Fondazione IRCCS
Istituto Nazionale dei Tumori

International benchmarking of childhood cancer survival by tumour stage

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Istituto Nazionale dei Tumori, Milan, Italy

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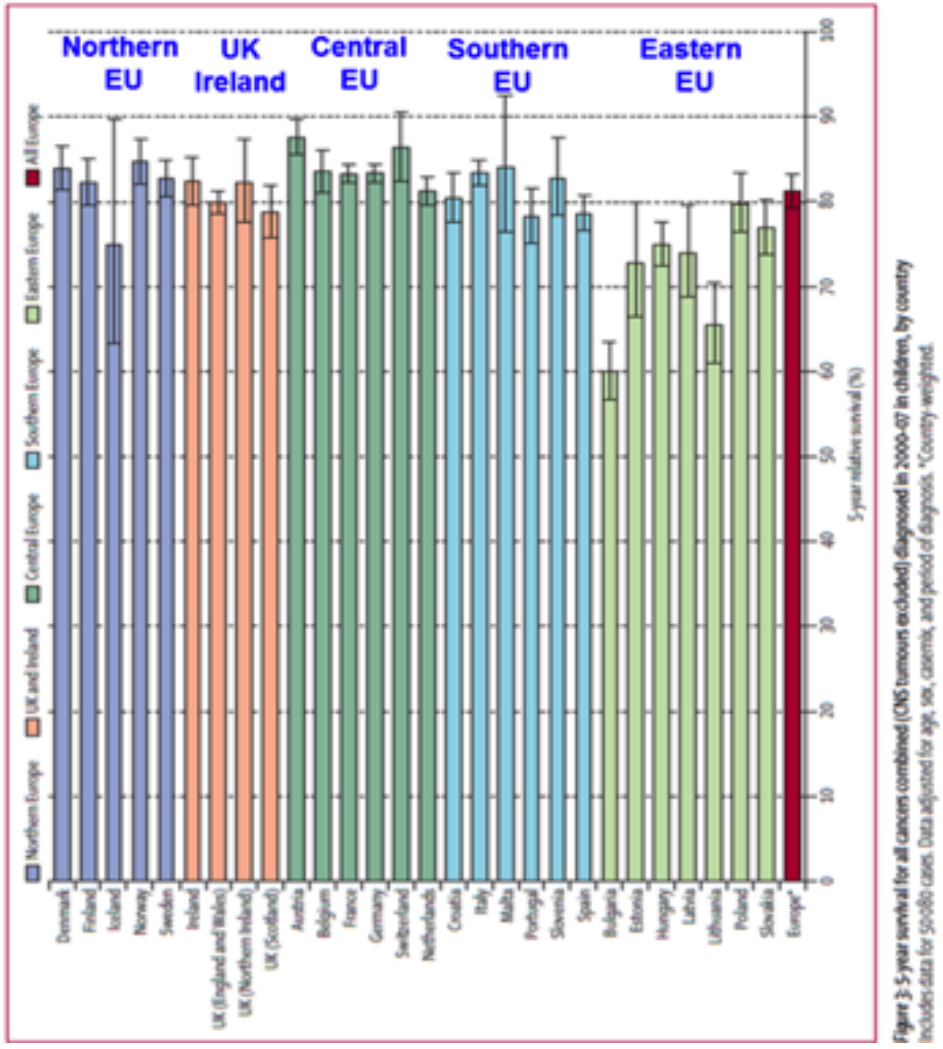
EUROCARE 5 (cases diagnosed 2000-2007)



EUROCARE 5, Gatta et al, Lancet Oncology 2014:**15**:35-47

Successive Population-based Cancer Registry (PBCR) studies have shown variation in overall survival rates for childhood cancer across Europe, more pronounced in brain tumours, and with no data for several countries

To understand basis for variation, we need to have more info on Patient & Tumour demographics:

- **Stage at diagnosis**
- **Other Non-Stage Prognostic (NSP) factors**
- Quality of diagnosis and risk stratification
- Treatment
- Follow up after treatment

DOI: 10.1002/pbc.29020

ONCOLOGY: RESEARCH ARTICLE

Pediatric Blood & Cancer | SIOP | aspho The American Society of Pediatric Hematology/Oncology | WILEY

benchista

Staging childhood cancers in Europe: Application of the Toronto stage principles for neuroblastoma and Wilms tumour. The JARC pilot study

Gemma Gatta[1] | Laura Botta[1] | Riccardo Capocaccia[2] | Adela Cañete[3] | Kathy Pritchard-Jones[4] | JARC Pilot Study Toronto Guidelines Working Group[#]

JARC
JOINT ACTION ON RARE CANCERS
2016-2019

Under the EU JARC project (2016-19), 25 European PBCRs performed a pilot study to test the feasibility of applying the international consensus "Toronto" staging guidelines to two solid tumours. *Pediatr Blood Cancer. 2021 Sep;68(9):e29020.*

Findings:

- Toronto stage could be assigned in 95% of both tumours diagnosed in 2014 or similar time period.
- This collaborative group of PBCRs, clinicians and epidemiologists worked well together to collect, analyse and publish the data.
- Expanded collaboration has succeeded in obtaining funding to take this to a full study – "BENCHISTA".

Specific questions to be addressed:

1. **Are childhood cancers diagnosed at a more advanced stage in some countries compared to others?**
   - Implies later diagnosis (differences in public awareness, child health surveillance and acute care practices)

2. **Do survival rates by tumour stage vary between countries/large geographic regions?**
   - Implies differences in diagnostic and treatment practices or tumour biology

PBCRs are asked to submit **all cases of 6 index childhood solid tumours diagnosed in a consecutive three-year window (2014-2017)** and staged according to the international consensus ”Toronto” guidelines (including non-staged cases)

- Osteosarcoma
- Ewing sarcoma
- Medulloblastoma
- Rhabdomyosarcoma
- Neuroblastoma
- Wilms tumour

BENCHISTA will include > 8.000 cases (compared to 1,115 in Pilot)

These six solid tumours chosen:

- Unambiguous coding for identification
- Pre-existing published evidence for international variation in tumour stage/size at diagnosis in multinational clinical trials
- Included in the International “Toronto” consensus guidelines for staging childhood cancers

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Paediatric cancer stage in population-based cancer registries: the Toronto consensus principles and guidelines

Sumit Gupta, Joanne F Aitken, Ute Bartels, James Brierley, Mae Dolendo, Paola Friedrich, Soad Fuentes-Alabi, Claudia P Garrido, Gemma Gatta, Mary Gospodarowicz, Thomas Gross, Scott C Howard, Elizabeth Molyneux, Florencia Moreno, Jason D Pole, Kathy Pritchard-Jones, Oscar Ramirez, Lynn A G Ries, Carlos Rodriguez-Galindo, Hee Young Shin, Eva Steliarova-Foucher, Lillian Sung, Eddy Supriyadi, Rajaraman Swaminathan, Julie Torode, Tushar Vora, Tezer Kutluk, A Lindsay Frazier

Gupta et al, Lancet Oncol 2016

Toronto Staging: Introduction (1)

- Adult cancers
  - International consensus: mainly TNM classification
- Paediatric cancers
  - Heterogeneous, many rare cancers
  - TNM not applicable for most paediatric cancers
  - Mostly staged by disease-specific staging systems
    - Different systems for the same disease
    - Differences between countries
- Need for consistency in paediatric cancer stage collection
  - Facilitate international comparisons and studies

Toronto Staging: Introduction (2)

- October 2014: international experts meeting in Toronto, Canada
- Development of a Tiered staging system for 18 major childhood malignancies: The “Toronto Staging System”
- Published in the Lancet Oncology (2016)


Paediatric cancer stage in population-based cancer registries: the Toronto consensus principles and guidelines

Sumit Gupta, Joanne F Aitken, Ute Bartels, James Brierley, Mae Dolendo, Paola Friedrich, Saad Fuentes-Alabi, Claudia P Garrido, Gemma Gatta, Mary Gospodarowicz, Thomas Grosa, Scott C Howard, Elizabeth Molyneux, Florencia Moreno, Jason D Pole, Kathy Pritchard-Jones, Oscar Ramirez, Lynn A G Ries, Carlos Rodriguez-Galindo, Hae Young Shin, Eva Steliarova-Foucher, Lillian Sung, Eddy Supriyadi, Rajaraman Swaminathan, Jude Torode, Tushar Vora, Taner Kutluk, A Lindsay Frazier

- Included in the UICC TNM 8th edition
- Clarified in an Australian guideline document (2017)
- Revised in a second expert meeting in Lyon (2019)

Toronto Staging: General principles (1)

- Consensus guidelines for collecting childhood cancer stage in population-based cancer registries
  - They are **not** intended to replace the staging systems of clinical trials
  - They are **not** intended to reflect or guide clinical decision making
  - They **are intended** to allow standardised comparisons of stage at diagnosis between populations.

- Tiered staging systems
  - Tier 1: limited resources and data access
  - Tier 2: more detailed criteria
  - Comprehensive and valid Tier 1 > Incomplete Tier 2

- Stage: the anatomical extent of the disease at diagnosis
  - Not after treatment

Toronto Staging: General principles (2)

- Tier 1 usually only indicates localised/limited or metastatic/advanced disease
    - Sometimes Tier 1 = Tier 2
- Tier 2 is more specific and more detailed
    - ➢ Register Tier 1 only when no info available to determine Tier 2
- For comparisons, Tier 2 categories may be collapsed to Tier 1 categories
- Missing info can lead to an unknown stage: Stage X

Toronto Staging:

CanStaging+ Tool

Developed by a collaboration between the Northern Ireland Cancer Registry (NICR), the International Agency for Research on Cancer (IARC), the Union for International Cancer Control (UICC)), and Cancer Council Queensland (CCQ).

Designed to help maximise the availability, standardisation and comparability of cancer staging internationally.

The tool provides:

- Automatic calculation of the international TNM staging classification versions 7 and 8 for a variety of tumour sites.
- Automatic **calculation of stage for childhood cancers using the business rules developed for the Toronto Paediatric Cancer Stage Guidelines**.

CanStaging+: an electronic staging tool for population-based cancer registries. I. Soerjomataram, M. Ervik, C. Fox, S.Hawkins, K. Yeung, G. Napolitano et al. August, 2021 LO, DOI:https://doi.org/10.1016/S1470-2045(21)00188-1 VOLUME 22, ISSUE 8, P1069].

Toronto Guidelines

Acute lymphoblastic leukaemia Toronto Paediatric Cancer Staging Guidelines	Hodgkin lymphoma Toronto Paediatric Cancer Staging Guidelines	Non-Hodgkin lymphoma Toronto Paediatric Cancer Staging Guidelines	Renal tumours (excluding renal cell carcinomas) Toronto Paediatric Cancer Staging Guidelines
Astrocytoma Toronto Paediatric Cancer Staging Guidelines	Malignant bone tumours Toronto Paediatric Cancer Staging Guidelines	Non-rhabdomyosarcoma soft tissue sarcoma Toronto Paediatric Cancer Staging Guidelines	Retinoblastoma Toronto Paediatric Cancer Staging Guidelines
Ependymoma Toronto Paediatric Cancer Staging Guidelines	Medulloblastoma and other CNS embryonal tumours Toronto Paediatric Cancer Staging Guidelines	Ovarian germ cell tumours Toronto Paediatric Cancer Staging Guidelines	Rhabdomyosarcoma Toronto Paediatric Cancer Staging Guidelines
Hepatoblastoma Toronto Paediatric Cancer Staging Guidelines	Neuroblastoma Toronto Paediatric Cancer Staging Guidelines		Testicular germ cell tumours Toronto Paediatric Cancer Staging Guidelines

benchista

CanStaging+ Home Sites Staging system ? Log in

Neuroblastoma

Toronto Guidelines

Tumour ID:	0 Auto
Tier1	
Age (in months)	Please Choose Reset
Distant metastatic disease at diagnosis	Yes No Don't know
Metastasis confined to skin, liver and/or bone marrow	Yes No Don't know
Locoregional tumour	Yes No Don't know
Tier2	
Age (in months)	Please Choose Reset
Distant metastatic disease at diagnosis	Yes No Don't know
Metastasis confined to skin, liver and/or bone marrow	Yes No Don't know
Tumour involves one or more Image Defined Risk Factors (IDRFs)	Yes No Don't know
Tumour confined within one body compartment	Yes No Don't know
	Reset form

https://canstaging.org/tool?tnm_version=Toronto

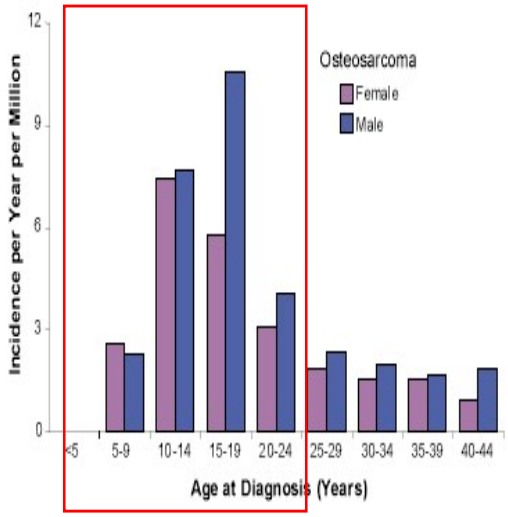
Osteosarcoma

Clinical expert: Dr Nathalie Gaspar

Osteosarcoma: Epidemiology

- Standardised Incidence in world population = 3 /million inhabitants/year
- 0,5% of cancers
- 5% of cancer in children and adolescents
- Pic incidence 14 years
- Male predominance

Children and AYA



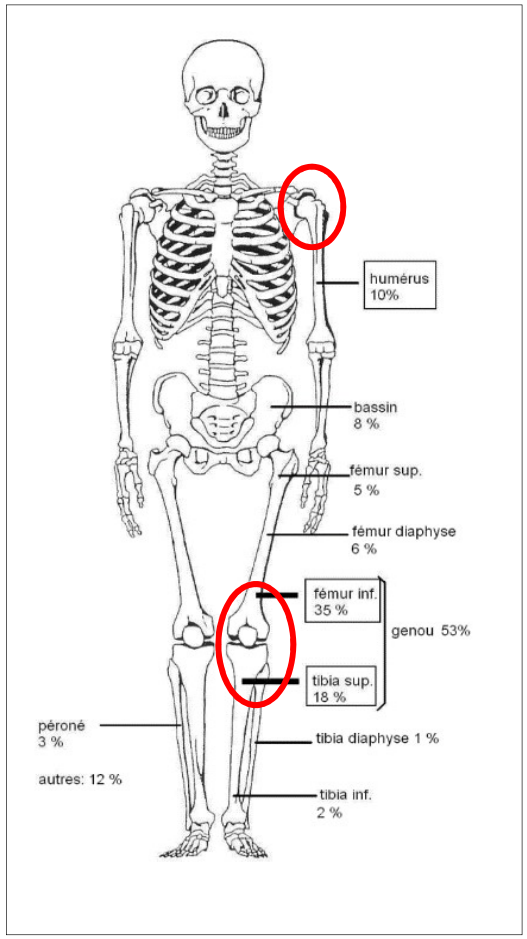
SEER database

Favouring factors

- Genetic
  - Li-Fraumeni
  - Rétinoblastome héréditaire
  - Rothmund-Thomson
- Radiations
- Pre-existing bone lesions

Osteosarcoma: Presentation

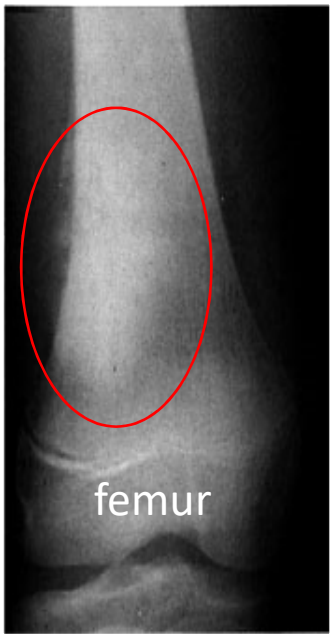
Long bones
Close to the knee, far from elbow

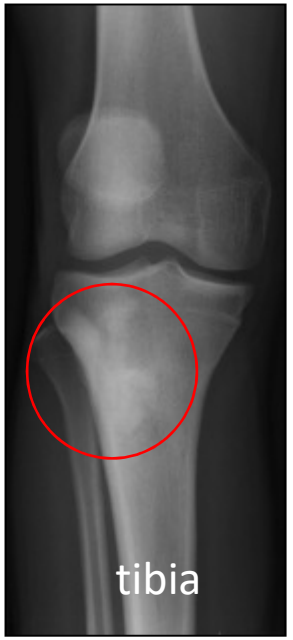


Bone axial and STS osteosarcoma are rare: genetic predisposition ?

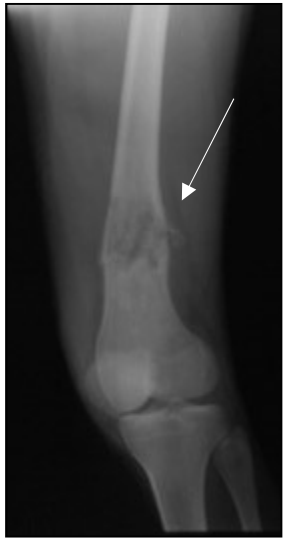
Pain +/- swelling

ostocondensant lesion of the metaphysis





Pathological fracture



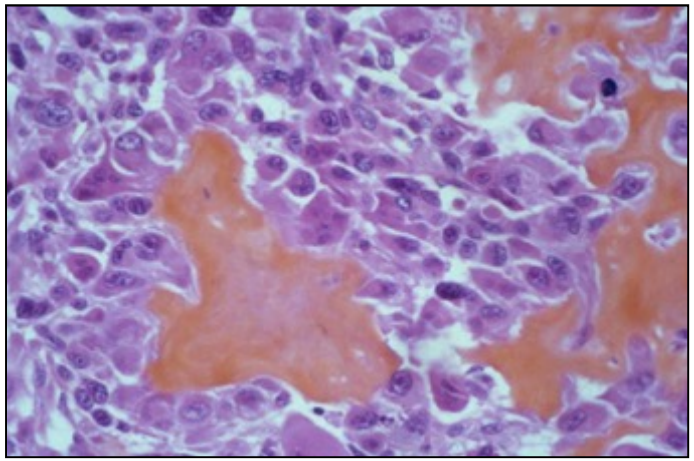
Standard radio

Osteosarcoma: Diagnostic

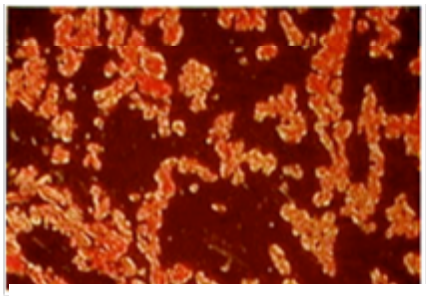
Biopsy in an expert center

To be interpreted with the Imaging

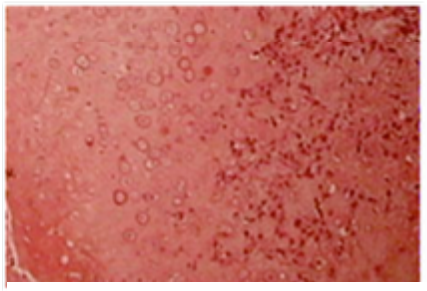
- Malignant tumour of the bone, with tumour cells producing osteoid tissue
- No specific markers



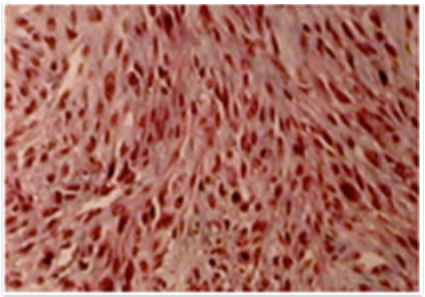
Several sub-types



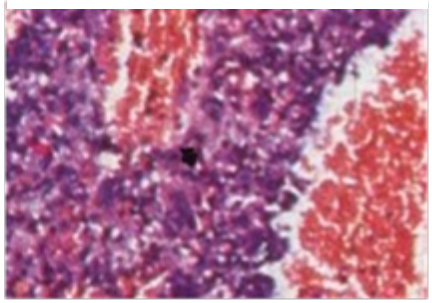
Osteoblastic



Chondroblastic



Fibroblastic

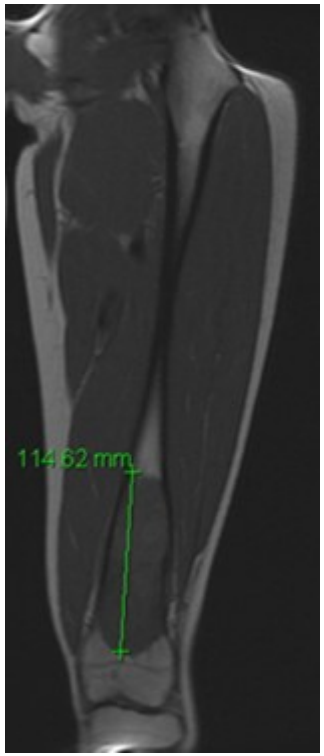


Telangiectasis

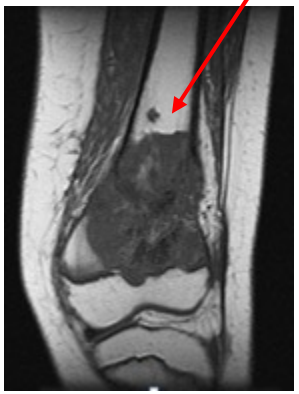
Osteosarcoma: Extension

Loco-regional extension

MRI of the whole bone
with upper and lower articulation



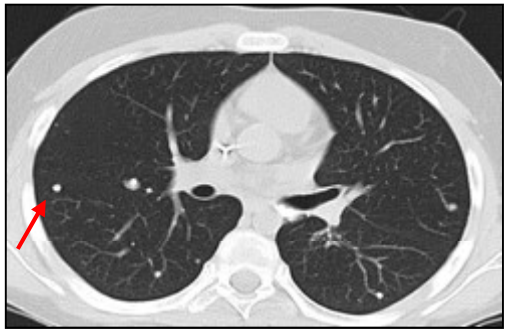
Skip metastasis
Small lesion on the same bone than primary tumour



Metastatic extension

25% of metastasis at diagnosis

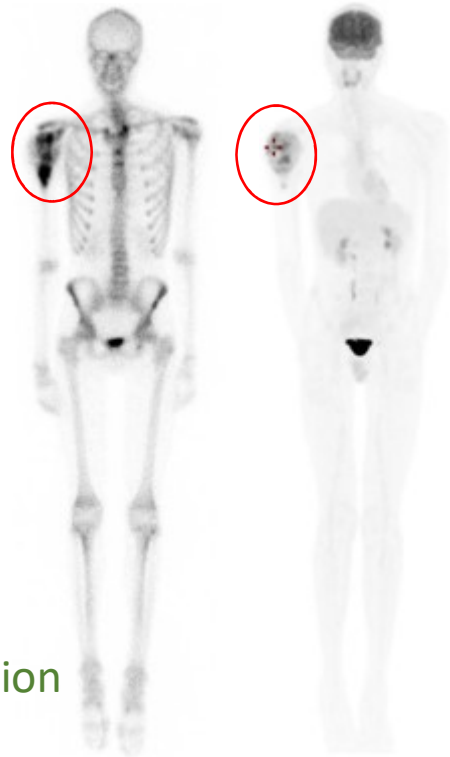
Lung = 80% of metastasis
Chest CT-scan



Other mets loc
= rare

Bone metastasis

Bone T99m scinti or **PET-scan**



Bone Formation

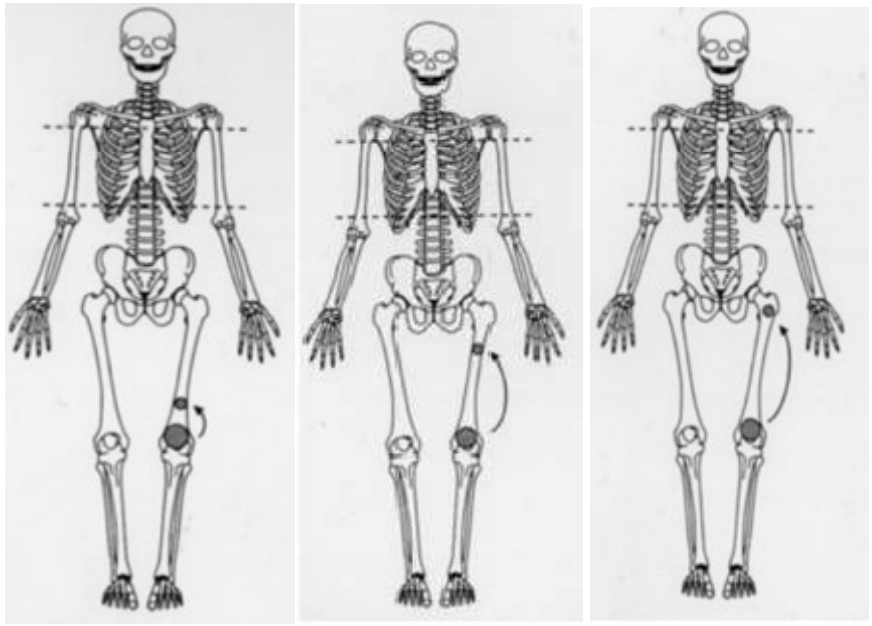
Pb of growth plate fixation

Osteosarcoma: Extension

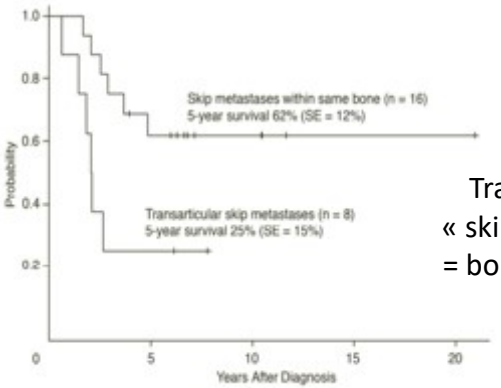
At diagnosis
IRM of the whole bone with upper and lower articulation
+ bone scinti And/or PET-scan

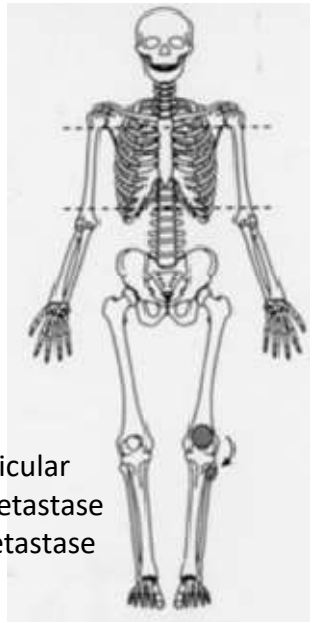
Skip metastasis are rare

Small bone metastasis in the same bone

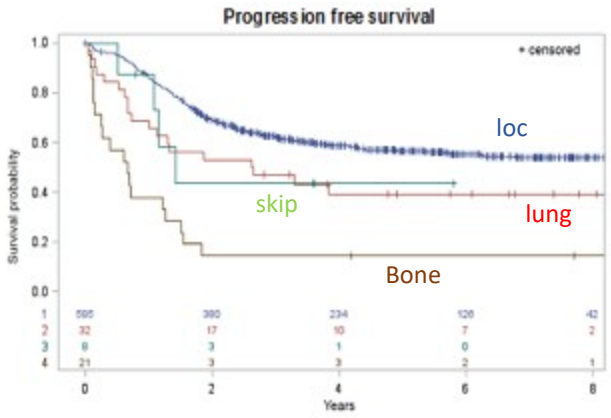


COSS experience
24 pts out of 1765 osteosarcomas
- 13 without othe mets
- 9 with associated lung mets





Transarticular
« skip » metastase
= bone metastase



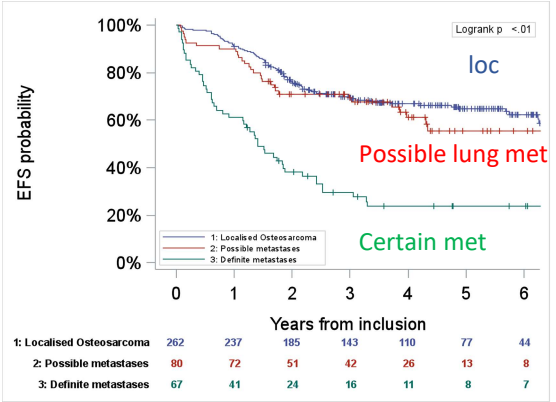
OS2006 experience
Skip metastasis
Prognostic close from lung metastatic patients

C Lervat SIOP 2019

Osteosarcoma: Extension

Definition of lung metastase

Lun mets	EURAMOS-1	OS2006
No	None	None
Possible	All other lesion	All other lesion
Certain	≥ 1 lesion ≥ 10mm ≥ 3 lesions ≥ 5mm	≥ 1 lesion ≥ 10mm ≥ 2 lesions, 5-9mm ≥ 5 lesion < 5mm, well limited



OS2006 MEI regimen
GASPAR N et al. EJC 2018

Chest CT-scan at diagnosis

Pathological report after lung surgery

Performed if lung lesions persist under treatment

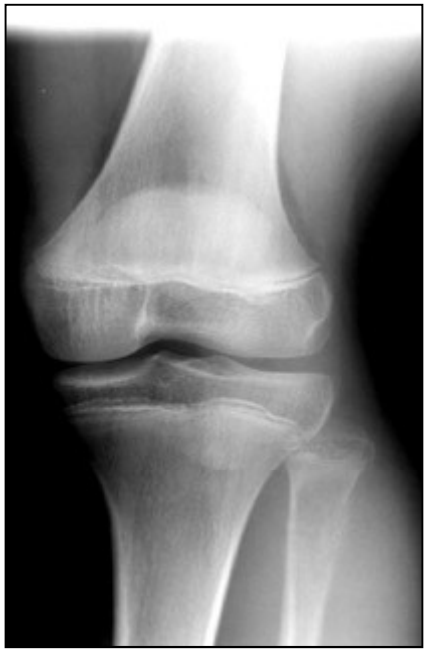
+/- surgery of residual lung metastasis

Neoadjuvant chemotherapy

PT SURGERY

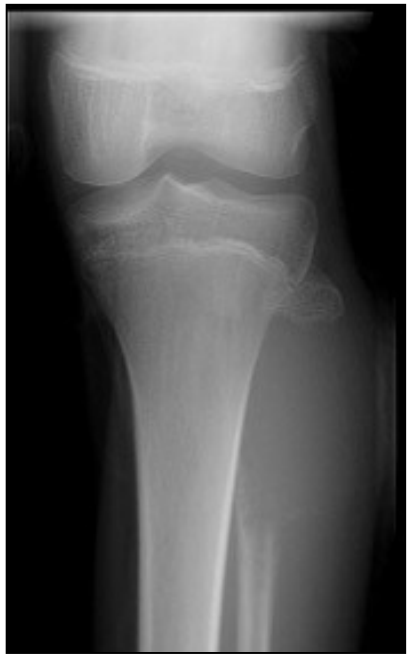
Post-operative chemotherapy

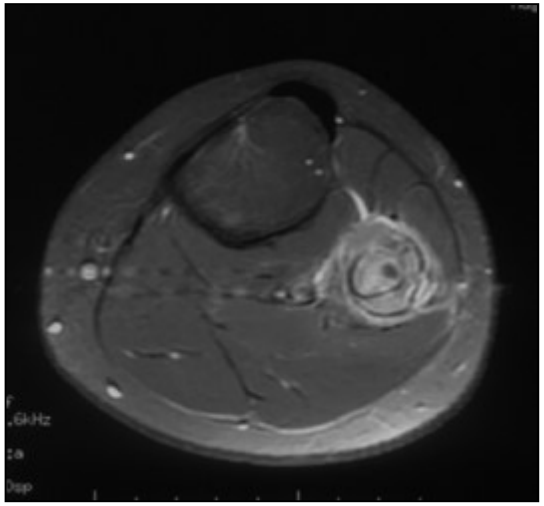
Osteosarcoma: An emergency

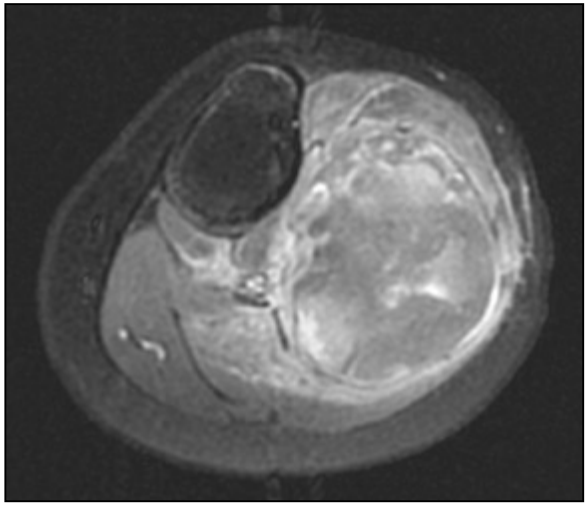


3 weeks later

- Complicates surgery
- Increase sequeal risk
- Might complicate interpretation of tumour evolution under chemotherapy







Osteosarcoma: Treatment

Methotrexate
Adramycine
Platinum
Ifosfamide
Etoposide

Conservative surgery / reconstruction

+/- surgery of residual lung metastasis

Early prophylaxis of metastases
To facilitate conservative surgery
Evaluation of histological response

prophylaxis of metastases

Biopsy

Neoadjuvant chemotherapy

PT

SURGERY

Post-operative chemotherapy

MAP

RADIOTHERAPY
Only for inoperable disease

MAP

Adapted to age

Adapted to risk factor of relapse

Adapted to PgP status

Osteosarcoma: Prognostic factors

benchista

At diagnosis

Metastatic status

The most powerful risk factor

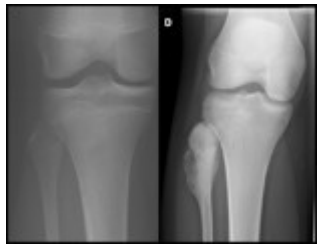
- Lung
- Bone

Primary tumour
Size ≥8cm

Elevated LDH

Neoadjuvant chemotherapy

Osteosarcoma size might not decrease
But the lesion might calcify



PT

SURGERY

During first line treatment

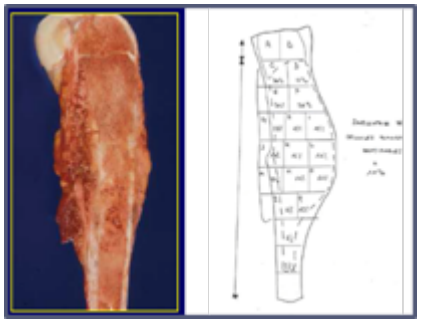
Doutfull lung lesions might be confirme or not at surgery

+/- surgery of residual lung metastasis

Post-operative chemotherapy

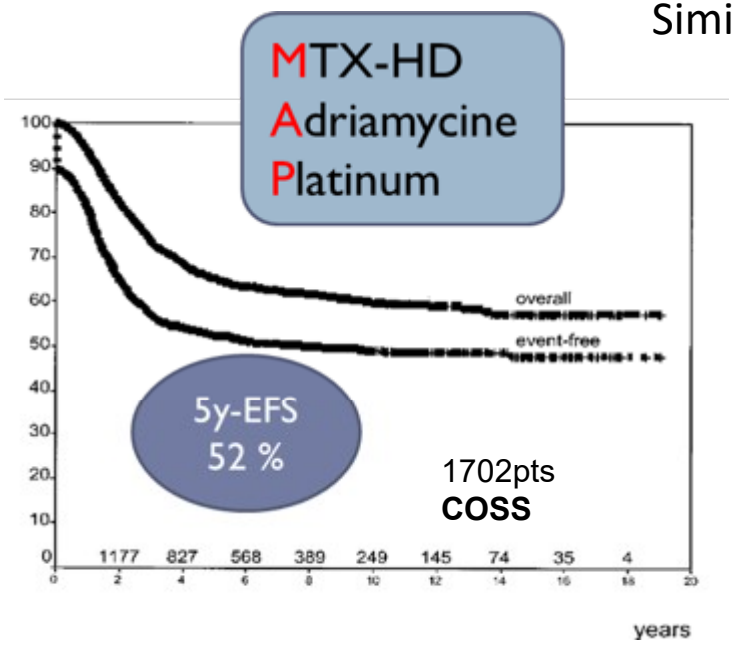
Histological response

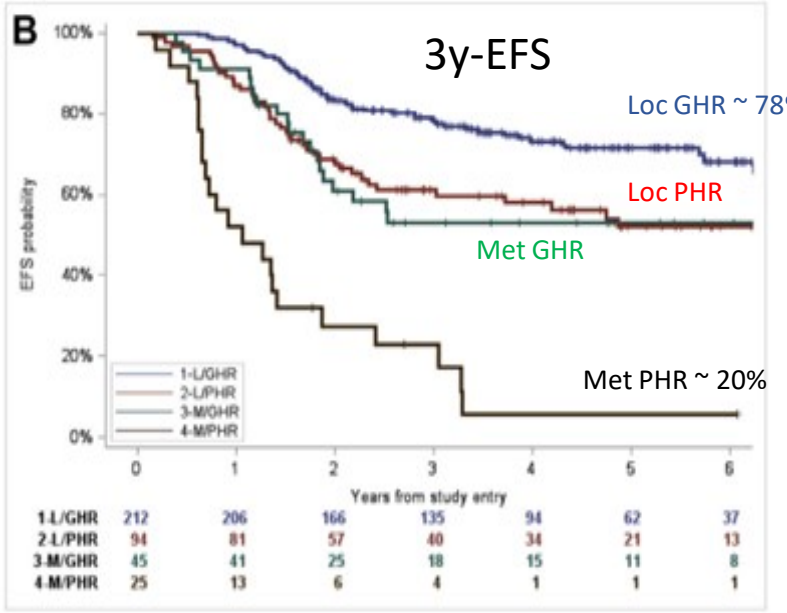
The most powerful risk factor in localised disease



Osteosarcoma: Survival

Similar to EURAMOS-1 data





OS2006 MEI regimen

GASPAR N et al. EJC 2018

Osteosarcoma: Exceptions

High-grade osteosarcoma

- Inoperable : radiotherapy can be proposed instead of surgery
- initial surgery : chemotherapy done on adjuvent setting, duration ?

Low grade osteosarcoma : surgery

T – Primary Tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour

Appendicular Skeleton, Trunk, Skull and Facial Bones

T1 Tumour 8.cm or less in greatest dimension
T2 Tumour more than 8.cm in greatest dimension
T3 Discontinuous tumours in the primary bone site

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

M – Distant Metastasis

M0 No distant metastasis
M1 Distant metastasis
M1a Lung
M1b Other distant sites

Stage – Appendicular Skeleton, Trunk, Skull and Facial Bones

Stage IA	T1	N0	M0	G1, GX Low Grade
Stage IB	T2, T3	N0	M0	G1, GX Low Grade
Stage IIA	T1	N0	M0	G2, G3 High Grade
Stage IIB	T2	N0	M0	G2, G3 High Grade
Stage III	T3	N0	M0	G2, G3 High Grade
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
Stage IVB	Any T	N0	M1b	Any G

Osteosarcoma: Non-stage prognostic factors

Solid Tumour	Essential	Additional	New and Promising	Comments
Osteosarcoma	None specified			Tumour response* not agreed as an NSP

*Response to therapy, either radiological or pathological, was excluded as an NSP to be collected by CRs given the wide variation at a population level in the treatment received, timepoint and modality of assessment, and definition of response.

Gupta et al. Development of paediatric non-stage prognosticator guidelines for population-based cancer registries and updates to the 2014 Toronto Paediatric Cancer Stage Guidelines. **Lancet Oncol 2020; 21: e444–51**

Ewing sarcoma

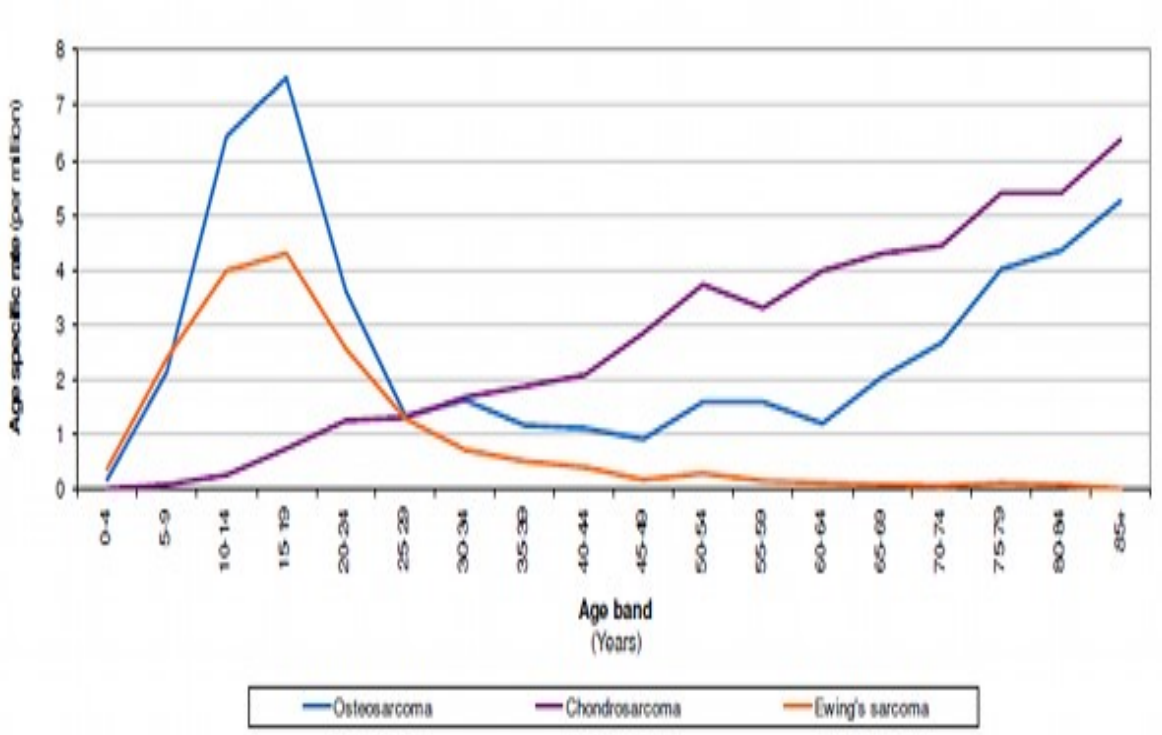
Clinical expert: Dr Sandra Strauss

Ewing sarcoma: Epidemiology

Rare tumour, 2nd most common primary bone tumour in children and teenagers

Incidence: 1- 2 per million

Peak incidence- 15-19 years. Very rare over 50 years



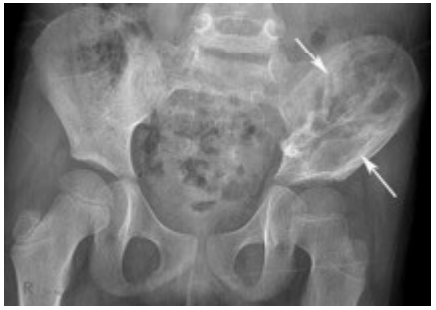
Male-to-female ratio 1.5:1

Highest in Caucasian pop

Whelan, et al , Int J Canc 2012

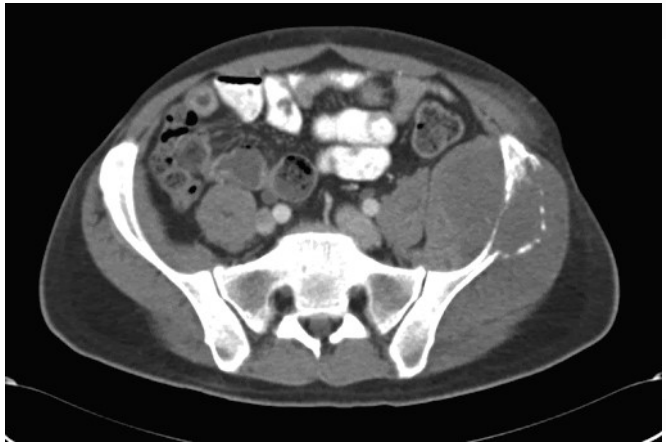
Ewing sarcoma: Presentation and primary sites

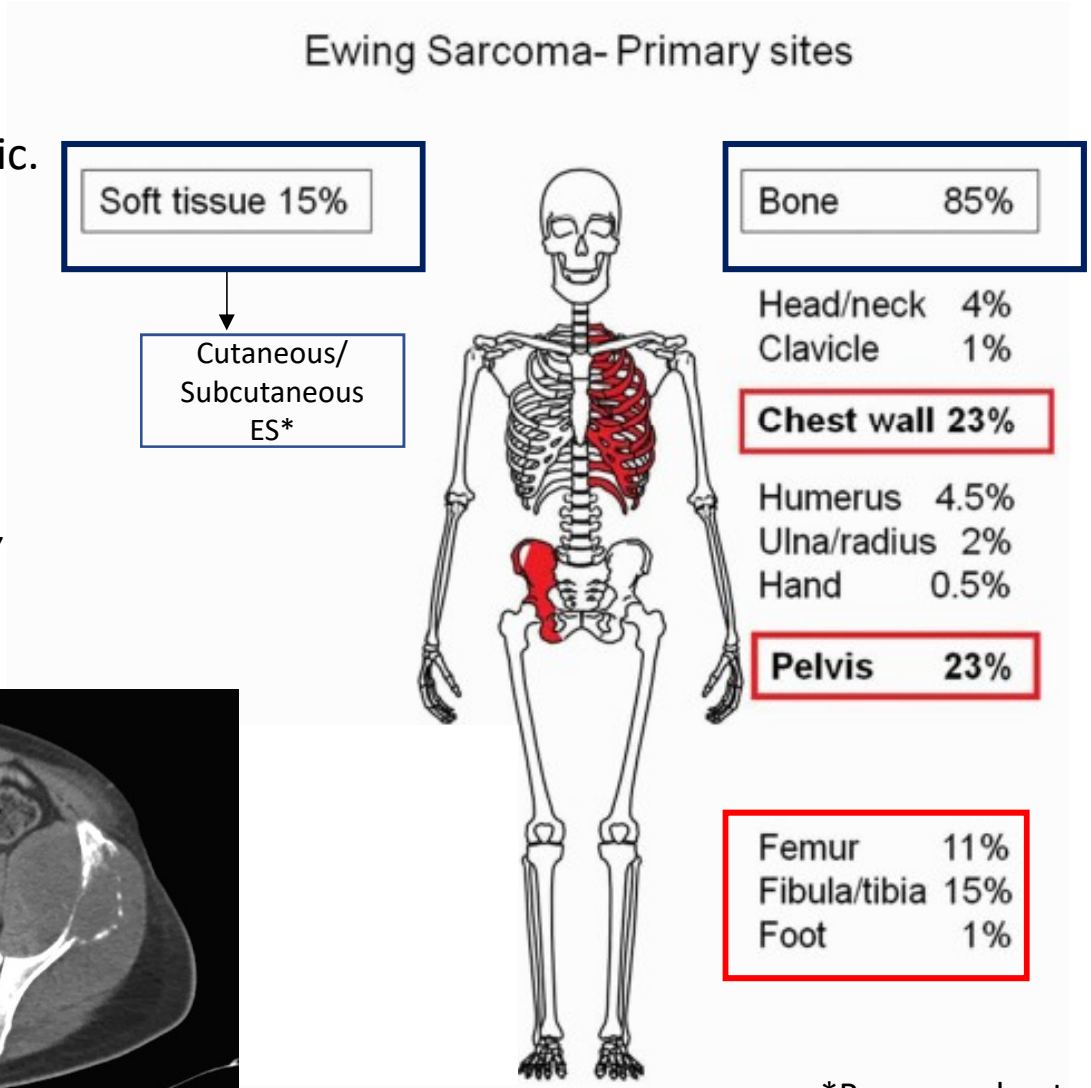
- Present with pain +/- lump
- Diagnosis can be delayed, partic. in pelvis
- Weight loss and fever



XRAY

MRI



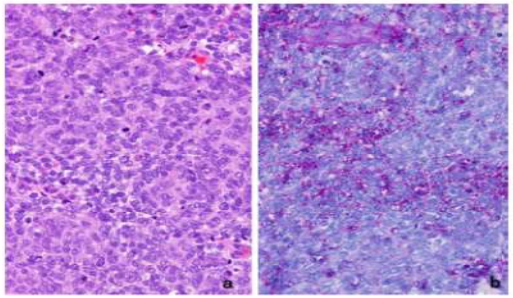


*Rare- good outcome

Ewing sarcoma:
Making the diagnosis

DIAGNOSIS ON A BIOPSY – USUALLY PERCUTANEOUS BUT ON OCCASION MAY BE A SURGICAL / OPEN BIOPSY

- Morphology: Small round blue cells
- IHC: CD99 positive



Molecular diagnosis

- Characterised by **specific rearrangement**
- EWSR1 with ETS family of genes: **most common EWSR1-FLI1**

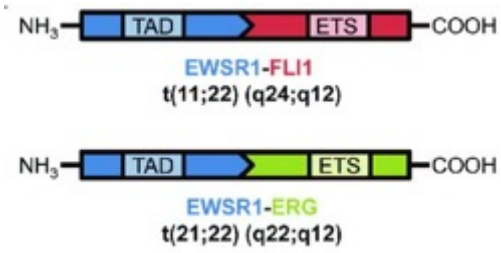


Table 2 Most common types of translocations found in Ewing sarcoma

Translocation	Fusion gene	% of tumors exhibiting EWS gene rearrangement
t(11;22)(q24;q12)	*EWSR1-FLI1*	85
t(21;22)(q22;q12)	*EWSR1-ERG*	10
t(7;22)(q22;q12)	*EWSR1-ETV1*	rare
t(17;22)(q21;q12)	*EWSR1-ETV4*	rare
t(2;22)(q35;q12)	*EWSR1-FEV*	rare

→ **Now is pre-requisite for diagnosis: FiSH or RT-PCR for translocation**

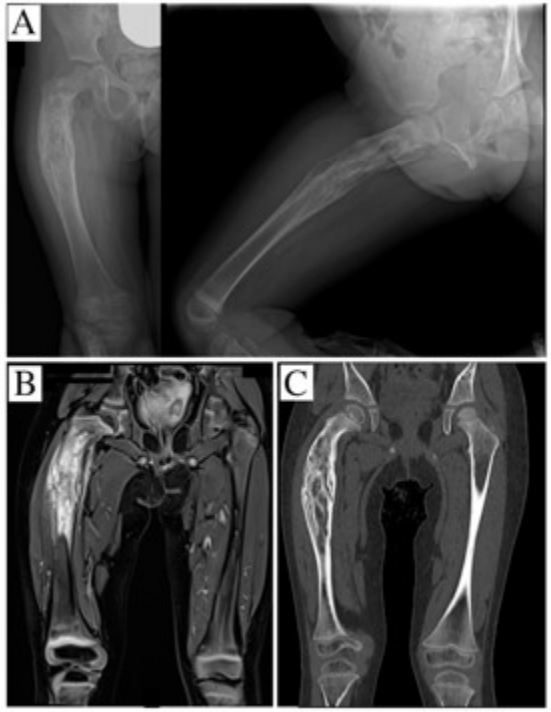
→ May not be available on **registries so analyses may include Ewing's–like tumours**

Ewing sarcoma:
Imaging of primary tumour

Primary tumour

MRI whole bone

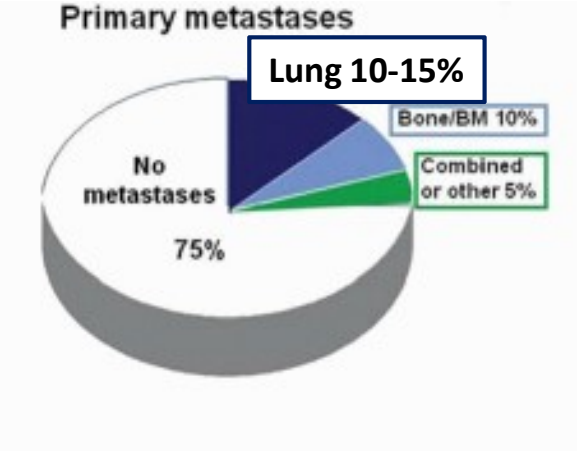
skip metastases not commonly seen in ES
but important to see full extent of disease
to plan local therapy as it needs to include the full volume



