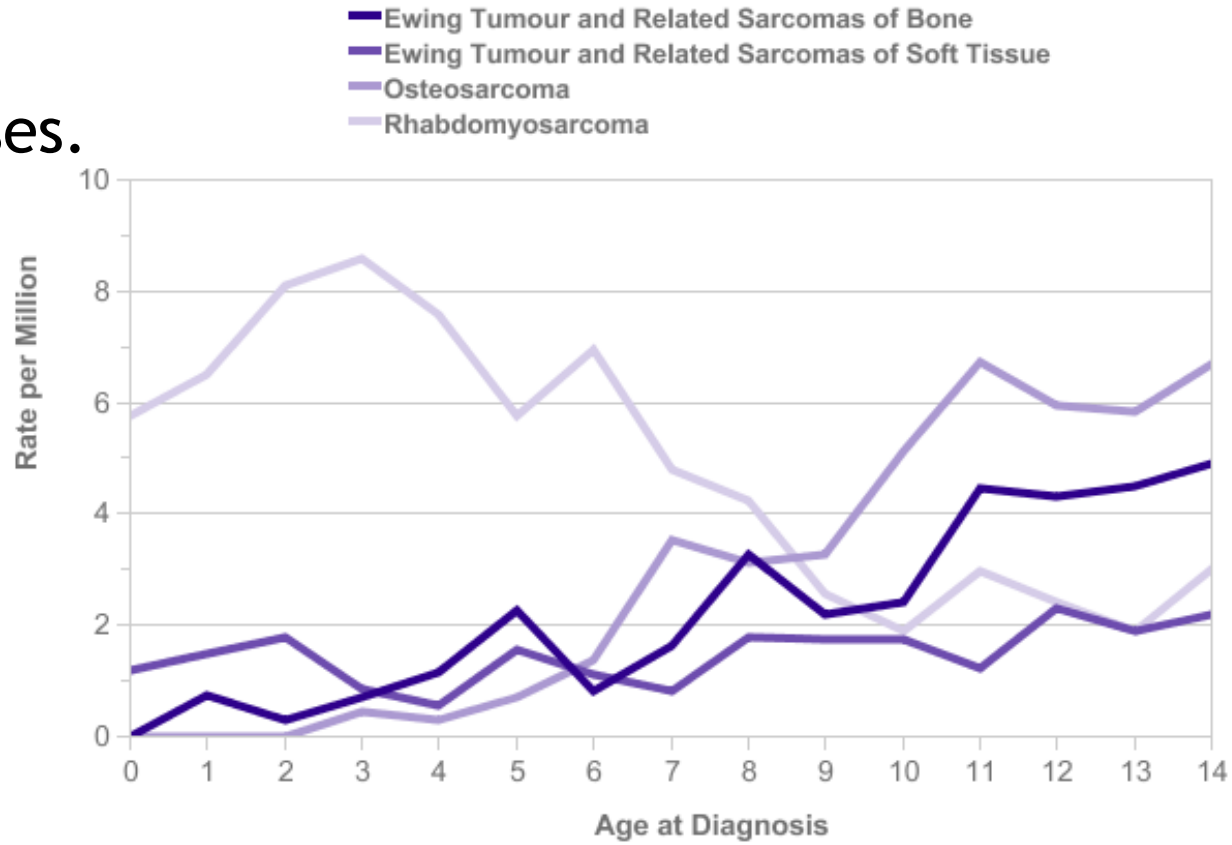
Imaging rhabdomyosarcoma

Prof. Rick R. van Rijn, MD. PhD.

Rhabdomyosarcoma - Incidence

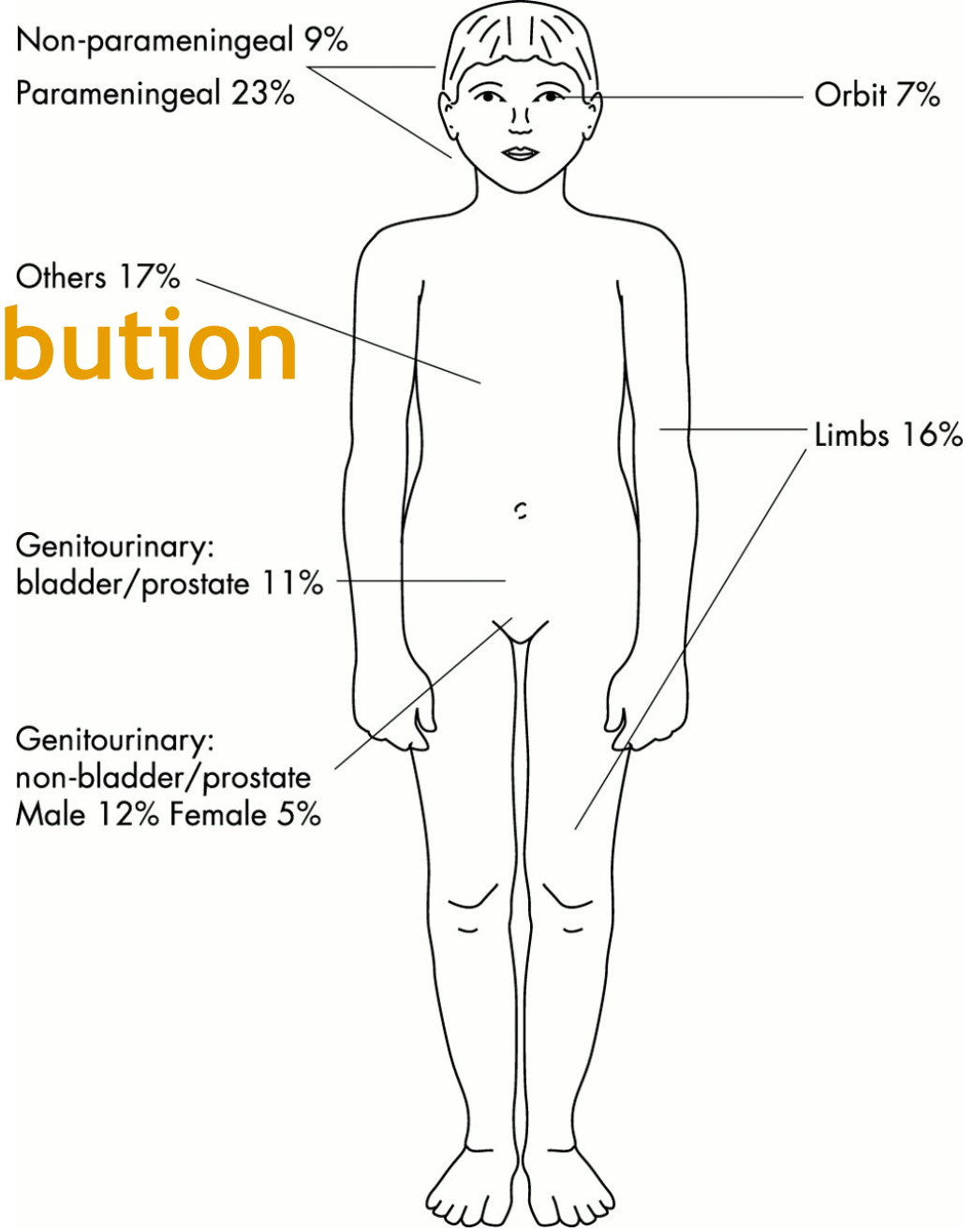
- Approximately 3-5 % of all cancer cases.
- Netherlands: ±20 patients annually.



Bone and Soft Tissue Sarcomas, Average Annual Age-Specific Incidence Rates per Million Population, Great Britain, 1996–2005. Source: https://www.cancerresearchuk.org/

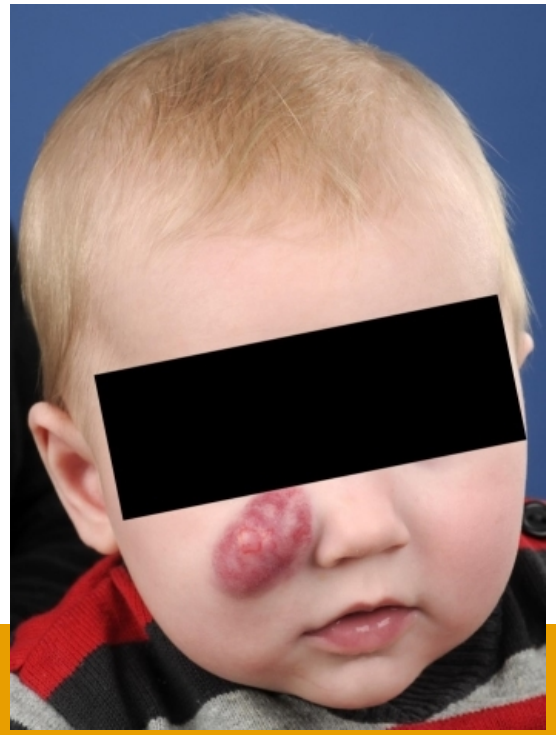
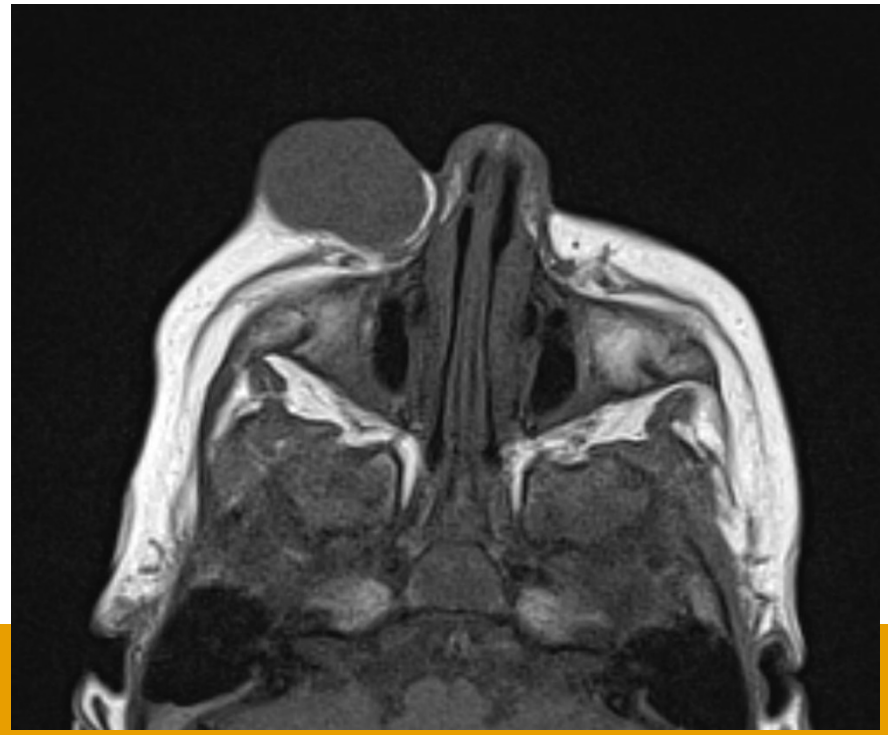
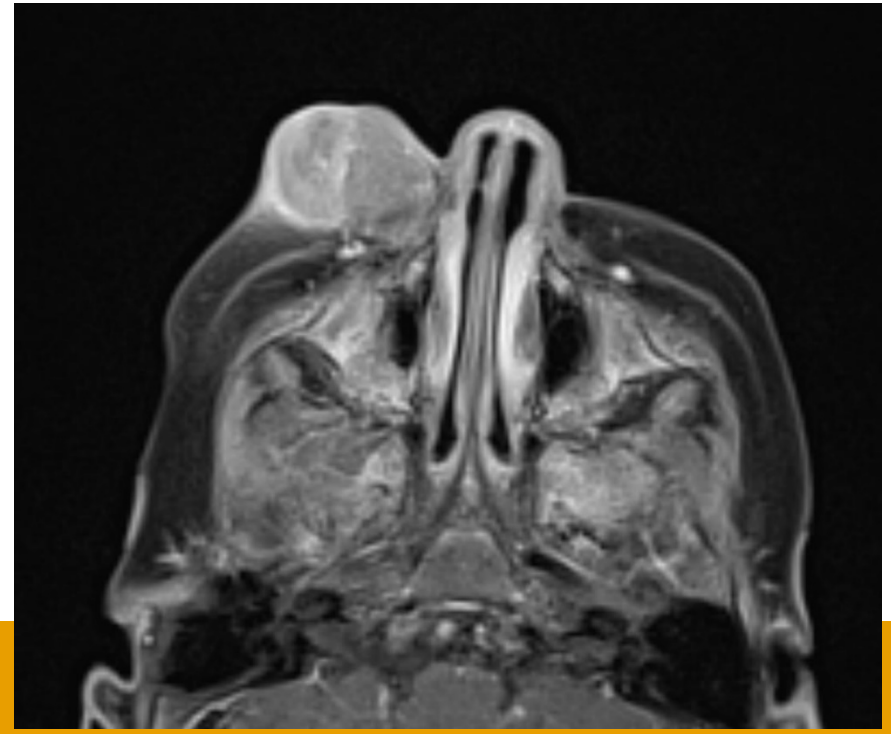
Rhabdomyosarcoma - Distribution

- Metastatic involvement:
  - Lung 39%
  - Bone marrow 32%
  - Lymph nodes 30%
  - Bone 27%
  - Soft tissue 16%

