SMALL ROUND BLUE CELL TUMOUR

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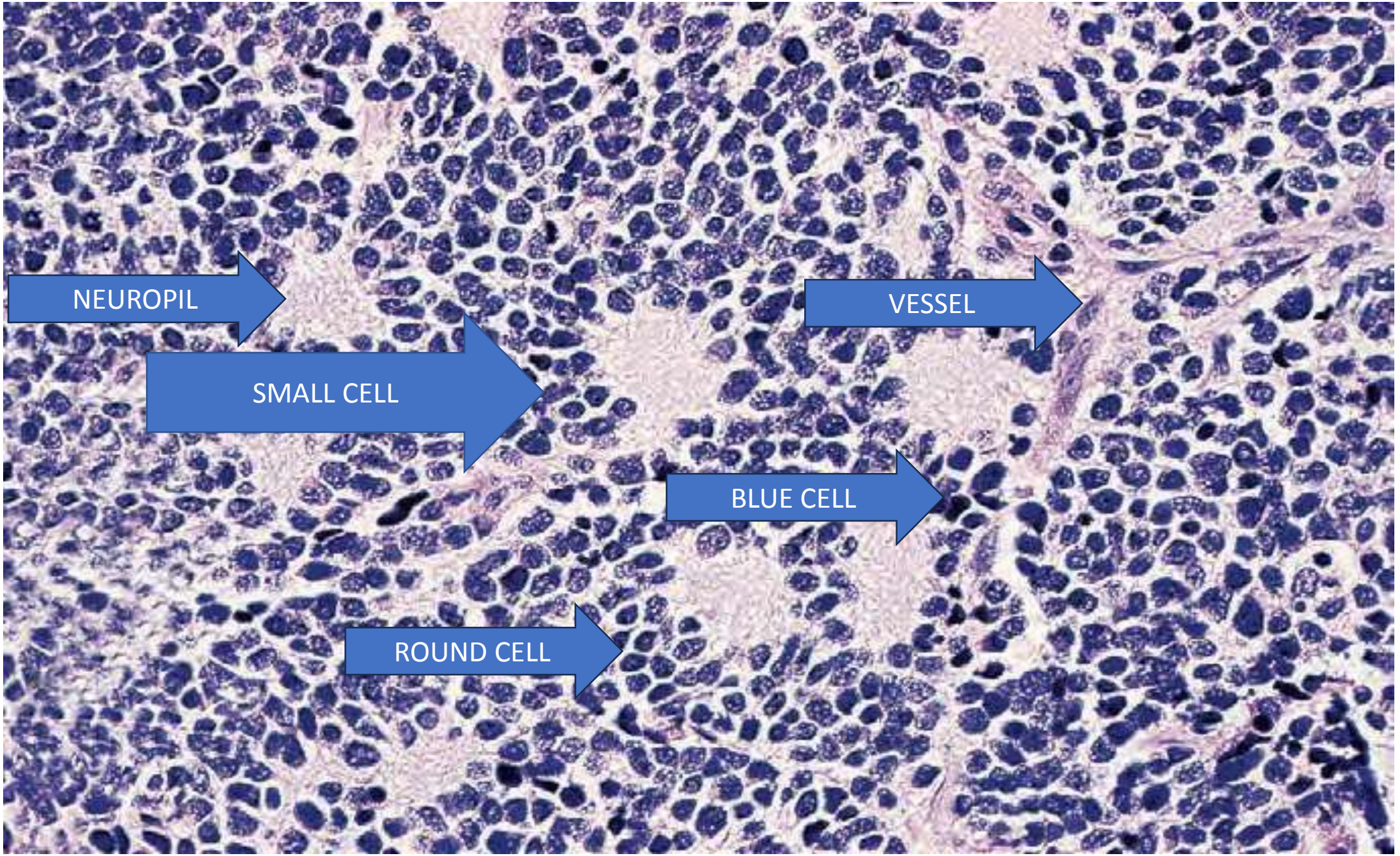
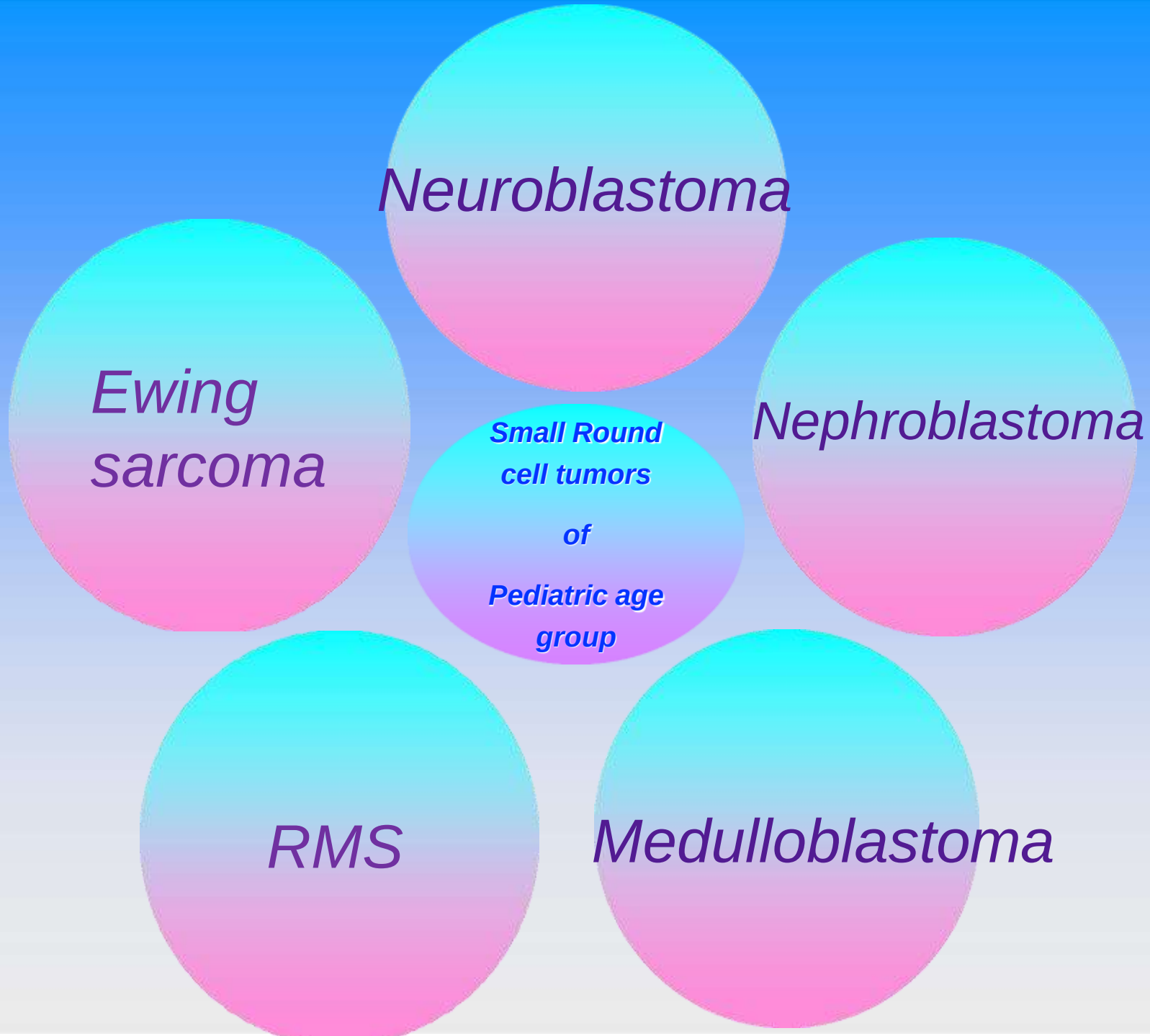
RGCIRC DELHI

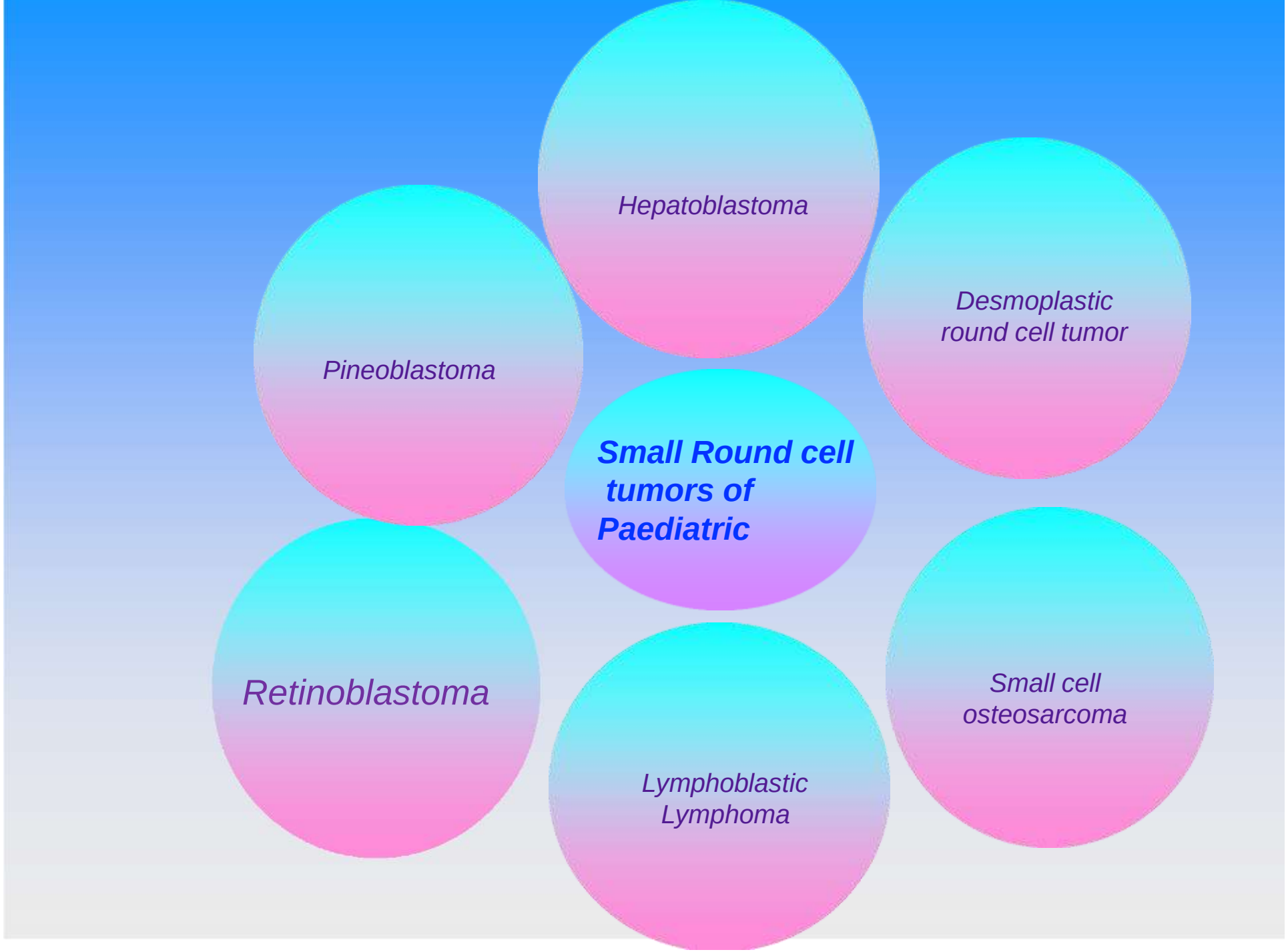
ROUND CELL NEOPLASM

Heterogeneous group of neoplasms are characterised by the sheets of poorly differentiated cells:

- Small (similar to lymphocyte in size)/air dried RBC
- Round (round nuclei and scanty cytoplasm)
- Blue (blue staining due to high nuclear/cytoplasmic ratios


NEUROPIL
SMALL CELL
VESSEL
BLUE CELL
ROUND CELL


Neuroblastoma
Ewing sarcoma
Small Round cell tumors of Pediatric age group
Nephroblastoma
RMS
Medulloblastoma


Hepatoblastoma
Pineoblastoma
Desmoplastic round cell tumor
Small Round cell tumors of Paediatric
Retinoblastoma
Lymphoblastic Lymphoma
Small cell osteosarcoma

I

I. **Neurogenic origin**:

Ewing's sarcoma
Neuroblastoma,
Retinoblastoma,
Medulloblastoma,
Merkel cell tumor,
Paragangliomas,
Small cell tumor of lung

II. **Mesenchymal origin**

- 1. Myogenic differentiation
  - a. ERMS
  - b. ARMS.

. 2. Osteoid differentiation

Small cell osteosarcoma.

- 3. Chondroid differentiation

Mesenchymal chondrosarcoma.

- 4. Adipose tissue like differentiation

Myxoid/round cell liposarcoma.

. 5.Wilms Tumour

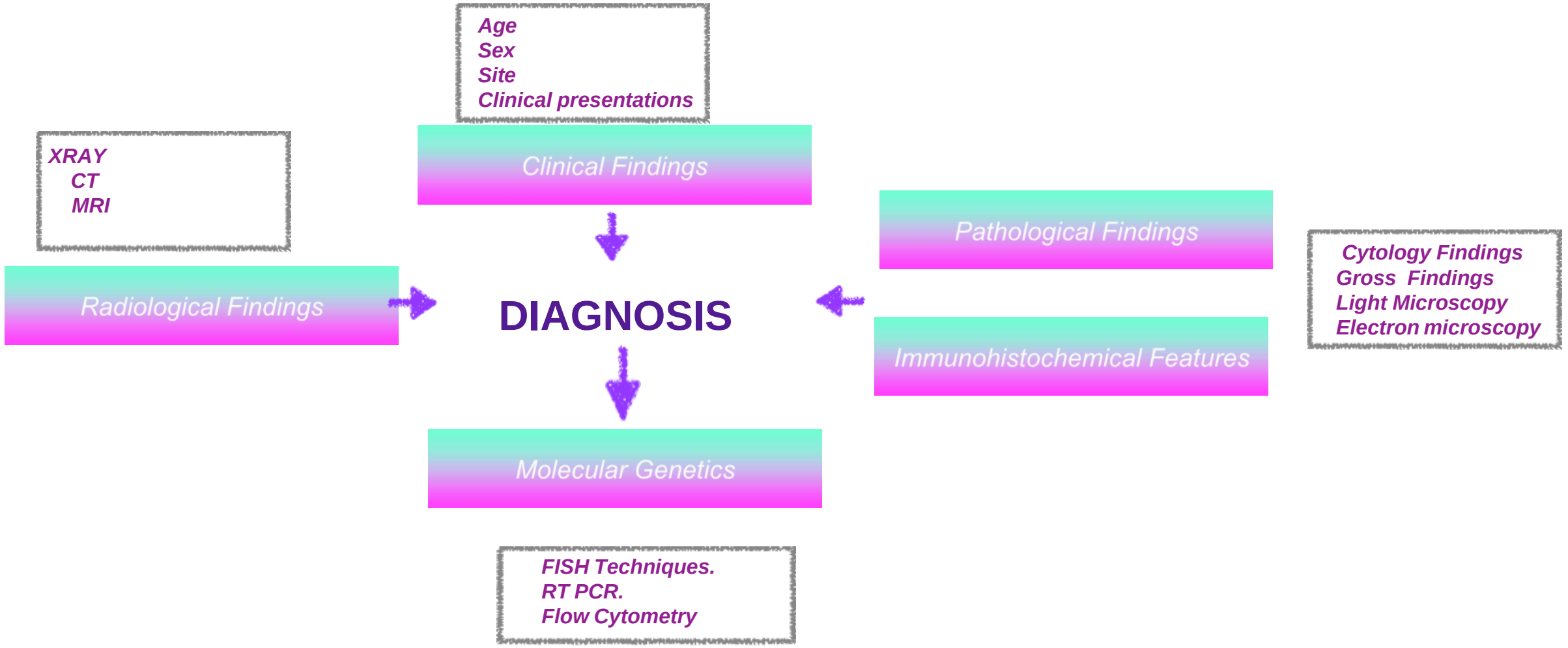
III Hematolymphoid origin

- Lymphoma/“reticulum cell sarcoma.”