Ewing sarcoma: Staging

75% localised

25% metastatic



~ 3% lymph node mets
(loco-regional disease)

Diagnosed on MRI of whole bone
+/- PET scan

Incorporated into local control strategies

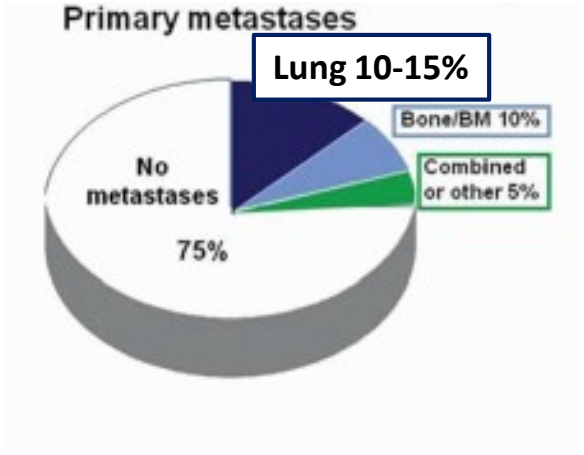
Impact on outcome not well-defined

Ewing sarcoma: Staging

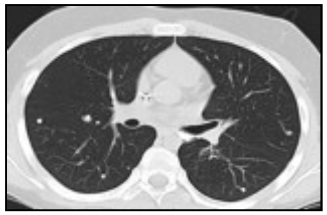
75% localised

25% metastatic

Lung



CT chest (high res)



Indeterminate pulm nodules (IPN) seen – one study 8.7% pt*

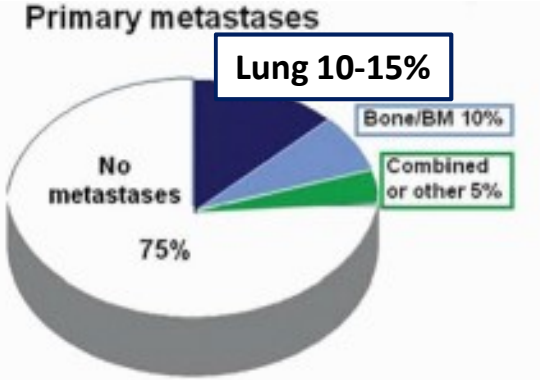
Impact on survival not well defined

Tsoi, et al. J Clin Orth, 2021

Ewing sarcoma: Staging

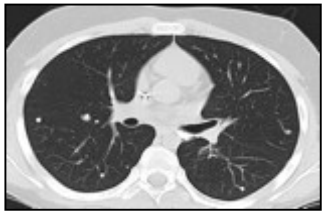
75% localised

25% metastatic



Lung

CT chest (high res)



Bone

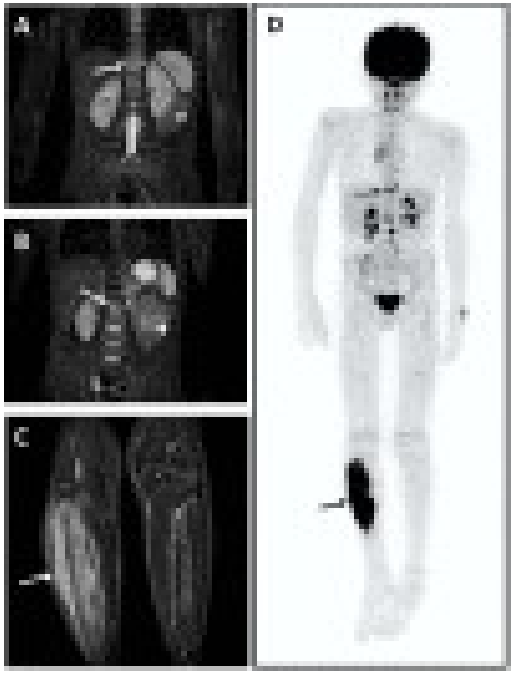
Skeletal imaging

Bone scan: traditional

****PET /CT or WB MRI***

- Increased sensitivity,

PET also detects BM mets

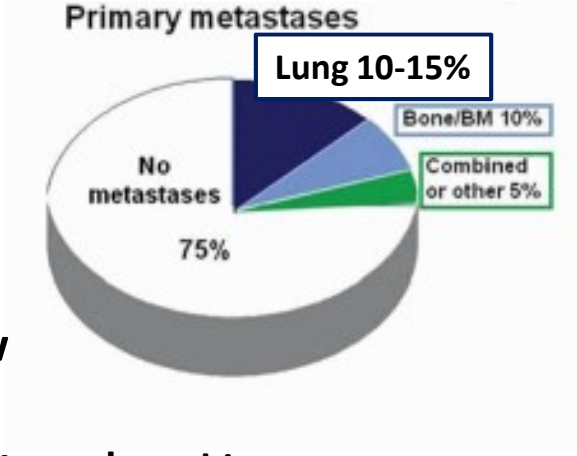


If indeterminate abnormality – pt would have a dedicated MRI and possibly a biopsy, particularly if oligo-metastatic

Ewing sarcoma: Staging

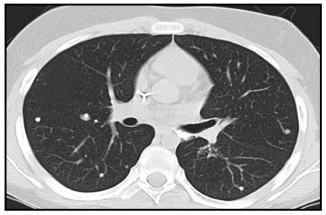
75% localised

25% metastatic



Lung

CT chest (high res)



Bone

Skeletal imaging

Bone scan: traditional

******PET /CT or WB MRI***

- Increased sensitivity,

PET also detects BM mets

If indeterminate abnormality – pt would have a dedicated MRI and rarely a biopsy, particularly if oligo-metastatic

Bone Marrow

bilateral aspirate and trephine – pathology diagnosis –reported by haematology

Recent reviews and new ESMO guidelines[1]
– BM not mandated outside clinical trials if had PET/CT or WB MRI as unlikely to influence management, however practice differs

- 1. Strauss et al, Ann Onc, 2021

Risk groups and clinical prognostic factors

Patient risk stratification

Localised disease

- **Standard risk (SR)**-small volume < 200ml
- **High risk (HR)**
  - **Large volume primary tumour > 200ml**
  - **Poor response to chemotherapy**

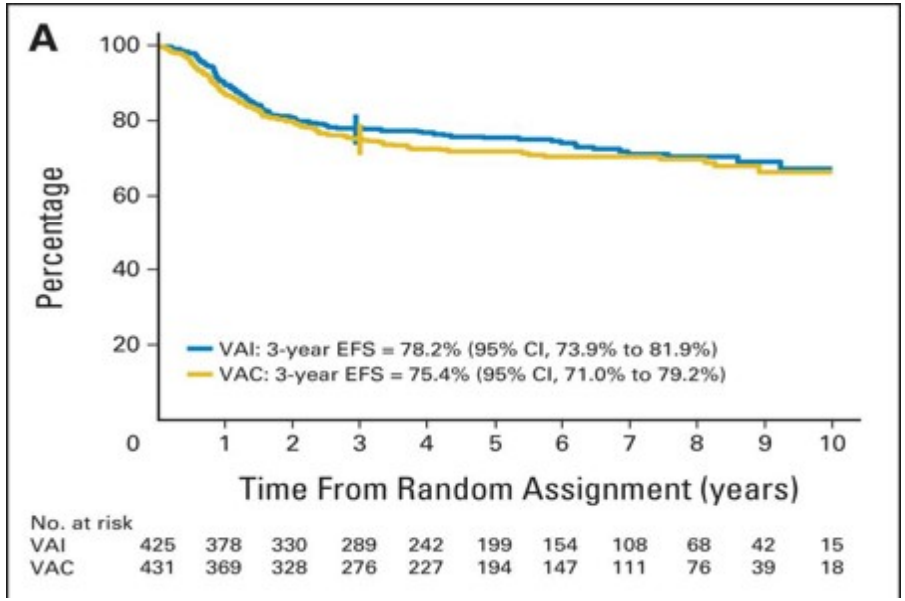
Metastatic

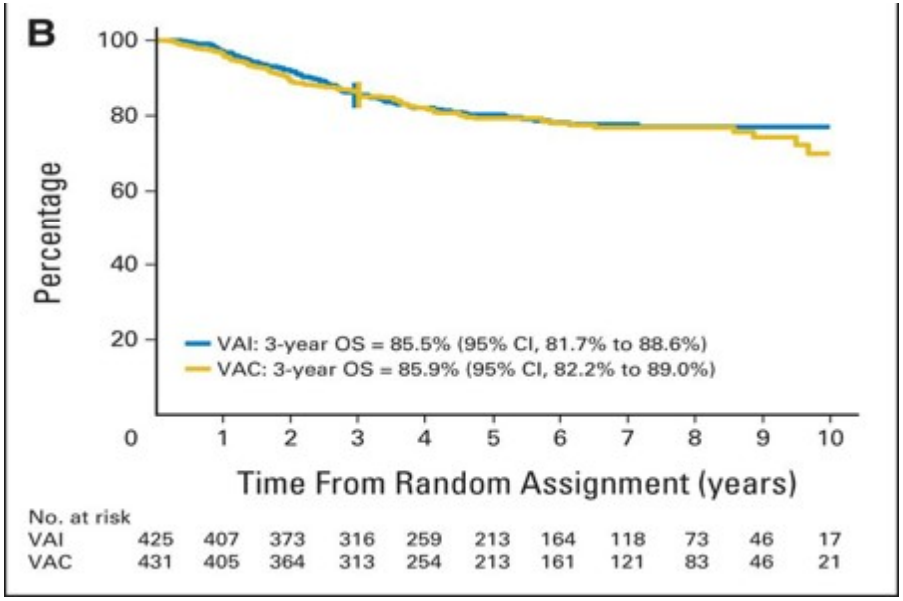
- **Lung metastases (R2)**
- **Extra pulmonary metastases (R3)– Bone and bone marrow +-/ other**

→ **Treatment has evolved through international collaborative clinical trials**

Survival: Localised Std Risk ES

EuroEwing 99- trial





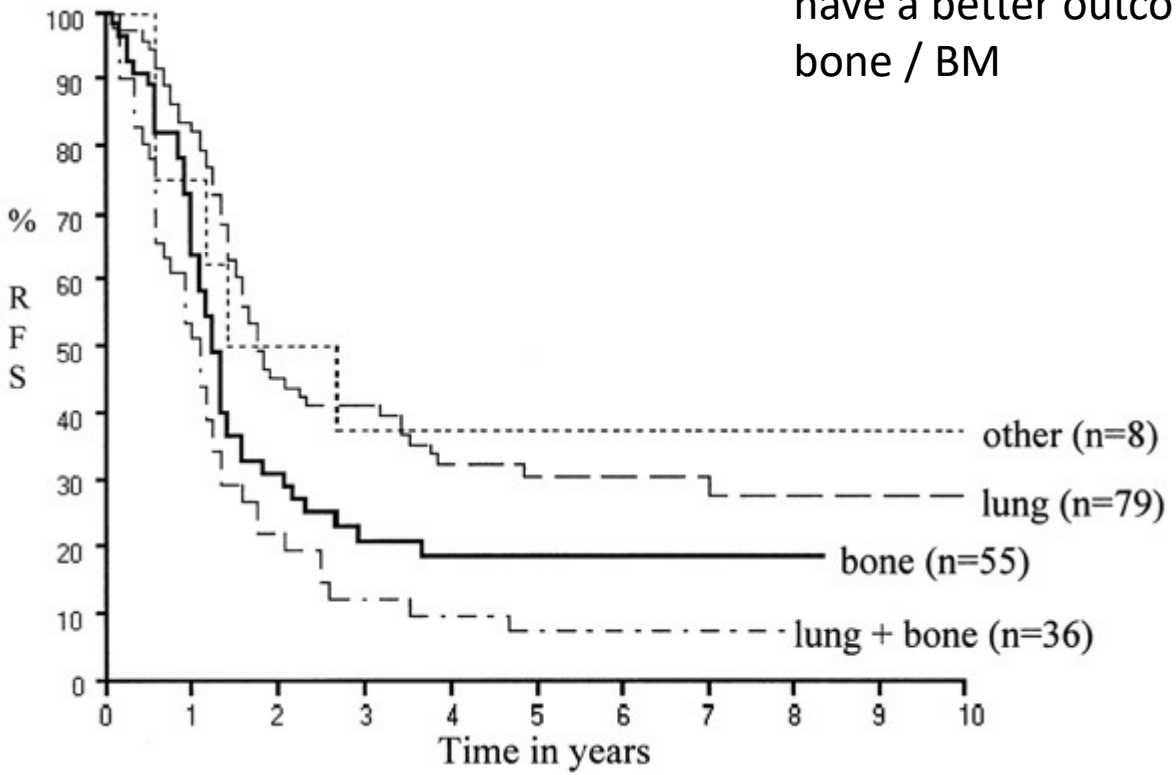
3 yr EFS = 78%

3 yr OS = 85%

Le Deley, et al, JCO, 2014

Survival: Metastatic Ewing sarcoma

Patients with lung metastases have a better outcome than bone / BM



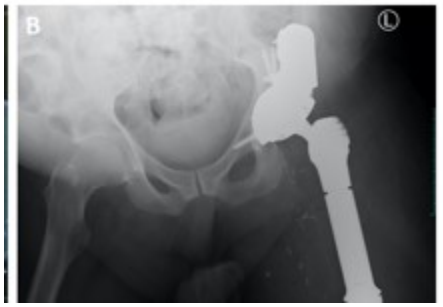
In recent clinical trials up to 50% pts with lung only mets survival 5 years

Bone/ BM:

< 20%

Ewing sarcoma: Treatment

LOCAL THERAPY



Surgery and / or Radiotherapy (RT)

- through discussion at expert tumour board

Depends on many factors:

- age, primary site, size and local extension

Overall surgery –has better outcomes – resect if possible

CONSOLIDATION TREATMENT:

- chemotherapy +/-whole lung radiotherapy +/- high dose chemotherapy (v selected patients**)**

Local therapy - Ewing sarcoma- sensitive to radiotherapy

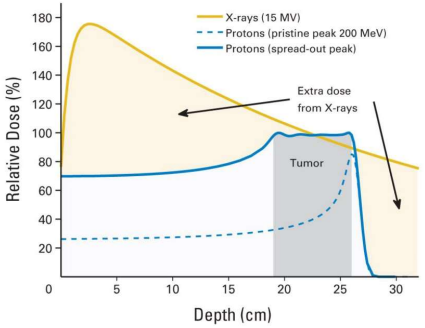
SURGERY RECOMMENDED where possible but if not

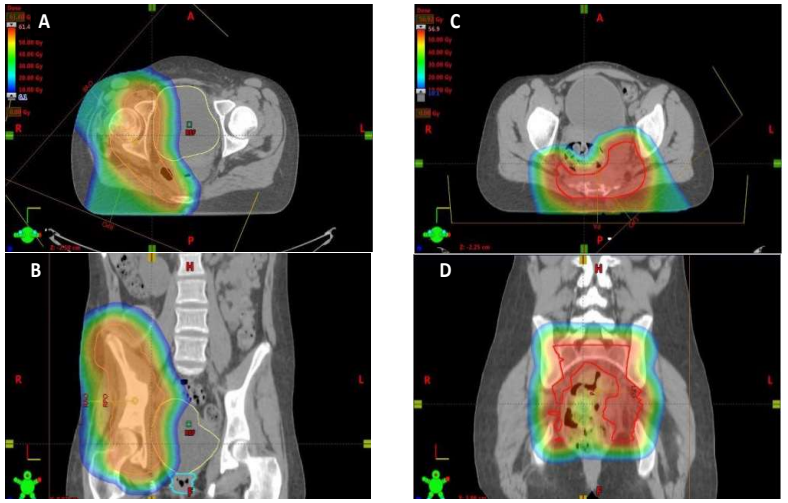
DEFINITIVE RADIOTHERAPY – can cure patients with inoperable disease

- eg: sacrum or pelvic tumours where morbidity too great
- Also spinal- often have decompressive surgery, further surgery not shown to improve outcome

Proton Beam Therapy

increasingly used particularly for pelvic, spinal and chest wall disease





Ewing sarcoma: post–operative radiotherapy (port)

RADIOTHERAPY

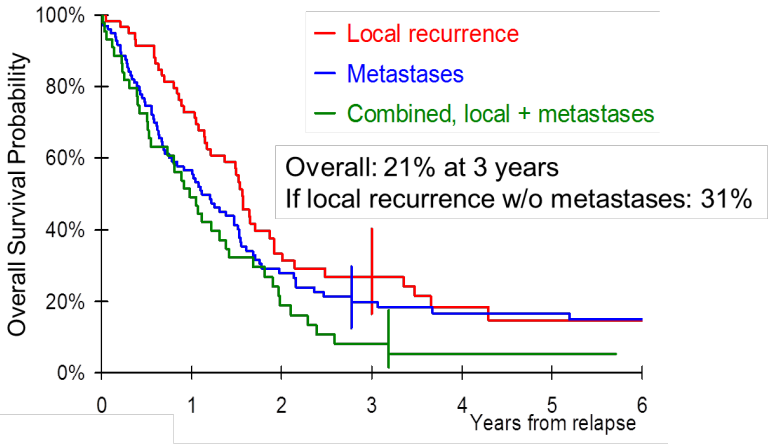
If tumour recurs at the primary site, outcome is poor, so need to optimise treatment at diagnosis

Statistical sig reduction in Local Recurrence if PORT (HR=0.43% (0.21-0.88, p=0.02) [1]

Most marked - large tumours (> 200mL)

→ **Recommended for all patients apart from small tumour with good response**

→ **If definitely having, then often given pre-operatively**



Radiotherapy –important in reducing local recurrence (halves) –only tumours that are not irradiated are small and good response (>90%). If definitely –pre-op. consider PBT

OTHER INDICATIONS

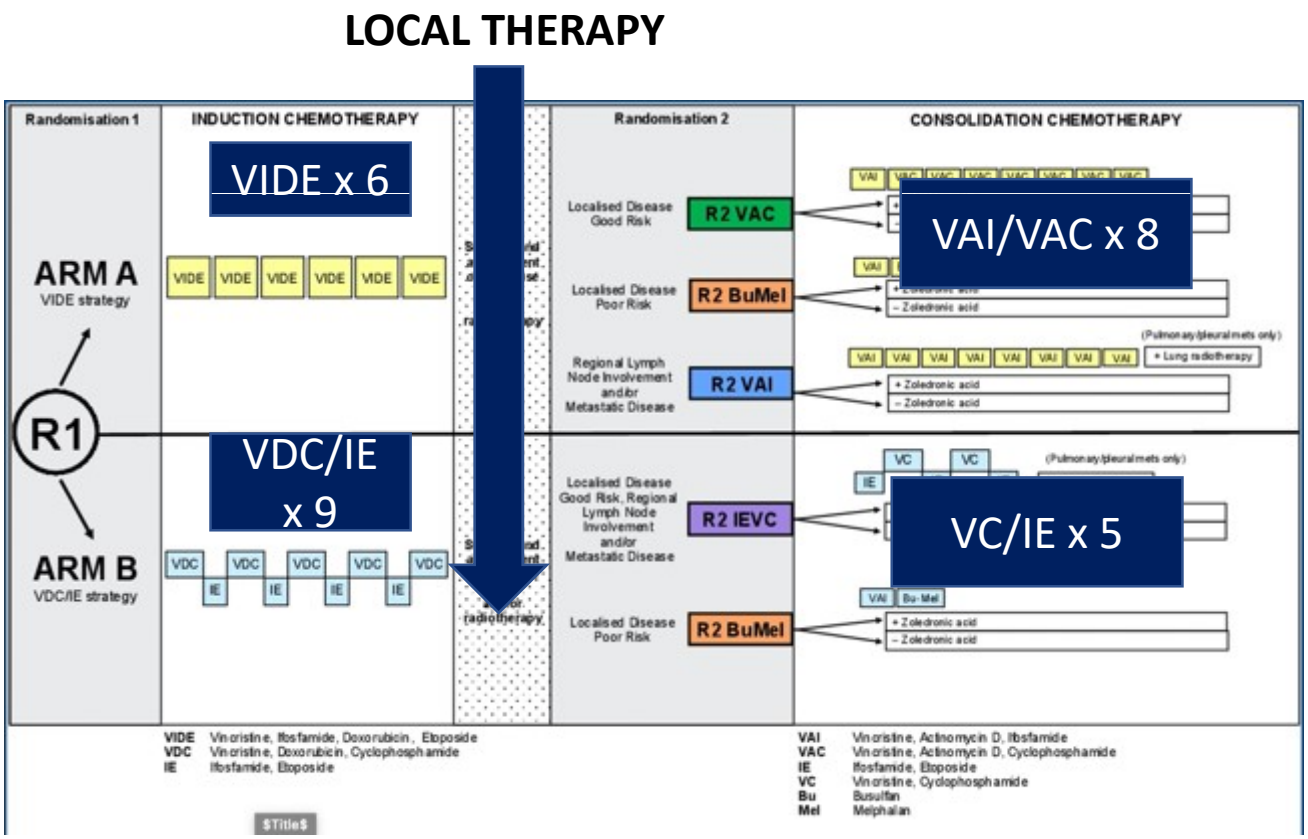
1. WHOLE LUNG RADIOTHERAPY – given at end of chemotherapy for patients with lung metastases, although no randomised evidence

2. **high dose (definitive RT) to patients with oligo-metastatic disease (one or two mets)**

Current Treatment Protocols

EuroEwing2012 - First line randomised trial

Compared two chemotherapy regimens: VIDE/VAI/VAC and VDC/IE (14 cycles)



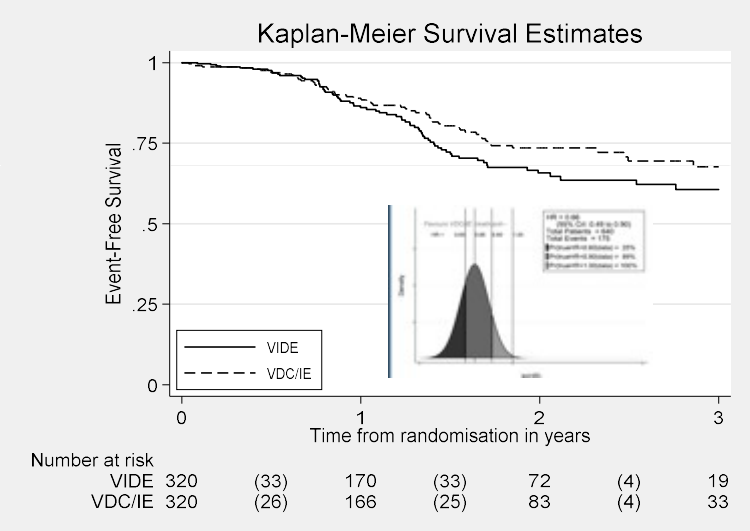
Randomisation 1 between the European standard of care and US

Randomisation 2 +/- zolendronic acid

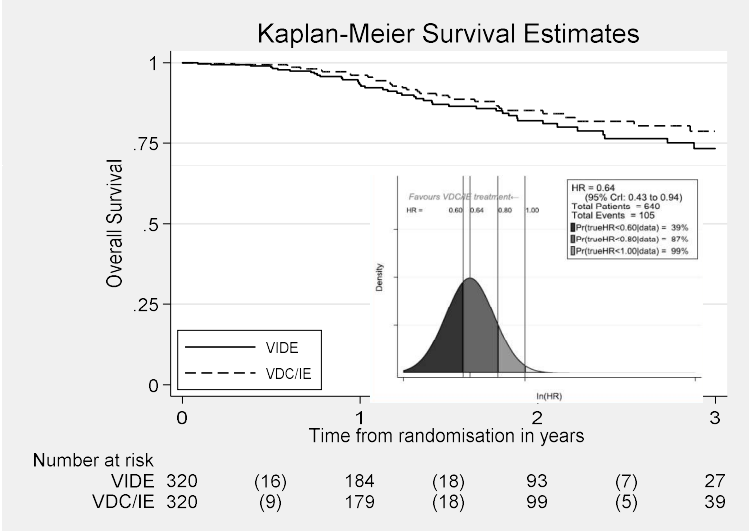
EuroEwing2012- First line randomised trial of adjuvant therapy

Recruited 640 patients across 14 countries in 5.5 years

Event-free survival



Overall survival



- **VDC / IE superior EFS and OS**

Brennan et al, ASCO 2020

- **VCD/IE standard of care for ES across all risk groups across Eu**

Ewing Sarcoma: Non-stage prognostic factors

Solid Tumour	Essential	Additional	New and Promising	Comments
Ewing sarcoma	None specified			Tumour response not agreed as an NSP

Gupta et al. Development of paediatric non-stage prognosticator guidelines for population-based cancer registries and updates to the 2014 Toronto Paediatric Cancer Stage Guidelines. **Lancet Oncol 2020; 21: e444–51**

Ewing sarcoma Summary

- Rare cancer- can arise in bone or soft tissue
- Metastasises to lung, bone, bone marrow
- Staging
    - CT chest to look for lung mets
    - skeletal staging varies across centres and countries
    - look for follow up imaging and additional pathology

Treatment:

- Induction chemotherapy, Local therapy (surgery and / or radiotherapy, consolidation chemotherapy
- +/- Whole lung RT; +/- high dose chemotherapy

Toronto Staging

Méric Klein, Belgian Cancer Registry

Dr Gemma Gatta, INT, Milan

Andrea Di Cataldo, University of Catania

Toronto Staging: Osteosarcoma and Ewing sarcoma

Tier 1 = Tier 2

- Only 2 stages
  - Localised or Metastatic
- Staging requires assessment of
  - Extent of disease

Localised	Metastatic
Tumour confined to the area of origin, including regional lymph nodes	Distant metastases present

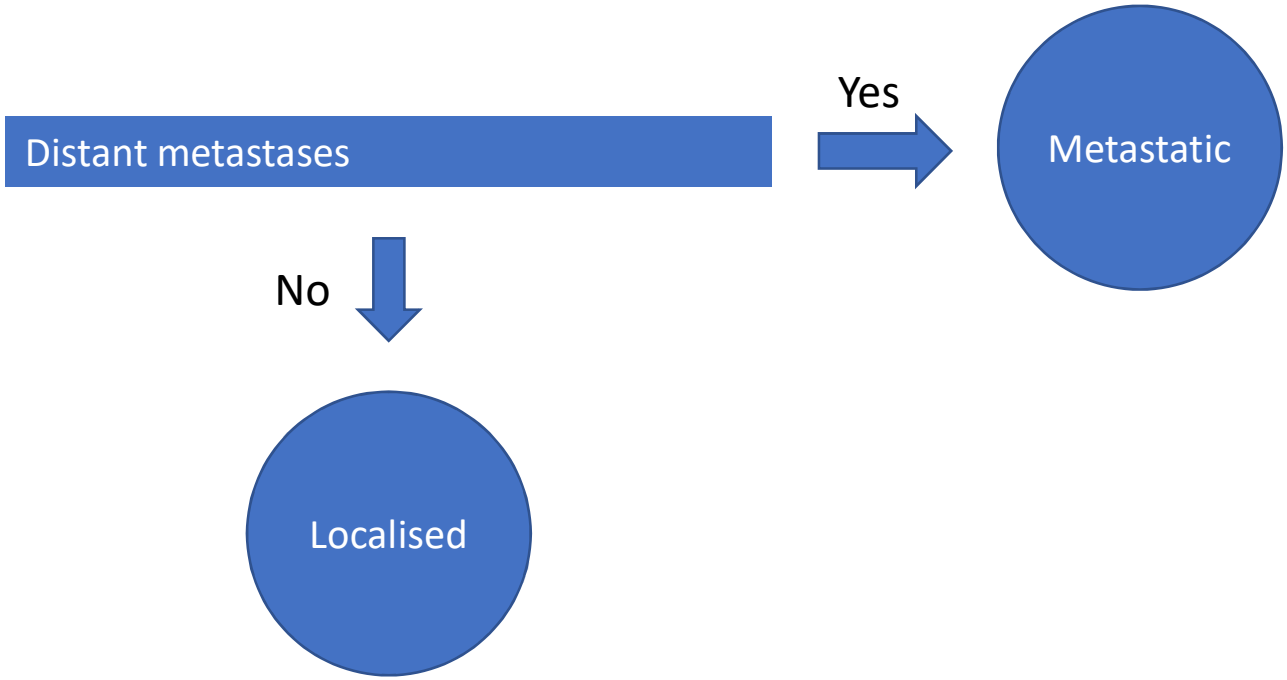
Skip lesions/skip metastases

Same bone → **Localised**

Different bone → **Metastatic**

Toronto Staging: Osteosarcoma and Ewing sarcoma

Tier 1 = Tier 2



Osteosarcoma and Ewing Sarcoma:

Exercises and Q&A

Exercise 1

A bulky tumour mass is found in the left ulna of a 8-year old patient. Left axillary lymph nodes are also involved. Further examination shows that this lesion is a 8cm long chondroblastic osteosarcoma.

What is the correct stage for this patient?

A. Localised

B. Metastatic

Exercise 2

A 10-year old girl comes in consultation because of pain of the right shin. Radiography and bone scintigraphy show a solitary focus of increased activity over the right tibial diaphysis.

MR imaging of the right tibia confirmed a diaphysis lesion, but also revealed another 1cm focus in the proximal tibial metaphysis.

Histological analysis is positive for an Ewing sarcoma of the right tibial diaphysis with a skip metastasis in the metaphysis.

CT scans of the chest were clear.

What is the correct stage for this patient ?

A. Localised

B. Metastatic

Exercise 3

- 8-year old patient
- MRI: 3cm lesion located on the head of the left humerus
- Biopsy: Ewing sarcoma
- CT scan of the chest: highly suspect lesion in the left lung

What is the correct stage for this patient ?

A. Localised
B. Metastatic

Exercise 4

A 7-year old patient suffers from an osteosarcoma of the right femur that also invades the left inguinal lymph nodes.

What is the correct stage for this patient ?

A. Localised

B. Metastatic

Exercise 5 (Osteosarcoma)

A ten year old boy with two tumour masses: one in the femur (4 cm) (C40.2, long bone lower limb) and one in the ankle joint (1.5 cm) (C40.3, short bone of lower limb), both lesions at right limb and are distinct. Histological analysis is positive for a chondroblastic osteosarcoma of the right lower limb.

What is the correct stage for this patient?

A. Localised

B. Metastatic

From: *Childhood cancer staging for population registries according to the Toronto Childhood Cancer Stage guidelines* by Aitken at al.

Osteosarcoma
Only two stages are recommended (localized or metastatic) for both Tier 1 and Tier 2.[2]

Definitions and notes
"Skip lesions", "skip metastases" or "seeding" in the same bone as the primary tumour are considered localized and not metastatic; if in a different bone to the primary tumour these are considered metastatic.

Staging criteria for osteosarcoma			
TIER 1		**TIER 2**	
Localized	Tumour confined to the area of origin including regional lymph nodes	**Localized**	Tumour confined to the area of origin including regional lymph nodes
Metastatic	Distant metastases present	**Metastatic**	Distant metastases present

Exercise 6 (Osteosarcoma)

- 8-year old patient
- MRI: 5 cm lesion located on the head of the left humerus
- Biopsy: small cell osteosarcoma
- Thorax Xray: suspected lesion of left lung measuring 4 mm, no other investigation to understand the nature of the lesion
- Start of pre surgery chemotherapy
- During chemotherapy, parents ask a second opinion to another hospital, here the CT scan of chest reports a small lesion suggesting a metastasis of osteosarcoma

What is the correct stage for this patient ?

A. Localised

B. Metastatic

From: *Childhood cancer staging for population registries according to the Toronto Childhood Cancer Stage guidelines* by Aitken at al.

General rules of staging

1. Stage is defined as extent of disease at diagnosis and is based on evidence acquired before treatment (with the exception of Wilms tumour, see page 34).

Exercise 7
(Ewing sarcoma of bone)

- 11-year old patient
- MRI: 5 cm lesion located on the pelvis
- Biopsy: Ewing sarcoma
- Before the start of treatment, all the investigations done, including bone marrow aspirate. All are negative, except the bone marrow aspirate the result of which arrives after the start of treatment and is positive.

What is the correct stage for this patient ?

A. Localised

B. Metastatic

Exercise 8
(Ewing sarcoma of bone)

- 11-year old patient
- MRI: 5 cm lesion located on the pelvis
- Biopsy: Ewing sarcoma
- Lung CT and PET are negative
- The result of bone marrow aspirate and trephine is: negative for pathological morphology and immunocytology, positive for molecular biology (specific transcript)

What is the correct stage for this patient ?

A. Localised

B. Metastatic

Exercise 9 (Osteosarcoma)

- 17-year old girl
- MRI: 5 cm lesion located on left part of the pelvis with highly suspected left inguinal nodes
- All the other investigations for staging are negative
- During surgical treatment, not anticipated by chemotherapy, discovery of two metastatic inguinal lymph nodes at left

What is the correct stage for this patient ?

A. Localised

B. Metastatic

Excel file Database Presentation: Osteosarcoma and Ewing Sarcoma

Fabio Didonè, Statistician,
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

The structure of the database (1)

The Database file is made up of 8 different excel sheets, the first is named "**Table 2**" and reflects the table 2 in the protocol, which contains six columns:

- The variable code
- The variable extended name
- The values that it can assume
- A brief description
- Explanatory notes (if necessary)
- The validation rules (if present)

The structure of the database (2)

- There are six excel sheets representing the **six different types of tumours.**

- The last excel page contains the **average time** to stage a patient with one of the six tumour type considered and the **data quality checks** (%DCO, %NOS, etc.)

The structure of the database (3)

The variables can be classified into the following '**macro areas**':

- Basic variables
- Imaging/examination performed before any treatment
- Source used for staging
- TG staging and NSPs (specific for every Tumour type)
- Primary treatment
- Relapse/recurrence/progression
- Follow-up.

Common Variables

- Basic variables
- Source used for staging
- Primary treatment
- Relapse/recurrence/progression
- Follow-up.

Common Variables: Basic Variables

	Variable name	values	Variable Description
Basic variables	Registry	alphabetic	Registry name, alphabetic
	Country	alphabetic	Country name, alphabetic
	Registry Patient Identification code	alphanumeric-10	Pseudo anonymized patient's ID code
	Year of birth	numeric- 4	Year of birth
	Age at diagnosis	numeric- 3	Age at diagnosis
	Year of diagnosis	numeric- 4	Year of diagnosis
	Sex	1,2,9	gender, boy/girl/unknown
	Base of diagnosis (as coded in the ENCR protocol)	0,1,2,4,5,6,7,9	DCO/Clinical/Clinical investigation/Specific tumou
	ICDO3-Topography	numeric- 3	only the numeric part of the ICD-O-3 topographic code
	ICDO3-Morphology	numeric- 4	malignant only, (behaviour=3)
	First previous cancer	1,0,9	Y/N/unknown presence of a first previous cancer
	First previous cancer definition	Ia, Ib, Ic, Id, Ie, IIa,	ICCC third edition code
	Year of diagnosis of the first previous cancer	numeric- 4	Year of diagnosis of the first previous cancer
	Second previous cancer	1,0,9	Y/N/unknown presence of a second previous cancer
	Second previous cancer definition	Ia, Ib, Ic, Id, Ie, IIa,	ICCC third edition code
	Year of diagnosis of the second previous cancer	numeric- 4	Year of diagnosis of the second previous cancer

Common Variables:
Source used for staging

	Variable name	values	Variable Description	Explanatory Notes
Source used for staging	Clinical report (hospital clinical records)	1,0,9	Y/N/unknown	was the data source a clinical report?
	Pathological report	1,0,9	Y/N/unknown	was the data source a pathological report?
	Administrative files (hospital discharge etc)	1,0,9	Y/N/unknown	was the data source an administrative file?
	Clinical study group	1,0,9	Y/N/unknown	was the data source a clinical study group?
	Others (string)	alphabetic-10	alphabetic	

Common Variables: Primary treatment

	Variable name	values	Variable Description
Primary Treatment defined as given within 1 year from diagnosis	*_Surgery	1,0,9	Y/N/unknown
	*_Chemotherapy	1,0,9	Y/N/unknown
	*_Chemotherapy type	1,2,3,4,9	Preoperative chemo/Postoperative chemo/ Both preoperative and postoperative chemo/ Chemotherapy only/Unknown
	*_Radiotherapy	1,0,9	Y/N/unknown

Note: *_ means the variable is optional

Common Variables:
Relapse or recurrence

	Variable name	values	Variable Description
Relapse/ recurrence/ progression	*_Relapse/ recurrence/ progression	1,0,9	Y/N/unknown
	*_Time in days from diagnosis to relapse/recurrence/progression	numeric	Time in days from diagnosis to relapse/ recurrence/progression, numeric

Note: *_ means the variable is optional

Common Variables: Follow up

	Variable name	values	Variable Description
Follow-up	Status of life	1,2,9	alive/dead/unknown
	*_Causes of death (CoD)	1,2,3,4,9	Toxicity of treatment, Tumor, Comorbidity previously present in the child, Others, unknown
	Time in days from diagnosis to death or last follow up	numeric	Time in days from diagnosis to death or last follow up, numeric

Note: *_ means the variable is optional

Specific Variables

- Imaging/examination performed before any treatment and their own results:
  - Imaging performed: 1='Yes', 0='No', 9='Unknown'
  - Imaging result: 0='Negative', 1='Positive', 2='Suspicious', 9='Unknown'
- TG staging and NSPs

Specific Variables: Imaging/examination performed for Osteosarcoma

Imaging/examination necessary for investigation of the **extension** of the disease are:

- CT/MRI primary site
- CT thorax
- Bone scan
- X-ray thorax
- PET
- Tissue biopsy (of non-primary sites suspicious for metastasis)

Note: the result of each exam performed is requested except for '*CT/MRI primary site*'

Specific Variables: Imaging/examination performed for Ewing Sarcoma

Imaging/examination necessary for investigation of the **extension** of the disease are:

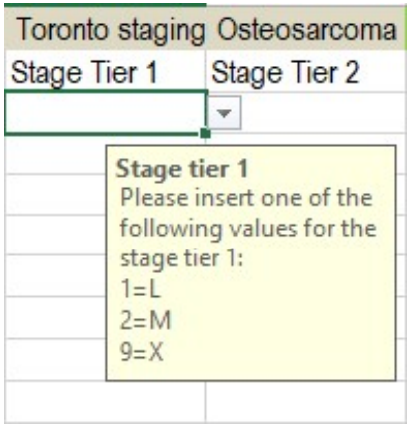
- CT/MRI primary site
- CT thorax
- Bone scan
- X-ray thorax
- PET
- Bone Marrow (BM) aspirate or BM biopsy

Note: the result of each exam performed is requested except for '*CT/MRI primary site*'

Specific Variables: TG staging and NSPs for Osteosarcoma and Ewing Sarcoma

Stage Tier 1 & Tier 2:

- L=Localized (Tumour confined to the area of origin including regional lymph nodes)
- M=Metastatic (Distant metastases present)
- X=Unknown



Note: "skip lesions", "skip metastasis" or "seeding" in the same bone as the primary tumour are considered localised and not metastatic; if in a different bone to the primary tumour these are considered metastatic.

	Essential	Additional	New and promising	Comments
Solid tumours				
Osteosarcoma	..	..	..	..
Ewing sarcoma	..	..	..	..

Table 2: The Lyon Paediatric Cancer Non-Stage Prognosticator Guidelines

Feedback of previous session focused on: Osteosarcoma and Ewing Sarcoma

Exercises overview

Important key points

- Cancer registries should routinely collect cancer stage for childhood cancer cases

- The Toronto Staging Guidelines are consensus guidelines for collecting childhood cancer stage in population based registries
  - Internationally consistent and comparable

- Toronto Stage is not intended for clinical practice / clinical decision making

When will we consider a lung metastasis ?

- Unlike for some clinical trials, no prescriptive definitions in the Toronto staging
- All the lesions might be considered as a metastasis, regardless their size
  - Histological confirmation → OK
  - Mention of “imaging positive for meta” → OK
  - Mention of “highly suspected” or “highly suspicious” lesion on imaging → OK
  - Mention of “suspect lesion” on imaging → Follow the opinion of the doctor
  - Mention of “possibly”, “maybe”, … → Do not record as metastatic

Be careful with the skip metastases located in the same bone than the primary tumour:

- Poorer prognosis than the tumours without skip metastasis.

  But this is an evolving adverse prognostic factor for risk stratification rather than staging at this point in time

- Still has to be classified as a Localised tumour

  - Stage as Metastatic only if located into another bone

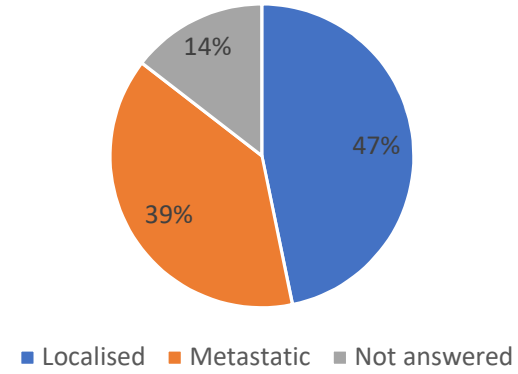
Exercise 4

A 7-year old patient suffers from an osteosarcoma of the right femur that also invades the left inguinal lymph nodes.

What is the correct stage for this patient ?

A. Localised

B. Metastatic



The regional lymph nodes for the lower limb are the ipsilateral popliteal and inguinal lymph nodes. Contralateral lymph nodes are thus distant metastases.

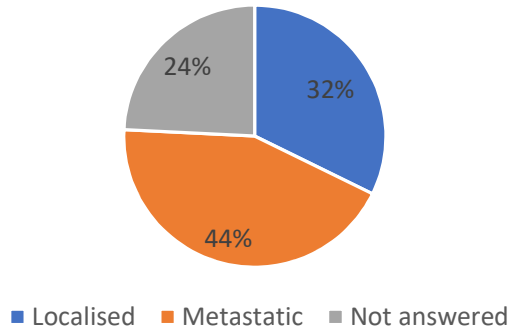
Exercise 5

A ten year old boy with two tumour masses: one in the femur (4 cm) (C40.2, long bone lower limb) and one in the ankle joint (1.5 cm) (C40.3, short bone of lower limb), both lesions at right limb and are distinct. Histological analysis is positive for a chondroblastic osteosarcoma of the right lower limb.

What is the correct stage for this patient?

A. Localised

B. Metastatic



Two histologically identical tumour masses in the bone. The smallest lesion is then considered as a distant metastasis of the biggest one. And since they are both located into a different bone, the lesion has to be classified as metastatic.

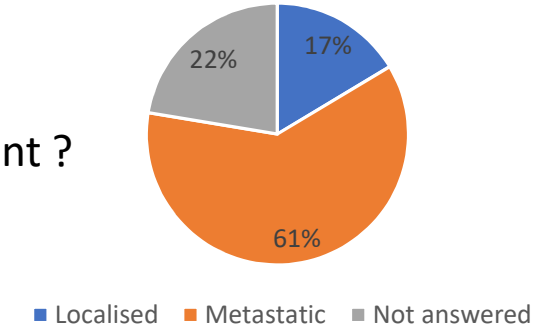
Exercise 6

- 8-year old patient
- MRI: 5 cm lesion located on the head of the left humerus
- Biopsy: small cell osteosarcoma
- Thorax Xray: suspected lesion of left lung measuring 4 mm, no other investigation to understand the nature of the lesion
- Start of pre surgery chemotherapy
- During chemotherapy, parents ask a second opinion to another hospital, here the CT scan of chest reports a small lesion suggesting a metastasis of osteosarcoma

What is the correct stage for this patient ?

A. Localised

B. Metastatic



Ambiguous case, discussion is needed with the pediatric hemato-oncologist for the correct staging

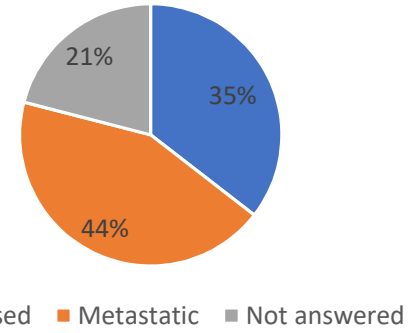
Exercise 8

- 11-year old patient
- MRI: 5 cm lesion located on the pelvis
- Biopsy: Ewing sarcoma
- Lung CT and PET are negative
- The result of bone marrow aspirate and trephine is: negative for pathological morphology and immunocytology, positive for molecular biology (specific transcript)

What is the correct stage for this patient ?

A. Localised

B. Metastatic



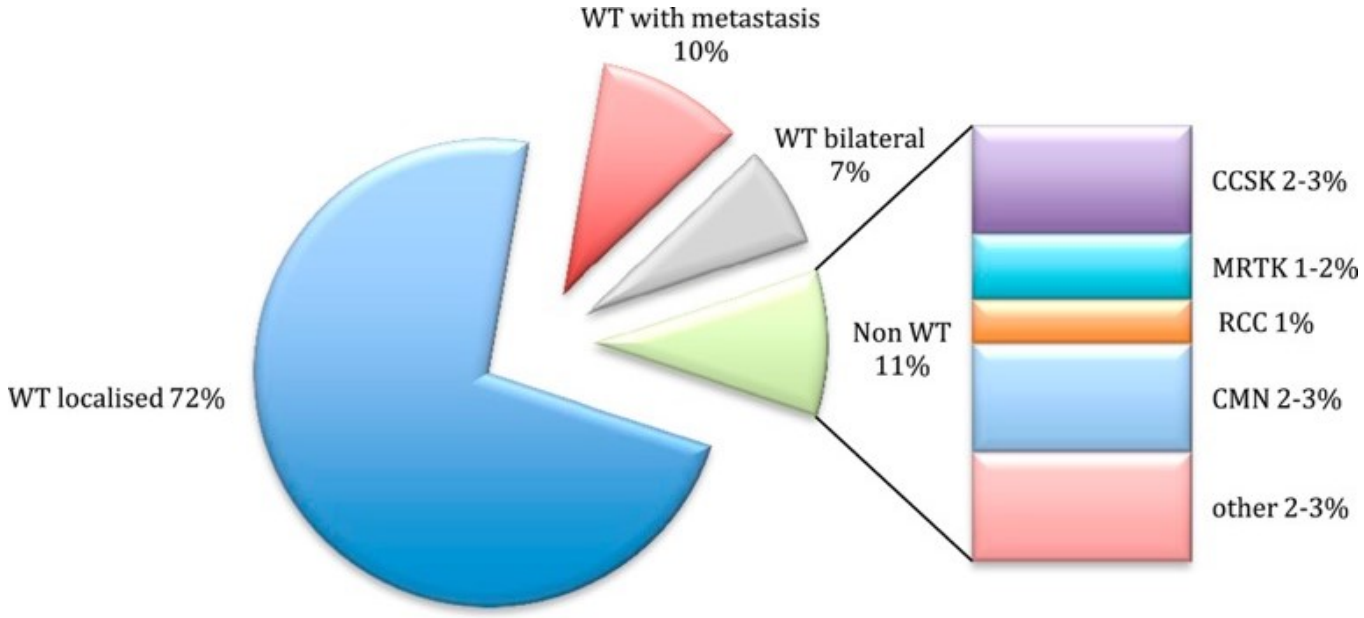
The implication of a positive result for the specific transcript in the bone marrow is not clear (as well clinically than for the prognosis), and this information should thus not be used.

