RETINOMICS, multimodal analysis of retinoblastoma: correlations between morphological MRI, radiomic analysis and molecular profiles of tumors

SARAH MEZGHANI

11/04/22

Epidemiology

- Retinoblastoma: the most common intraocular malignancy of infancy
- Incidence of 1/15,000 births
- Median age at diagnosis of 2 years

Aerts et al., Arch Pediatr. 2016

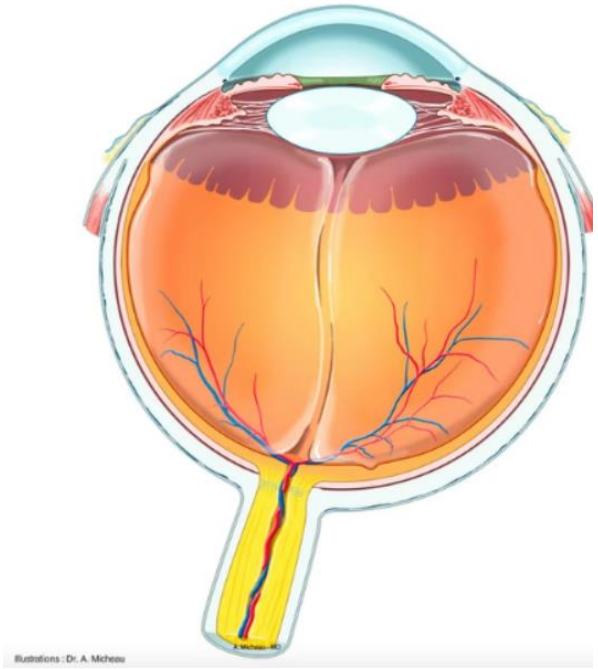
Clinical aspects

- Leukocoria (white reflection in the pupil) and strabismus : the most frequent clinical manifestations of retinoblastoma

Aerts et al., Arch Pediatr. 2016
COUF 2021

Origin

- Originating from a maturing cone precursor in the developing retina



Liu et al., *Nat Commun*, 2021

Imaios

Origin

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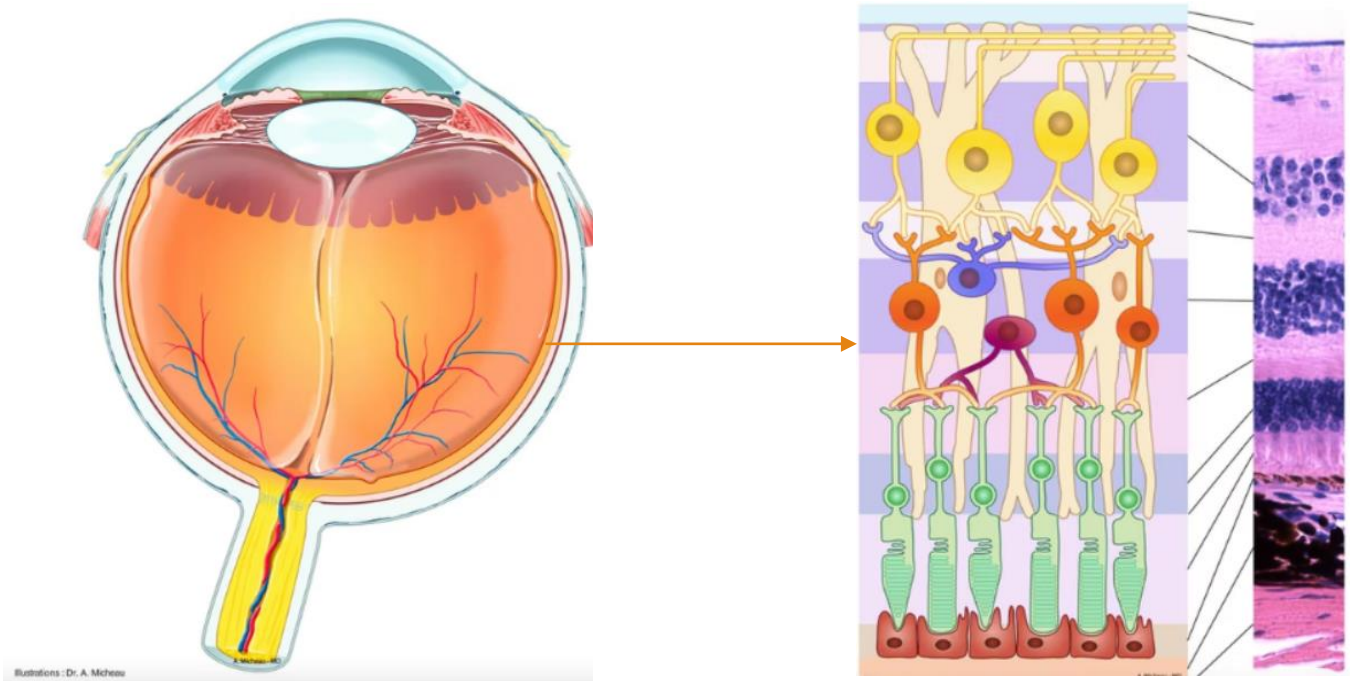
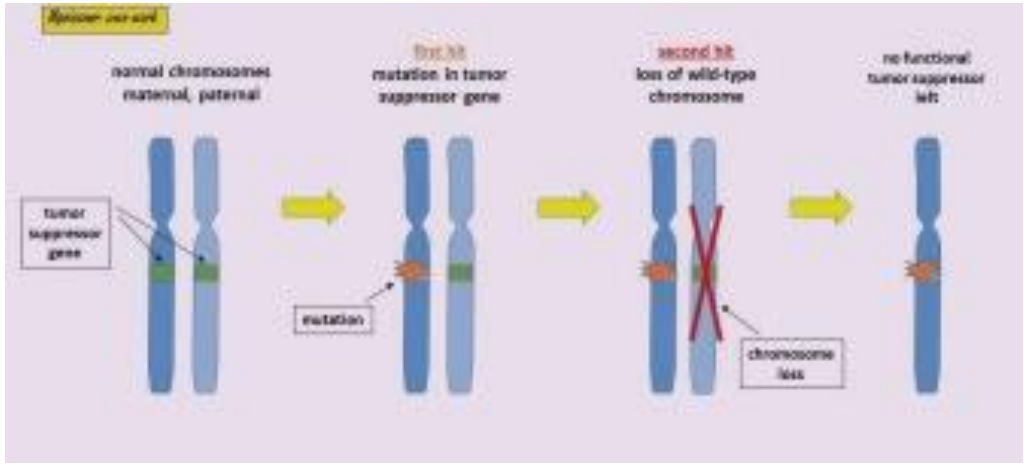


Liu et al., *Nat Commun*, 2021

Imaios

Genetic aspects

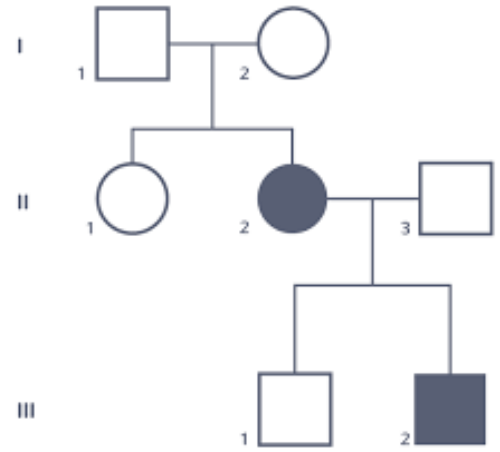
- Inactivation of the *RB1* tumor suppressor gene (13q14)
- Hereditary retinoblastomas (bilateral) versus non-hereditary cases (most unilateral)
- Autosomal dominant transmission with high penetrance



