastine based chemotherapy (b)

Diagnostic workup for Suspected NHL

1	History and physical exam	Symptomatic large mediastinal masses, epidural or paraspinal tumors, should be recognized on examination and dealt with as an emergency. Steroids can be initiated before diagnostic confirmation but biopsy should not be delayed.	
2	Laboratory	Baseline labs CBC, Renal function test, Liver function test, serum electrolytes LDH Coagulation profile, (a) Viral Markers(b) Bone marrow aspirate and biopsy (a) CSF cytospin and morphology (a)	
3	Imaging	CXR (a) CT scan neck chest abdomen and pelvis (a) OR PET scan whole body (b) Ultrasound for certain intra-abdominal masses (b) 2 D ECHO (a)	For initial staging of tumor and response assessment (Treatment modality is based on site of lesion and best suited modality at that particular center on a case by case basis)
4	Histology	Biopsy (a) Excision biopsy or core biopsy Histopathology(a) Immunohistochemistry (a) as in appendix Flowcytometry on pleural effusion or ascitic fluid where possible (b)	NHL is a heterogenous group of disorders. Common Pediatric NHLs include • Aggressive mature B cell NHLs (Burkitt lymphoma and Diffuse large B cell lymphoma) • Lymphoblastic lymphoma T/B cell type • Primary mediastinal large B cell lymphoma (PMBCL) • Anaplastic large cell lymphoma (ALCL) Miscellaneous NHL
5	Molecular studies (b)	Burkitt lymphoma t(8;14)(q24;q32) t(2;8) or t(8;22)(b) Anaplastic large cell lymphoma t(2;5)(p23;q35)(b)	

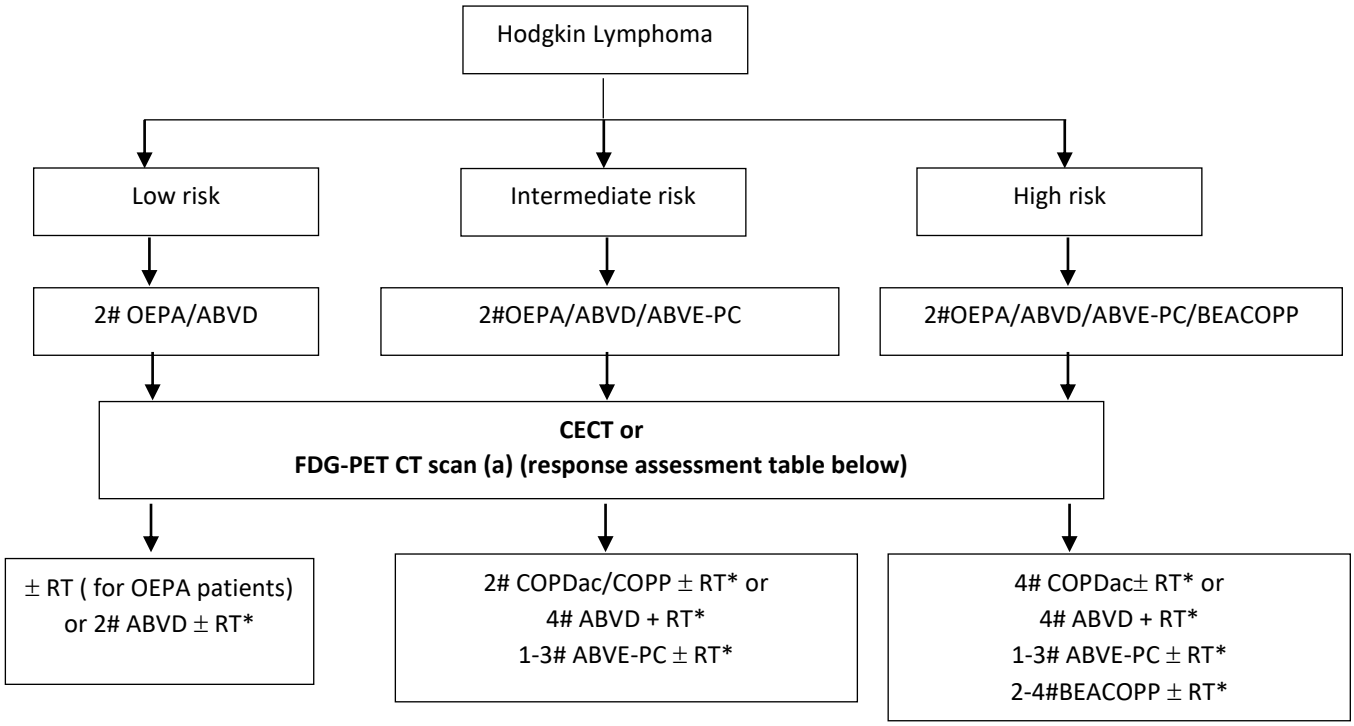
Staging (Due to high incidence of extra-nodal disease Murphy's staging is used for NHL)
Burkitt's and DLBCL are stratified as mentioned subsequently.

Stage I	Involvement of a single tumor or nodal area excluding the abdomen and mediastinum
Stage II	Disease extent is limited to a single tumor with regional node involvement, two or more tumors or nodal areas involved on one side of the diaphragm, or a primary gastrointestinal tract tumor (completely resected) with or without regional node involvement.
Stage III	Tumors or involved lymph node areas occur on both sides of the diaphragm. Stage III NHL also includes any primary intrathoracic (mediastinal, pleural, or thymic) disease, extensive primary intra-abdominal disease, or any paraspinal or epidural tumors.
Stage IV	In stage IV childhood NHL, tumors involve the bone marrow and/or CNS, regardless of other sites of involvement.

- Bone marrow involvement is defined as 5% or more malignant cells the bone marrow, with normal peripheral blood counts and smears.
- Patients with lymphoblastic lymphoma with more than 25% malignant cells in the bone marrow are considered to have Acute Lymphoblastic Leukaemia and to be treated on ALL protocols.
- Patients with Burkitt's lymphoma with >25% blasts are considered as Burkitt'sleukaemia but treated on Burkitt's lymphoma protocol as stage IV disease with higher intensity of chemotherapy
- CNS disease is any malignant cell present in the CSF regardless of cell count.

PEDIATRIC HODGKIN LYMPHOMA

Treatment algorithm: Pediatric Hodgkin Lymphoma



Chemotherapy regimens

BEACOPP: Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisone

ABVD: Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine

ABVE-PC: Doxorubicin, Bleomycin, Vincristine, Etoposide, Prednisone, Cyclophosphamide

OEPA: Vincristine, Etoposide, Prednisone, Doxorubicin

COPDac: Cyclophosphamide, Vincristine, Prednisone, Dacrbazine

***RT indicated only for inadequate response (PET)/ bulky disease denoted as (X) in the staging at presentation**

RT doses ranging from 19.8 cGy to 25 cGy

Diagnostic workup		
1	History and physical examination	B symptoms (any one is sufficient) Fever (oral temp >38'C) Night sweats Weight loss > 10% in last 6 months
2	Laboratory	Baseline labs CBC, Renal function test, Liver function test, serum electrolytes LDH Coagulation profile, Viral Markers (b) Bone marrow aspirate and biopsy for stage IV only (b) CSF cytospin and morphology only if indicated (b)
3	Imaging	CXR CT scan chest abdomen and pelvis (if PET not available) OR PET scan whole body (a) 2D ECHO (a)
4	Histology	Excision biopsy of a peripheral lymph node or Core biopsy of mediastinal or abdominal lymph node if no accessible enlarged peripheral node Immunohistochemistry as in appendix (a)

Staging information (Ann-Arbor staging system)	
Stage I	Involvement of a single lymphatic site (ie. nodal region, Waldeyer's ring, thymus, spleen) (Stage I); or involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (Stage IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (Stage II) or localized involvement of a single extra lymphatic organ or site in association with regional lymph node involvement with out without involvement of other lymph node regions on the same side of the diaphragm (Stage IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (Stage III) which may also be accompanied by extra lymphatic extension in association with adjacent lymph node involvement (Stage IIIE) or by involvement of the spleen or both (Stage III ES)
Stage IV	Diffuse or disseminated involvement of one or more extra lymphatic organs, with or without associated lymph node involvement; or isolated extra lymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver or bone marrow, lungs (note) or CSF.

The substage classification A,B,E,S,X amend each stage based on defined features
B - B symptoms, A - absence of B symptoms. S - Spleen Involvement E - extra-nodal extension which most commonly involves lung, pleura, pericardium or bone when there is contiguous extension of lymph node disease or the site is proximal to an involved draining lymph node. X - Bulky disease defined differently by various study groups. Bulky peripheral lymphadenopathy is defined as single or conglomerated lymph nodal mass >6cm in longest diameter. Bulky mediastinal disease is defined as a mediastinal mass with a horizontal tumor diameter ≥1/3rd the thoracic diameter.