Wilms Tumour

Clinical expert: Dr Filippo Spreafico

Renal tumours: Epidemiology

- Malignant renal tumours comprise 5% of all cancers in children <15 years of age; WT (also known as nephroblastoma) is the most common of these tumours

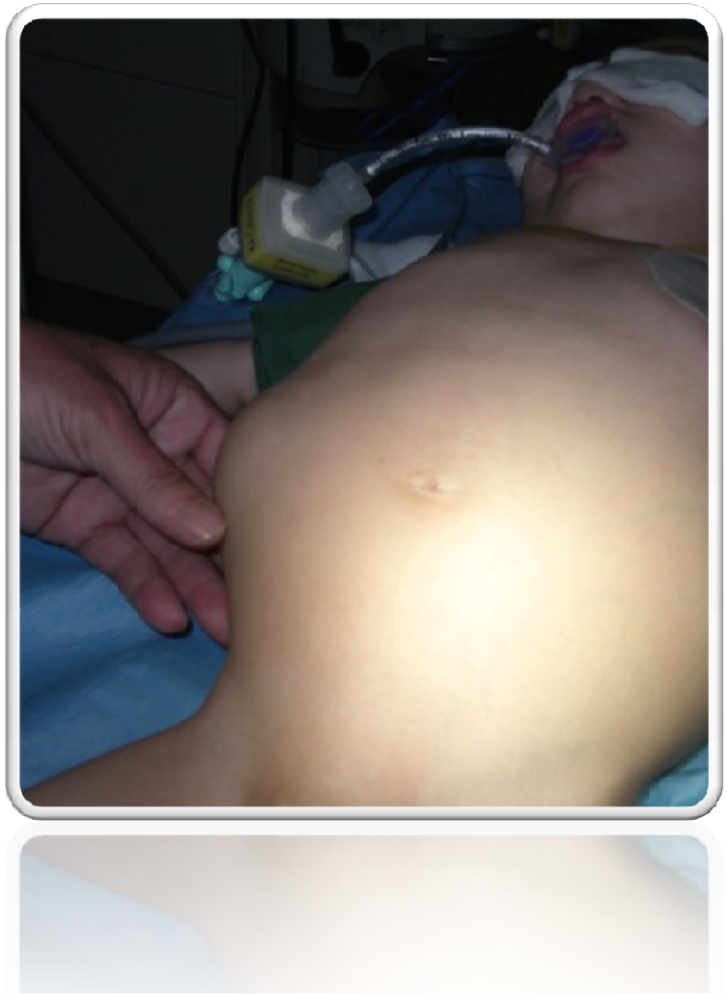


Brok J, et al. Biology and treatment of renal tumours in childhood. Eur J Cancer. 2016

Wilms tumours: Epidemiology

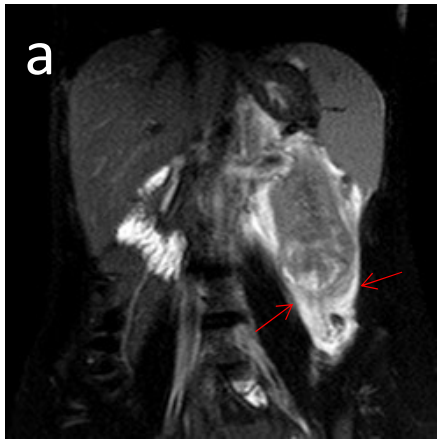
- WT incidence varies between regions and ethnicities: the annual incidence in East Asia (4.3 per million) is lower than in North America or Europe (8–9 per million)
- WT is ~10% more common in girls than in boys
- WT presents between ages 2-5 yrs, and its incidence in children >10 yrs is rare
- Overall survival rate >90% in high-income countries, yet survival disparities within and between countries exist

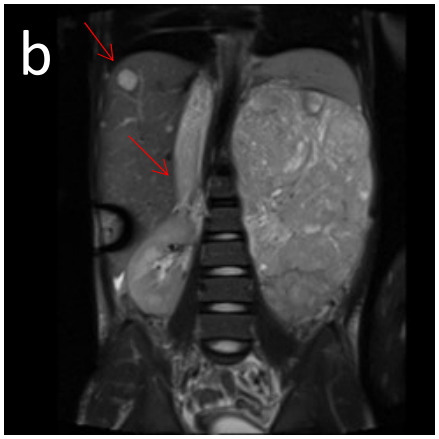
Wilms tumours: Clinical presentation

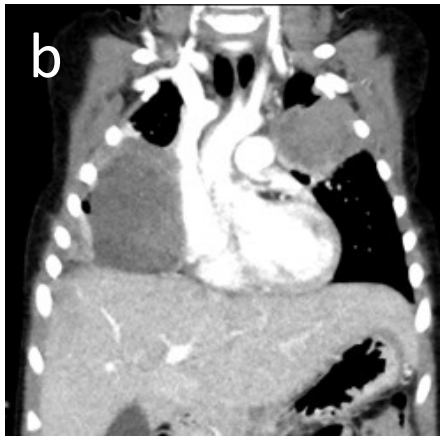


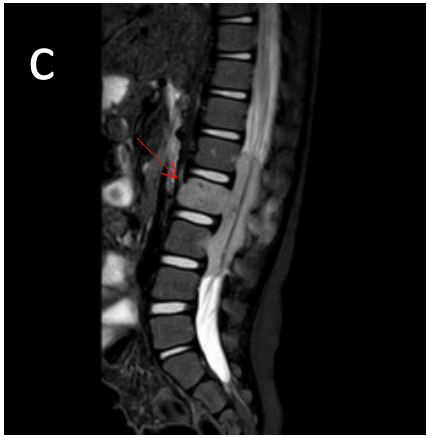
- Most children are asymptomatic at presentation and predominantly have a distended abdomen with a palpable mass
- Only one in five children have signs/symptoms; pain (40%), haematuria (25%), fever, hypertension (30%), constipation and weight loss are among the most common
- Presence of symptoms do not influence stage assignment

Wilms tumours: Unusual clinical presentation









a. Rarely, a patient can present with an acute abdomen in the setting of tumour rupture and bleeding into surrounding tissue

b. Symptoms related to metastases, such as dyspnoea (**lung**), abdominal pain (**liver**) or tumour **thrombus in the renal vein or vena cava**, or varicocele rarely occur

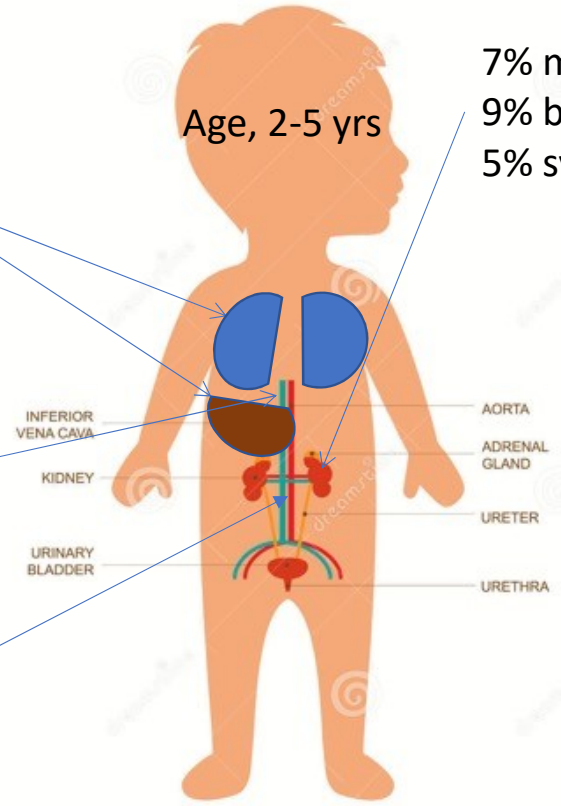
c. Non-pulmonary and non-hepatic metastases are very rare at primary diagnosis of non-anaplastic WT

Wilms tumours: Clinical presentation, summary

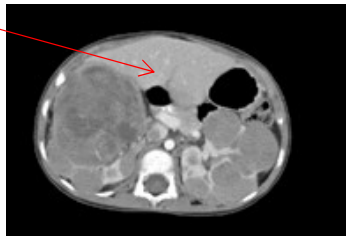
10-12%: hematogenous metastases (80% lung; 15% liver; very rare: <1% bone, brain)

Intravascular extension (4-10%)

WT spreads to local (retroperitoneal) lymph nodes in 15% to 20%



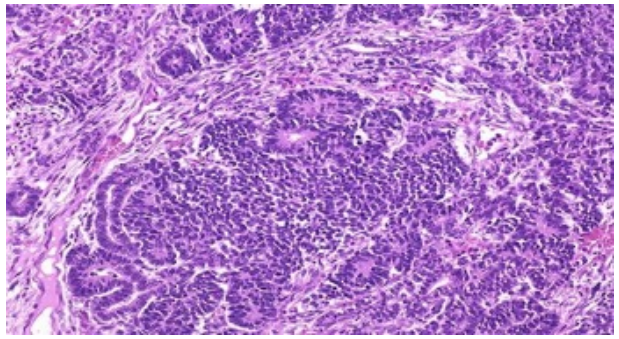
7% multifocal unilateral tumour
9% bilateral *disease*;
5% synchronous bilateral WT



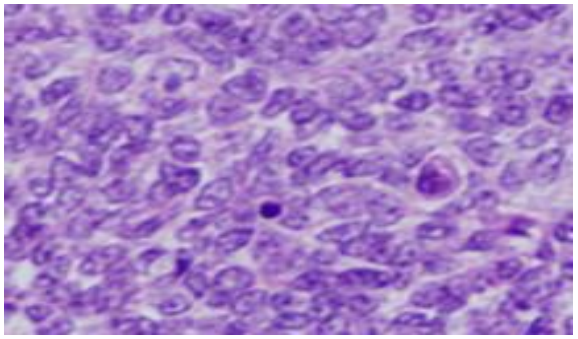
Few rare extrarenal locations have been reported (retroperitoneum, sacrococcygeal region, testis, uterus, inguinal canal, mediastinum)

~10% of WT occur as part of predisposition syndromes; screening, using renal ultrasound, is offered to children with predisposition syndromes & WT risk >5%

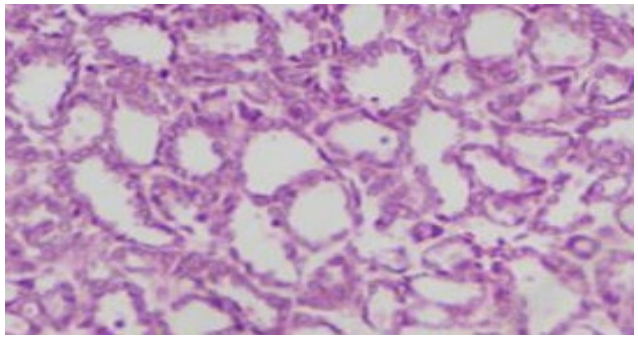
Wilms tumours: Introduction to WT subtypes



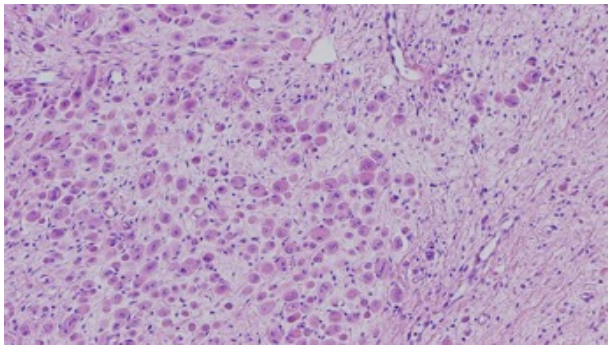
Classic triphasic



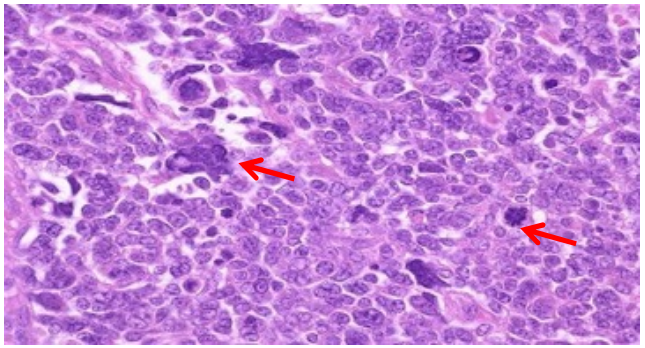
Blastemal



Epithelial



Stromal, including heterologous differentiation



Anaplasia = cells with hyperchromatic, pleomorphic nuclei that are three times larger than adjacent cells and have abnormal mitotic figures (**morphological criteria for definition**)

Wilms tumours: Anaplastic histology

- ~7–8% of WTs demonstrate anaplasia
- The definition of anaplasia further specifies whether it is *diffuse* or *focal* based on the anatomical distribution of anaplastic cells
- Anaplastic tumour frequently harbour oncogenic *TP53* mutations
- 65%: advanced stage at diagnosis
- Patient median age: 56.5 months
- Anaplasia is a most important factor regardless of the treatment protocol adopted

Wilms tumours: (current) Diagnostic workup

Abdominal ultrasound (+colour-Doppler)	YES	Clarifies the organ of origin, extension into the renal and inferior cava veins, contralateral kidney, associated urogenital abnormalities, liver or lymph node metastases
Chest X-Ray	Optional	To assess lung nodules
Chest CT scan (unenhanced)	YES	
Abdominal CT scan + i.v. iodinated contrast	YES	CT can be used interchangeably with MRI for diagnostic purposes
Abdominal MRI (± gadolinium)	YES	Preferably, for better assessment of potential nephrogenic rests and their distinction from true WT
FDG-PET	No	Not routinely used for WT
Bone scan	Clinical need	Reserved for patients with signs/symptoms suspicious for distant extra-pulmonary metastases
Cross-sectional imaging of other sites	Clinical need	
The usual labs are not specific for WT but need to be ordered to look for other pathologies and to start chemotherapy		

Wilms tumours: Clinical presentation & diagnosis

- The diagnosis of WT can be suspected with reasonable certainty based on patient's age, history, physical examination and abdominal imaging (centrally reviewed), without tumour biopsy

Wilms tumours: Staging

Main differences in the staging workup between COG and SIOP are not in the type of imaging used, but rather in their interpretation in the light of pre-nephrectomy chemotherapy		
	SIOP	**COG**
AT DIAGNOSIS	Localised vs metastatic; Bilateral vs unilateral	Localised vs metastatic; Bilateral vs unilateral
	Stage III if open surgical biopsy	Stage III if biopsy (any type); Stage III if inoperable tumour and preoperative chemotherapy done
AT NEPHRECTOMY	(Delayed) Define 'local' stage	(Upfront) Define 'local' stage

Wilms tumour: Definition of lung metastases

- Possible stage shift across subsequent protocols due to **pulmonary metastases detected only by CT scan (<1 cm) but not by chest x-rays** (as in older protocols)
- Different CT studies found lung nodules in 15% to 33% of patients with normal chest x-rays[1]
- Up to 1/3 of nodules <1 cm in diameter may be benign nodules[2]

CHEST CT SCAN FOR STAGING (i.e. for detecting lung metastases) ACCROSS PROTOCOLS		
1986-2002	2005-onwards	
Optional in NWTS-4 & 5	**Mandatory** (COG AREN03B2 - AREN0533 protocol)	
	2001-2016	2018-onwards
	Optional (SIOP 2001 Trial & Study)	**Mandatory** (Umbrella protocol)

[1]Owens et al. *J Clin Oncol*. 2002;20:2768; Grundy et al. *Ped Blood Cancer* 2012
[2]Meisel et al. *Int J Radiat Oncol Biol Phys* 1999

Wilms tumour: Definition of lung metastases

Current research protocols include central review of **CT scan** to homogeneously classify lung nodules

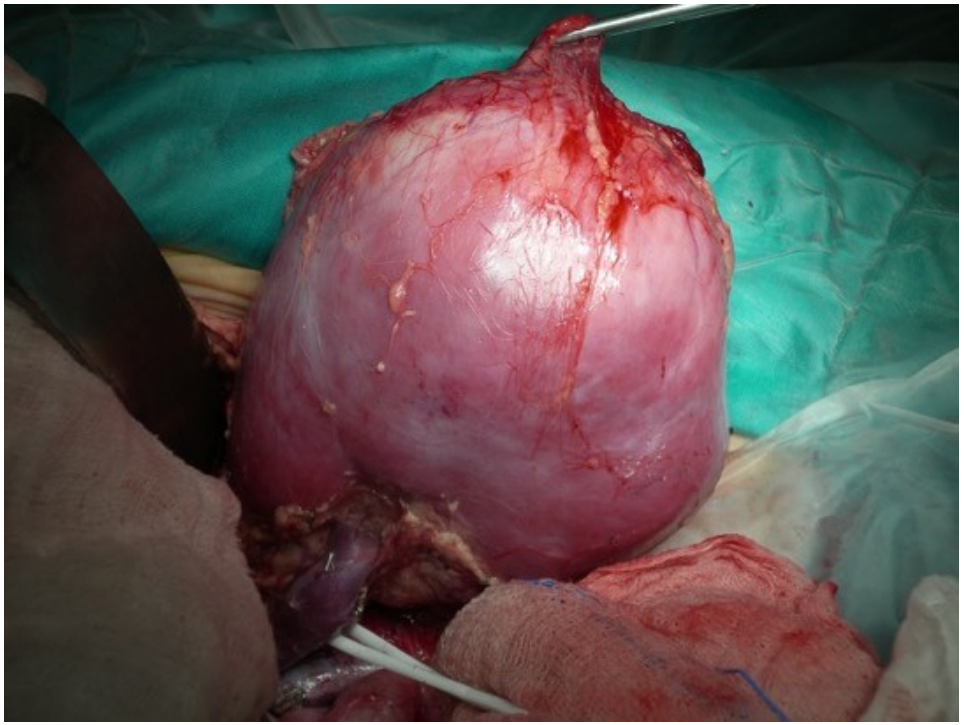
Lung nodules classified as metastases:

- COG: round, noncalcified lung nodules not in a fissure visible on chest CT scan, regardless of size
- SIOP: round, with sharp margins, with a transverse diameter ≥3 mm (on CT scan) and centrally-reviewed imaging appearance suspicious for metastatic origin

Wilms tumours: Common protocols in use

Child with imaging typical for Wilms tumour	
SIOP APPROACH	**COG APPROACH**
Preoperative chemotherapy (Diagnostic biopsy evaluated in select cases) Primary nephrectomy for age < 6 months	**Primary nephrectomy** (Neo-adjuvant chemotherapy in unresectable or select cases)
4-week in localised tumour; 8-week in metastatic tumour	Histologic, molecular and staging assessment
Response assessment of tumour and metastases	Response assessment of metastases
Delayed nephrectomy	**Postoperative treatment**
Histologic risk and stage assessment	According to tumour stage, anaplasia, molecular markers (in chemo-naïve tumour)
Postoperative treatment	
According to tumour stage and histological risk group	

Wilms tumours: Standard surgical approach

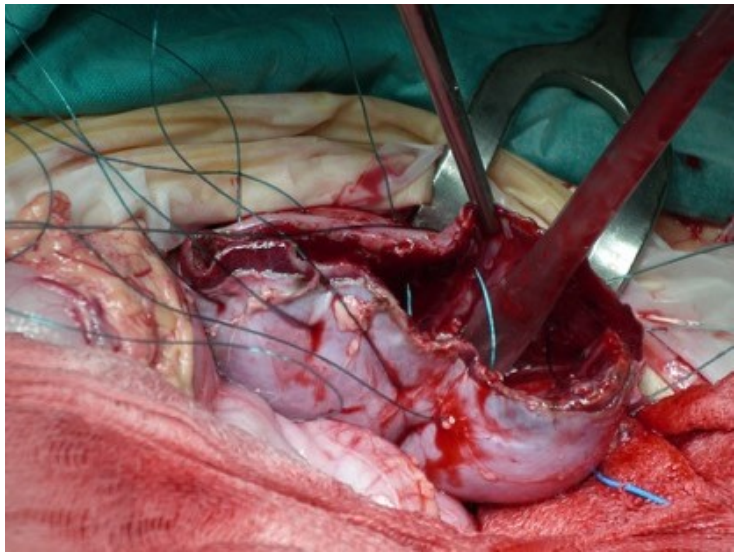


Conventional surgical approach:

- Nephrectomy (laparotomy) with adequate lymph node sampling

Godzinsky et al. Eur J Pediatr Surg 2014; Lopyan et al. Surg Oncol Clin N Am 2021

Wilms tumours: Nephron sparing surgery



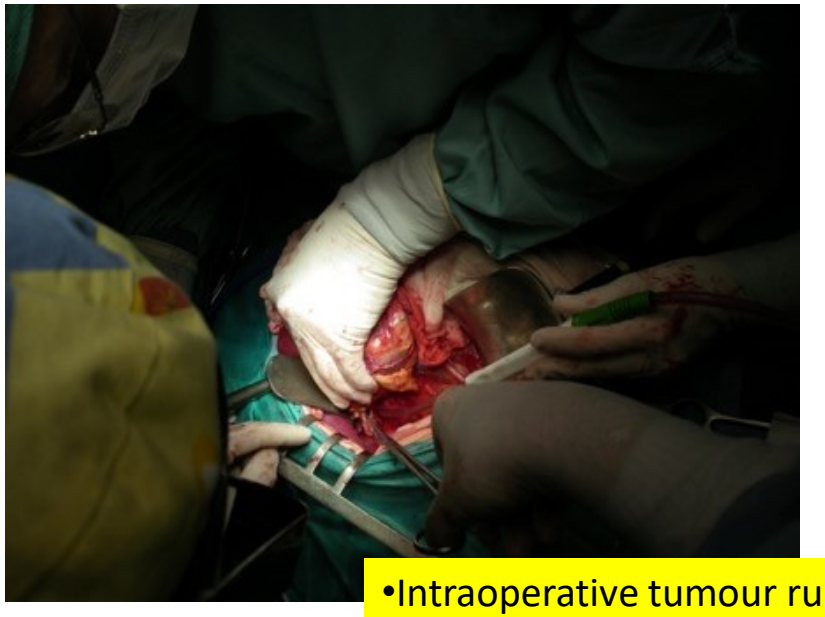
NSS is a standard surgical approach in:

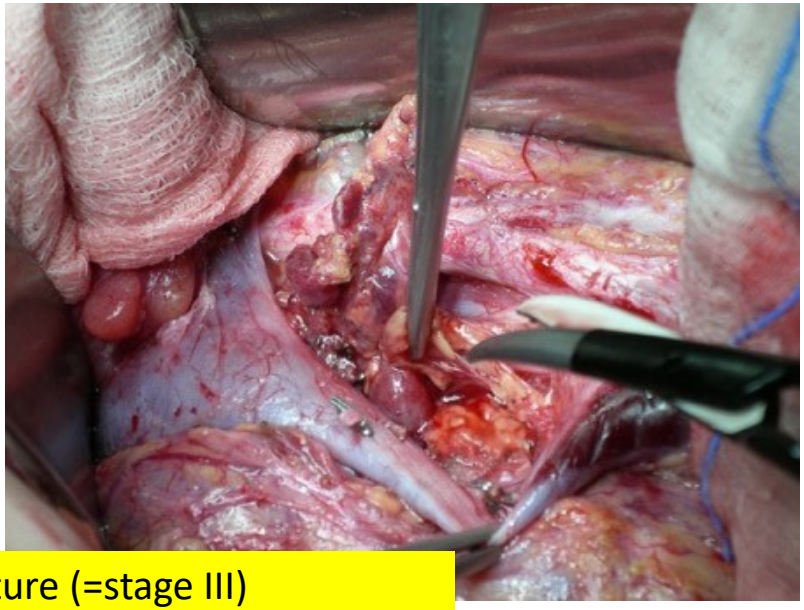
- Bilateral WT
- WT in genetic predisposition syndrome
- WT & underlaying renal function impairment

- *Sometime stage assignment is challenging*

Godzinsky et al. Eur J Pediatr Surg 2014; Lopyan et al. Surg Oncol Clin N Am 2021

‘Abdominal’ staging in WT done at the time of surgery





- Intraoperative tumour rupture (=stage III)
- Lack of lymph node sampling (=risk of understaging)
- Incomplete tumour resection (=stage III)
- Peritoneal tumour implants (=stage III)

Spreafico et al. *Int J Radiat Oncol Biol Phys* 2012

Wilms tumours: Staging

	COG	SIOP
Stage I	• Tumour limited to kidney, completely resected. • The renal capsule is intact. • **The tumour was not ruptured or biopsied prior to removal.** • The vessels of the renal sinus are not involved. • There is no evidence of tumour at or beyond the margins of resection.	• Tumour is limited to the kidney. • Tumour is present in the perirenal fat but is surrounded by a fibrous (pseudo)capsule. The (pseudo)capsule might be infiltrated by viable tumour, which does not reach the outer surface. • Tumour might show protruding (botryoid) growth into the renal pelvis or the ureter but does not infiltrate their walls. • The vessels or the soft tissues of the renal sinus are not involved by tumour. Intrarenal vessel involvement might be present.
Stage II	• The tumour is completely resected and there is no evidence of tumour at or beyond the margins of resection. • The tumour extends beyond kidney, as is evidenced by any one of the following criteria: a. there is regional extension of the tumour (i.e. penetration of the renal capsule, or extensive invasion of the soft tissue of the renal sinus); b. blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumour	• **Viable** tumour is present in the perirenal fat and is not covered by a (pseudo)capsule, but is completely resected (resection margins are clear). • **Viable** tumour infiltrates the soft tissues of the renal sinus. • **Viable** tumour infiltrates blood and/or lymphatic vessels of the renal sinus or of the perirenal tissue, but it is completely resected. • **Viable** tumour infiltrates the wall of the renal pelvis or of the ureter. • **Viable** tumour infiltrates the vena cava or adjacent organs (except the adrenal gland) but is completely resected.

Wilms tumours: Staging

	COG	SIOP
Stage III	• Residual nonhaematogenous tumour present following surgery, and confined to abdomen. Anyone of the following may occur: a. lymph nodes within the abdomen or pelvis are involved by tumour (note: lymph node involvement in the thorax, or other extra-abdominal sites is a criterion for stage IV); b. the tumour has penetrated through the peritoneal surface; c. tumour implants are found on the peritoneal surface; d. gross or microscopic tumour remains postoperatively (e.g., tumour cells are found at the margin of surgical resection on microscopic examination); e. the tumour is not completely resectable because of local infiltration into vital structures; f. tumour spillage occurring either before or during surgery; **g. the tumour is treated with preoperative chemotherapy** (with or without a biopsy regardless of type- tru-cut, open or fine needle aspiration) before removal; h. tumour is removed in greater than one piece (e.g. tumour cells are found in a separately excised adrenal gland; a tumour thrombus within the renal vein is removed separately from the nephrectomy specimen). Extension of the primary tumour within vena cava into thoracic vena cava and heart is considered stage III, rather than stage IV even though outside the abdomen.	• Viable tumour is present at a resection margin. **Nonviable tumour or chemotherapy induced changes** present at a resection margin are not regarded as stage III. • Abdominal lymph node involvement is present by either viable or nonviable tumour. • Preoperative or intraoperative **tumour rupture, if confirmed by microscopic examination** (viable tumour at the surface of the specimen at the area of the rupture). • Viable or nonviable tumour thrombus is present at resection margins of ureter, renal vein, or vena cava inferior (always discuss resection margins with the surgeon). • Viable or nonviable tumour thrombus, which is attached to the inferior vena cava wall, is removed piecemeal by a surgeon. • **Wedge or open tumour biopsy before preoperative chemotherapy or surgery**. • Tumour implants (viable or nonviable) are found anywhere in the abdomen. • Tumour (viable or nonviable) has penetrated through the peritoneal surface.

Wilms tumours: Stage III remarks, COG

Few staging factors have raised as much controversy over the years as that of tumour "spillage“

- Current **COG** criteria indicate that a tumour that "spills" or ruptures preoperatively or intraoperatively should be designated as stage III, regardless of the degree or localization of the spillage
- Any preoperative biopsy is considered as a spill (whether, tru-cut, open or fine needle aspiration)
- If pre-nephrectomy therapy is given, with or without a needle biopsy, the local tumour should be considered to be stage III

Wilms tumours: Stage III remarks, SIOP

Some of previous stage III criteria have undergone important changes in SIOP UMBRELLA protocol in comparison with the SIOP–2001 trial criteria

- The presence of nonviable tumour or chemotherapy-induced changes only at a resection margin is no longer regarded as stage III
- The UMBRELLA protocol now states that the presence of tumour rupture at diagnosis on imaging studies (i.e., prechemotherapy) is only considered as pathological stage III if viable tumour is seen microscopically at the rupture site of the nephrectomy specimen
- Abdominal lymph node involvement is present by either viable or nonviable tumour

Vujanic et al. *Nat Rev Urol*. 2018 Nov;15(11):693-701

Wilms tumours: Staging

	COG	SIOP
Stage IV	• Haematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdominopelvic region are present. (The presence of tumour within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present).	• Haematogenous metastases (for example, lung, liver, bone and brain) or lymph node metastases outside the abdominopelvic region.
Stage V*	• Bilateral tumours at diagnosis; **each side should be substaged according to the above criteria**.	• Bilateral renal tumours at diagnosis; **each side should be substaged according to the above criteria**.

*In the BENCHISTA project, the higher tumour stage of the two sides (or stage IV if overall metastatic) should be documented. The presence of bilateral disease can be documented as a separate data field.

SIOP vs COG, prognostic factors in clinical use

Factors	SIOP	COG	notes
Stage	Y	Y	But differences
Initial biopsy	does not matter (only open biopsy)	stage III (any type of biopsy)	
Anaplasia	Y (diffuse)	Y (focal & diffuse)	
Histologic response (blastemal type; completely necrotic type)	Y	Only in bilateral tumors	
LOH 1p/16q	N	Y	
Patient age/tumour weight <550g	N	Y	
Tumour volume after pre-op CT	Y (in some histologies)	N	
Completeness of lung nodule response	Y	Y	

Wilms tumour, Survival (NWTS-5)

Stage	Favorable Histology		Diffuse anaplastic	
	EFS (%)	OS (%)	EFS (%)	OS (%)
I	94.2	98.4	68.4	78.9
II	84.4	97.2	82.6	81.5
III	86.5	94.4	64.7	66.7
IV	75.1	85.2	33.3	33.3

Wilms tumour, Survival (SIOP 2001)

Histologic risk	Stage I	Stage II	Stage III	Stage IV
Low-Risk				
2-year EFS	97%	100%	100%	91%
5-year OS	99%	100%	100%	94%
Intermediate-Risk				
EFS	92%	89%	88%	81%
OS	98%	97%	94%	89%
High-Risk				
EFS	91%	84%	68%	31%
OS	97%	82%	70%	35%

Brok J, et al. Biology and treatment of renal tumours in childhood. Eur J Cancer. 2016

Wilms Tumour: Non-stage prognostic factors, SIOP

Solid Tumour	Essential	Additional	New and Promising	Comments
Wilms Tumour	Histology (low-risk; intermediate-risk, high-risk – but only anaplasia is included in current Toronto NSPs)	Tumour volume after pre-operative chemotherapy; rapidity of lung metastases response after chemotherapy	Gain on chromosome 1q; residual blastemal volume	Histological sub-classification assessed after adjuvant chemotherapy

Gupta et al. Development of paediatric non-stage prognosticator guidelines for population-based cancer registries and updates to the 2014 Toronto Paediatric Cancer Stage Guidelines. **Lancet Oncol 2020; 21: e444–51**

Wilms Tumour: Non-stage prognostic factors, COG

Solid Tumour	Essential	Additional	New and Promising	Comments
Wilms Tumour	Histology (anaplasia, focal or diffuse)	Patient age <2 yrs + stage I + tumour weighting <550g*; rapidity of lung metastases response after chemotherapy; loss of heterozygosity on both chromosome 1p and 16q	Gain on chromosome 1q; *loss of heterozigosity (LOH)/loss of imprinting (LOI) at chromosome 11p15	*to define select Very Low-Risk patients

Gupta et al. Development of paediatric non-stage prognosticator guidelines for population-based cancer registries and updates to the 2014 Toronto Paediatric Cancer Stage Guidelines. **Lancet Oncol 2020; 21: e444–51**

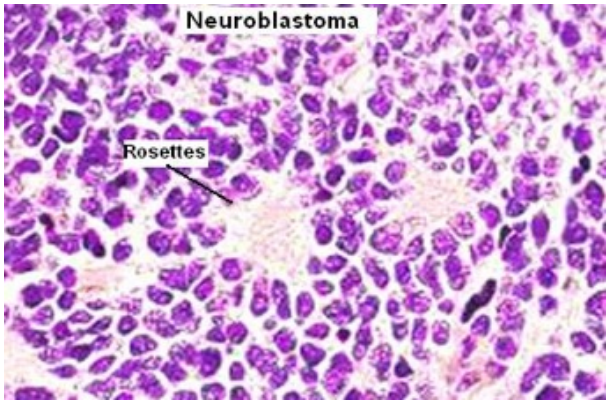
Wilms tumours: Summary

- Minimal staging workup at diagnosis (imaging of chest and abdomen)
- A prognostic factor can only be evaluated in the context of the treatment given: this principle is relevant to WT as COG studies advocate for immediate nephrectomy whereas SIOP studies advocate for preoperative chemotherapy
- Tumour stage and histology important across different protocols
- Tumour biology currently adopted as risk factor only in COG protocols

Neuroblastoma

Clinical expert: Dr Adela Cañete

Neuroblastoma: Introduction and general aspects



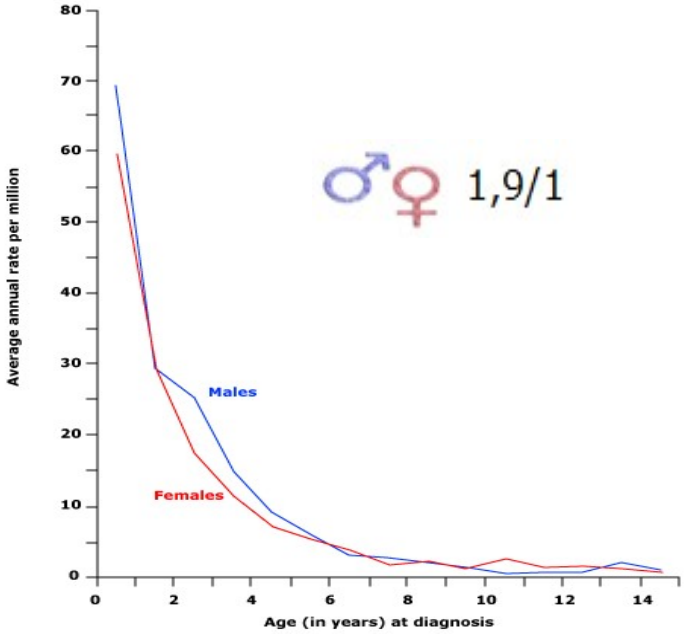
Tumour cells are usually described as small, rounded, bluish-blue, rosette-patterned cells (Homer-Wright pseudorosettes).

•Most common extracranial solid tumour in children.
•Mean age: 17.3 months.

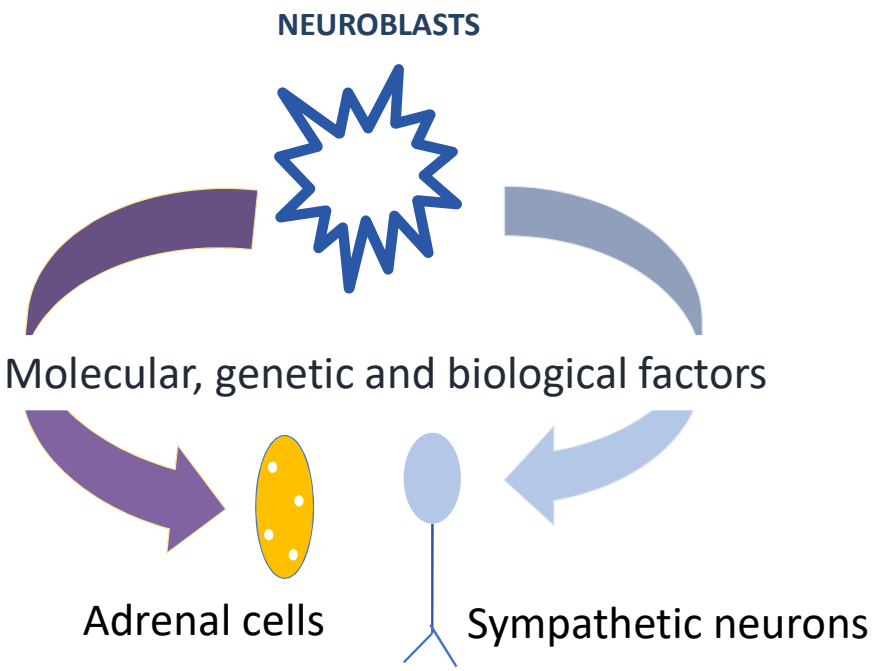
•Incidence: 9,9 x 10*6.

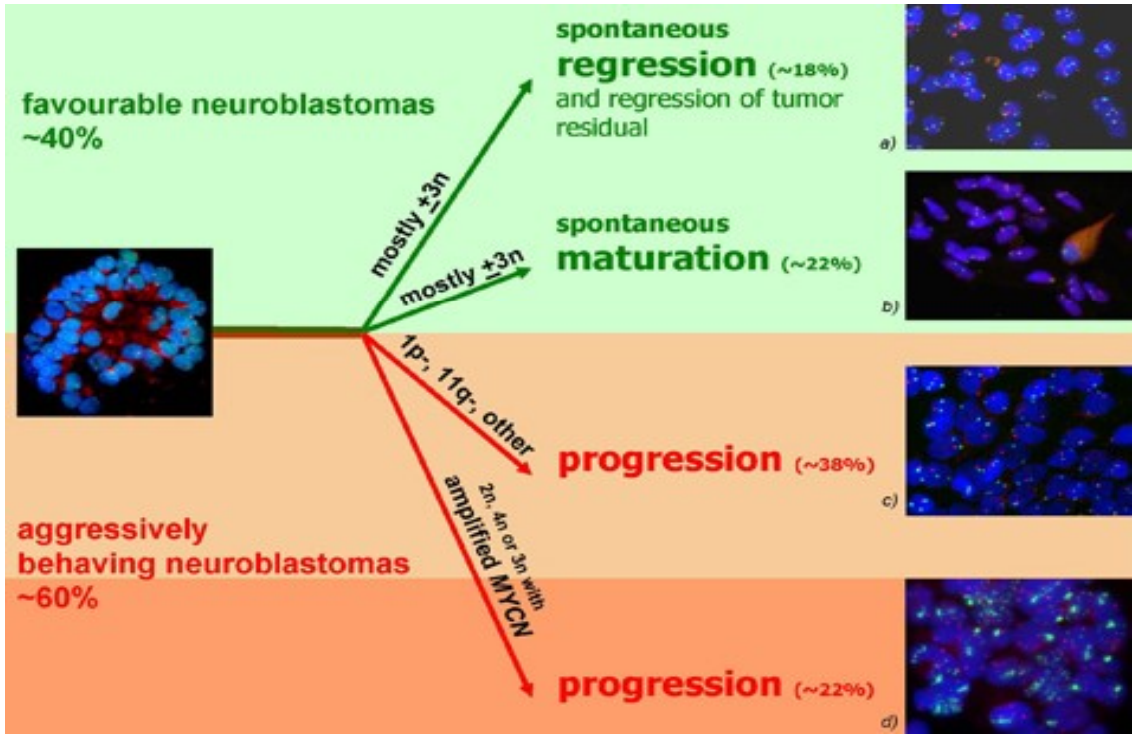
•It originates from adrenal medulla cells or paraspinal ganglia of the sympathetic nervous system..

• Biomarker: Increase of catecholamin metabolits in urine (VM and HVA).

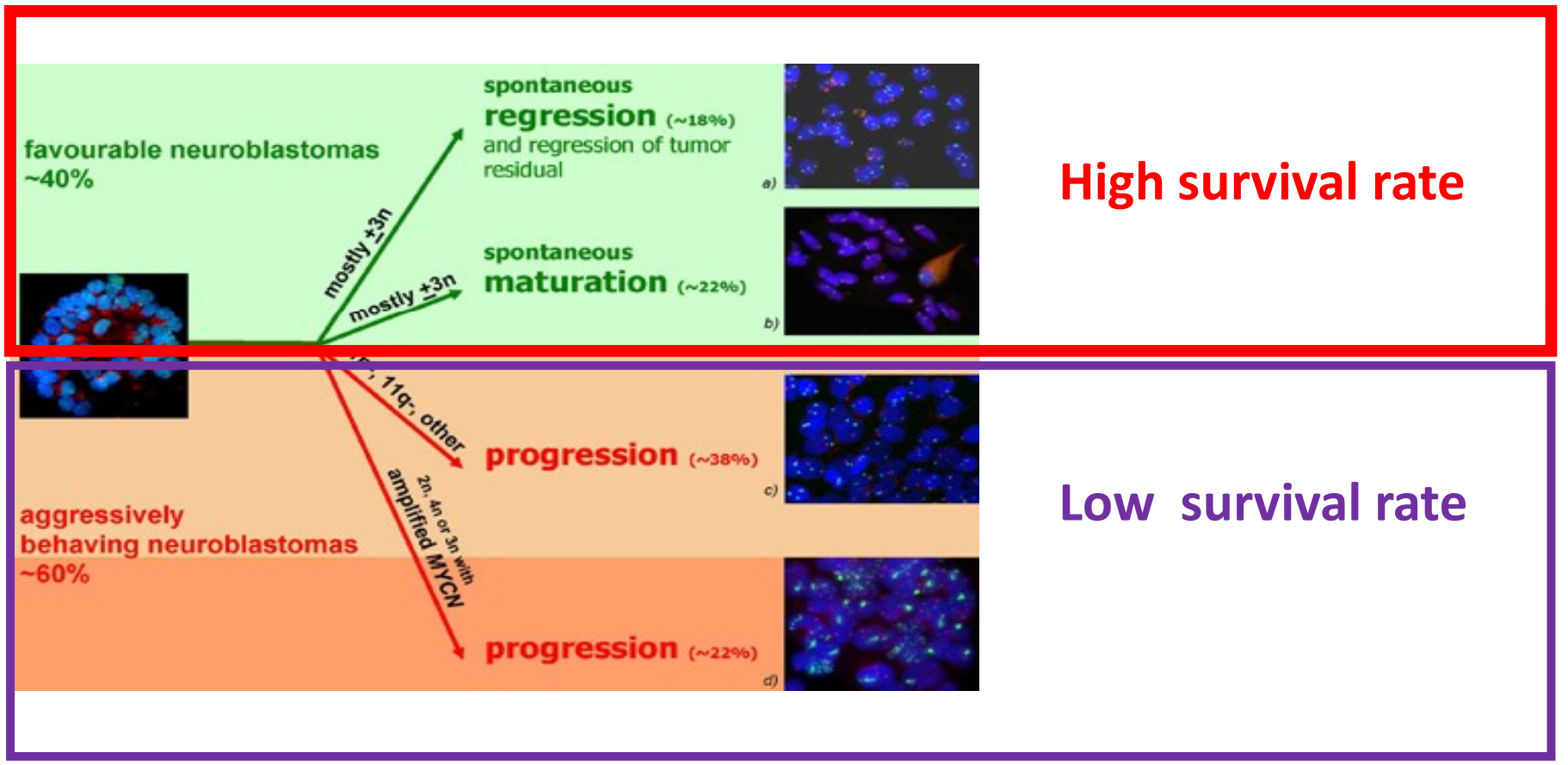


Biological and clinical heterogeneity

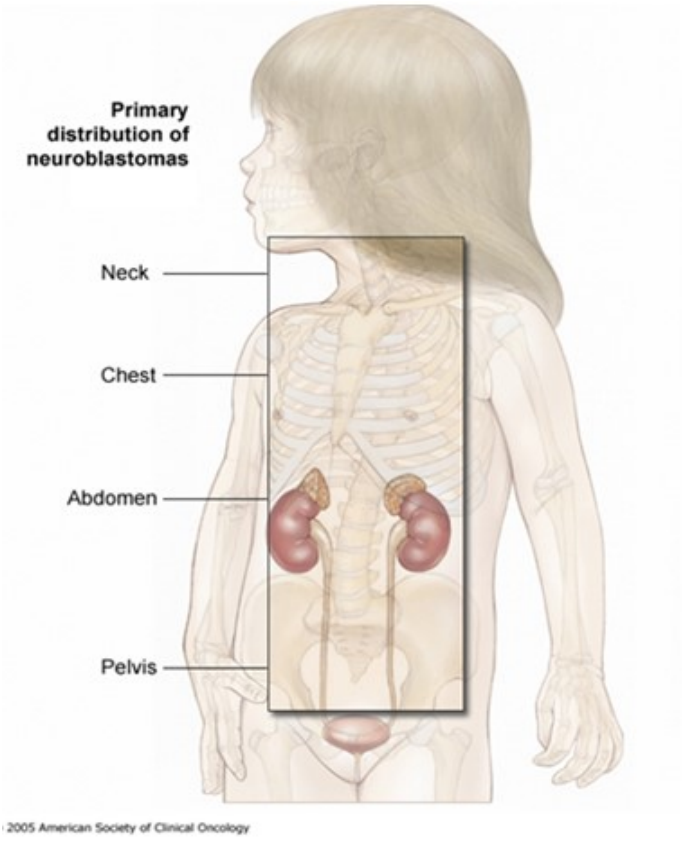


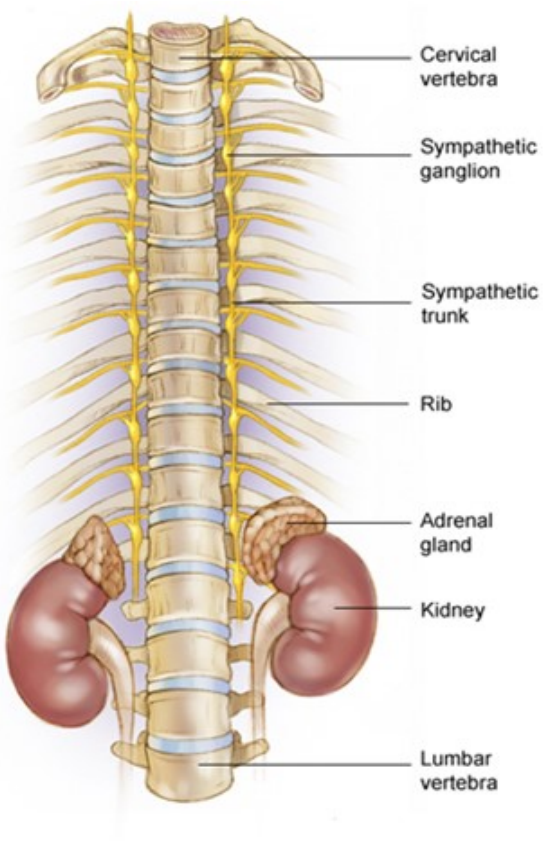


Neuroblastoma: Introduction and general aspects



Clinical heterogeneity: Location and dissemination





METASTASES

- ✓LYMPHATIC NODES
- ✓ BONE MARROW
- ✓ CORTICAL BONE
- ✓ ORBIT
- ✓LIVER
- ✓SKIN

- Child, 4 years old
- Tiredness, fever,
- ”Abdominal swelling”, pain
- Bruising around the eyes.
- Moaning and with pain in the lower extremities.
- BP 120/90
- Tumour in right hemiabdomen, mistaken for liver.

Newborn.

Prenatal ultrasound detected an adrenal mass.

No other clinical findings.

Infant, 9 month

Right Leg monoparesy

Neurogenic bladder in ultrasound examination

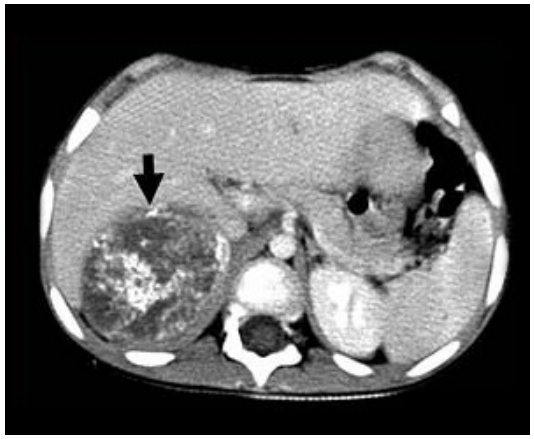
9-month-old infant

3 months: oculogyric movements and hypotonia.

Hepatomegaly study

Elevated catecholamines.

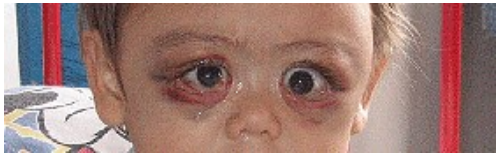
Central retroperitoneal mass



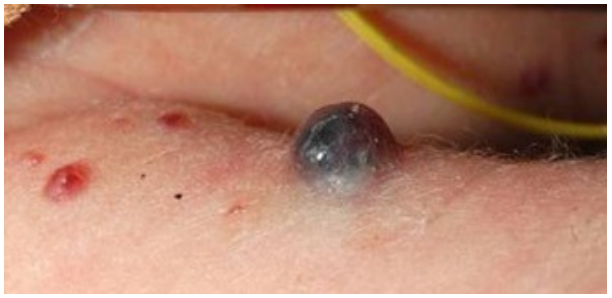
5 year old boy

Fever and cough. X-ray: mass in posterior mediastinum present one year ago in another X-ray. .

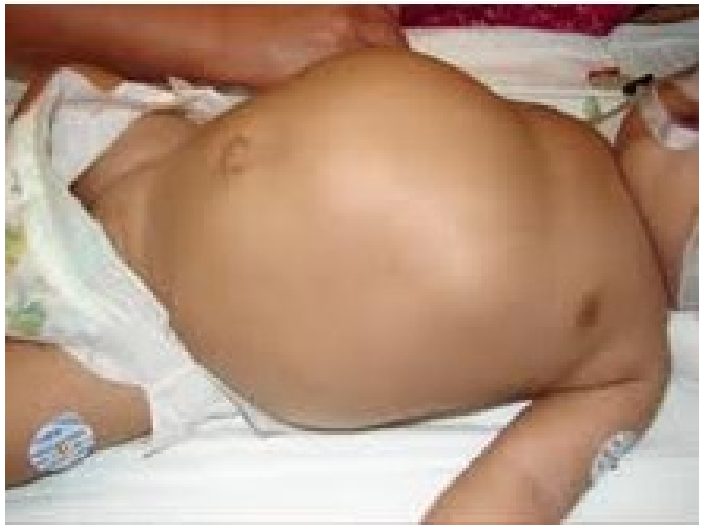
Raccon eyes



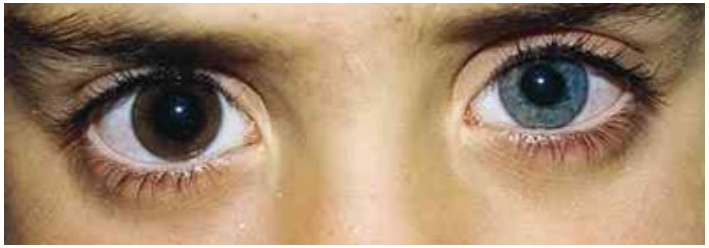
Blueberry muffin skin nodules



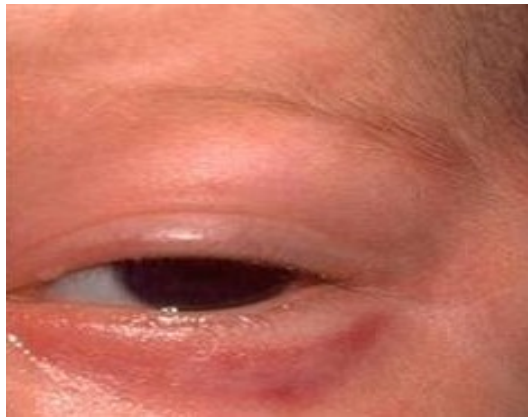
Hepatomegaly



Heterochromia iris



Claudio Bernard Horner Sdr.



Neuroblastoma: Introduction and general aspects

We, as clinicians, need to predict tumour behaviour in order to…

Adapt the therapeutic strategy to the risk of relapse (Risk groups) using different factors...

INRG: International Neuroblastoma Risk Group.

INRG Stage	Age	Diagnostic Category Tumor Grade	*MYCN*	Unb 11q aberration	Ploidy	Pre-treatment Risk Group
L1		GN maturing GNB intermixed	NA			A Low
		Any, except GN maturing or GNB intermixed	NA			B Low
			Amp			H High
L2		GN maturing GNB intermixed				A Low
	<18m	Any, except GN maturing or GNB intermixed	NA	No		D Intermediate
				Yes		I High
	≥18m	GNB nodular, differentiating NB, differentiating	NA	No		E Intermediate
		GNB nodular, poorly differentiated or undifferentiated	NA	Yes		J High
		NB, poorly differentiated or undifferentiated	NA	(Any)		J High
	(Any)		Amp			N Ultra-High
M	<18m		NA		Hyperdiploid	F Intermediate
					Diploid	G Intermediate
			Amp			O Ultra-High
	≥18m					P Ultra-High
MS	<18m		NA	No		C Low
				Yes		K High
			Amp			Q Ultra-High

Cohn S et a.J Clin Oncol 2008, 27:289-297.

SURVIVAL according to risk factors:

Pre-treatment Group	5-year EFS	Proportion of Patients (%)
Low	≥ 85%	28.2
Intermediate	75-<85%	26.8
High	50-<75%	9.0
Ultra-High	<50%	36.1

Cohn S et a.J Clin Oncol 2008, 27:289-297

Neuroblastoma: Introduction and general aspects

TABLE 1
International Classification of Childhood Cancer, Third Edition: Main Classification Table

Diagnostic group	ICD-O-3 code(s)[10] Morphology	Topography
IV. Neuroblastoma and other peripheral nervous cell tumors		
a. Neuroblastoma and ganglioneuroblastoma	9490, 9500	
b. Other peripheral nervous cell tumors	8680–8683, 8690–8693, 8700, 9520–9523 9501–9504	C00.0–C69.9, C73.9–C76.8, C80.9

International Classification of Childhood Cancer, Third Edition

Eva Steliarova-Foucher, Ph.D.[1]
Charles Stiller, M.Sc.[2]
Brigitte Lacour, M.D.[3]
Peter Kaatsch, Ph.D.[4]

[1] International Agency for Research on Cancer,

BACKGROUND. The third edition of the International Classification of Diseases for Oncology (ICD-O-3), which was published in 2000, introduced major changes in coding and classification of neoplasms, notably for leukemias and lymphomas, which are important groups of cancer types that occur in childhood. This necessitated a third revision of the 1996 International Classification of Childhood Cancer (ICCC-3).