IV Malignant soft tissue tumors of uncertain type

- a. Desmoplastic small round cell tumor (DSRCT)
- b. Poorly differentiated synovial sarcoma

Diagnostic Approach

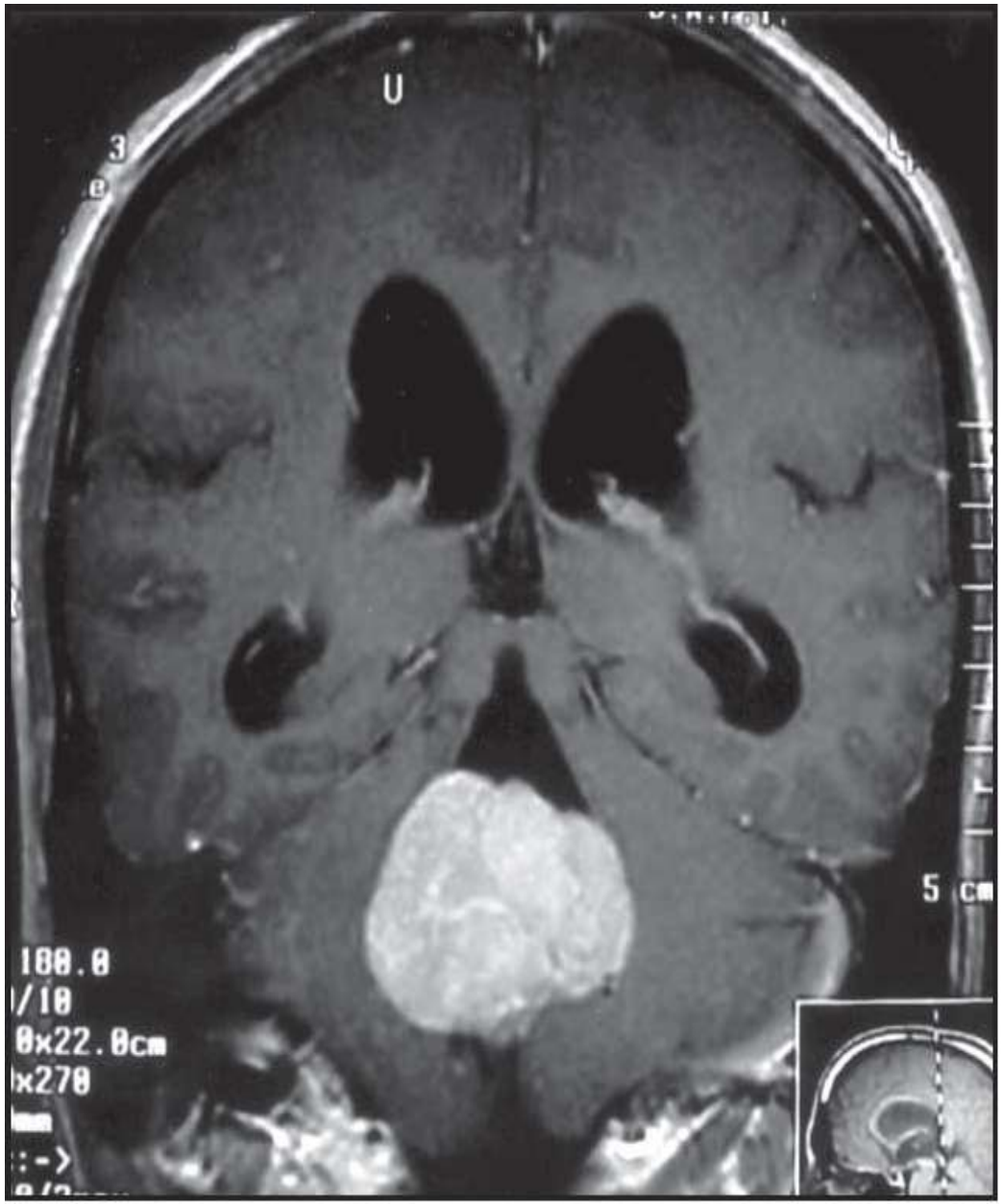


CNS SRBCT

MEDULLOBLASTOMA

- *Age: 5-10 yr*
- *Sex:M>F*
- *Site: Commonly arise from Cerebellar vermis.*
- *Presentations:*
  - *Truncal ataxia*
  - *Disturbed gait*
  - *Lethargy*
  - *Headache*
- *Morning emesis*

- *Mostly sporadic.*
- *Heritable cases are associated with:*
  - *Type 2 Turcot syndrome*
  - *Nevoid basal cell carcinoma – or ‘Gorlin’ – syndrome*
  - *Li–Fraumeni syndrome*
  - *Rubinstein–Taybi syndrome*
  - *Coffin–Siris syndrome*



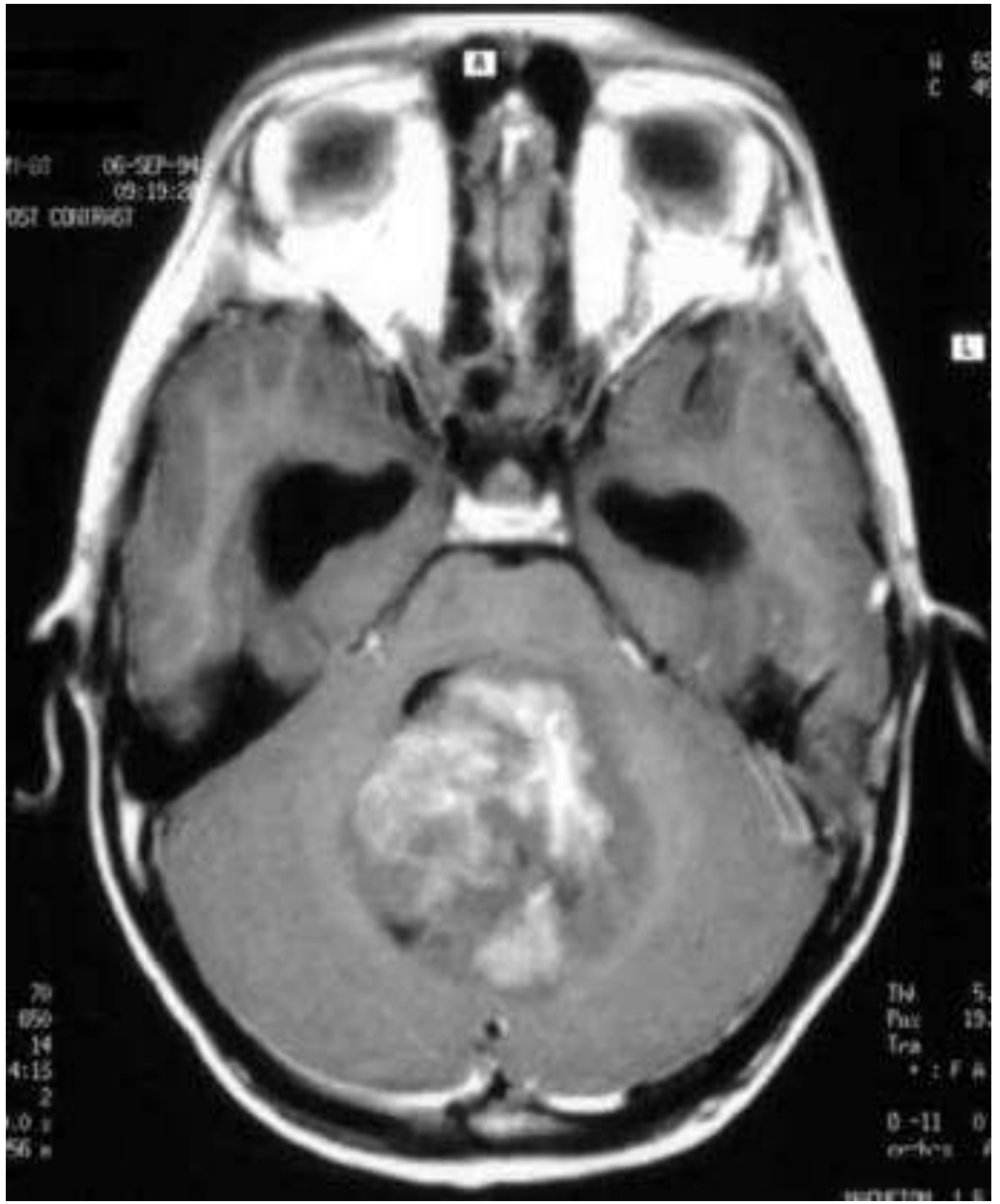


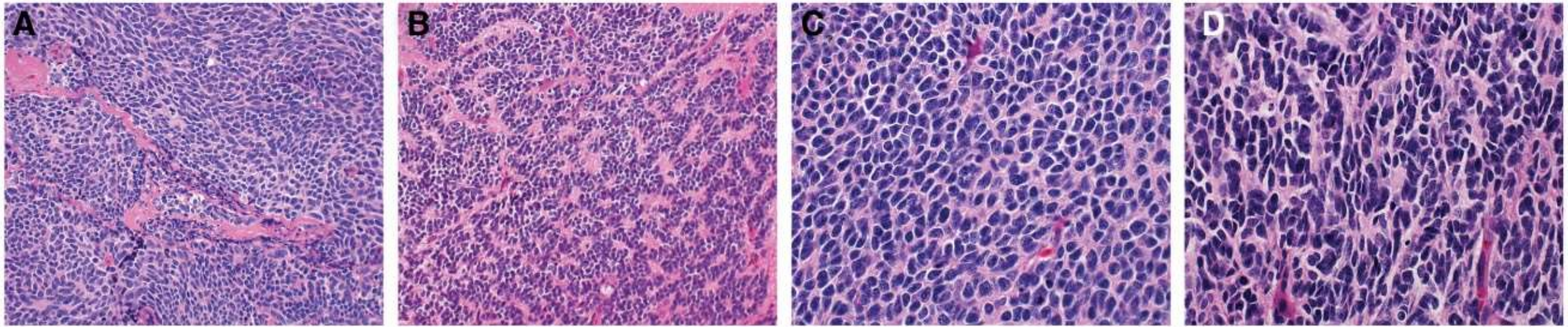
Fig 4. Coronal T1 weighted MRI after contrast injection revealing

Medulloblastoma is classified by an integrative diagnosis including a histologically as well as genetically defined compound.

Medulloblastoma, histologically defined
Medulloblastoma, classic
Medulloblastoma, desmoplastic/nodular
Medulloblastoma with extensive nodularity
Medulloblastoma, large cell/anaplastic
Medulloblastoma, genetically defined
Medulloblastoma, WNT-activated
Medulloblastoma, SHH-activated, TP53 mutated
Medulloblastoma, SHH-activated, TP53 wild-type
Medulloblastoma, non-WNT/non-SHH
Medulloblastoma, group 3
Medulloblastoma, group 4

- *The histological patterns have their own specific clinical associations. In turn, molecularly defined medulloblastomas demonstrate specific associations with certain histological patterns*
- *The four principal molecular groups of medulloblastoma are associated with clinicopathological and genetic features that provide clinical utility: diagnostic/prognostic/therapeutic implications*
- *The current molecular classification reflects biological heterogeneity that can be demonstrated by the clustering of medulloblastomas into groups using transcriptome or DNA methylation profiling.*

- Classic medulloblastoma — good prognosis
- Desmoplastic/nodular medulloblastoma — Intermediate prognosis
- Medulloblastoma with extensive nodularity — Intermediate prognosis
- Large cell/Anaplastic medulloblastoma — poor prognosis

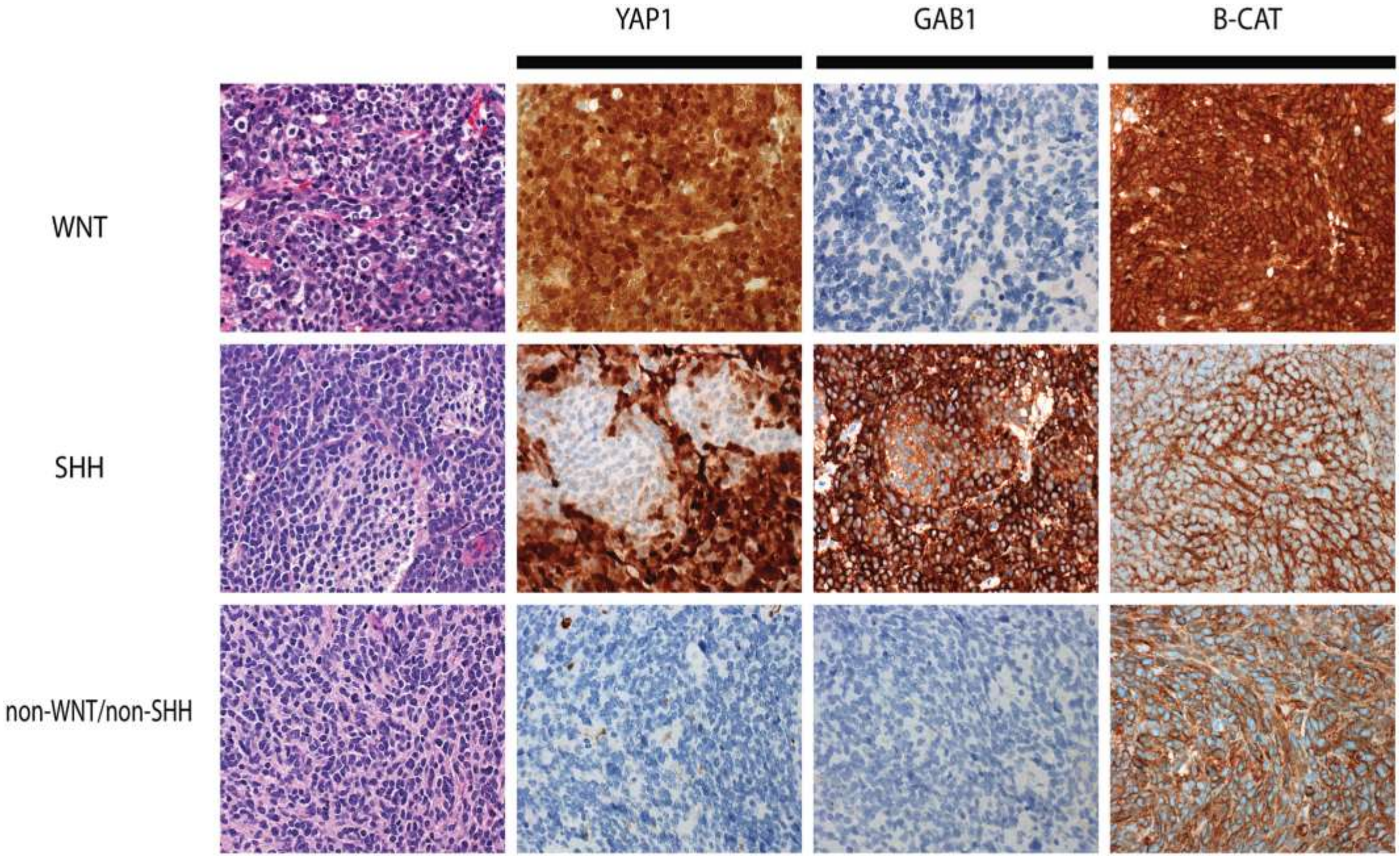


- Sheets of small cells with round to ovoid nuclei
- Frequent Homer Wright rosettes
- No significant cytologic pleomorphism or cell molding
- No desmoplasia

Medulloblastomas, molecularly defined

- 4 principal molecular subgroups
  1. Wnt
  2. Shh
  3. Group 3
  4. Group 4

  } non-WNT/non-SHH
- The Wnt (Wingless) & Shh (Sonic Hedgehog) were named for the signaling pathways involved in the pathogenesis of that subgroup
- Since less is known about the biology of the remaining two subgroups, the consensus was to retain generic names for the present until the underlying biology driving these subgroups was better delineated
- There is evidence for the existence of subtypes within the subgroups


YAP1
GAB1
B-CAT
WNT
SHH
non-WNT/non-SHH

Management-Surgical technique

- Complete surgical resection is ideal
- Not always be safe or feasible
- Tumor which are large so that it extends beyond the limits of the floor of the fourth ventricle into the cisterna magna-in or extending into brain stem in such cases, tumor decompression should be done

Management-Post-operative Molecular risk Stratification

Risk category	WNT	SHH	Group 3	Group 4	Others
Low Risk (expected survival >90%)	<16 years				
Standard Risk (expected survival 75-90%)		TP53 wild type No MYC amplification Non-metastatic	All of the following No MYC amplification Non-metastatic	All of the following Non-metastatic Chr 11 loss	
High Risk (expected survival 50-75%)		One or both MYC amplification Metastatic		All of the following Non-metastatic No Chr 11 loss	
Very High Risk (expected survival <50%)		TP53 mutation (metastatic or non-metastatic)	Metastatic	Metastatic	
Unknown	Metastatic		Non-metastatic with MYC amplification; anaplasia; isochromosome 17q	Anaplasia	Melanotic medulloblastoma Medullomyoblastoma Indeterminate between groups 3/4

Molecular Subgroups of Medulloblastoma

CONSENSUS	WNT	SHH	Group 3	Group 4
Cho (2010)	C6	C3	C1/C5	C2/C4
Northcott (2010)	WNT	SHH	Group C	Group D
Kool (2008)	A	B	E	C/D
Thompson (2006)	B	C', D	E, A	A, C

DEMOGRAPHICS

Age Group: infant, child, adult

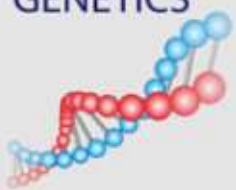
Gender:

	WNT	SHH	Group 3	Group 4
Age Group				
Gender	♂♂:♀♀	♂♂:♀♀	♂♂:♀	♂♂:♀

CLINICAL FEATURES

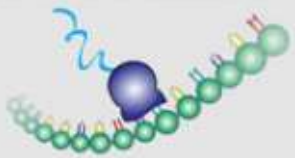
	WNT	SHH	Group 3	Group 4
Histology	classic, rarely LCA	desmoplastic/nodular, classic, LCA	classic, LCA	classic, LCA
Metastasis	rarely M+	uncommonly M+	very frequently M+	frequently M+
Prognosis	very good	infants good, others intermediate	poor	intermediate

GENETICS



	WNT	SHH	Group 3	Group 4
	6-	3q+, 9q-, 10q-	7+, 1q+, 17q+, 18q+, 11p-, 8-, 5q-, 10q-, 16q-	7+, 17q+, 18q+, 11p-, X-, 8-
	CTNNB1 mutation	*PTCH1/SMO/SUFU* mutation *GLI2* amplification *MYCN* amplification	i17q *MYC* amplification	i17q *CDK6* amplification *MYCN* amplification

GENE EXPRESSION



	WNT	SHH	Group 3	Group 4
	WNT signaling	SHH signaling	Photoreceptor/GABAergic	Neuronal/Glutamatergic
	MYC +	*MYCN* +	*MYC* +++	minimal *MYC* / *MYCN*

DIFFERENTIAL DIAGNOSIS

1. Atypical Teratoid/Rhabdoid Tumor

- Common in posterior fossa; mimics medulloblastoma
- Generally more nuclear pleomorphism and more cytoplasm, but occasionally small cell morphology
- IHC: EMA, GFAP, CK, Synaptophysin (+)
- Loss of nuclear immunostaining for INI1

2. Embryonal Tumor With Multilayered True Rosettes (ETMR)

- Formerly, embryonal tumor with abundant neuropil and true rosettes (ETANTR)
- Defined by presence of genetic features
- Any CNS embryonal tumor with C19MC amplification or fusion given ETMR designation, including those without rosettes
- Prominent neuropil, not in discrete islands as in D/N medulloblastoma
- True (lumen-containing) rosettes

3. Anaplastic Glioma and Glioblastoma

- May be radiation-induced 2nd primary
- Microvascular proliferation and necrosis with pseudopalisading more common
- IHC: GFAP, Olig2 (+)

4. Ependymoma

- Generally sharper tumor-cerebellum interface, Less involvement of subarachnoid space
- More prominent perivascular pseudorosettes
- True (lumen-containing) rosettes, in some cases
- Microvascular proliferation more common
- IHC: GFAP, EMA(+), Synaptophysin usually (-), but can be focally (+)