Indovina et al., oncotarget, 2015

Genetic aspects

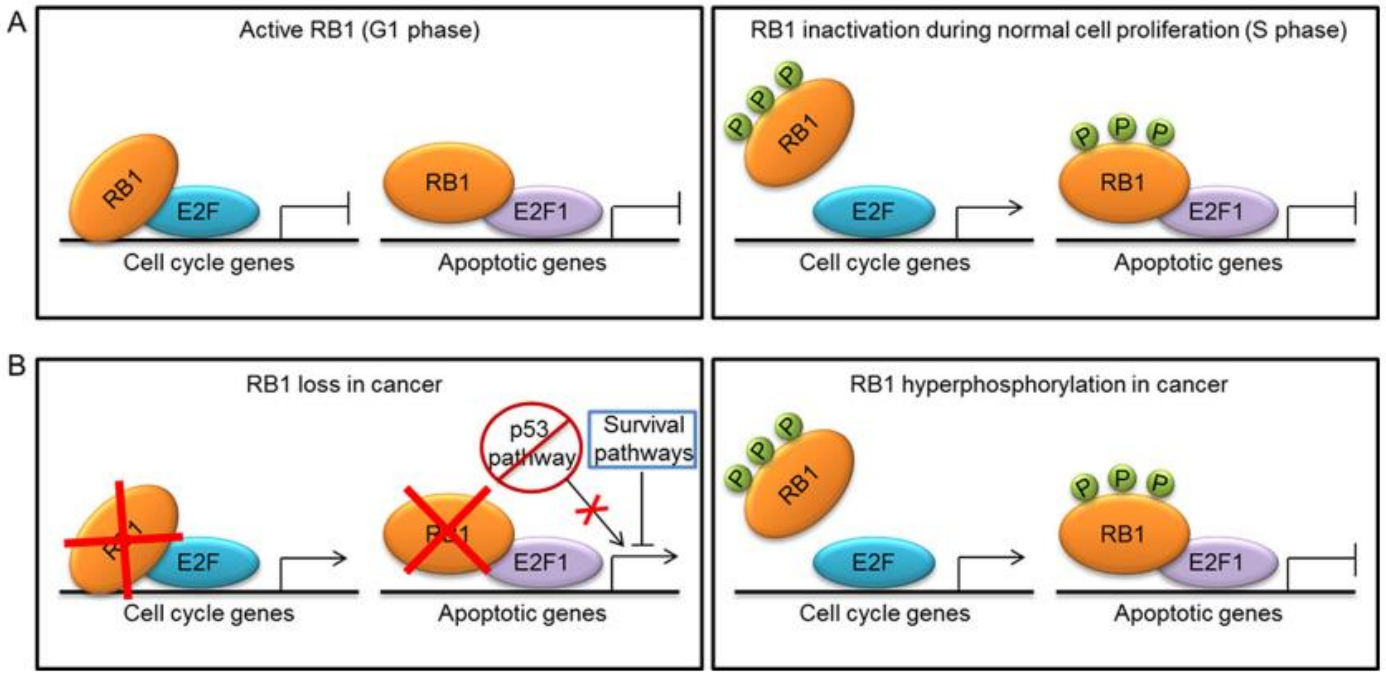
- Inactivation of the *RB1* tumor suppressor gene (13q14)
- Hereditary retinoblastomas (bilateral) versus non-hereditary cases (most unilateral)
- Autosomal dominant transmission with high penetrance
- ≠ Familial form with two case in a family



Indovina et al., oncotarget, 2015

Genetic aspects

- Biallelic inactivation of the *RB1* tumor suppressor gene (13q14)



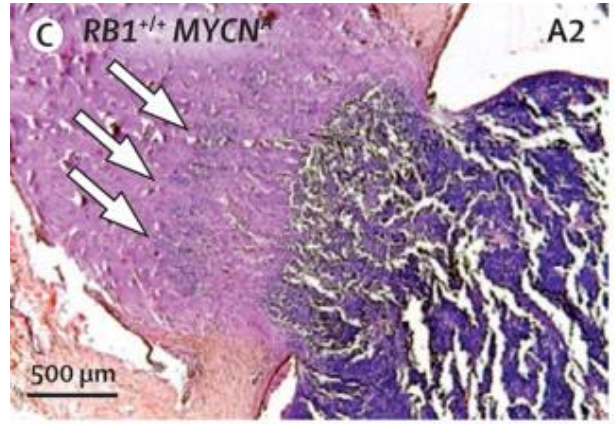
Indovina et al., oncotarget, 2015

Genetic aspects

Other alterations:

- *MYCN*-amplification without *RB1* inactivation (<2%)

- Positive correlation between high copy-number alterations, age at diagnosis, and other clinical and histopathological variables, including aggressivity and local invasion



Indovina et al., oncotarget, 2015

Rushlow et al., the lancet oncology, 2013

Molecular aspects

- The need of a better understanding of the the biology and clinical behavior of retinoblastoma

Liu et al., *Nat Commun*, 2021

Molecular aspects

- 3 centers (France, Argentina, Spain) with a total of 102 analysed retinoblastomas

- Multi-omics data with integrative analysis of
- Transcriptome
- Methylome
- DNA copy-number alteration

69/72 classified (subtype 1 or 2)

Liu et al., *Nat Commun*, 2021

Molecular aspects

- 3 centers (France, Argentina, Spain) with a total of 102 analysed retinoblastomas

- Multi-omics data with integrative analysis of
  - Transcriptome
  - Methylome
  - DNA copy-number alteration

→ 69/72 classified (subtype 1 or 2)

- Nine-CpG-based classifier

→ 27/30 classified (subtype 1 or 2)

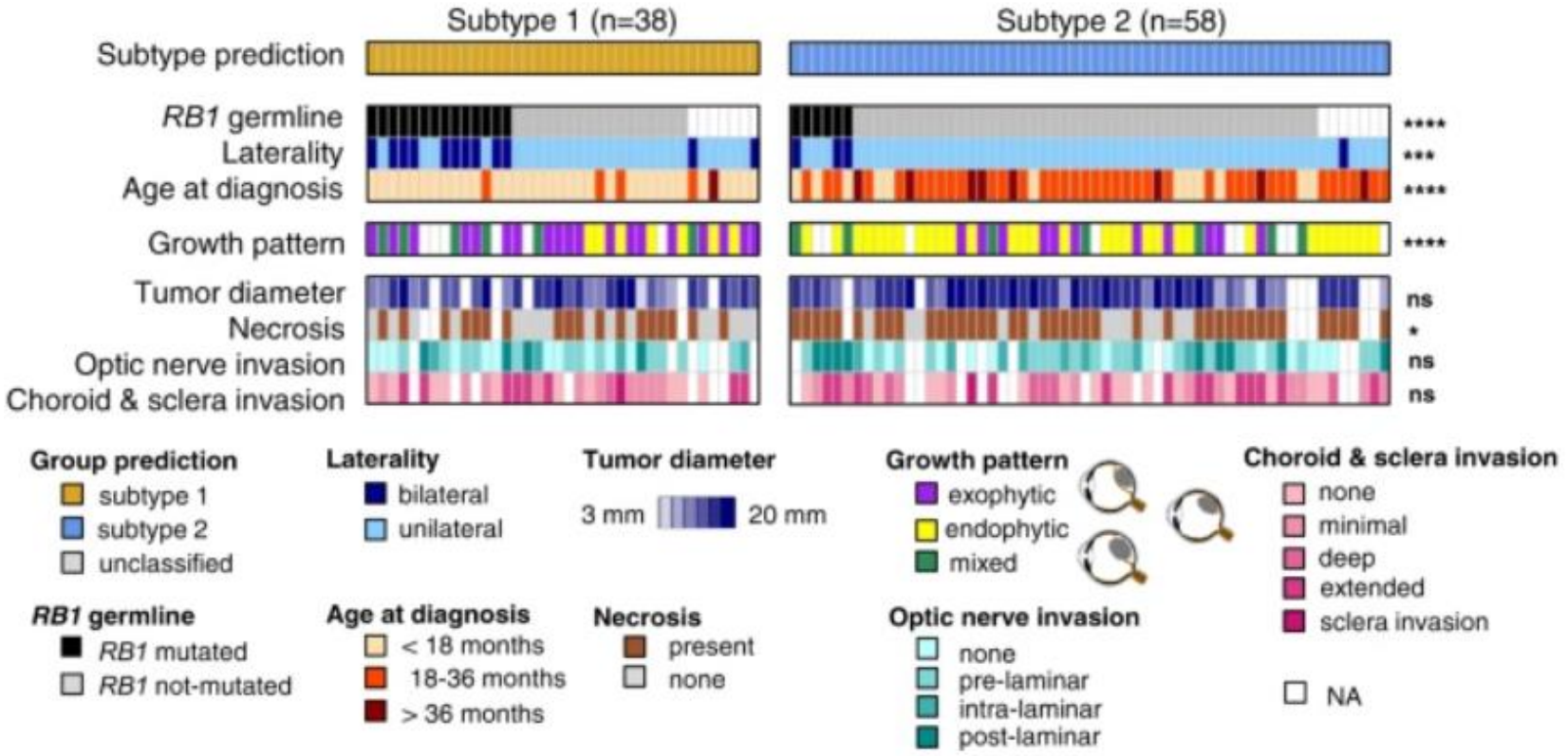
Liu et al., *Nat Commun*, 2021

Molecular aspects

- Two subtypes of retinoblastoma associated with different clinical and pathological features
- Arguments for a maturing cone precursor as the cell-of-origin of retinoblastoma