Neuroblastoma: Introduction and general aspects

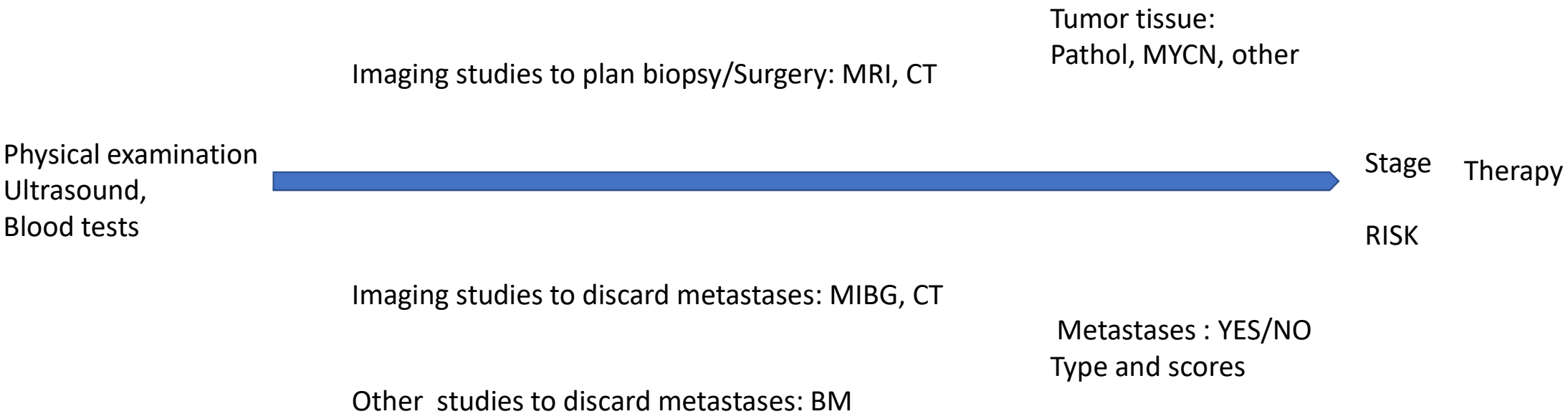
Tips

- Biological heterogeneity.
- Clinical heterogeneity, from ”mild disease” to “severe, life-threatening or functional threatening” disease.
- Very young children: the younger, the better…
- Risk factors that remains over years:
  - ✓Age
  - ✓Stage

  - ✓N-myc amplification

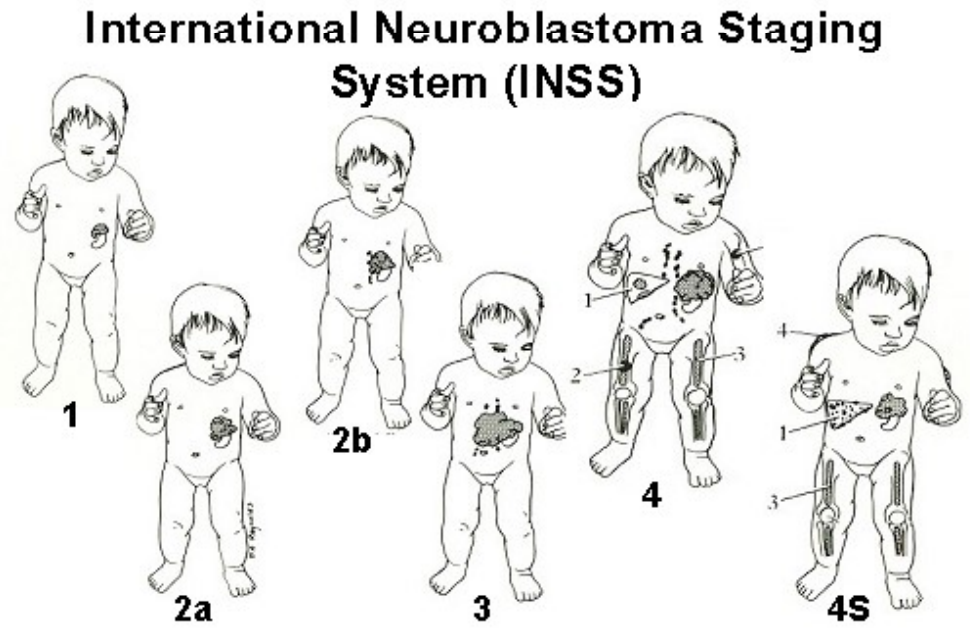
Neuroblastoma: Diagnosis & Staging

- How is it diagnosed?



Neuroblastoma: Diagnosis & Staging

- In 1988, International staging criteria were agreed: INSS.
- However, the application of these criteria (especially with regard to the primary tumour) was uneven among the co-operative groups.



Brodeur GM et al.
J Clin Oncol 6:1874-1881, 1988

Neuroblastoma: Diagnosis & Staging

INRGSS: International Neuroblastoma Risk Group Staging System

A major review and new consensus emerged in 2009, based on the work by European surgeons who published the results of LNESG1 and defined:

Surgical risk factors determined by imaging: IDRF

- Universal
- Inclusive: includes all neuroblastomas
- No surgery-dependent
- No pathology-dependent
- Comparable

Monclair T, J Clin Oncol 2009, 27:298-303.

Neuroblastoma: Diagnosis & Staging

INRGSS: International Neuroblastoma Risk Group Staging System

- Universal
- Inclusive
- Independent
- Comparable

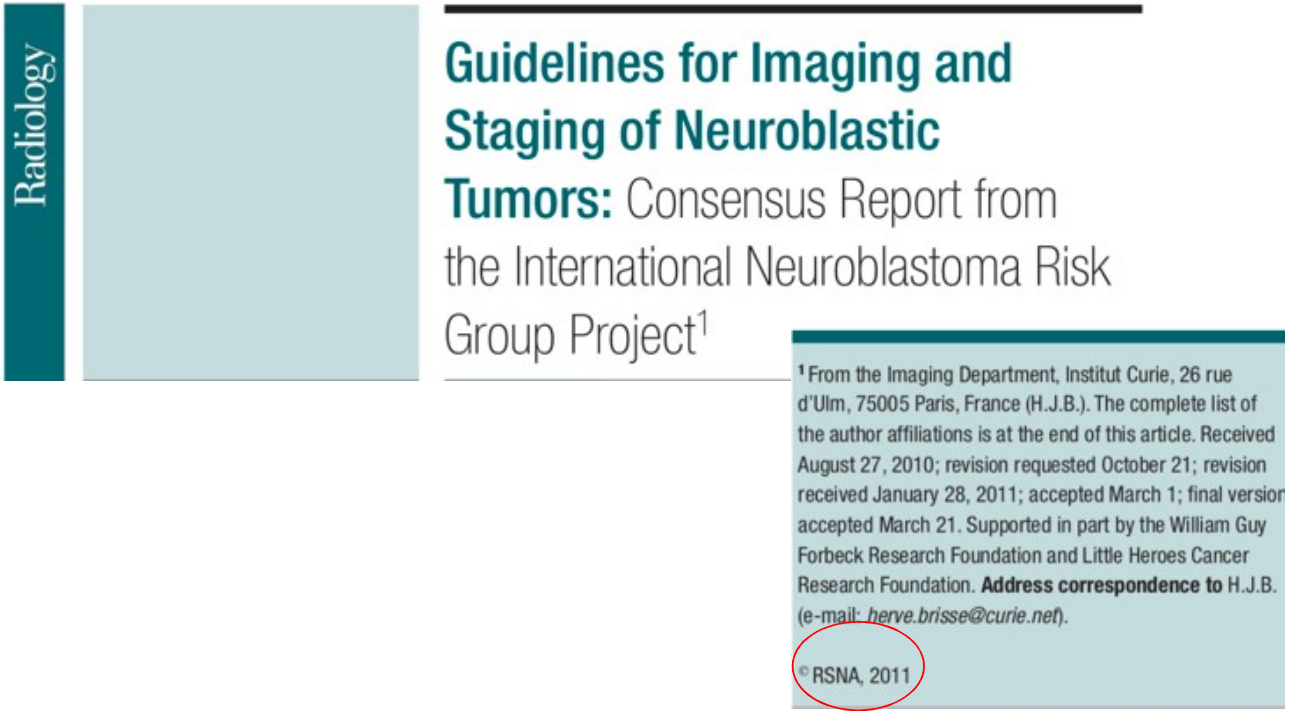
Table 2

Descriptions of New INRG Tumor Stages

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

Source.—Reference 8. Complete definitions of these stages are cited in the text. IDRFs = image-defined risk factors.

Neuroblastoma: Diagnosis & Staging


Radiology

Guidelines for Imaging and Staging of Neuroblastic Tumors: Consensus Report from the International Neuroblastoma Risk Group Project[1]

[1] From the Imaging Department, Institut Curie, 26 rue d'Ulm, 75005 Paris, France (H.J.B.). The complete list of the author affiliations is at the end of this article. Received August 27, 2010; revision requested October 21; revision received January 28, 2011; accepted March 1; final version accepted March 21. Supported in part by the William Guy Forbeck Research Foundation and Little Heroes Cancer Research Foundation. **Address correspondence to** H.J.B. (e-mail: *herve.brisse@curie.net*).

Primary tumor

L1 or L2?

=

Are there IDRF?

Brisse H, Radiology: Volume 261: Number 1—October 2011

Neuroblastoma: Diagnosis & Staging

Table 3

Descriptions of IDRFs

Anatomic Region	Description
Multiple body compartments	Ipsilateral tumor extension within two body compartments (ie, neck and chest, chest and abdomen, or abdomen and pelvis)
Neck	Tumor encasing carotid artery, vertebral artery, and/or internal jugular vein Tumor extending to skull base Tumor compressing trachea
Cervicothoracic junction	Tumor encasing brachial plexus roots Tumor encasing subclavian vessels, vertebral artery, and/or carotid artery Tumor compressing trachea
Thorax	Tumor encasing aorta and/or major branches Tumor compressing trachea and/or principal bronchi Lower mediastinal tumor infiltrating costovertebral junction between T9 and T12 vertebral levels
Thoracoabdominal junction	Tumor encasing aorta and/or vena cava
Abdomen and pelvis	Tumor infiltrating porta hepatis and/or hepatoduodenal ligament Tumor encasing branches of superior mesenteric artery at mesenteric root Tumor encasing origin of celiac axis and/or origin of superior mesenteric artery Tumor invading one or both renal pedicles Tumor encasing aorta and/or vena cava Tumor encasing iliac vessels Pelvic tumor crossing sciatic notch
Intraspinal tumor extension	Intraspinal tumor extension (whatever the 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 adjacent organs and structures	Pericardium, diaphragm, kidney, liver, duodenopancreatic block, and mesentery

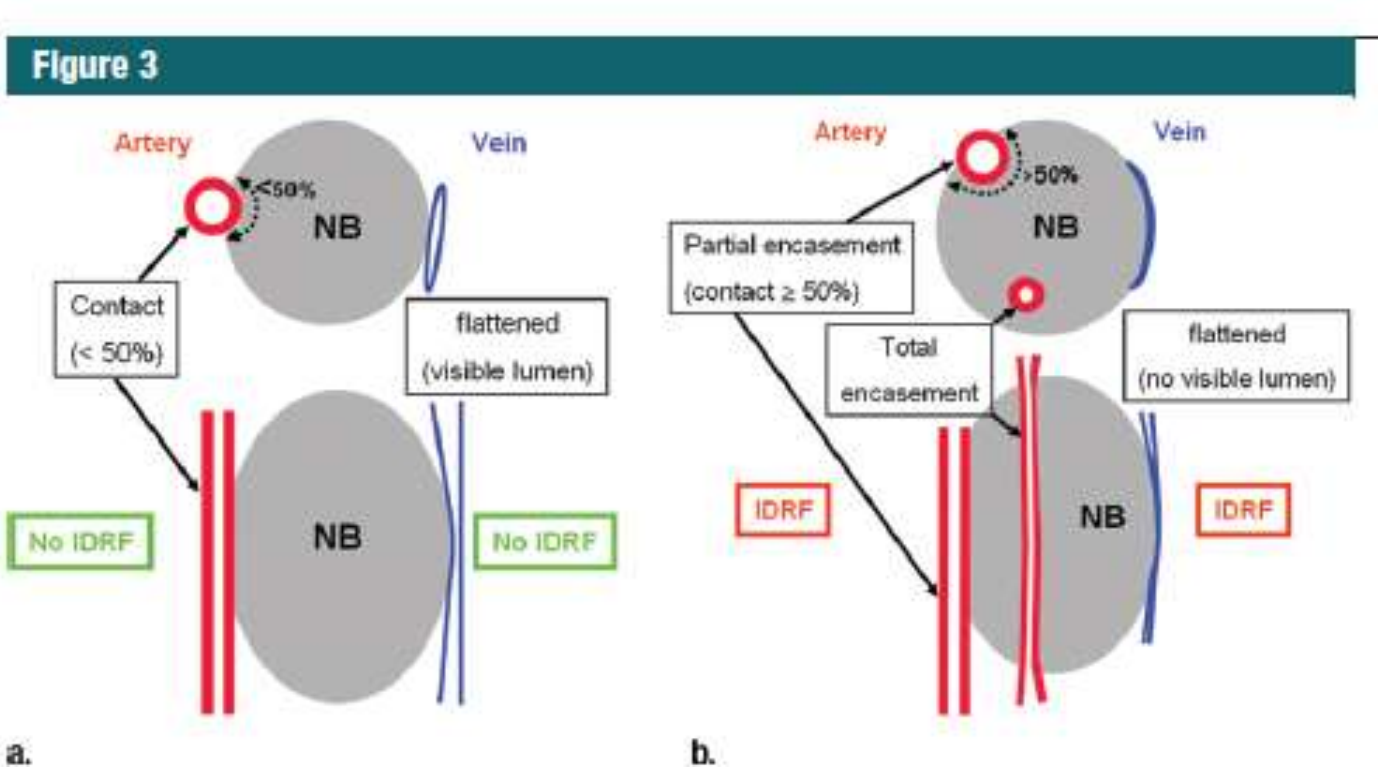
Source.—Reference 8. Conditions that should be recorded but are not considered IDRFs are multifocal primary tumors, pleural effusion with or without malignant cells, and ascites with or without malignant cells.

1/ Important definitions

2/ Anatomical sites.

- Carried out by radiologists
- Written in the radiological reports and tumor board reports.

Important definitions for IDRF in MRI/CT



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No IDFR criteria:

Separation:

there is a visible layer, usually fat

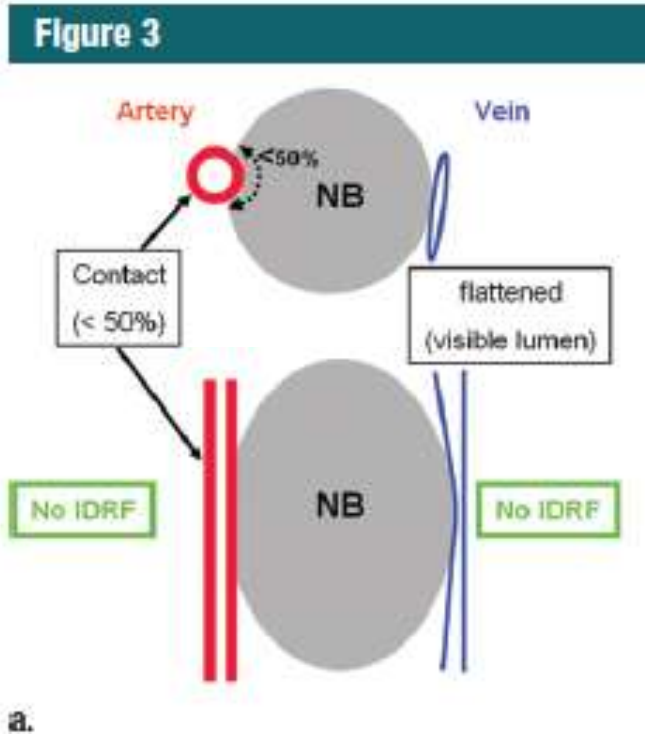
between the tumour and neighbouring structures..

Contact:

There is no visible layer between tumour and neighbouring structures.

If in contact with a vessel, it is < al 50% of circumference

Vessels can be disminished and collapsed but lumen visible.



- EXCEPTION: RENAL VESSELS: ANY CONTACT = IDRF.

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IDFR criteria:

<u>Encasement:</u> Structures surrounded by tumour.

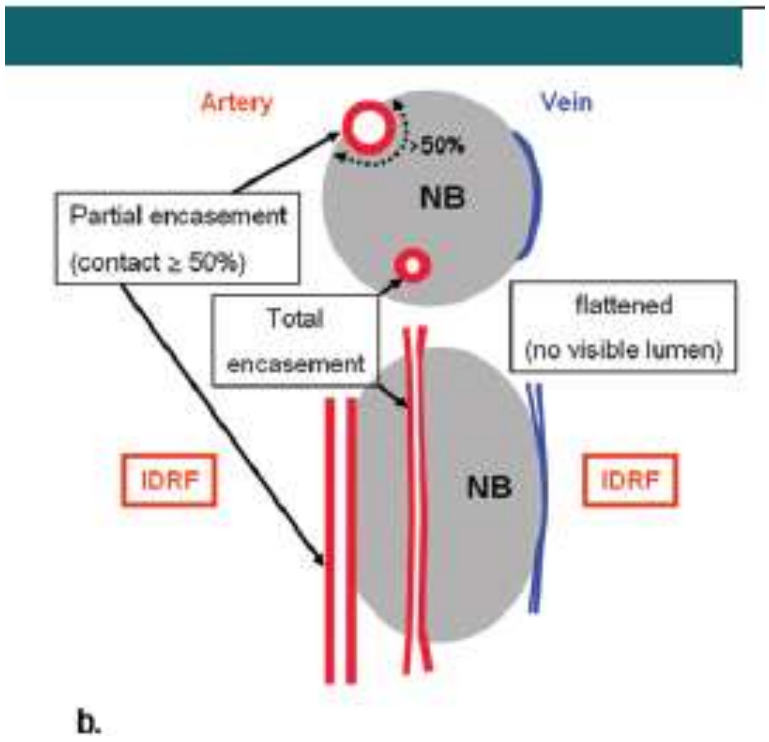
Vessels: more than 50% circumference in contact with tumour.

A vessel where lumen cannot be distinguished= encased.

<u>Compression</u>: it refers to trachea being compressed by tumour: ; change in the diameter of trachea´s lumen = IDRF.

<u>Infiltration</u>: extension of the tumor to neighbouring organs.

It is considered IDRF.



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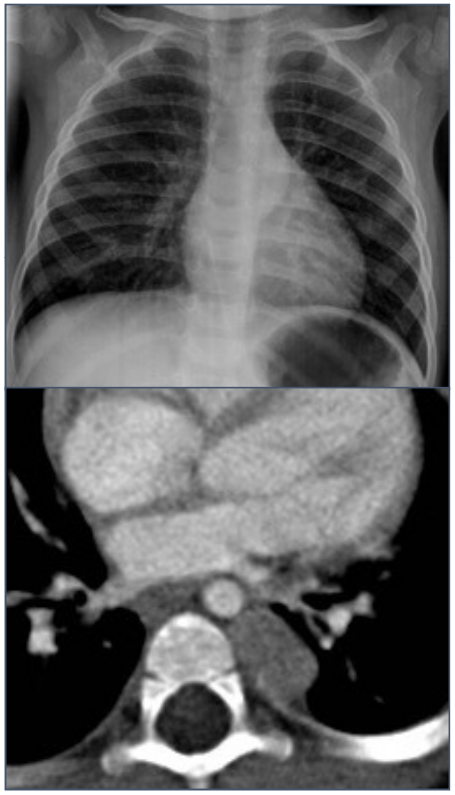
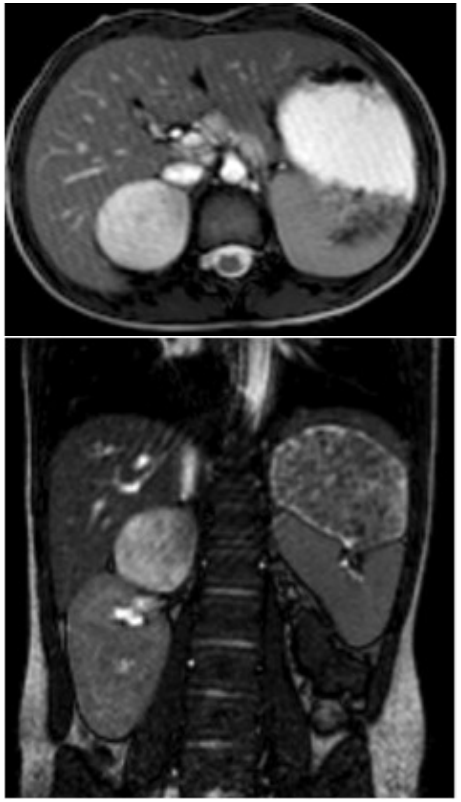
IDRF

Separation

- Good layer, no IDRF

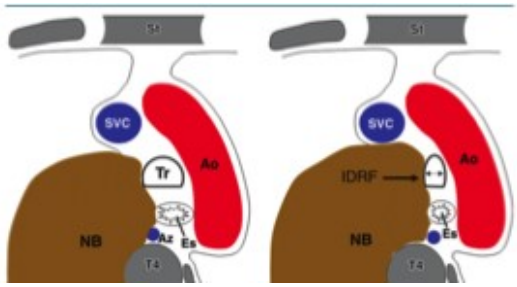


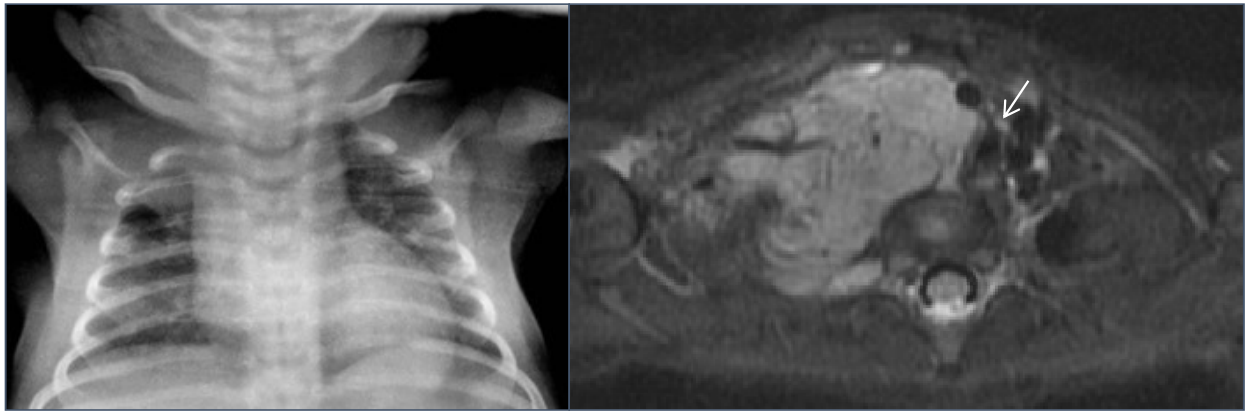


IDRF

Compression

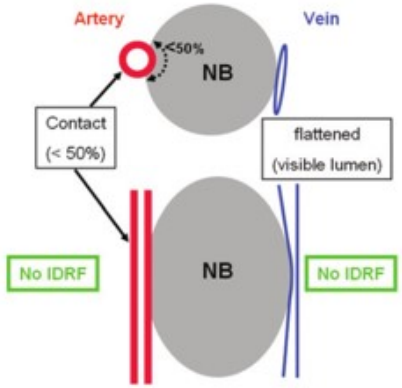
- Airway
- IDRF

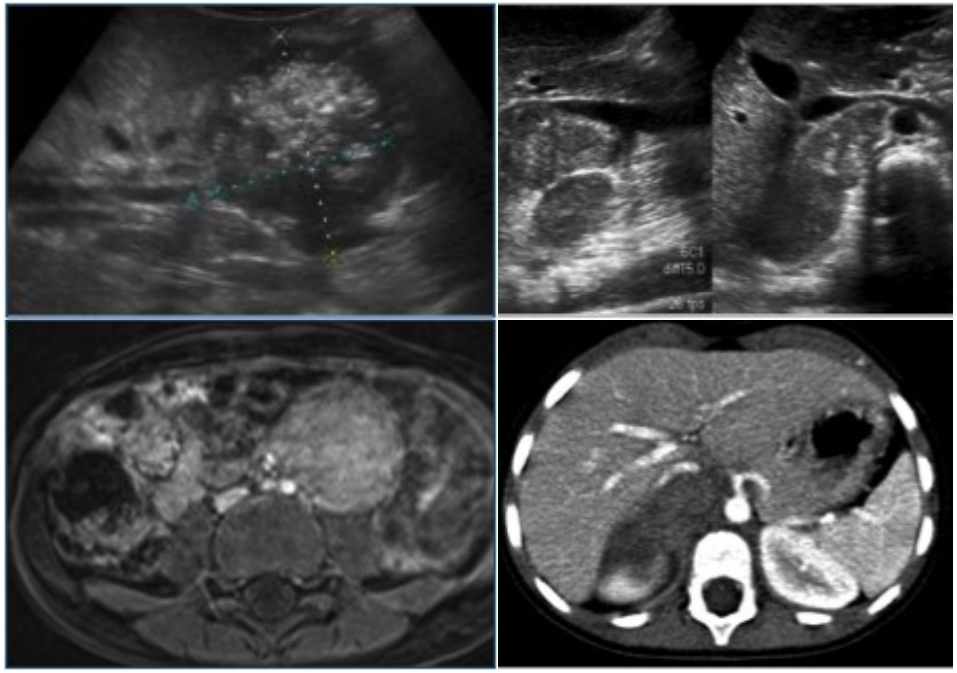




IDRF

Contact

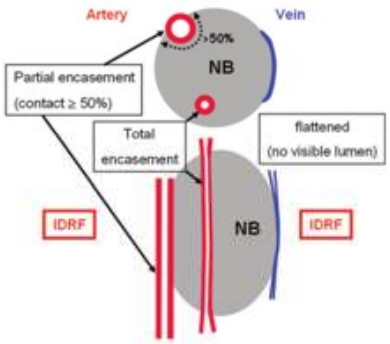


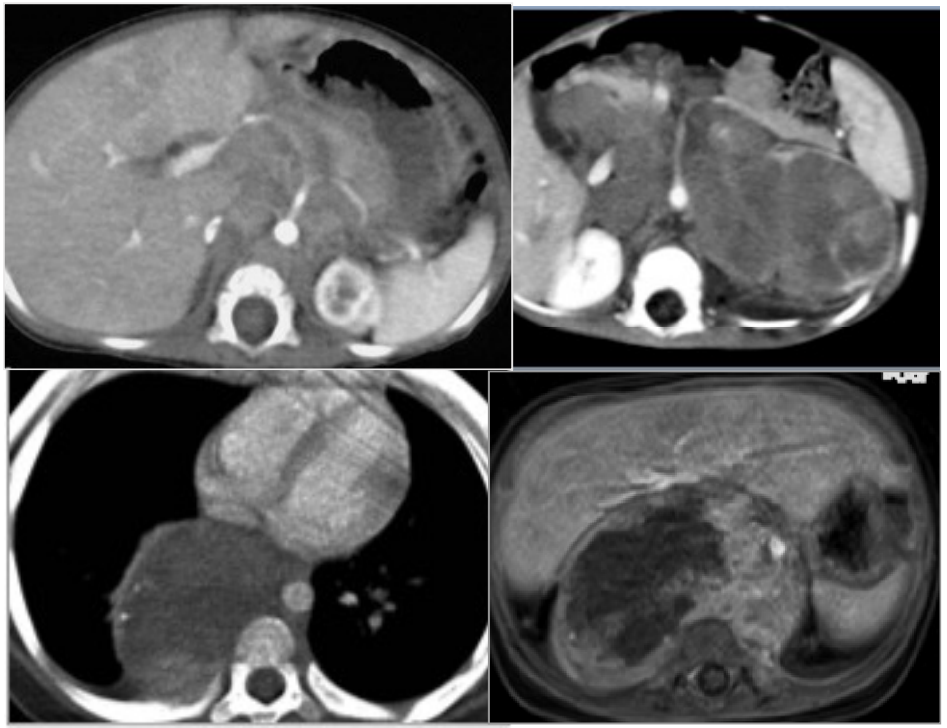


- Exception: Renal vessels = Contact = IDRF

IDRF

Encasement

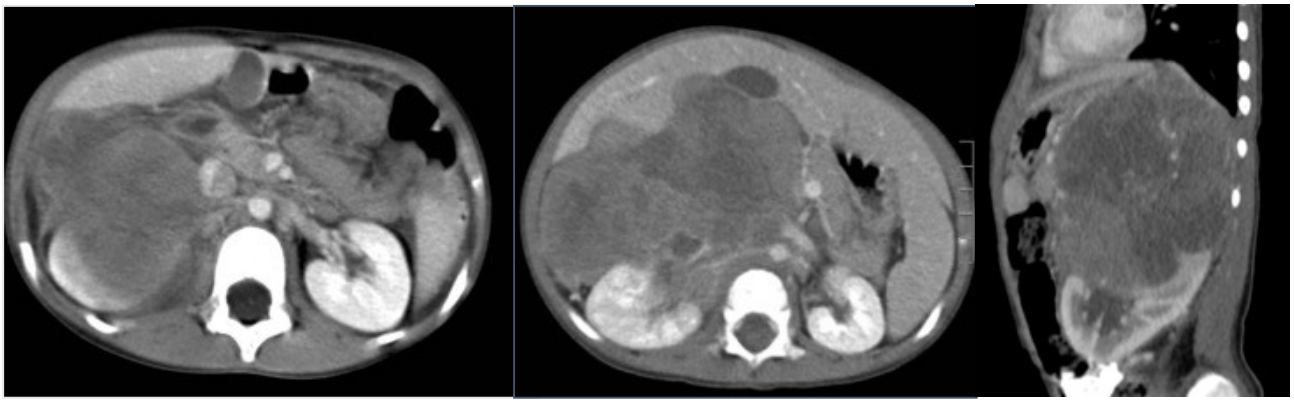




IDRF

Infiltration

- Extension to a neighbouring organ without layer of separation = IDRF



IDRF by anatomical compartiments:

- **Cervical neuroblastoma**: arises from the cervical sympathetic chain behind the internal carotid artery. IDRFs are present if it engulfs the cervical vessels, compresses the trachea or extends to the base of the skull. It rarely becomes intraspinal at this level.

- **Cervicothoracic neuroblastoma**: arises from the area of the stellate ganglion. It is an area of high surgical difficulty. IDRFs exist if the tumour involves the roots of the brachial plexus, subclavian and cervical vessels and compresses the trachea.

- **Thoracic neuroblastoma**: arises from the posterior mediastinal paraspinal sympathetic chain. Intraspinal invasion is frequent in this location, if it is greater than 1/3 of the spinal canal, if there is CSF obliteration in the leptomeningeal space or alteration in the medulla, it indicates IDRFs present.

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IDRF by anatomical compartiments:

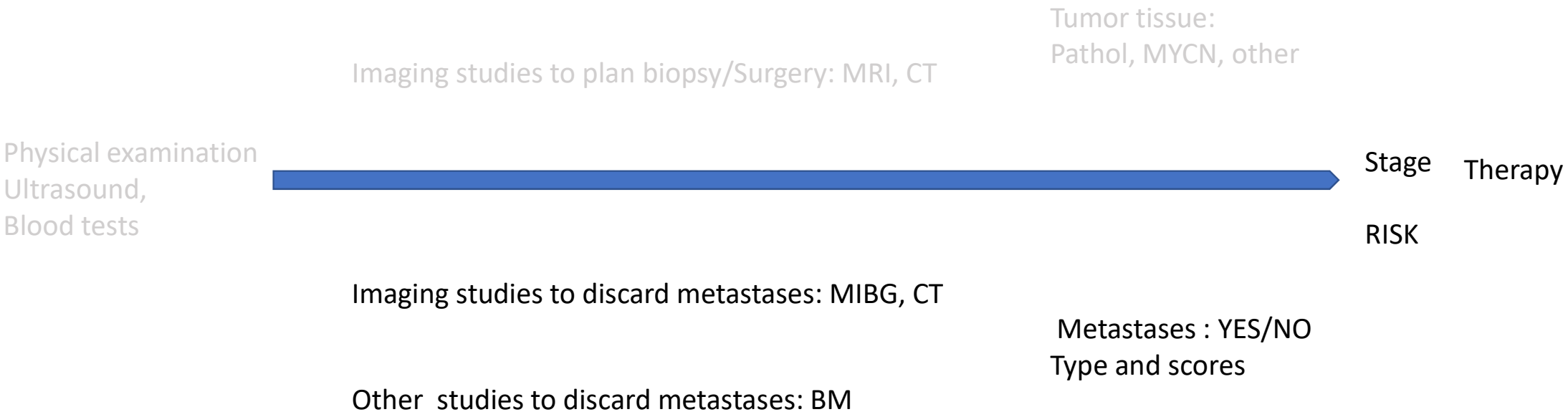
- **Inferior mediastinal neuroblastoma**: infiltration of the costovertebral junction between levels T9 to T12 indicates IDRF due to the presence of the anterior spinal artery (Adamkievicz artery). Also at this level, the relationship of the tumour with the descending aorta, pulmonary pedicles, compression of the bronchi, and infiltration of the pleura, pericardium and diaphragm are assessed.

- **Abdominal neuroblastoma**: originates in the adrenal gland of the abdominal sympathetic chain, Zuckerkandl's organ. The close relationship of the tumour with the abdominal vessels (celiac trunk, mesenteric, renal and iliac vessels) makes it highly complex surgery. In addition, the structures adjacent to the tumour must be assessed: porta hepatis, diaphragm, kidneys, mesentery.

- **Pelvic neuroblastoma**: arises from the hypogastric sympathetic plexus or presacral sympathetic ganglia. They extend towards the lumbosacral foramina and iliac vessels. Extension below L2 towards the foraminal foramina results in radicular involvement rather than spinal cord compression. Extension through the sciatic notch is important when considering IDRF.

Neuroblastoma: Diagnosis & Staging

- How is it diagnosed?



Neuroblastoma: Diagnosis & Staging

<u>Consensus report for pathology:</u>

IHC: NB-84, Tirosin-hidroxilasa (TH), CD-56 (N-CAM), Synaptofisin, y Protein S-100 .

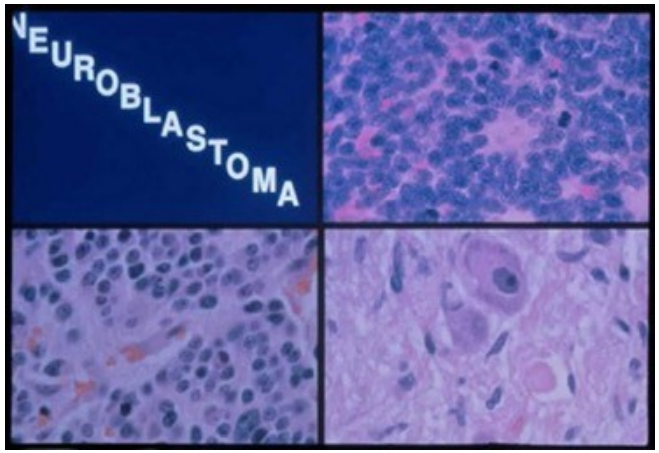
Mitosis –Kariorrexis index.

Presence/abscence calcification.

Surgical margins.

Node invasión

% Neuroblasts / Schwanian cells

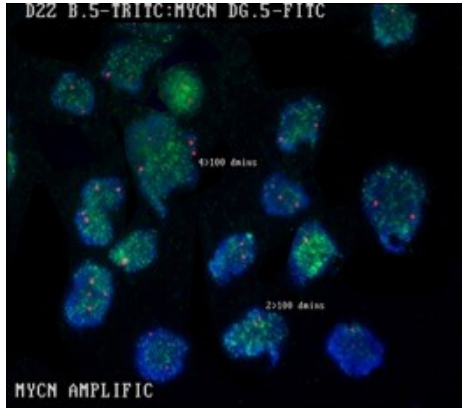


Shimada H, Ambros IM, Dehner LP, et al. The International neuroblastoma pathology classification (the Shimada system). Cancer 1999; 86:364-72.

b) MYCN, TERT and ALT-FISH, SNParray/CGH/IcWGS, NGSpanel; Research projects on i.e. cell free DNA (cfDNA) will be carried out

Genetic studies: MYC-N amplification !:

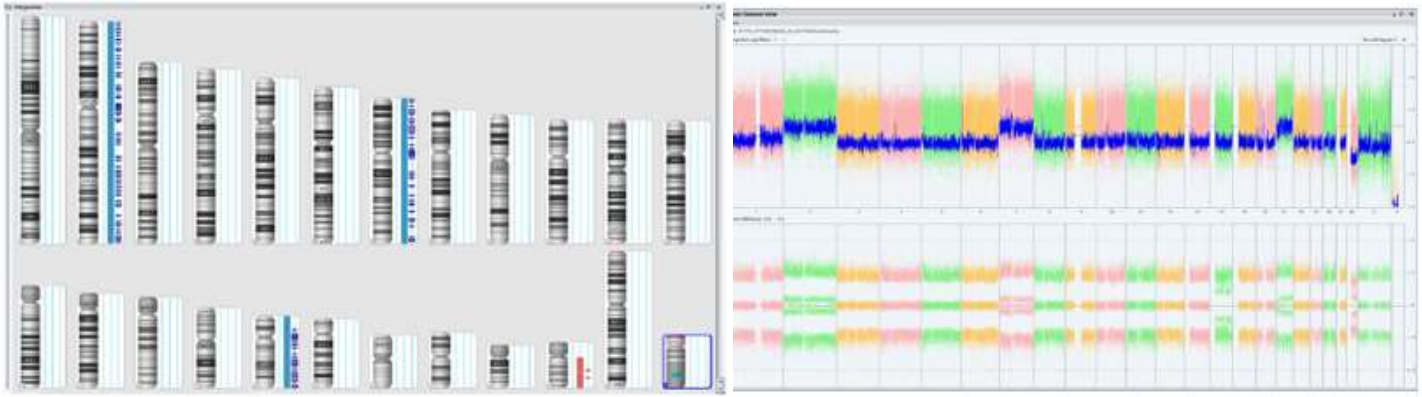
- Oncogen N-myc: cromosoma 2.
- **Over 10 copies = bad prognosis always!.**
- FISH: Gold standard in most clinical laboratorios.



- Other studies:
  - Copy number variations by different techniques (SNP array(CGH,IcWGS

- Alteraciones numéricas (NCA): SÍ. +2, +7, LOH 14, +17, -22.

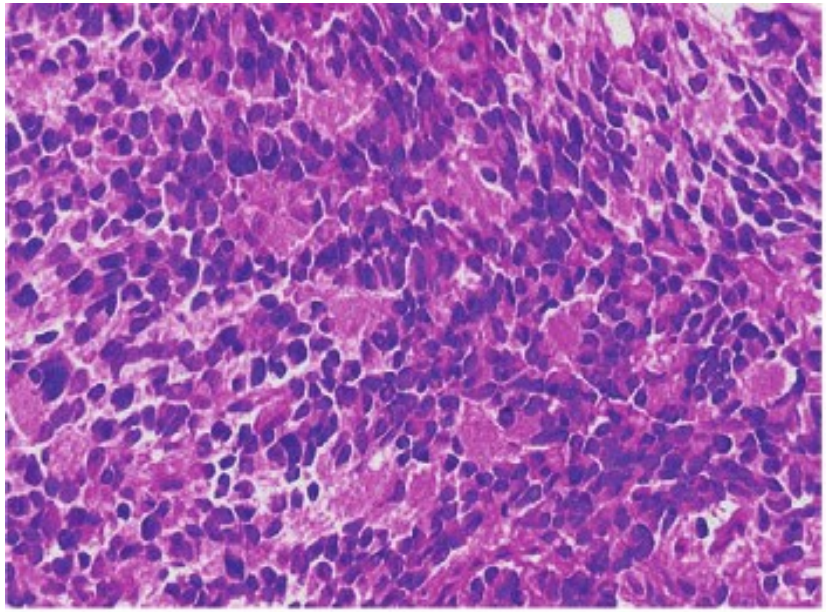
- Alteraciones cromosómicas segmentarias (SCA): NO.

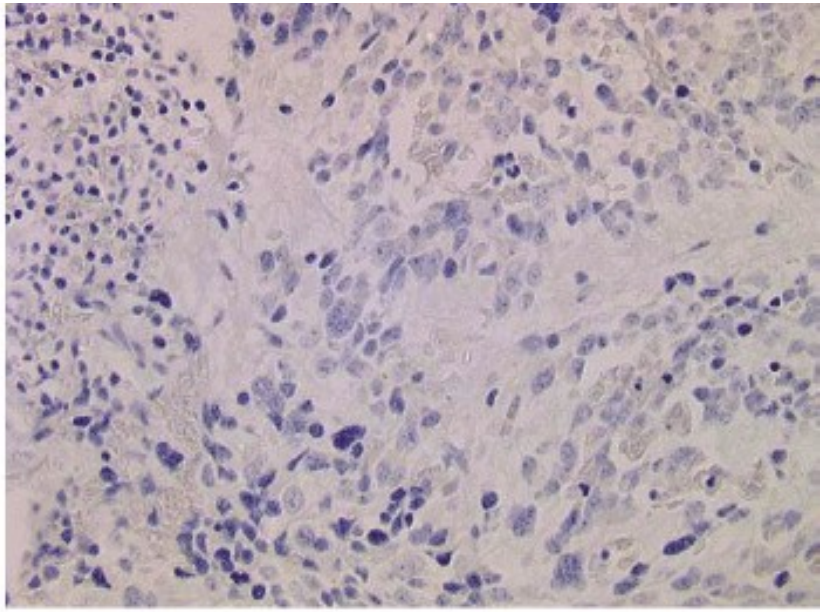


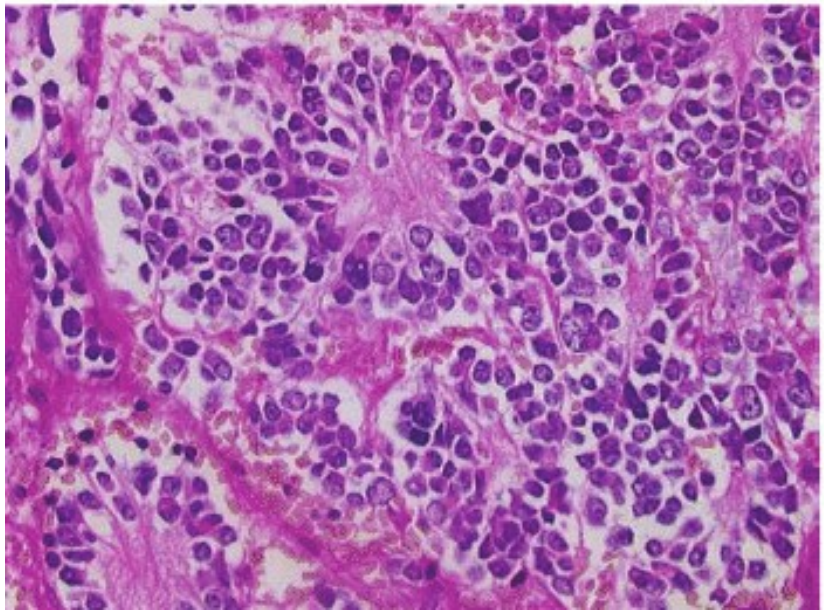
Neuroblastoma: Staging

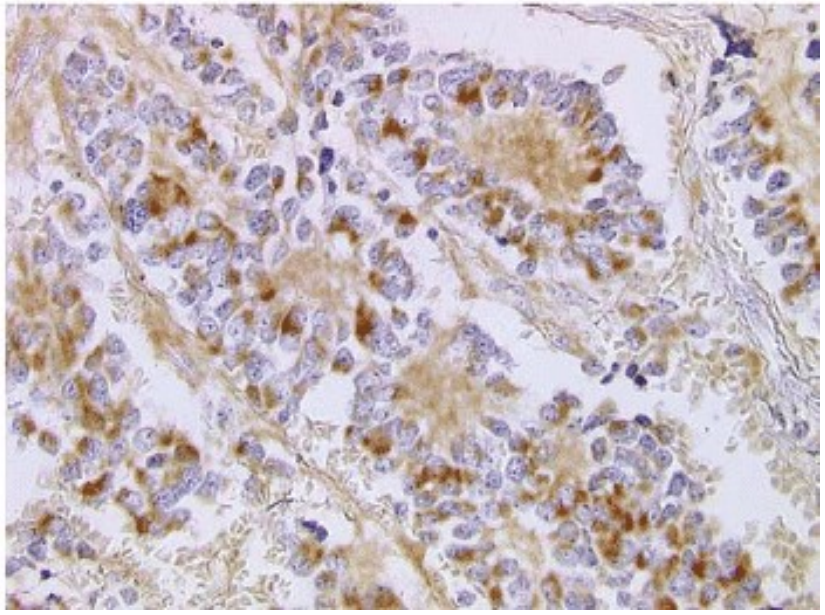
Bone marrow staging: INSS 1988

- From two different sites: 2 bone marrow aspirations and 2 bone marrow biopsies.
- Bone cylinders must be evaluable: 1 cm.
- Complex in infants and very Young children (more BMA can be carried out).
- Pathological criteria.



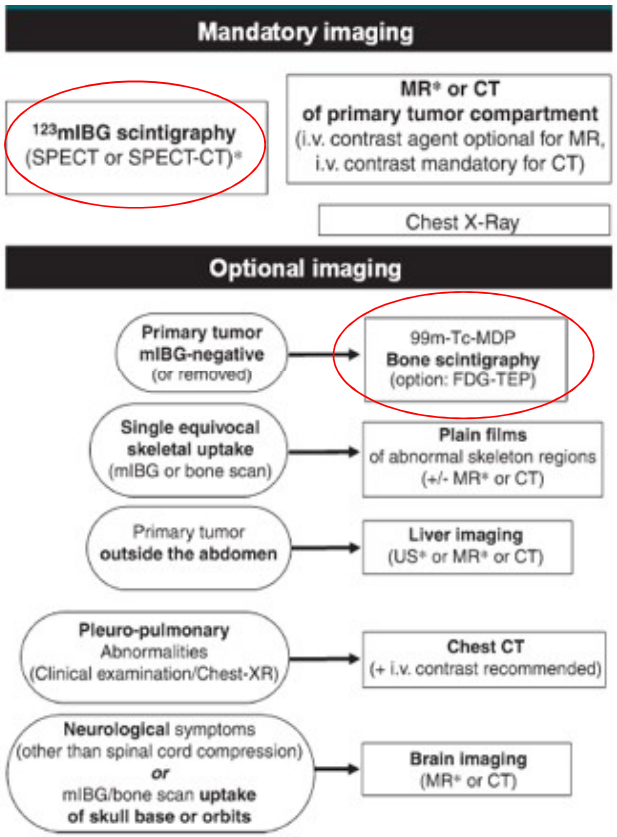






benchista

GUIDELINES FOR IMAGING AND STAGING OF NEUROBLASTIC TUMORS: CONSENSUS REPORT FROM THE INTERNATIONAL NEUROBLASTOMA RISK GROUP PROJECT 2011



123MIBG SCINTIGRAPHY (OSTEOMEDULLARY)

Physiological uptake: salivary glands, miocardium, thyroid, liver, bladder.

Distant metastases : Bone marow and bone

MIBG is not uptaken physiologically in BM
It detects osteo-medullary targets

Sensitivity 90% and Specificity 100%

To assess extent and response:
"Semi-quantitative scale".

Neuroblastoma: Diagnosis & Staging

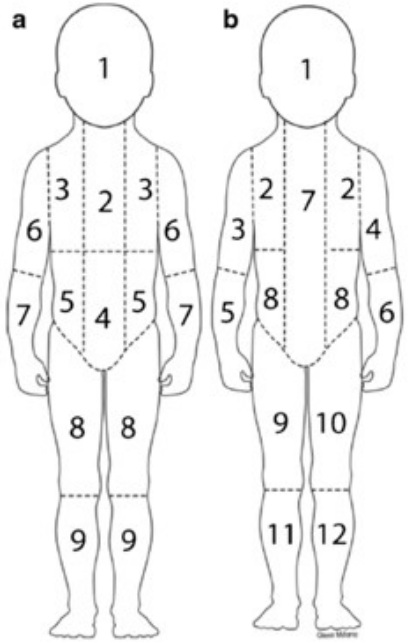
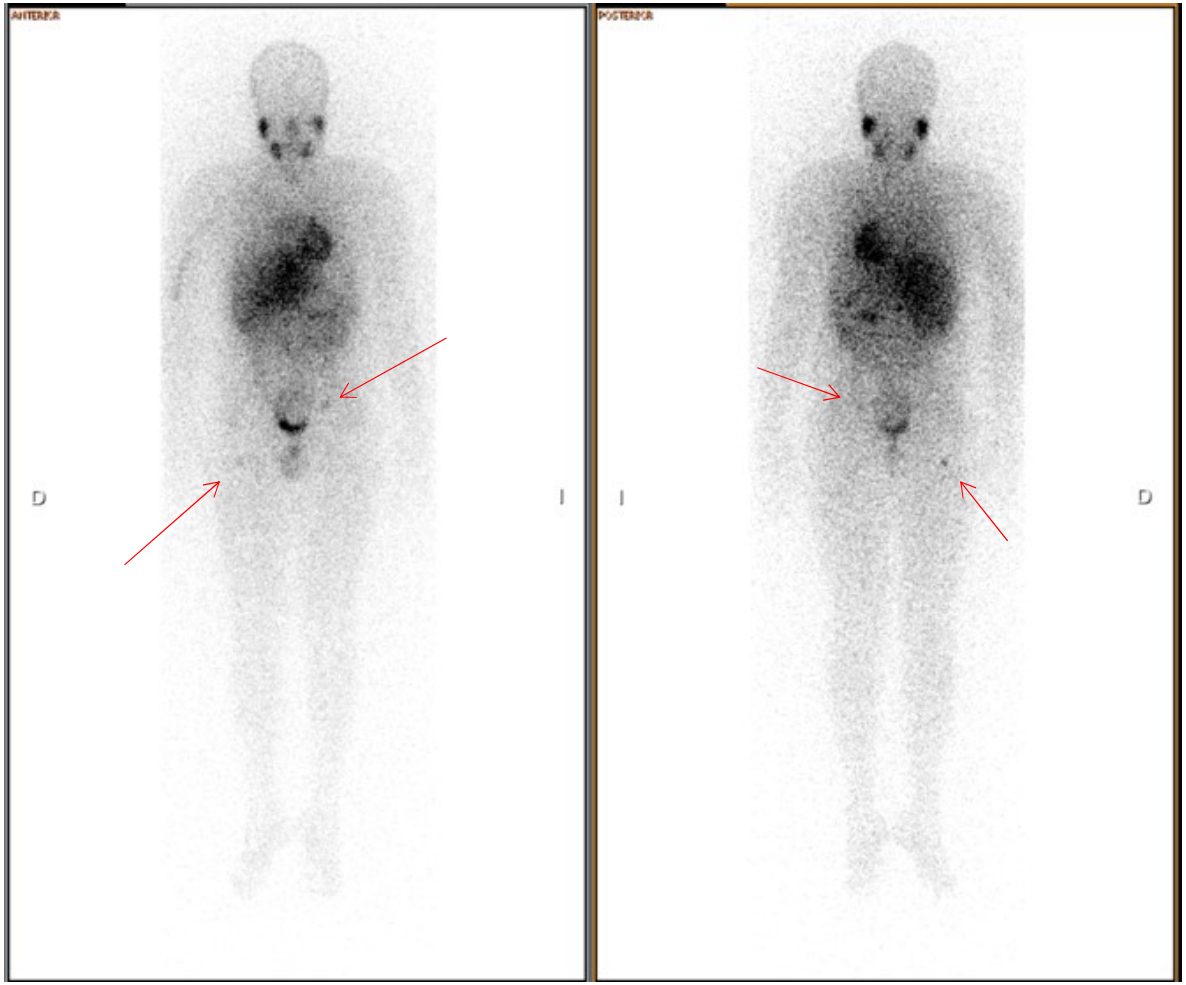


Fig. 1 Semiquantitative mIBG scoring systems. **a** The Curie scoring system divides the skeleton into nine segments as shown, with a tenth segment designated for soft tissue disease. **b** The SIOP-EN scoring system divides the skeleton into 12 segments; there is no segment for soft tissue involvement (from Sharp et al. [35])

1/ Good thyroid block.

2/ Whole body, including full hands and feet.