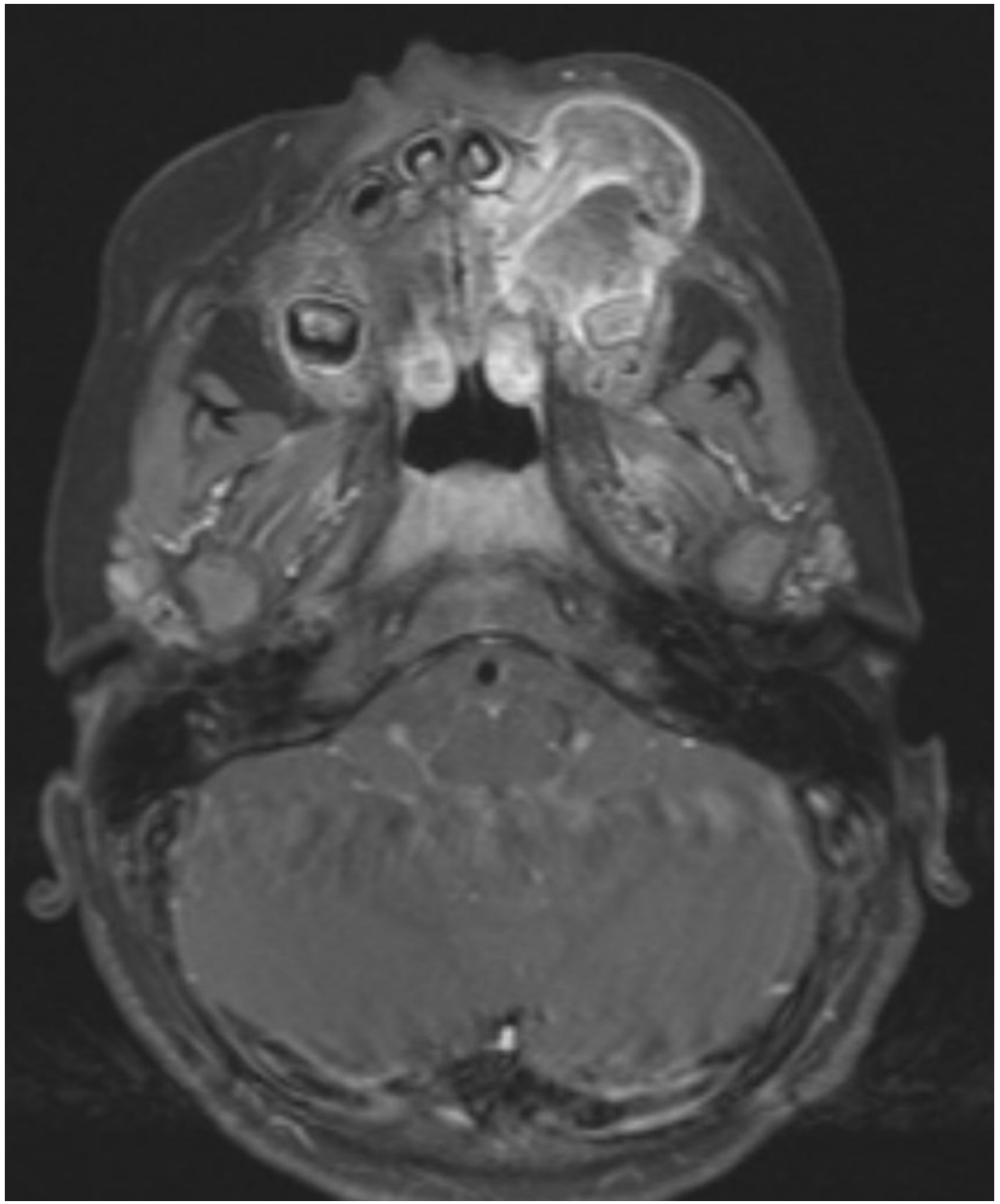


Rhabdomyosarcoma - Presentation

- Highly dependent on tumor location.
  - Visible or palpable mass

Site	Signs and symptoms
Head & neck	Proptosis
	Ophthalmoplegia
	Nasal/sinus congestion
	Nasal discharge
	Cranial nerve palsies
	Headache
	Vomiting
	Systemic hypertension
Genitourinary	Haematuria
	Urinary obstruction
	Abdominal mass
	Extrusion of mucosanguineous tissue
	Mucosanguineous discharge
	Constipation
	Unilateral scrotal/inguinal swelling
Extremity	Swelling
	Pain
Abdomen/pelvis	Palpable mass
	Abdominal pain
	Intestinal obstruction
Biliary tract	Obstructive jaundice



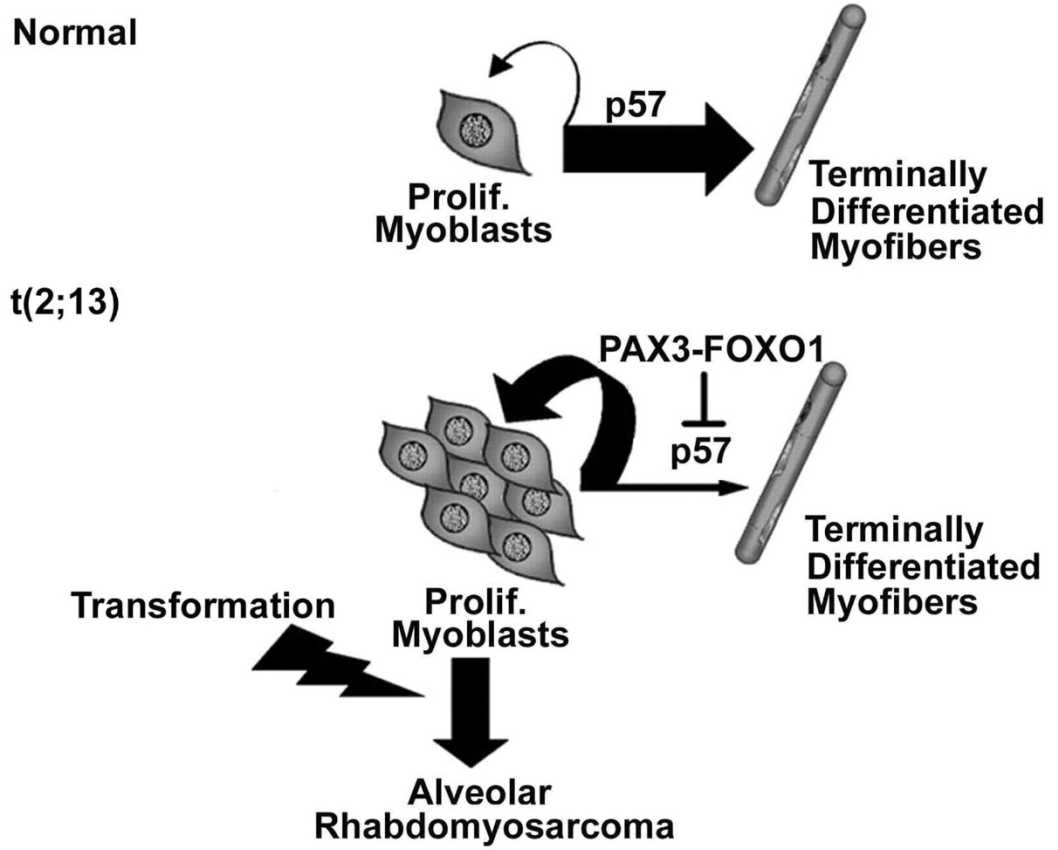
Jawad N, McHugh K. Pediatr Radiol. 2019 Oct;49(11):1516-1523.

Rhabdomyosarcoma – Associated conditions

- History of radiation therapy for treatment of another condition
- Li-Fraumeni syndrome
- *DICER1* syndrome
- Neurofibromatosis
- Costello syndrome
- Beckwith-Wiedemann syndrome
- Noonan syndrome

Rhabdomyosarcoma – Risk stratification

- Fusion status:
  - Favourable = PAX-FOXO1 fusion negative
  - Unfavourable = PAX-FOXO1 fusion positive



Wendy Roeb et al. PNAS 2007;104:46:18085-18090

Rhabdomyosarcoma – Risk stratification

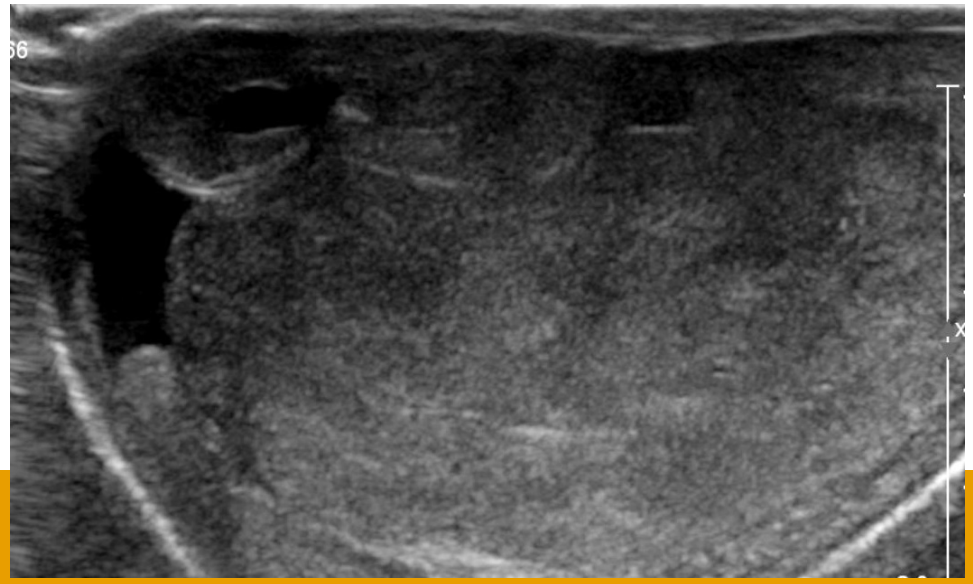
- Fusion status:
  - Favourable = PAX-FOXO1 fusion negative
  - Unfavourable = PAX-FOXO1 fusion positive

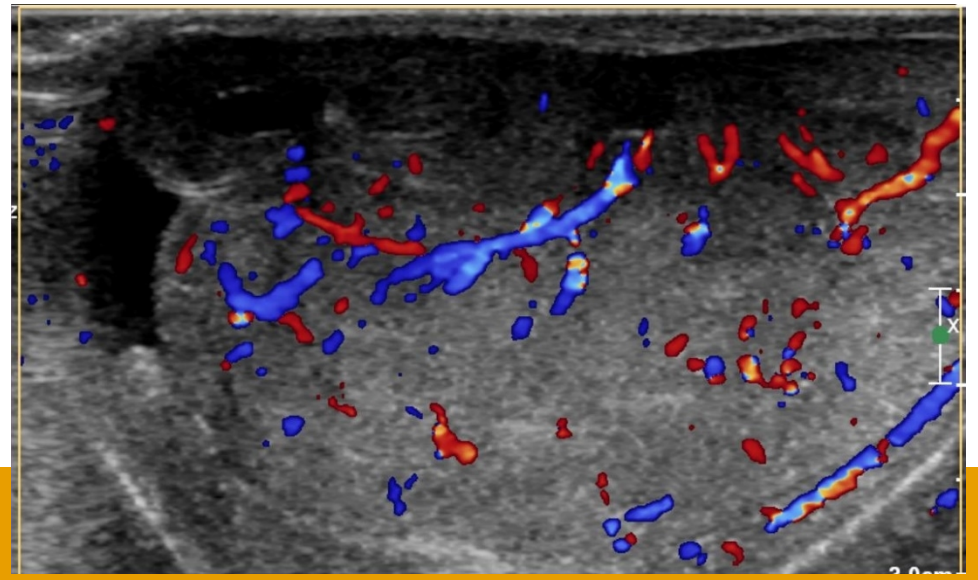
- IRS stage:
  - Group I = Primary complete resection (R0)
  - Group II = Microscopic residual (R1) or primary complete resection but N1
  - Group III = Macroscopic residual (R2)
  - Group IV = Metastatic disease.

IRS = Intergroup Rhabdomyosarcoma Study

Rhabdomyosarcoma – Risk stratification

- Site:
  - Favourable = Orbit, GU bladderprostate, GU non bladder prostate (i.e. paratesticular and vagina/uterus) and non PM head & neck