Liu et al., *Nat Commun*, 2021

Molecular Subtype

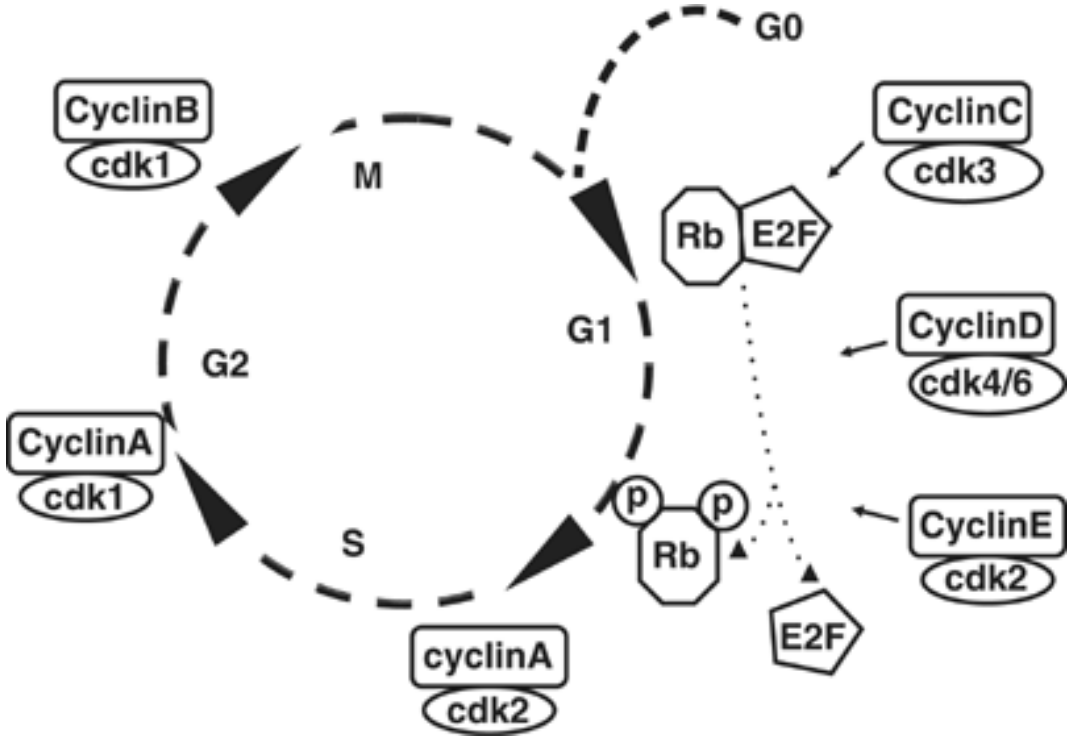


Liu et al., *Nat Commun*, 2021

Molecular Subtype

Subtype 1:

- Differentiated
- Bilateral
- Younger patients
- Rb1



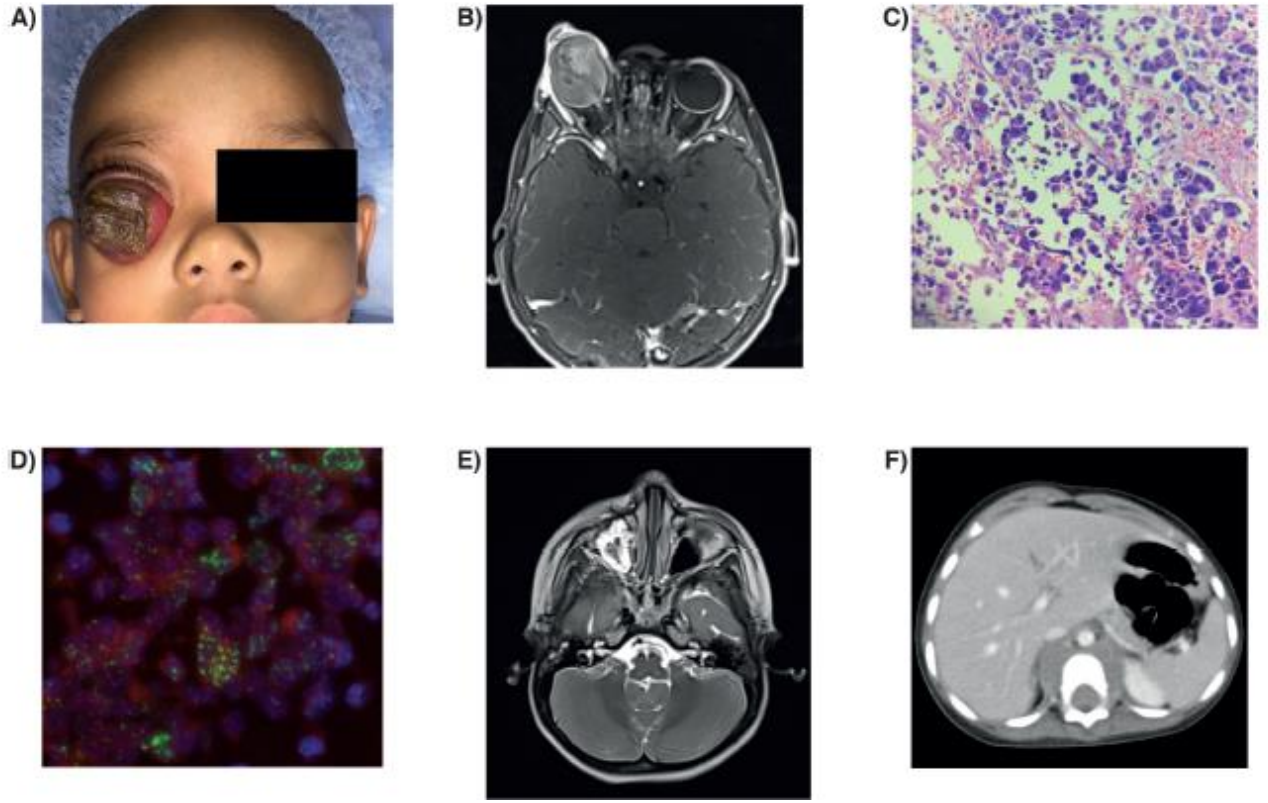
Liu, J et al., . *Nat Commun*, 2021

Molecular Subtype

Subtype 2:

- Less differentiated
- Expression of neuronal/ganglion cell markers
- Marked inter- and intratumor heterogeneity
- Other recurrent genetic alterations,including *MYCN* aplifications

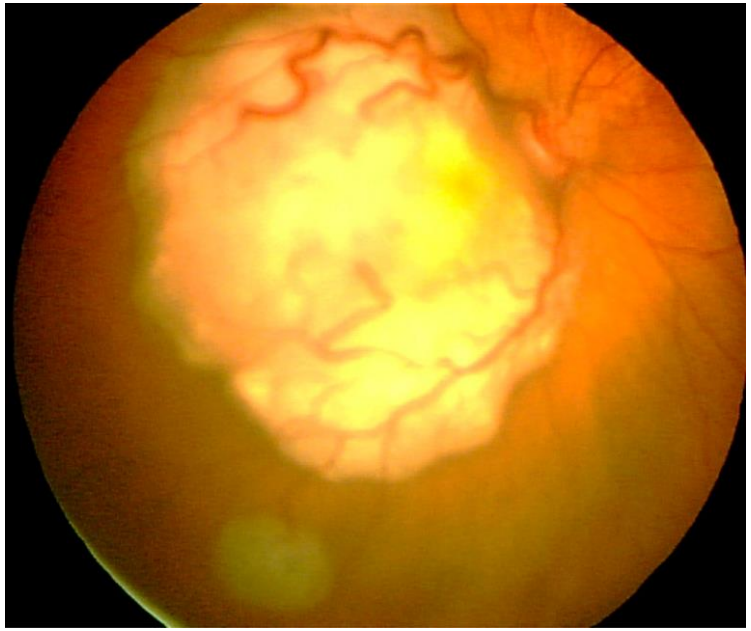
- Metastasis+



Liu, J et al., . *Nat Commun*, 2021
S. Zugbi et al., cancers, 2020

Diagnosis

- Diagnosis is made by fundoscopy with general anesthesia
- Memorization of images
- Specific wide-angle camera
- Precise assessment of intra ocular lesions:
  - Reese-Elworth
  - IRC



de Graaf, Pim et al., Pediatric radiology vol. 42,1 (2012)