3/ SPECT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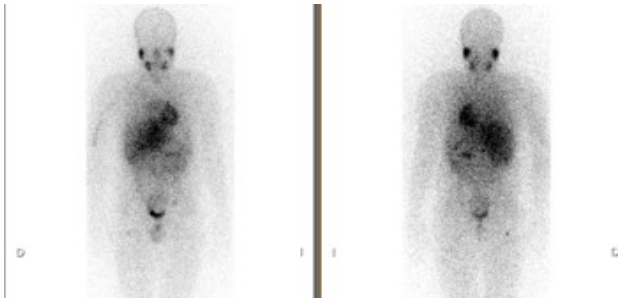

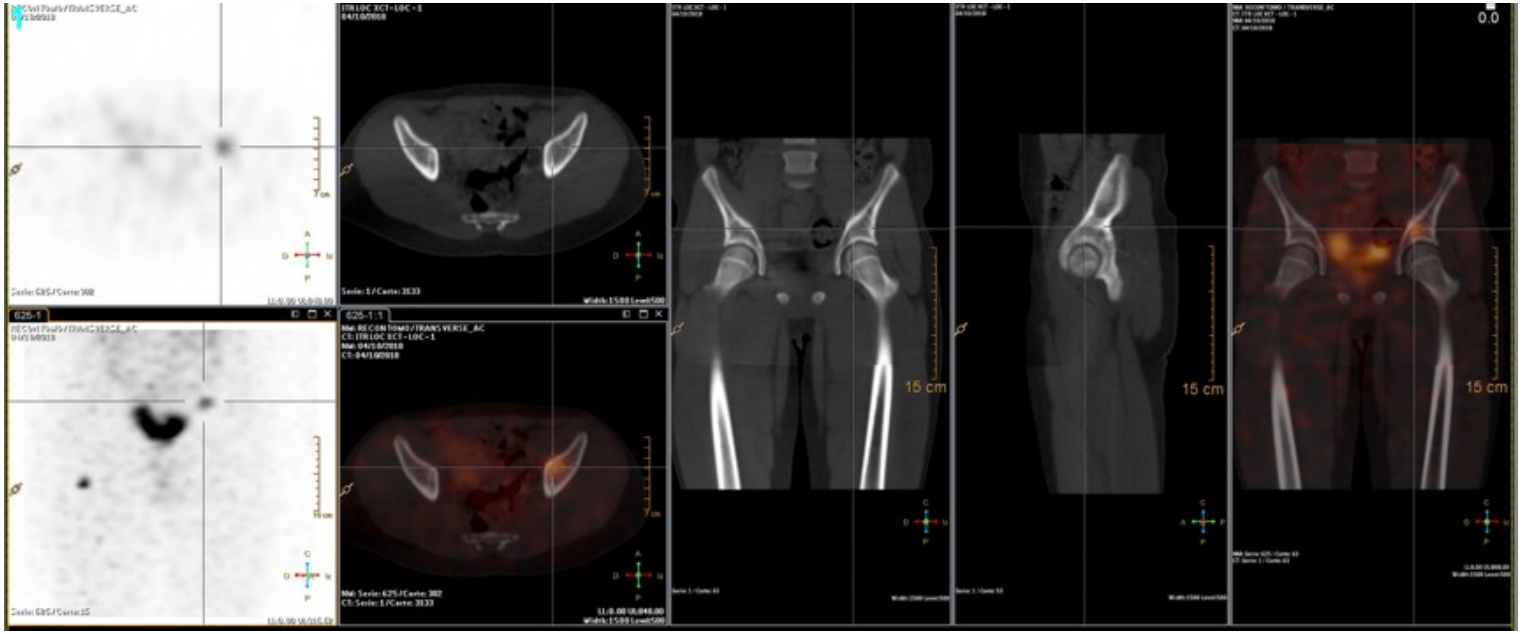
15 cm
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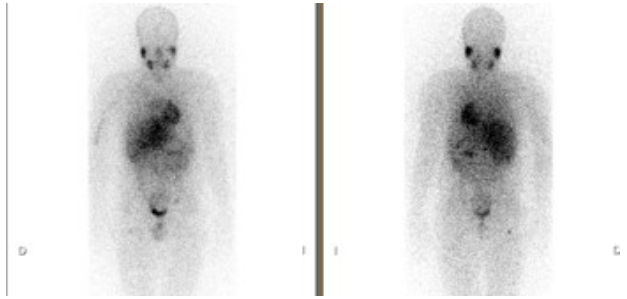
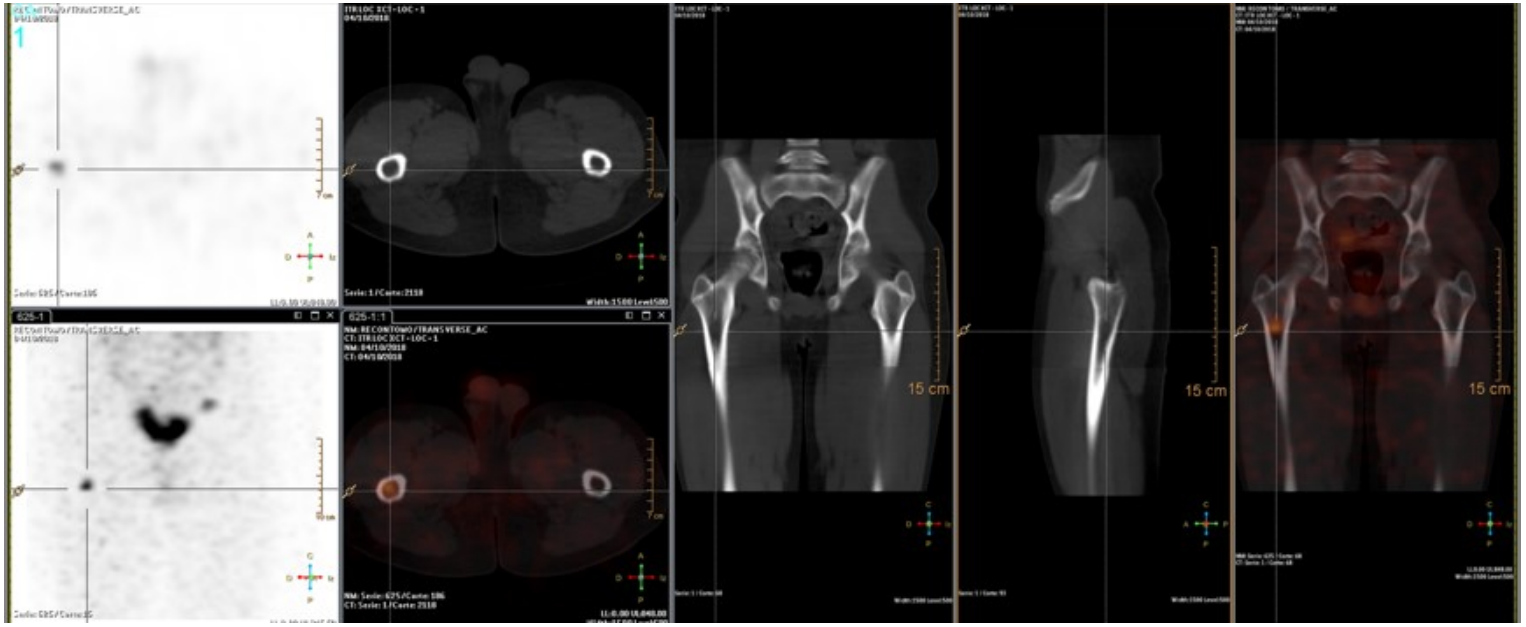



15 cm
15 cm
15 cm

- Child, 4 years old
- Tiredness, fever,
- "abdominal swelling", pain
- bruising around the eyes.
- Moaning and with pain in the lower extremities.
- BP 120/90
- Tumour in right hemiabdomen, mistaken for liver.

Newborn.

Prenatal ultrasound detected an adrenal mass.

No other clinical findings.

Infant, 9 month

Right Leg monoparesy

Neurogenic bladder in ultrasound examination

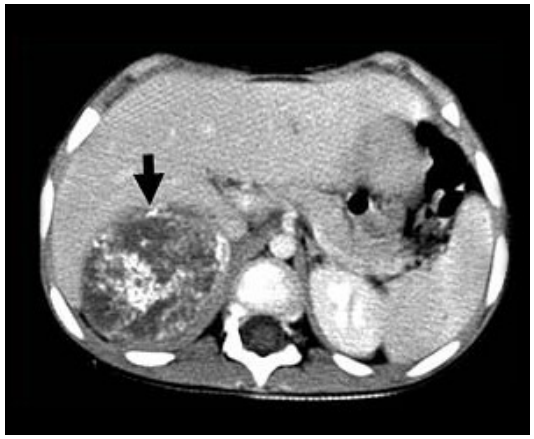
9-month-old infant

3 months: oculogyric movements and hypotonia.

Hepatomegaly study

Elevated catecholamines.

Central retroperitoneal mass



5 year old boy

Fever and cough. X-ray: mass in posterior mediastinum present one year ago in another X-ray. .

- Child, 4 years old
- Tiredness, fever,
- abdominal swelling", pain
- bruising around the
- Moaning and the lower extremities
- Bl
- Tumour in right hemiabdomen, mistaken for liver.

M stage

Newborn.

Prenatal ultrasound revealed an adrenal mass.

No other clinical findings.

L1 stage

Infant, 9 month

Right Leg monoparesis

Neurogenic bladder. Ultrasound examination

L2 stage

9-month-old infant

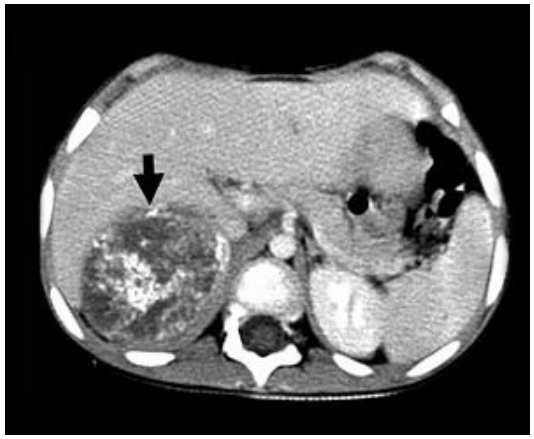
3 months: oculogyric crisis and hypotonia.

Hepatomegaly

Elevated catecholamines.

Central abdominal mass

Ms stage

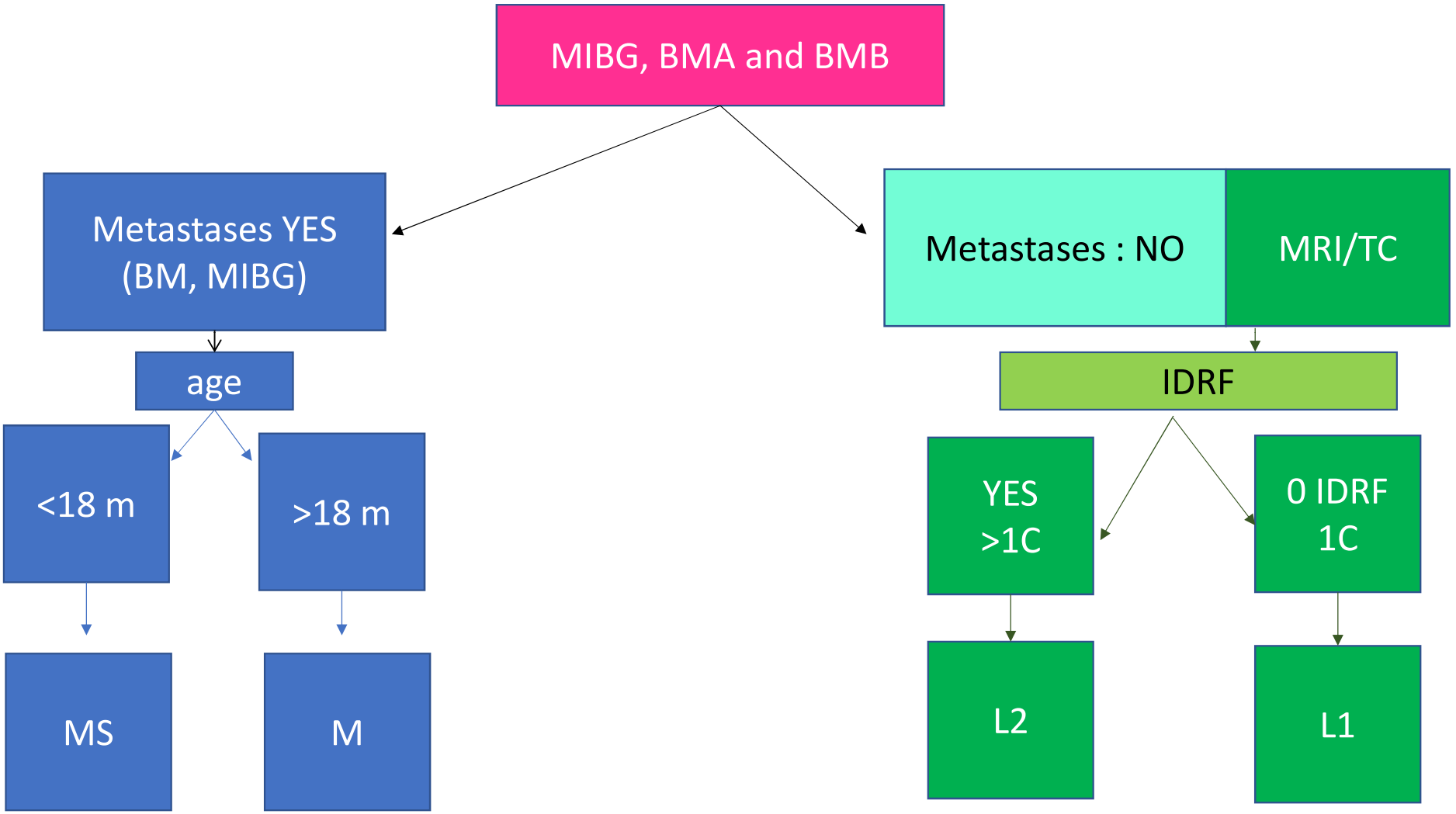


5 year old boy

Fever and abdominal mass in posterior abdomen present one year ago. Another X-ray. .

L2 stage

Road map for staging in neuroblastoma:



Neuroblastoma: Diagnosis & Staging

- How is it diagnosed? : Main/usual diagnostic procedures used?

1. Aim: Biopsy of primary tumor by surgery or tru-cut.
2. If not feasible, Bone marrow infiltrated is diagnostic.
3. If not feasible neither both of them: MIBG+ and increased of catecholamins.

Enough material to secure not only diagnosis, but pathological classification (INPC) and biological studies (MycN amplification).

Other genetic / biological studies in research.

Neuroblastoma: Diagnosis & Staging

- What investigations are used for tumour staging and how are they interpreted?
  - Primary tumor: MRI is the gold-standard. If not feasible: CT. Ultrasound only for daily clinics.
  - Metastases: ^{123}I-MIBG (thyroide blockade) and Bone marrow studies (biopsy, BMA). Infants: bone marrow aspirations.

  - INRGSS: Define IDRF and presence/abscence of metastases.

T. S second tier for Neuroblastoma: INRGSS.

Level 2 follows the International Neuroblastoma Risk Group Staging System (INRGSS).

Level 1 criteria are simplified equivalents of Level 2, which do not require assessment of image-guided risk criteria in situations where cross-sectional imaging is not available or does not exist.

L1: Localized without IDRF. One compartiment
L2: Localized, at least one **IDRF**. Two contigous compartiments
M: Metastases, except MS
MS: < 18 months with metastases: skin, liver, BM (>10%). L1 or L2 locally.

Neuroblastoma: Therapy and non-stage prognostic factors

Pre-treatment Group	5-year EFS	Proportion of Patients (%)
Low	≥ 85%	28.2
Intermediate	75-<85%	26.8
High	50-<75%	9.0
Ultra-High	<50%	36.1

Decrease treatment to avoid sequelae

Different approaches: no consensus

Multimodal intensive treatment

Experimental and new approaches

Multimodal intensive treatment:
Induction chemotherapy- Surgery- Consolidation (BMT)- Radiotherapy- MRD treatment

Neuroblastoma: Non-stage prognostic factors

Solid Tumour	Essential	Additional	New and Promising	Comments
Neuroblastoma	Age Stage	N-myc	CNV 11q ALK mutation TERT	MYCN copy number is essential for clinical risk stratification but is not uniformly available to cancer registries

Gupta et al. Development of paediatric non-stage prognosticator guidelines for population-based cancer registries and updates to the 2014 Toronto Paediatric Cancer Stage Guidelines. **Lancet Oncol 2020; 21: e444–51**

Neuroblastoma: Summary

- Clinical heterogeneity.
- INRGSS for staging = T2 Toronto staging.
- Follow in-house road map for staging
- IDRF important to define local staging and initial biopsy (L1/L2).
- Metastases: Bone marrow (biopsy, aspiration) and MIBG (Bone and other).
- Age is an important factor : The younger … the better. 18 months!
- Nmyc amplification.
- Therapy according to risk stratification:
  - low : decrease therapy safely in those that can be decreased (Biology /LTS).
  - Intermediate: ?
  - High: multimodal everywhere!.

Toronto Staging

Méric Klein, Belgian Cancer Registry

Gemma Gatta (Fondazione IRCCS, INT, Milan)
Andrea Di Cataldo (University of Catania)

Leisa O'Neill - Australian Childhood Cancer Registry

Wilms tumours:
Toronto Staging

Toronto Staging: Wilms tumours

Tier 1

Localised	Metastatic
Tumour confined to the area of origin	Distant metastases present at diagnosis

Toronto Staging: Wilms tumours

Tier 2 = COG/SIOP

- 2 different staging systems
  - Children's Oncology Group 'COG'
    - When **NO** chemotherapy is given prior to surgery
  - International Society of Paediatric Oncology 'SIOP'
    - When chemotherapy is given prior to surgery
    - Identified by the prefix "y"
  - Both are based on findings at surgery (except for stage IV)
- Staging requires assessment of
  - Diagnostic imaging (regardless of upfront chemo/surgery)
  - Results of surgical excision

Toronto Staging: Wilms tumours

Tier 2 = COG/SIOP

COG - When **NO** chemotherapy is given prior to surgery

Stage I	Stage II	Stage III	Stage IV
Tumour limited to kidney and completely excised	Tumour extends beyond kidney but is completely resected	Residual tumour or non-haematogenous metastases confined to abdomen	Haematogenous metastases or spread beyond abdomen at diagnosis

Toronto Staging: Wilms tumours

Tier 2 = COG/SIOP

COG - When **NO** chemotherapy is given prior to surgery

- Some conditions to interpret the stages

Stage I	Stage II	Stage III	Stage IV
Renal capsule intact, not penetrated by tumour. No tumour invasion of veins or lymphatics of renal sinus. No nodal or haematogenous metastases. No prior biopsy. Negative margins.	Tumour penetrates renal capsule. Tumour in lymphatics or veins of renal sinus. Tumour in renal vein with margin not involved. No nodal or haematogenous metastases. Negative margins.	Involved abdominal nodes. Peritoneal contamination or tumour implant. Tumour spillage of any degree occurring before or during surgery. Gross residual tumour in abdomen. Biopsy of tumour (including fine-needle aspiration) prior to removal of kidney. Resection margins involved by tumour.	

Toronto Staging: Wilms tumours

Tier 2 = COG/SIOP

SIOP - When chemotherapy is given prior to surgery

Stage y-I	Stage y-II	Stage y-III	Stage IV
Tumour limited to kidney and completely resected	Tumour extends beyond kidney but is completely resected	Incomplete excision of the tumour (gross or microscopic extension beyond resection margins)	Haematogenous metastases or spread beyond abdomen at diagnosis

Toronto Staging: Wilms tumours

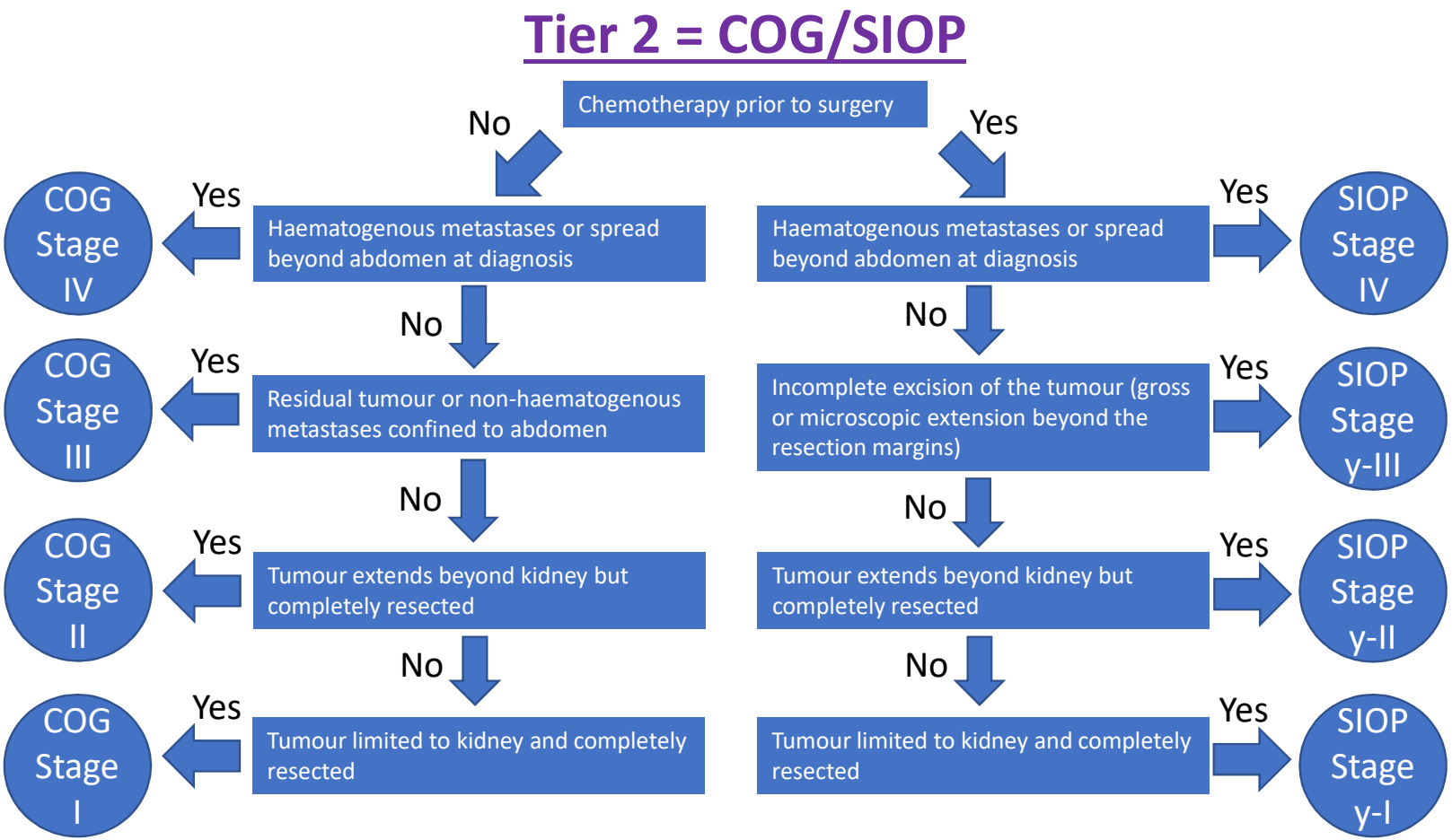
Tier 2 = COG/SIOP

SIOP - When chemotherapy is given prior to surgery

- Some conditions to interpret the stages

Stage y-I	Stage y-II	Stage y-III	Stage IV
Renal capsule may be infiltrated by tumour, but tumour does not reach the outer surface. Tumour may protrude or bulge into the pelvic system or ureter, but does not infiltrate. Vessels of renal sinus not involved.	Tumour penetrates renal capsule into perirenal fat. Tumour infiltrates the renal sinus and/or invades blood and lymphatic vessels outside renal parenchyma but is completely resected. Tumour infiltrates adjacent organs or vena cava but is completely resected.	Involved abdominal lymph nodes, including necrotic tumour or chemotherapy induced changes. Tumour rupture before or intraoperatively. Tumour has penetrated the peritoneal surface. Tumour thrombi present at resection margins. Surgical biopsy prior to resection (does not include needle biopsy).	

Toronto Staging: Wilms tumours



NSP: Wilms tumours

- Registration of Non-Stage Prognostic Factors NSP
  - ➢Presence or absence of diffuse or focal anaplasia

- The laterality is also important!
  - ✓Right
  - ✓Left
  - ✓Bilateral

Wilms tumours: Exercises

Available in the Kahoot application until November 10, 2021 at the following link:

https://kahoot.it/challenge/04834060?challenge-id=7382f979-7345-44c6-9f85-9268fb87bef4_1634207300136

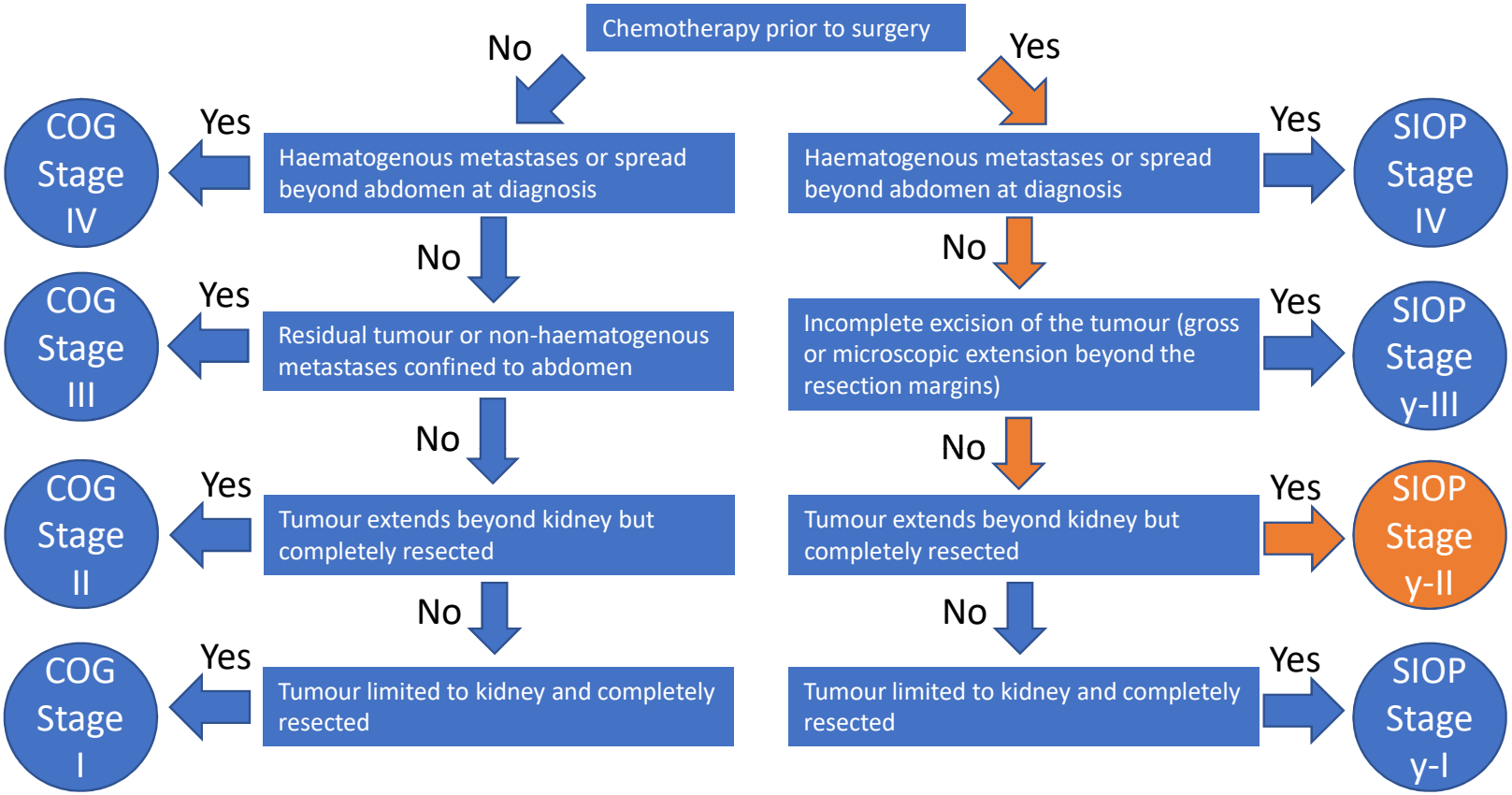
Exercise 1

A 1-year old patient is diagnosed with a nephroblastoma on the left kidney. A left nephrectomy is realised after neo-adjuvant chemotherapy and shows a well-defined encapsulated nephroblastoma (epithelial subtype). The tumour is 6.5cm in greatest dimension with a focal involvement of the vena cava. Resection margins are negative.

What is the correct stage for this patient ?

A. Stage I
B. Stage II
C. Stage y-I
D. Stage y-II

Exercise 1 - Answer



Infiltration of the vena cava is considered as an extension beyond kidney.

Exercise 2

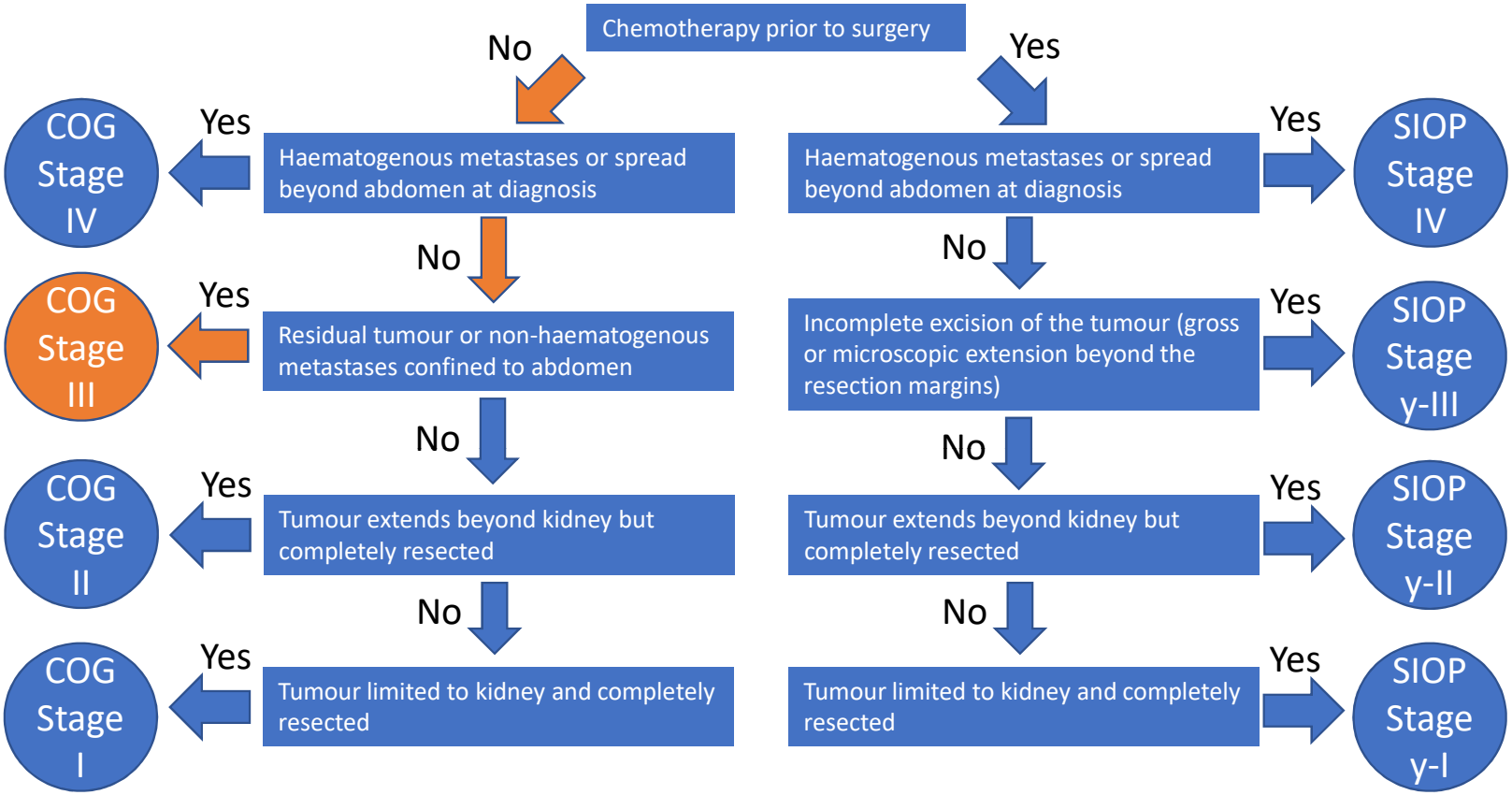
A Wilms tumour is found in the right kidney of a 5-year old patient. Whether or not the tumour is confined to the kidney is unclear on diagnostic imaging, but there is no evidence of tumour spill.

A complete resection is performed and confirms that the primary tumour extends beyond the kidney. 6 abdominal lymph nodes have also been removed, 1 of them is found positive.

What is the correct stage for this patient ?

A. Stage II
B. Stage III
C. Stage y-II
D. Stage y-III

Exercise 2 - Answer



One abdominal lymph node is involved, which corresponds to a non-haematogenous metastasis confined to the abdomen.

Exercise 3

- A 5 -year-old boy
- surgical exploration in emergency to stop internal bleeding at the local hospital. As the tumour was very large and adjacent to large vessels, radical resection was impossible.
- Biopsy was performed, and the pathological diagnosis revealed Wilms tumour
- Chemotherapy (vincristine) was given in specialised hospital
- Ultrasound and intravenous pyelography (IVP) showed a right retroperitoneal solid mass causing compression and deformation of the renal pelvis and calyx. There was no evidence of pulmonary metastasis.
- Intraoperatively was found that the tumour was 15 x 15 x 20 cm and located at the retroperitoneum, invading the ascending duodenum and mesocolon. Kidneys, liver and spleen were normal with no evidence of disease involvement.

What is the correct stage for this patient?

A. Stage III
B. Stage y-III
C. Stage IV
D. Case not to be included in the study

Exercise 3 - Answer

Only Wilms tumours from the kidney have to be included in the BENCHISTA project !!!

This one is located in the retroperitoneum, with both kidneys being normal with no evidence of disease involvement.

Exercise 4

Boy 2 years old, imaging shows a mass involving the left kidney

- All investigations performed before surgery exclude metastases except Chest X-ray which mentions ‘suspicious lesion’ of lung. Tumour is completed excised. CT scan thorax performed immediately after surgery and prior to any chemotherapy confirms presence of a definite lung metastasis.

What is the correct stage for this patient?

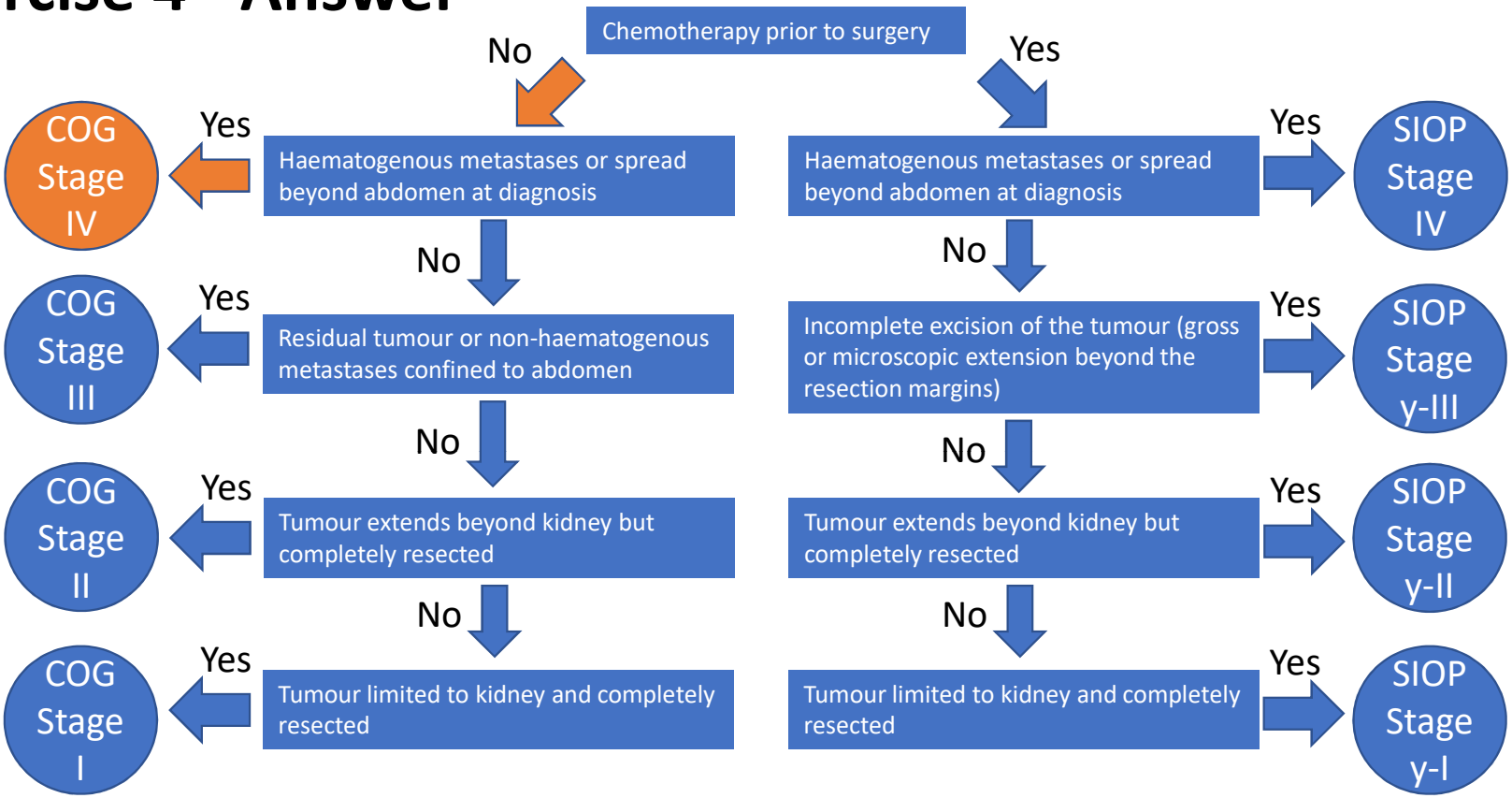
A. Stage I

B. Stage III

C. Stage IV

D. Stage X

Exercise 4 - Answer



The suspect lesion is confirmed positive before any treatment might alter its nature. We would recommend to encode this as Stage IV.

Neuroblastoma: Toronto Staging

Toronto Staging: Neuroblastoma

Tier 1

Localised	Locoregional	Metastatic	MS
Localised tumour confined to one body compartment and not involving vital structure	Locoregional tumour with spread	Distant metastatic disease, except stage MS	Patient less than 18 months (547 days) with a metastatic disease confined to skin, liver and/or bone marrow

Toronto Staging: Neuroblastoma

Tier 2 = International Neuroblastoma Risk Group Staging 'INRGSS'

- Staging requires assessment of
  - Extent of disease
  - Location and invasion
    - ➢Image-Defined Risk Factors IDRFs

L1	L2	M	MS
Localised tumour confined to one body compartment, neck, chest, abdomen or pelvis, and with the absence of IDRFs.	Locoregional tumour with the presence of one or more IDRFs.	Distant metastatic disease, except stage MS. Non-regional (distant) lymph node involvement is considered as metastatic disease.	Patient less than 18 months (547 days) with a metastatic disease confined to skin, liver and/or bone marrow.

Toronto Staging: Neuroblastoma

Tier 2 = International Neuroblastoma Risk Group Staging 'INRGSS'

L1	L2	M	MS
The isolated finding of intraspinal tumour extension that does not fulfill the criteria for an IDRF is consistent with stage L1.	The tumour may be ipsilaterally contiguous within body compartments (ie, a left-sided abdominal tumour with left-sided lung, bone or pleura involvement should be considered stage L2). However, a clearly left-sided abdominal tumour with right-sided lung, bone or pleura (or vice-versa) involvement is defined as a metastatic disease.	An upper abdominal tumour with enlarged lower mediastinal nodes or a pelvic tumour with inguinal lymph node involvement is considered as a locoregional disease. Ascites and/or pleural effusion, even with malignant cells, do not constitute metastatic disease unless they are remote from the body compartment of the primary tumour.	MIBG scintigraphy must be negative in bone and bone marrow. Provided there is MIBG uptake in the primary tumour, bone scans are not required.

Toronto Staging: Neuroblastoma

Tier 2 = International Neuroblastoma Risk Group Staging 'INRGSS'

➢ **Image-Defined Risk Factors IDRFs** are identified by imaging at diagnosis, so prior to any resection.

- *Ipsilateral tumour extension within two body compartments*
  - Neck-chest, chest-abdomen, abdomen-pelvis
- *Neck*
  - Tumour encasing carotid and/or vertebral artery and/or internal jugular vein
  - Tumour extending to base of skull
  - Tumour compressing the trachea
- *Cervico-thoracic junction*
  - Tumour encasing brachial plexus roots
  - Tumour encasing subclavian vessels and/or vertebral and/or carotid artery
  - Tumour compressing the trachea
- *Thorax*
  - Tumour encasing the aorta and/or major branches
  - Tumour compressing the trachea and/or principal bronchi
  - Lower mediastinal tumour, infiltrating the costo-vertebral junction between T9 and T12

Toronto Staging: Neuroblastoma

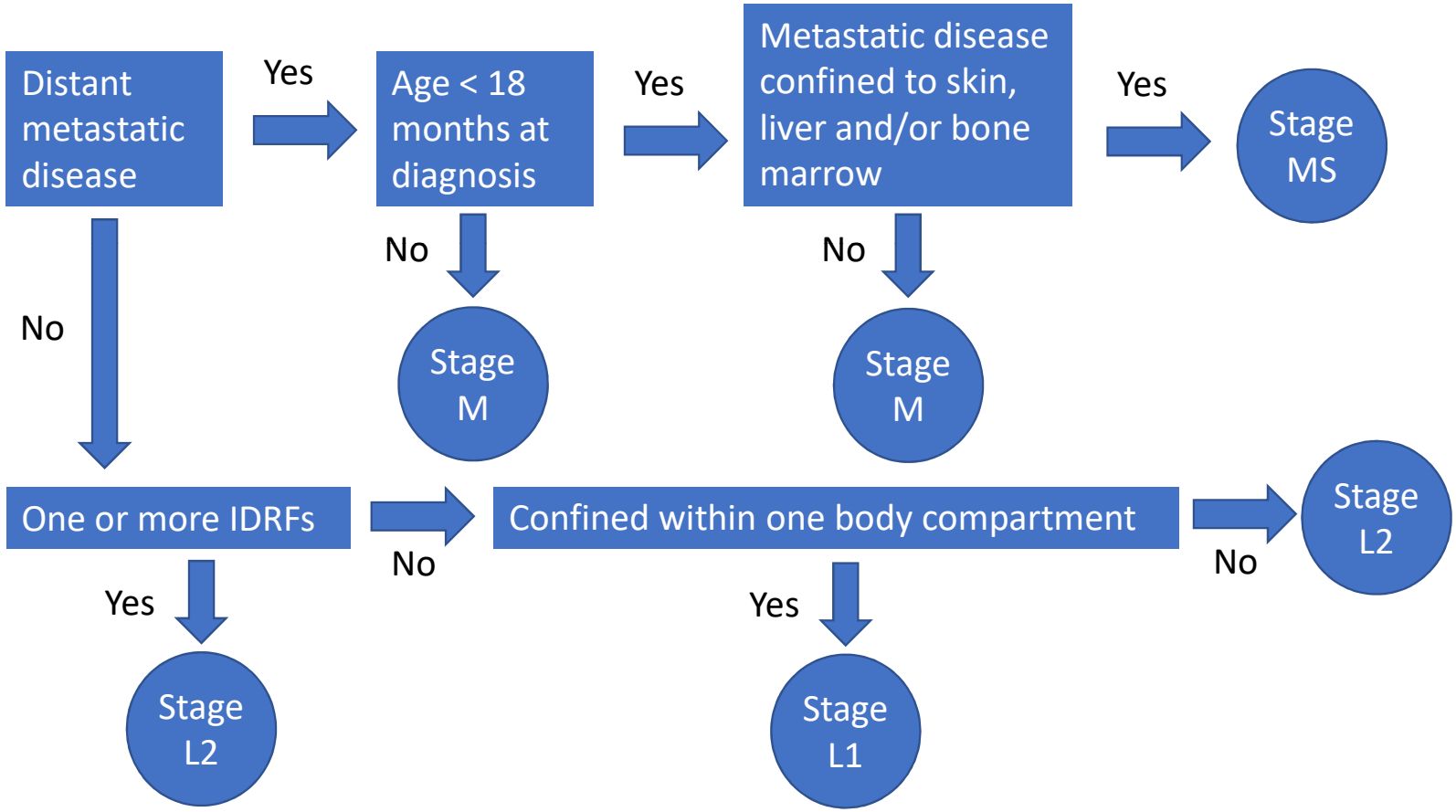
Tier 2 = International Neuroblastoma Risk Group Staging 'INRGSS'

➢ **Image-Defined Risk Factors IDRFs** are identified by imaging at diagnosis, so prior to any resection.

- *Thoraco-abdominal*
  - Tumour encasing the aorta and/or vena cava
- *Intraspinal tumour extension whatever the location provided that:*
  - More than one third of the spinal canal in the axial plane is invaded and/or peri medullary eptomeningeal spaces are not visible and/or the spinal cord signal is abnormal
- *Abdomen/pelvis*
  - Tumour infiltrating the porta hepatis and/or the hepatoduodenal ligament
  - Tumour encasing branches of the superior mesenteric artery at the mesenteric root
  - Tumour encasing the origin of the coeliac axis, and/or of the superior mesenteric artery
  - Tumour invading one or both renal pedicles
  - Tumour encasing the aorta and/or vena cava
  - Tumour encasing the illiac vessels
  - Pelvic tumour crossing the sciatic notch
- *Infiltration of adjacent organs/structures*
  - Pericardium, diaphragm, kidney, liver, duodenopancreatic block and mesentery

Toronto Staging: Neuroblastoma

Tier 2 = International Neuroblastoma Risk Group Staging 'INRGSS'



NSP: Neuroblastoma

- Registration of Non-Stage Prognostic Factors NSP
  - ➢Assessment of the N-MYC gene amplification

- The laterality is also important!
  - ✓Not applicable
  - ✓Right
  - ✓Left
  - ✓Unilateral NOS
  - ✓Bilateral
  - ✓Unknown

Neuroblastoma: Exercises

Available in the Kahoot application until November 10, 2021 at the following link:

https://kahoot.it/challenge/02504881?challenge-id=7382f979-7345-44c6-9f85-9268fb87bef4_1634207440160

Exercise 1

A 3-year old patient is diagnosed with a N-Myc amplified neuroblastoma of the adrenal gland.

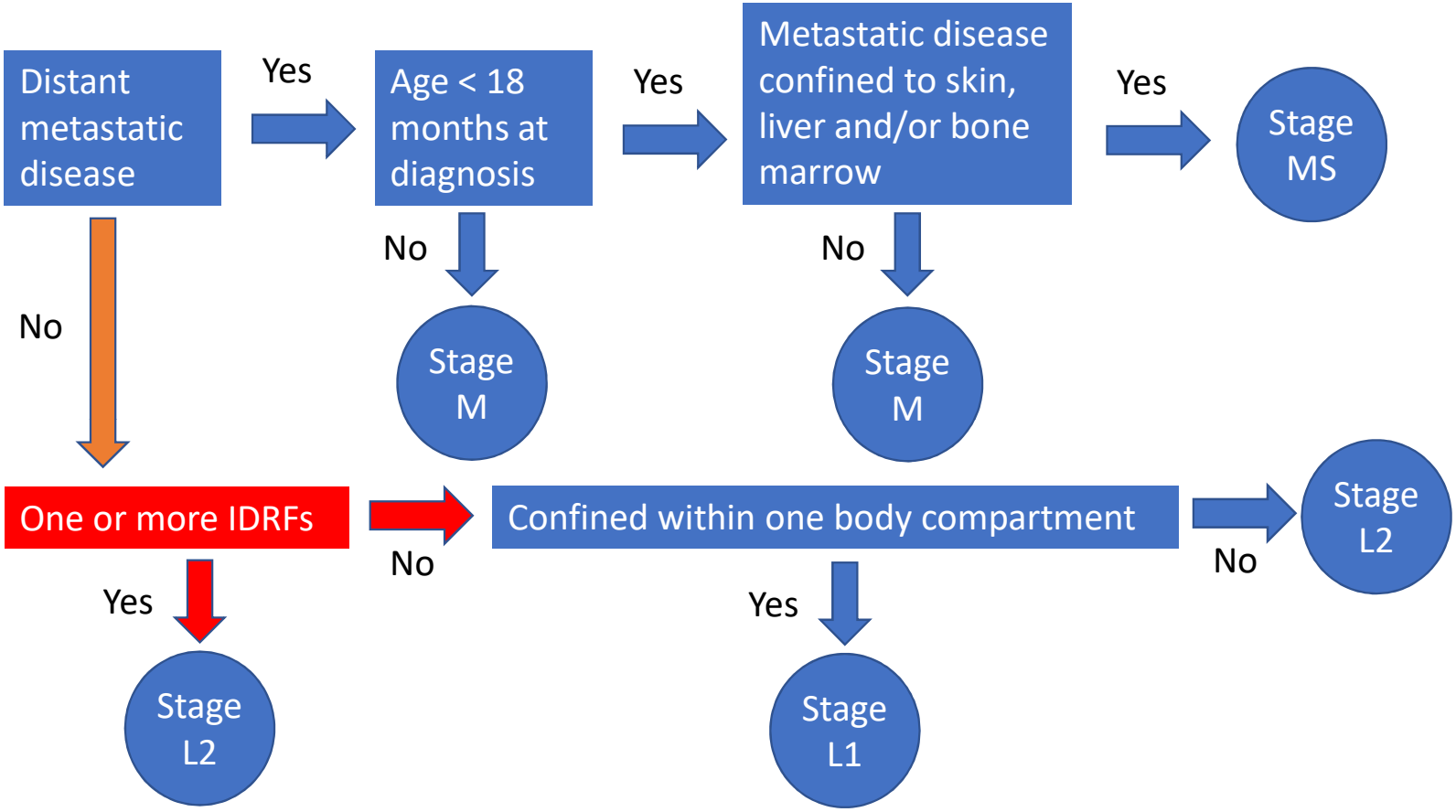
No imaging is realised.

A puncture of the paraaortic lymph nodes is made, and shows the involvement of those regional lymph nodes.

What is the correct stage for this patient ?

A. Localised
B. Locoregional
C. L1
D. L2

Exercise 1 - Answer



For this patient, Tier 2 classification requires an imaging examination to know if one (or more) IDRF is present. Since not realised, we can only assign a Tier 1. The correct answer is thus Locoregional, since regional lymph nodes are involved.

Exercise 2

An intra-abdominal mass is found in a 7-year old patient. The diagnosis of a neuroblastoma is made. Imaging shows an infiltration of the left kidney. Bone metastases are also seen, and confirmed by biopsy.

What is the correct stage for this patient ?