APPENDIX A (FLOWCYTOMETRY)

A. Acute Leukemia- Essential panel (a)

1. Smears stained with a Romanowsky stain and Myeloperoxidase or Sudan Black B
2. NSE, toluidine blue and Iron stain as required.

Note: Morphology is followed by flow cytometricimmunophenotyping and other ancillary techniques including cytogenetics and molecular diagnostics. The final diagnosis is based on a combination of all these modalities.

Essential		
Common markers	CD45, CD38, HLADR	
Markers of immaturity	CD34	
	Lineage associated	Lineage Specific
B-cell	CD10, CD19, CD20, surface or cytoplasmic CD22, CyCD79a	
T-cell	CD1a, CD4, CD5, CD7, CD8, TCRγδ	Surface and Cytoplasmic CD3
Myeloid	CD13, CD33, CD117	cyMPO or Cytochemical Myeloperoxidase or Sudan Black B
Monocytic	CD36, CD64	Non Specific Esterase
Megakaryoblastic	X	
NK-cell	CD56	
Plasmacytoid dendritic cells	CD123	

B. Acute leukemia – Optimal panel (b)

Essential + additional markers as below

Optimal	Lineage associated	Lineage Specific
B - cell	CD73, CD86, CD25, CD304	
T - cell		
Myeloid	CD15	
Monocytic	CD11c, CD14	
Megakaryoblastic	CD41, CD61	
NK – cell		
Plasmacytoid dendritic cells		

C. Acute leukemia – Optional panel (c)

Optional		
Common markers	CD25, CD45Ra	
Markers of immaturity	CD133, TdT	
	Lineage associated	Lineage Specific
B - cell	CD58, CD81, NG2, CRLF2	IgM, Kappa & Lambda chains
T - cell	CD2, CD99, TCRαβ	
Myeloid	CD15, CD11b, CD16, CD65, CD66c	
Monocytic	CD86, CD300e	
Megakaryoblastic	CD42b	
NK-cell	CD94, CD161	
Plasmacytoid dendritic cells	CD303, CD304	
Mast cells	CD203c	
Erythroid lineage	CD49d, CD71, CD105	CD235a

D. DNA ploidy by flow cytometry for B-ALL – Optimal (b)

Propidium Iodide
FxCycle Violet
DRAQ5
DAPI (4',6-Diamidino-2-phenyl Indole)

E. B-ALL Minimal Residual Disease Panel Essential (a) + Optional (c)

Essential	**Optimal**	**Optional**
CD10, CD19, CD20, CD34, CD38, CD45, CD73, CD123, CD86, CD304		CD25, CD44, CD66c, CD81, CD200, CD58
Nuclear dye such as Syto13, Syto16, Syto44		

Recommendations for processing

- Use Euroflow recommended Bulk-lysis method
- Acquire minimum 10,00,000 CD45-positive events
- Minimum 8-color antibody panel
- Use the template-based analysis
- Should be done in a laboratory with workload of minimum 30 acute leukemia samples per month
- Mention the limit of detection and limit of quantitation of MRD assay
- Mentioned the number of events studied
- Control sample should be evaluated atleast once in month

F. T-ALL MRD Optimal (b) + Optional (c)

Optimal	**Optional**
CD4, CD5, CD7, CD8, CD16, CD34, CD38, CD45, CD56, Surface and cytoplasmic CD3	CD1a, CD2, CD48, CD99, TdT
Nuclear dye such as Syto13, Syto16, Syto44	-

G. AML MRD Optimal (b) + Optional (c)

	Optimal	**Optional**
Deviation from normal	CD13, CD14, CD15, CD33, CD34, CD36, CD38, CD45, CD64, CD117, CD123, HLADR	CD11b, CD65, CD66c, CD71,
Leukemia associated Immunophenotypic markers	CD7, CD19, CD56	CD2, CD4, CD5,

H. Lymphoproliferative disorders/Lymphoma Essential (a) + Optimal (b) + Optional (c)

B-cell NHL

Essential	**Optimal**	**Optional**
CD5, CD10, CD19, CD20, CD23, CD45, CD200, Kappa & Lambda light chains	CD22, CD38, IgM,	CD27, CD43, CD44, CD49d, CD72, CD79b, CD81, CD123, CD148, CD180, CD305, IgD, IgG, FMC7, ROR1, Ki67, BCL2, BCL6, Mum-1

T- NHL

Essential	**Optimal**	**Optional**
CD3, CD4, CD5, CD7, CD8, CD10, CD16, CD25, CD26, CD45, CD56	CD2, CD30, CD94, CD161, CD185, CD279, ALK-1, Perforin, Granzyme	CD38, CD45RA, CD45RO, TCL1, TCRVβ-repertoire, KIR, Ki67, TIA-1

<u>Important</u>: The laboratory without expertise in diagnosing hematolymphoid neoplasms and with inadequate IHC/Flow cytometricimmunophenotyping panels should refer the sample to any specialized lab dealing with such neoplasms. There cannot be any definite algorithms for diagnosing hematolymphoid neoplasms as each lesion is different and number of reagents used may vary case to case basis.

APPENDIX B

Histopathology for lymphomas

Tissue /lymph node processing guidelines

Essential

- Tissue preservation (avoid frozen processing)
    - Fixative: 10% neutral buffered formalin
- Fixation:
    - Lymph nodes/tissue thicker than 0.8 -1.0cms; should be bisected and large tissue should be serially sliced, perpendicular to the long axis.
    - Tissue ≤4 cm in greatest dimension should be processed in entirety
    - Should be put for fixation within 30 – 60 minutes of biopsy
    - Fixation volume should be at 3-4 times the volume of the tissue
    - Should not be left in the fixative for more than 48 hrs; and should be processed in 12-24 hrs time (in cases of inevitable delay; should be kept in cold temperature [refrigerator], preferably at 4 degrees centigrade)
- Routine processing and embedding
    - 2-3 micron thick sections with Hematoxylin and eosin stained slides of each paraffin block
    - Immunohistochemistry set up
    - Microscopic evaluation

Optional (Immunohistochemistry and Molecular diagnostic laboratories)

**For transportation – Either by immersing tissue in the adequate formalin in a sealed container or by paraffin blocks*

<u>Lymphoma Tissue Diagnosis</u>

Essential: (a)

- Diagnosis:
    - Histological evaluation, i.e. biopsy as a method of investigation with comprehensive IHC panels.
    - Only in instances of inability of get adequate, a fine needle aspiration (FNA) based flow cytometric evaluation should be considered for diagnosis
- Staging
    - Bone marrow biopsy, aspirate and imprint smear

Optional/extended work-up: (b)

- Diagnosis:
    - Fine needle aspiration (FNA) based flow cytometricimmunophenotyping along with the biopsy
    - Molecular work-up (c)
- Staging:
    - Flow cytometricimmunophenotypic evaluation (for Non-Hodgkin Lymphoma) (c)

<u>A. Hodgkin lymphoma</u>

(cHL) classical Hodgkin Lymphoma and (NLPHL) Nodular Lymphocyte Predominant Hodgkin Lymphoma-requisites for diagnosis

Classic Hodgkin lymphoma (cHL)

- Essential: (a)
    - CD3, CD20, CD30, CD15, Pax5, ALK-1**
- Optimal/extended work-up: (b)
    - LCA, CD3, CD20, CD30, CD15, Pax-5, Oct2, Bob1, EBV-LMP1/EBER, Gata 3

Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)

- Essential: (a)
    - CD20, CD3, CD30, CD15, Pax5
- Optimal/extended work-up: (b)
    - CD3, CD20, CD30, CD15, Pax-5, EBVLMP1/EBER, PD1, Oct2, Bob1, Gata3, CD4, CD8

** Rule out a possibility of ALK+ve ALCL

B. Non-Hodgkin Lymphoma

1. CD20 positive BNHL: large cell morphology

- Essential: (a)
    - IHC: LCA, CD20, CD3, MIB-1
- Optimal/extended work-up:
    - IHC: CD3, CD20, MIB-1, cyclin D1, CD5, CD10, Bcl6, Mum1, cmyc, Bcl-2, CD30, EBV-LMP1/EBER
    - FISH: CMYC/BCL2/BCL6 gene rearrangement
    - Gene expression/methylation studies – COO subtyping