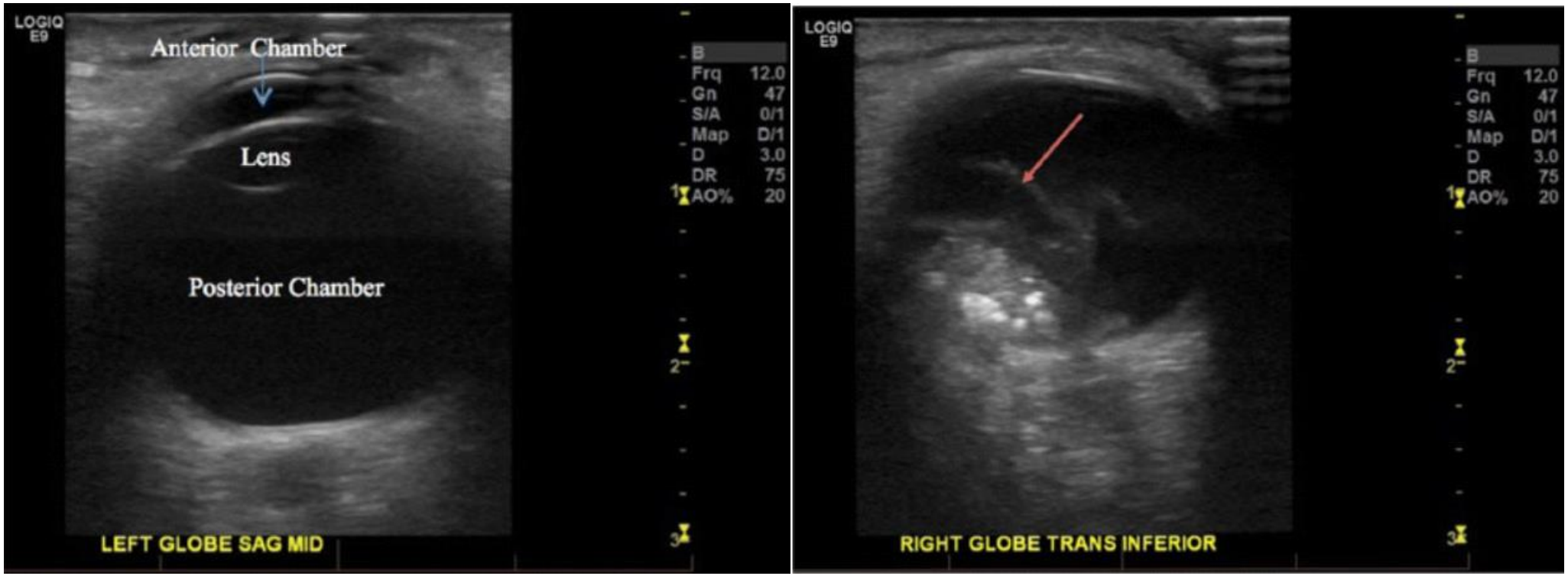
Imaging findings

- Ultrasound and magnetic resonance imaging (MRI) contributing both to diagnosis and assessment of the extension of the disease.

- Differential diagnosis:
  - Coats' disease
  - Persistent fetal vasculature
  - Retinal dysplasias

de Graaf, Pim et al., Pediatric radiology vol. 42,1 (2012)

US

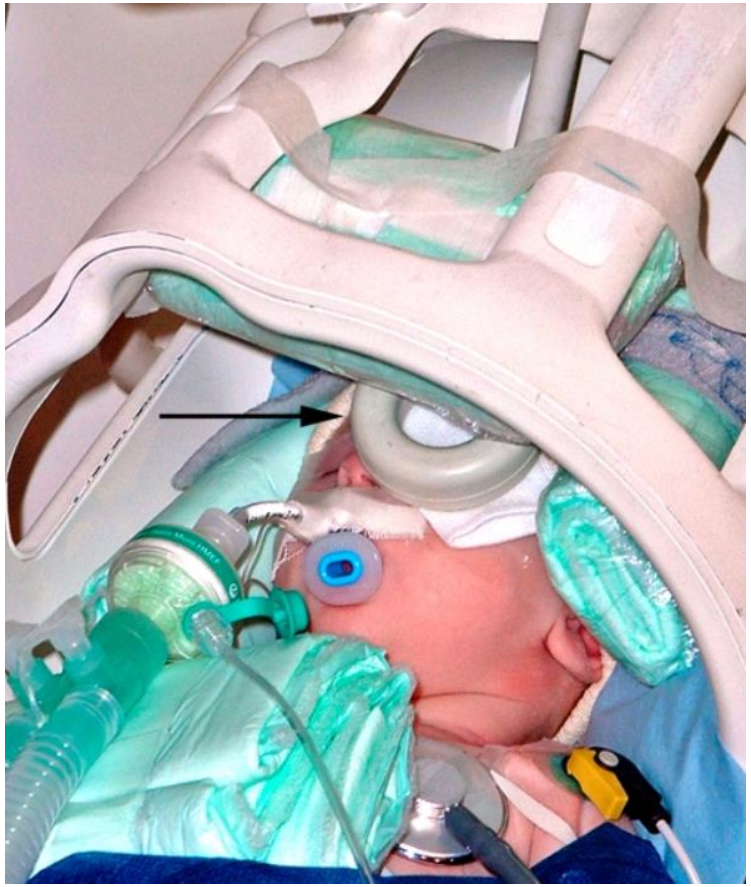


Sutton S et al., Journal of Diagnostic Medical Sonography. 2016

MRI

Protocole

- High-resolution MRI in retinoblastoma
- Under general anesthesia



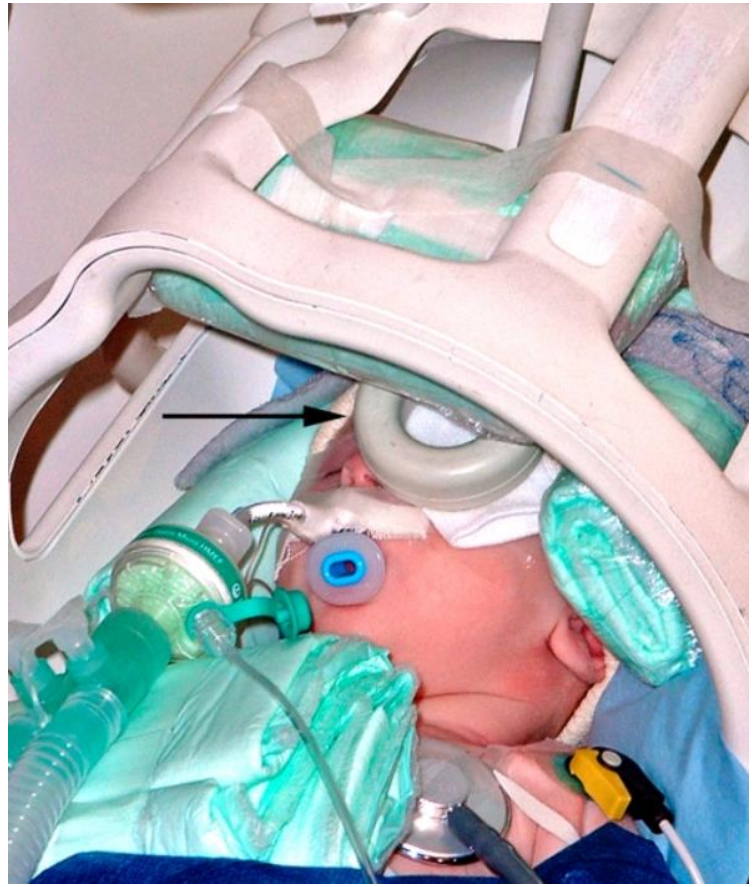
de Graaf P et al., Pediatr Radiol. 2012

Protocole

- Field strength above 1 T

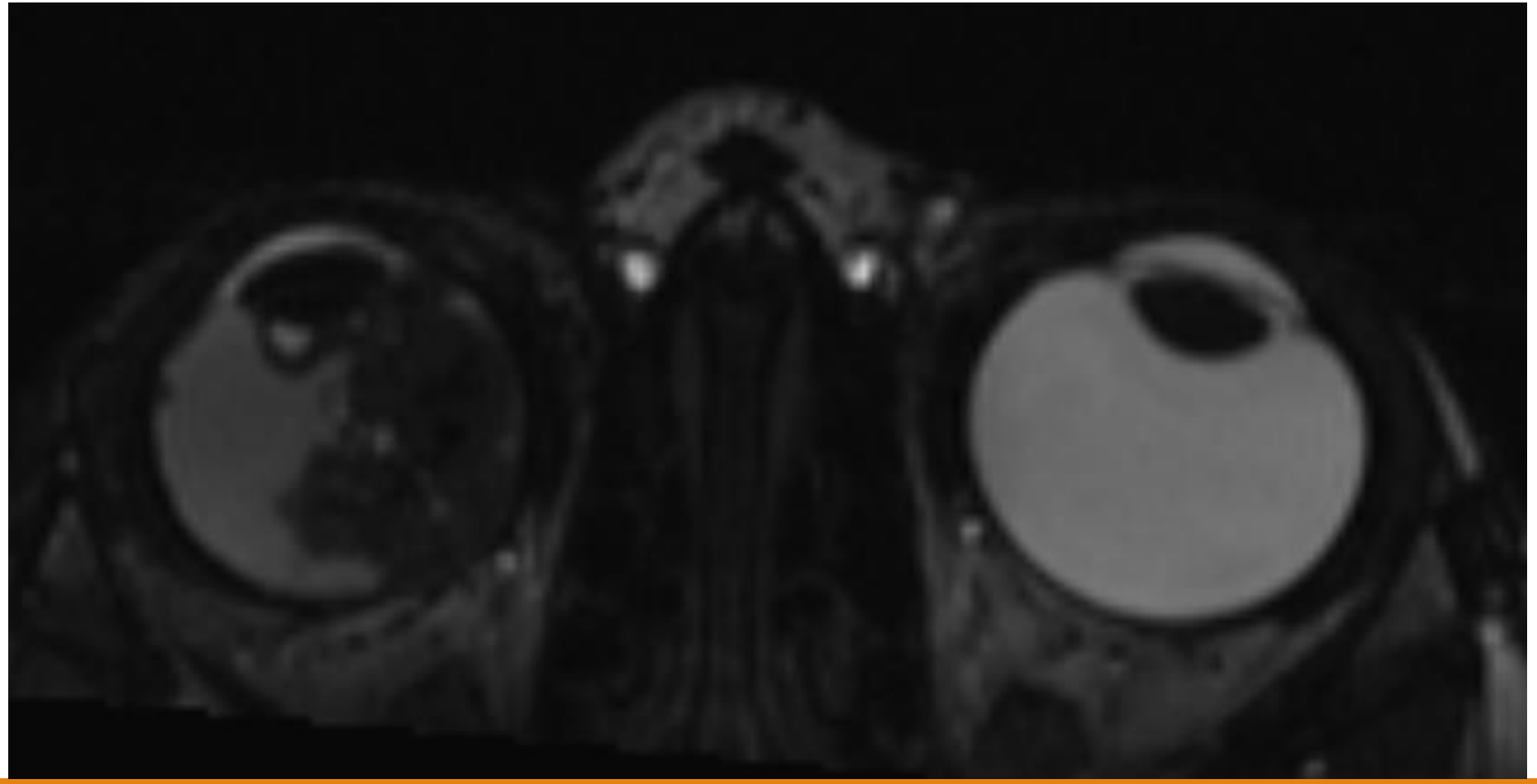
- 1.5-T system combined with one or two small surface coils, (diameter < 5 cm)