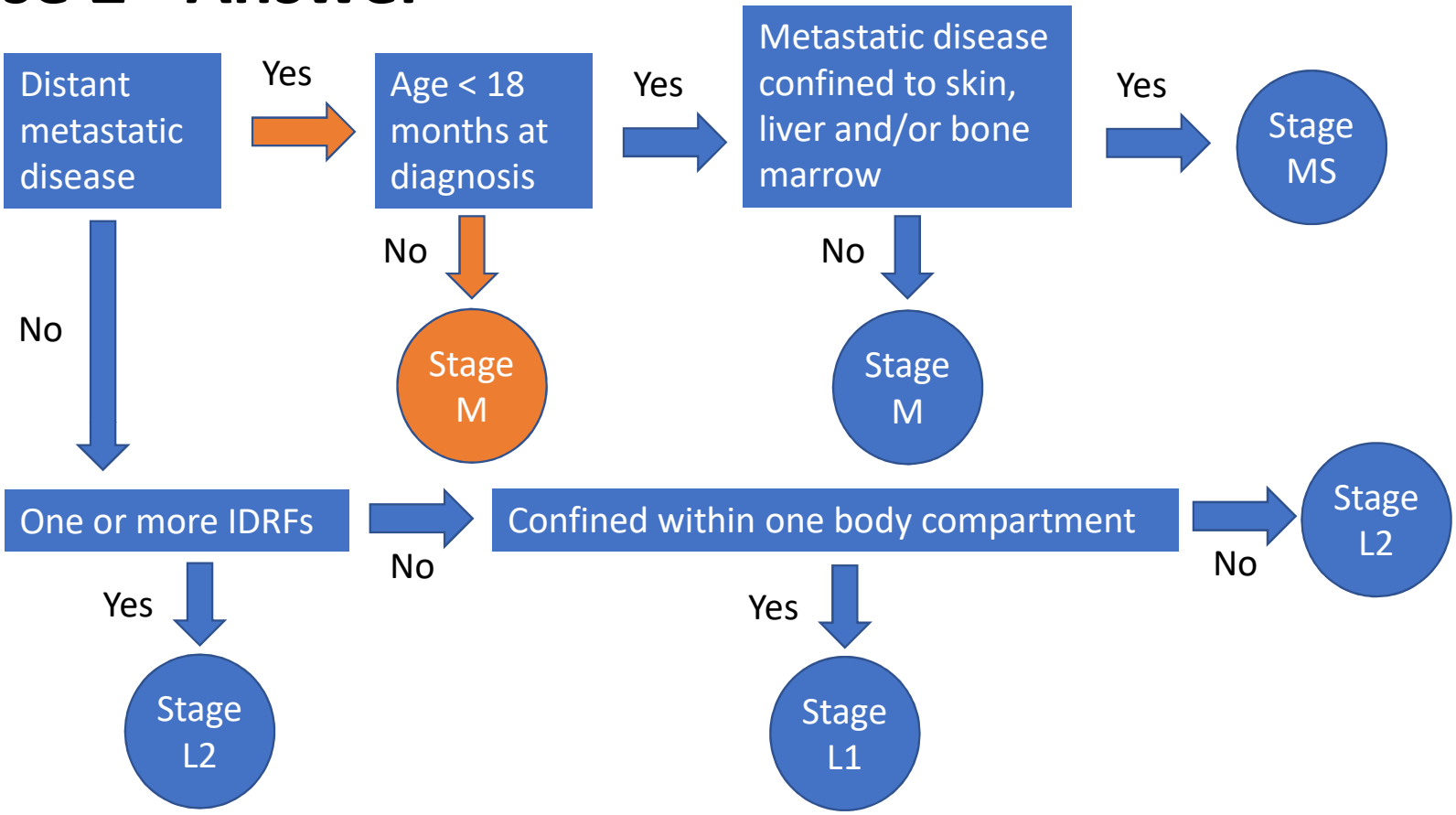
A. L2

B. Metastatic

C. M

D. MS

Exercise 2 - Answer



7 years old patient with a metastatic neuroblastoma. Since Tier 2 classification is more specific than Tier 1, it should be preferred when possible.
So, in this case, stage M should be recorded instead of stage Metastatic.

Exercise 3

A neuroblastoma is found in the adrenal gland of a 11 months old patient.

Imaging showed no image-defined risk factor, but identified a metastasis located in the liver.

What is the correct stage for this patient ?

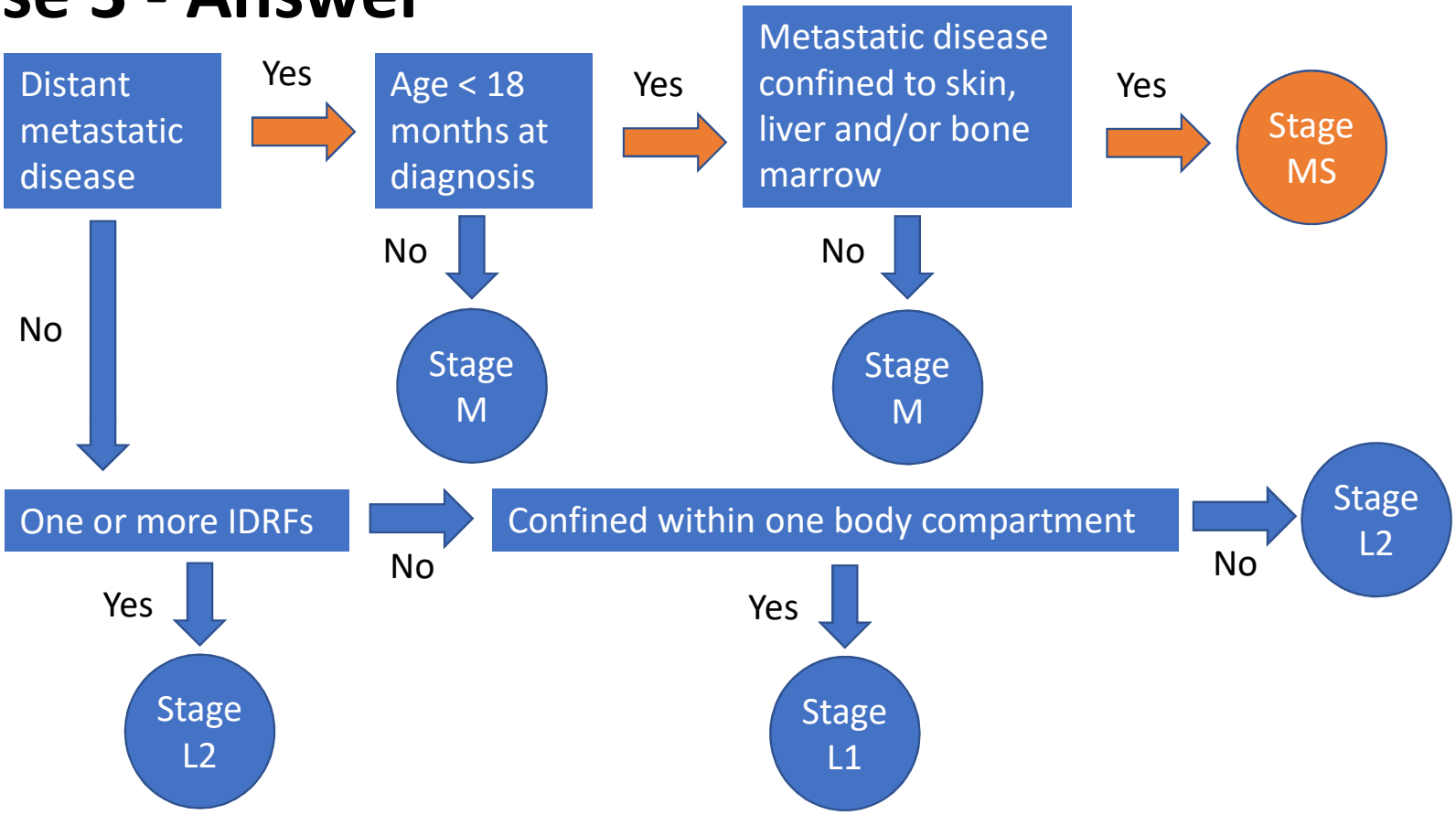
A. L1

B. L2

C. M

D. MS

Exercise 3 - Answer



Metastatic disease that meets the two conditions required for stage MS.

Exercise 4

A 7 years old girl from clinical record

- Bone marrow biopsy of left anterior iliac crest → total infiltration of neuroblastic tumour
- Bone marrow aspirate of left and right iliac crest → both infiltrated
- Chest X-ray negative
- CT rounded mass on the para-aortic right side (32 x 15 mm) which extends at bridge on the abdominal aorta also extending versus the left paraaortic and encases the right renal vein

What is the correct stage for this patient?

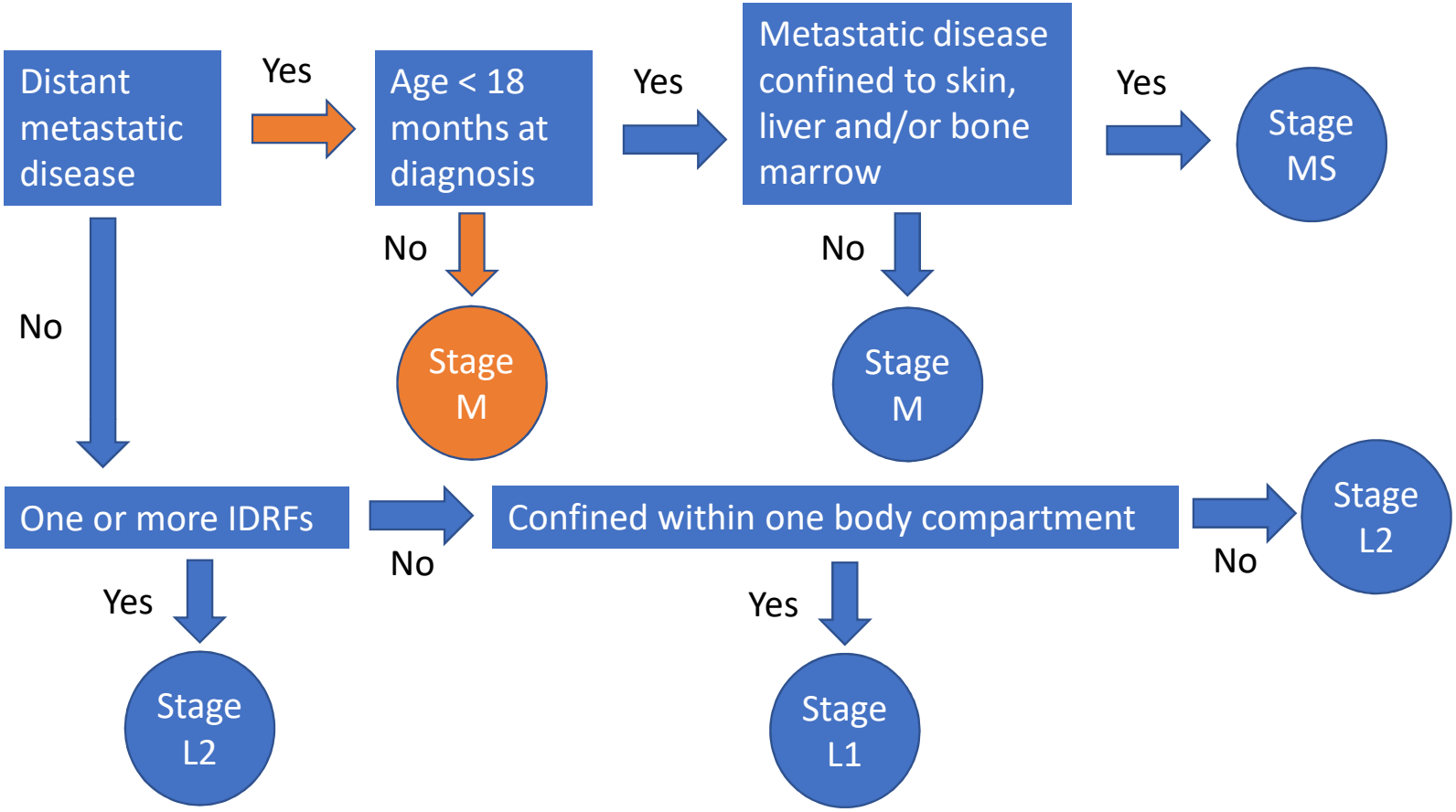
A. L1

B. L2

C. M

D. MS

Exercise 4 - Answer



Para-aortic lesion with metastases located in the bone marrow. The patient is 7 years old, and can thus not be staged as MS.

Exercise 5

A 17 months old boy, from clinical record

- diagnosed with a N-Myc not amplified neuroblastoma of the right adrenal gland.
- CT abdomen shows tumour is invading the porta hepatis and encasing some mesenteric vessels and is highly suspicious for invasion of the upper pole of the right kidney.
- Other staging investigations (bone marrow, MIBG scan, CT chest) are negative for distant metastases.
- Surgical excision is performed after a period of chemotherapy. The surgeon achieves complete macroscopic excision. Pathology finds positive resection margins.

What is the correct stage for this patient?

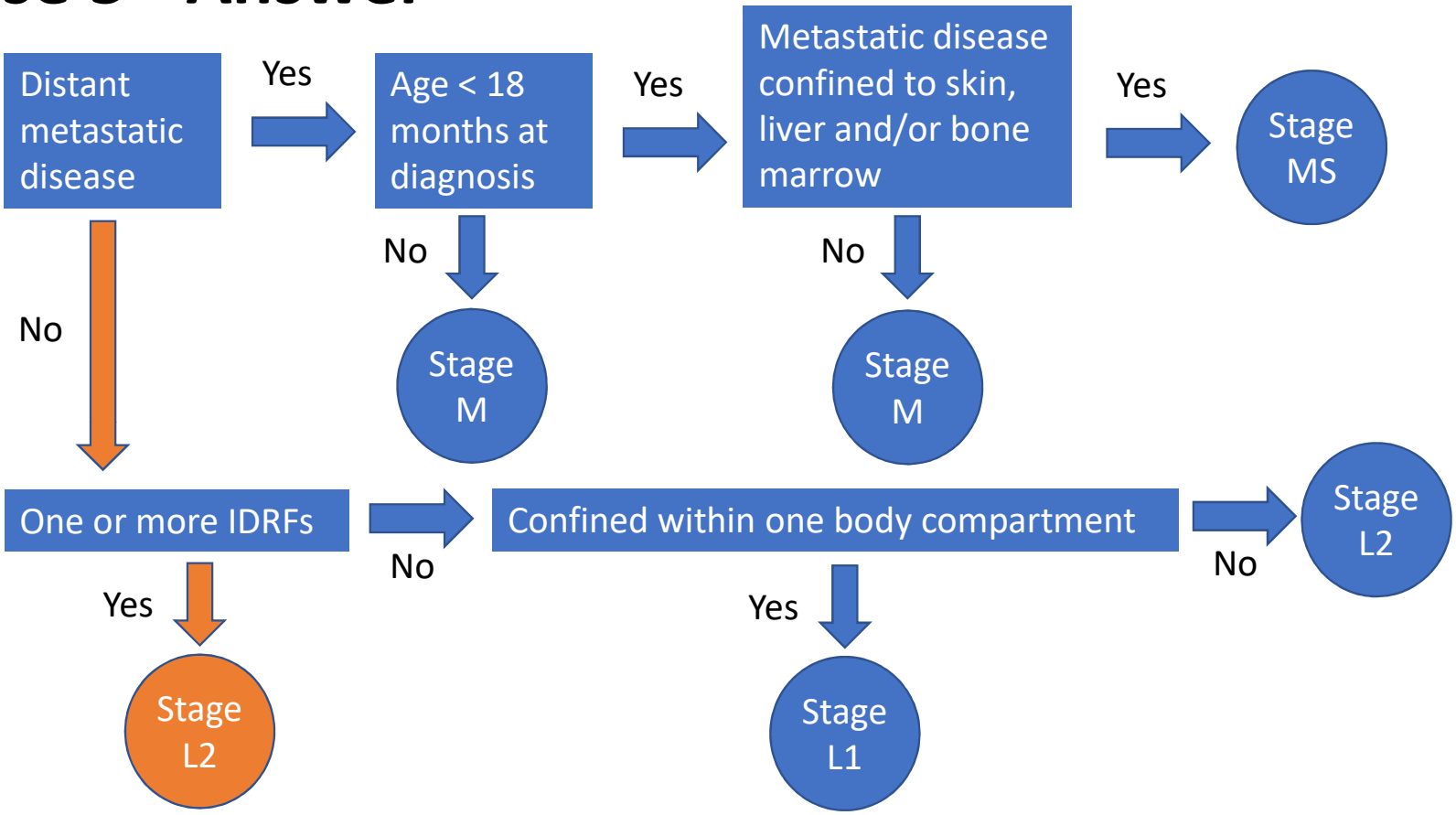
A. L1

B. L2

C. MS

D. M

Exercise 5 - Answer



Neuroblastoma of the right adrenal gland without any distant metastasis. The correct stage is L2 since we have the presence of IDRFs (tumour invading the porta hepatis and encasing some mesenteric vessels according to the CT scan of the abdomen).

Excel file Database Presentation: Wilms Tumour and Neuroblastoma

Fabio Didonè, Statistician,
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

Specific Variables: Imaging/examination performed for Neuroblastoma

Imaging/examination necessary for investigation of the **extension** of the disease are:

- CT/MRI primary site
- MIBG scan
- Abdominal ultrasound
- Bone scan
- X-ray Thorax
- Bone marrow (BM) aspirate or BM biopsy
- Tissue biopsy (of non-primary sites suspicious for metastasis)

Note: the result of each exam performed is requested except for '*CT/MRI primary site*'

Specific Variables: Imaging/examination Performed for Wilms tumour

Imaging/examination necessary for investigation of the **extension** of the disease are:

- CT/MRI primary site
- CT Thorax
- Abdominal Ultrasound
- X-ray Thorax
- Tissue biopsy (of non-primary sites suspicious for metastasis)

Note: the result of each exam performed is requested except for '*CT/MRI primary site*'

Specific Variables:
TG staging and NSPs

	Variable name	values	Variable Description
Toronto staging, Neuroblastoma	Stage Tier 1	1,2,3,4,9	L/LR/M/MS/X
	Stage Tier 2	1,2,3,4,9	L1/L2/M/MS/X
	Laterality	0,1,2,3,4,9	Not applicable/Right/Left/Unilateral NOS/Bilateral//Unknown
	*_NSP: NMYC	1,0,9	Y/N/Unknown
Toronto staging, Wilms tumour	Stage Tier 1 after pre-surgery chemotherapy	1,2,9	L/M/X
	Stage Tier 2 after pre-surgery chemotherapy	1,2,3,4,9	y-I/y-II/y-III/IV/X
	Stage Tier 1 after immediate surgery (Or surgery first)	1,2,9	L/M/X
	Stage Tier 2 after immediate surgery	1,2,3,4,9	I/II/III/IV/X
	Laterality	1,2,3,9	R/L/B/Unknown
	*_NSP: Presence of anaplasia	0,1,2,3,9	No/Yes, unknown/Yes, Focal/Yes, diffuse/unknown

	Essential	Additional	New and promising	Comments
Solid tumours				
Neuroblastoma	..	N-myc	..	..
Wilms tumour	Histology	..	Specific aberrations on chromosomes 1p, 16q, or 1q	Histological sub-classification will depend on if assessed before or after adjuvant chemotherapy; see main text for details

Table 2: **The Lyon Paediatric Cancer Non-Stage Prognosticator Guidelines**

Specific Variables: TG staging and NSPs for Neuroblastoma

Laterality:

- 0=Not applicable
- 1=Right
- 2=Left
- 3=Unilateral NOS (Not Otherwise Specified)
- 4=Bilateral
- 9=Unknown

NSP: NMYC amplification

- 1=Yes
- 2=No
- 9=Unknown

Specific Variables: TG staging and NSPs for Wilms tumour

Laterality:

- 1=Right
- 2=Left
- 3=Bilateral
- 9=Unknown

NSP: Presence of Anaplasia

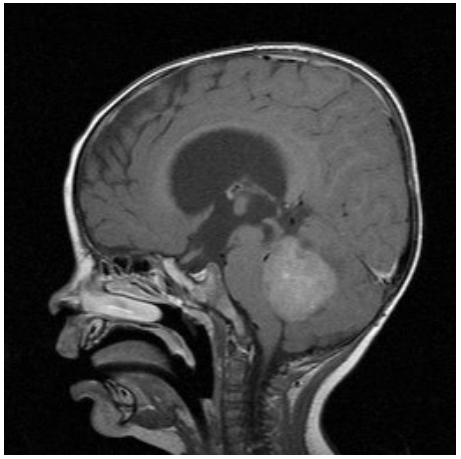
- 0=No
- 1=Yes, unknown subtype
- 2=Yes, focal
- 3=Yes, diffuse
- 9=Unknown

Medulloblastoma

Clinical expert: Prof Simon Bailey

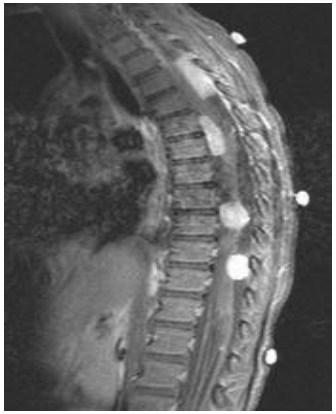
Background

- 15 -20 % of CNS neoplasms in children
- Initially described by Bailey and Cushing in 1925
- Put in broad PNET group in 1973
- Peak incidence of 4 - 7 years
- M:F 1.7 :1.
- Metastatic spread in up to 35 %
- By definition primary is in the posterior fossa



Chang Staging

M0: No evidence of metastatic disease
M1: positive CSF cytology
M2: Metastasis within the cranial vault
M3: MRI visible spinal metastatic disease.
M4: Metastasis outside the CNS (usually bone)



Staging Notes

- Staging is by MRI of head and spine.
- Distant metastatic disease outside the CNS is not routinely looked for in most places and only done if bone pain or abnormal bone chemistry unless cancer predisposition syndrome.
- Staging in simplest form is metastatic or non metastatic (Toronto staging).
- The highest stage is the one recorded e.g., if metastatic disease in the brain and spine it becomes M3.
- M1 is when the CSF shows cells and nothing outside the posterior fossa is seen on MRI scan this is only done on day 14 and often needs searching for in the notes. If positive before day 14 then needs repeating at this date.
- IF CSF is not done then it is usually recorded as MO/1 (M1 is rare (about 4%)).
- Stratification of treatment is done by MRI, Histological subtype and biology.

History

~ 650 EU cases / year

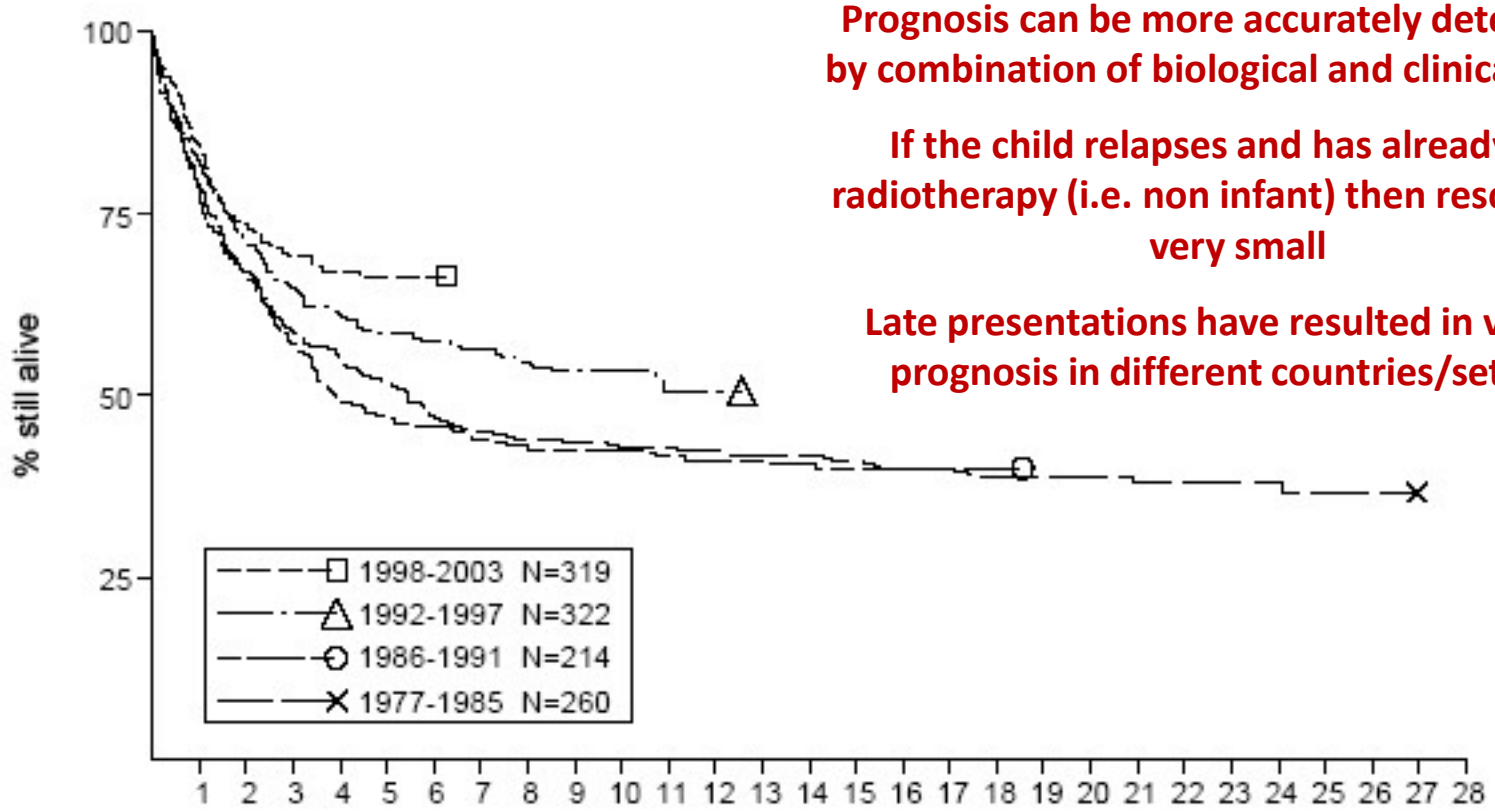
~ 250 deaths

Long-term disabilities

Prognosis can be more accurately determined by combination of biological and clinical factors

If the child relapses and has already had radiotherapy (i.e. non infant) then rescue rates very small

Late presentations have resulted in varying prognosis in different countries/settings



Cure vs burden of survival

VOLUME 31 · NUMBER 28 · OCTOBER 1 2013
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Processing Speed, Attention, and Working Memory After Treatment for Medulloblastoma: An International, Prospective, and Longitudinal Study

Shawna L. Palmer, Carol Armstrong, Arzu Onar-Thomas, Shengjie Wu, Dana Wallace, Melanie J. Bonner, Jane Schreiber, Michelle Swain, Lynn Chapieski, Donald Mabbott, Sarah Knight, Robyn Boyle, and Amar Gajjar

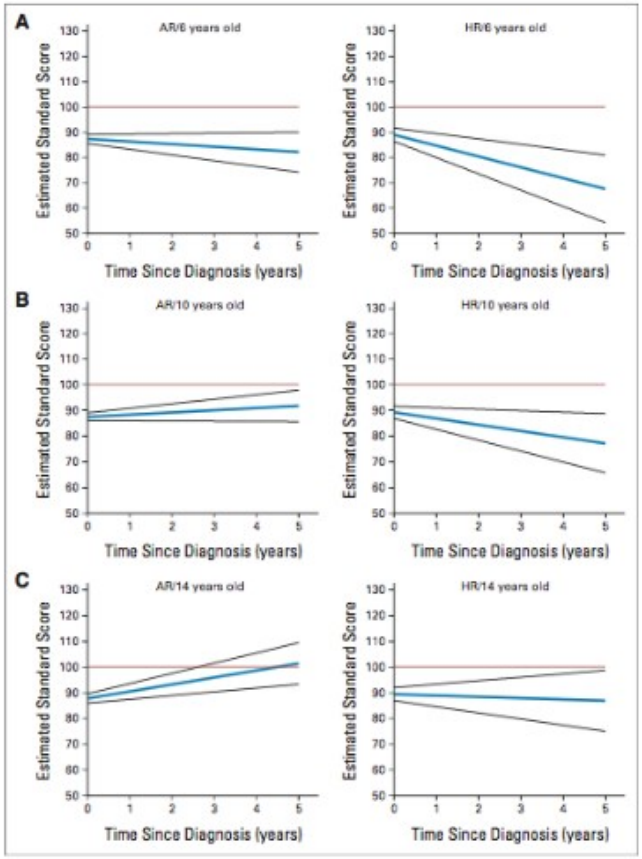


Fig 1. Estimated change in processing speed standard score (blue line; 95% CI, black lines) over time (years) for patients diagnosed at (A) 6, (B) 10, and (C) 14 years old with either average-risk (AR) or high-risk (HR) medulloblastoma. Population mean, 100 (red line).

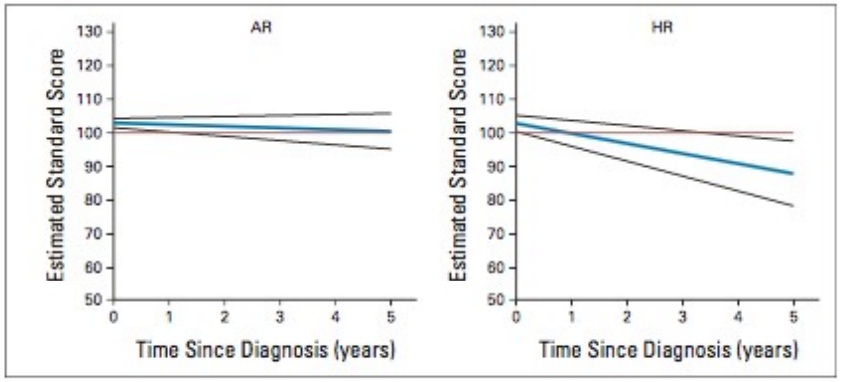


Fig 2. Estimated change in working memory standard score (blue line; 95% CI, black lines) over time (years) for patients diagnosed with either average-risk (AR) or high-risk (HR) medulloblastoma. Population mean, 100 (red line).

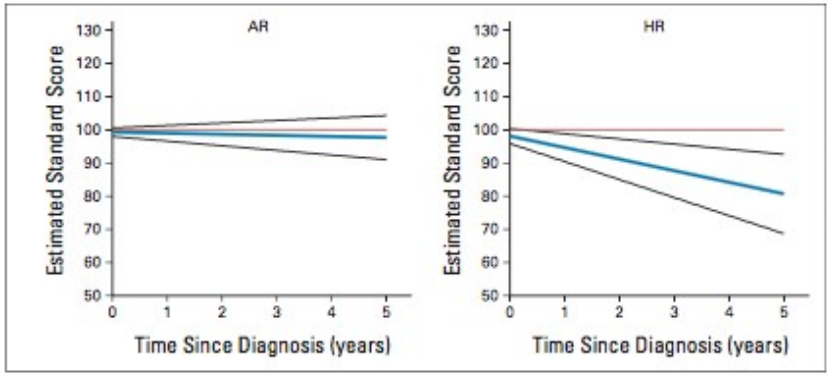
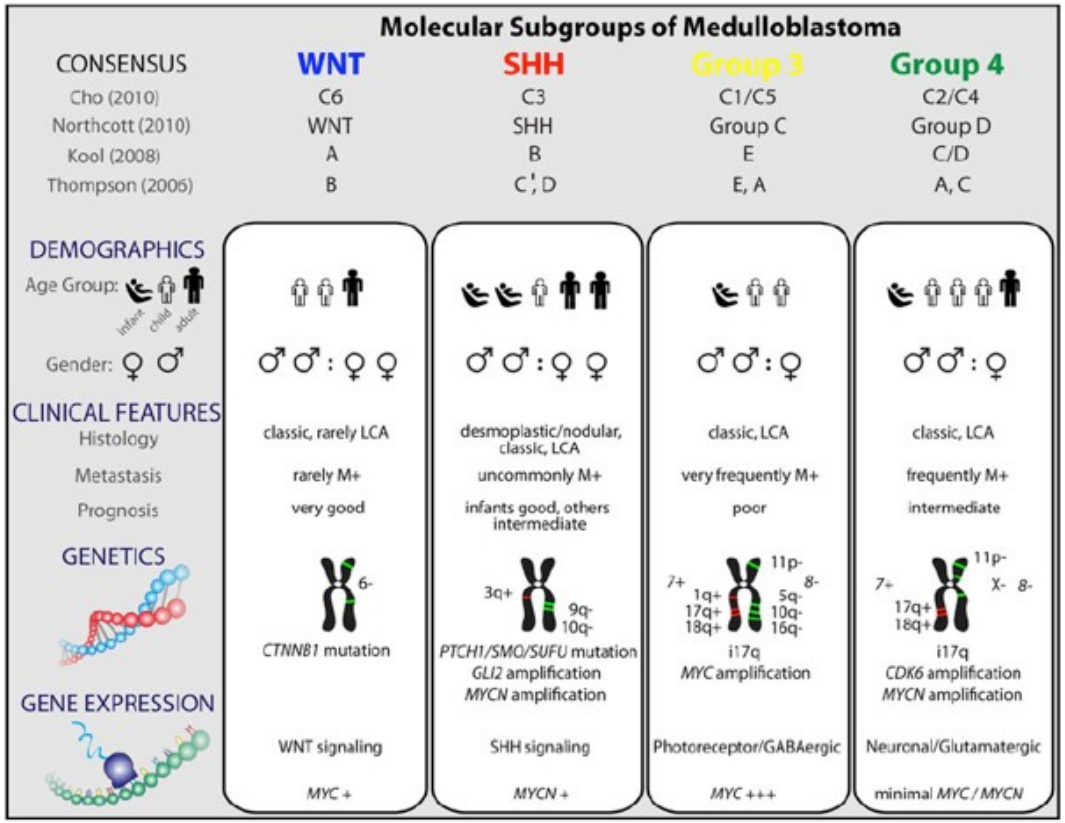


Fig 3. Estimated change in broad attention standard score (blue line; 95% CI, black lines) over time (years) for patients diagnosed with average-risk (AR) or high-risk (HR) medulloblastoma. Population mean, 100 (red line).



Taylor 2012

	Subgroup	WNT	SHH			
	Subtype		α	β	γ	δ
Demographics	Frequency (%)	100	29	16	21	34
	Age (bar height corresponds with percentage)	0–3 3–10 10–17 17+	0–3 3–10 10–17 17+	0–3 3–10 10–17 17+	0–3 3–10 10–17 17+	0–3 3–10 10–17 17+
	Gender (%)	45 ♀ ♂ 55	63 ♀ ♂ 37	47 ♀ ♂ 53	55 ♀ ♂ 45	69 ♀ ♂ 31
Clinical features	Histology	Classic	Classic > desmoplastic > LCA	Desmoplastic > classic	Desmoplastic > MBEN classic	Classic > desmoplastic
	Metastasis (%)	12	20	33	9	9
	5-year OS (%)	98	70	67	88	89
Molecular features	Cytogenetics	6–	9p+ 9q– 10q– 17p–	2+	9q–	9q– 14q–
	Driver events	*CTNNB1*, *DDX3X* or *SMARCA4* mutation	• *MYCN* or *GLI2* amplification • *TP53* mutation • *PTCH1* mutation (less)	• *PTCH1* or *KMT2D* mutation • *SUFU* mutation/ deletion • *PTEN* deletion	• *PTCH1*, *SMO* or *BCOR* mutation • *PTEN* deletion	• *PTCH1* mutation • *TERT* promoter mutation

	Subgroup	Group 3							Group 4
	Subtype	I	II	III	IV	V	VI	VII	VIII
Demographics	Frequency (%)	4	13	9	10	8	9	22	25
	Age (bar height corresponds with percentage)	0–3 3–10 10–17 17+	0–3 3–10 10–17 17+	0–3 3–10 10–17 17+	0–3 3–10 10–17 17+	0–3 3–10 10–17 17+	0–3 3–10 10–17 17+	0–3 3–10 10–17 17+	0–3 3–10 10–17 17+
	Gender (%)	60 ♀ ♂ 40	77 ♀ ♂ 23	78 ♀ ♂ 22	68 ♀ ♂ 32	71 ♀ ♂ 29	67 ♀ ♂ 33	66 ♀ ♂ 34	75 ♀ ♂ 25
Clinical features	Histology	Classic > desmoplastic	LCA, classic	Classic > LCA	Classic	Classic	Classic	Classic	Classic
	Metastasis (%)	35	57	56	58	62	45	45	50
	5-year OS (%)	77	50	43	80	59	81	85	81
Molecular features	Cytogenetics	Balanced	8+ 1q+ i17q (less)	7+ i17q 10q–	14+ 7+ no i17q 8– 10– 11– 16–	7+ i17q 16q–	7+ i17q 8– 11–	7+ i17q (less) 8–	i17q
	Driver events	• *GFI1* and *GFI1B* activation • *OTX2* amplification	• *MYC* amplification • *GFI1* and *GFI1B* activation • *KBTBD4*, *SMARCA4*, *CTDNEP1* or *KMT2D* mutation	*MYC* amplification (less)	No common driver events	*MYC* or *MYCN* amplification	• *PRDM6* activation • *MYCN* amplification (less)	*KBTBD4* mutation	• *PRDM6* activation • *KDM6A*, *ZMYM3* or *KMT2C* mutation

Hovestadt 2020

WHO 2021

- Medulloblastoma, genetically defined
- Medulloblastoma, WNT-activated
- Medulloblastoma, SHH-activated and *TP53*-mutant
- Medulloblastoma, SHH-activated and *TP53*-wildtype
- Medulloblastoma, non-WNT/non-SHH Medulloblastoma (encompassing Group 3 and Group 4)

New

- Medulloblastoma, histologically defined
- Classic medulloblastoma
- Desmoplastic/nodular medulloblastoma
- Medulloblastoma with extensive nodularity
- Large-cell / anaplastic medulloblastoma

Diagnostic pathway

Pre op MRI head and spine (reviewed centrally for trials)

Surgery + Frozen tissue

Postop Scan head within 72 hours to assess residual disease

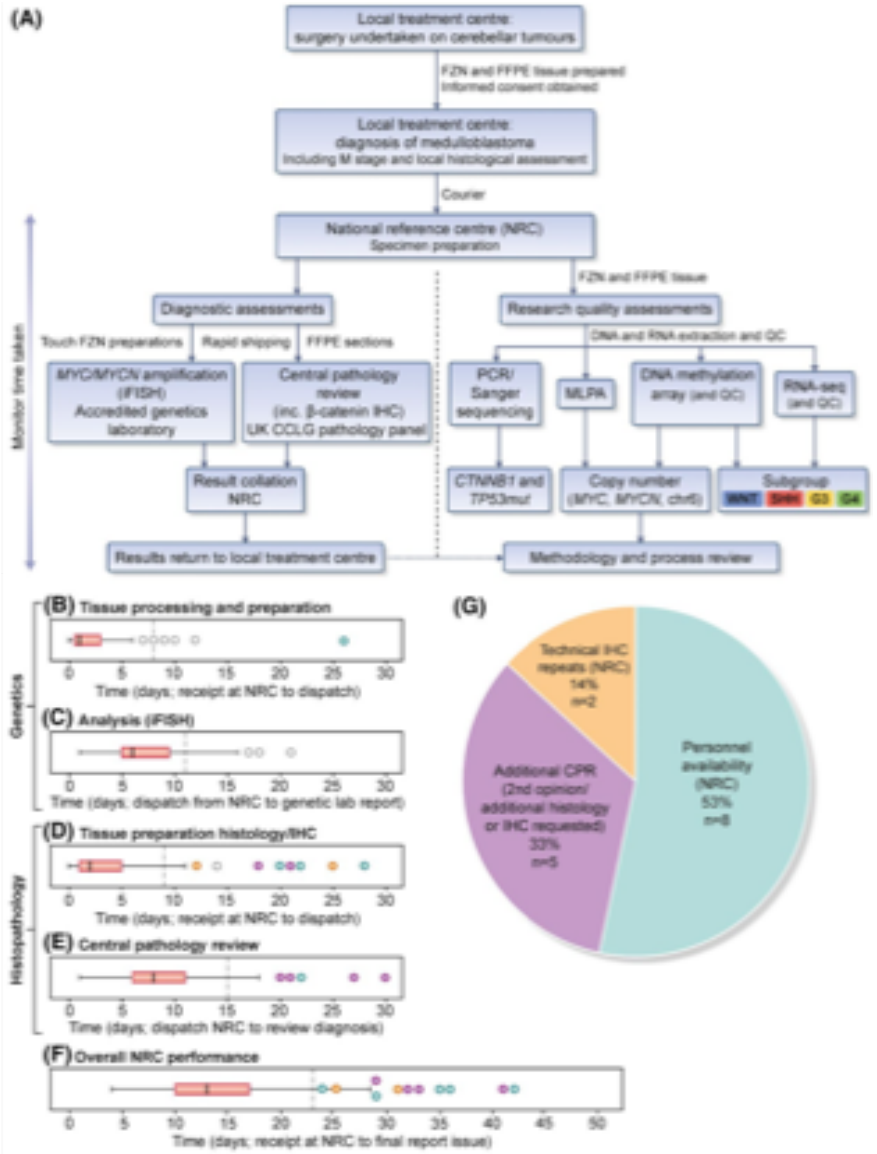
Local Pathology to diagnose medulloblastoma

Central Reference

CSF for cytology done at 14 days – usually same time as central line insertion

Result with biology in 28 days ideally

Appropriate treatment



Mandatory diagnostic testing HIC

Current

Pathology review
H&E
IHC panel: GFAP, synaptophysin, NFP, EMA, INI-1, vimentin, Ki-67 and reticulin special stain

WNT subgroup assignment
IHC: β-catenin
CTNNB1 mutation
Chromosome 6 status – iFISH or SNP array

MYC and *MYCN* amplification
iFISH or SNP array

Testing in accredited labs - Mandatory

Core research evaluations (all patients)
RNA-seq (Newcastle)
850K array (Newcastle/Heidelberg)
Panel-seq (Heidelberg)

Current amendment:

Pathology review to WHO (2016) criteria:
Add GAB1, YAP1, filamin A, Lin28 to 2014 panel

Subgroup assignment: WNT, SHH, G3, G4
Consensus from 2 independent methods, from…
1. IHC (above)
2. 850K/EPIC DNA methylation array
3. Methylation signature assay (e.g. Sequenom)

WNT subgroup assignment
CTNNB1 mutation plus subgroup assignment (above)

MYC and *MYCN* amplification
As 2014

Somatic mutation analysis of *PTCH, SUFU, TP53* (SHH patients)
Perform by Sanger or Panel; Validate by Sanger

Germline mutation testing – all relevant syndromes
Perform if tumour *PTCH, SUFU* or *TP53* mutation-positive
*Optional testing for *APC* (*CTNNB1* –ve WNT), Fanconi (*BRCA2/PALB2*).
Rapid genetics referral for germline patients

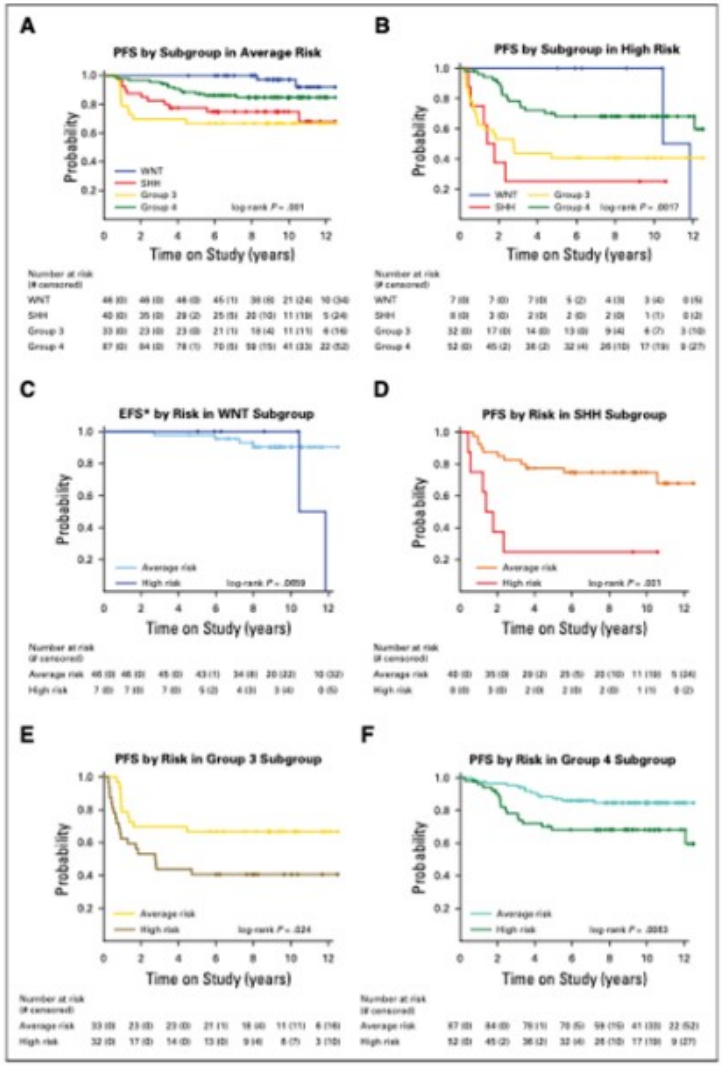
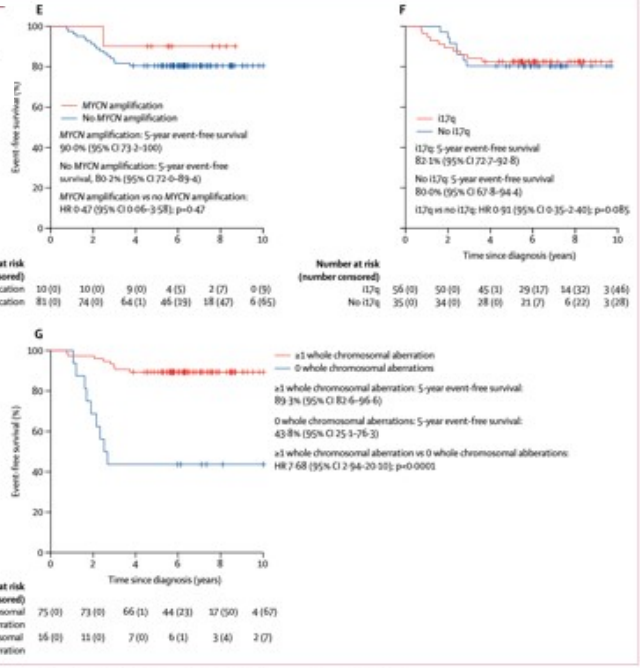
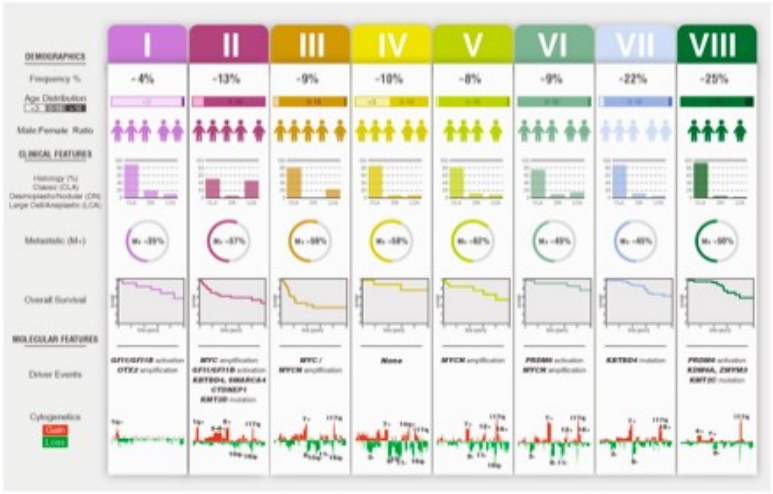


FIG 4. Survival analysis by molecular subgroup and subtype: PFS (A) by subgroup in average risk, (B) by subgroup in high risk, (C) EFS by risk in the WNT subgroup, (D) by risk in the SHH subgroup, (E) by risk in the group 3 subgroup, (F) by risk in the group 4 subgroup, (G) by SHH subtype, and (H) by group 3 or group 4 subtype. EFS, event-free survival; PFS, progression-free survival; SHH, Sonic Hedgehog; WNT, Wingless.

Prognostic effect of whole chromosomal aberration signatures in standard-risk, non-WNT/non-SHH medulloblastoma: a retrospective, molecular analysis of the HIT-SIOP PNET 4 trial





<table>
<tr><th>Risk Category</th><th>Low Risk</th><th>Standard Risk</th><th>High Risk</th><th>Very High Risk</th></tr>
<tr><td>Survival (%)</td><td>>90</td><td>75-90</td><td>50-75</td><td><50</td></tr>
<tr><td rowspan="3">Subgroup, clinical and molecular characteristics</td><td rowspan="2">Non-metastatic</td><td>Non-metastatic, TP53 WT and no MYCN amplification</td><td rowspan="2">One or both:
• Metastatic
• MYCN amplification</td><td rowspan="2">TP53 Mutation</td></tr>
<tr><td rowspan="2">Non-metastatic and no MYC amplification</td></tr>
<tr><td>Non-metastatic and Chromosome 11 loss</td><td>Non-metastatic and no chromosome 11 loss</td><td>Metastatic</td><td>Metastatic</td></tr>
</table>

FIG. 3. Proposed risk stratification for noninfant medulloblastoma, based on data from the following reference.[50] Box color represents the subgroup and the text reflects clinical and molecular criteria (WNT: *blue*, SHH: *red*, group 3: *yellow*, group 4: *green*). WT = wild type. Figure is available in color online only.

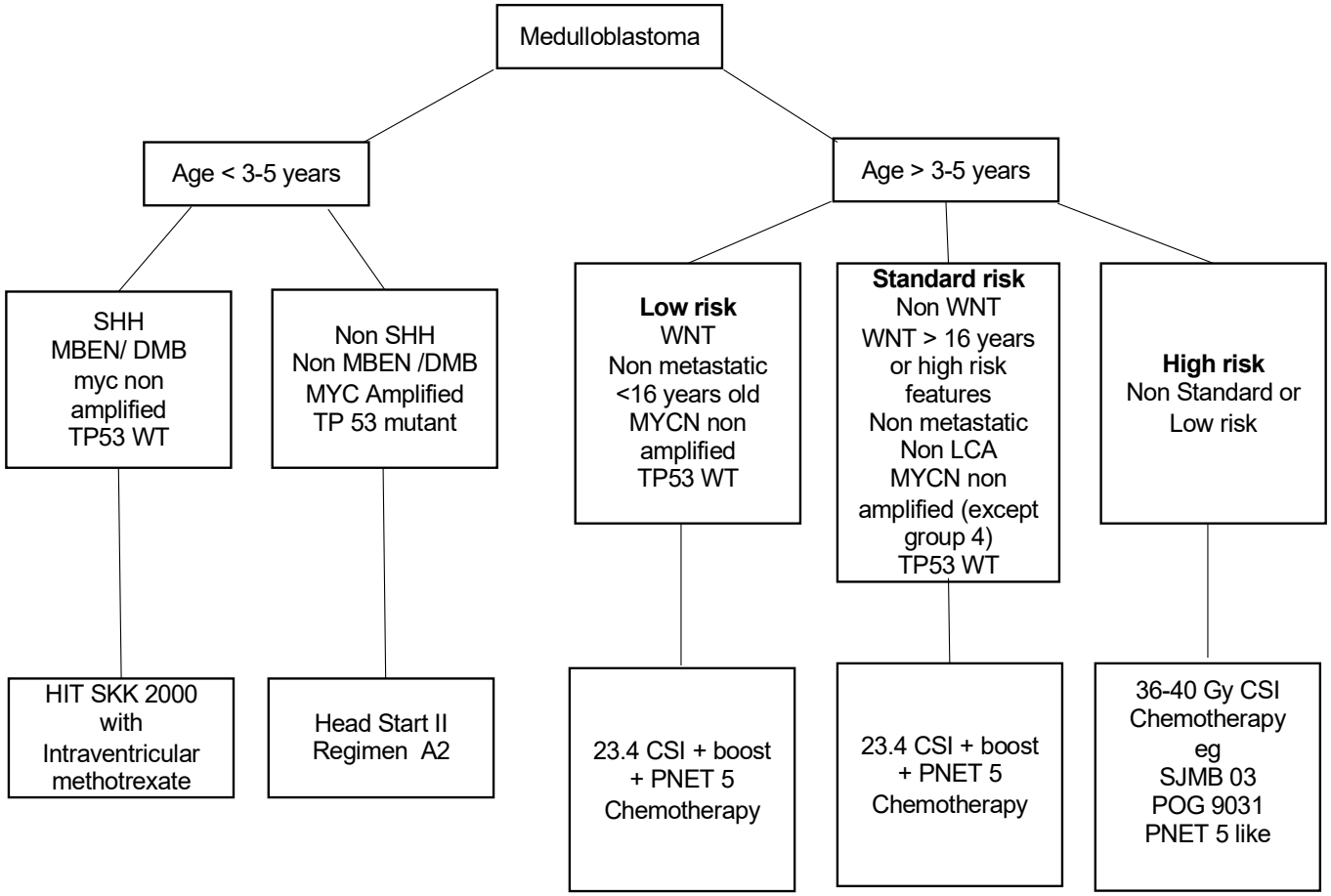
Treatment

- Surgery – maximal safe resection of primary
- Chemotherapy
  - Many combinations and trials
  - May include treatment prior to radiotherapy (high risk disease)
  - May include chemotherapy with radiotherapy
  - Almost always includes chemotherapy after radiation therapy
- Radiotherapy
  - Usually craniospinal with boost (protons or photons – no difference in outcome)
  - May be focal in younger children although less common now
  - Try to avoid in younger children (under 3-5 depending on country)

Additional Notes

- M1 disease confers worse outlook – not universally accepted as detailed analysis together with biological factors not done in trial setting yet.
- Generally prolonged chemotherapy prior to radiotherapy (bar infants and French High dose High risk study) shown to be less effective (PNET 3 and early German HIT Study).
- Prolonged time to radiation (>49 days) been shown in number of studies to confer worse prognosis.