Rhabdomyosarcoma – Risk stratification

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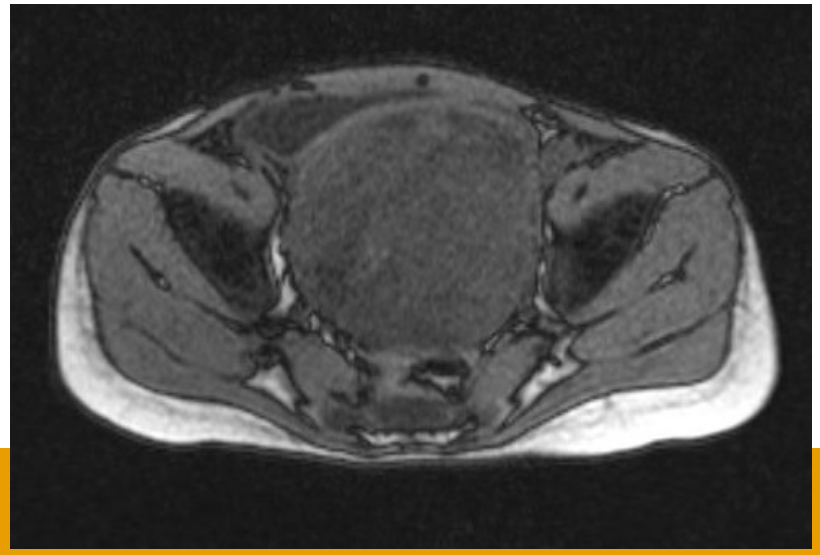
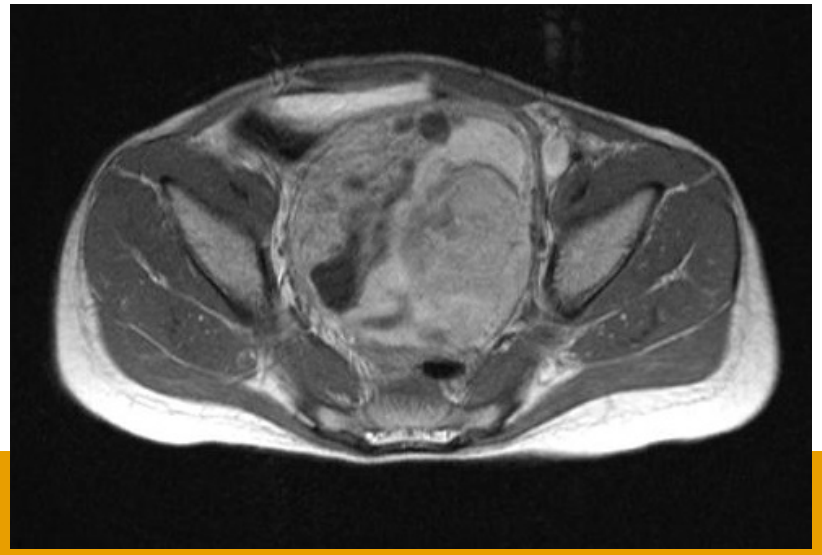
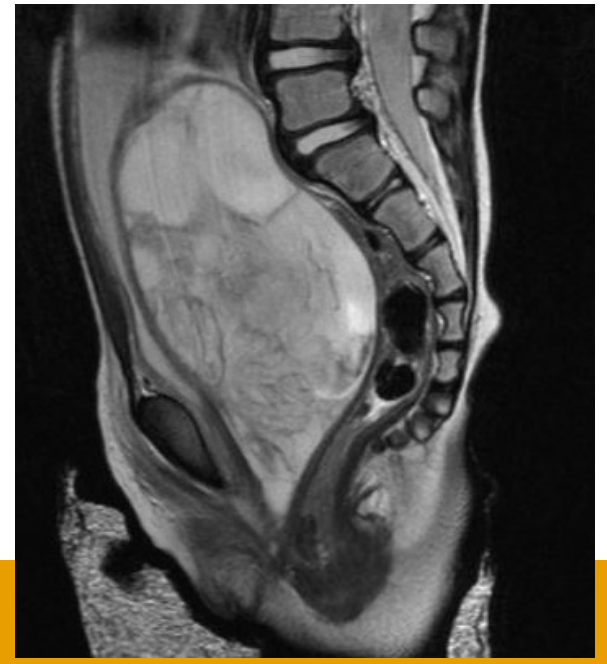
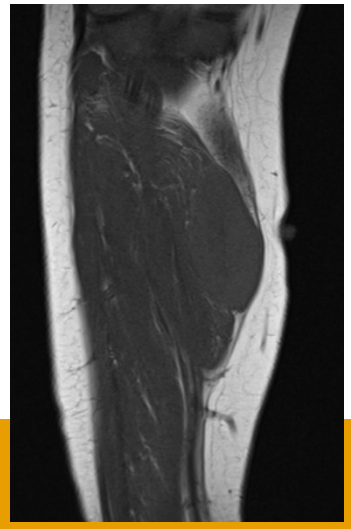
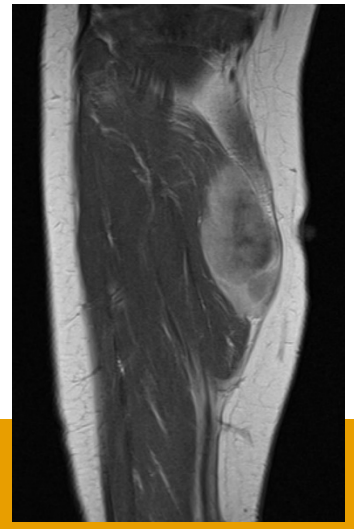
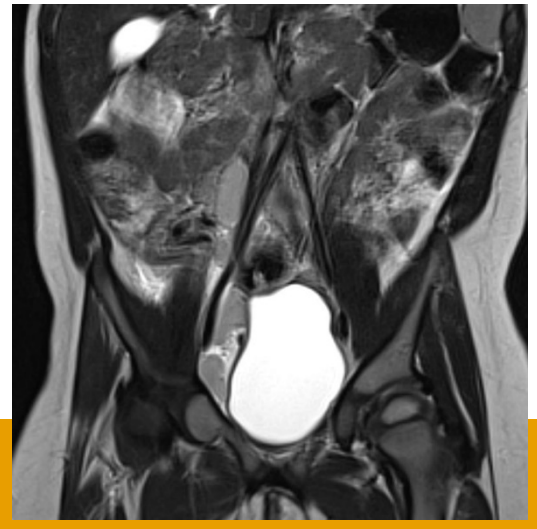
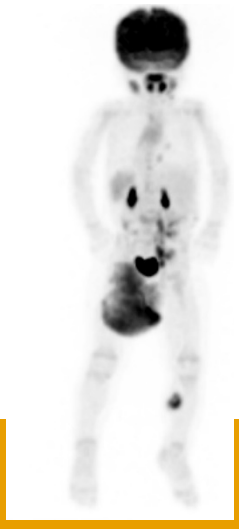






Rhabdomyosarcoma – Risk stratification

- Site:
  - Favourable = Orbit, GU bladderprostate, GU non bladder prostate (i.e. paratesticular and vagina/uterus) and non PM head & neck
  - Unfavourable = All other sites (parameningeal, extremities and “other site”)

Rhabdomyosarcoma – Risk stratification

- Site:
  - Favourable = Orbit, GU bladderprostate, GU non bladder prostate (i.e. paratesticular and vagina/uterus) and non PM head & neck
  - Unfavourable = All other sites (parameningeal, extremities and “other site”)

- Node stage (According to the TNM classification):
  - N0 = No clinical or pathological node involvement
  - N1 = Clinical or pathological nodal involvement

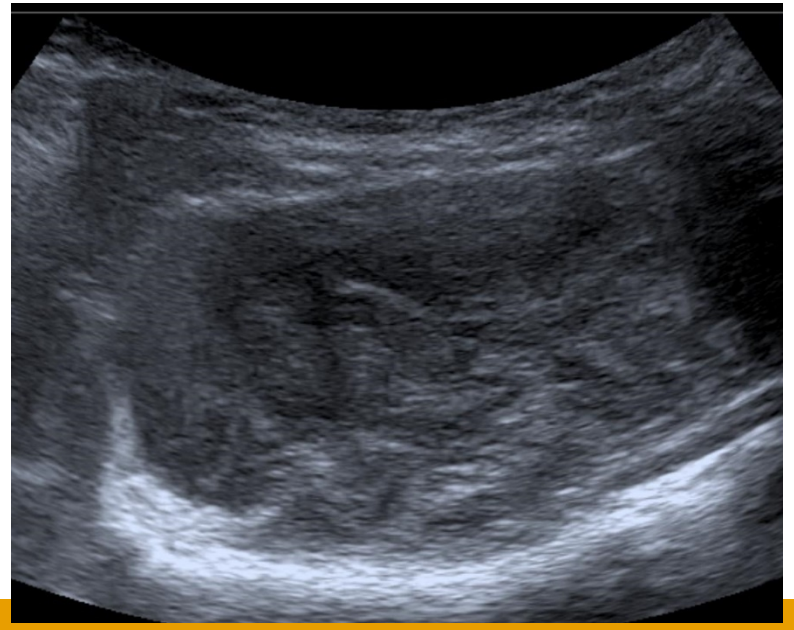
Rhabdomyosarcoma – Risk stratification

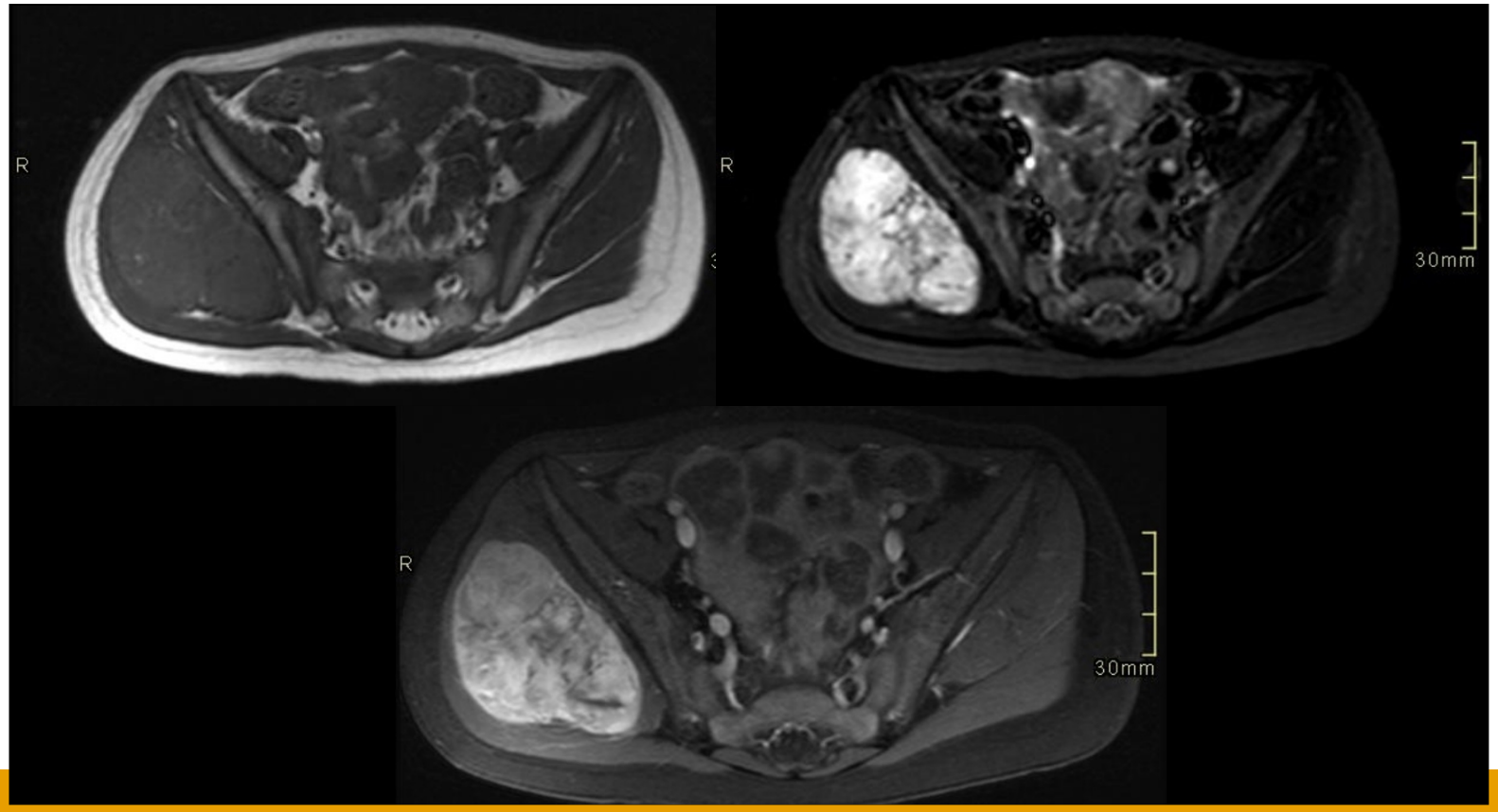
- Size & Age:
  - Favourable = Tumour size (maximum dimension) ≤5 cm or Age ≤10 years)
  - Unfavourable = All others (i.e. Size >5 cm or Age >10 years)

Risk group	Sub-group	Fusion status	Post Surgical stage	Site	Node stage	Size & 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	N	Any
Very high risk	G	Positive	II, III	Any	N1	Any
	H	Any	IV	Any	Any	Any

Rhabdomyosarcoma - Imaging

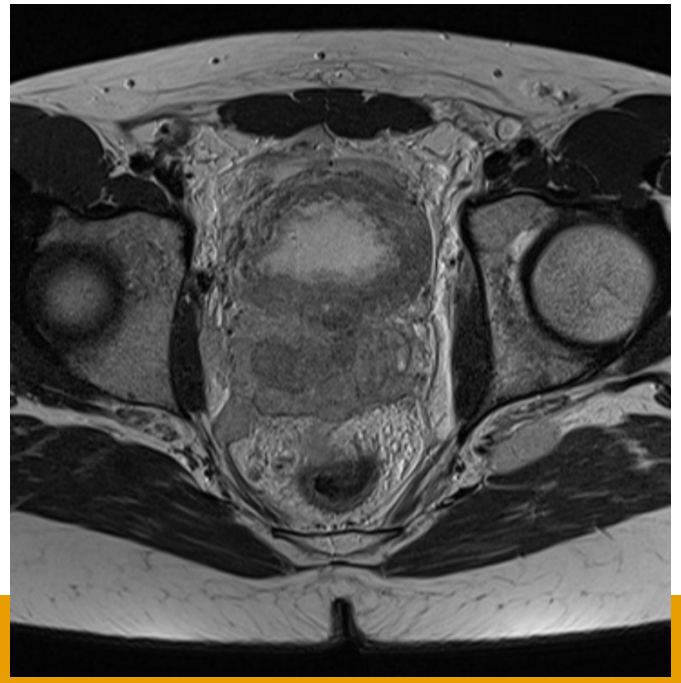
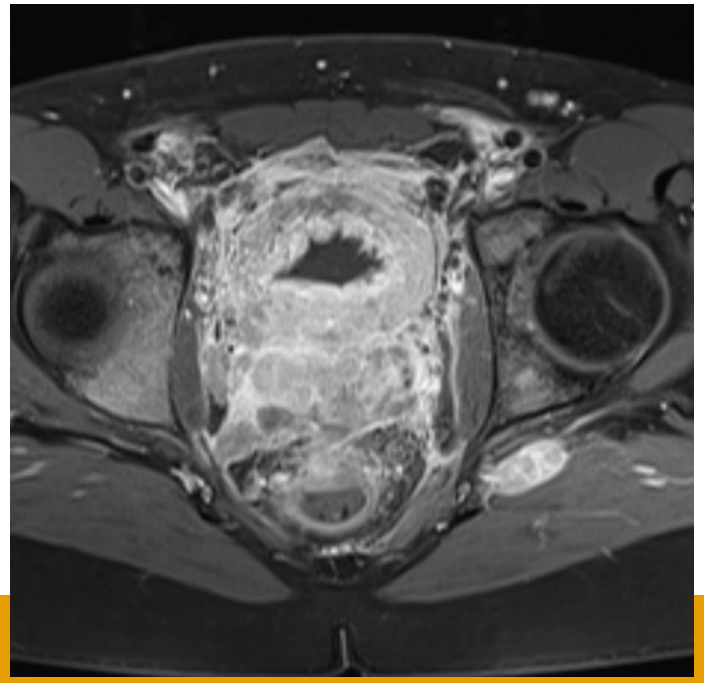
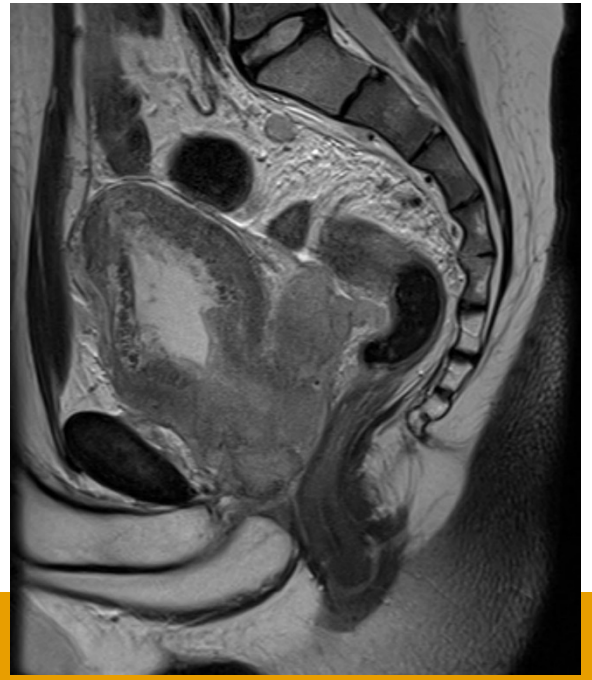
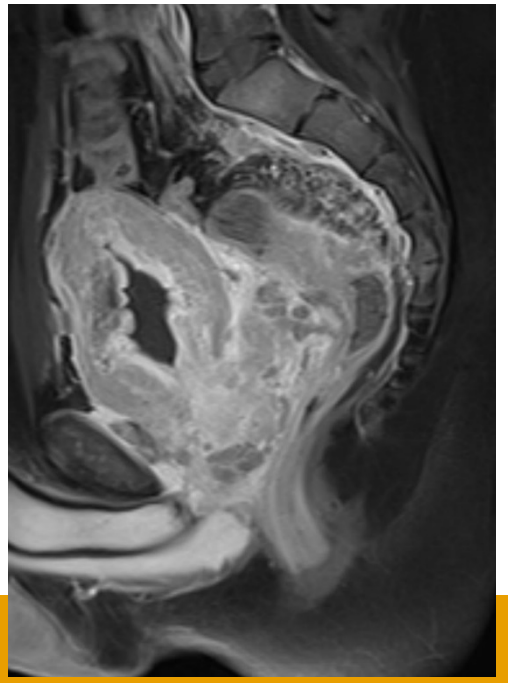
- Initial imaging modality:
  - US