- 3.0-T system combined with multichannel head coil



de Graaf P et al., Pediatr Radiol. 2012

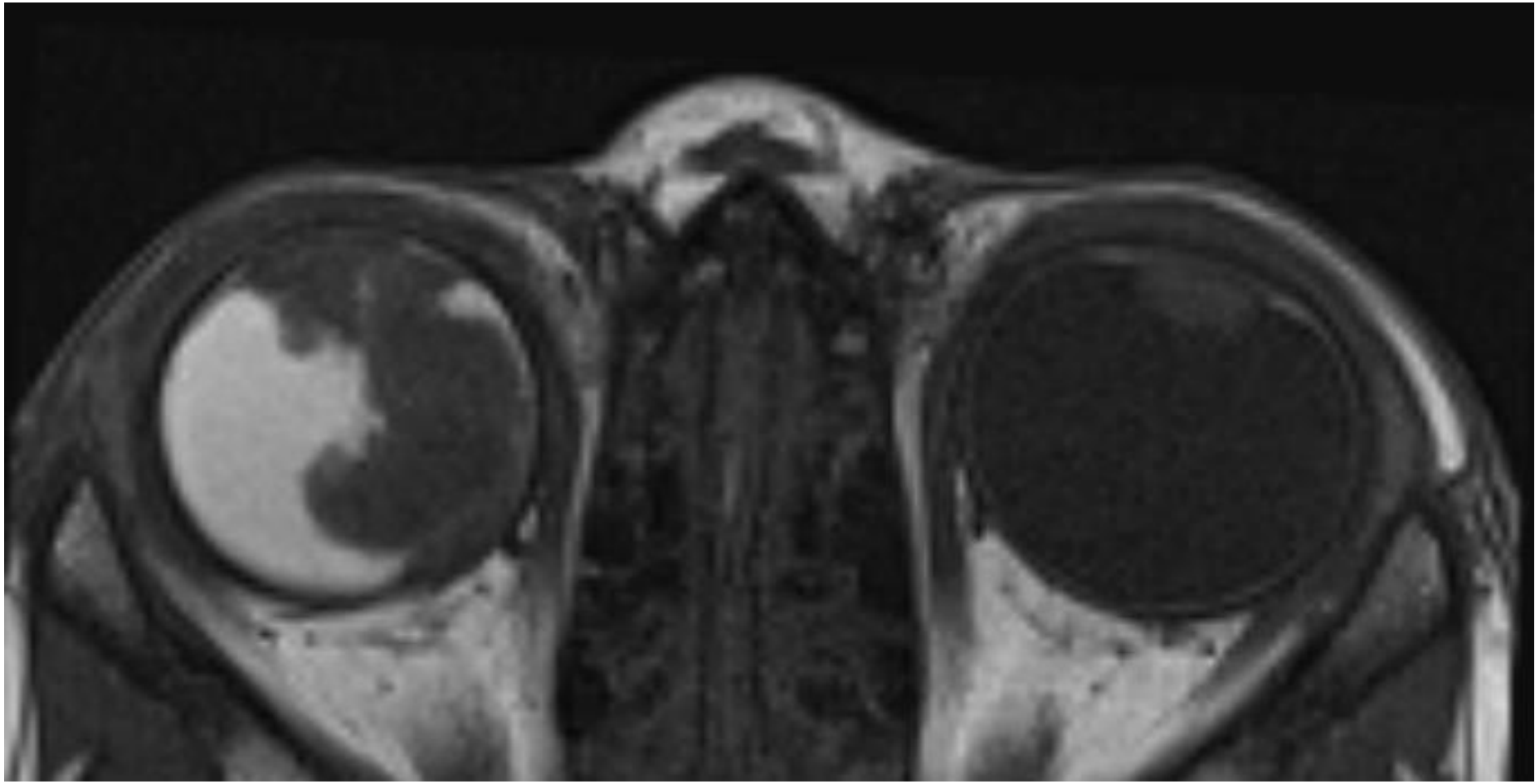
Transaxial T2-W



AX 3D CISS
iso_0.7 PETIT FOV
FLEX

- 1.5 T
- 63.6768
- 3D
- 0.7 mm
- TE 4.7 ms
- TR 11 ms

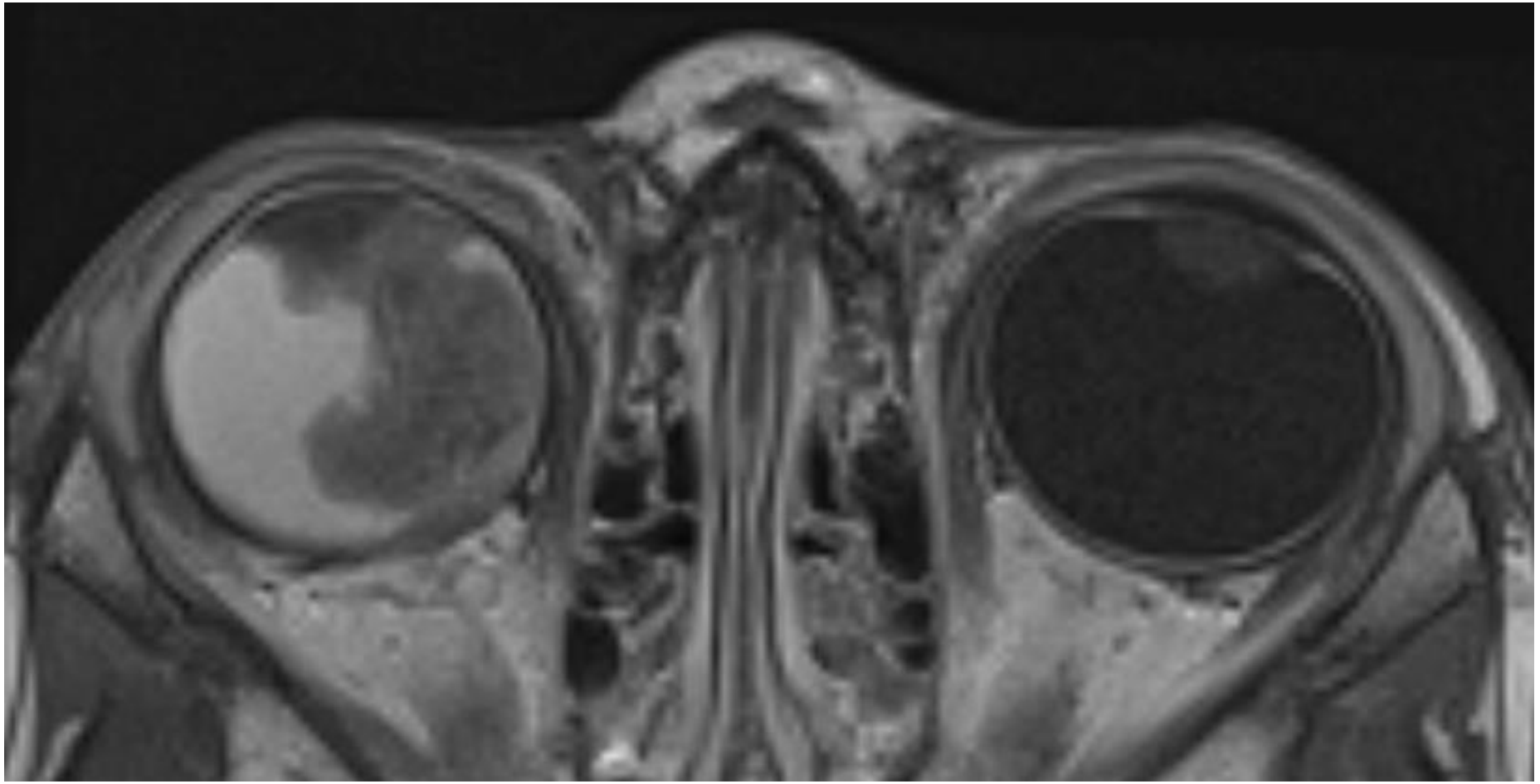
Precontrast T1-W



AX T1 SE FLEX 2 mm

- 1.5 T
- 63.6768
- 2D
- 2 mm
- TE 12 ms
- TR 331 ms

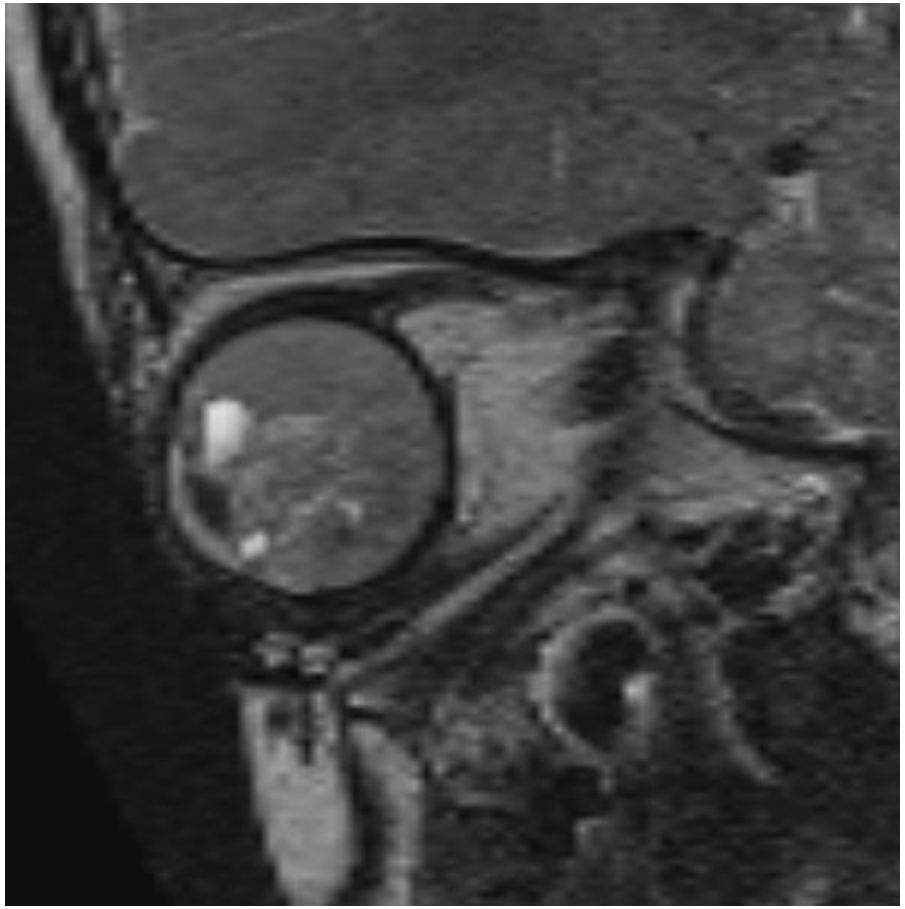
Post contrast T1-W



AX T1 SE FLEX 2 mm

- 1.5 T
- 63.6768
- 2D
- 2 mm
- TE 12 ms
- TR 331 ms

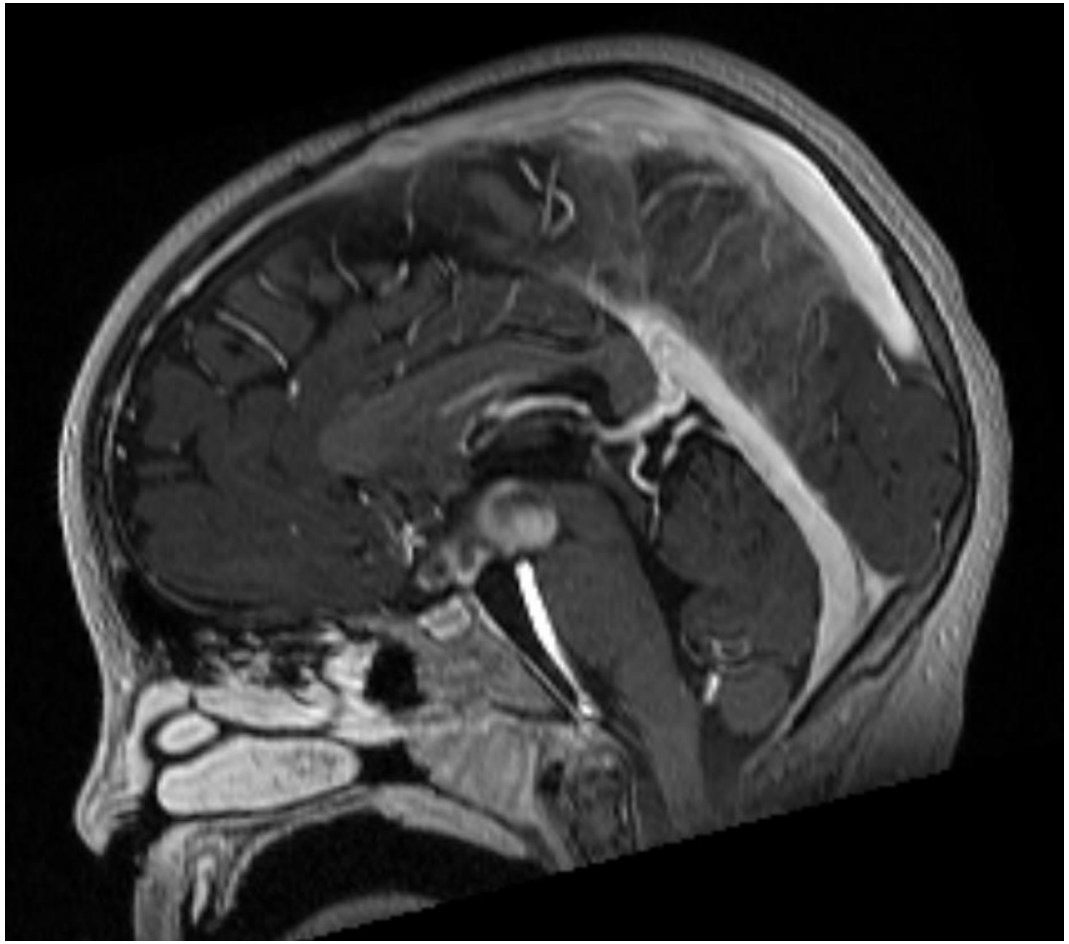