2. CD20 positive BNHL: non-large cell morphology

- Essential: (a)
    - IHC: LCA, CD20, CD3, MIB-1, CD5, CD23, CD10, bcl6, cyclin D1 (if blastic morphology, please add AMPO, ckit, CD10, CD19/Pax5, Tdt, CD34)
- Optimal/extended work-up: (b)
    - IHC: Mum1, cmyc, Bcl-2, EBV-LMP1/EBER, CD43, CD138, Sox11
    - FISH: CMYC/BCL2/BCL6; IFR4 gene rearrangement
    - Sequencing: MYD88 mutation

3. CD3 positive NHL: large cell morphology

- Essential: (a)
    - IHC: CD20, CD3, CD30, MIB-1, ALK-1, CD4
- Optimal/extended work-up :
    - IHC: CD3, CD20, CD4, CD8, CD2, CD5, CD7, MIB-1, CD56, CD30, ALK-1, CD10, Bcl6, PD1, Mum1, EBV-LMP1/EBER, CD123, Gata3
    - FISH: DUSP22 gene rearrangement

4. CD3 positive NHL: non-large cell morphology

- Essential: (b)
    - IHC: CD20, CD3, CD2, CD5, CD7, CD4, CD8, MIB-1, cyclin D1, Tdt, CD34, CD30, ALK-1
- Optimal/extended work-up :
    - IHC: CD56, CD10, Bcl6, PD1, Mum1, EBER-ISH, CD123, Gata3, CXCLl13, CXCR5, ICOS
    - FISH: DUSP22 gene rearrangement

5. CD3 and CD20 negative NHL- requisites for diagnosis

- IHC: LCA, CD3, CD20, CD30, CD19, Pax-5, CD138, ALK-1, CD5, CD10, Bcl6, Mum1, EBV-LMP1/EBER, CD56, CD7, CD4, CD8, CD123, MIB-1, c-kit, MPO, CD41, CD61, CD33, CD34, Tdt, CD1a, CD163, S-100 protein, EMA, CD23, CD21, kappa, lambda, MIB-1

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APPENDIX C

Response assessment for Lymphomas

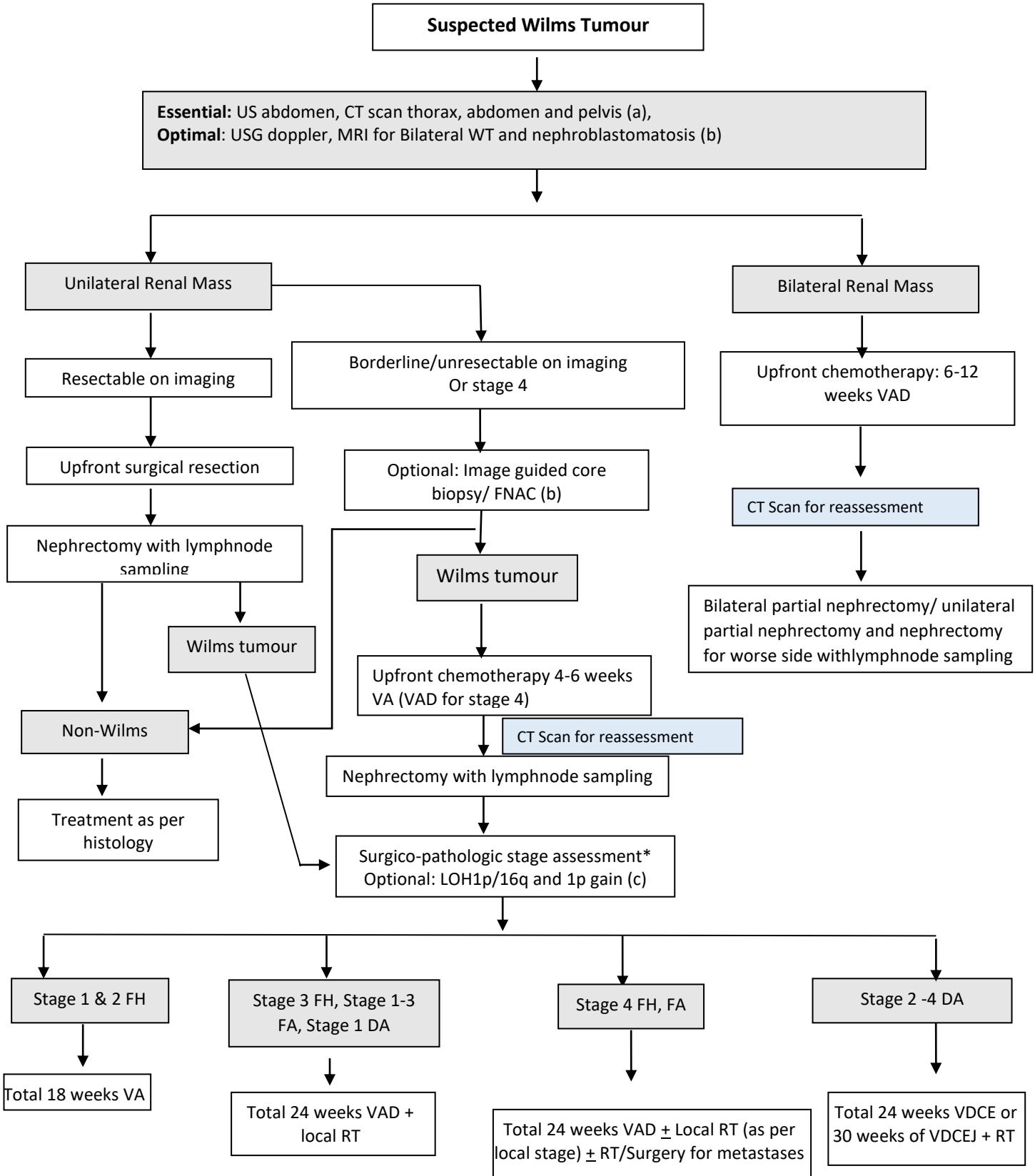
Deauville score

1	No FDG uptake
2	FDG uptake ≤ mediastinum
3	FDG uptake > mediastinum but ≤ liver
4	FDG uptake > liver at any site
5	FDG uptake > liver and new sites of disease
x	New areas of FDG uptake unlikely to be related to lymphoma

PEDIATRIC SOLID TUMORS

WILMS TUMOUR

Treatment Algorithm: Wilms Tumor



- FH=Favourable Histology
- V= Vincristine, A= Actinomycin D, D= Doxorubicin, C= Cyclophosphamide, E= Etoposide, J= Carboplatin
- RT= Radiotherapy
- DA- diffuse anaplasia, FA-focal anaplasia

- Tumours weighing <550g in children aged <24 months and with favorable histology may be observed after surgery
- In centres adopting the SIOP approach to management of Wilms tumor, post-operative chemotherapy is given as per operative staging and post-operative histology as per table below:

Risk Stratification

Disease	**Treatment**		
	Stage I	Stage II	Stage III
Low-risk	None	AV (27 weeks)	AV (27 weeks)
Intermediate-risk, all subtypes <500ml	AV (4 weeks)	AV (27 weeks)	AV (27 weeks) + flank RT
Intermediate-risk, stromal or epithelial-type >500 ml	AV (4 weeks)	AV (27 weeks)	AV (27 weeks) + flank RT
Intermediate-risk, nonstromal, nonepithelial	AV (4 weeks)	AVD (27 weeks)	AVD (27 weeks) + flank RT
High-risk blastemal type and diffuse anaplasia Wilms tumour	AVD (27 weeks)	DCEJ (34 weeks) flank RT in DA	DCEJ (34 weeks) + flank RT

Staging of Wilms Tumour

Stage 1	Tumour limited to the kidney and completely excised.
Stage 2	Tumour extends beyond the kidney but is completely excised The tumour infiltrates the renal sinus and/or adjacent organs or vena cava but is completely resected
Stage 3	Residual nonhematogenoustumor confined to the abdomen; lymph-node involvement, peritoneal spillage, peritoneal implants, either gross or microscopic tumor beyond the surgical margin, or tumor not completely removed.
Stage 4	Hematogenous metastases to lung, liver, bone, brain or other organ.
Stage 5	Bilateral renal involvement at diagnosis.