Rhabdomyosarcoma - Imaging

- Main imaging modality:
  - MRI

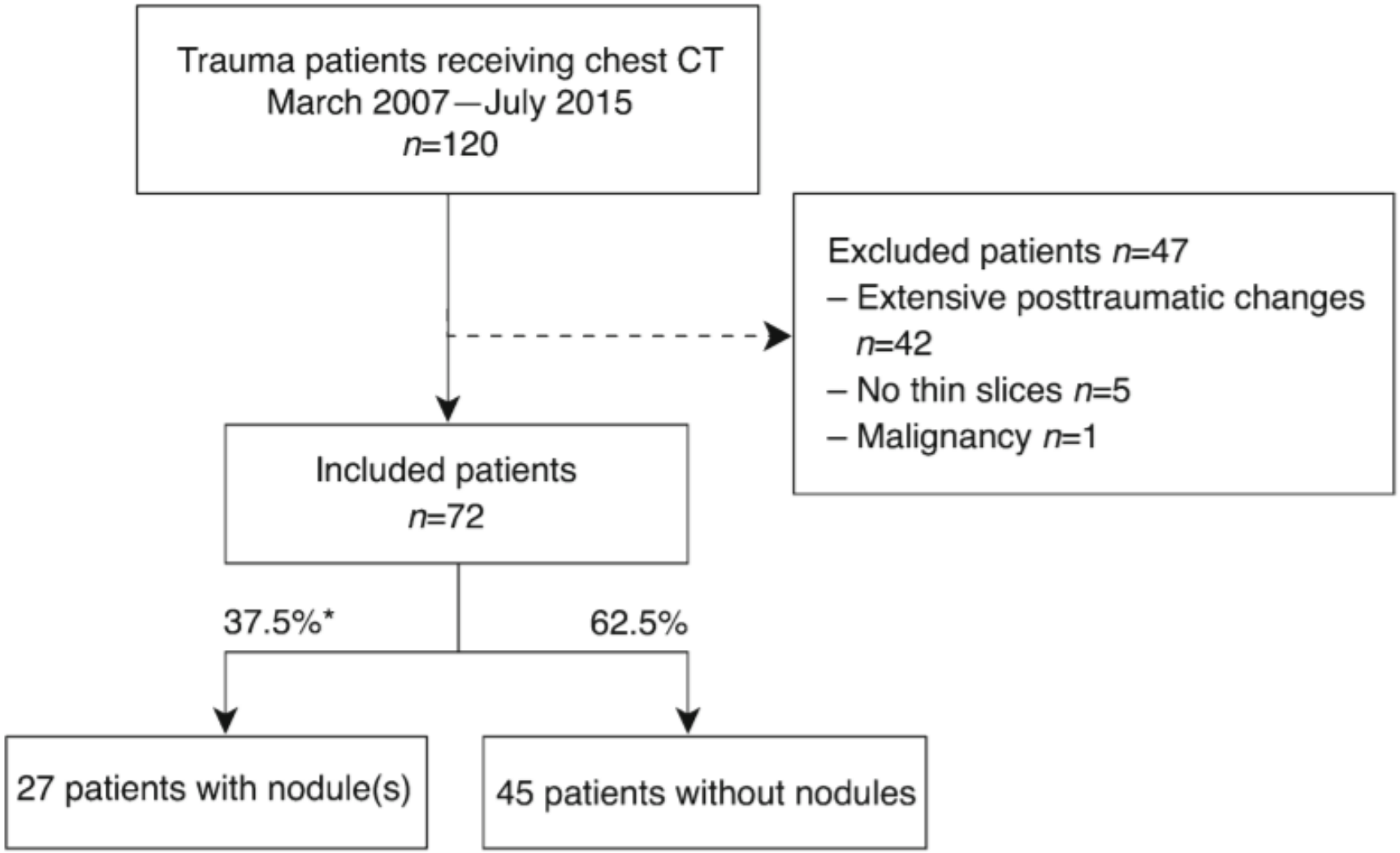
Rhabdomyosarcoma – Imaging lungs

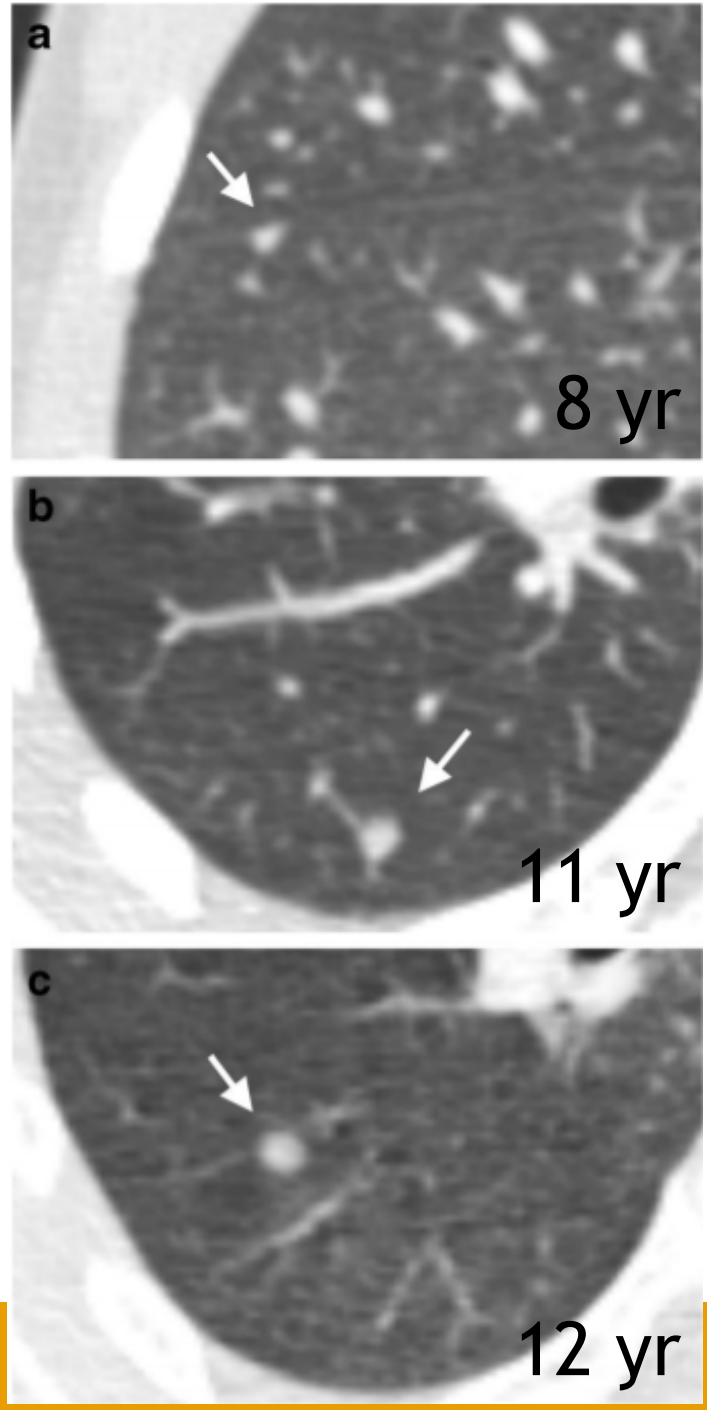
- Always CT of the chest at diagnosis.
- Follow-up CR.

Frequency and characteristics of pulmonary nodules in children at computed tomography

Atia Samim[1] · Annemieke S. Littooij[1] · Marry M. van den Heuvel-Eibrink[2] · Frank J. Wessels[1] · Rutger A. J. Nievelstein[1] · Pim A. de Jong[1]

Pediatr Radiol (2017) 47:1751–1758


Trauma patients receiving chest CT
March 2007—July 2015
n=120
Excluded patients n=47
– Extensive posttraumatic changes n=42
– No thin slices n=5
– Malignancy n=1
Included patients
n=72
37.5%*
62.5%
27 patients with nodule(s)
45 patients without nodules


a
8 yr
b
11 yr
c
12 yr

Rhabdomyosarcoma – Imaging lungs

- E*p*SSG Definition:
  - No lesions: Normal CT.
  - Indeterminate lesions: No more than 4 nodules of <5 mm OR
    1 nodule between 5 and 10 mm
  - Metastatic disease: 1 or more pulmonary nodules of ≥ 10 mm OR
    2 or more well-defined nodules of 5 to 10 mm OR
    5 or more well-defined nodules < 5 mm

Indeterminate Pulmonary Nodules at Diagnosis in Rhabdomyosarcoma: Are They Clinically Significant? A Report From the European Paediatric Soft Tissue Sarcoma Study Group

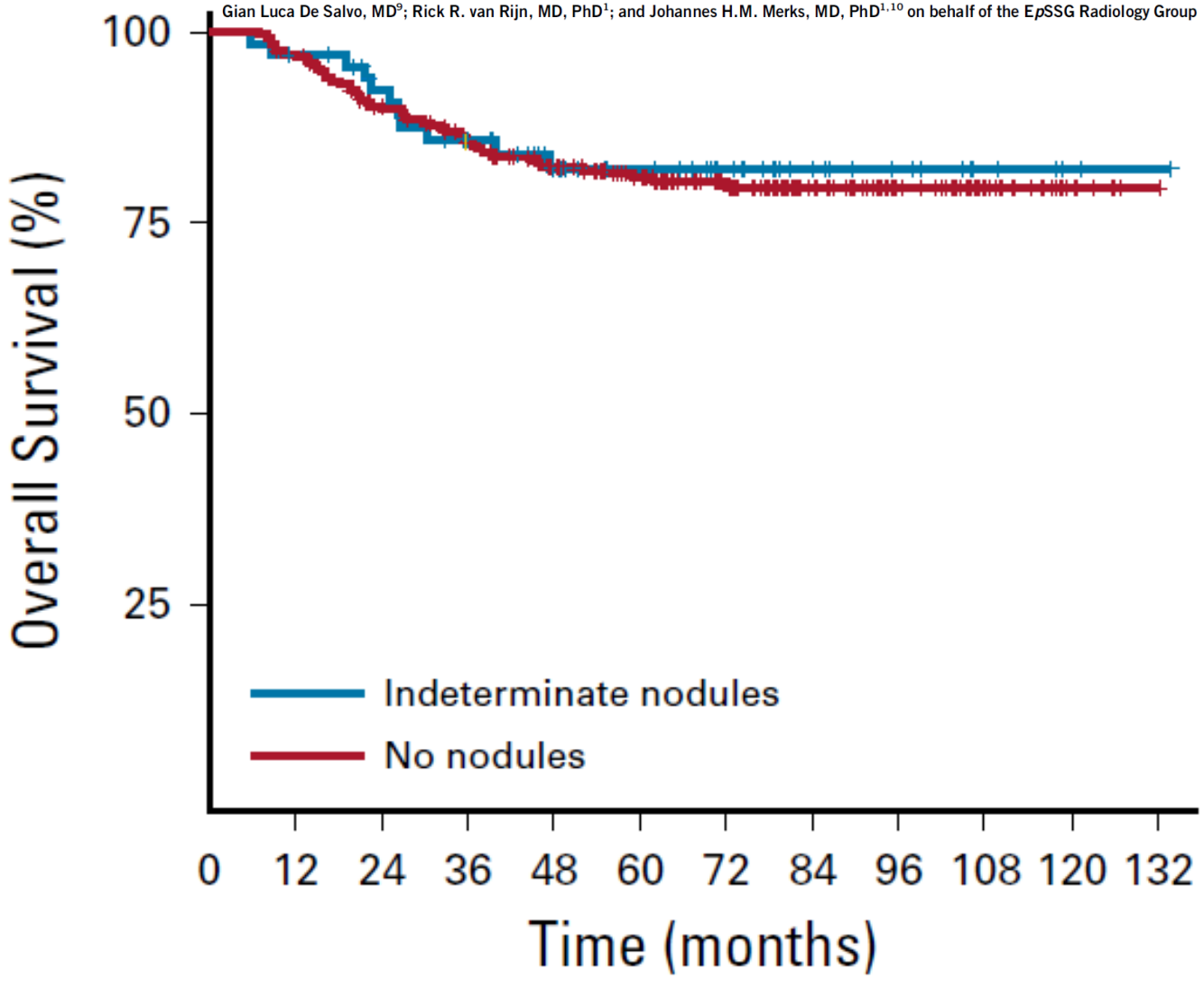
Bas Vaarwerk, MD[1,10]; Gianni Bisogno, MD, PhD[2]; Kieran McHugh, MD[3]; Hervé J. Brisse, MD, PhD[4]; Carlo Morosi, MD[5]; Nadège Corradini, MD[6]; Meriel Jenney, MD[7]; Daniel Orbach, MD[4]; Julia C. Chisholm, MD, PhD[8]; Andrea Ferrari, MD[5]; Ilaria Zanetti[2]; Gian Luca De Salvo, MD[9]; Rick R. van Rijn, MD, PhD[1]; and Johannes H.M. Merks, MD, PhD[1,10] on behalf of the E*p*SSG Radiology Group