Management-Radiation therapy

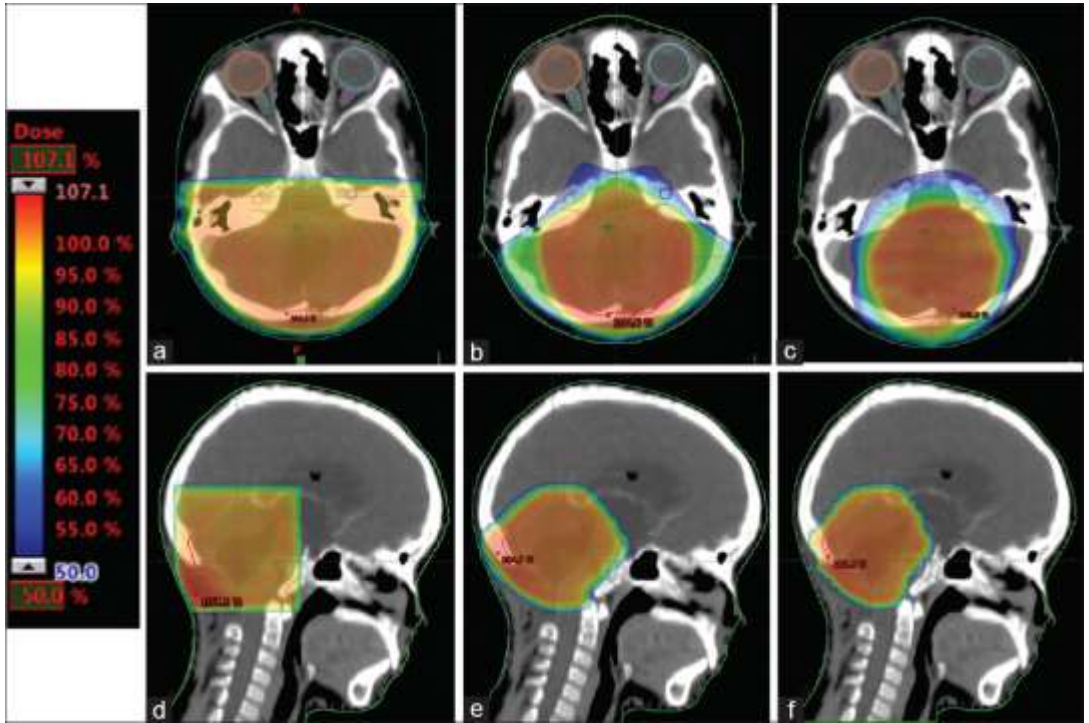
- Adjuvant radiation therapy (RT) remains an integral component and cornerstone of therapy in the curative-intent treatment
- Leptomeningeal dissemination, treatment of the entire neuraxis, i.e. craniospinal irradiation (CSI) --→ boost irradiation(tumor bed/posterior fossa)

Management-Radiotherapy prescription

Risk Stratification	CSI	Posterior Fossa Boost	Chemotherapy
Standard Risk(Dose Reduces)	23.4Gy/13# @1.8Gy/1#	30.6Gy/17# @1.8Gy/1#	Present
High Risk	35-36Gy/20-21# @1.8Gy/1#	18-19.8Gy/10-11# @1.8Gy/1#	Nil
Standard Risk	35-36Gy/20-21# @1.8Gy/1#	18-19.8Gy/10-11# @1.8Gy/1#	Unavailable
Accurate staging not done	35-36Gy/20-21# @1.8Gy/1#	18-19.8Gy/10-11# @1.8Gy/1#	Nil
Diffuse leptomeningeal dissemination	35-36Gy/20-21# @1.8Gy/1# With 5.4-9Gy/3-5# boost	18-19.8Gy/10-11# @1.8Gy/1# With 5.4-9Gy/3-5# boost	Nil

Management-Boost irradiation planning

Risk-stratification	Boost Irradiation
High Risk And Very High Risk Disease	Entire Posterior Fossa Is Presently Recommended.
Low Risk And Standard Risk	Pre-operative Tumor-bed With Appropriate Margins (Typically 1-1.5cm Around The Tumor Bed)



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Review of the impact of molecular analysis on the therapy of medulloblastoma

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Risk adapted therapy

ABSTRACT

Medulloblastoma (MB) is a brain tumor composed of distinct molecularly defined subgroups. Recent advances in genomics and transcriptomics have revealed >12 subtypes within the previously identified four subgroups. Molecular classification has improved clinical outcome predictions and facilitated introduction of risk-adjusted therapy. Newer subtyping of MB has the potential to rapidly guide the development of clinical trials that further explore risk-adjusted therapies. This review summarizes recent advances in the molecular characterization of medulloblastoma and evaluates subgroup directed treatment.

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Molecular Analysis: Clinical Impact

- The molecular classification of MB has evolved to include subtypes beyond the original four consensus subgroups of WNT, SHH, Group 3, and Group 4 MB.
- Molecular subgrouping has shown improved survival with better risk-adapted strategies.
- The original four subgroups have had a limited impact in identifying novel therapeutic strategies, while identified additional subdivisions (“subtypes”) of MBs are not yet widely used, they have the potential to improve risk stratification in future clinical trials.
- The molecular subgrouping may allow us to better predict patient outcomes, any attempts at therapy reduction should only take place in the context of a clinical trial.
- Efforts are underway to translate new information learned from these subtypes into better risk stratification and identify targeted therapies to improve outcomes

ABDOMINAL SRBCT

NEUROBLASTOMA

WILMS

DSRBCT

RENAL EWING

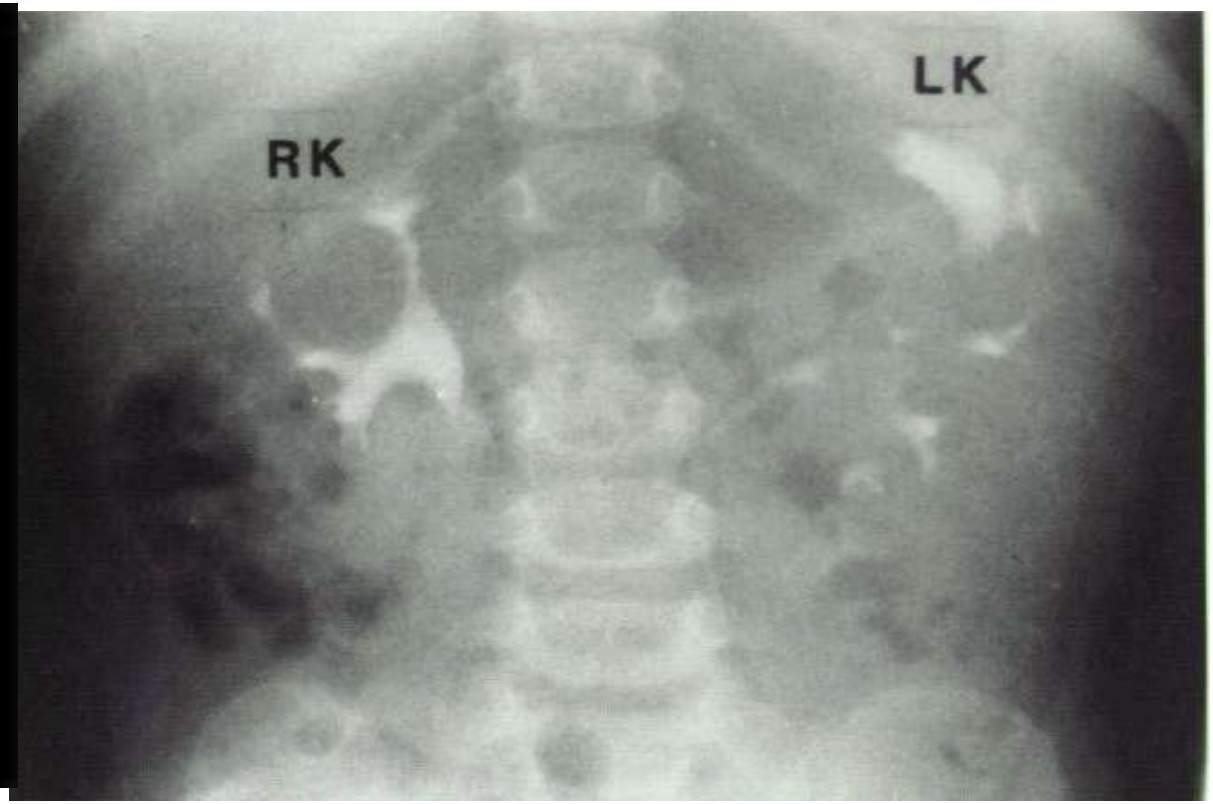
WILMS TUMOUR

- *Age:Infants (primarily), less than 3 years (50%) & less than 6 years (90%)*
- *Sex:M=F*
- *Site: Kidney;*
- ***Presentations:****Large abdominal mass*
  Hematuria
  Pain in abdomen
  Hypertension

Conditions associated with wilms' tumor are

- *WAGR syndrome*
- *Beckwith wiedemann Syndrome*
- *Denys Drash Syndrome*

Radiological Findings
Nephroblastoma

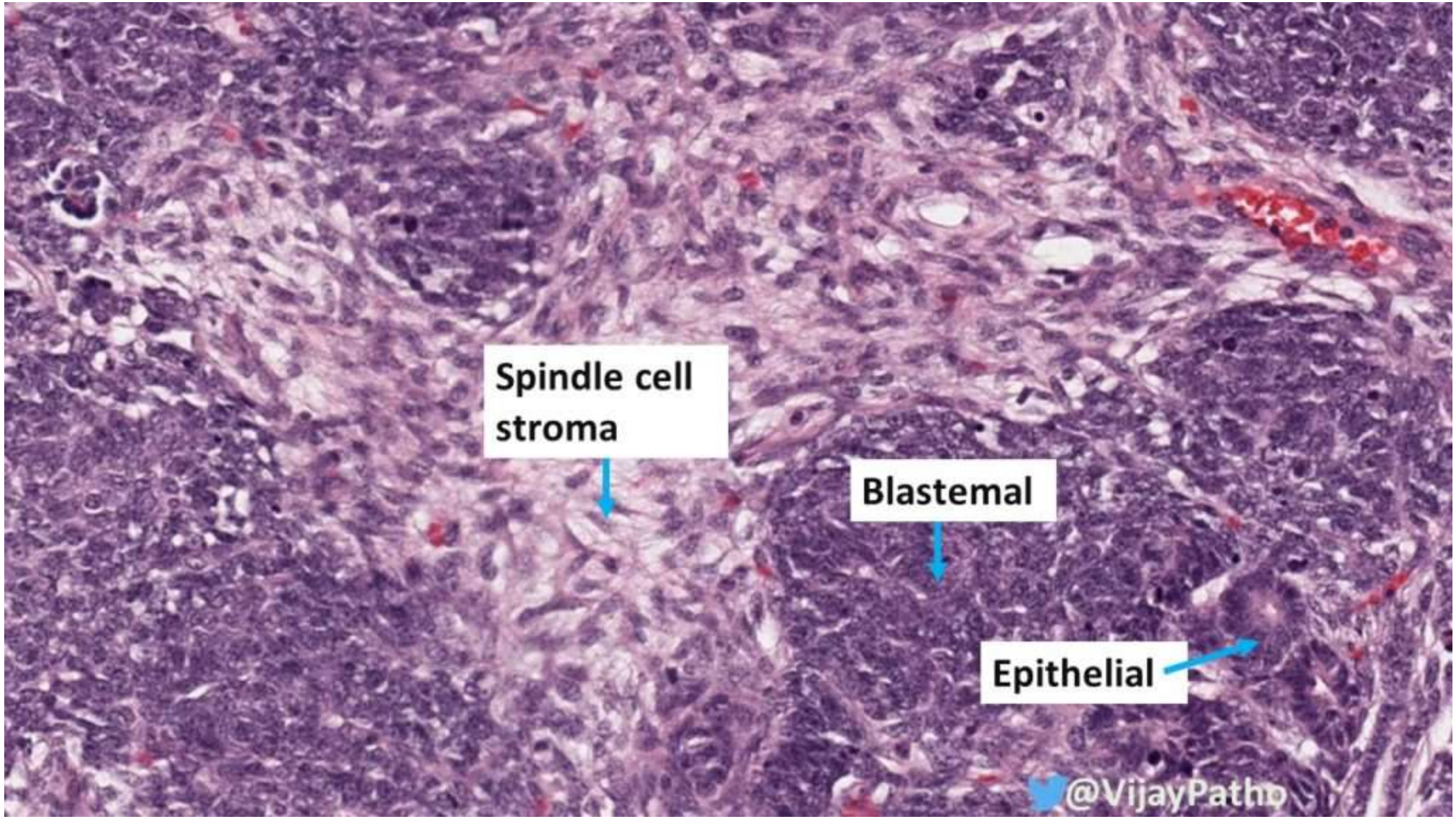


Neuroblastoma

1. Calcifications are common
2. Younger age, less than 2 yrs
3. Poorly marginated
4. Dumbell shaped tumors
5. Bone metastases common
6. Spinal canal extension common
7. RP LN more commonly seen
8. Blueberry muffin sign
9. Not seen

Wilms Tumors

1. Calcifications are uncommon
2. Older age group
3. Well circumscribed
4. Claw sign of kidney
5. Bone mets uncommon, lung common
6. Spinal canal extension uncommon
7. RP LN uncommon
8. Haemorrhage common
9. Extension in IVC/RV seen


Spindle cell stroma
Blastemal
Epithelial
@VijayPatho

IHC

- ***Reactivity for***
- *Vimentin* → ***Blastematous elements***

- *Keratin*
- *Epithelial membrane antigen* → ***Epithelial elements***

- *Myogenin*
- *Desmin* → ***Mesenchymal /Stromal elements***

- *Neuron specific enolase*
- *S-100*
- *Glial fibrillary acid protein* → ***Neural elements***
- *WT-1(90%)*
- *CD56(96%)*
- *Type I insulin-like growth factor*

MOLECULAR GENETICS

- LOH at 16q and 1p have higher relapse and mortality rates.
- Novel WT suppressor gene on the X chromosome, Anaplastic tumors - *TP53* deletion and specific genomic loss or underexpression on 4q and 14q and focal gain of *MYCN.*
- Rhabdoid tumors - genetic loss of the *SMARCB1/hSNF5/INI-1 (*chromosome 22q11.)
- gain of 1q is a promising biomarker for patients with favorable histology WT.
- *Mutations of B catenin gene-14-20%*
- *WT1 (located on chromosome11p 13)- Dennys Drash*
- *WT2 (located on chromosome 11p15.5)- Beckwith Weidman*

COG PROTOCOL

Treatment Outline

- Patients are classically treated with immediate nephrectomy followed by adjuvant Chemotherapy as per the stage and histological features
- Radiation therapy is delivered according to the abdominal stage.
- Radiation therapy and Chemotherapy are classically avoided in very young infants (< 6 months)

Neoadjuvant Chemotherapy

- Indicated is some select situations like:
  - Tumor is deemed inoperable:
    - Tumor thrombus in Rt Atrium / IVC
    - Extensive tumor with anticipated morbidity
    - Invasion of surrounding organs (Liver/ Spleen/ intestines)
  - Disseminated disease (Stage IV)
  - WT occurring in some special situations:
    - Bilateral WT
    - WT in unilateral kidney
    - WT in presence of genetic syndromes
    - WT in horseshoe kidneys

Nephrectomy alone

- Presently indicated in:
  - Age < 2 yrs
  - Favourable Histology
  - Stage I tumors
  - Weight < 550 gms
- Still under protocol study – NWTS 5 found lesser RFS.

Post nephrectomy management

Histology	Stage	Chemotherapy	Radiation therapy
Favourable	I II	Actinomycin D + Vincristine (EE4A)	Not needed
	III – IV	Act-D + VCR+ Dox (DD4A)	Stage adapted radiation therapy
Focal Anaplasia	I II	Actinomycin D + Vincristine (EE4A)	Not needed
	III–IV	Act-D + VCR+ Dox (DD4A)	Stage adapted radiation therapy
Diffuse Anaplasia	I	Actinomycin D + Vincristine (EE4A)	Not needed
	II-IV	Regimen I	Stage adapted radiation therapy
CSSK	I-IV	Regimen I	Stage adapted radiation therapy
Rhabdoid Tumors	I-IV	Regimen RTK	Stage adapted radiation therapy

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

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DOI: 10.1002/pbc.30090
Pediatric Blood & Cancer
aspho The American Society of Pediatric Hematology/Oncology
WILEY

SPECIAL REPORT

Harmonica consensus, controversies, and future directions in radiotherapy for pediatric Wilms tumors

Mary Frances McAleer[1] | Patrick Melchior[2] | Jeannette Parkes[3,4] | Luke Pater[5] | Christian Rübe[2] | Daniel Saunders[6] | Arnold C. Paulino[1] | Geert O. Janssens[7,8] | John Kalapurakal[9]

There are multiple knowledge gaps and opportunities for future research including:

1. Impact of molecular biomarkers including loss of heterozygosity at 1p, 16q, and 1q gain on RT indications

2. Mitigation of reproductive toxicity following RT with modern techniques like IMRT, IGRT, PBT

NEUROBLASTOMA

Age: Under 4 yrs (21 month)

Sex:M=F

Site: Retroperitoneum (70%), and the majority of these involve adrenal gland.