Simplified Treatment Strata



Medulloblastoma: Non-stage prognostic factors

CNS Tumour	Essential	Additional	New and Promising	Comments
Medulloblastoma		Molecular classification (WNT vs SHH vs group 3 / 4)		Molecular classification according to the ICD-O-3 classification. Extent of resection not agreed as an NSP for collection by PBCRs due to its availability. It will be collected as an optional variable in BENCHISTA.

Gupta et al. Development of paediatric non-stage prognosticator guidelines for population-based cancer registries and updates to the 2014 Toronto Paediatric Cancer Stage Guidelines. **Lancet Oncol 2020; 21: e444–51**

Summary

- Medulloblastoma may be complicated to get the stratification and biology information to enable the correct treatment.
- Main things to look for though remain metastatic stage (M1 most difficult to find in the notes) and histology (LCA = high risk)
- Exclusive pre radiotherapy chemotherapy not used routinely anymore.
- Protons vs photons do not alter EFS but may reduce long term effects.

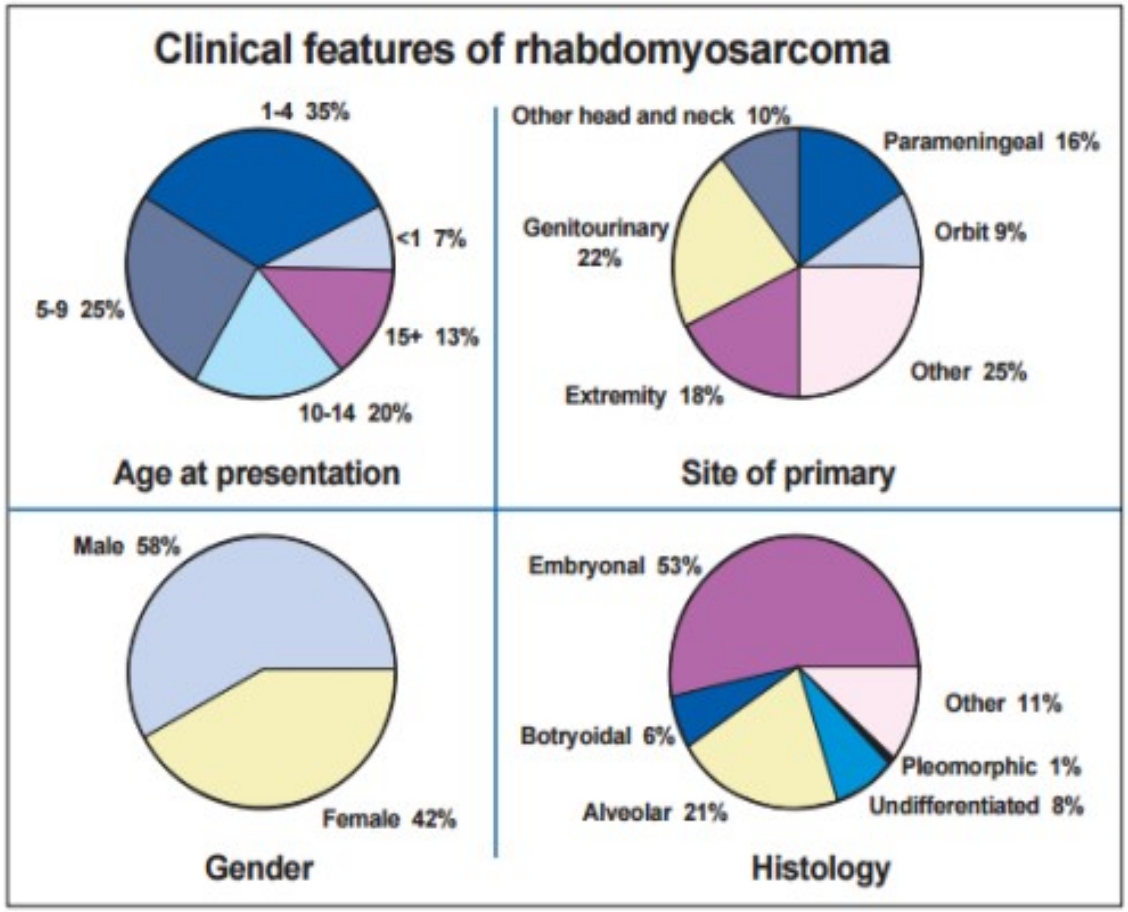
Rhabdomyosarcoma

Clinical expert: Dr Lisa Hjalgrim

Epidemiology

- Rhabdomyosarcoma (RMS) is thought to arise from primitive mesenchymal cells committed to develop into striated muscles.
- It is a high-grade malignant neoplasm.
- It can be found virtually **anywhere** in the body, including those sites where striated muscles are not normally found.
- It is the commonest form (50%) of soft tissue sarcoma in children and young adults and accounts for approximately 4 - 5 % of all childhood malignancy.

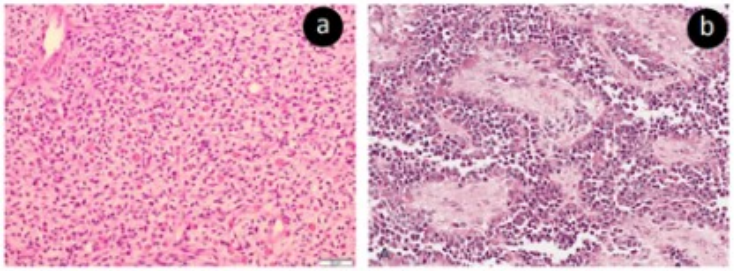
Clinical characteristics



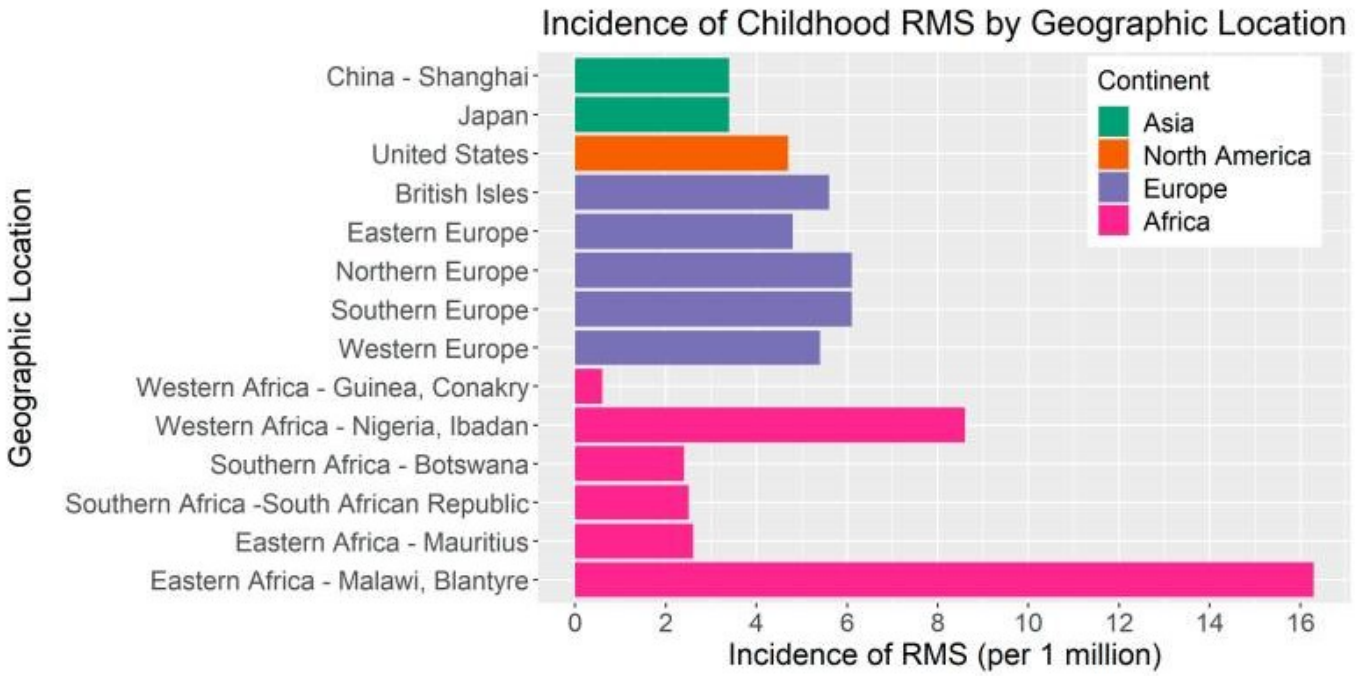
- 2/3 children < 10 years
- H&N, GU tract, extremities common sites
- Slight male predominance

a: Embryonal RMS (ERMS): dense spindle areas, loose myxoid stroma (60%)

b: Alveolar RMS (ARMS): nests with dense stroma, pseudoalveolar spaces (20-25%)



Epidemiology

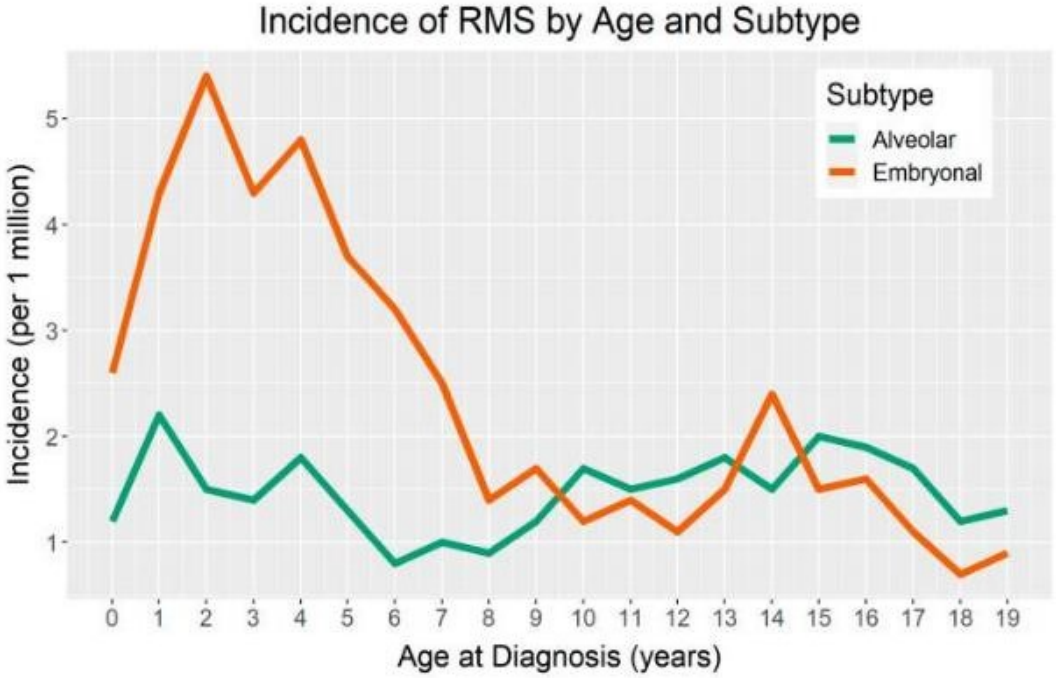


US 350 new patients/year
UK 40 new patients/year
DK 6 new patients/year

Variations in incidence – not many studies. No clear pattern regarding ethnicities
An annual incidence of approx. 5 per million children under the age of 15

BA. Martin-Giacalone: J.Clin.Med.2021, 10, 2028

Epidemiology



- Incidence stable over time.
- The peak incidence is seen early in childhood with a median age at diagnosis of about 5 years for embryonal RMS.
- Alveolar more stable across ages.

BA. Martin-Giacalone: J.Clin.Med.2021, 10, 2028

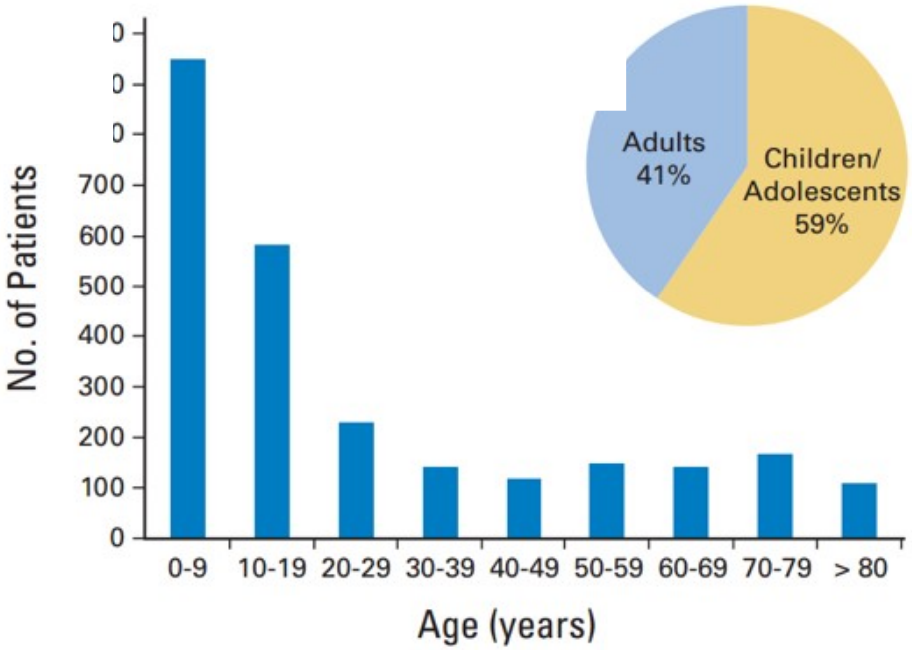
Risk factors – Genetic predisposition

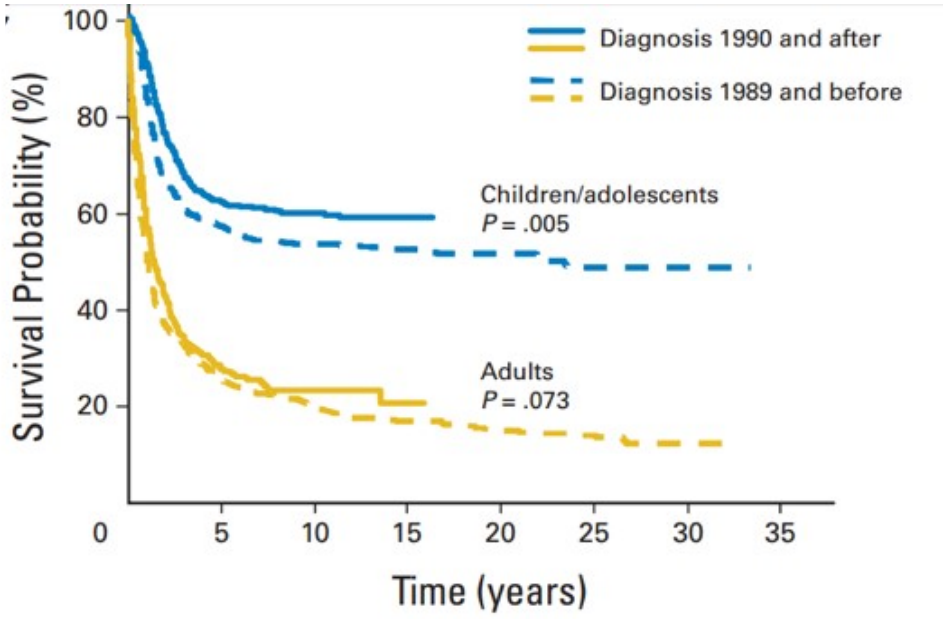
Heritable syndromes associated with an increased risk of RMS

Syndrome	Phenotype	Associated gene(s)
Li-Fraumeni	Cancer susceptibility syndrome	*TP53*
Neurofibromatosis type 1	Systemic effects	*NF1*
DICER1	Cancer susceptibility syndrome	*DICER1*
Costello	Systemic effects	*HRAS*
Noonan	Systemic effects	*BRAF; KRAS; NRAS; PTPN11; RAF1; SOS1*
Beckwith-Wiedemann syndrome	Overgrowth disorder	*IGF2; CDKN1C; H19; KCNQ1OT1*

Skarpek et al, Nat rev Dis Primers, 2020

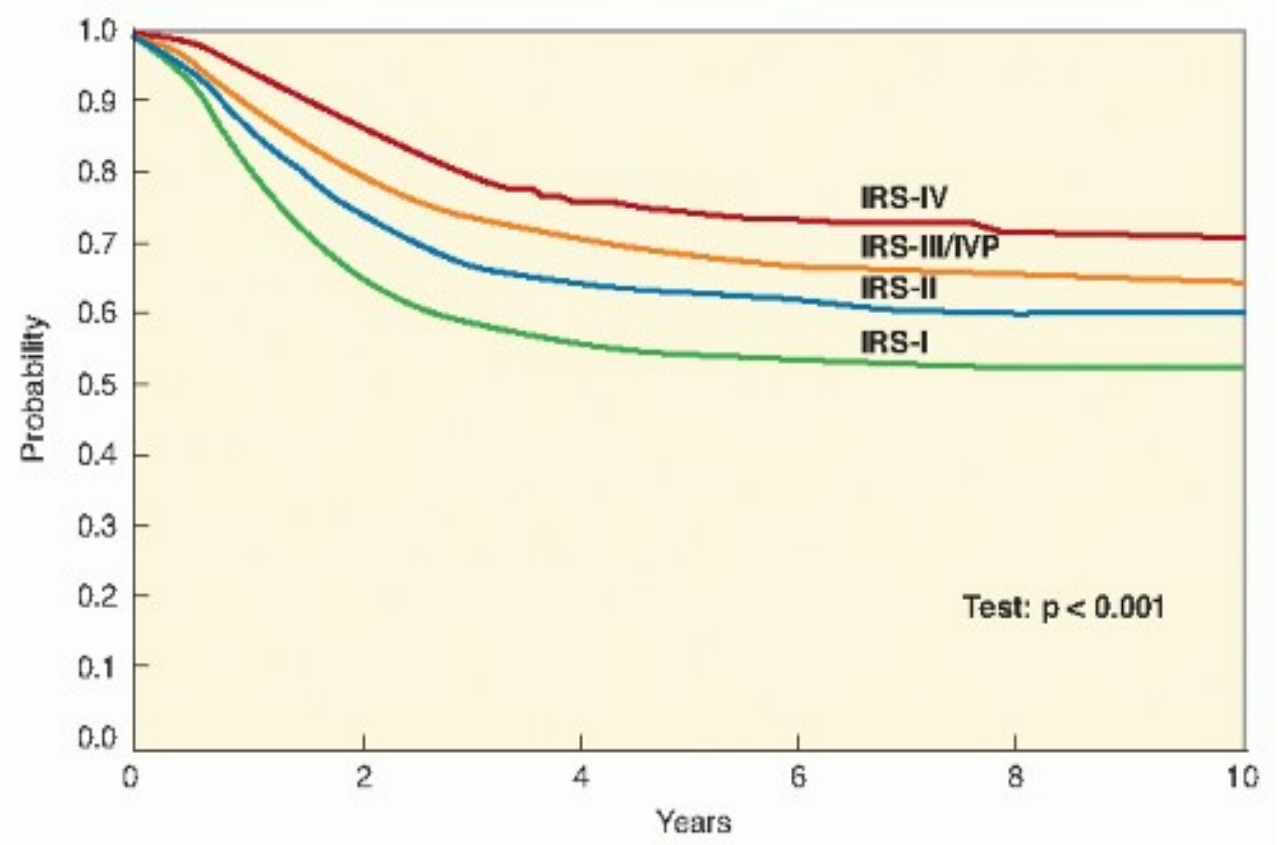
Age at onset and overall outcome





Sultan I, JCO, 2009

Survival



Improvement in 5-year survival of children with RMS treated on the IRS trials. (From Wexler L, Meyer WH, Helman LJ. Rhabdomyosarcoma and the undifferentiated sarcomas.

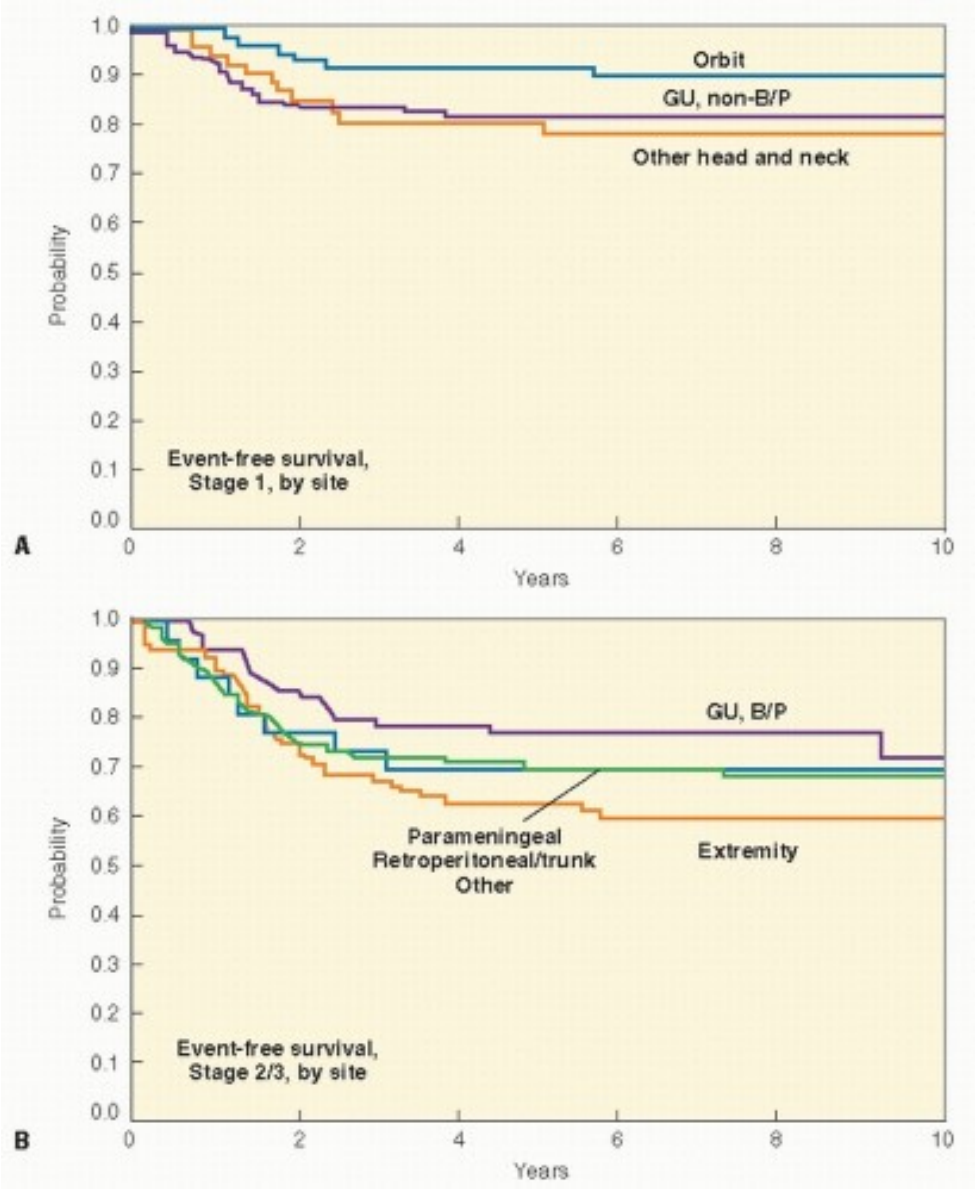
In: Pizzo P, Poplack D, eds. *Principles and Practice of Pediatric Oncology*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006:988,

Event-free survival of patients treated on Intergroup Rhabdomyosarcoma Study IV by stage and site.

A: nonmetastatic “favorable” site tumors (stage 1).

B: nonmetastatic unfavorable site tumors (stage 2 or 3)

(From Pizzo P, Poplack D, eds. Principles and Practice of Pediatric Oncology. Philadelphia, PA: Lippincott-Raven; 2006:991



Survival in metastatic RMS

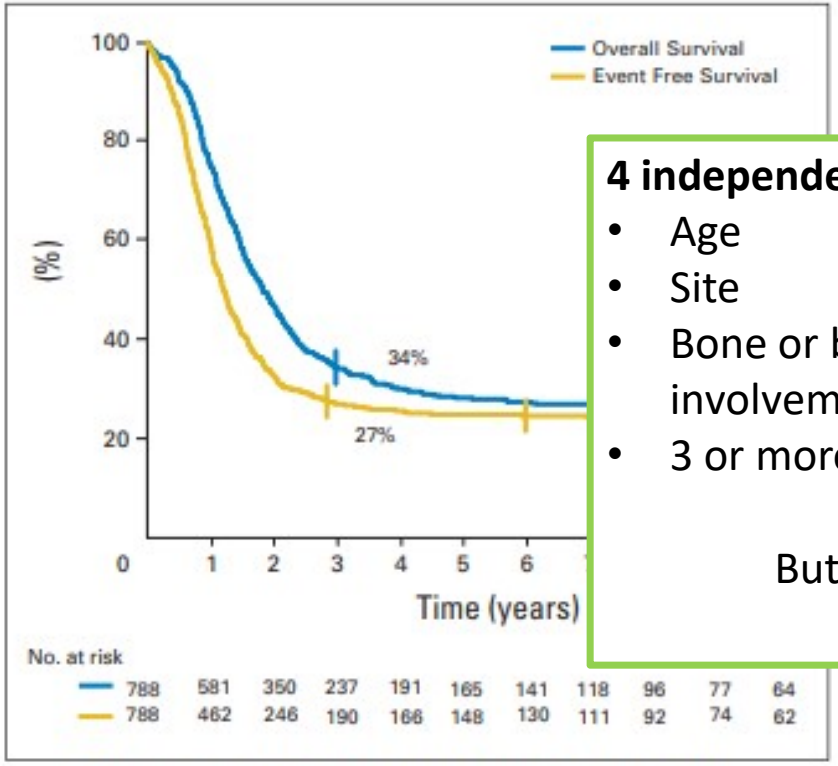


Fig 1. Overall survival and event-free survival of all 788 patients.

4 independent risk factors defined:

- Age
- Site
- Bone or bone marrow involvement
- 3 or more metastatic sites

But NOT histology!

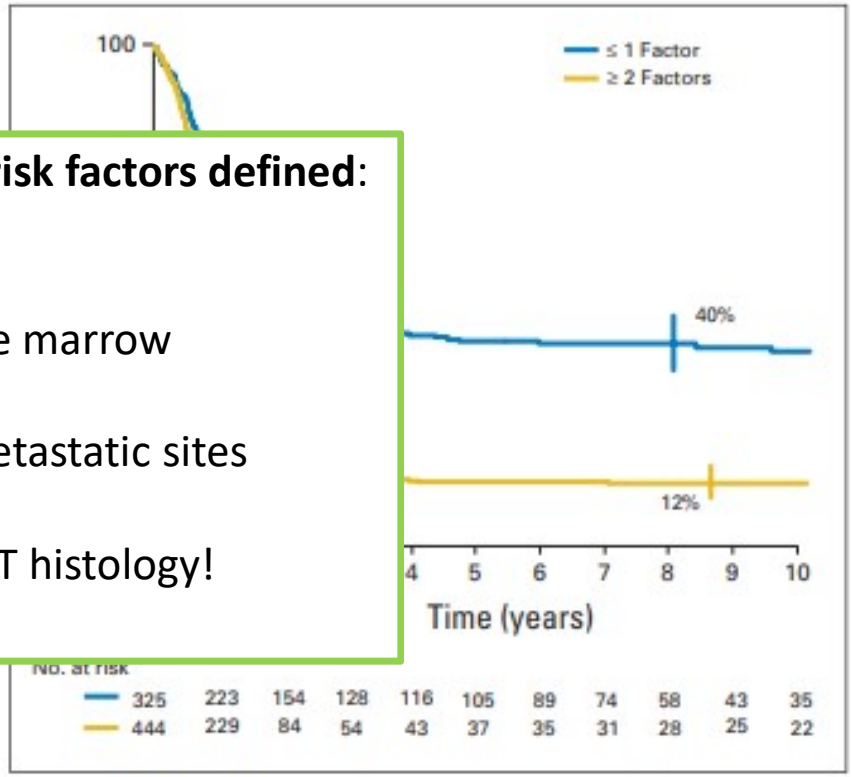


Fig 3. Event-free survival of patients according to risk score.

Oberlin O. et al, JCO 26, 2008

Clinical presentation

Head-neck	Asymptomatic mass, may mimick enlarged lymph node
Orbit	Proptosis, chemosis, ocular paralysis, eyelid mass
Nasopharynx	Snoring, nasal voice, epistaxis, rhinorrhoea, local pain, dysphagia, cranial nerve palsies
Paranasal sinuses	Swelling, pain, sinusitis, obstruction, epistaxis, cranial nerve palsies
Middle ear	Chronic otitis media, haemorrhagic discharge, cranial nerve palsies, extruding polypoid mass
Larynx	Hoarseness, irritating cough
Trunk	Asymptomatic mass (usually)
Biliary tract	Hepatomegaly, jaundice
Retroperitoneum	Painless mass, ascites, gastrointestinal or urinary tract obstruction, spinal cord symptoms
Bladder/prostate	Haematuria, urinary retention, abdominal mass, constipation
Female genital tract	Polypoid vaginal extrusion of mucosanguineous tissue, vulval nodule
Male genital tract	Painful or painless scrotal mass
Extremity	Painless mass, may be very small but with secondary lymph node involvement

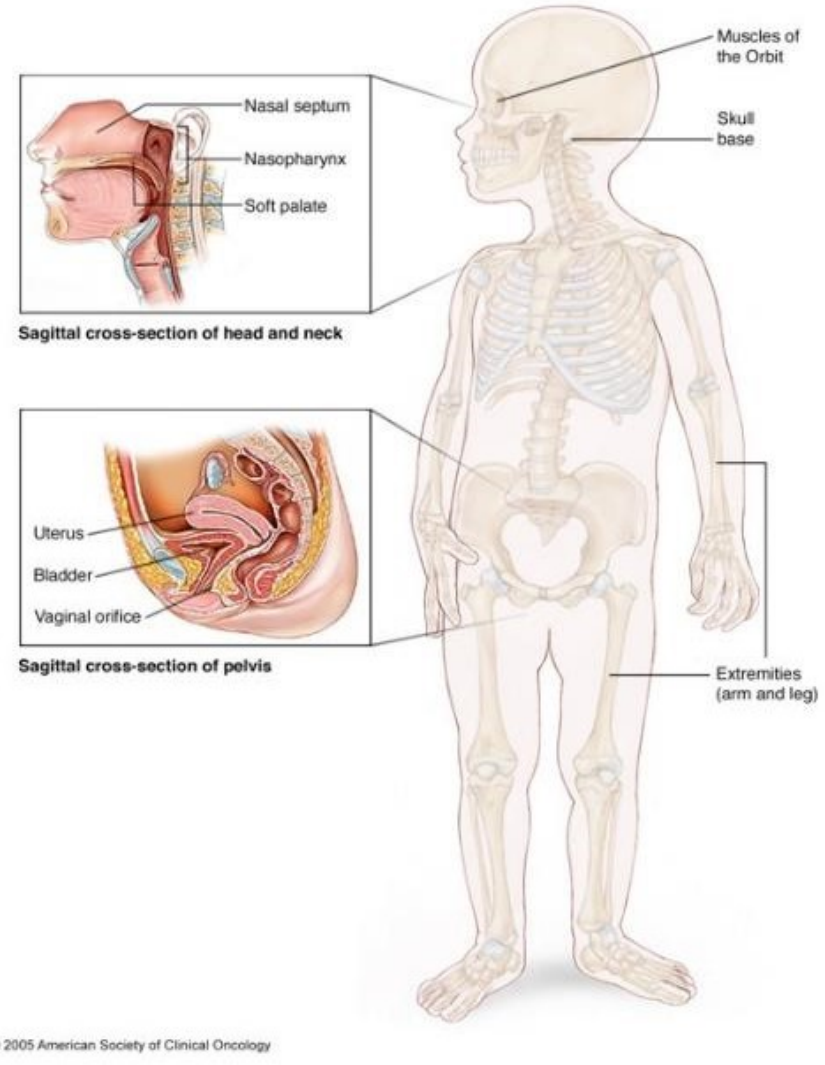
Usually present with anatomical mass

Diagnostic work up

- Surgical open biopsy.
- Bone marrow examination (bilateral) – mandatory.
- In cases of para-meningeal disease – lumbar puncture should be done.

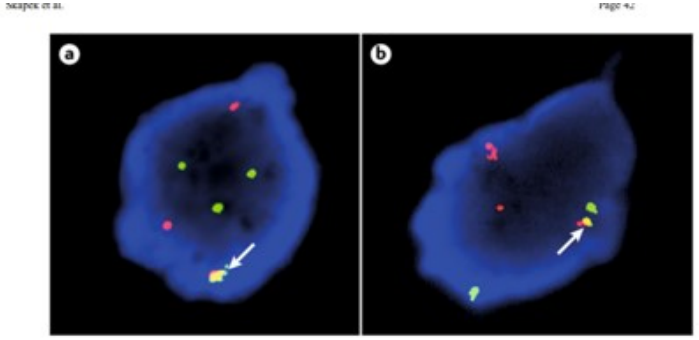
Imaging at diagnosis

- MRI of primary tumor and regional lymph node - mandatory
- Chest CT – mandatory
- PET CT – distant metastases - now mandatory (bone scan in case PET is not available)
- *Ultrasound – regional lymph nodes*



Pathology

- Accurate pathology required
- H and E
- Immunohistochemistry (Myogenin, Desmin, MyoD)
- Molecular genetics
  - ERMS: Loss of heterozygosity at 11p15 locus
  - ARMS: **t(2;13)** – Translocation between long arms of chr 2 and 13 fusing FOX01 transcription facto to PAX3 or **t(1;13) –** Fuses FOX01 to PAX7



REVIEW

WILEY

Pathology of childhood rhabdomyosarcoma: A consensus opinion document from the Children's Oncology Group, European Paediatric Soft Tissue Sarcoma Study Group, and the Cooperative Weichteilsarkom Studiengruppe

Erin R. Rudzinski | Anna Kelsey | Christian Vokuhl | Corinne M. Linardic | Janet Shipley | Simone Hettmer | Ewa Koscielniak | Douglas S. Hawkins | Gianni Bisogno

Skarpek et al, Nat rev Dis Primers, 2020

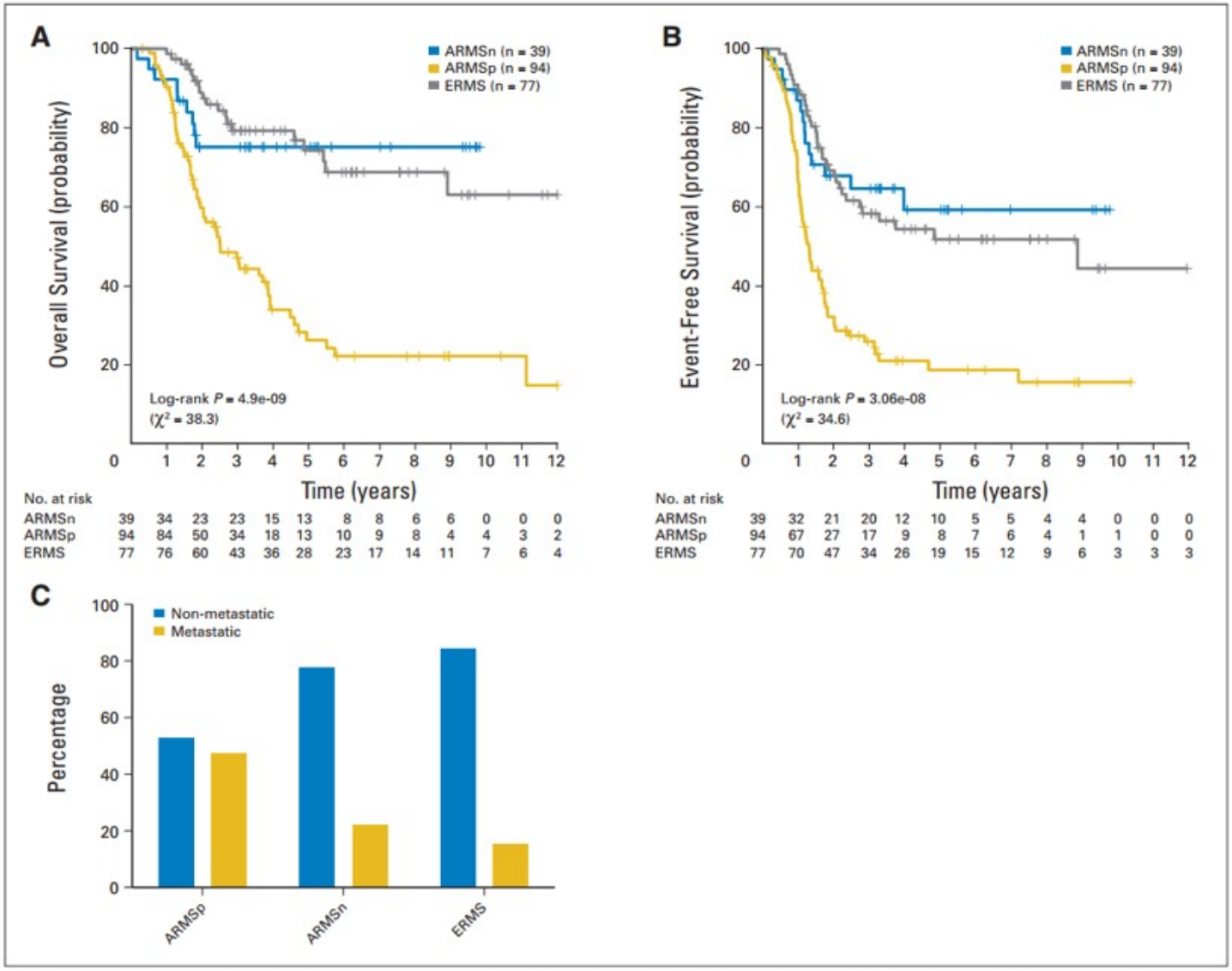
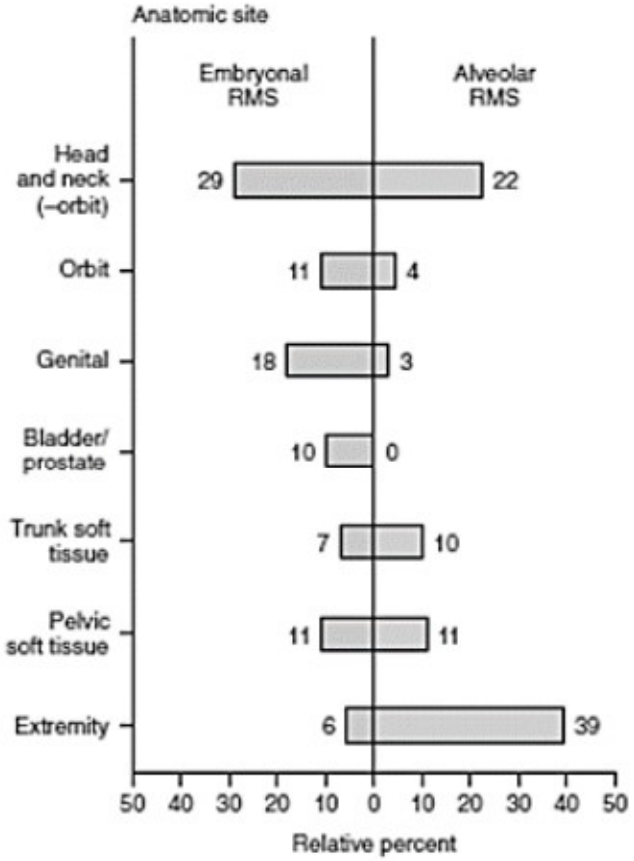


Fig 1. Kaplan-Meier curves showing significant poorer prognosis in (A) overall survival and (B) event-free survival for patients with fusion gene–positive alveolar rhabdomyosarcoma (ARMSp). Survival of patients with fusion gene–negative ARMS (ARMSn) and embryonal RMS (ERMS) is not significantly different. (C) Percentage frequency of metastases is significantly higher in ARMSp than in ARMSn or ERMS. Three ERMS patients who survived and did not relapse for 12.3, 16.7, and 17.2 years were left out of the plot for presentational purposes but were included in the calculation of the statistics.

- ✓ **Fusion-gene-negative ARMS is clinically and molecularly indistinguishable from ERMS**
- ✓ **Fusion-gene status is useful in risk stratification**

Wiliamsen D. et al, JCO, 2009



	Embryonal	Alveolar
Age	Younger	Older
Location	Central	Peripheral
Invasion	Low-moderate	High
Metastases	Lungs	Other
Prognosis	40-90%	30-60%

Nathan and Oski's Hematology and Oncology of Infancy and Childhood 8th ed, 2015

Treatment (COG, EpSSG, CWS)

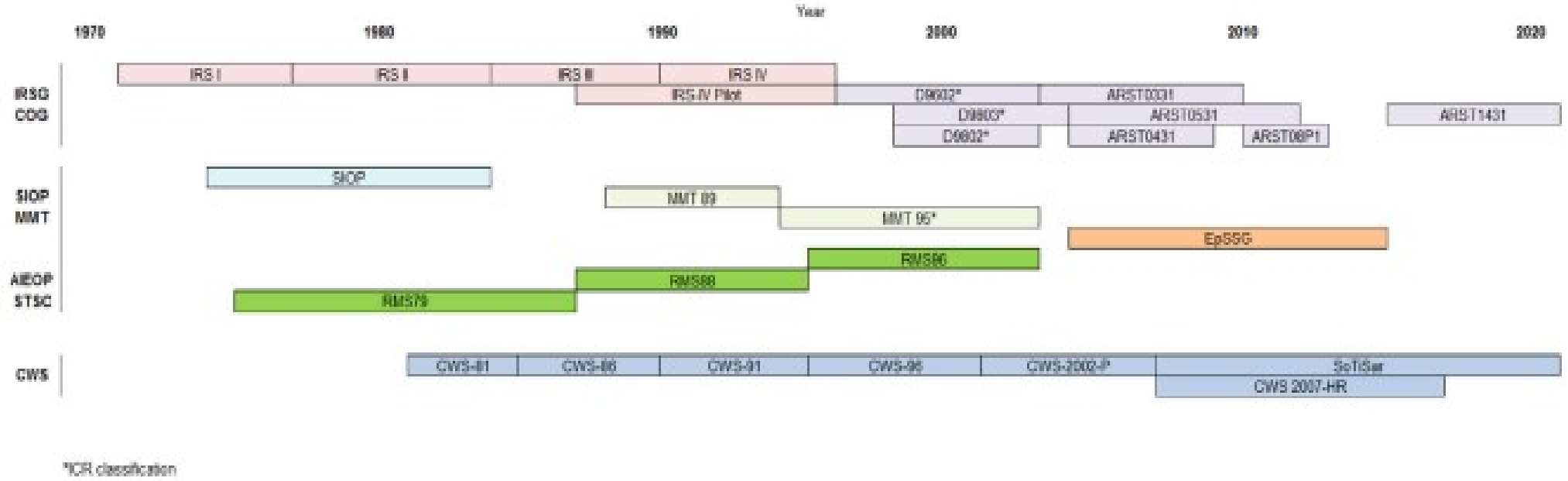


FIGURE 1 Pediatric oncology cooperative group clinical trial studies across the Children's Oncology Group (COG), the European Paediatric Soft Tissue Sarcoma Group (EpSSG), and the Cooperative Weichteilsarkom Studiengruppe (CWS)

Rudzinski et al: Pediatr Blood Cancer, 2021

Regional nodes

- ✓ Nodal involvement indepedent risk factor.
- ✓ 23 % at diagnosis.
- ✓ Pathological non-regional lymph node = metastatic disease.

Pediatric Radiology (2021) 51:1940–1951
https://doi.org/10.1007/s00247-021-05081-0

ESPR

European guideline for imaging in paediatric and adolescent rhabdomyosarcoma — joint statement by the European Paediatric Soft Tissue Sarcoma Study Group, the Cooperative Weichteilsarkom Studiengruppe and the Oncology Task Force of the European Society of Paediatric Radiology

Roelof van Ewijk[1] · Reineke A. Schoot[1] · Monika Sparber-Sauer[2] · Simone A. J. ter Horst[1,3] · Nina Jehanno[4] · Lise Borgwardt[5] · Bart de Keizer[1,3] · Johannes H. M. Merks[1] · Alberto de Luca[6,7] · Kieran McHugh[8] · Thekla von Kalle[9] · Jürgen F. Schäfer[10] · Rick R. van Rijn[11] · On behalf of the Cooperative Weichteilsarkom Studiengruppe Imaging Group, the European Society of Paediatric Radiology Oncology Task Force and the European Paediatric Soft Tissue Sarcoma Study Group Imaging Committee

Pediatr Radiol (2021) 51: 1940-1951

REGIONAL NODAL BASINS FOR RHABDOMYOSARCOMA

Extremity
Lower Extremity –inguinal, femoral, popliteal nodes (rarely involved)
Upper extremity – axillary, brachial, epitrochlear, infraclavicular nodes (infraclavicular)

Genitourinary
Bladder/Prostate – pelvic, retroperitoneal nodes at renal artery level or below
Cervix and Uterus– pelvic, retroperitoneal nodes at renal artery level or below
Paratesticular – pelvic, retroperitoneal nodes at renal artery level or below
Vagina – retroperitoneal, pelvic nodes at or below common iliacs inguinal nodes
Vulva – inguinal nodes

Head and Neck
Head/Neck – ipsilateral cervical, jugular, preauricular, occipital, supraclavicular nodes for laterally placed tumors (excluding scalp); may have bilateral adenopathy with centrally placed tumors
Orbit/Eyelid – ipsilateral jugular, preauricular, cervical nodes

Intrathoracic
Internal mammary, mediastinal nodes

Retroperitoneum/Pelvis –
Pelvic, retroperitoneal nodes

Trunk
Abdominal Wall – inguinal, femoral nodes
Chest Wall – axillary, internal mammary, infraclavicular nodes

OTHER
Biliary/Liver – liver hilar nodes
Perianal/Perineal – inguinal, pelvic nodes; may be bilateral

Non-regional node involvement

- Evidence of nodal involvement beyond the regional lymph nodes must be interpreted as distant metastasis and the patient must be treated according to the protocol for metastatic RMS.
- Examples:
  - Perineal tumour with nodes above the pelvis
  - Thigh tumour with iliac or periaortic nodes
  - Intrathoracic tumour with subdiaphragmatic nodes
  - Unilateral tumour with contralateral involved lymph nodes (except in the head and neck).

Evaluation of lymph nodes (MRI+ PET)

- Oval shaped nodes (with a preserved hilum at sonography) and a short axis diameter of less than 1 cm are considered normal nodes.
- Lymph node short axis >= 1.5 cm = pathological.
- Pet Pos lymph nodes < 1.5 cm considered suspicious.
- All suspicious (doubtful) lymph nodes merit biopsy or another form of nodal sampling.
- Surgical sampling of locoregional nodes **is mandatory** for all limb primaries, paratesticular > 10 years and probably also head and neck alveolar (**regardless** of imaging findings).
- *Sentinel node examination (alveolar tumors, large tumors, extremities).*

Pediatr Radiol (2021) 51: 1940-1951

Metastases

- 20% of RMS patients have metastatic disease at diagnosis.

Lung	39%
Bone Marrow	32%
Lymph Nodes	30%
Bone	27%
Omentum/Ascites	16%
Soft Tissue	16%

Lung metastases - definition

- One or more pulmonary nodules of 10 mm or more diameter or;
- Two or more well-defined nodules of 5 to 10 mm diameter or;
- 5 or more well-defined nodules smaller than 5 mm;
- Hence, 4 or less small nodules (<5mm) at diagnosis will **not** be considered as pulmonary metastatic disease and should be classified only as "**non-specific pulmonary lesions**". Biopsy is NOT recommended.

European guideline for imaging in paediatric and adolescent rhabdomyosarcoma — joint statement by the European Paediatric Soft Tissue Sarcoma Study Group, the Cooperative Weichteilsarkom Studiengruppe and the Oncology Task Force of the European Society of Paediatric Radiology

Pediatr Radiol (2021) 51: 1940-1951

Peritoneal metastatic

- For patients with pleural effusion or ascites, examination of the fluid is strongly recommended.
- If malignant cells are found on morphology = metastatic.
- If peritoneal or pleural nodules are evident on imaging, the tumour will be considered as metastatic and treated accordingly.

Paramenigeal site

- Middle ear, Nasal Cavity and Para nasal Sinuses, Nasopharynx Infratemporal Fossa/Pterygopalatinand Parapharyngeal Area, Orbital tumours with bone erosion.
- Tumours involving vessels or nerves with direct intracranial connection (Arteria carotis interna, vertebralis, N. opticus, trigeminus, facialis etc).
- All intracranial and intraspinal tumours (but tumours arising from the paraspinal muscles with intraspinal extension should be designated as paraspinal, see “Other site” definition).
- All tumors with cranial nerve paresis
  - (excluding parotid tumours with facial nerve palsy)
- CSF Tumour cell positive patients.

Staging of RMS

- The TMN stage
- The clinical group
- The fusion gene status

Staging TMN

Characteristic	Definition
Tumor	
T(site)1	Confirmed to anatomic site of origin
a	≤ 5 cm in diameter in size
b	> 5 cm in diameter in size
T(site)2	Extension and/or fixative to surrounding tissue
a	≤ 5 cm in diameter in size
b	> 5 cm in diameter in size
Regional nodes	
N0	Regional nodes not clinically involved
N1	Regional nodes clinically involved by neoplasm
Nx	Clinical status of regional nodes unknown (especially sites that preclude lymph node evaluation)
Metastasis	
M0	No distant metastasis
M1	Metastasis present

Pre-treatment TNM staging in RMS

Table 2. Pretreatment TNM Staging System for Rhabdomyosarcoma

Stage	Sites	Tumor	Size	Node	Metastasis
1	Orbit, H… …uding para… …rinary: nonbladder/nonprostate, biliary tract	T1 or T2	a or b	N0 or N1 or Nx	M0
2	Bladder/prostate, extremity, cranial…	T1 or T2	a	N0 or Nx	M0
3	Bladder/prostate, extremity, cranial…	T1 or T2	a	N1	M0
			b	N0 or N1 or Nx	M0
4	All	T1 or T2	a or b	N0 or N1	M1

NOTE. Staging before treatment requires thorough clinical examination and laboratory and imaging examinations. Biopsy is required to establish the histologic diagnosis.