E*p*SSG-RMS-2005 cohort (n = 1,274)

Eligible patients in selected centers (n = 376)

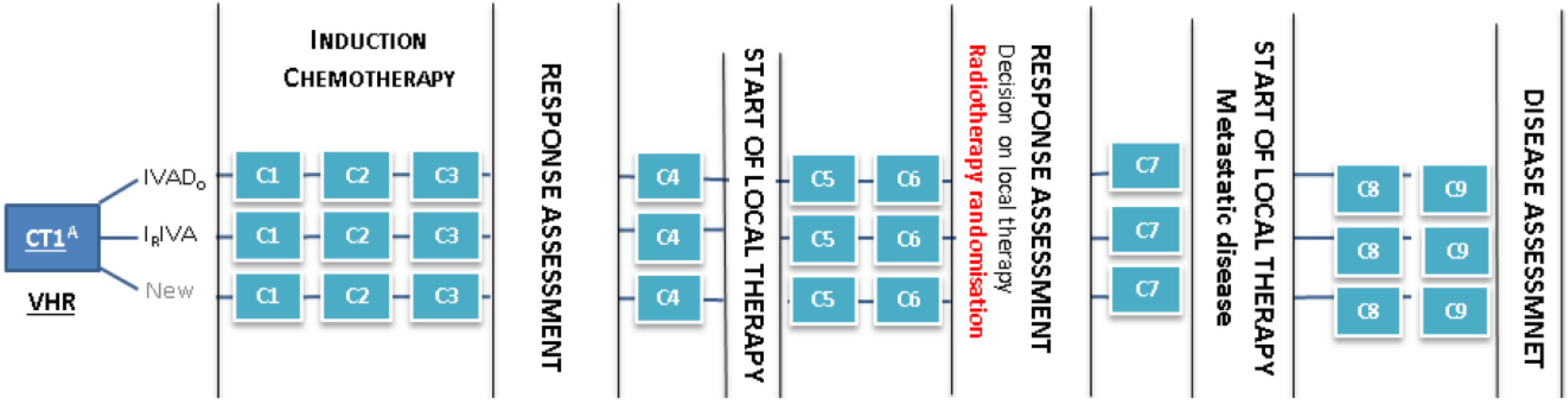
Reason for exclusion	(n = 60)
Chest CT not available	(n = 55)
Chest CT inadequate quality	(n = 1)
Surgical resection of nodules	(n = 2)
Metastatic nodules, according to E*p*SSG-RMS 2005 definitions	(n = 2)

Patients with reviewed chest CT (n = 316)



Rhabdomyosarcoma – Multimodality treatment

- At diagnosis biopsy.
- *Induction (multidrug) chemotherapy.*



$IVAD_O$ (Ifosfamide, Vincristine, Actinomycin D, Doxorubicin) or I_RIVA (Irinotecan, Ifosfamide, Vincristine, Actinomycin D)

Rhabdomyosarcoma – Multimodality treatment

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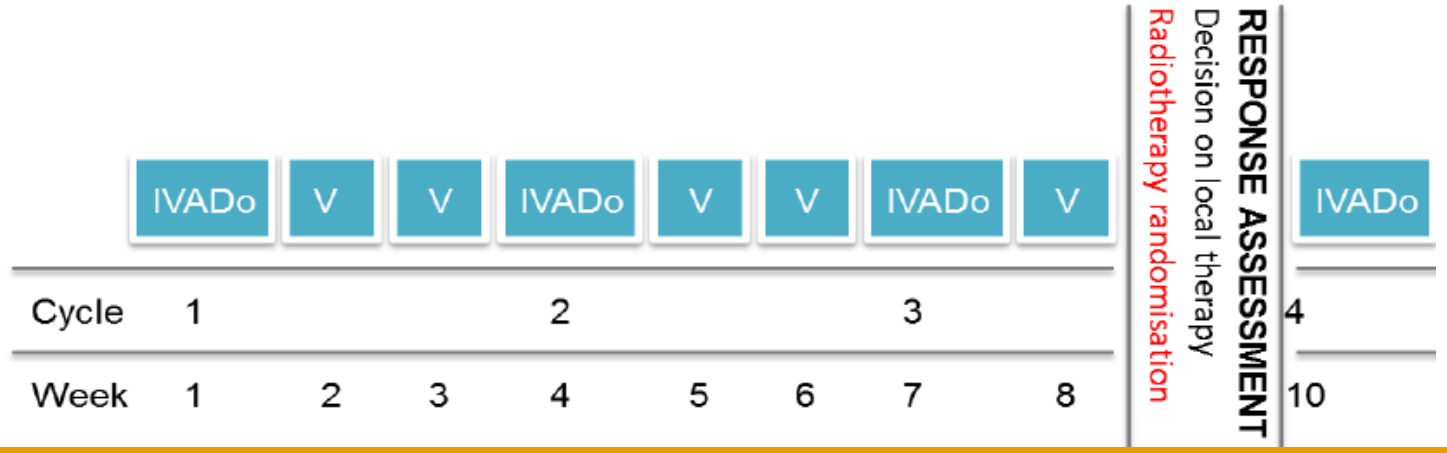
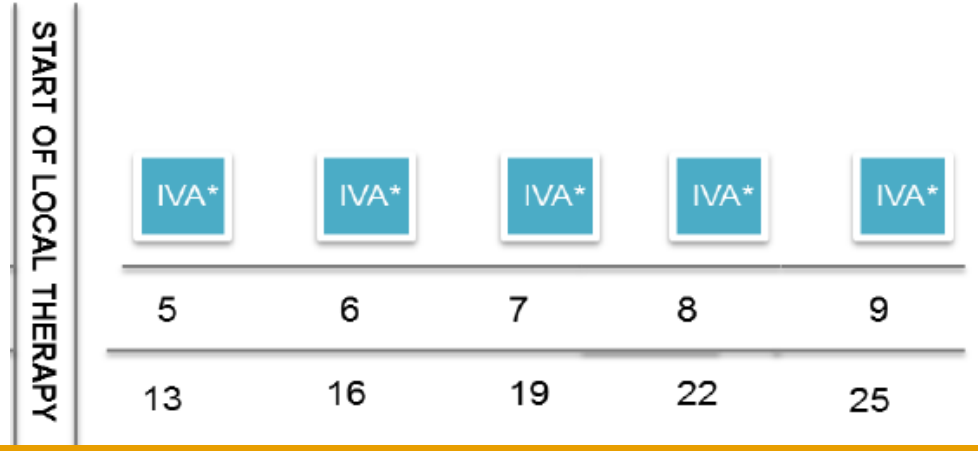


$IVAD_O$ (Ifosfamide, Vincristine, Actinomycin D, Doxorubicin)

Rhabdomyosarcoma – Multimodality treatment

- At diagnosis biopsy.
- Induction (multidrug) chemotherapy.
- Surgery and/or radiotherapy.
- *Adjuvant chemotherapy.*



$IVAD_O$ (Ifosfamide, Vincristine, Actinomycin D, Doxorubicin). * During RTx no Doxorubicin.

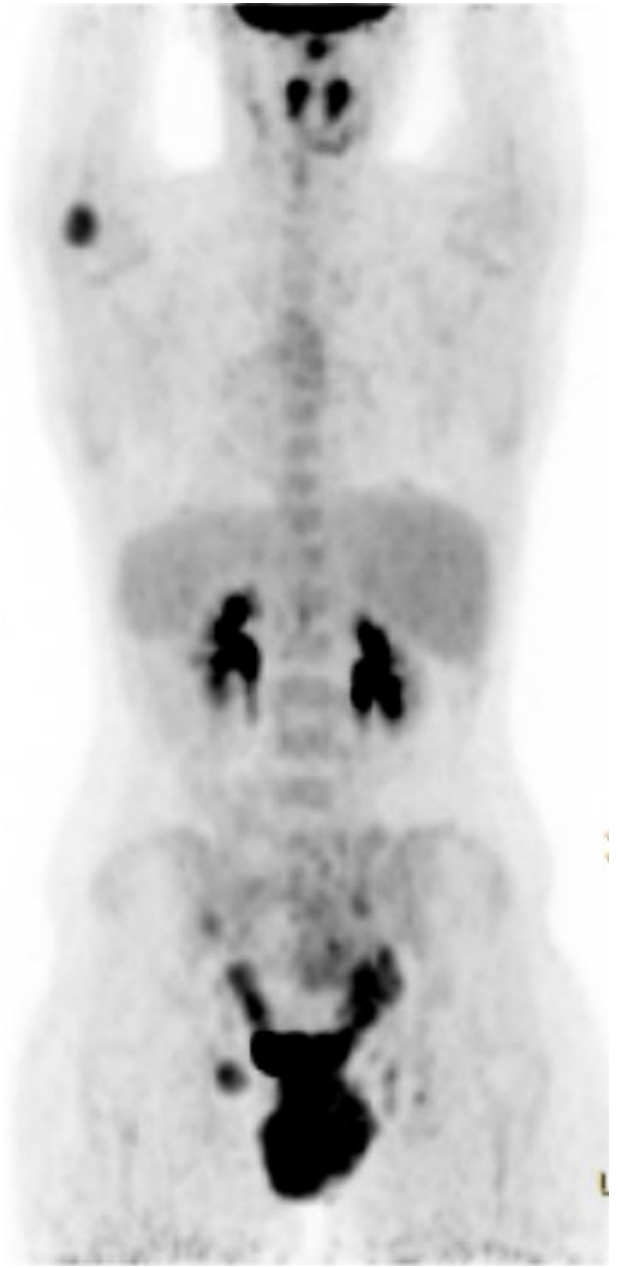
Rhabdomyosarcoma - Outcome

- Localized disease:
  - 5-year event-free survival (EFS): ± 75%
  - Overall survival (OS): 80%

Rhabdomyosarcoma - Outcome

- Localized disease:
  - 5-year event-free survival (EFS): ± 75%
  - Overall survival (OS): 80%

- Metastatic disease:
  - 5-year overall survival (OS): 10-50%



Rhabdomyosarcoma – Treatment response

- European protocols (before FaR-RMS):
  - Insufficient response: tumor volume reduction < 33%
    - Change to second line chemotherapy regimen.
- USA protocols:
  - Tumor progression
    - Change to second line chemotherapy regimen.

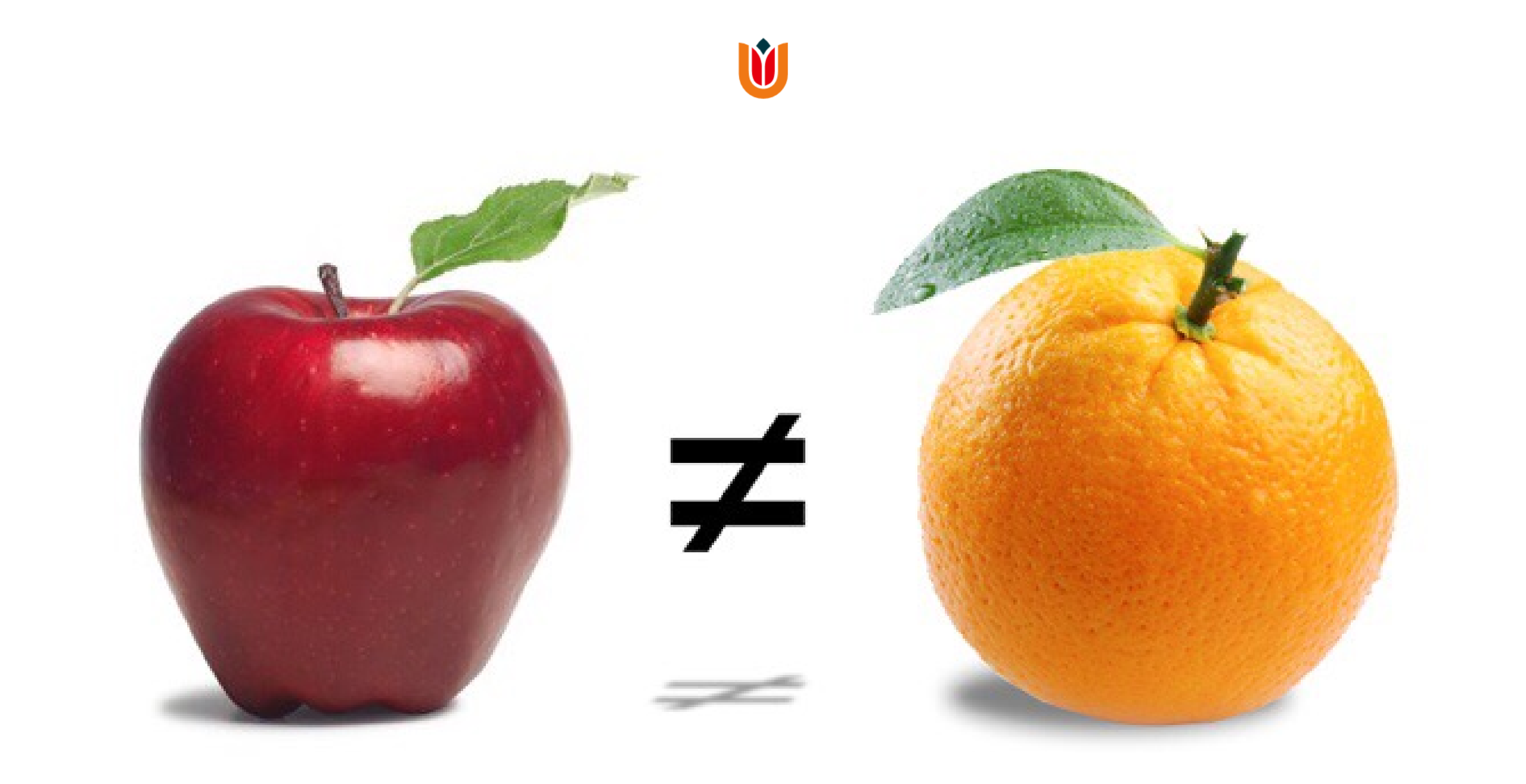
Response Assessment in Pediatric Rhabdomyosarcoma: Can Response Evaluation Criteria in Solid Tumors Replace Three-dimensional Volume Assessments?[1]

Reineke A. Schoot, MD
Kieran McHugh, MD
Rick R. van Rijn, MD, PhD
Leontien C. M. Kremer, MD, PhD
Julia C. Chisholm, MD, PhD
Huib N. Caron, MD, PhD
Johannes H. M. Merks, MD, PhD

Radiology: Volume 269: Number 3—December 2013

EpSSG Guidelines	Unadjusted RECIST			
	CR (100% Decrease)	PR (≥30% but <100% Decrease)	SD (Neither PR nor PD)	PD (≥20% Increase)
CR (100% decrease)	0	0	0	0
PR (≥66% but <100% decrease)	0	35	5	0
mPR (>33% but <66% decrease)	0	3	9	0
SD (neither mPR nor PD)	0	0	11	0
PD (≥40% increase)	0	0	1	0

Note.—CR = complete remission, mPR = minor partial response, PD = progressive disease, PR = partial response, SD = stable disease.