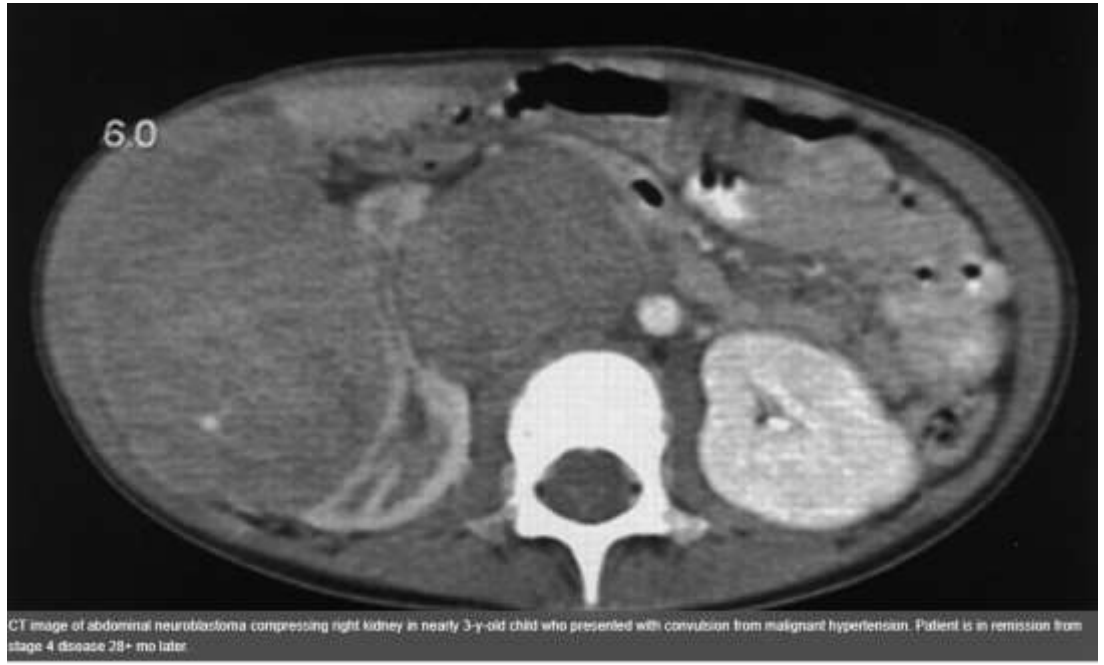
Other sites:

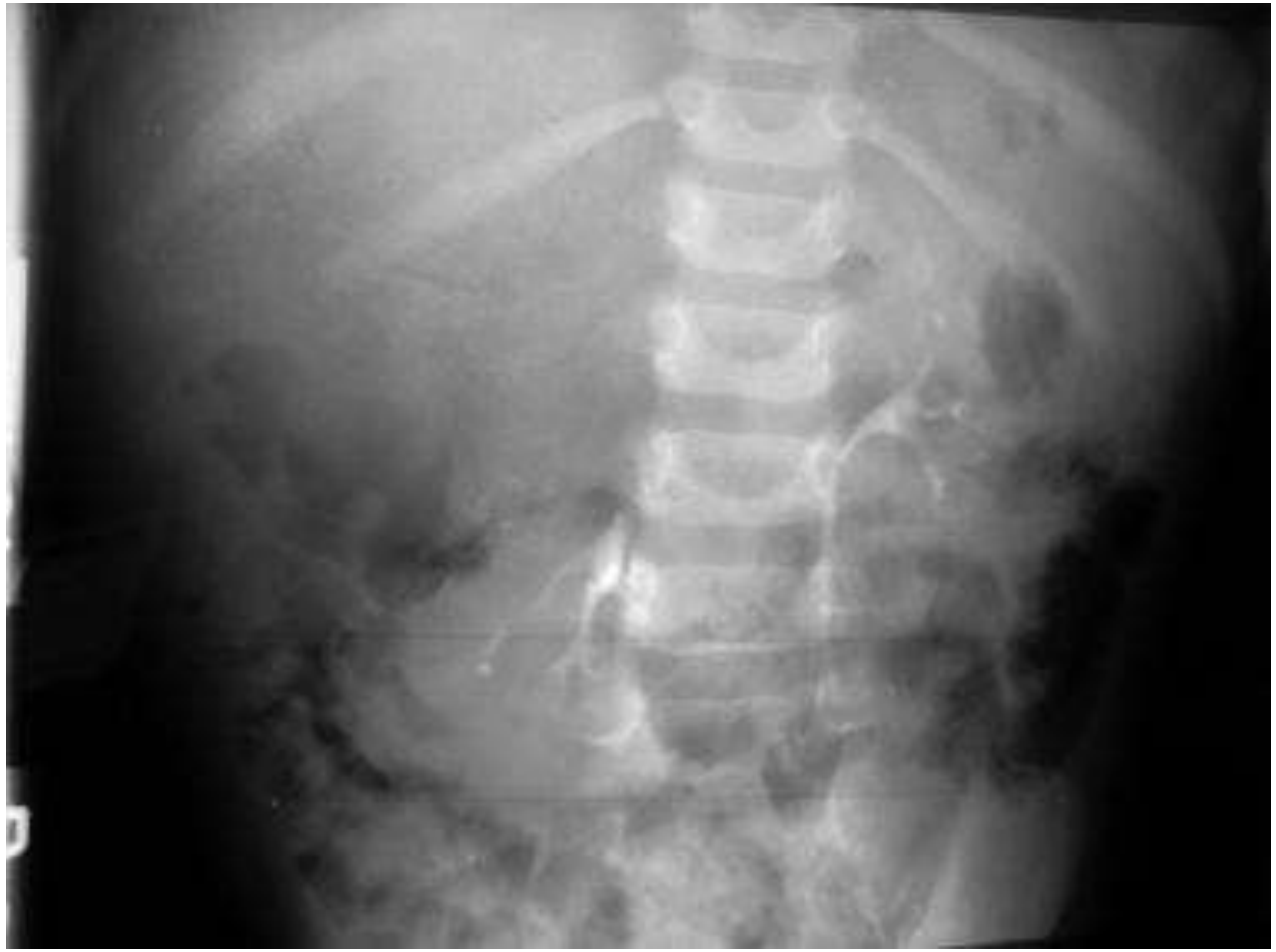
along sympathetic chain, post mediastinum, neck, brain, adrenal medulla (30% to 40%) and paraspinal ganglia in the abdomen or pelvis (25%). Thoracic (15%) and head and neck primary(5%)

Presentations

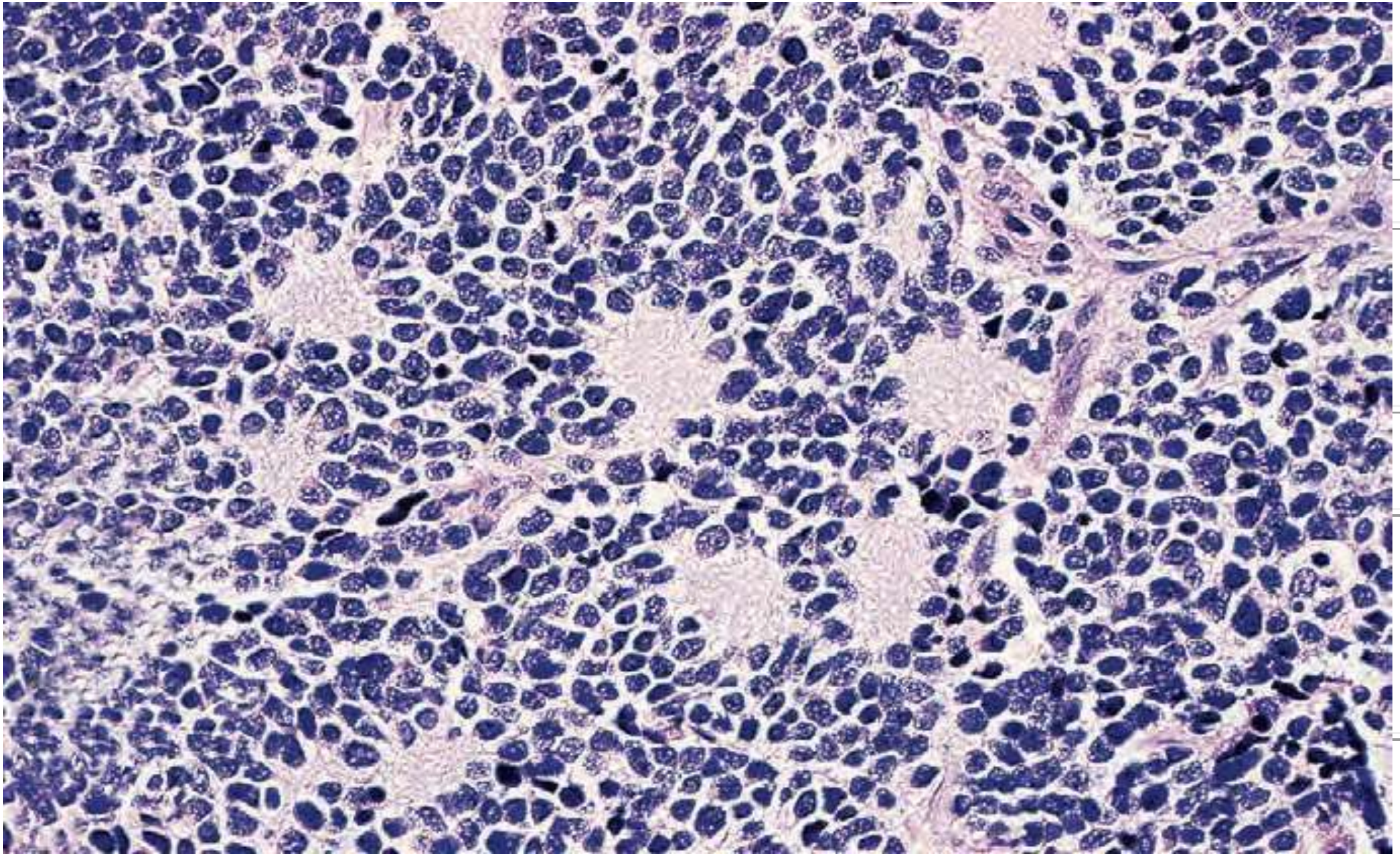
- *An abdominal mass first noted by the parents.*
- *Rarely watery diarrhea,Cushing syndrome,heterochromia iridis and horner syndrome (in cervical or mediastinal tumors) and opsoclonus/myoclonus*

Radiological Findings
Neuroblastoma





An intravenous pyelogram (IVP) shows an inferiorly displaced kidney on the right. Above the right kidney are stippled calcifications. These findings are consistent with those of a neuroblastoma.



IHC

Amplification of the N-myc oncogene detected by FISH technique

Several molecular targets or pathways of NB studied, such as GD2, MYCN, ALK, p53/MDM2, PI3K/Akt/mTOR/, and RAS/MAPK signaling

- Secretogranin II
- Vasoactive intestinal peptide
- Microtubule-associated proteins
- Growth factor receptors, and other neural-related

- Antigen including cell surface ganglioside GD_2.

Current Pharmacology Reports (2023) 9:43–58
https://doi.org/10.1007/s40495-022-00306-8

NANODRUGS (ATY LAU, SECTION EDITOR)

Promising Molecular Targets and Novel Therapeutic Approaches in Neuroblastoma

Xu Yang[1] · Jixia Li[2,3] · Jigang Yang[1]

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- Anti-GD2 monoclonal antibodies have been approved to treat high-risk NB.
- Inhibitors targeting MYCN, ALK, p53/MDM2, RAS/MAPK, and PI3K/Akt/mTOR are being tested in phase I/II clinical trials.
- Most research on molecularly targeted therapy stays at the preclinical level.
- More valuable targets need to be identifed, and more effcient therapies need to be developed.
- Further, exploration of new combinations using inhibitors targeting multiple targets and conventional therapy is still the most important research direction in future, which would advance treatment regimens, improve outcomes, and prolong survival in children with high-risk NB.

original reports

Revised Neuroblastoma Risk Classification System: A Report From the Children's Oncology Group

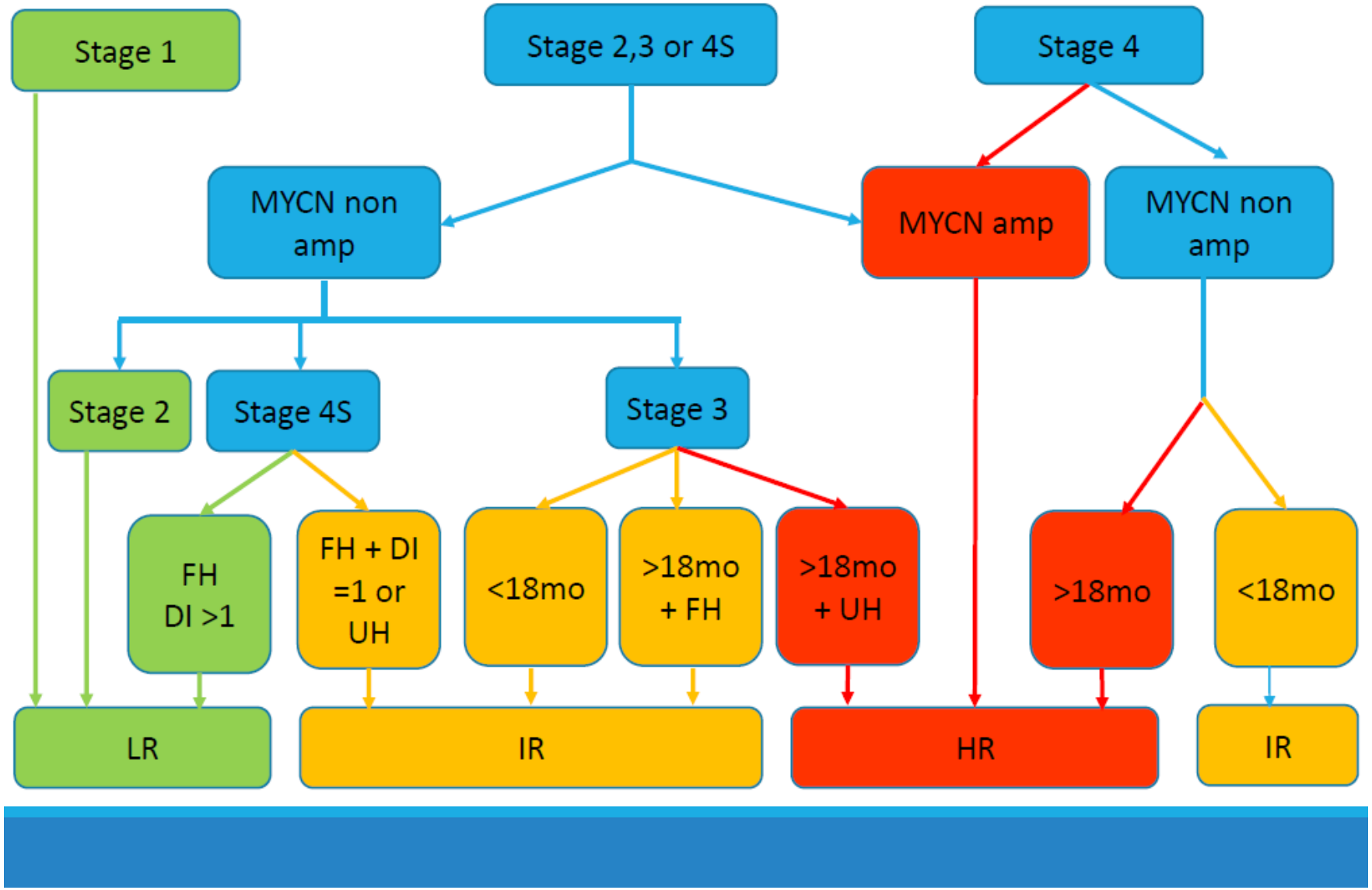
Meredith S. Irwin, MD[1]; Arlene Naranjo, PhD[2]; Fan F. Zhang, MSc[3]; Susan L. Cohn, MD[4]; Wendy B. London, PhD[5]; Julie M. Gastier-Foster, PhD[6,7]; Nilsa C. Ramirez, MD[6,7]; Ruthann Pfau, PhD[6,7]; Shalini Reshmi, PhD[6,7]; Elizabeth Wagner, MSc[6]; Jed Nuchtern, MD[8]; Shahab Asgharzadeh, MD[9]; Hiroyuki Shimada, MD, PhD[10]; John M. Maris, MD[11]; Rochelle Bagatell, MD[11]; Julie R. Park, MD[12]; and Michael D. Hogarty, MD[11]

METHODS Newly diagnosed patients enrolled on the COG neuroblastoma biology study ANBL00B1 between 2007 and 2017 with known age, International Neuroblastoma Staging System, and INRGSS stage were identified (N = 4,832). Tumor *MYCN* status, ploidy, SCA status (1p and 11q), and International Neuroblastoma Pathology Classification histology were determined centrally. Survival analyses were performed for combinations of prognostic factors used in COG risk classification according to the prior version 1, and to validate a revised algorithm (version 2).

CONCLUSION A revised 2021 COG neuroblastoma risk classifier (version 2) that uses the INRGSS and incorporates SCAs has been adopted to prospectively define COG clinical trial eligibility and treatment assignment.