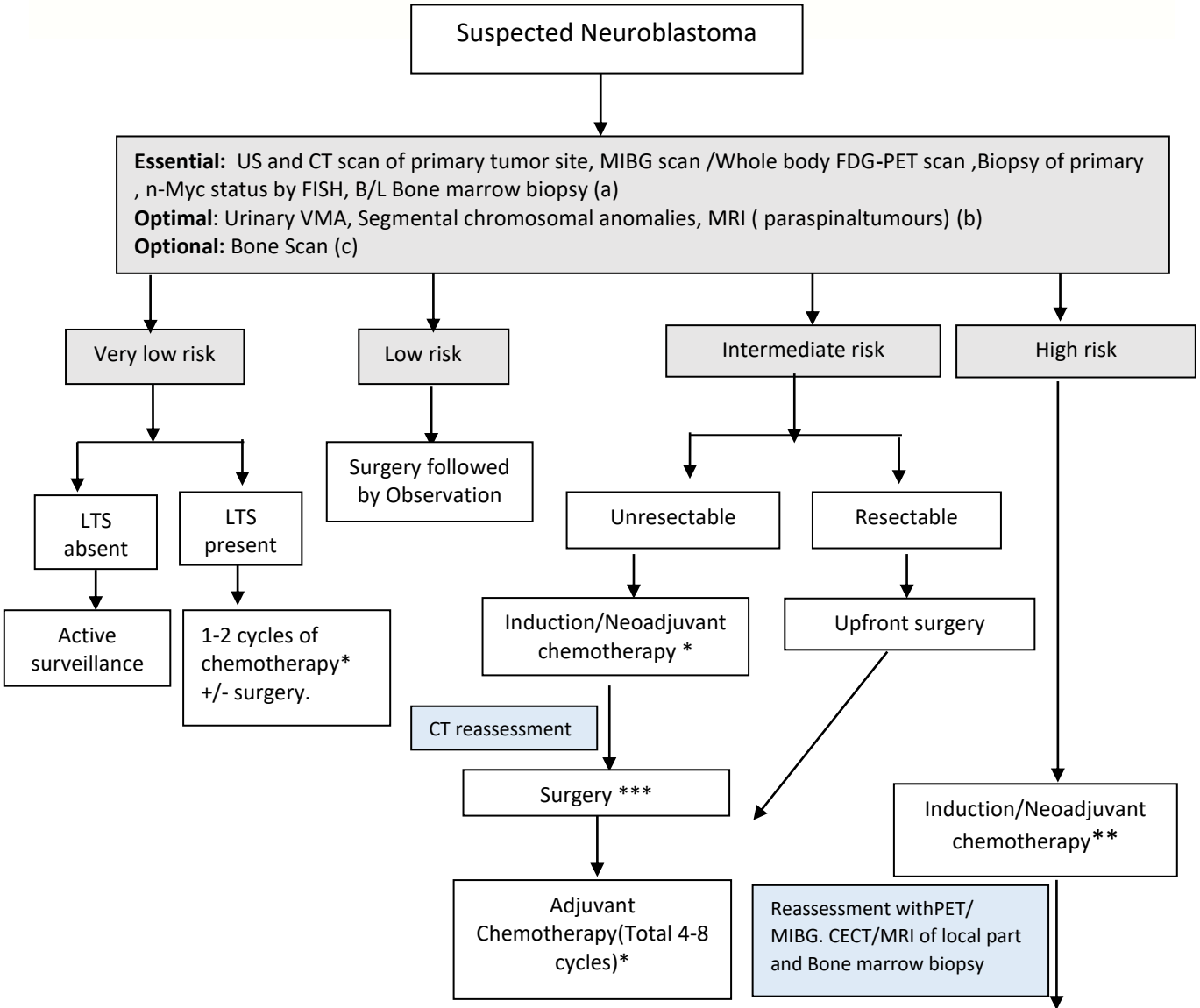
RT guidelines in Wilms Tumour

	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)

- Whole-lung irradiation may be omitted in cases of FH with complete response (pulmonary) after 6 weeks of VAD (provided there is no extrapulmonary metastases or LOH 1p/16q)
- 3D Conformal RT and Intensity Modulated RT are standard forms of delivery of RT in children with WT

NEUROBLASTOMA

Treatment Algorithm: Neuroblastoma



LTS: Life threatening symptoms
*Chemotherapy regimens for low/Intermediate Risk Neuroblastoma
-Carboplatin and Etoposide,
-Cyclophosphamide and doxorubicin
**Chemotherapy regimens (NACT) for High risk Neuroblastoma
-OPEC/OJEC:vincristine, cisplatin, etoposide, cyclophosphamide, and carboplatin
-Rapid COJEC: carboplatin, etoposide, vincristine, cisplatin and cyclophosphamide
-ICE: Ifosfamide, Cisplatin, Etoposide
-N7 protocol: cyclophosphamide, doxorubicin, vincristine, cisplatin and etoposide
*** May consider local radiation therapy or MIBG therapy in inoperable tumours

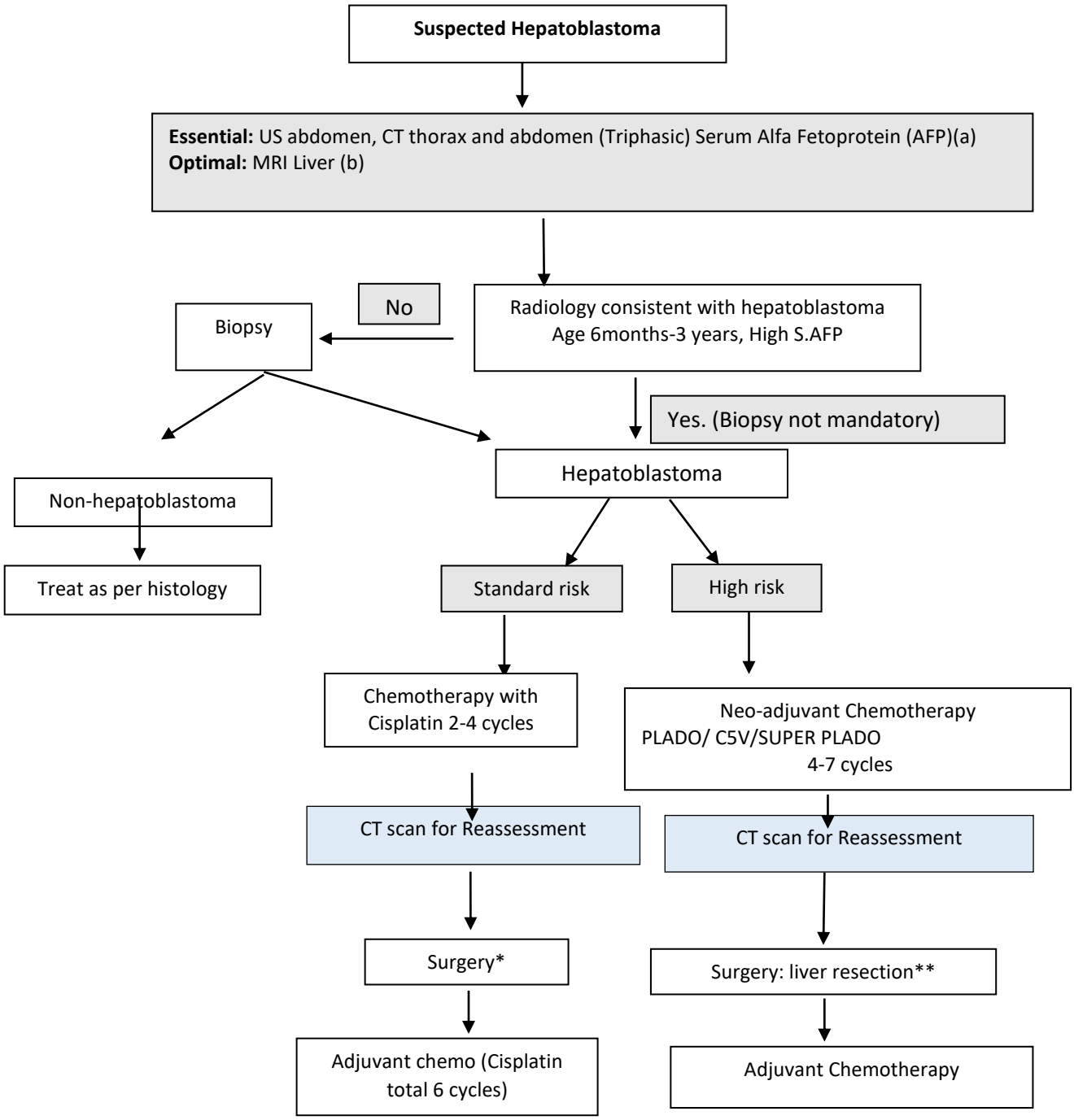
Risk Stratification

International Neuroblastoma Risk Grouping Staging System (INRGSS)	
Stage	**Description**
L1	Localized tumor not involving vital structures as defined by the list of Image defined Risk Factors (IDRFs) and confined to one body compartment.
L2	Loco regional tumor with presence of one or more image defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 547 days and metastases confined to skin, liver and/or bone marrow (< 10% of total nucleated cells on smears or biopsy)