Favourable

Unfavourable

Unfavourable

Meza J, JCO, 2006

Clinical grouping (IRS)

Table 1. Surgical-Pathologic Grouping System of the Intergroup Rhabdomyosarcoma Study

Group	Definition
Group I	Localized disease, completely resected
Group II	Total gross resection with evidence of regional spread
a	Grossly resected tumor with microscopic residual disease
b	Regional disease with involved nodes, completely resected with no microscopic residual disease
c	Regional disease with involved nodes, grossly resected but with evidence of microscopic residual disease and/or histologic involvement of the most distal regional node (from the primary site) in the dissection
Group III	Incomplete resection with gross residual disease
Group IV	Distant metastatic disease present at onset

Meza J, JCO, 2006

Risk group assigment at diagnosis

- **Fusion status:** Where fusion gene status is unavailable histopathology will be used. Non-alveolar disease should be defined as fusion gene negative and alveolar disease should be defined as fusion gene positive.
- **Site:** Favourable sites are: **GU (non-bladder-prostate*)**, head & neck non-parameningeal, orbit (no bone involvement) and **biliary primaries**. Unfavourable sites are: all other sites.
- **Node Stage**: N0 = 0 positive lymph nodes, N1 = 1 ≥ positive lymph nodes.
- **Age:** Favourable is defined as age over 1 and under 10 years of age at diagnosis.
- **Size:** Favourable primary tumour is ≤ 5 cm in longest diameter, patients that are assessed as not evaluable, they will be included in >5cm group).

**Has changed to favorable in the FaR-RMS - trial*

EpSSG – FaR-RMS

Table 3: Risk Group Assignment

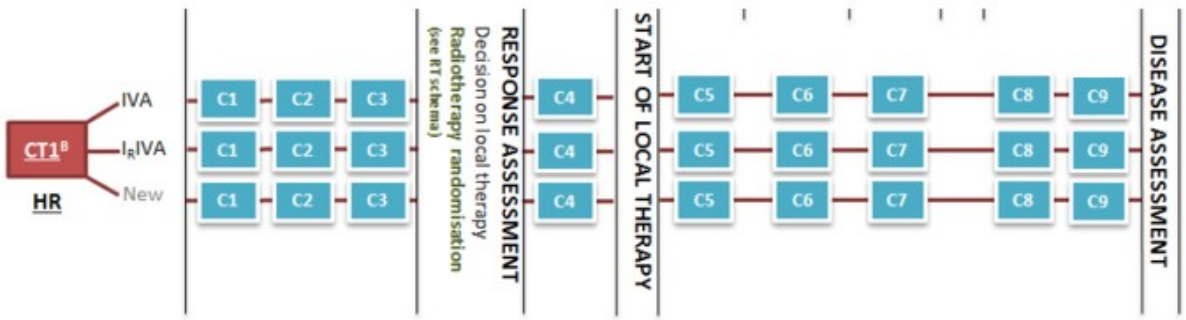
Risk Group	Subgroup	Fusion Status	IRS Group	Site	Node Stage	Size or Age
Low Risk	**A**	Negative	I	Any	N0	Both Favourable
Standard Risk	***B***	Negative	I	Any	N0	One or both Unfavourable
	C	Negative	II, III	Favourable	N0	Any
High Risk	***D***	Negative	II, III	Unfavourable	N0	Any
	E	Negative	II, III	Any	N1	Any
	F	Positive	I, II, III	Any	N0	Any
Very High Risk	***G***	Positive	II, III	Any	N1	Any
	H	Any	IV	Any	Any	Any

Treatment principle

- Local control
  - Surgery (not – debulking)
  - Radiotherapy
- Systemic control
  - Chemotherapy, localised diasease require systemic treatment to eradicate micrometastic diasease typically present at diagnosis.

VAC/IVA/VI/IVADo

Figure 6: HR CT1^{B} schema



Rhabdomyosarcoma: Non-stage prognostic factors

Solid Tumour	Essential	Additional	New and Promising	Comments
Rhabdomyosarcoma	Histology Anatomical location Size	Cytogenetics (FKHR-PAX3 or FKHR-PAX7)	MYOD1	Histological categories based on ICD-O-3 classification; and anatomical location captured through ICD-O-3 topography codes. BENCHISTA captures clinical TNM (cTNM).

Gupta et al. Development of paediatric non-stage prognosticator guidelines for population-based cancer registries and updates to the 2014 Toronto Paediatric Cancer Stage Guidelines. **Lancet Oncol 2020; 21: e444–51**

Rhabdomyosarcoma: Summary

- Diagnostic work up at diagnosis extremely important for correct risk assigment.
- Common imaging guidelines across protocols.
- Pre-treatment stage and clinical stage equal across protocols.
  - Site (will change over time)
  - Size
  - Node status
  - Metastasis
  - **Fusion status – NPS**
- Risk assigment and treatment not the same across protocols.
- Treatment principles equal across protocols.

Toronto Staging

Méric Klein, Belgian Cancer Registry

Supported by:
Gemma Gatta (Fondazione IRCCS, INT, Milan)
Andrea Di Cataldo (University of Catania)

Toronto Staging:

CanStaging+ Tool

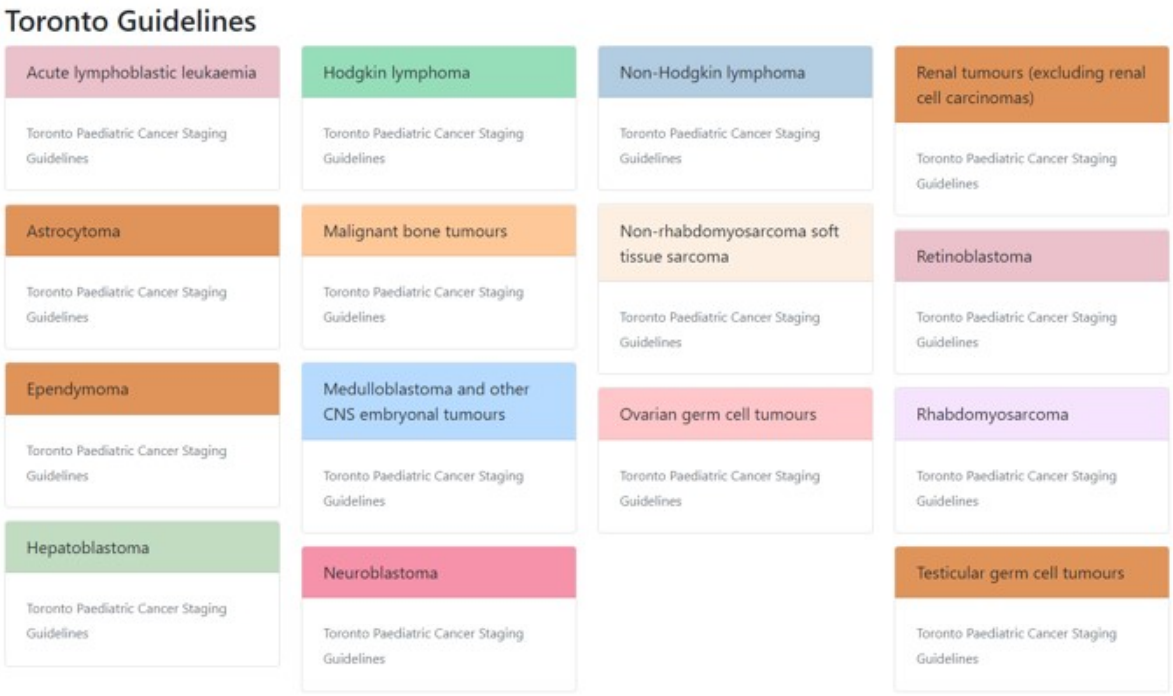
Developed by a collaboration between the Northern Ireland Cancer Registry (NICR), the International Agency for Research on Cancer (IARC), the Union for International Cancer Control (UICC)), and Cancer Council Queensland (CCQ).

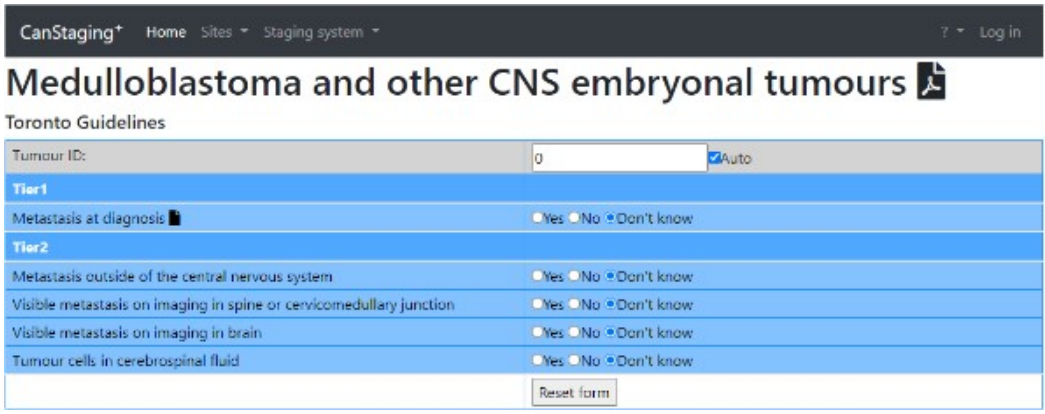
Designed to help maximise the availability, standardisation and comparability of cancer staging internationally.

The tool provides:

- Automatic calculation of the international TNM staging classification versions 7 and 8 for a variety of tumour sites.
- Automatic **calculation of stage for childhood cancers using the business rules developed for the Toronto Paediatric Cancer Stage Guidelines**.

CanStaging+: an electronic staging tool for population-based cancer registries. I. Soerjomataram, M. Ervik, C. Fox, S.Hawkins, K. Yeung, G. Napolitano et al. August, 2021 LO, DOI:https://doi.org/10.1016/S1470-2045(21)00188-1 VOLUME 22, ISSUE 8, P1069].





https://canstaging.org/tool?tnm_version=Toronto

CanStaging+ Home Sites Staging system ?

Rhabdomyosarcoma

https://canstaging.org/site/rms

Toronto Guidelines

Tumour ID:	0 Auto
Tier1	**L**
Distant metastasis at diagnosis	Yes No Don't know
Tier2	**1**
Distant metastasis at diagnosis	Yes No Don't know
Regional lymph nodes involved	Yes No Don't know
Tumour size (greatest dimension)	>5cm
Favourable anatomic site	Yes No Don't know

Tier1	**L**
Distant metastasis at diagnosis	Yes No Don't know
Tier2	**3**
Distant metastasis at diagnosis	Yes No Don't know
Regional lymph nodes involved	Yes No Don't know
Tumour size (greatest dimension)	>5cm
Favourable anatomic site	Yes No Don't know

Medulloblastoma: Toronto Staging

Toronto Staging: Medulloblastoma

Tier 1

Localised	Metastatic
Localised disease	Disease beyond local site

Toronto Staging: Medulloblastoma

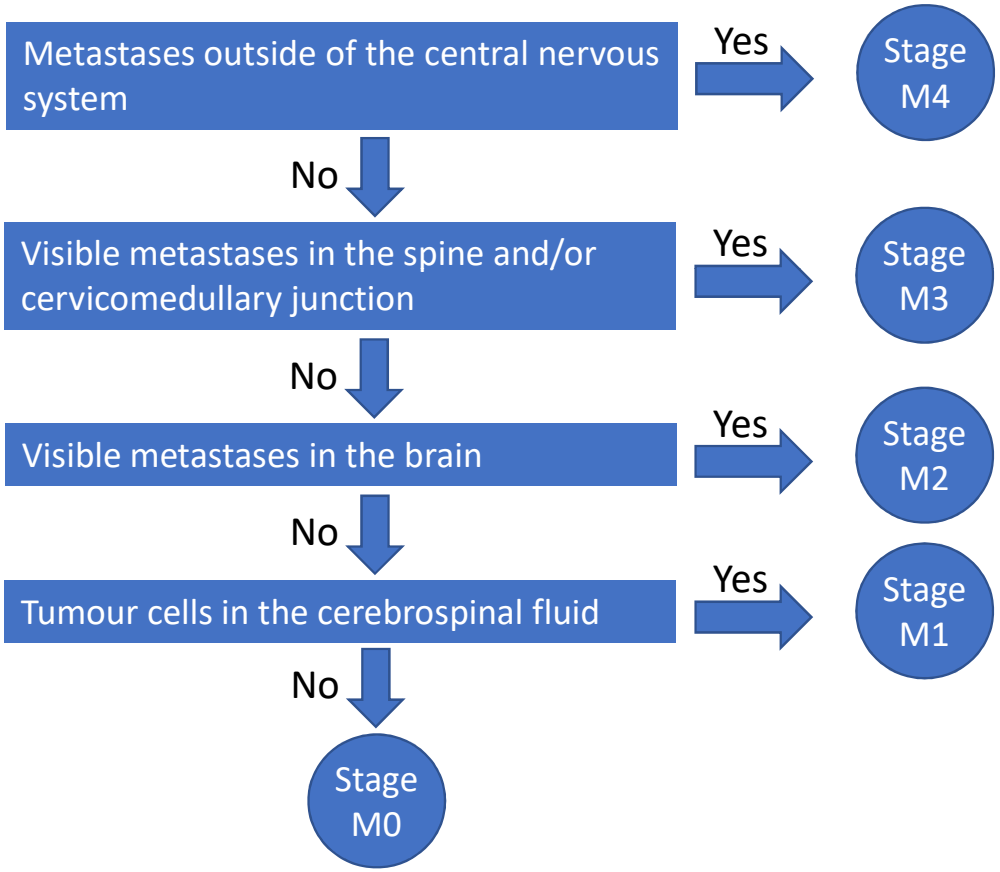
Tier 2 = M staging system

- Staging requires assessment of
  - Extent of disease

M0	M1	M2	M3	M4
No visible disease on imaging beyond primary site of disease (MRI brain and spine) AND No tumour cells in the cerebrospinal fluid	Tumour cells in the cerebrospinal fluid	Visible metastasis in brain	Visible metastasis in spine OR Visible metastasis in cervicomedullary (junction)	Metastasis outside of the central nervous system

Toronto Staging: Medulloblastoma

Tier 2 = M staging system



NSP: Medulloblastoma

- Registration of Non-Stage Prognostic Factors NSP
  - ➢ Molecular classification (according to the ICD-O-3.2)
    - ✓ Wingless (WNT) medulloblastoma (10-15%)
    - ✓ Sonic Hedgehog (SHH) medulloblastoma (30%)
    - ✓ Group 3 / Group 4 medulloblastoma (Non-WNT/ non-SHH)

- Evaluation of post-operative residual disease volume
  - ✓ R0 = No residual cerebellar tumour
  - ✓ R1 = Residual tumour ≤ 1.5 cm^2
  - ✓ R2 = Residual tumour > 1.5 cm^2
  - ✓ R+ = Residual tumour with unknown volume
  - ✓ Unknown = Unknown presence of residual tumour

Medulloblastoma: Exercises

Available in the Kahoot application until November 14, 2021 at the following link:

https://kahoot.it/challenge/03305576?challenge-id=7382f979-7345-44c6-9f85-9268fb87bef4_1634549115290

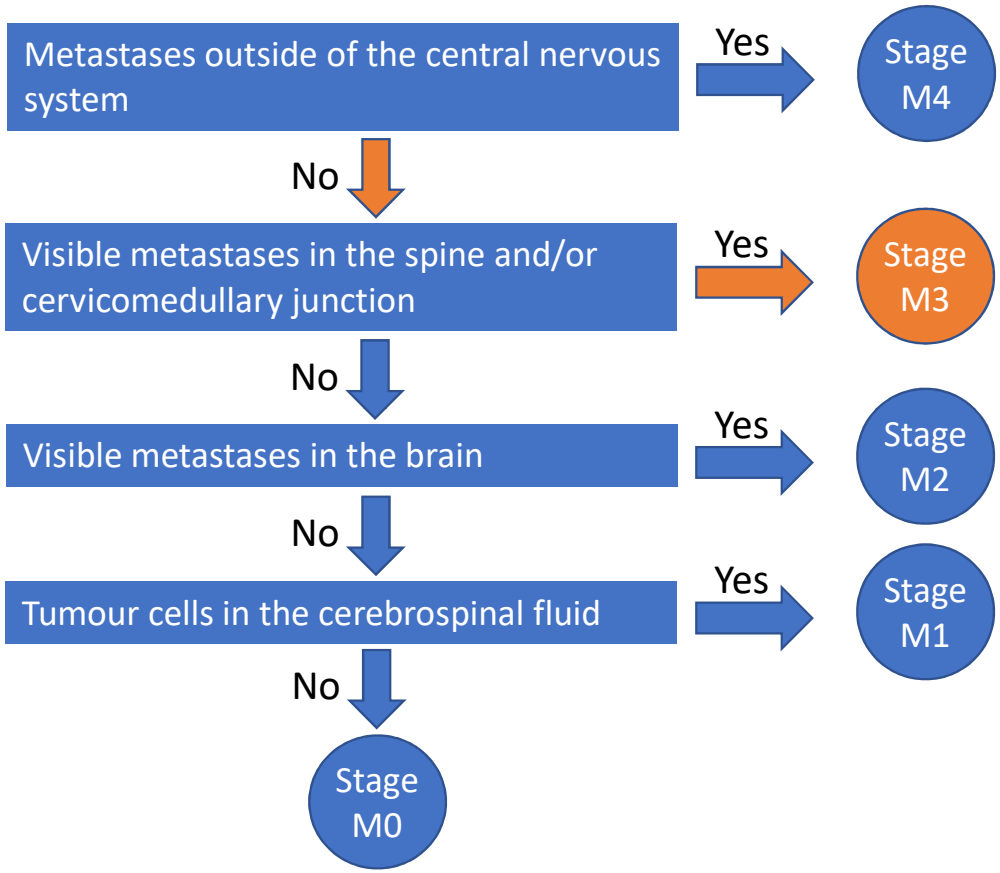
Exercise 1

A 2-year old patient is diagnosed with a WNT-activated medulloblastoma in the posterior cranial fossa. Tumour cells are present in the cerebrospinal fluid at the day 14 lumbar puncture. There is also evidence of spinal metastasis.

What is the correct stage for this patient ?

A. M1
B. M3
C. M4

Exercise 1 - Answer



Medulloblastoma with tumours cells in the cerebrospinal fluid and spinal metastasis. The highest stage has to be recorded, so the stage is M3 and not M1.

Exercise 2

A MRI of the brain performed on a 9-year old patient suffering from headaches shows a solitary posterior fossa tumour. This is subsequently identified as a group 3 medulloblastoma.

A MRI of the spine shows nothing suspicious. The cerebrospinal fluid is analysed, but no tumour cells are found.

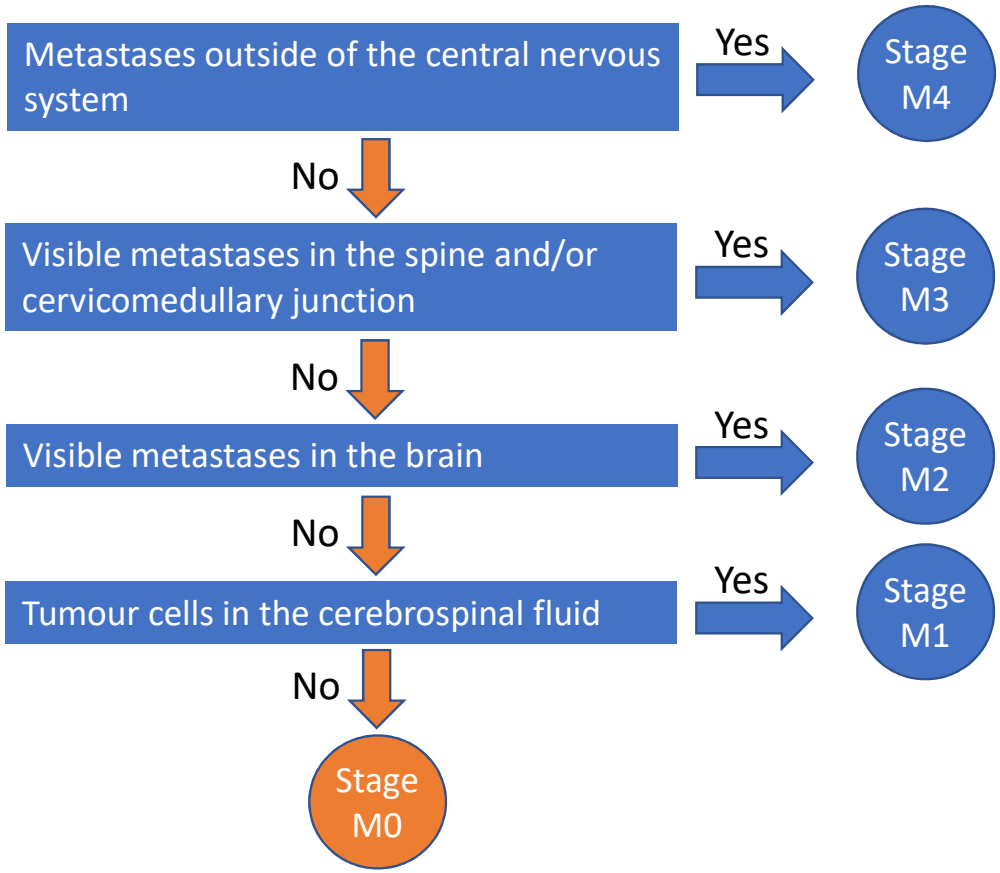
What is the correct stage for this patient ?

A. M0

B. M2

C. M4

Exercise 2 - Answer



No metastasis identified for this patient, so the correct stage is M0.

Exercise 3

A SHH-activated medulloblastoma is described as being metastatic without further details in a 12-year old patient.

What is the correct stage for this patient ?

A. M1
B. M3
C. M4
D. Metastatic

Exercise 3 - Answer

Tier 2 classification can not be used in this case, since it would require clarifications about how metastases were found, and at which anatomical site.

Since you do not have those information, you have to use the Tier 1 classification, and record the patient as Metastatic.

Exercise 4

A 3-year old patient hospitalised for vomiting and disturbances of balance.

- CT of brain: lesion of the posterior cranial fossa that could be a choroid plexus papilloma or an ependymoma of the 4th ventricle, which gives hydrocephalus.
- MRI confirms the lesion. An offshoot of this lesion insinuates itself into the left lateral recess of the 4th ventricle. Dissemination in spine of nodules located at the posterior spinal cord at T2. No clear metastatic lesions in the brain. The imaging concludes to a possibly disseminated medulloblastoma.
- No CSF analysis performed
- Surgically treated two days later

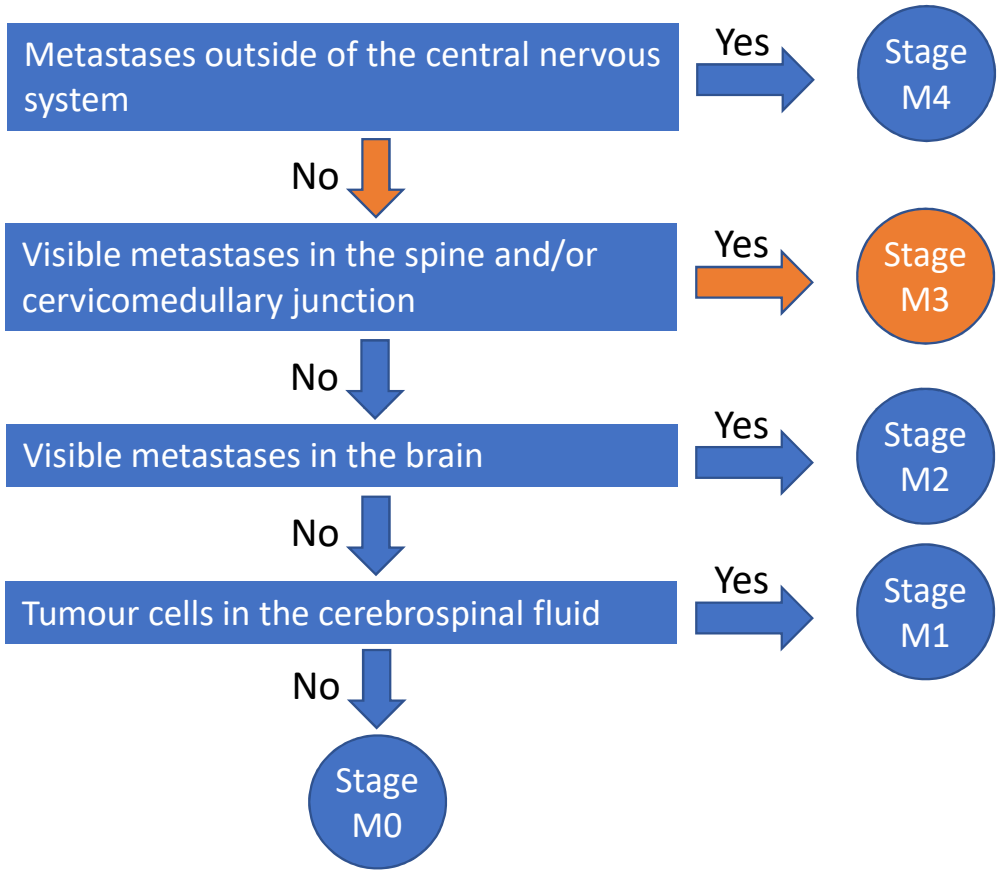
What is the correct stage for this patient ?

A. M1

B. M2

C. M3

Exercise 4 - Answer



Medulloblastoma of the posterior cranial fossa with dissemination in the spine.

Exercise 5

The same 3-year old patient:

- CT of brain at diagnosis: lesion of the posterior cranial fossa that could be a choroid plexus papilloma or an ependymoma of the of the 4th ventricle, which gives hydrocephalus
- MRI confirms the lesion; the imaging concludes to a possibly disseminated medulloblastoma.
- Surgically treated two days later
- Some days later, MRI post surgery: primary lesion completely resected. Persistence in the spine of a pathological enhancement, identified as leptomeningeal carcinomatosis, less evident comparing with the pre surgery imaging.

What is the correct answer about the evaluation of postoperative residual disease?

A. R0

B. R1

C. R+

D. Unknown

Exercise 5 - Answer

The postoperative residual disease corresponds to the volume of the primary tumour.

So, in this case, even if leptomeningeal carcinomatosis is still present, the primary tumour is completely resected, and the correct answer is thus R0.

Rhabdomyosarcoma: Toronto Staging

Toronto Staging: Rhabdomyosarcoma

Tier 1

Localised	Metastatic
Tumour confined to the area of origin, including regional lymph nodes	Distant metastases present

Toronto Staging: Rhabdomyosarcoma

Tier 2 = modified TNM

- Several factors involved for prognosis
  - TNM classification
  - Favourable and unfavourable anatomic site

=> TNM revised to incorporate the anatomic site

- Staging requires assessment of
  - Paediatric TNM
  - Anatomic site

Stage I	Stage II	Stage III	Stage IV
Favourable site Any T Any N M0	Unfavourable site T1a or T2a N0 M0	Unfavourable site T1a or T2a N1 M0 **OR** Unfavourable site T1b or T2b Any N M0	Any site Any T Any N M1

Toronto Staging: Rhabdomyosarcoma

Tier 2 = modified TNM

- ***Favourable anatomic sites:***
  - ✓ Orbit
  - ✓ Head and neck (excluding parameningeal tumours)
  - ✓ Genitourinary sites (excluding bladder and prostate tumours)

- ***Unfavourable anatomic sites:***
  - ✓ Bladder
  - ✓ Prostate
  - ✓ Extremity
  - ✓ Cranial
  - ✓ Parameningeal
  - ✓ Trunk
  - ✓ Retroperitoneum
  - ✓ All other sites not noted as favourable

Toronto Staging: Rhabdomyosarcoma

Tier 2 = modified TNM

➢ ***Paediatric TNM classification of rhabdomyosarcoma:***

TNM Classification of Malignant Tumours, 8th edition, page 248

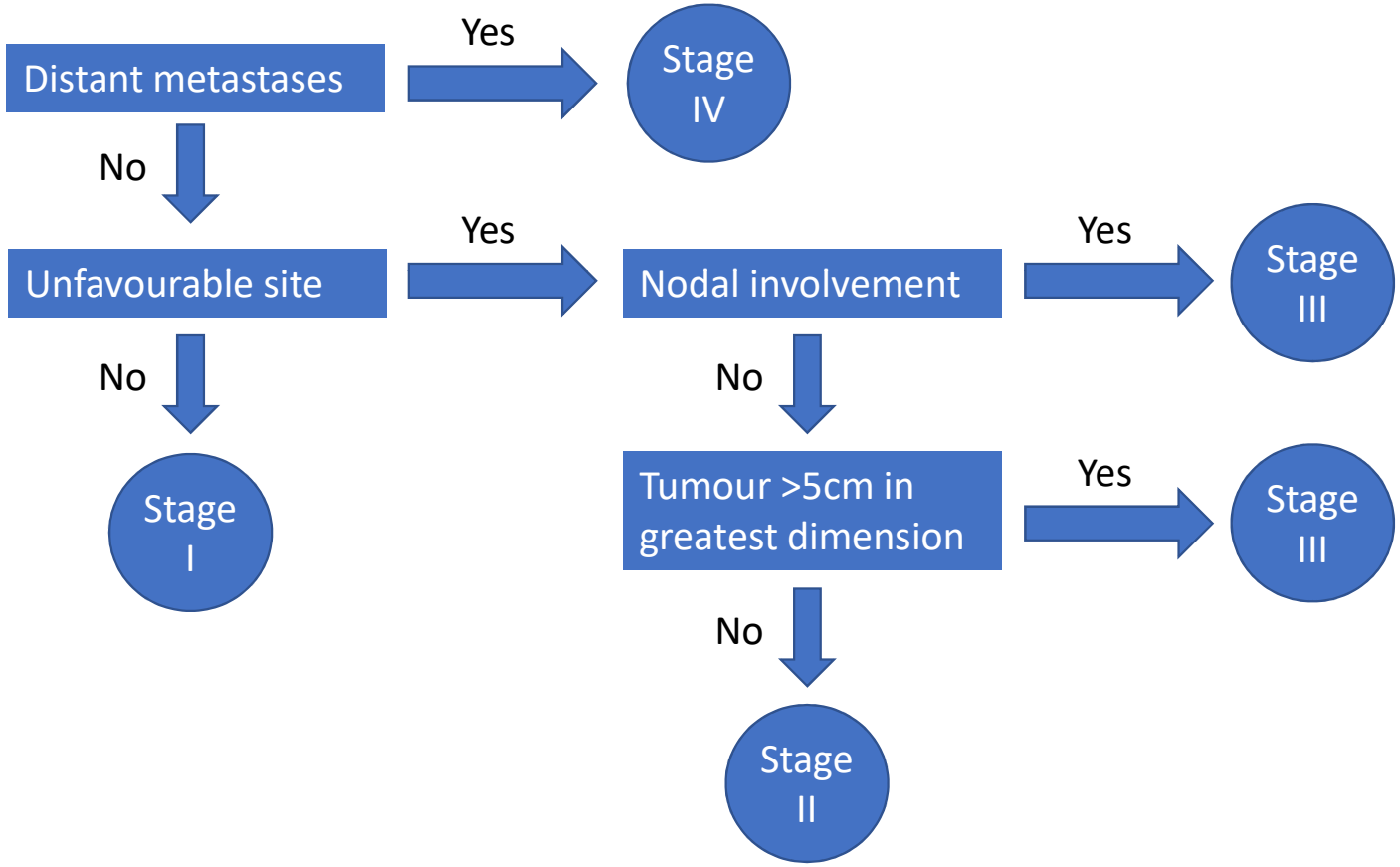
- T – Primary tumour
  - TX: Primary tumour cannot be assessed
  - T0: No evidence of primary tumour
  - T1: Confined to a single anatomic site
    - T1a: Tumour 5cm or less in greatest dimension
    - T1b: Tumour more than 5cm in greatest dimension
  - T2: Extension beyond anatomic site
    - T2a: Tumour 5cm or less in greatest dimension
    - T2b: Tumour more than 5cm in greatest dimension

- N – Regional lymph nodes
  - NX: Regional lymph nodes cannot be assessed
  - N0: No regional lymph node metastasis
  - N1: Regional lymph node metastasis

- M – Distant metastasis
  - M0: No distant metastasis
  - M1: Distant metastasis

Toronto Staging: Rhabdomyosarcoma

Tier 2 = modified TNM



NSP: Rhabdomyosarcoma

- Registration of Non-Stage Prognostic Factors NSP
  - Genetic expression
    - ✓FKHR-PAX3
    - ✓FKHR-PAX7

Rhabdomyosarcoma: Exercises

Available in the Kahoot application until November 14, 2021 at the following link:

https://kahoot.it/challenge/02598258?challenge-id=7382f979-7345-44c6-9f85-9268fb87bef4_1634549175471

Exercise 1

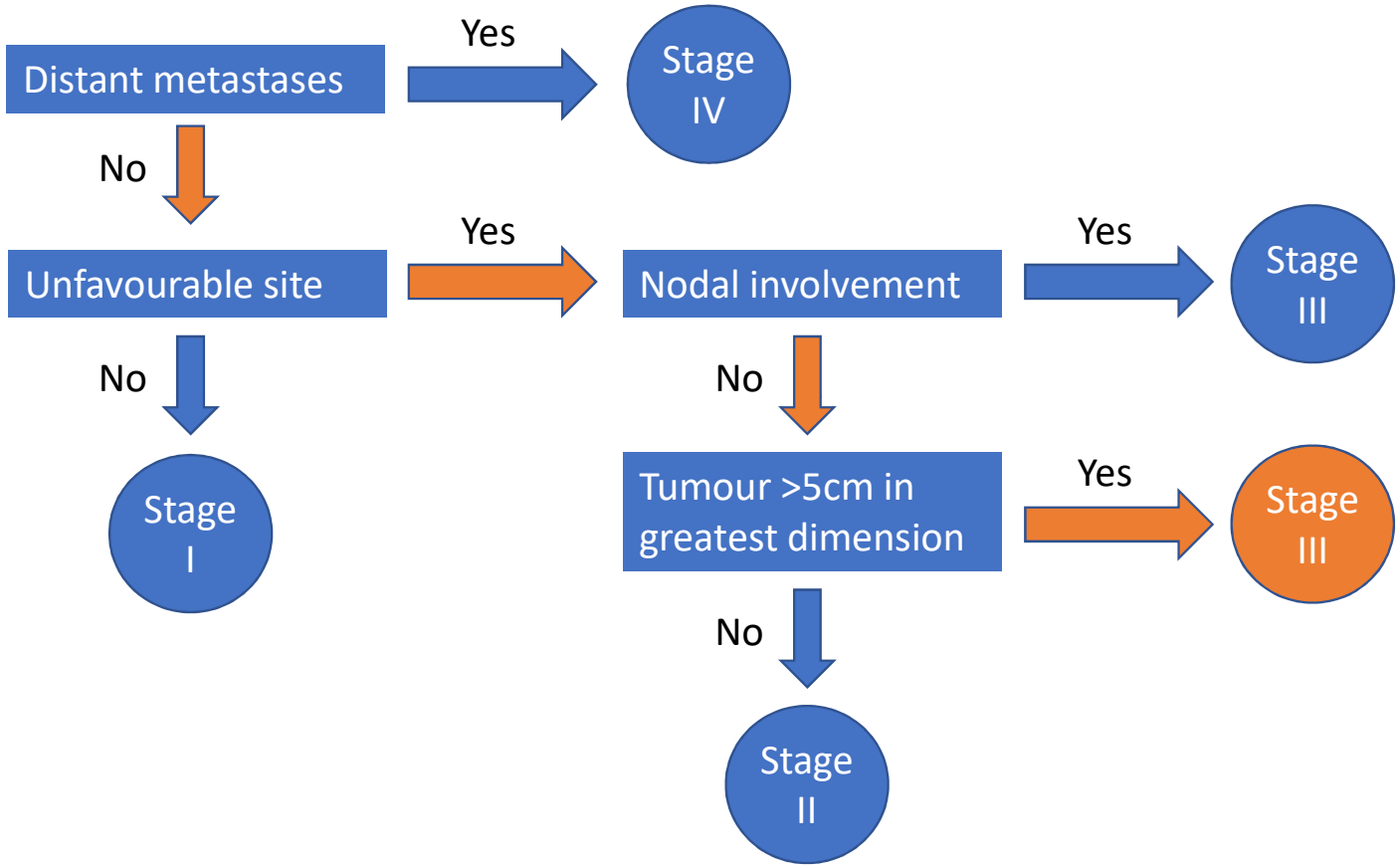
A rhabdomyosarcoma is found in the bladder of a 6-year old patient. The tumour is 3.9x3x5.2cm in greatest dimension, and invades the seminal vesicle.

Imaging of regional lymph nodes and investigations for distant metastases are negative.

What is the correct stage for this patient ?

A. Stage I
B. Stage II
C. Stage III

Exercise 1 - Answer



Tumour located in the bladder, an unfavourable site, without any distant metastasis nor regional lymph node involvement. The tumour is 5.2cm in greatest dimension, and the correct stage is thus III.

Exercise 2

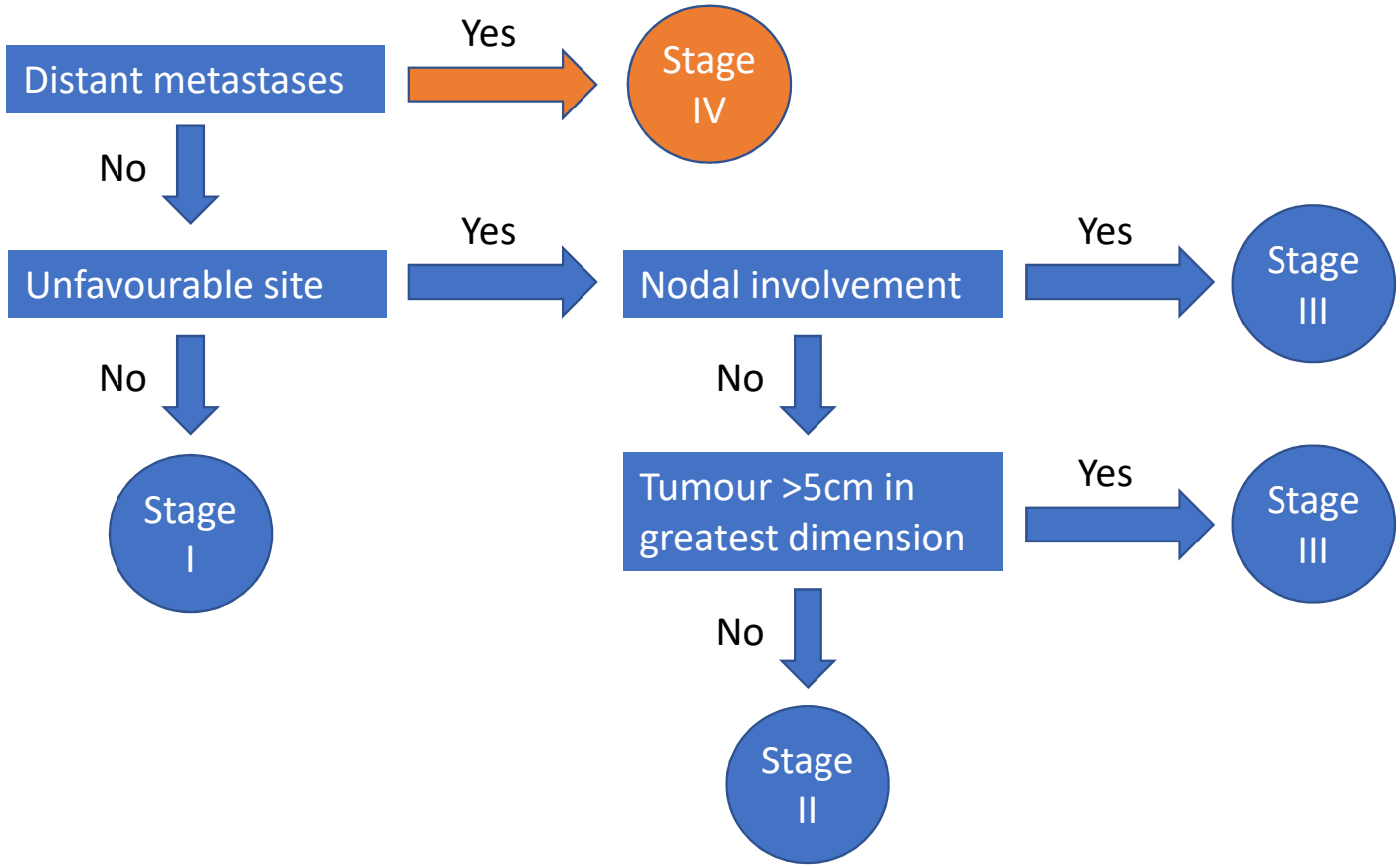
A metastasis of a spindle cell rhabdomyosarcoma is found in the lung of a 7-year old patient.

No primary tumour can be identified.

What is the correct stage for this patient ?

A. Metastatic
B. Stage III
C. Stage IV

Exercise 2 - Answer



The primary tumour location is not required for staging, if we know that distant metastases are present.

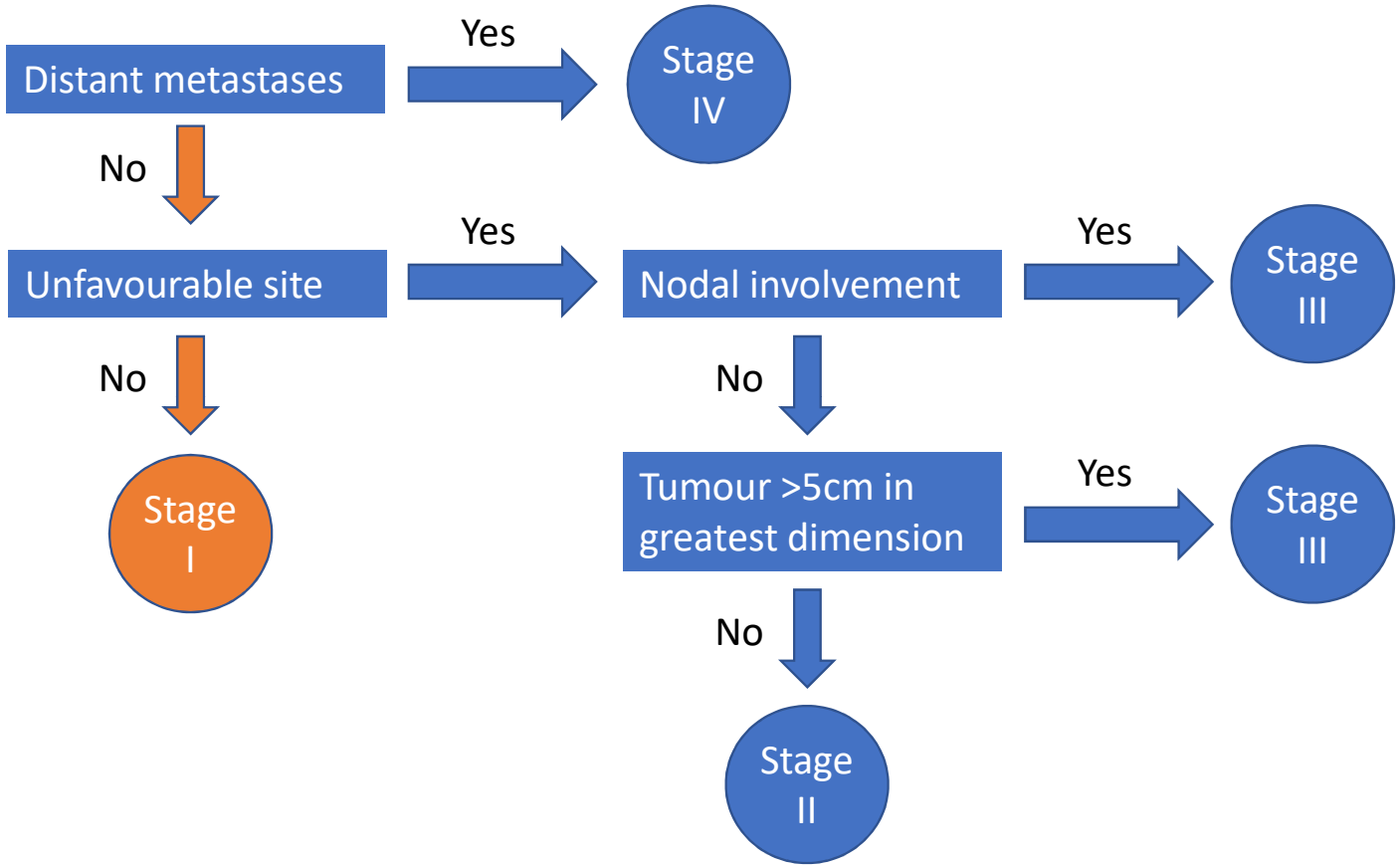
Exercise 3

A confined rhabdomyosarcoma of 3.6cm is diagnosed in the scalp of a 12-year old patient. There are no regional or distant metastases.

What is the correct stage for this patient ?

A. Stage I
B. Stage II
C. Stage III

Exercise 3 - Answer



The scalp is a favourable site. Since there are no distant metastases, this tumour is classified Stage I.

Exercise 4

13-year old boy with a painful, swollen, with functional limitation right lower limb, and homolateral inguinal lymphadenomegaly (9 cm).

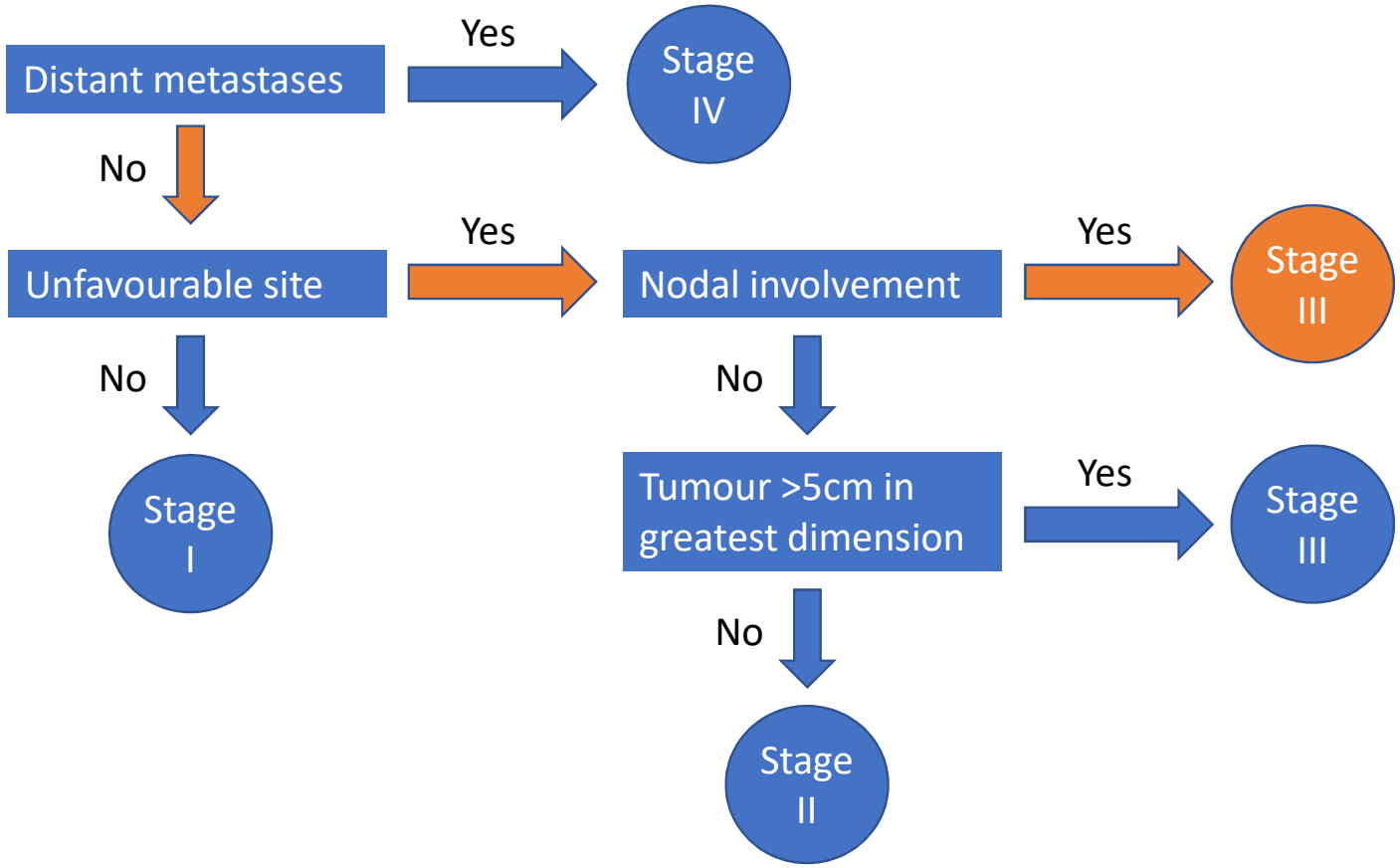
Biopsy of lymph node → rhabdomyosarcoma

A more detailed clinical inspection showed the primary lesion in the sole of the right foot (3 cm). All the major investigations confirmed the extension of the tumour.

What is the correct stage for this patient ?

A. Stage I
B. Stage III
C. Stage X

Exercise 4 - Answer



The sole of the foot is an unfavourable site. There is a regional lymph node involvement, so the tumour has to be classified as Stage III.

Excel file Database Presentation: Medulloblastoma and Rhabdomyosarcoma

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Specific Variables: Imaging/examination performed for Medulloblastoma

Imaging/examination necessary for investigation of the **extension** of the disease are:

- CT/MRI primary site
- MRI whole neuraxis
- CSF (Cerebrospinal fluid)

- Note: the result of each exam performed is requested except for '*CT/MRI primary site*'

Specific Variables: Imaging/examination Performed for Rhabdomyosarcoma

Imaging/examination necessary for investigation of the **extension** of the disease are:

- CT/MRI primary site
- CT thorax
- Imaging of regional lymph nodes
- Bone scan
- Bone Marrow (BM) aspirate or BM biopsy
- X-ray thorax
- PET
- Tissue biopsy (of non-primary sites suspicious for metastasis)

- Note: the result of each exam performed is requested except for '*CT/MRI primary site*'

Specific Variables:
TG staging and NSPs for Medulloblastoma and Rhabdomyosarcoma

	Variable name	values	Variable Description
Toronto staging, Medulloblastoma	Stage Tier 1	1,2,9	L/M/X
	Stage Tier 2	0,1,2,3,4,9	M0/M1/M2/M3/M4/X
	*_Evaluation of postoperative residual disease	0,1,2,3,9	R0/R1/R2/R+/Unknown
	*_NSP: Wingless (WNT)	1,0,9	Y/N/unknown
	*_NSP: Sonic Hedgehog (SHH)	1,0,9	Y/N/unknown
Toronto staging, Rhabdomyosarcoma	Stage Tier 1	1,2,9	L/M/X
	Stage Tier 2	1,2,3,4,9	I/II/III/IV/X
	*_NSP: FKR-PAX3	1,0,9	Y/N/unknown
	*_NSP: FKR-PAX7	1,0,9	Y/N/unknown

	Essential	Additional	New and promising	Comments
Solid tumours				
Rhabdomyosarcoma	Histology; anatomical location	Cytogenetics	..	Histological categories based on ICD-O-3 classification; and anatomical location captured through ICD-O-3 topography codes
CNS tumours				
Medulloblastoma	..	Molecular classification	..	Molecular classification according to the ICD-O-3 classification

Table 2: The Lyon Paediatric Cancer Non-Stage Prognosticator Guidelines

Specific Variables: TG staging and NSPs for Medulloblastoma

Evaluation of postoperative residual disease:

- 0=R0 (no residual cerebellar tumour)
- 1=R1 (residual tumour ≤ 1,5 cm^2)
- 2=R2 (residual tumour > 1,5 cm^2)
- 3=R+ (residual tumour with unknown volume)
- 9=Unknown

NSP: Wingless (WNT)

- 1=Yes
- 0=No
- 9=Unknown

NSP: Sonic Hedgehog (SHH)

- 1=Yes
- 0=No
- 9=Unknown

Specific Variables: TG staging and NSPs for Rhabdomyosarcoma

benchista

NSP: Presence of FKR-PAX3

- 1=Yes
- 0=No
- 9=Unknown

NSP: Presence of FKR-PAX7

- 1=Yes
- 0=No
- 9=Unknown

BENCHISTA Contact

Any questions?

Please feel free to email the BENCHISTA Team in case there are further questions/queries or guidance is required:

benchista@istitutotumori.mi.it

Thank you for your participation!