J Clin Oncol 39:3229-3241. © 2021 by American Society of Clinical Oncology

COG Neurobloastoma risk groups



Management : Low & Int. Risk

- **Low risk**
- ◦ Surgery alone for stage 1 or 2 disease
- ◦ Short course chemo for symptomatic cord compression or respiratory compromise
- ◦ Stage 4S – supportive care or short course of chemotherapy
- ◦ Survival - 90-95%
- **Intermediate risk**
- ◦ Primary resection + standard dose multiagent chemotherapy for 4-8 months
- ◦ Survival >80%
- Radiotherapy
- ◦ Life or function threatening situation
- ◦ Unresectable primary disease after chemotherapy
- ◦ Regional recurrences not controlled with chemotherapy

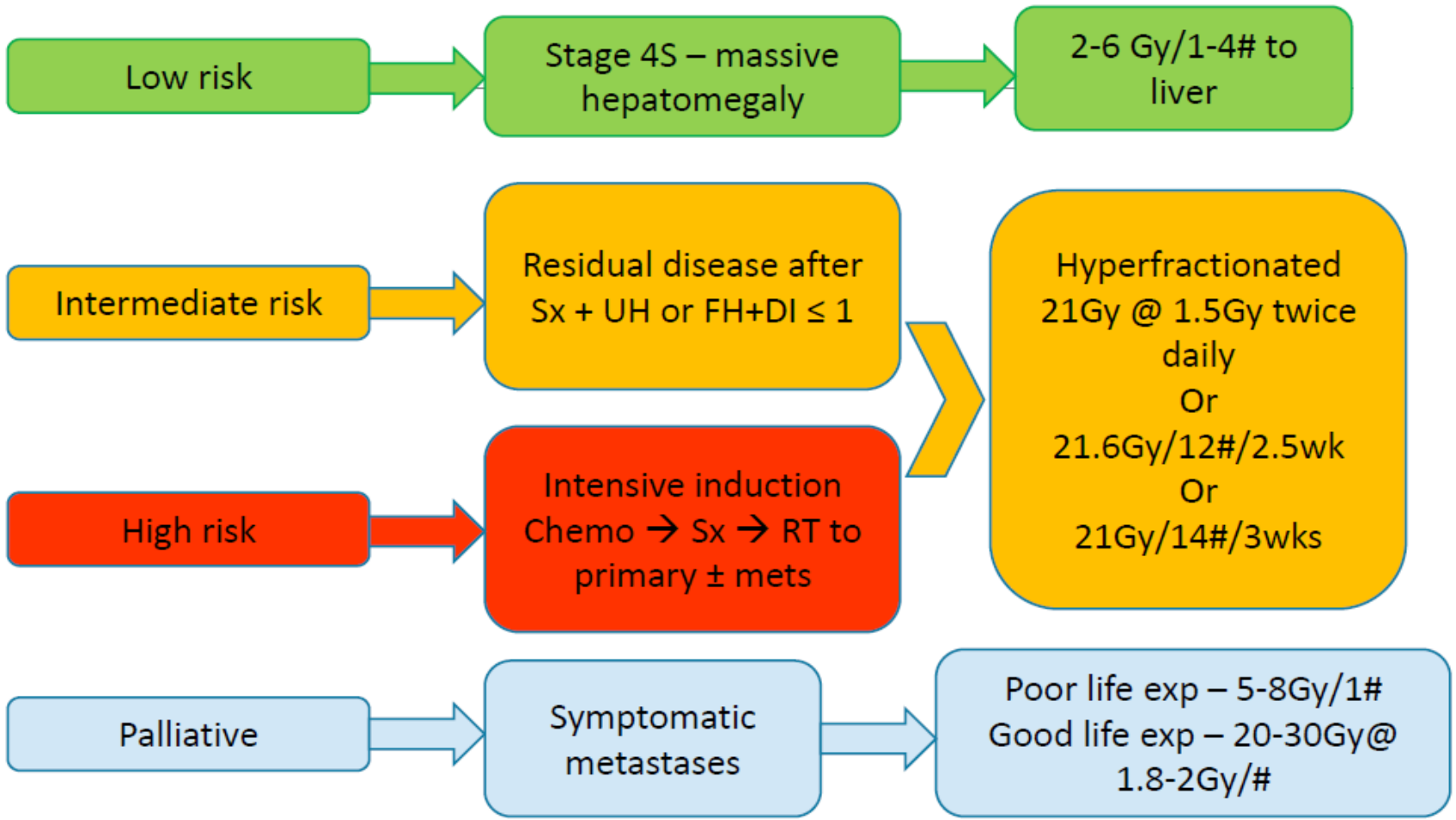
Management: *High Risk*

- Four general components

1. Induction chemotherapy
2. Surgical resection of all gross disease
3. Consolidation therapy- which generally includes Myeloablative chemotherapy with stem cell rescue and Radiation to the tumor bed.
4. Management of Minimal Residual Disease

- Radiotherapy
  - Local RT for bulky primary (complementary to surgery)
  - TBI: as part of myeloablative conditioning regimen if HDC/ASCT is planned.

Role of RT in Neuroblastoma



DSRBCT

- sharply demarcated islands of uniform small round cells- abundant desmoplastic stroma - loose extracellular matrix.

- **IHC- polyphenotypic** differentiation- co-expression of epithelial, myogenic, mesenchymal and neural markers
- EWSR1-WT1 fusion oncogene

BONE AND SOFT TISSUE

EWING

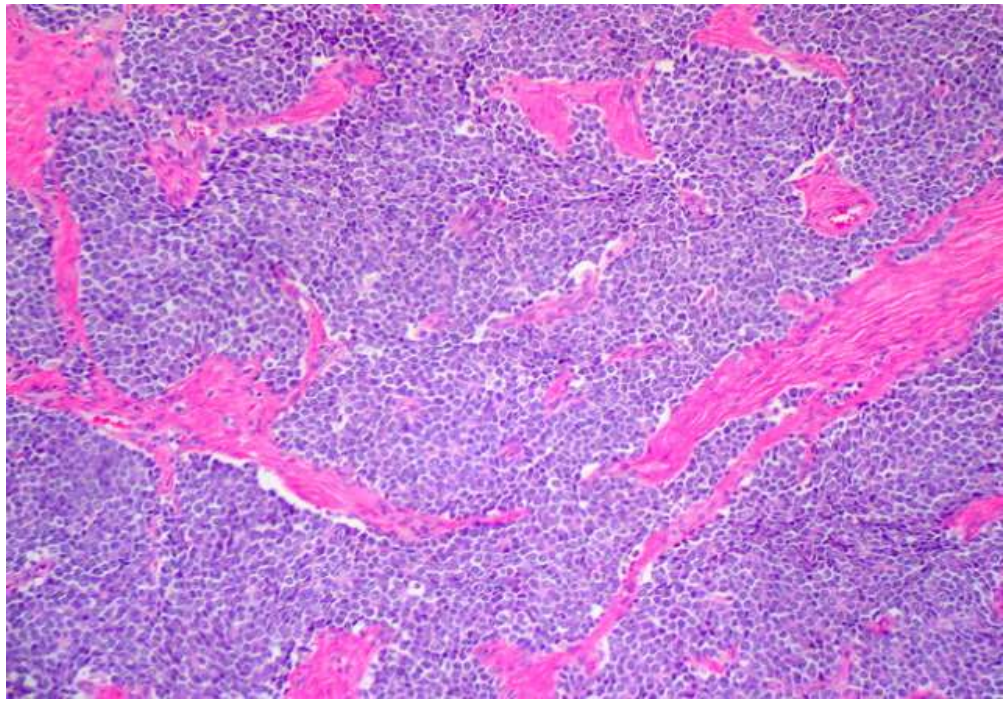
SMALL CELL OSTEOSARCOMA

MESENCHYMAL CHONDROSARCOMA

LYMPHOMA

SYNOVIAL SARCOMA

ARTHUR PURDY STOUT



James Ewing

EWINGS SARCOMA

Age: 5-20yrs. Sex:M>F 1.4:1

Site:-Bone:Medulla of diaphysis or metaphysis of femur, pelvis, tibia,humerus, ribs and fibula.

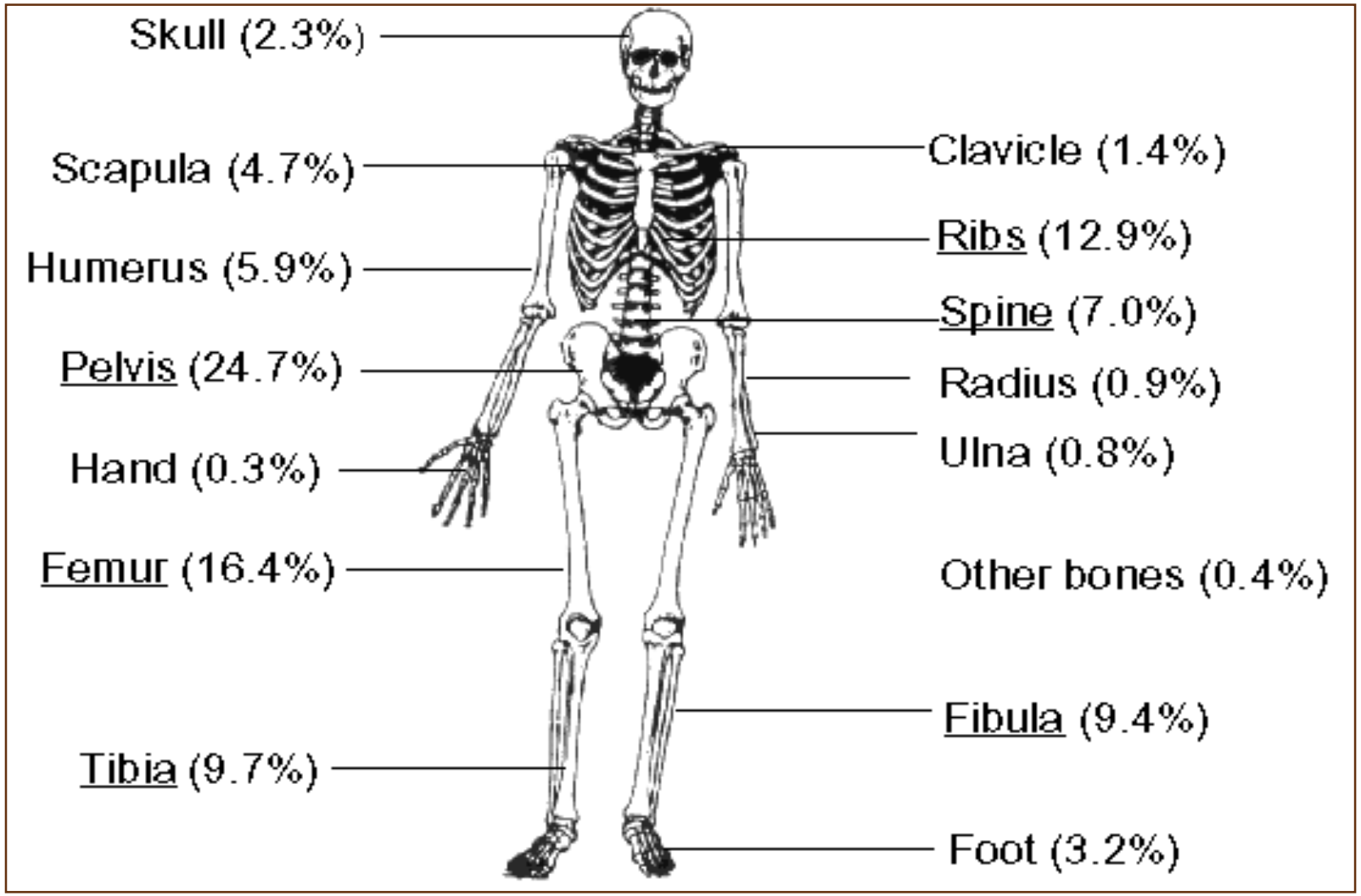
-Soft tissue: Deep soft tissue of extremities

Presentations:

Bone: Clinically the tumor may simulate osteomyelitis

Soft tissue: Rapidly growing, deeply located mass measuring 5-10cm in greatest diameter.

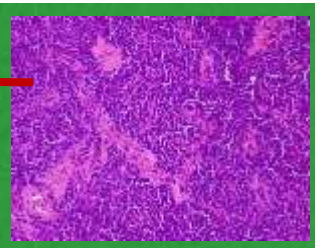
EWINGS SARCOMA



~~Primitive Neuroectodermal Tumors~~

(Neural crest tumor)

Batsakis et al(1996)



Based on the tissue of origin

Tumors derived from the central nervous system

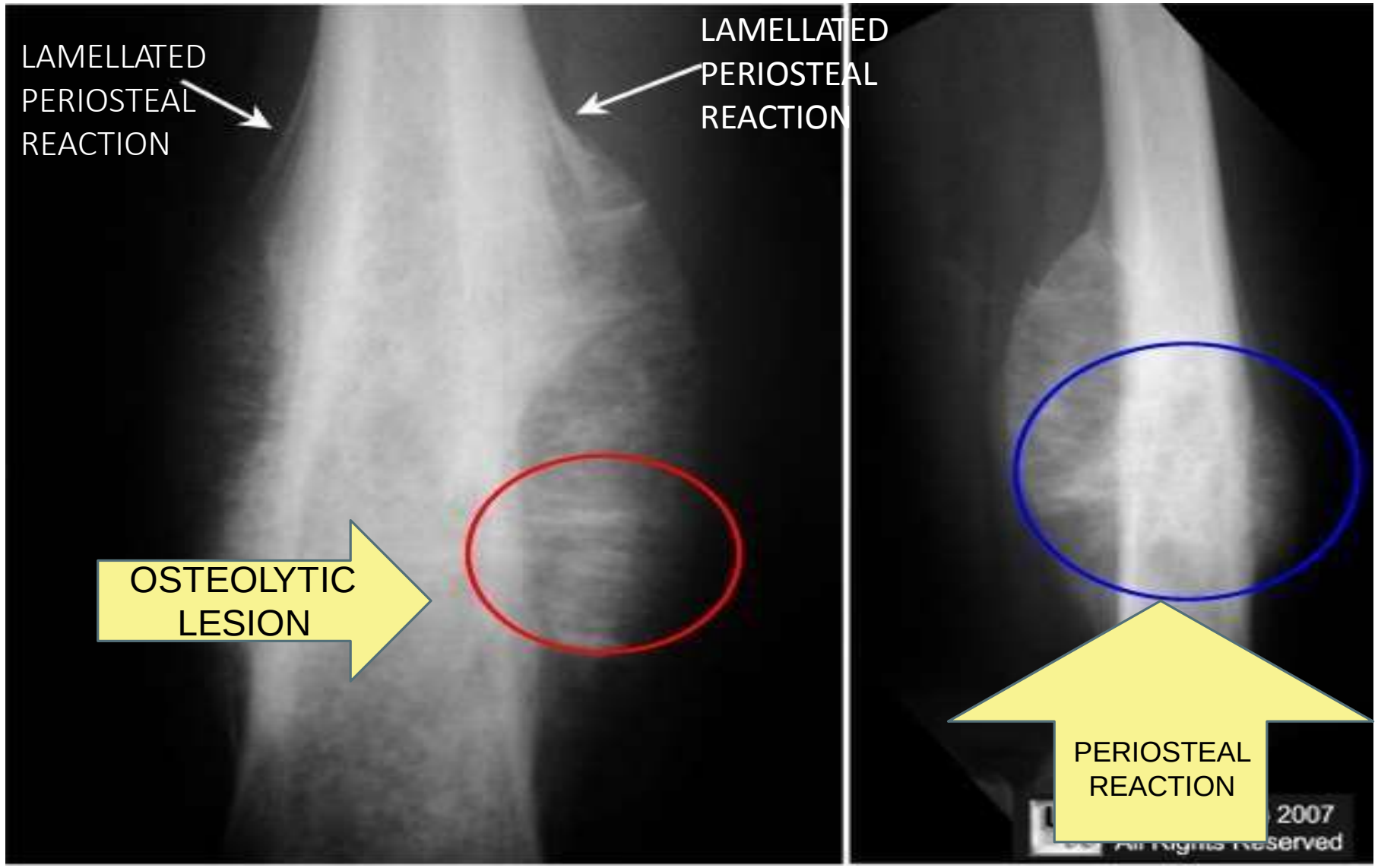
Tumors derived from the autonomic nervous system

Tumors derived from tissues outside the central and autonomic nervous system

- CNS PNETs
- Neuroblastoma
- ~~Peripheral PNETs~~/ Ewing Family of tumors
  - Ewing sarcoma
  - Malignant peripheral PNETs
  - Askin tumor
  - *Other

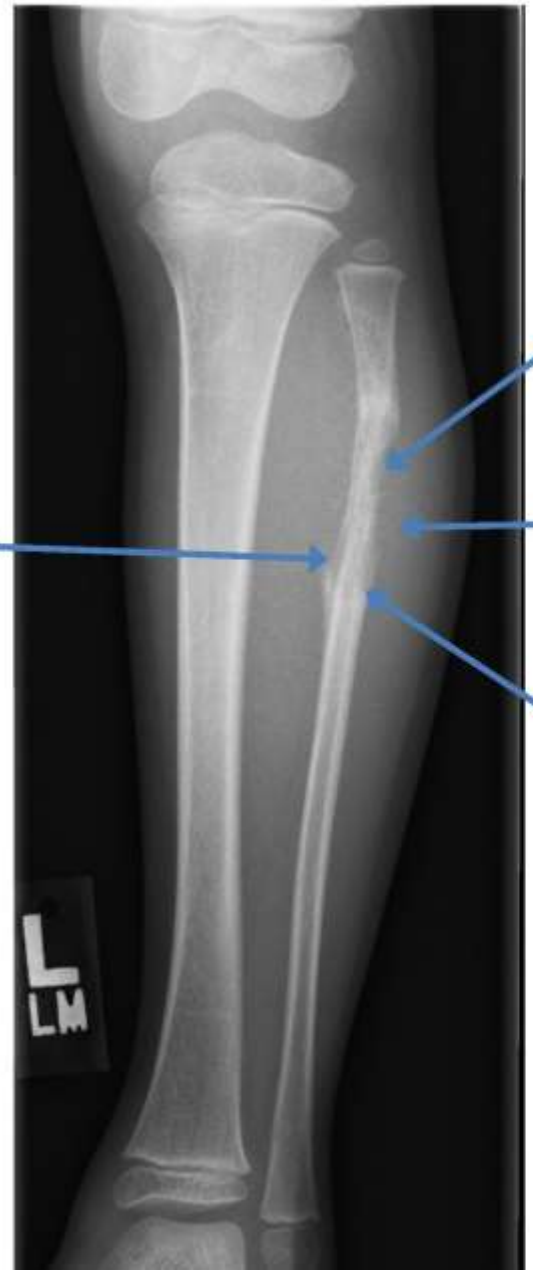
Neuroectodermal tumor, ectomesenchymoma, peripheral medulloepithelioma. These tumors were thought to arise directly from nerves.