International Neuroblastoma Risk Grouping	
Very low Risk	Infant (<18 months) asymptomatic, no high-risk molecular features, Ganglioneuroma any age
Low Risk	Infant (<18 months) NB L2 or stage II/III (non-metastatic)
Intermediate Risk	Stage M infant (<18 months) NB, Stage II/III, L2 non-infantile NB, infant (<18 months) NB L2 or stage II/III with 11q aberration
High Risk	Any NMYC amplified tumour, Metastatic Stage M(non-infant), infant NB MS with 11q aberration

HEPATOBLASTOMA

Treatment Algorithm: Hepatoblastoma



*Upfront surgical resection may be feasible in selected cases of Standard Risk hepatoblastoma
**Orthotopic liver transplant indicated in selected cases of high risk hepatoblastoma requiring extensive resection(multifocal/ pretext IV)

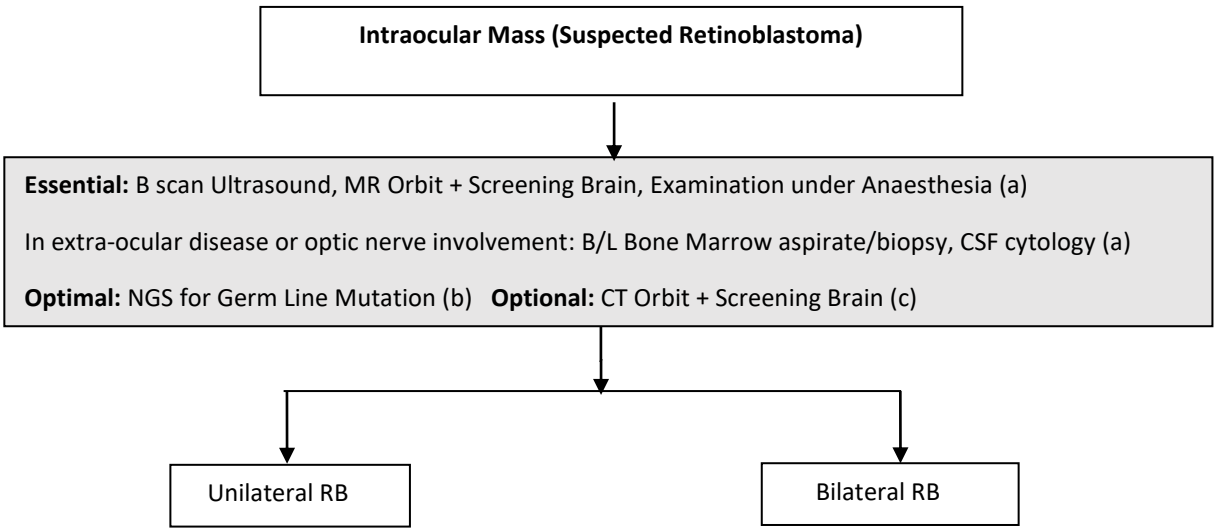
- PLADO: Cisplatin + Doxorubicin, (Total 6 cycles)
- C5V – Cisplatin + 5-fluorouracil+ Vincristine (Total 6 cycles)
- SUPERPLADO : Alternating cycles of Carboplatin/Doxorubicin and Cisplatin (total 10 cycles)

Risk Stratification

High risk: Patients with any of the following	**Standard risk**
Serum alpha-fetoprotein <100 µg/l	All other patients
PRETEXT IV	
Small cell undifferentiated subtype	
Additional PRETEXT criteria:	
Extrahepatic intra-abdominal disease (E).	
Distant metastases (M),	
Nodal metastases (N1, N2)	
Tumor extension into the main and/or both branches of the portal vein (P2, P2a)	
Tumor extension into the vena cava or all three hepatic veins (V3, V3a)	
Intraperitoneal Haemorrhage (H1)	

RETINOBLASTOMA

Treatment Algorithm: Retinoblastoma



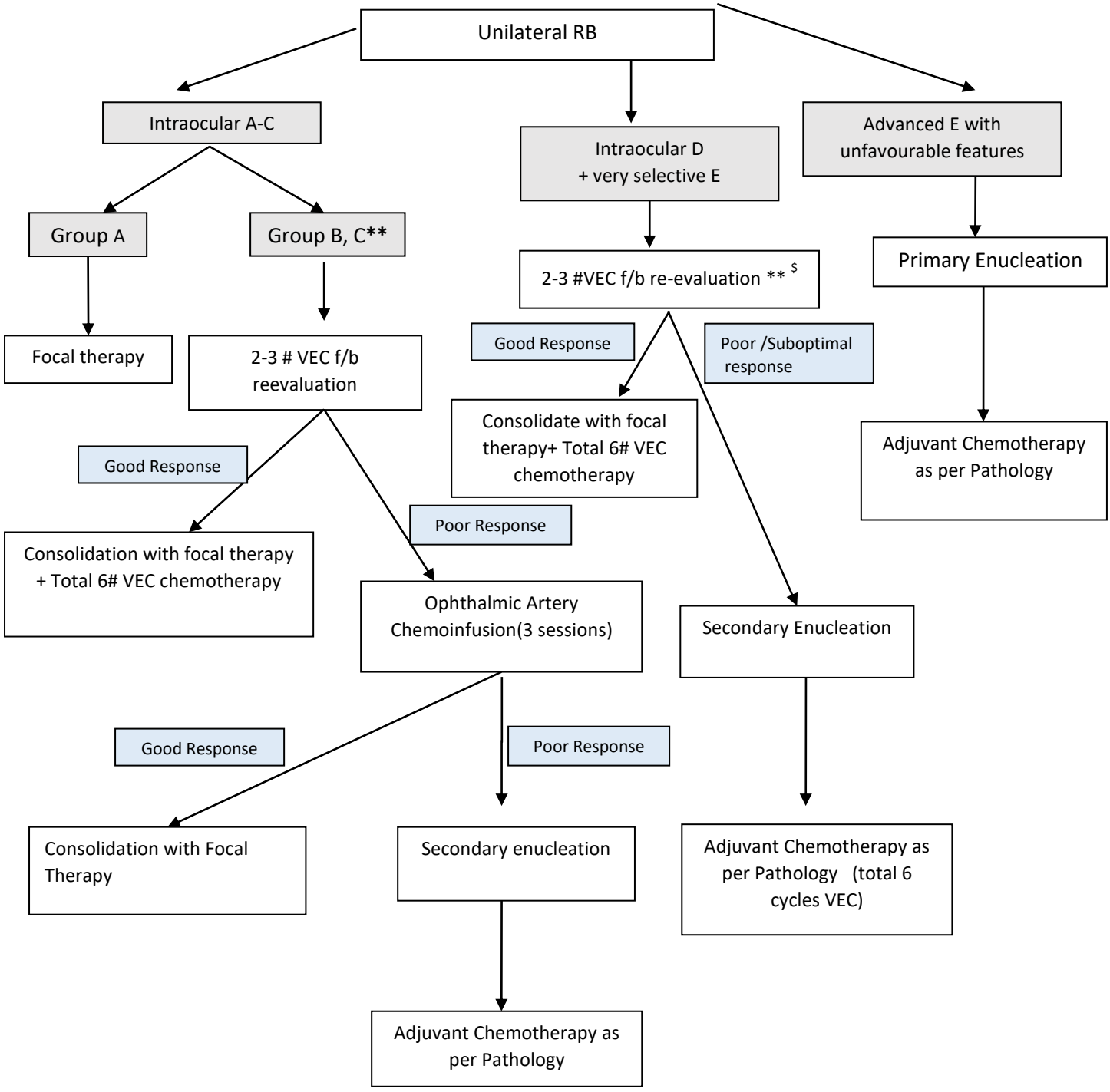
Grouping for Intraocular Retinoblastoma

Group A	Small tumors away from foveola and disc • Tumors < 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 tumors confined to the retina • all other tumors confined to retina and not in Group A • Subretinal fluid (without subretinal seeding) <3 mm from the base of the tumor.
Group C	Local vitreous or subretinal seeding • Subretinal fluid alone > 3mm and < 6 mm from the tumor • Vitreous or subretinal seeding < 3mm from the tumor
Group D	Diffuse vitreous or subretinal seeding • Subretinal fluid alone > 6 mm from the tumor • Vitreous or subretinal seeding > 3mm from the tumor
Group E	Presence of any one or more of these poor prognosis features • More than 2/3 of the globe filled with tumor • Tumor in anterior segment or anterior to vitreous • Tumor in ciliary body • Iris neovascularisation • Neovascular glaucoma • Opaque media from hemorrhage • Tumor necrosis with aseptic orbital cellulitis • Phthisis bulbi