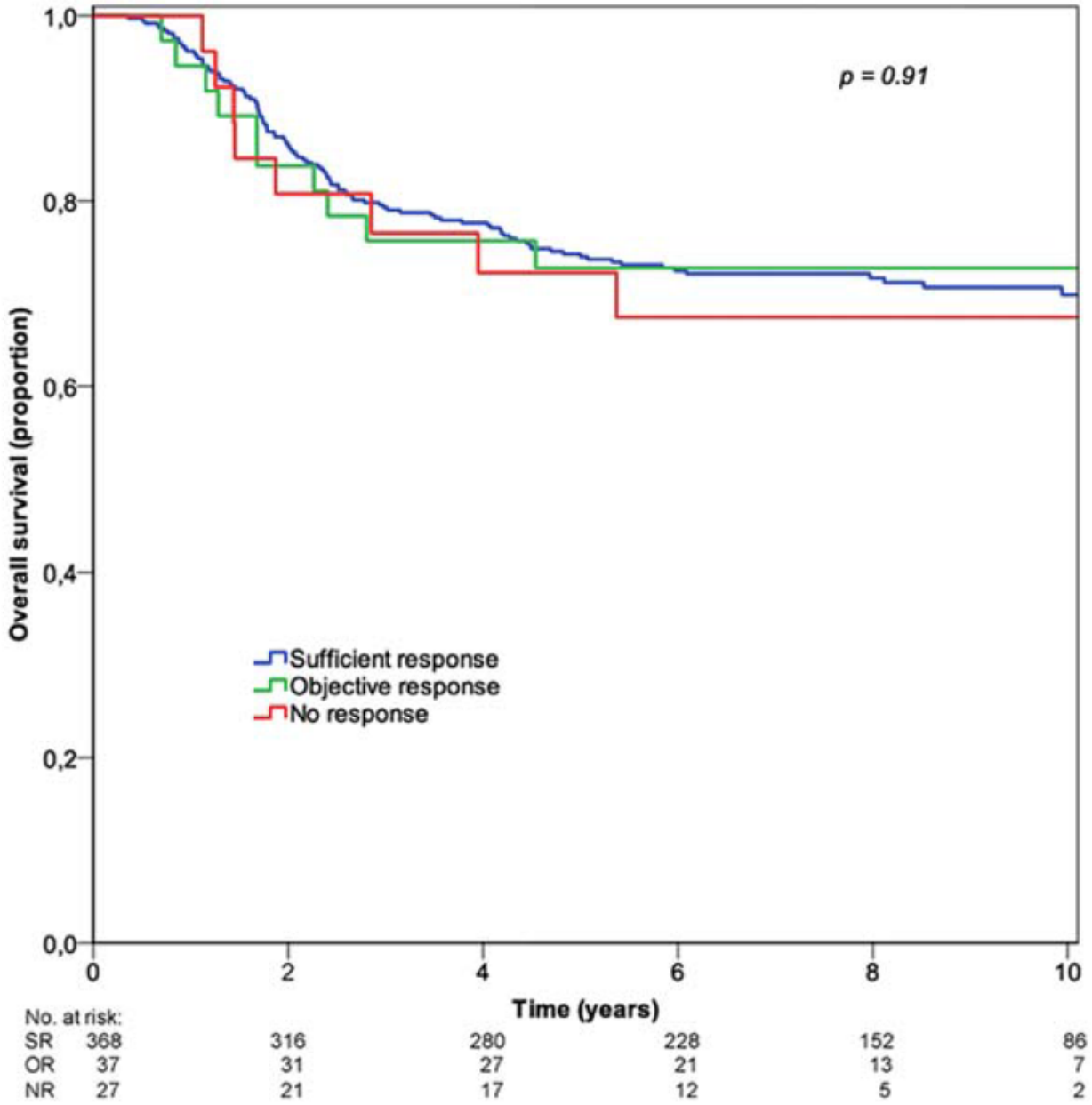


Different treatment decisions in 14 patients (22%; 95% CI: 12-32)

Cancer March 1, 2018

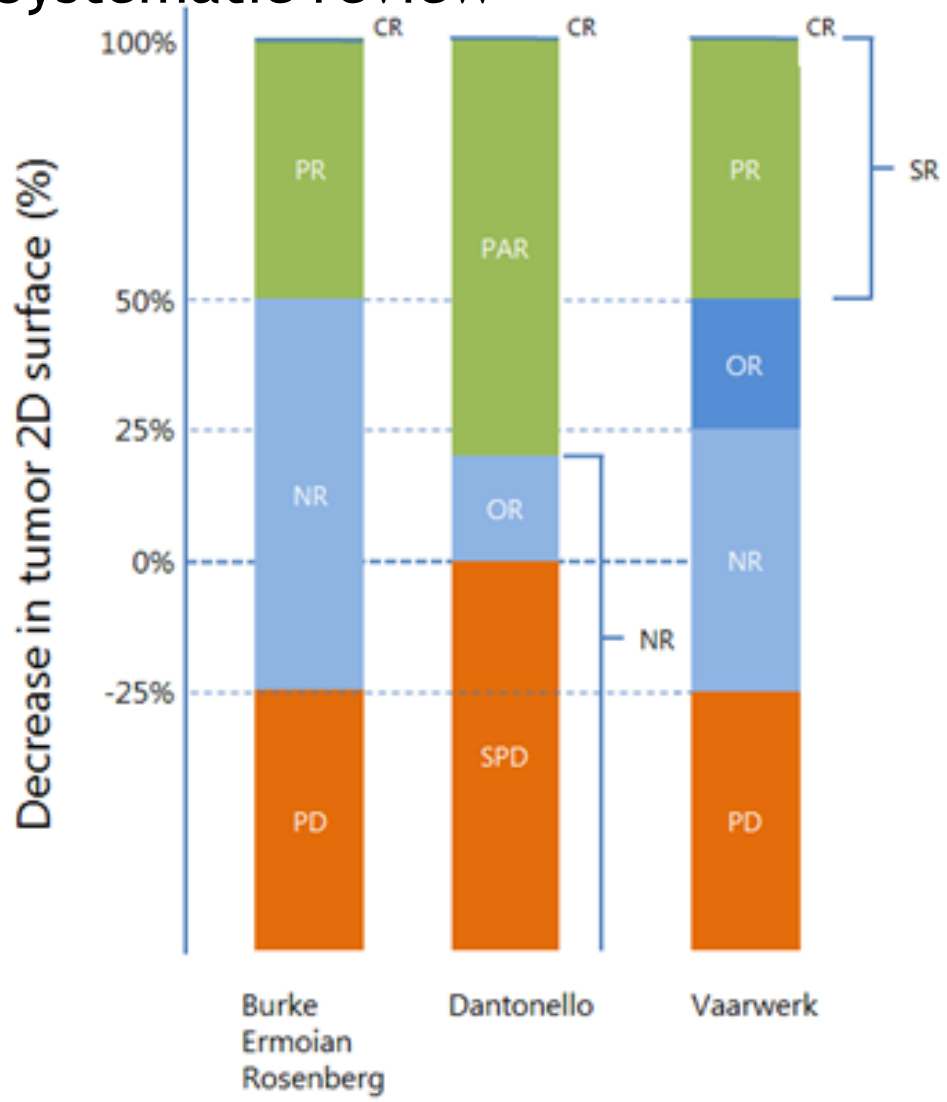
Prognostic Relevance of Early Radiologic Response to Induction Chemotherapy in Pediatric Rhabdomyosarcoma: A Report From the International Society of Pediatric Oncology Malignant Mesenchymal Tumor 95 Study

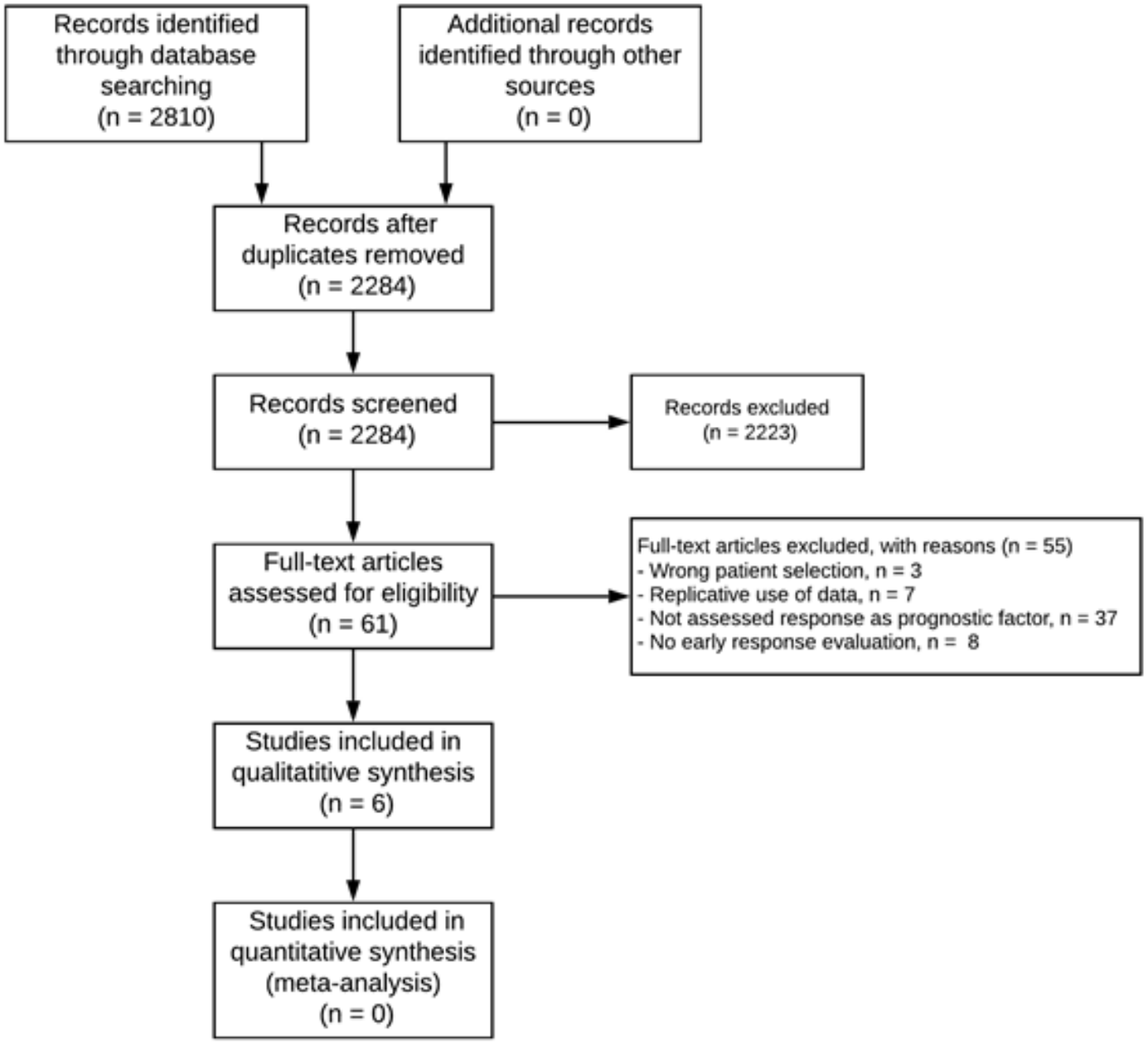
Bas Vaarwerk, MD[1]; Johanna H. van der Lee, MD, PhD[2]; Willemijn B. Breunis, MD, PhD[1]; Daniel Orbach, MD[3]; Julia C. Chisholm, MD, PhD[4]; Nathalie Cozic, MSc[5]; Meriel Jenney, MD[6]; Rick R. van Rijn, MD, PhD[7]; Kieran McHugh, MD[8]; Soledad Gallego, MD, PhD[9]; Heidi Glosli, MD, PhD[10]; Christine Devalck, MD[11]; Mark N. Gaze, MD[12]; Anna Kelsey, MD[13]; Christophe Bergeron, MD[14]; Michael C. G. Stevens, MD[15]; Odile Oberlin, MD[16]; Veronique Minard-Colin, MD, PhD[16]; and Johannes H. M. Merks, MD, PhD[1]



NR, no response; OR, objective response; SR, sufficient response.

- Systematic review





CR – Complete Response; PR/PAR – Partial Response; OR – Objective Response; NR – No Response; SPD – Stable/Progressive Disease; PD – Progressive Disease; SR – Sufficient Response

Rhabdomyosarcoma – Treatment response

- Patient outcome as parameter!

- 6 studies
  - 2 show response is an outcome parameter
    - PD included.
  - 4 show response is no outcome parameter
    - PD excluded.

➲ PD is a prognostic factor for poor outcome!