RADIOGRAPH: Ewings sarcoma/PNET



Representative X-ray appearance of a primary malignant bone tumor *(Ewings Sarcoma)*

See associated slide on malignant bone tumors for the pathogenesis behind these x-ray findings



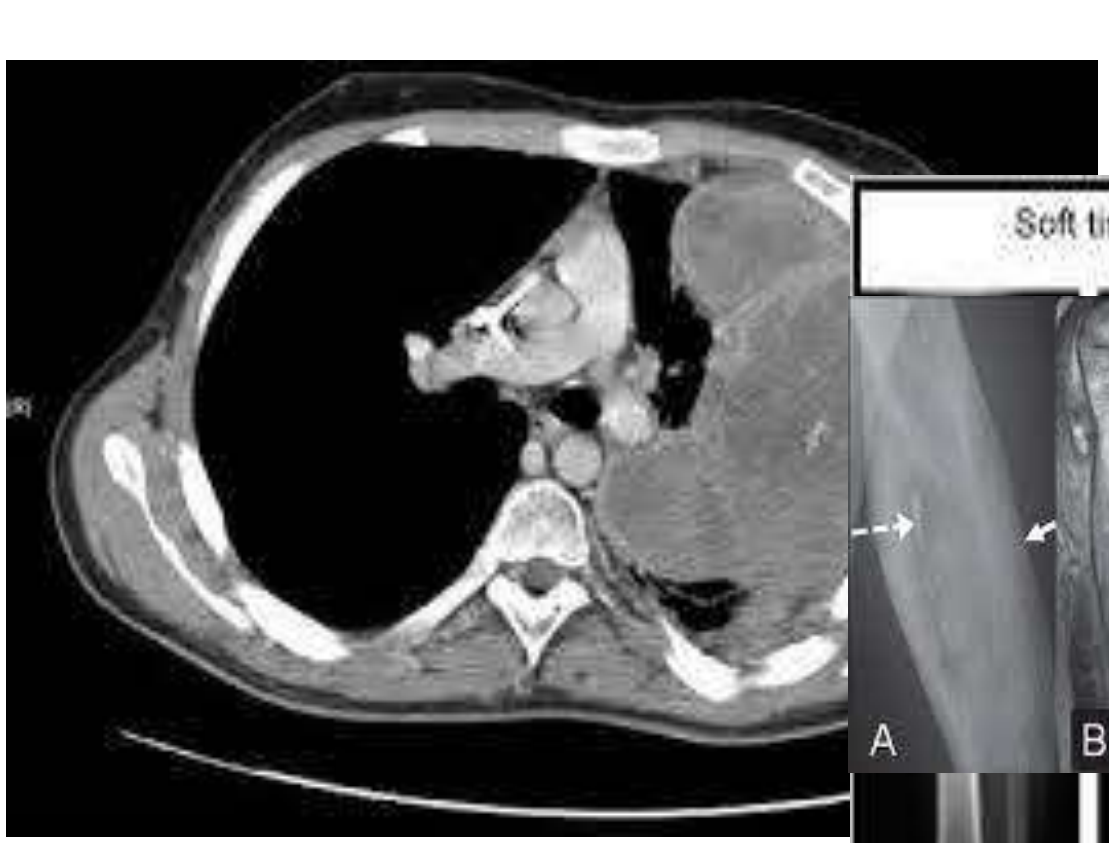
Spen

Interrupted periosteal reaction

"Moth-eaten", permeative bone destruction

Soft-tissue mass accumulation around the bone tumor

Wide zone of transition between bone and tumor *(Ill-defined border)*



EWING RIB

EWING HUMERUS

RADIOLOGICAL DIFFERENTIALS

Differential diagnc

- other Ewing sarcoma family c
  - pPNET: large soft tissue c
  - Askin tumor: chest wall
- osteosarcoma:
  - more often has amorphou
  - classically perimetaphyse
  - more prevalent around th sarcoma is the more frequ
- osteomyelitis
- metastatic disease
- hematological malignancy
- eosinophilic granuloma [9]
- neuroblastoma (age <5) [10]

Undifferentiated small round cell sarcomas of bone and soft tissue

Ewing sarcoma

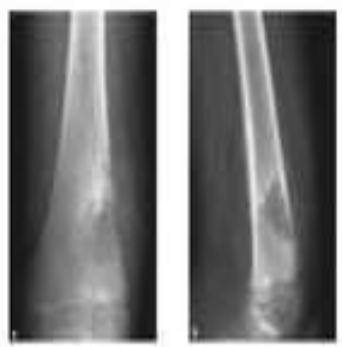
Round cell sarcoma with EWSR1-non-ETS fusions

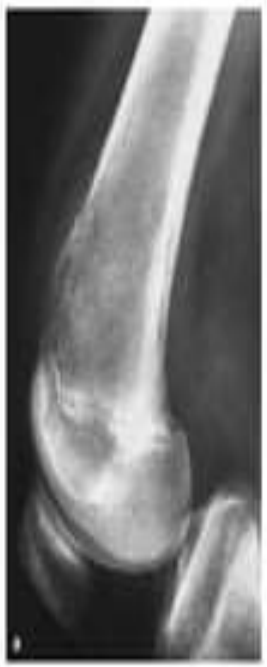
CIC-rearranged sarcoma

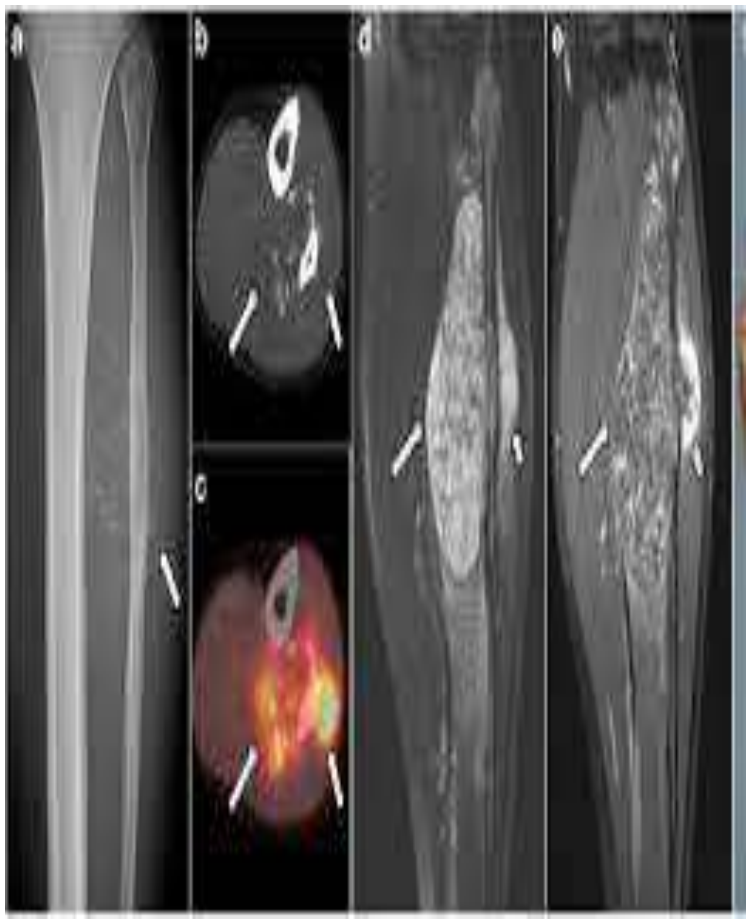
Sarcoma with BCOR genetic alterations

Small Cell Osteosarcoma

- Rare
- High grade
- Uniform small size tumor cells.
- Diffuse pattern of growth.
- Resemble Ewing sarcoma or Lymphoma



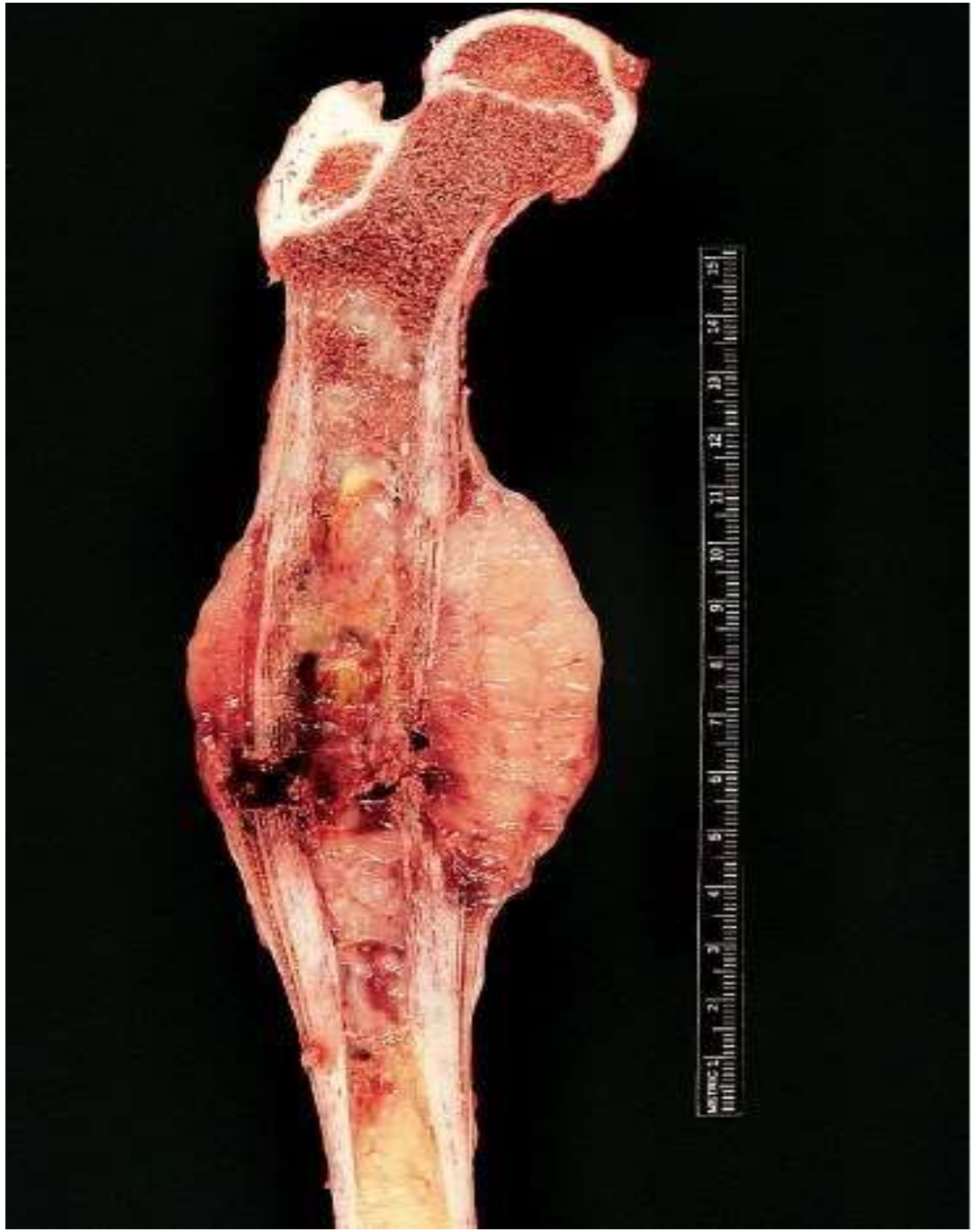




MESEN- CHONDROSARCOMA

GROSS

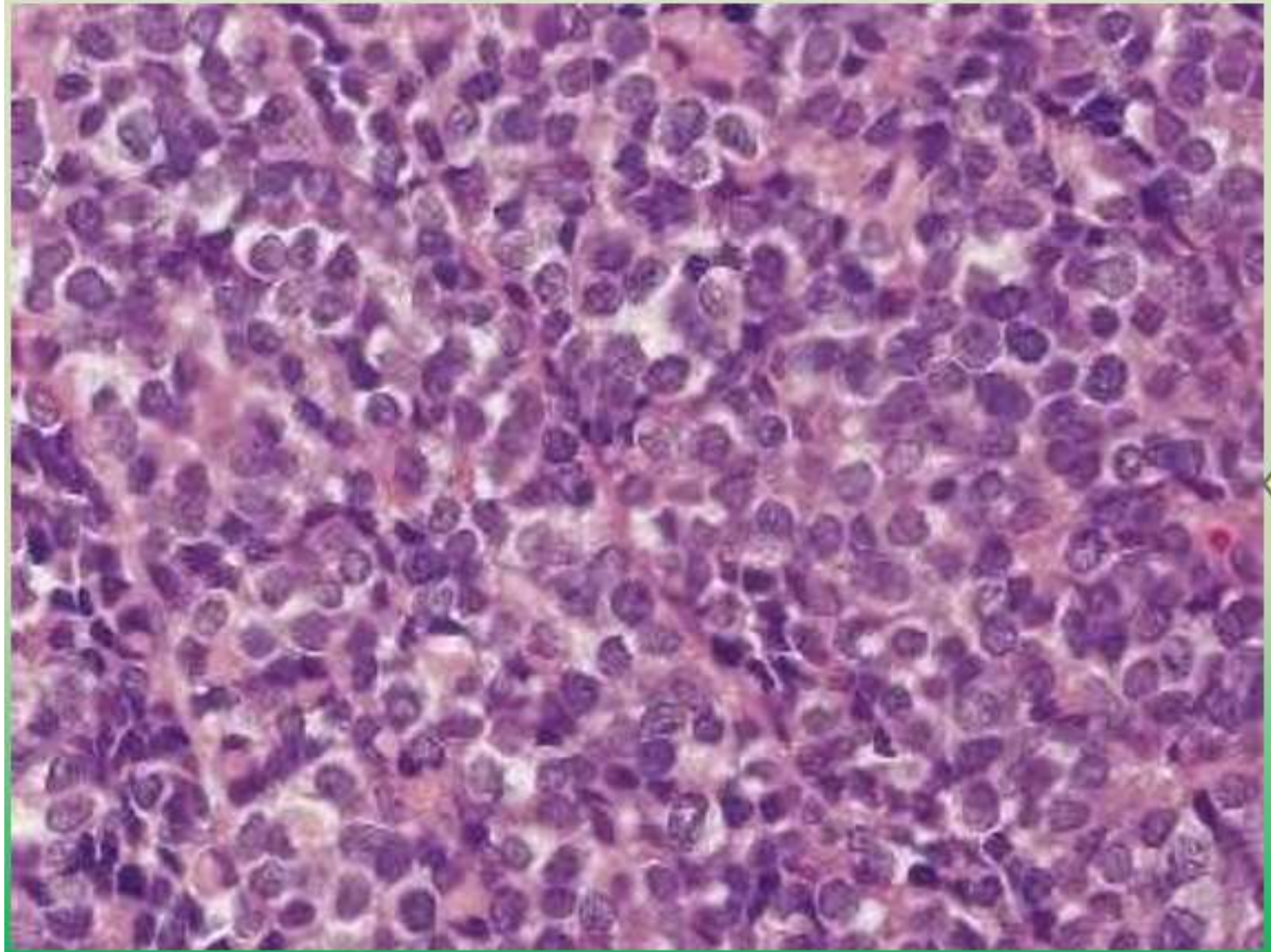
- Generally arises in medullary cavity of shaft from which it permeates cortex and invades soft tissue
- Rarely, periosteal
- Soft, tan-white, areas of haemorrhage and necrosis



MICROSCOPY:Ewings sarcoma/PNET

1. Classic or conventional (typical) Ewing sarcoma
2. Atypical Ewing sarcoma

- Same immunohistochemical and molecular features, differing only in the extent of neural differentiation.
- *Each subtype* is considered a *high-grade tumor*.



sheets of uniform population of cells; round nuclei ; finely granular chromatin; indistinct cell borders; necrosis common; mitotic activity usually not prominent

SPECTRUM OF LIGHT MICROSCOPIC FEATURES ACROSS ES/PNET FAMILY OF TUMORS

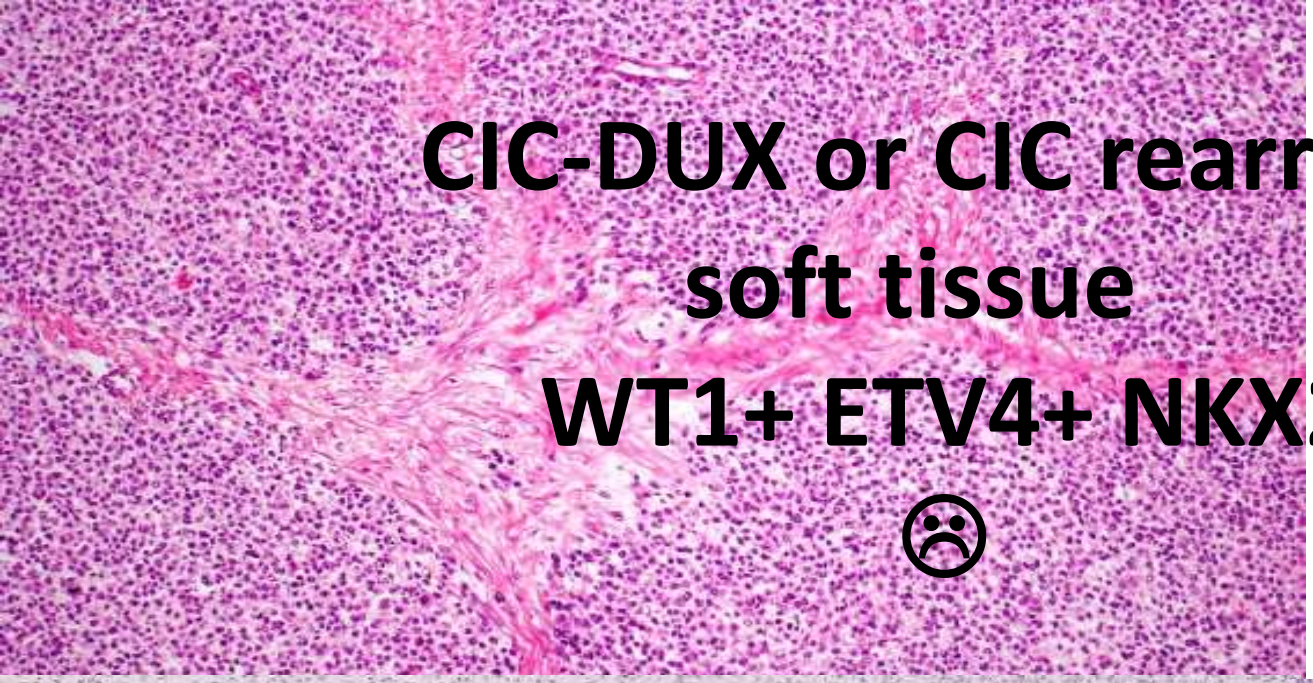
Feature	Classic Ewing's sarcoma	Atypical Ewing's sarcoma
Cell shape	Uniform, round	Irregular
Chromatin	Fine	Coarse
Nucleoli	Pinpoint	More prominent
Glycogen	Abundant	Moderate
Rosettes	Absent	Absent

SPECTRUM OF ULTRASTRUCTURAL FEATURES ACROSS THE FAMILY OF TUMORS

Feature	Classic Ewing's sarcoma	Atypical Ewing's sarcoma
Organelles	Scarce	Moderate
Dense-core granules	Absent	Rare
Neurotubules	Absent	Rare
Neuritic processes	Absent	Rare

ATYPICAL-*most difficult group* to recognize

- Great degree of *cytologic variability* and/or *unusual growth patterns* e.g. large nuclei with irregular nuclear membranes and prominent nucleoli; abundant eosinophilic cytoplasm imparting a rhabdoid appearance.