Genetic counseling needs to be done in all families, with genetic testing indicated in cases of suspected heritable disease

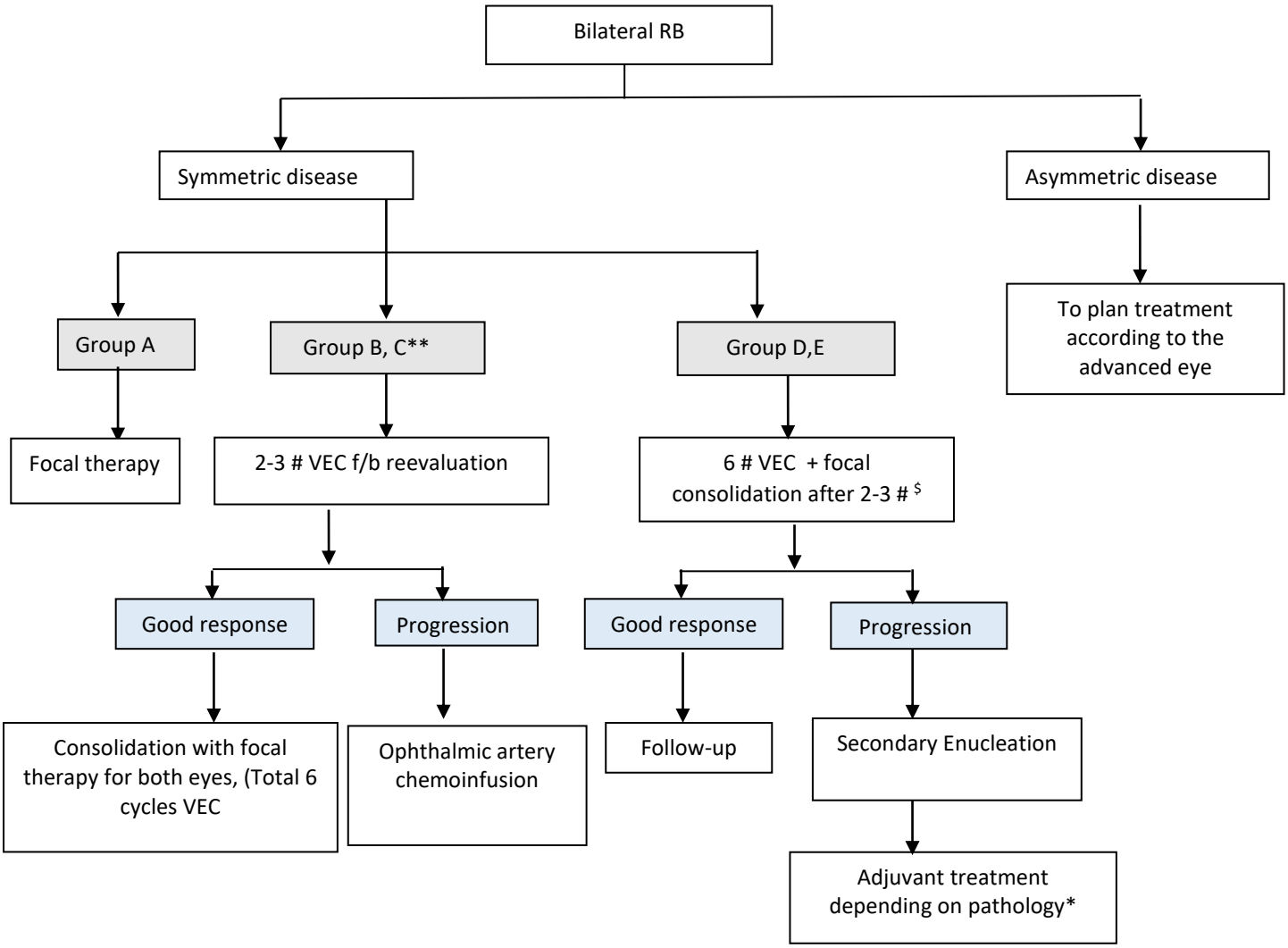
Screening of all siblings less than 7 years of age should be done

Treatment Algorithm: Retinoblastoma- Unilateral



- **Extraocular disease:** 12 cycles of chemotherapy(VEC), Secondary Enucleation (after 2-4 cycles) and EBRT
- **Response assessment**
  -Intraocular disease : by Examination Under Anaesthesia (EUA) and periodic B-ultrasound (a)
  -Extraocular disease : Additionally, requires MRI (a)

Treatment Algorithm: Retinoblastoma- Bilateral



- **Extraocular disease:** 12 cycles of chemotherapy(VEC), Secondary Enucleation (after 2-4 cycles) and EBRT
- **Response assessment**
  -Intraocular disease : by Examination Under Anaesthesia (EUA) and periodic B-ultrasound (a)
  -Extraocular disease : Additionally, requires MRI (a)

Unfavorable features in group E disease: Phthisis bulbi, Intraocular haemorrhage, neovascular glaucoma, anterior chamber involvement

Focal therapies

-Laser photocoagulation
-TranspupillaryThermo Therapy
-Cryotherapy
-Plaque RT

** To consider **ophthalmic artery chemoinfusion/ intra-arterial chemotherapy** case to case basis and where expertise available

$ To consider **intravitreal chemotherapy** in group D/E

Chemotherapy details

Chemotherapy :VEC (Vincristine, etoposide, Carboplatin)

-6 cycles for Intraocular disease

-12 cycles for extraocular/stage 3 disease (plus EBRT)

Other chemotherapy Options:

-High dose carboplatin

-Vincristine/doxorubicin/cyclophosphamide (refractory group E tumours/ stage 3 disease)

Stage 4 Bone Marrow disease:

-Chemotherapy including high dose chemotherapy with Autologous BMT /Stem Cell Transplant

Stage 4 Central nervous system disease.

-Treatment intent to be decided on a case-to case basis by MDT. To consider palliation

***Indications for Adjuvant Chemotherapy:**

-Massive choroidal infiltration

-Post-laminar optic nerve involvement (PLONI)

-Scleral or Extra-scleral spread (on radiology or HPR)