sagittal T2-W

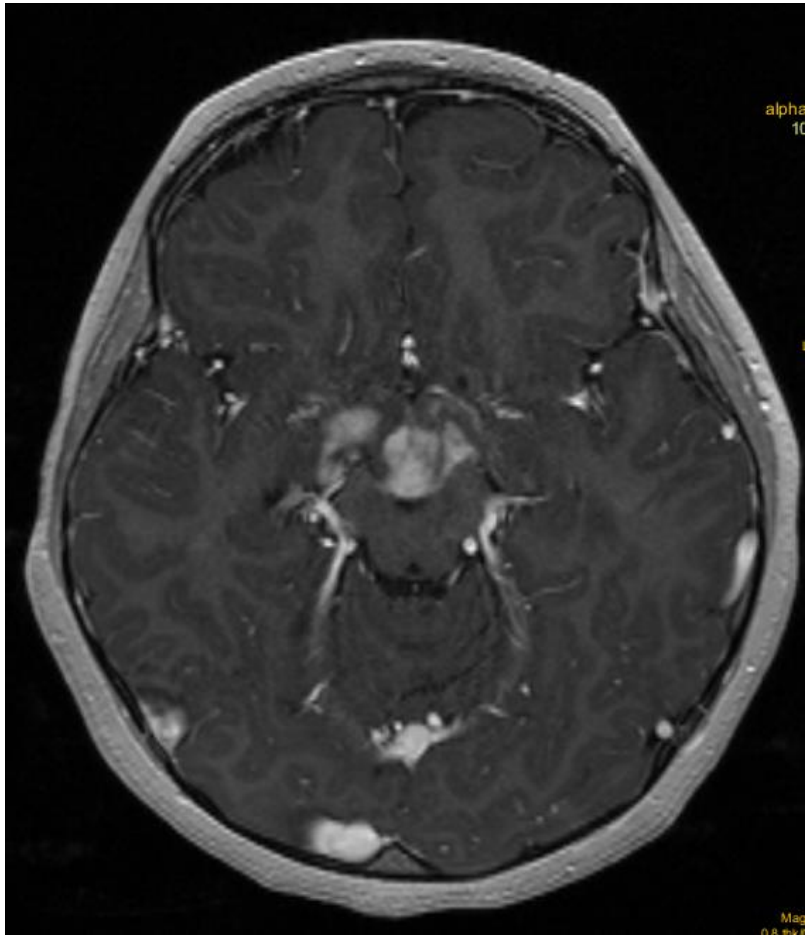


PNOTO T2 OEIL DROIT TSE FLEX 2D

- 2D
- 2 mm
- TE 128 ms
- TR 3790 ms

Brain Postcontrast T1-W

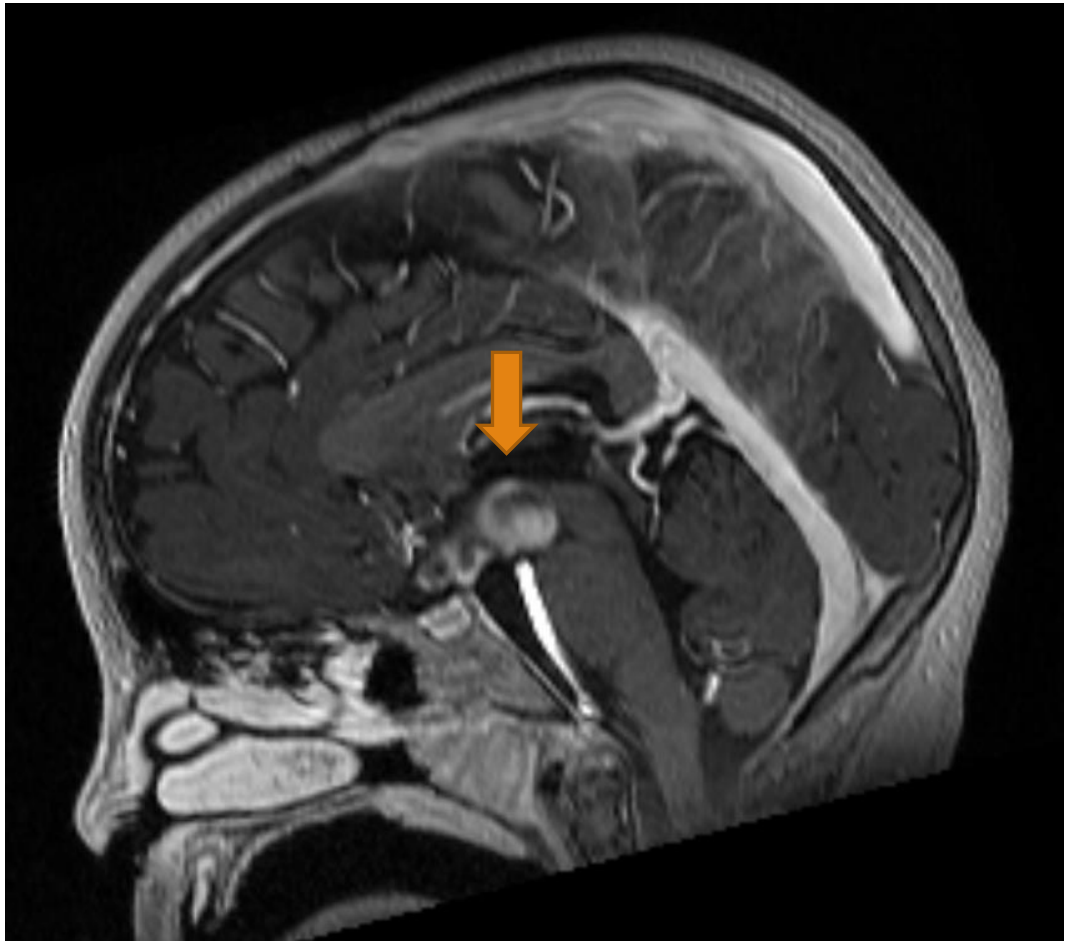


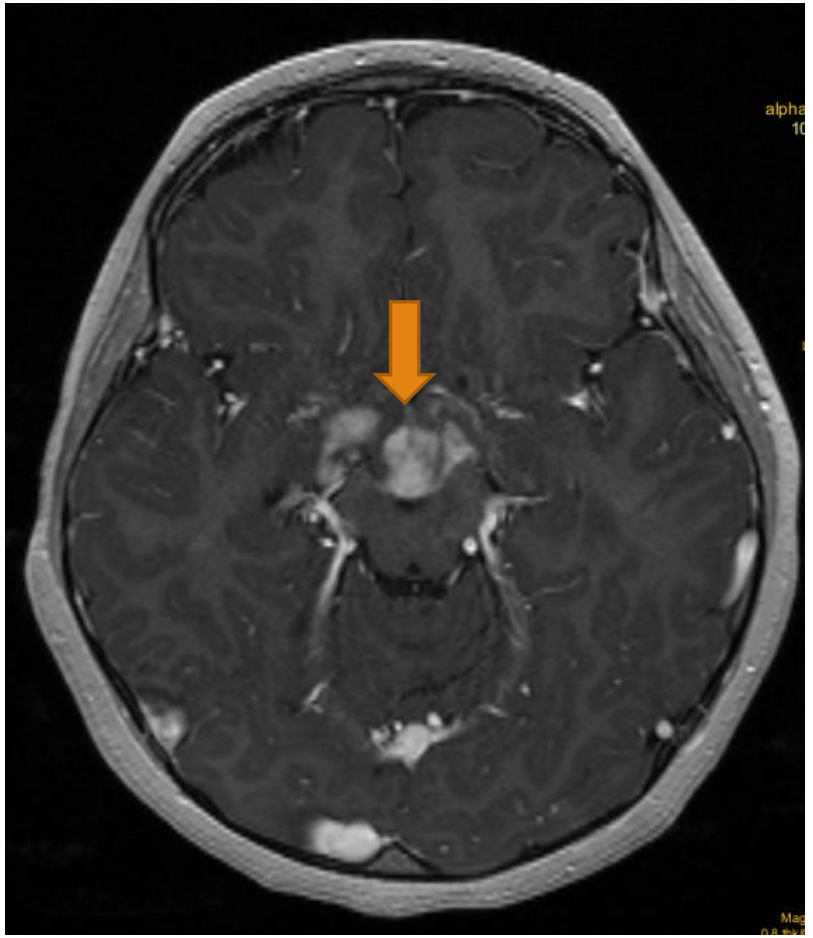


AX FLASH 3D IV

- 3D
- 1 mm
- TE 5.3 ms
- TR 11 ms

Brain Postcontrast T1-W





AX FLASH 3D IV

- 3D
- 1 mm
- TE 5.3 ms
- TR 11 ms

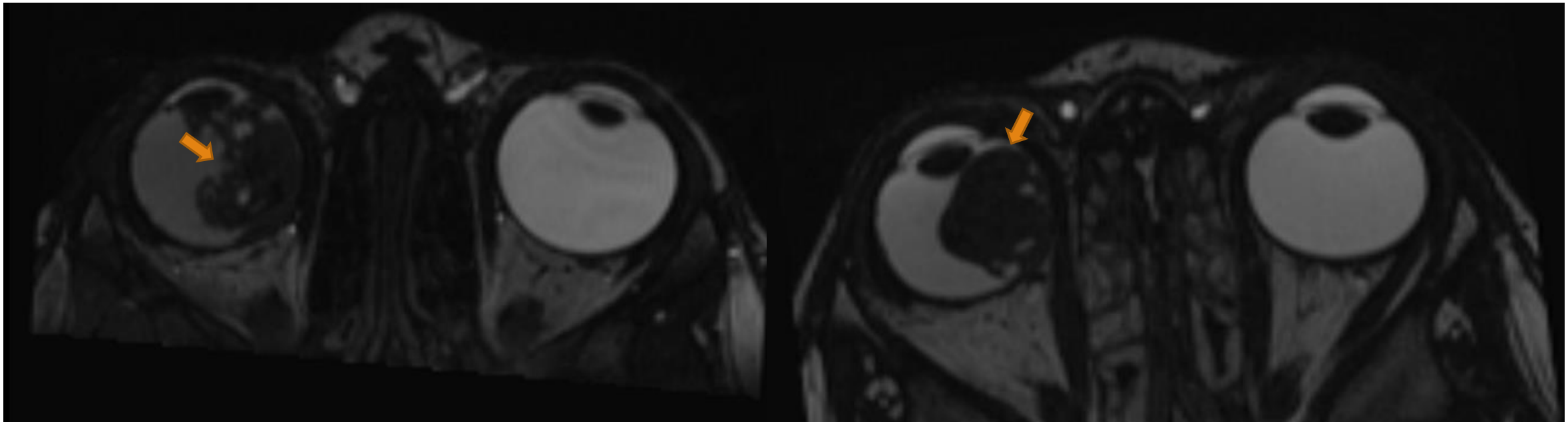
Atlas morphologique

F1 Eye size
F2 Tumor location
F3 Growth pattern
F4 Retinal detachment
F5 Subretinal composition
F6 Shallowness of the anterior eye chamber
F7 Number of lesions
F8 Dominating shape of largest tumor lesion
F9 Calcifications
F10 Tumor cavitation(s)
F11 Definition of the tumor margin
F12 Tumor homogeneity
F13 Compactness of the entire mass
F14 Enhancement quality
F15 Proportion Contrast Enhancing Tumor (CET)
F16 Proportion necrosis
F17 Presence of non-contrast enhancing non-necrosis tumor mass
F18 Enhancement anterior eye segment
F19 Vitreous hemorrhage
F20 Vitreous seedings
F21 Subretinal seedings
F22 Uveitis
F23 Orbital cellulitis
F24 Dislocated eye lens