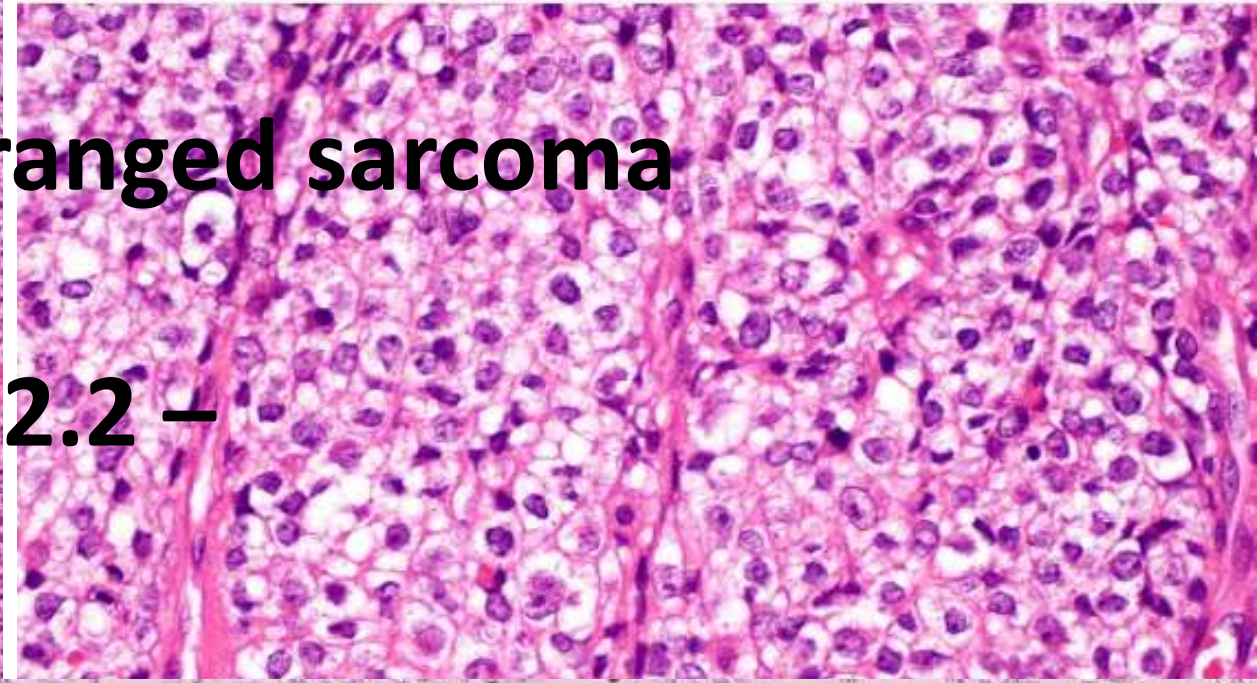


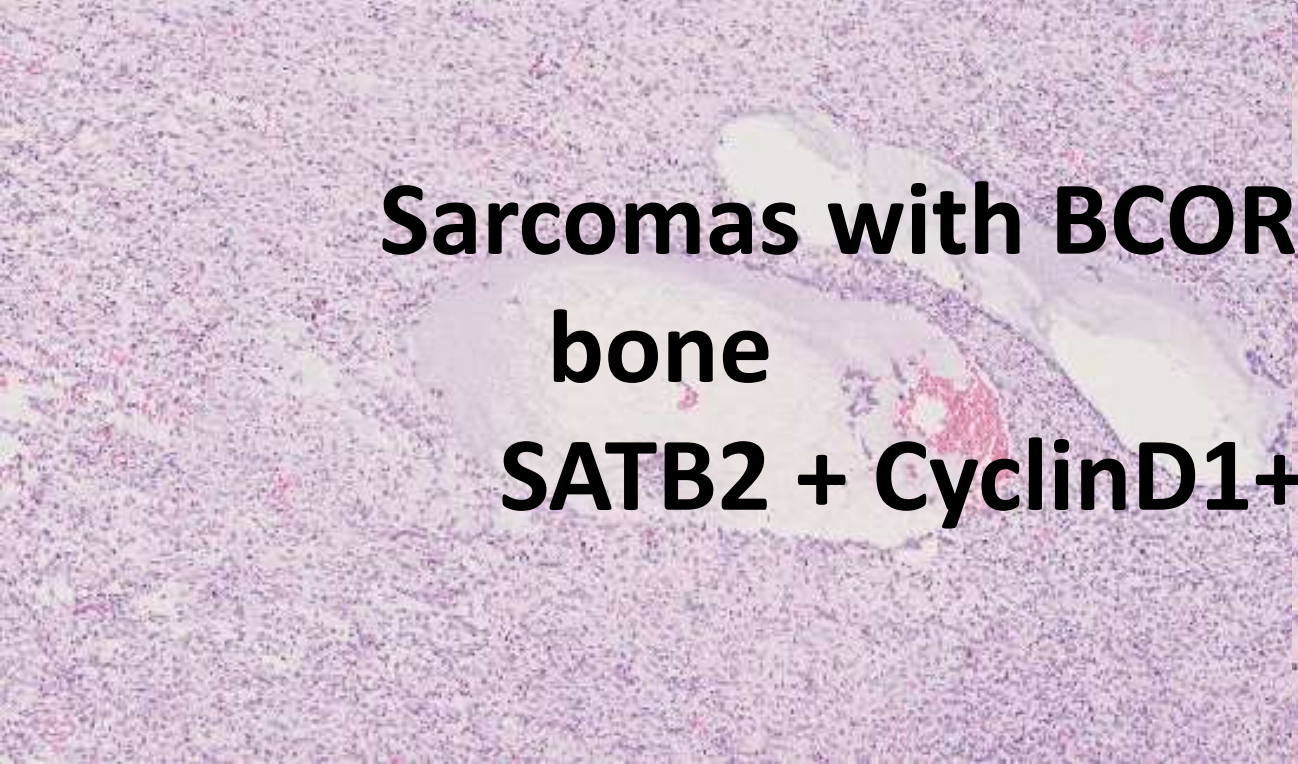
CIC-DUX or CIC rearranged sarcoma

soft tissue

WT1+ ETV4+ NKX2.2 –

☹

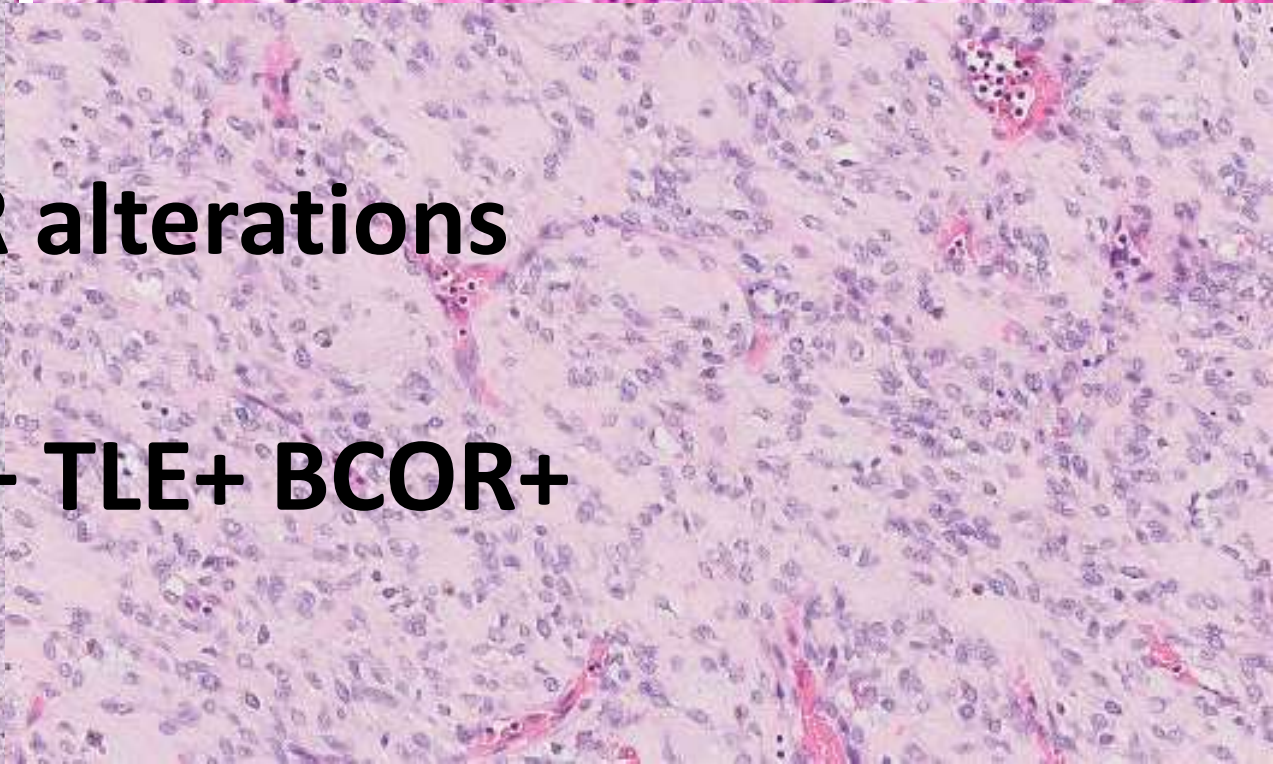




Sarcomas with BCOR alterations

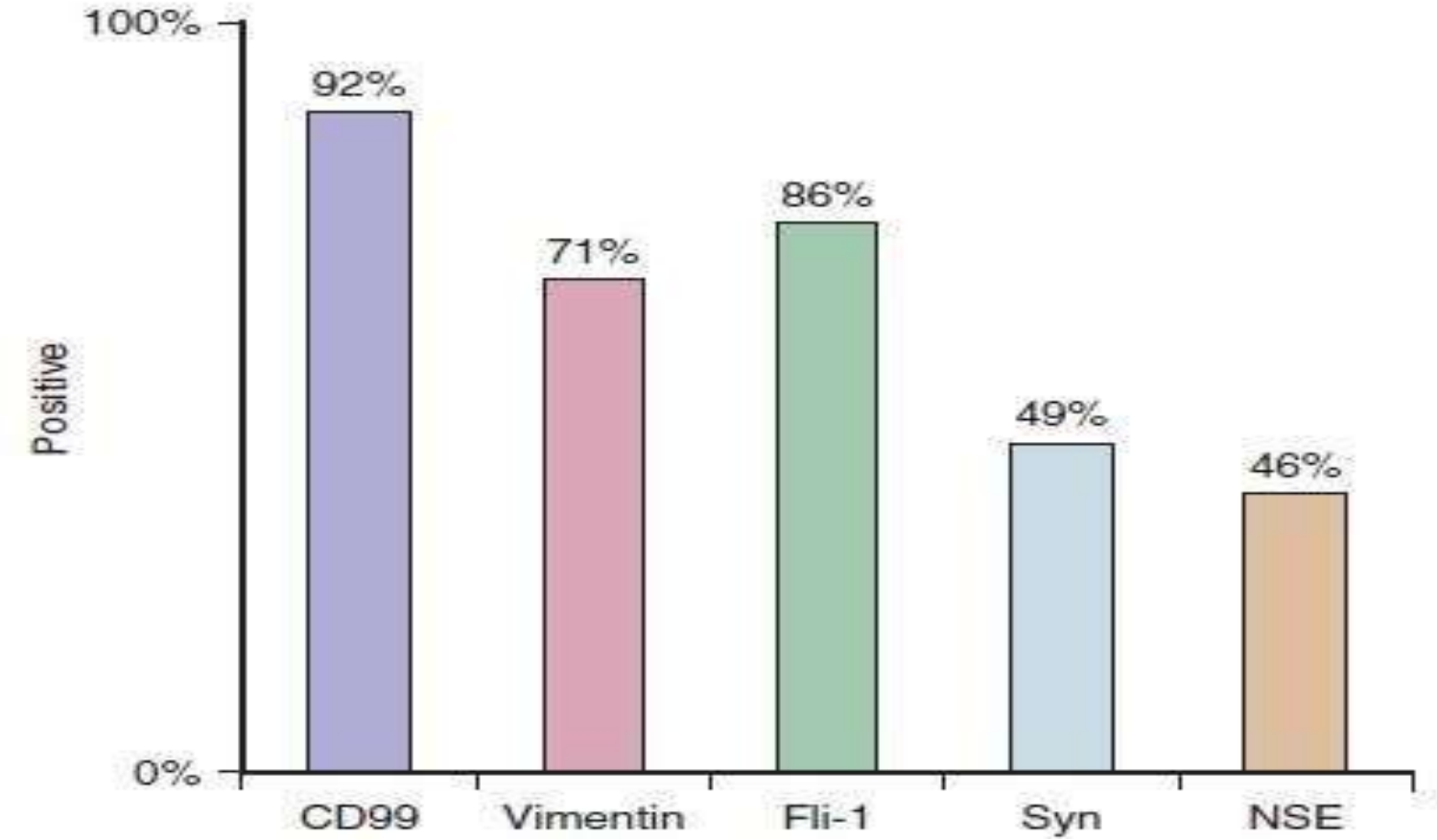
bone

SATB2 + CyclinD1+ TLE+ BCOR+



- IHC
  - CD99
  - FLI1/ERG
  - NKX2.2
  - Dot like CK (1/3rd cases)**
  - +/- desmin

IMMUNOHISTOGRAM OF EWINGS SARCOMA/PNET



Non reactive for chromogranin, glial fibrillary protein, *desmin, muscle specific actin, myogenin* and CD45.

- **CD99**- *strong, diffuse membranous staining* pattern-84-100% sensitive - *NOT A SPECIFIC MARKER*

- CD99 is important for distinction between Ewings sarcoma/PNET and metastatic neuroblastoma

-

CD99 NEGATIVE-highly unlikely to be Ewing sarcoma

NKX2.2 DIAGNOSTIC

- **FLI1**- Only *nuclear staining* is considered positive
  NOT SPECIFIC MARKER

But also positive in
Lymphoblastic lymphoma, myeloid neoplasms, DSRCT, Malignant melanoma, merkel cell carcinoma,synovial sarcoma, and some vascular neoplasms.

MOLECULAR GENETIC FEATURES

Reciprocal translocation t(11;22)(q24;q12)

Fusion of EWSR1 gene(encodes for RNA binding protein) at 22q12 with FLI1 gene(member of ETS family of transcription factors)

- The t(21;22)(q12;q12) translocation involves the gene ERG, which is located on chromosome 21
- t(7;22)(p22;q12) translocation involves a gene known as ETV1 at 7p22.
- Recently a translocation involving chromosomes 4 and 9 with CIC and DUX4 gene has been identified

- FISH for *EWSR1* genomic rearrangements

is highly sensitive (>95%) but *nonspecific* because other tumours may show rearrangement of this locus.

- RT-PCR for *EWSR1* fusion genes - highly sensitive (>95%) and specific (100%).

- Rearrangements of *EWSR1* with non–ETS-family genes—including *NFATc2*,*POU5F1*, *SMARCA5*, *ZSG,* and *SP3*—are also rarely identified
-

LYMPHOBLASIC LYMPHOMA

- *TdT*
- *CD1*
- *CD2*
- *CD3*
- *CD43*
- *CD99*
- *bcl2*
- *CD71*
- *LCA+*

B and T cell markers

- **SMALL CELL OSTEOSARCOMA**

→ SATB2

- **MESENCHYMAL-CHONDROSARCOMA**

→ NKX2.2 and 3.1

- **SYNOVIAL SARCOMA**

→TLE1/CK/SYNAPTOPHYSIN DIFFUSE+

RHABDOMYOSARCOMA

- Only two categories show small round cell picture on histology:
    1. Embryonal rhabdomyosarcoma
    2. Alveolar rhabdomyosarcoma

EMBRYONAL RHABDOMYOSARCOMA

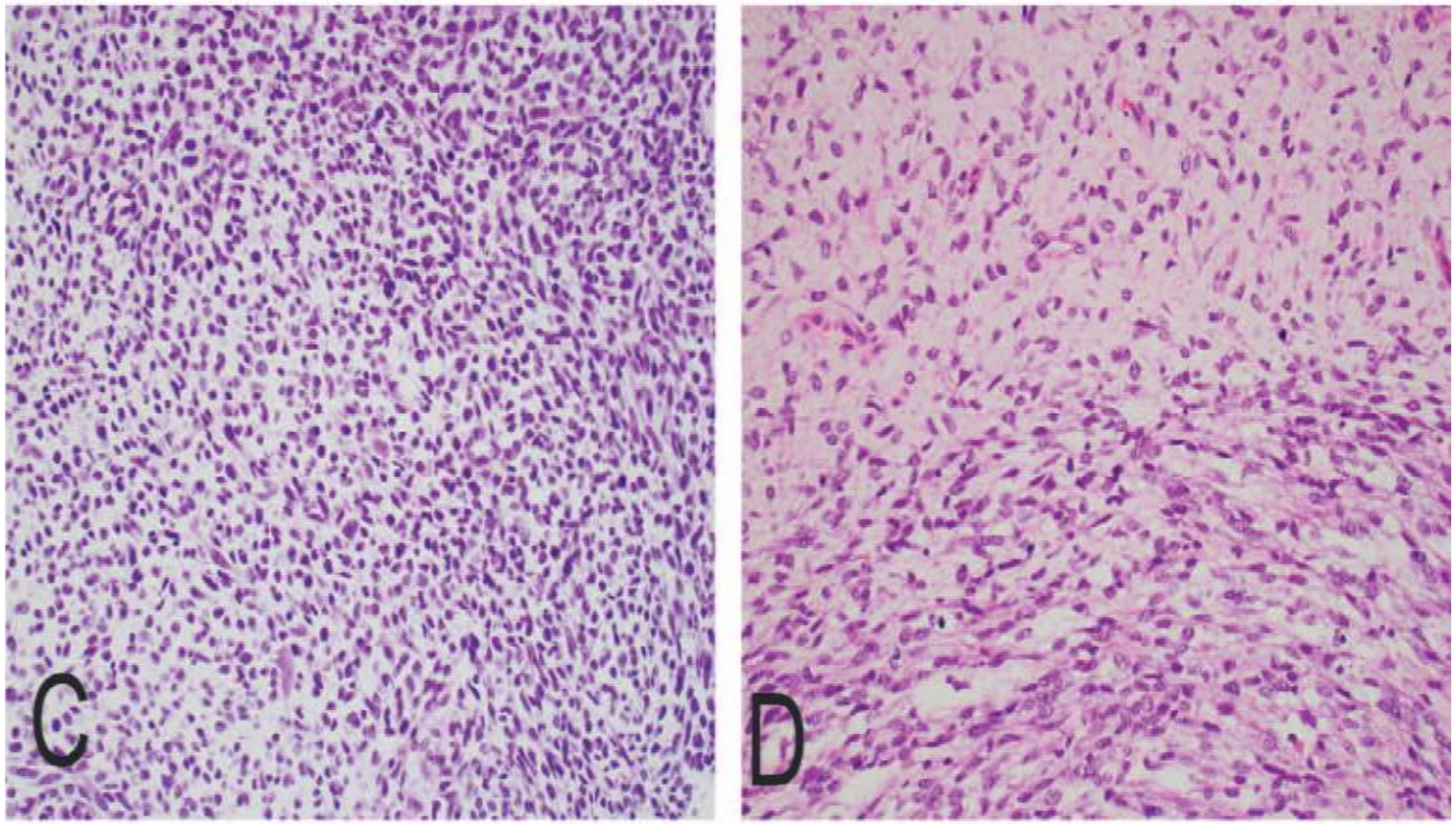
- Arises from unsegmented and undifferientiated mesoderm
- SITE- head and neck region- orbit, nasopharynx, middle ear
  retroperitoneum
  bile ducts
  urogenital tract
- AGE- 3-12 years
- GROSS- poorly circumscribed, white, soft