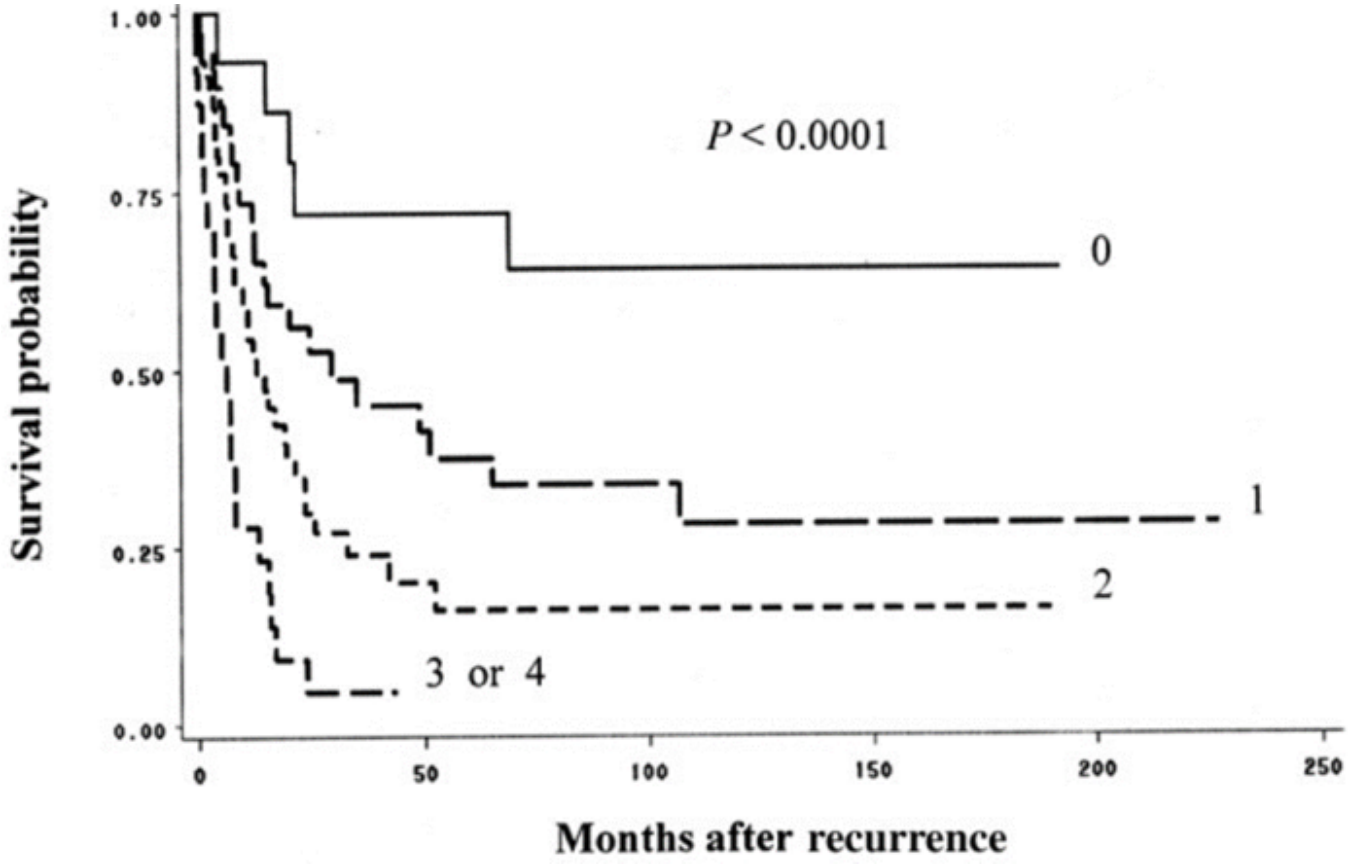
1) Alveolar subtype
2) Parameningeal or “other” sites
3) Systemic recurrence
4) Recurrence on therapy

Rhabdomyosarcoma – Follow-up

EpSSG-RMS 2005 protocol.

Standardized follow-up:

- Y1: @ 3 months
- Y2: @ 4 months
- Y3: @ 4 months
- Y4: @ 12 months
- Y5: @ 12 months



Mazzoleni S, et al. Cancer. 2005 Jul 1;104(1):183-90.

SCAN • XIETY

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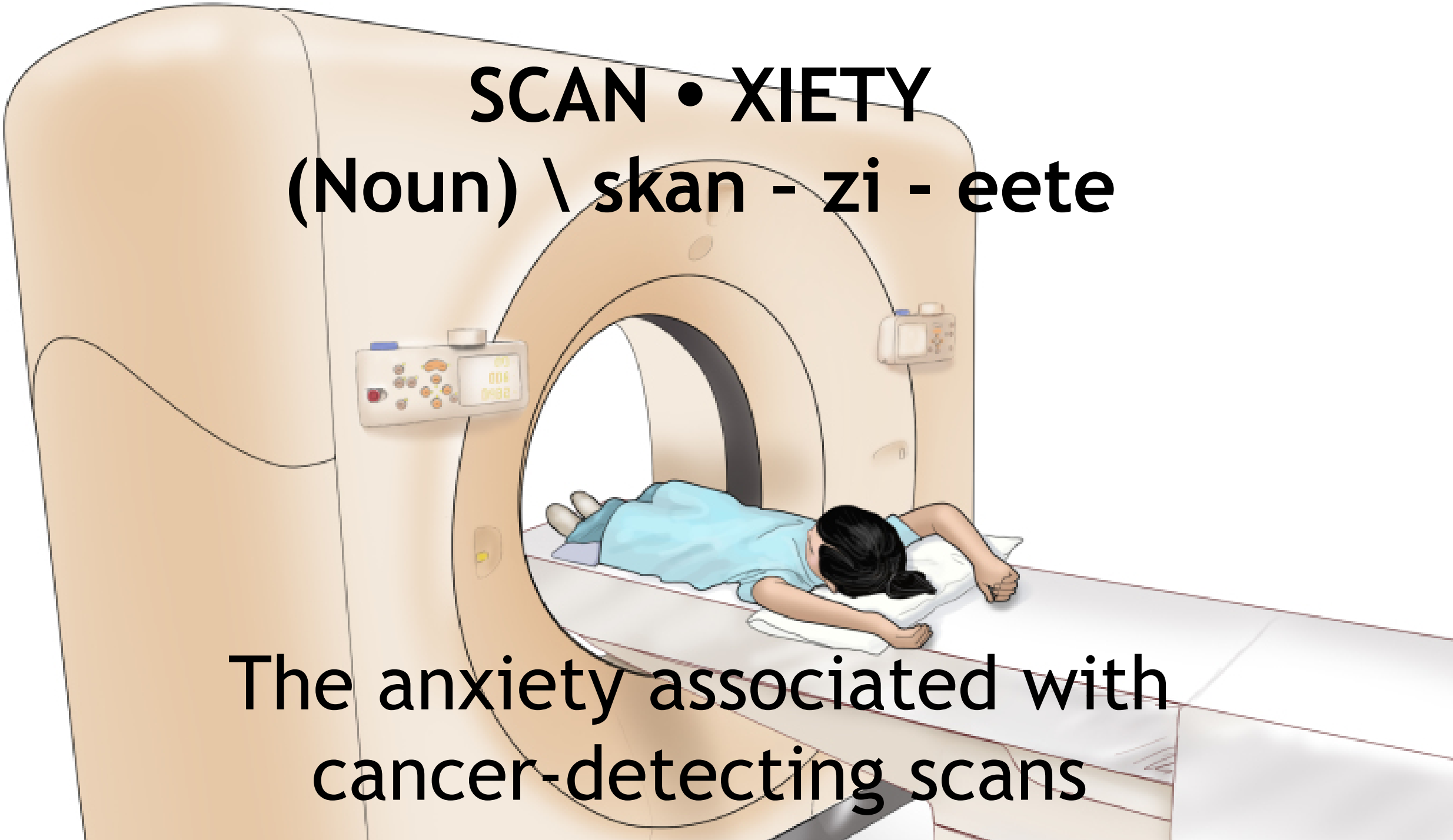


The anxiety associated with cancer-detecting scans

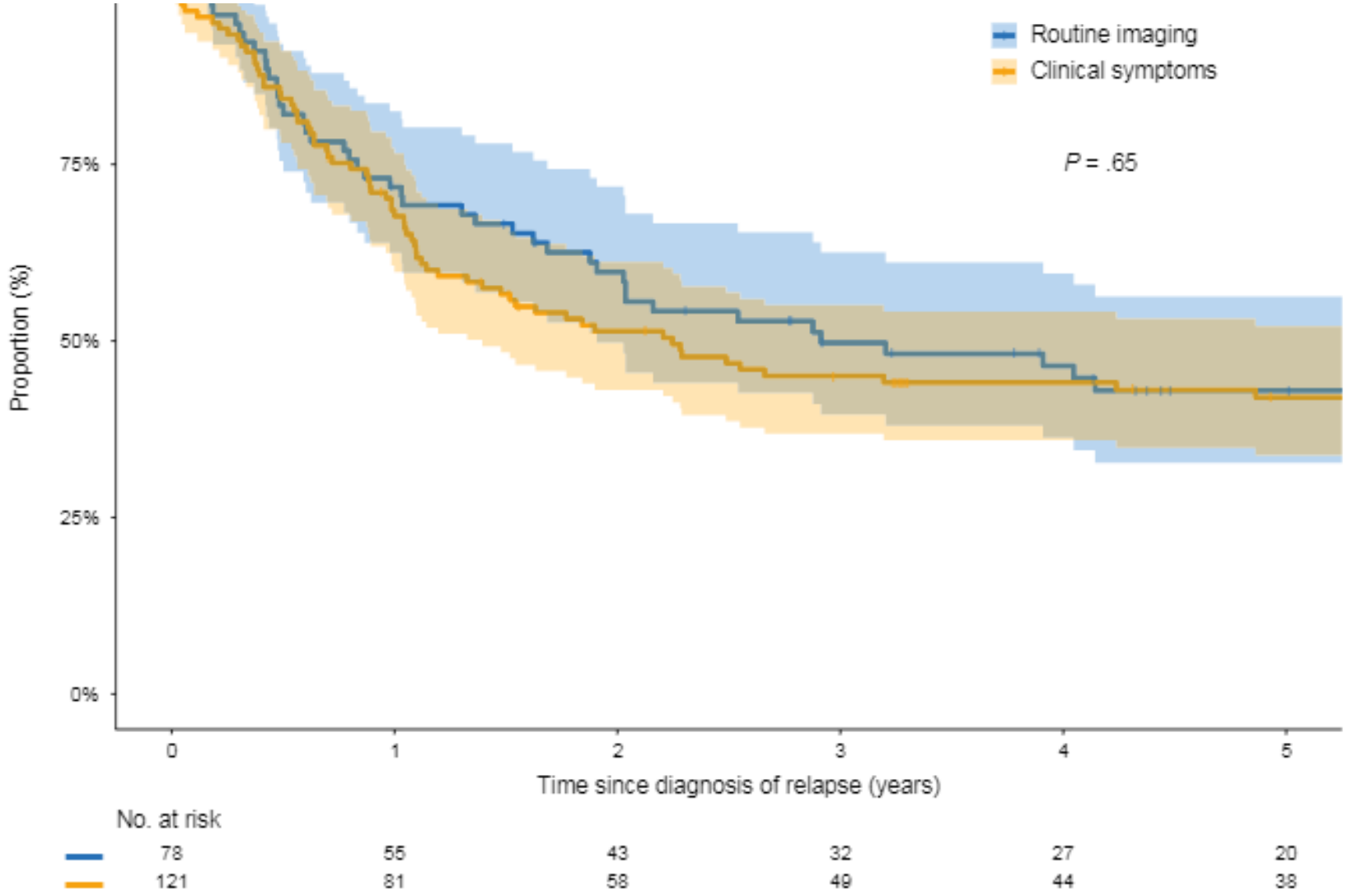
Rhabdomyosarcoma – Scanxiety

Mother, RMS, 35 months	"The first year, I was getting nervous a month before the follow-up"
Mother, ES, 50 months	"You just want the five years to get over"
Father, RMS, 29 months	"On the day of the imaging I am always more agitated"
Mother, RMS, 12 months	"You get more confident over the years"
Father, ES, 50 months	"Especially the first few times I was really anxious"
Mother, ES, 51 months	"It would be nice if the different specialists would also discuss their individual advice with each other"
Mother, ES, 52 months	"I know that the outpatient clinic from our oncologist is open on Monday and Friday, so we always arrange the imaging on Friday to have the results on Monday."

Vaarwerk B, et al. Support Care Cancer. 2019 Oct;27(10):3841-3848.

Is Surveillance Imaging in Pediatric Patients Treated for Localized Rhabdomyosarcoma Useful? The European Experience

Bas Vaarwerk, MD [1,2]; Coralie Mallebranche, MD[3]; Maria C. Affinita, MD[4]; Johanna H. van der Lee, MD, PhD[5]; Andrea Ferrari, MD[6]; Julia C. Chisholm, MD, PhD[7]; Anne-Sophie Defachelles, MD[8]; Gian Luca De Salvo, MD[9]; Nadège Corradini, MD[10]; Veronique Minard-Colin, MD, PhD [11]; Carlo Morosi, MD[6]; Hervé J. Brisse, MD, PhD[3,12]; Kieran McHugh, MB[13]; Gianni Bisogno, MD, PhD [4]; Rick R. van Rijn, MD, PhD [14]; Daniel Orbach, MD[3]; and Johannes H. M. Merks, MD, PhD [1,2]

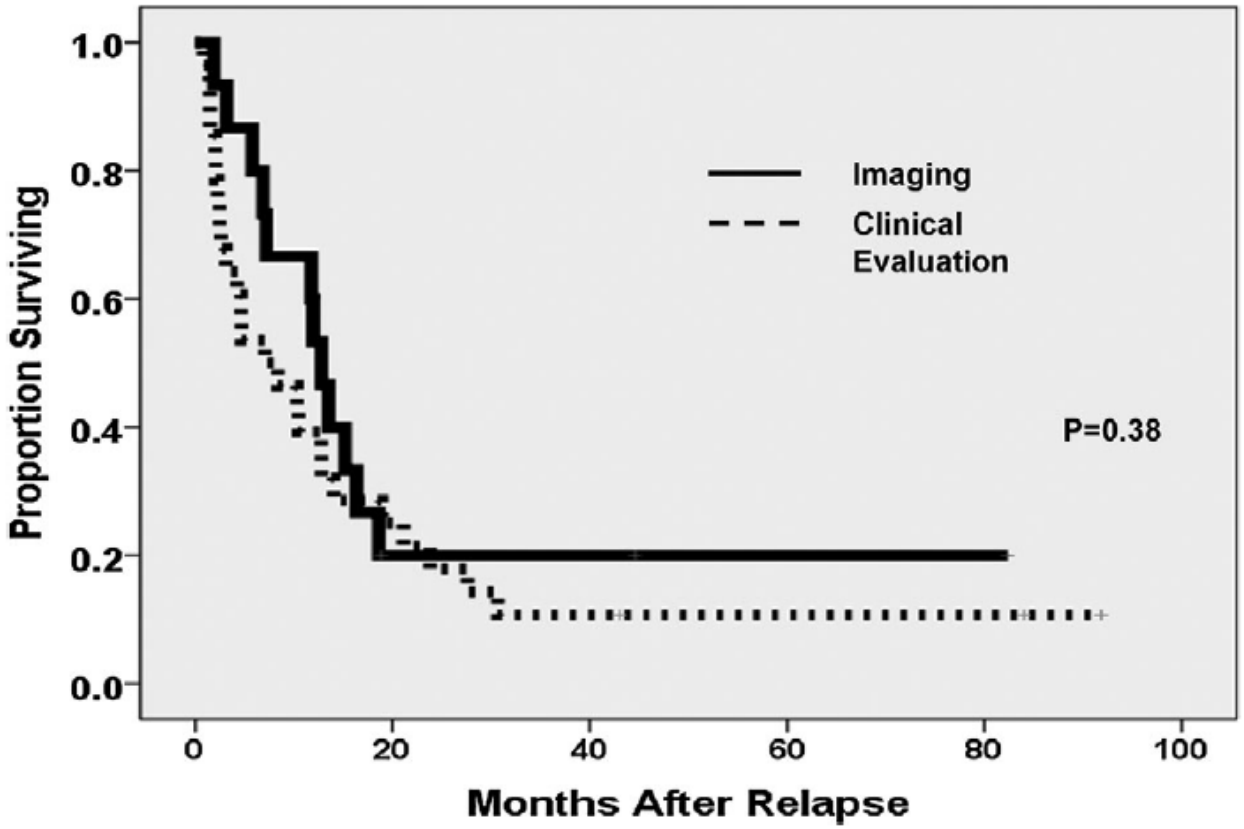


Overall survival after relapse (including 95% confidence intervals)

Pediatr Blood Cancer 2016;63:202–205

Does Routine Imaging of Patients for Progression or Relapse Improve Survival in Rhabdomyosarcoma?