-Cut-margin of Optic Nerve positive for tumor,

-Optic Nerve involvement upto the apex at presentation on MRI

***Indications for Adjuvant Radiotherapy:**

-Extra-scleral spread

-Cut-margin of Optic Nerve positive for tumor on histology

-Extra-ocular mass at presentation

-Optic Nerve involvement upto the apex at presentation on MRI

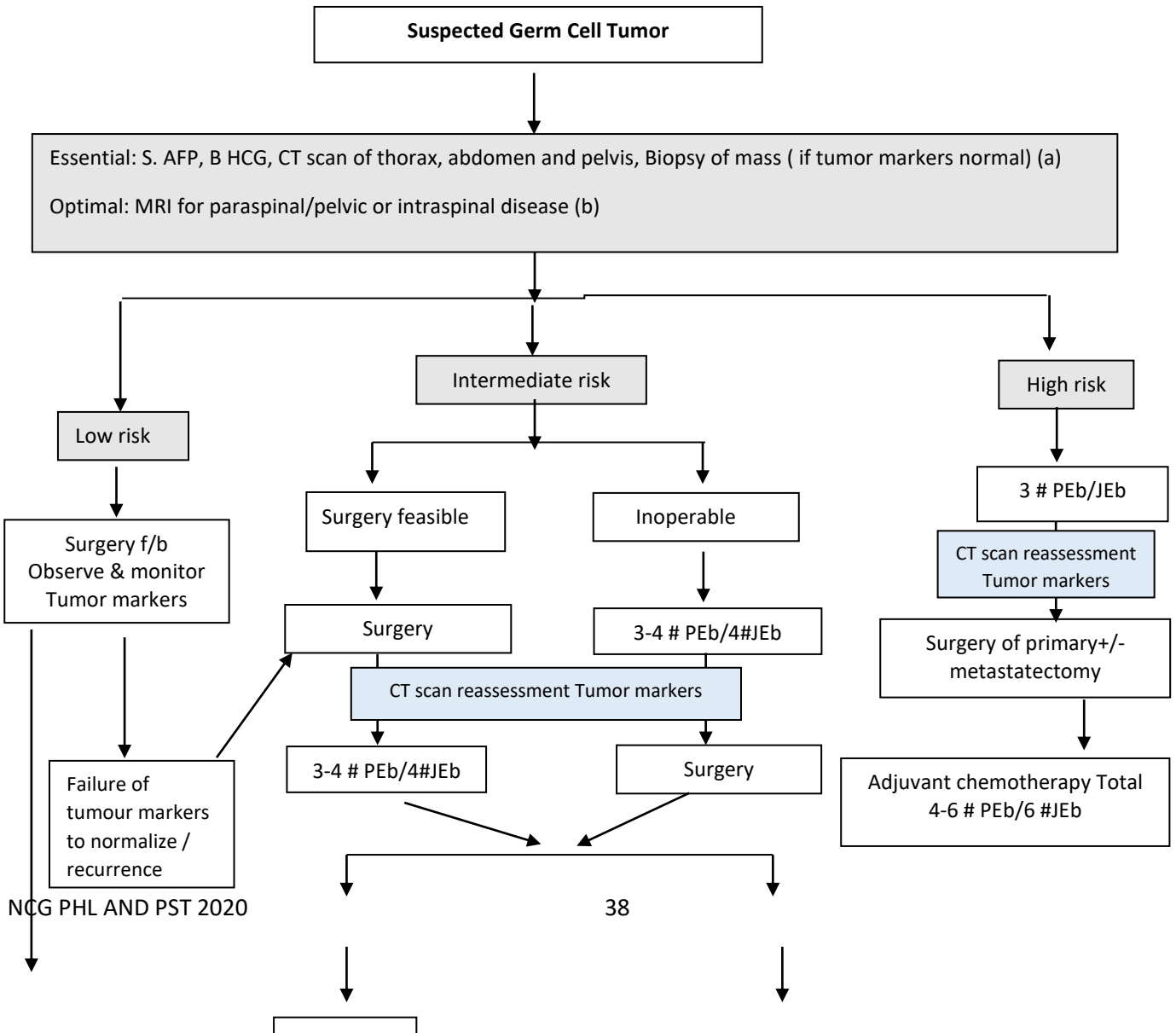
Radiotherapy doses:

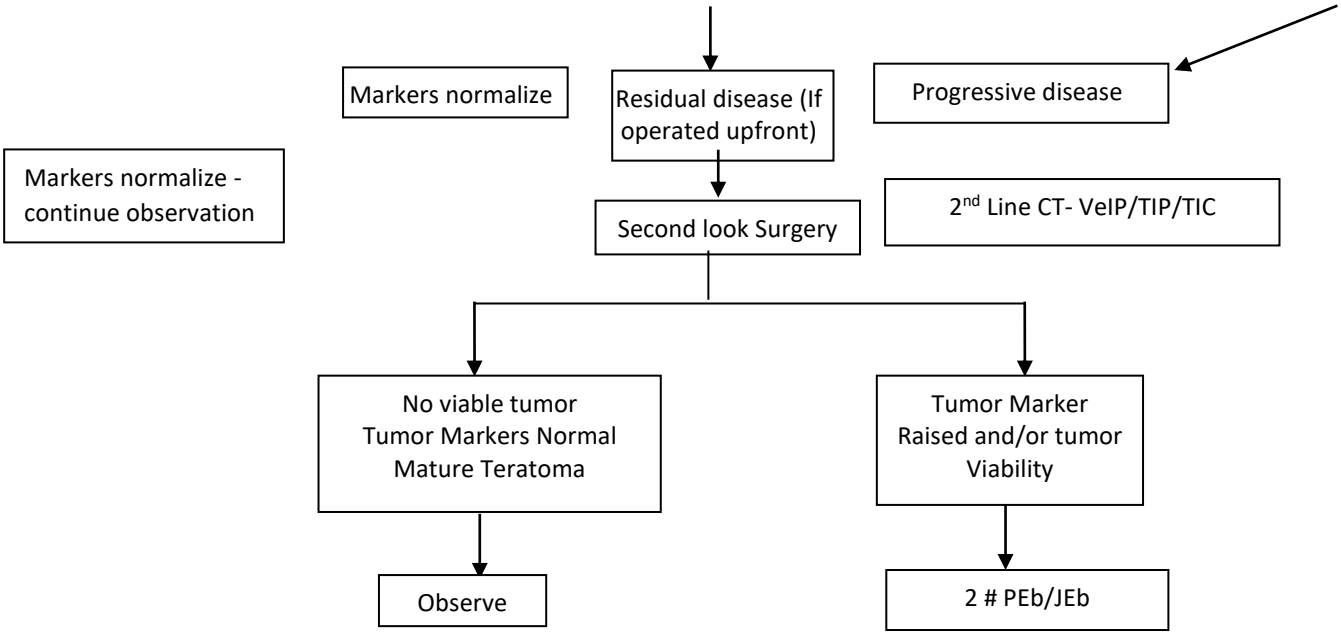
-Definitive RT 45Gy/25#s over 5 weeks with conformal portals

-Adjuvant RT 39.6Gy/22#s over 5 weeks with conformal portals

EXTRACRANIAL GERM CELL TUMOUR

Treatment Algorithm: Extra Renal Germ Cell Tumor





Chemotherapy:

PEb: Cisplatin d1-d5, Etoposide d1-d5, Bleomycin d1 (3-4 cycles in Intermediate Risk and 4-6 cycles in High Risk)

JEb: Carboplatin d1, Etoposide d1-d3, Bleomycin d1 (4 cycles in Intermediate Risk and 6 cycles in High Risk)

VeIP: Vinblastine d1, Ifosfamide d1-d5, Cisplatin d1-d5 (6 cycles)

TIP: Paclitaxel d1,Ifosfamide d2-d5, Cisplatin d2-d5 (4-6 cycles)

TIC: Paclitaxel d1, Ifosfamide d2-d5, Carboplatin d1 (4-6 cycles)

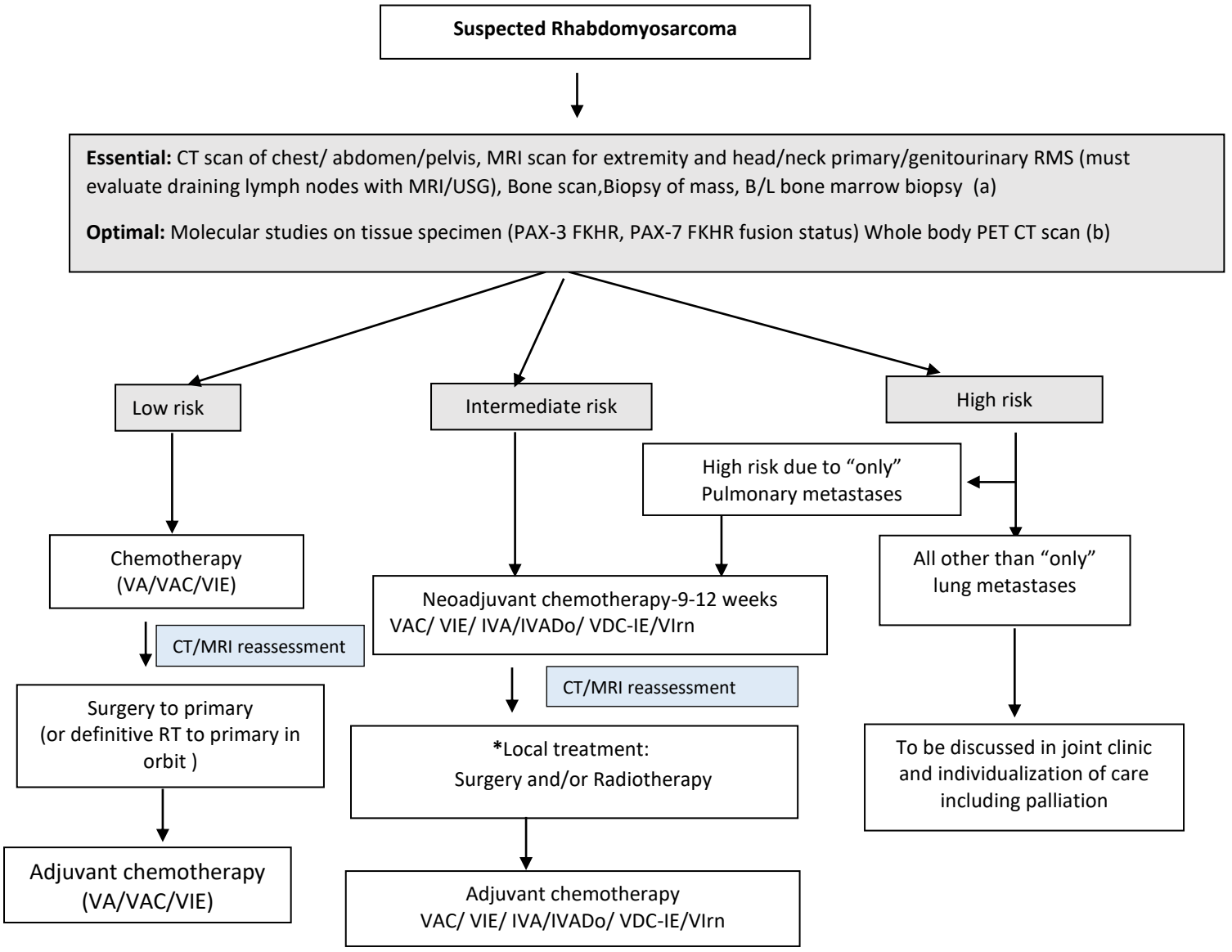
Risk stratification

Low risk:	Stage I testes Stage I ovary All immature teratoma (completely excised)
Intermediate risk:	Stage II- IV testes Stage II-III ovary Stage I-II Extragonadal Immature teratoma (incompletely excised)
High risk:	Stage IV ovary Stage III-IV Extragonadal