ALVEOLAR RHABDOMYOSARCOMA

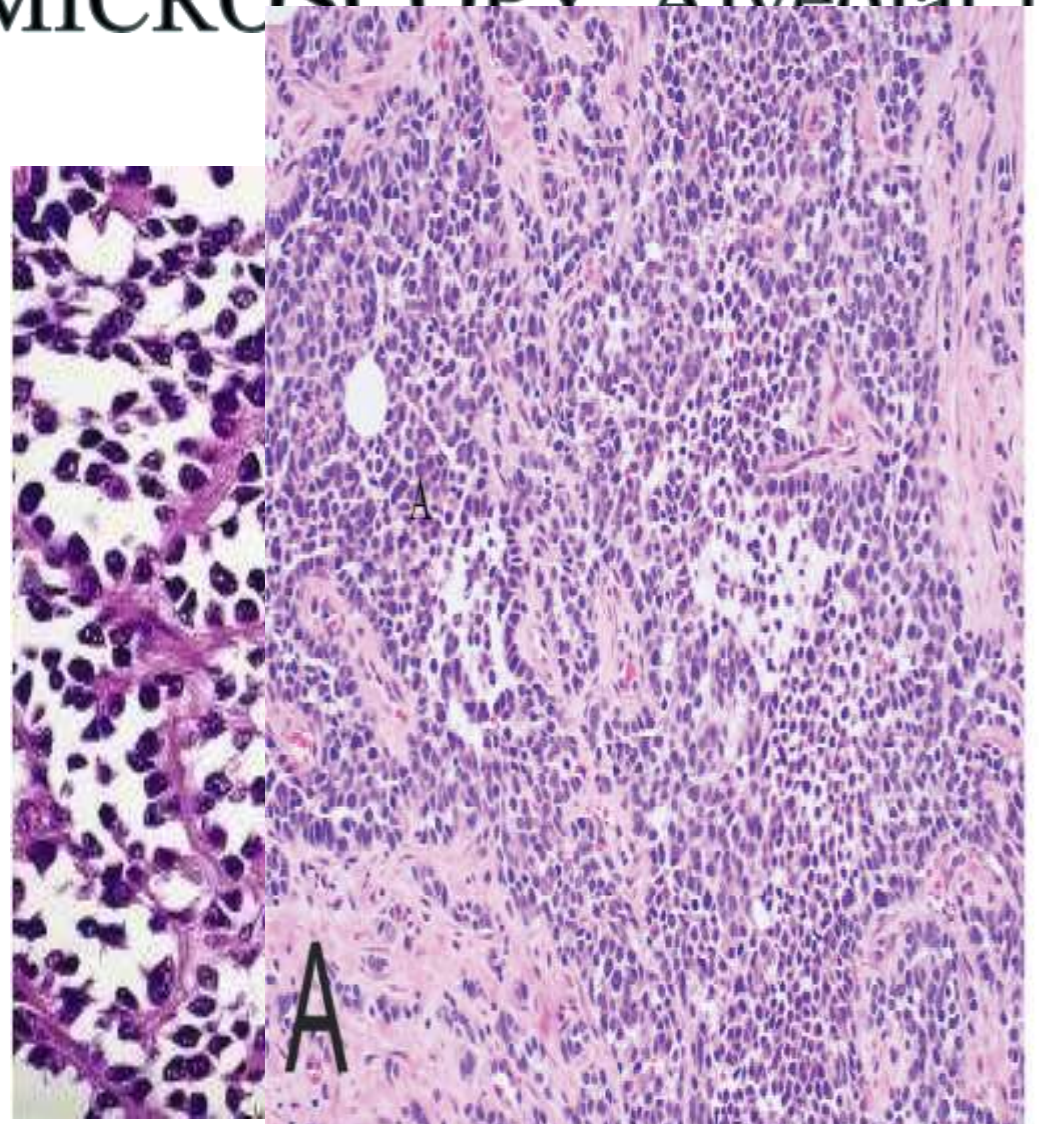
- AGE- 10- 25 years
- SITE- Extremities- forearm,arms, perirectal, perineal regions

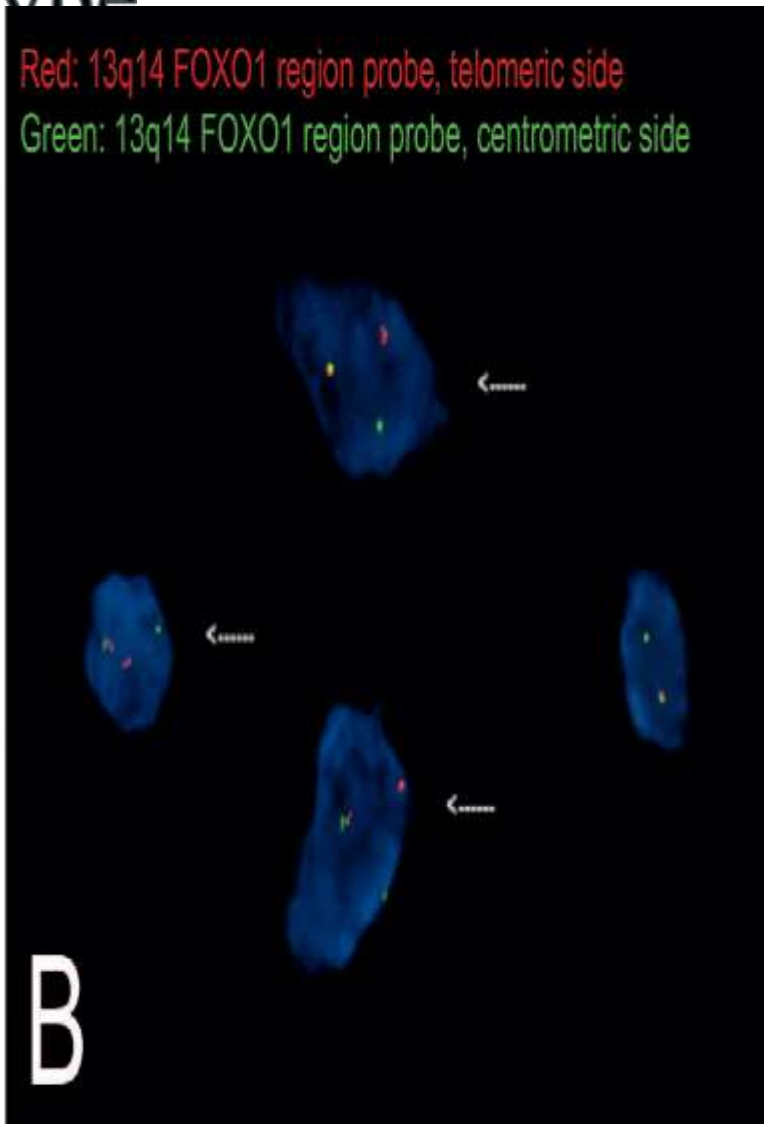
Most common sites of metastatic involvement → bone marrow, lungs, soft tissues, lymph nodes

MICROSCOPY: Embryonal type

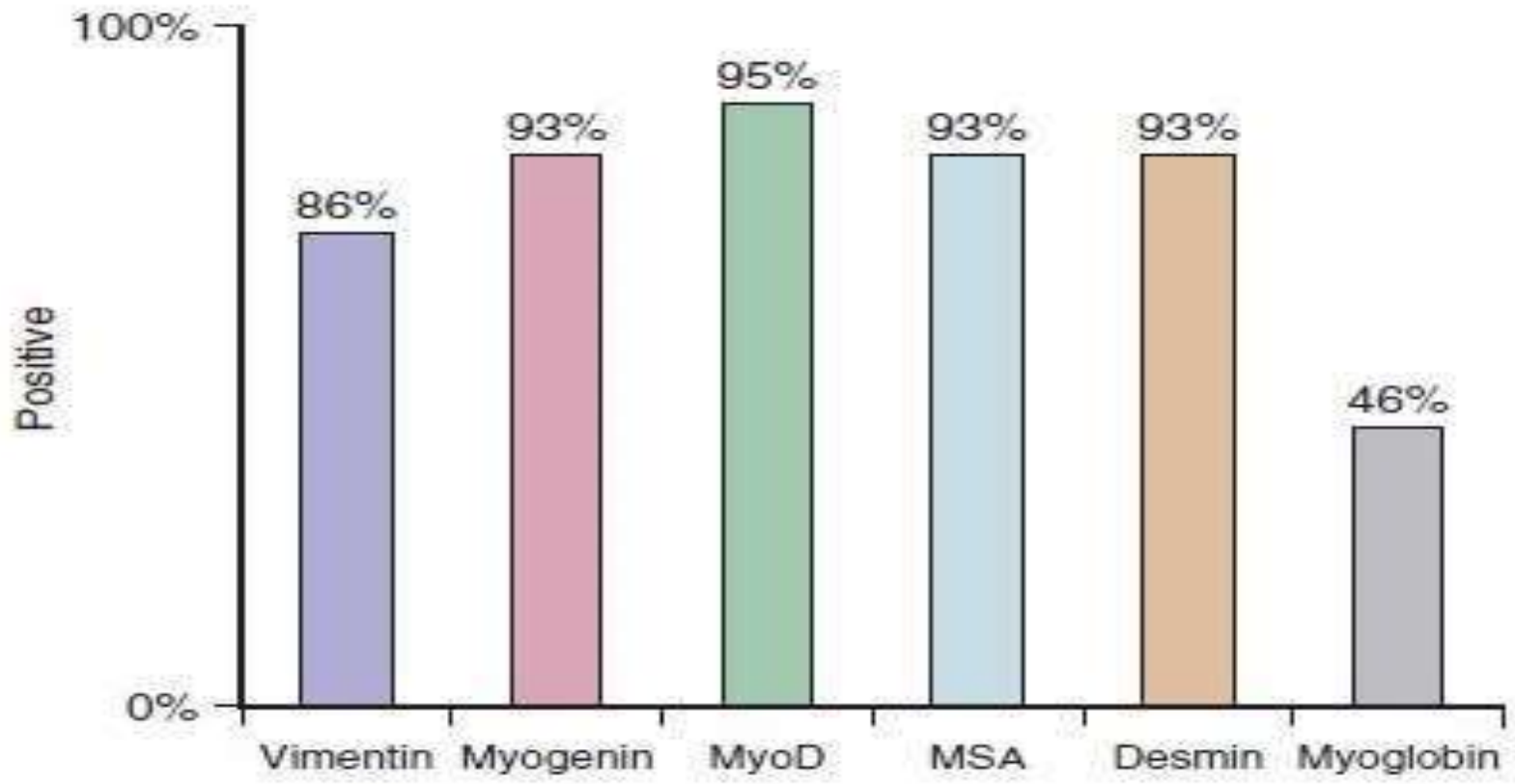


MICROSCOPY: Alveolar type



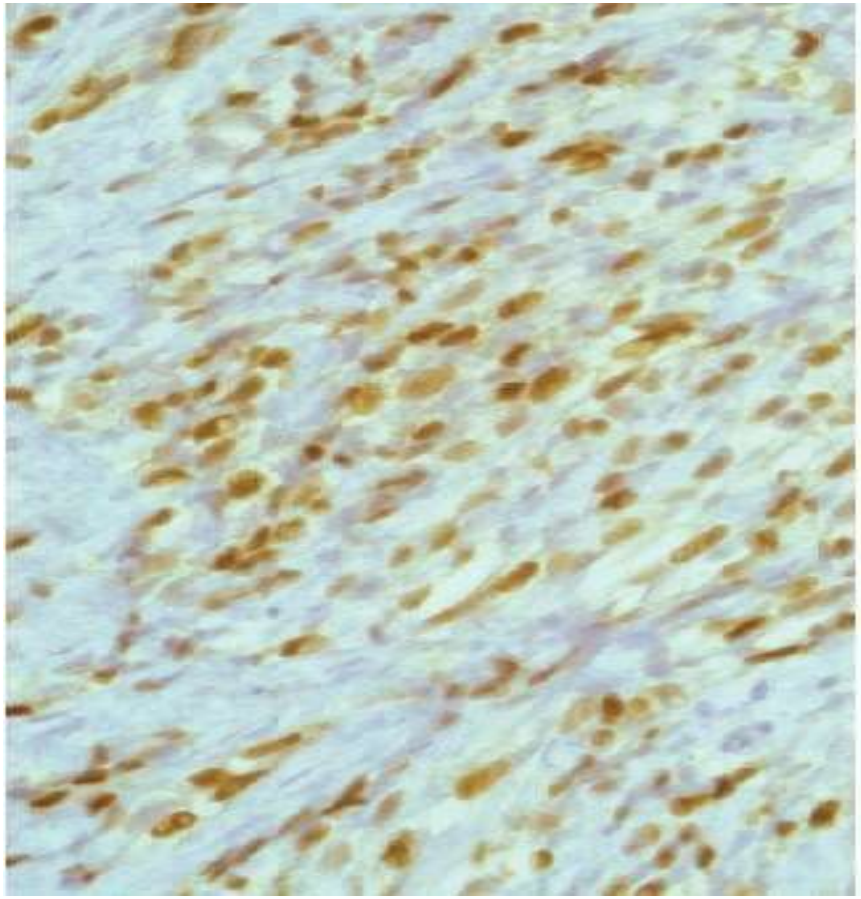


IMMUNOHISTOCHEMISTRY

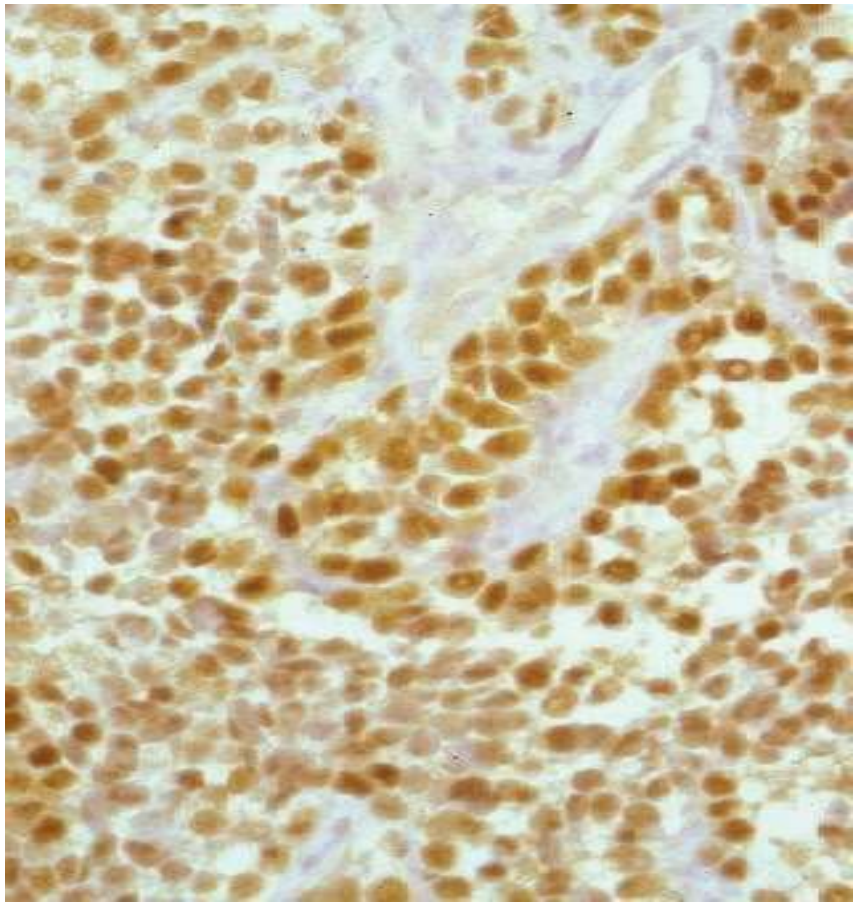


IMMUNOHISTOGRAM OF RHABDOMYOSARCOMA

MYOGENIN REACTIVITY



Embryonal rhabdomyosarcoma



Alveolar rhabdomyosarcoma

MOLECULAR DIAGNOSTICS: CLINICAL IMPLICATIONS

Fusion status rather than histology may be the more important driver of clinical outcomes

Fusion-negative alveolar RMS is more similar to embryonal -histology both clinically and molecularly- LESS aggressive therapy

75% of children- alveolar RMS exhibit t(2;13)(q35;q14), and occasionally a t(1;13)-→ abnormal fusion genes involving *PAX3-FOXO1* and *PAX7-FOXO1*, respectively

Fusion positive is considered ARMS

Dense form of ERMS(Similar pattern like ARMS) = Fusion negative ARMS

Percentages of Positivity for Pertinent Immunomarkers in Malignant Small Round Cell Tumors of Soft Tissue and Bone

Antigen Tumor	KER	EMA	DES	MYOG/MYF-4	SYN	S-100P	CD45	CD99
A-RMS	30[†]	0	>95	>95	20[†]	<10	0	10
E-RMS	<5	0	>95	>90	LD	<10	0	<10
ES/PNET	20[†]	0	<1[†]	0	65	<10	0	>95
DSRCT	85	90	90	0	15	<5	0	<5
Lymphoma	0	0	0	0	0	0	>95	50[§]

THANK YOU