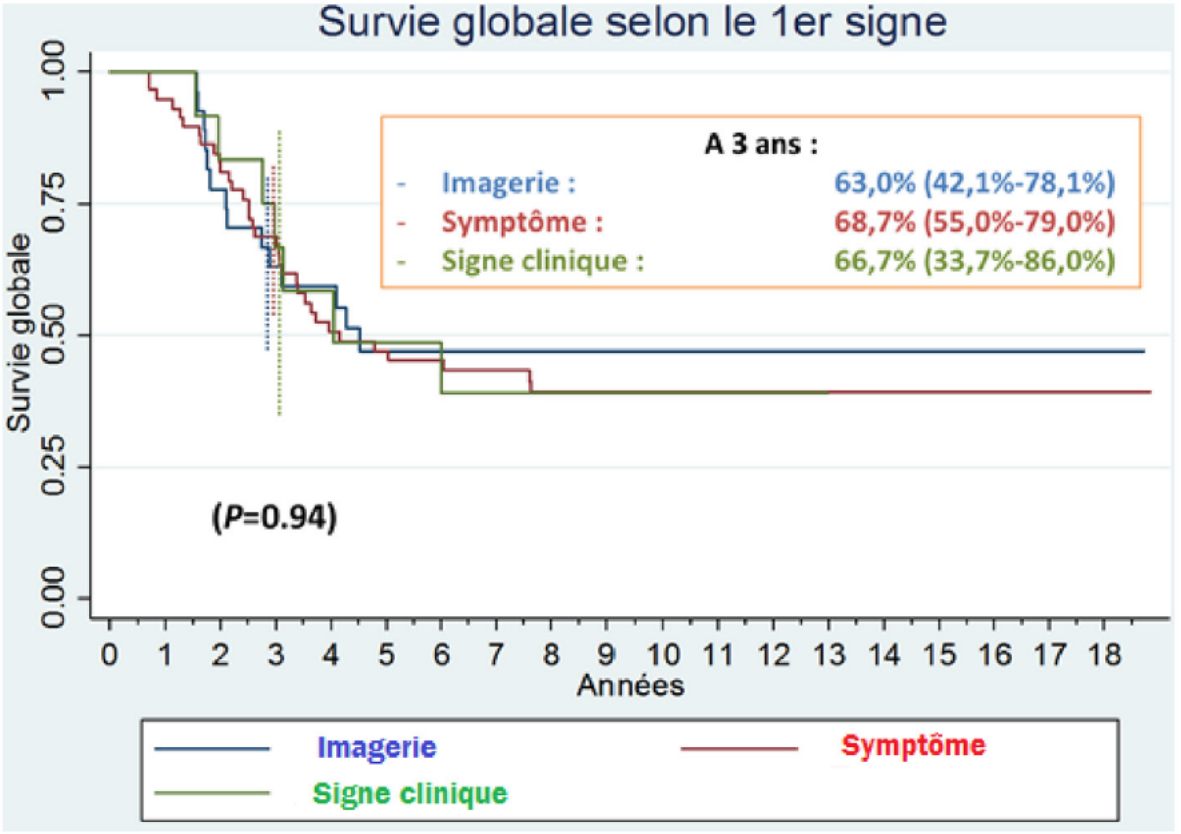
Jody L. Lin, MD,[1] R. Paul Guillerman, MD,[2] Heidi V. Russell, MD,[3] Philip J. Lupo, PhD,MPH,[3] Lauren Nicholls, MD,[3] and M. Fatih Okcu, MD, MPH[3]*



Bull Cancer 2017

Rôle de la surveillance dans la détection précoce et la survie après rechute d'un rhabdomyosarcome de l'enfant et de l'adolescent

Coralie Mallebranche [1,8], Matthieu Carton [2], Véronique Minard-Colin [3], Anne-Sophie Desfachelle [4], Angélique Rome [5], Hervé J. Brisse [6], Véronique Mosseri [2], Estelle Thébaud [7], Isabelle Pellier [8], Hélène Boutroux [9], Virginie Gandemer [10], Nadège Corradini [11], Daniel Orbach [1]



Rhabdomyosarcoma – Ongoing research

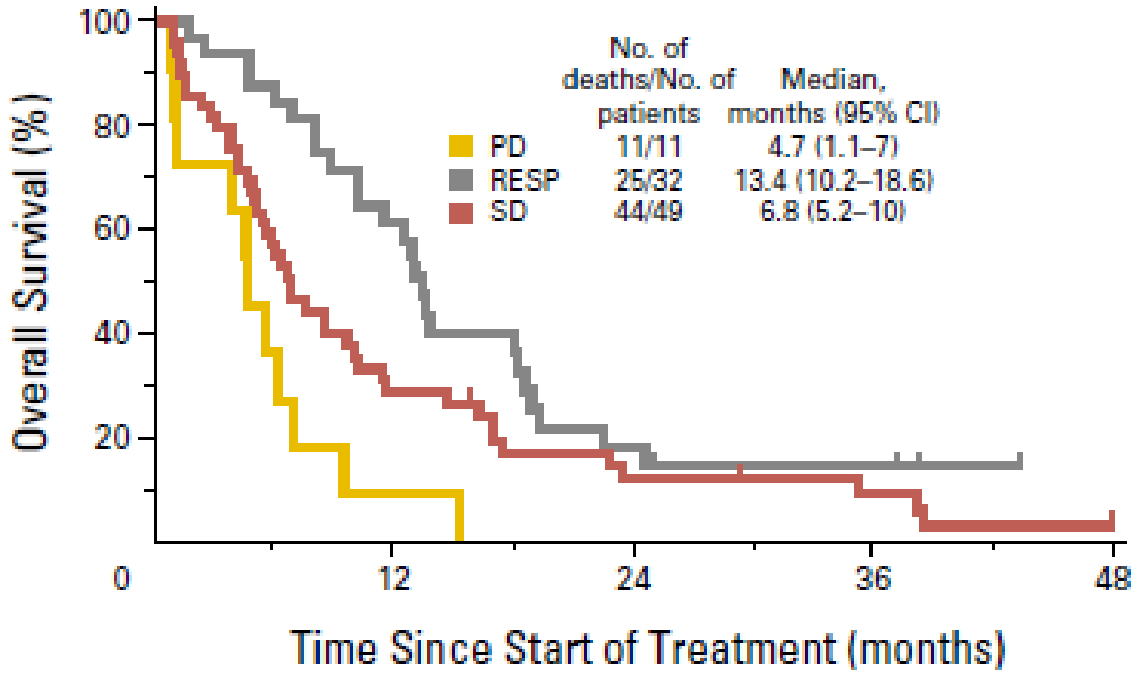
FaR-RMS

An overarching study for children and adults with Frontline and Relapsed RhabdoMyoSarcoma

Estimated Enrollment: 1,672 participants

Rhabdomyosarcoma – Ongoing research

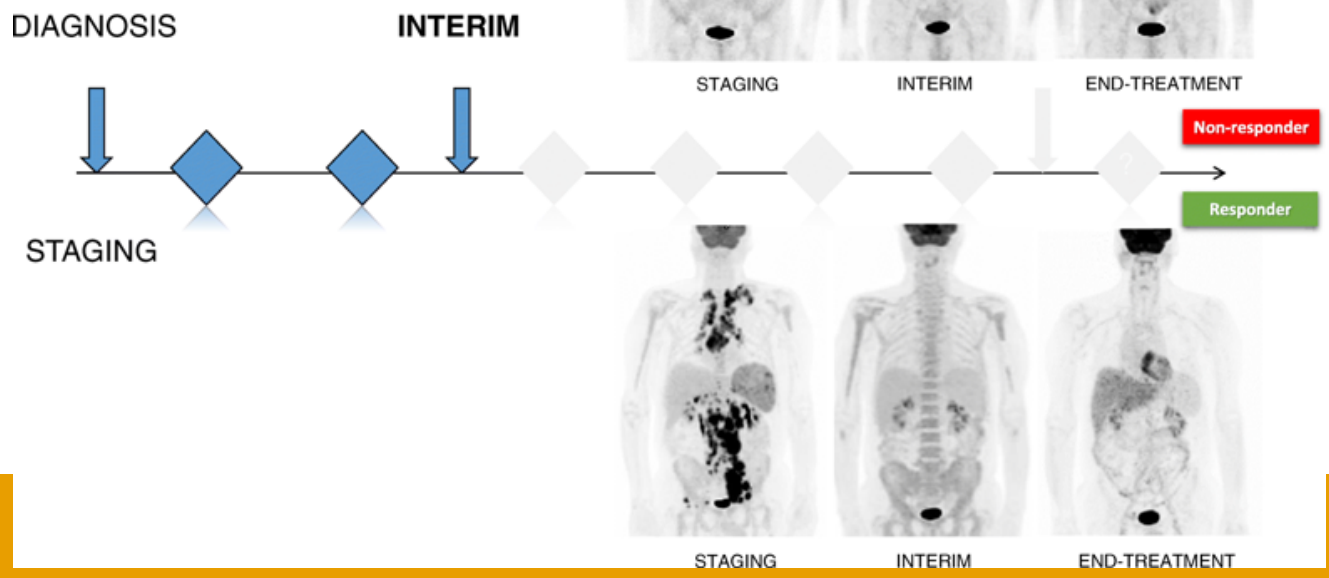
- FDG PET-CT sub-study
  - Leads: Nina Jehanno, Bart de Keizer, Lise Borgwardt, Arthur Braat & Simon Wan
- Response assessment according to:
  - PERCIST 1.0 criteria.



Rhabdomyosarcoma – Ongoing research

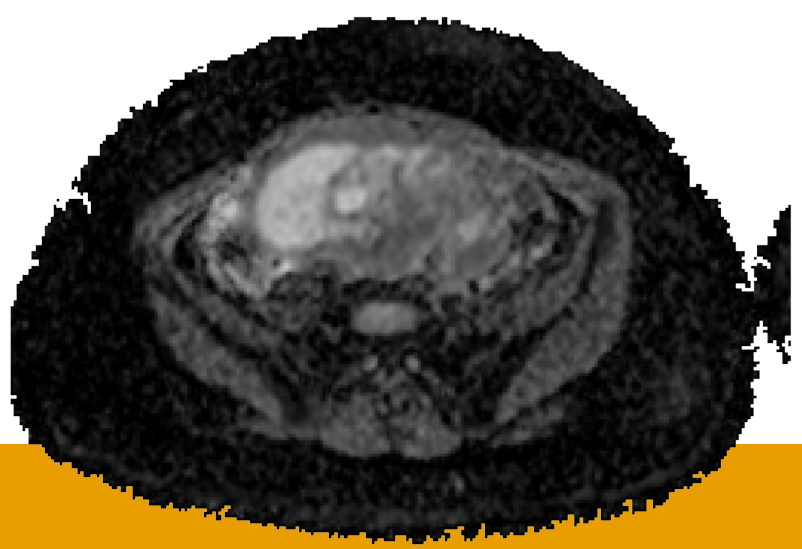
- FDG PET-CT sub-study
  - Leads: Nina Jehanno, Bart de Keizer, Lise Borgwardt, Arthur Braat & Simon Wan

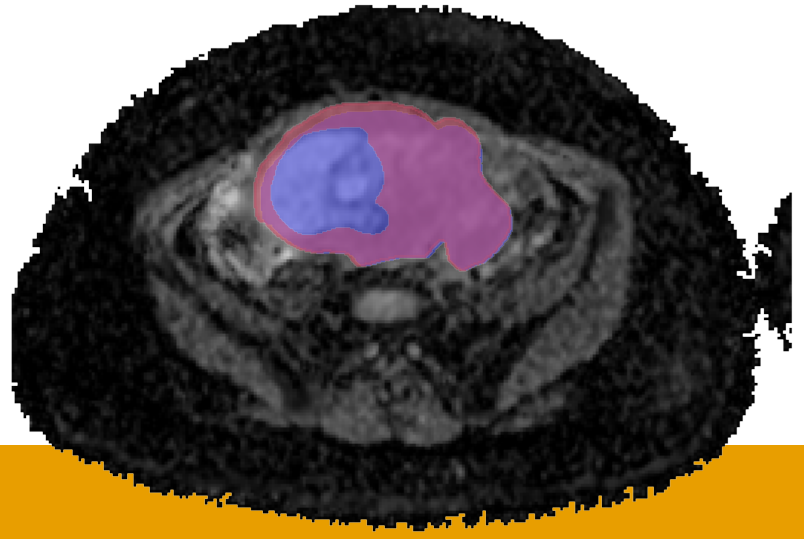
- Response assessment according to:
  - PERCIST 1.0 criteria.
  - Visual ‘Deauville like’ criteria.



Rhabdomyosarcoma – Ongoing research

- MRI DWI sub-study
  - PhD students: Roelof van Ewijk, Isabelle de Vries, Laura Adriaanse, Cyrano Chatziantoniou
  - Leads: Reineke Schoot, Alberto de Luca, Alexander Leemans, Hans Merks, Rick van Rijn





We need YOU!

Thanks for your attention