Tumour markers (Serum Alfa-fetoprotein, AFP and Serum Beta HCG) to be done at diagnosis. If raised, monitoring of disease status may be done by measurement of tumor markers after each cycle of chemotherapy, surgery and at end of treatment. Post treatment surveillance to be done using tumor markers.

RHABDOMYOSARCOMA

Treatment Algorithm: Neuroblastoma



Chemotherapy Options:

- **VA**: Vincristine, Dactinomycin (for low risk only)
- **VAC:** Vincristine, Dactinomycin, Cyclophosphamide
- **VIE**: Vincristine, Ifosfamide, Etoposide
- **IVA**: Ifosfamide, Vincristine, Dactinomycin
- **IVADo**: Ifosfamide, Vincristine, Dactinomycin, Doxorubicin
- **VDC-IE :**Vincristine, Doxorubicin, Cyclophosphamide/Ifosfamide, Etoposide
- **VIrn :**Vincristine/Irinotecan

***Local Therapy options**:Complete surgical excision only (upfront surgery)

Complete Surgical excision followed by Radiotherapy(or brachytherapy)

Definitive Radiotherapy (inoperable)

(Indications and doses for adjuvant radiation are given below)

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
3.	Group III		
	All	Pre - Chemotherapy primary site	50.4Gy (45 Gy for orbital tumors in complete remission)
	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	

Staging based on the TNM and site of disease:

Stage	**Sites of Primary Tumor**	**T Stage**	**Tumor Size**	**Regional Lymph Nodes**	**Distant Metastasis**
I	Favorable sites	T1 or T2	Any size	N0 or N1 or NX	M0
II	Unfavorable sites	T1 or T2	a- 5 cm	N0 or NX	M0
III	Unfavorable sites	T1 or T2	a- 5 cm	N1	M0
			b- > 5 cm	N0 or N1 or NX	
IV	Any site	T1 or T2	Any size	N0 or N1 or NX	M1
M0 = absence of metastatic spread; M1 = presence of metastatic spread beyond the primary site; N0 =					

absence of nodal spread; N1 = presence of nodal spread beyond the primary site; X = unknown N status.

Grouping based on the surgico-pathological resection

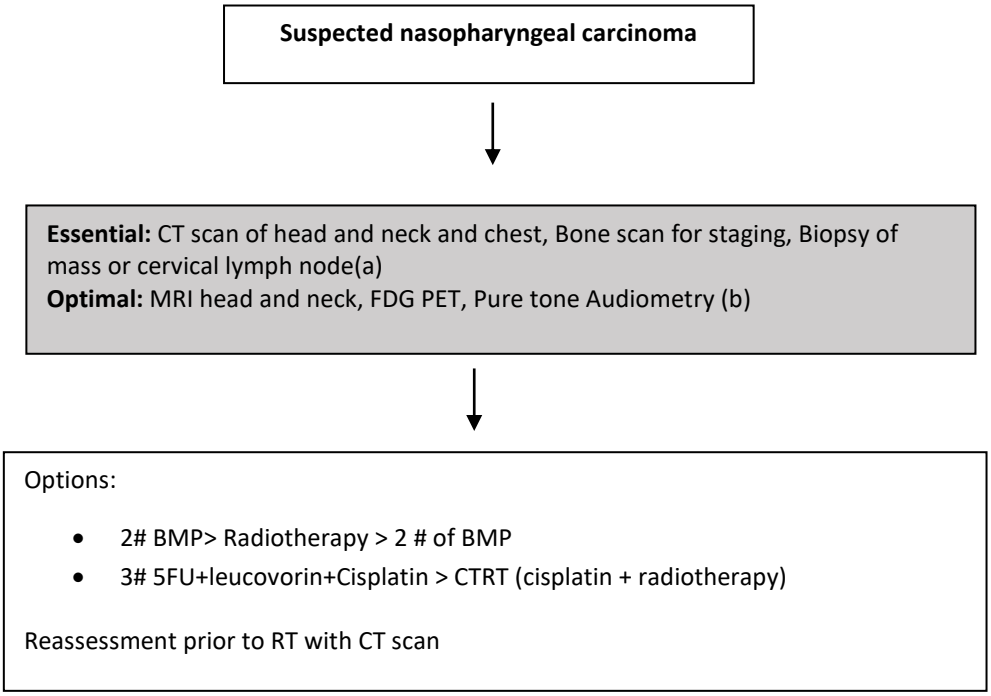
Group	Definition
I	A localized tumor that is completely removed with pathologically clear margins and no regional lymph node involvement.
II	A localized tumor that is grossly removed with (a) microscopic disease at the margin, (b) involved, grossly removed regional lymph nodes, or (c) both (a) and (b).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

Risk stratification of RMS

Risk Group	Histology	Stage	Group
Low risk	Embryonal / (Fusion negative)	1	I, II, III
	Embryonal / (Fusion negative)	2, 3	I, II
Intermediate risk	Embryonal / (Fusion negative)	2, 3	III
	Alveolar / (Fusion positive)	1, 2, 3	I, II, III
High risk	Embryonal or Alveolar (Fusion negative/positive)	4	IV

NASOPHARYNGEAL CARCINOMA

Treatment Algorithm: Nasopharyngeal Carcinoma



Chemotherapy:

BMP: Bleomycin, Methotrexate, Cisplatin

5FU+CDDP: 5 Fluorouracil+/- Leucovorin, cisplatin

Radiotherapy :

Dose: 55-70 Gy given in fractions of 1.6-2.1 Gy in 33 fractions over 7 weeks

Intensity modulated radiotherapy with/without image guidance

ANNEXURE -1

DIAGNOSTIC INVESTIGATIONS FOR COMMON PAEDIATRIC SOLID TUMOURS

Tumor	Local/staging Essential (a)	Local Staging Optimal (b)/Optional (c)
All Paediatric Solid tumours	USG abdomen to be part of basic diagnostic workup	
Neuroblastoma	CT scan of primary tumor site MIBG scan/Whole body FDG-PET scan Biopsy of mass n-Myc status by FISH B/L Bone marrow biopsy	Urinary VMA Segmental chromosomal anomalies MRI (paraspinaltumours) (b) Bone Scan (c)
Wilms Tumor	CT scan thorax, abdomen and pelvis	USG doppler MRI for Bilateral WT and nephroblastomatosis (b)
Hepatoblastoma	CT thorax and abdomen (Triphasic) Serum Alfa Fetoprotein (AFP)	MRI Liver (b)
Rhabdomyosarcoma	CT scan of chest/ abdomen/pelvis MRI scan for extremity and head/neck primary/genitourinary RMS Bone scan Biopsy of mass B/L Bone marrow biopsy	Molecular studies on tissue specimen (PAX-3 FKHR, PAX-7 FKHR fusion status) Whole body PET CT scan (b)
Germ Cell Tumor	S. AFP, B HCG CT scan of thorax, abdomen and pelvis Biopsy of mass (if tumor markers normal)	MRI for paraspinal/pelvic or intraspinal disease (b) Whole body PET CT scan (c)
Retinoblastoma	B scan Ultrasound MR Orbit + Screening Brain Examination under Anaesthesia In extra-ocular disease or optic nerve involvement: B/L Bone Marrow biopsy, CSF cytology	NGS for Germ Line Mutation (b) CT Orbit + Screening Brain (c)
Nasopharyngeal Carcinoma	CT scan of head and neck and chest Bone scan for staging Biopsy of mass or cervical lymph node	MRI head and neck, FDG PET Pure tone Audiometry (b)