F3 growth pattern

Exophytic

Endophytic

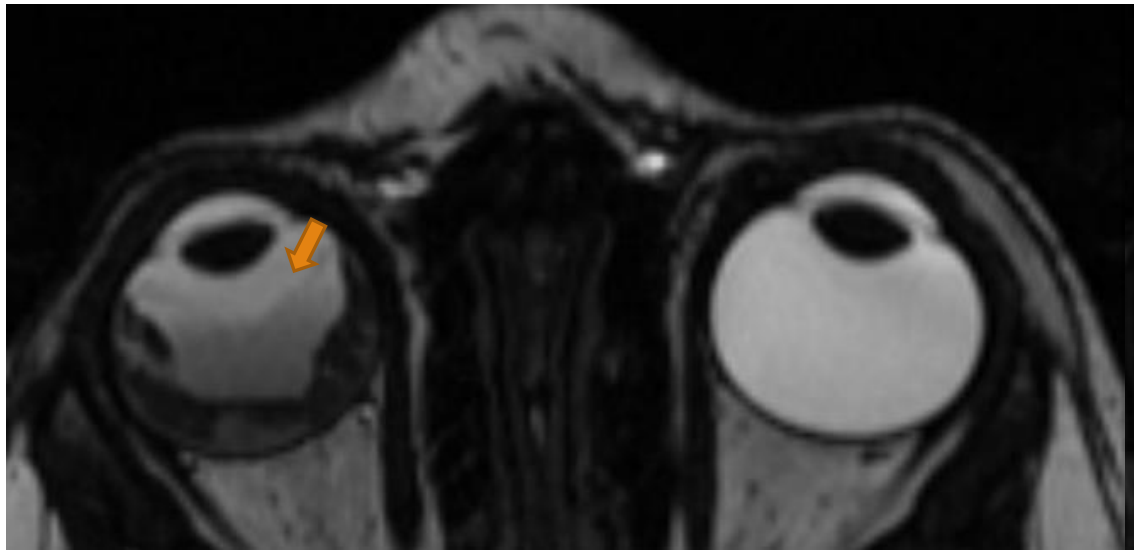


CISS

CISS

F5 subretinal composition

Protein rich



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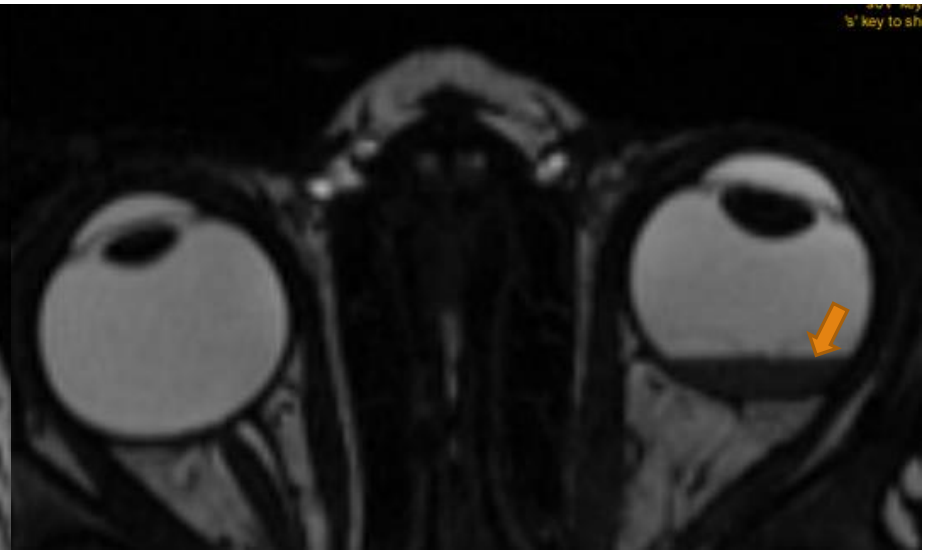
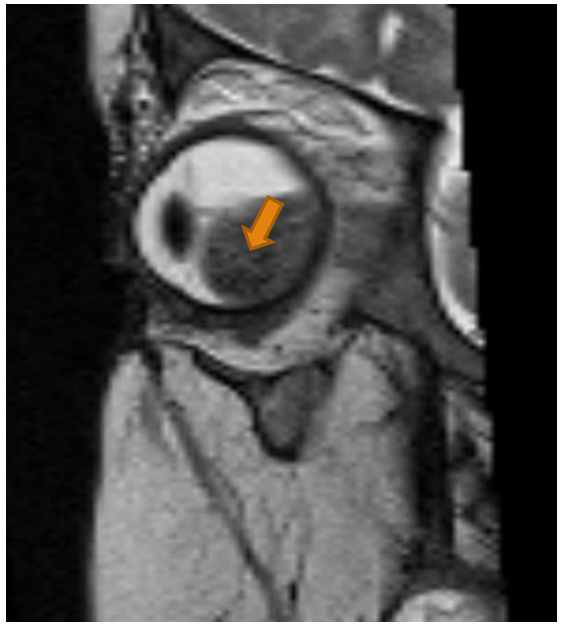
Subretinal hemorrhage



CISS

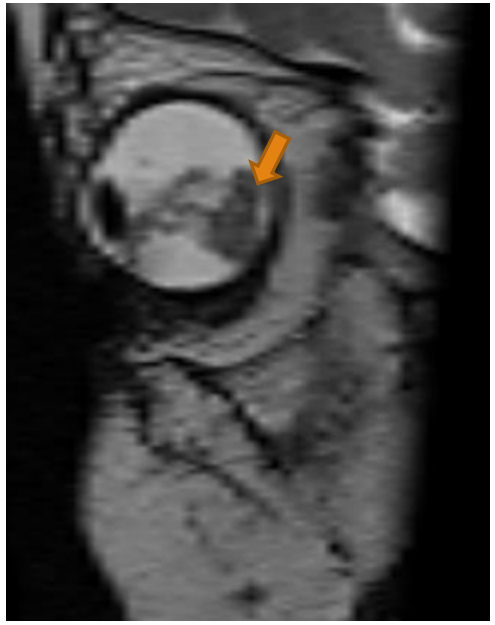
F9 calcifications

Massive calcifications



T2w

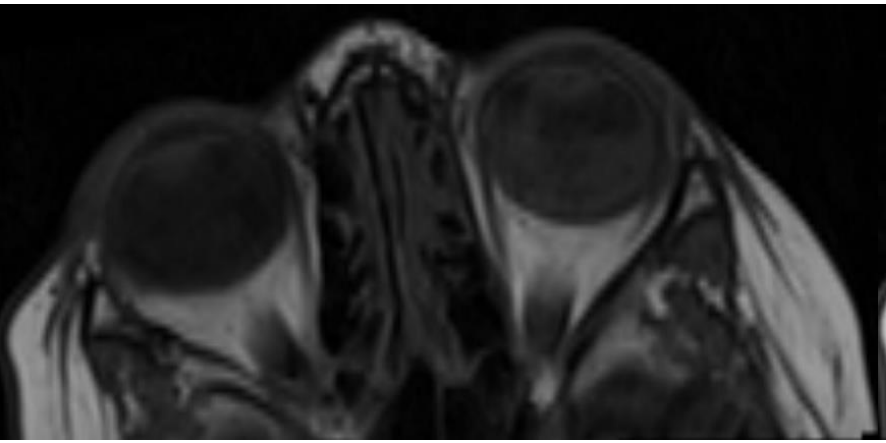
Focal spot of calcifications



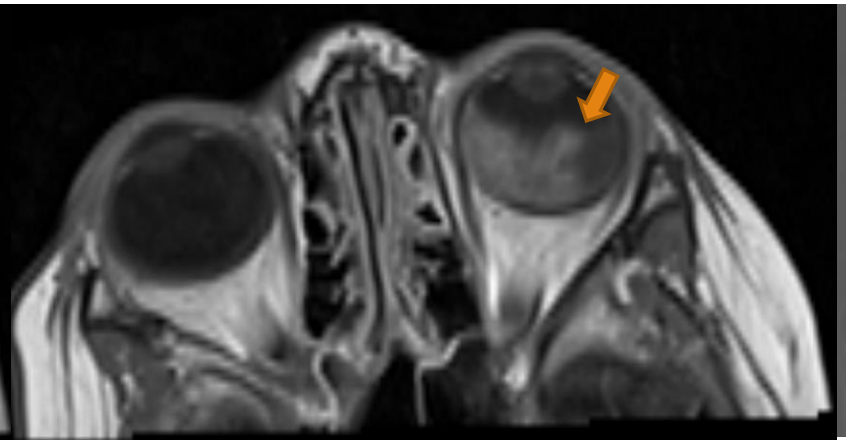
T2w

F14 Enhancement quality

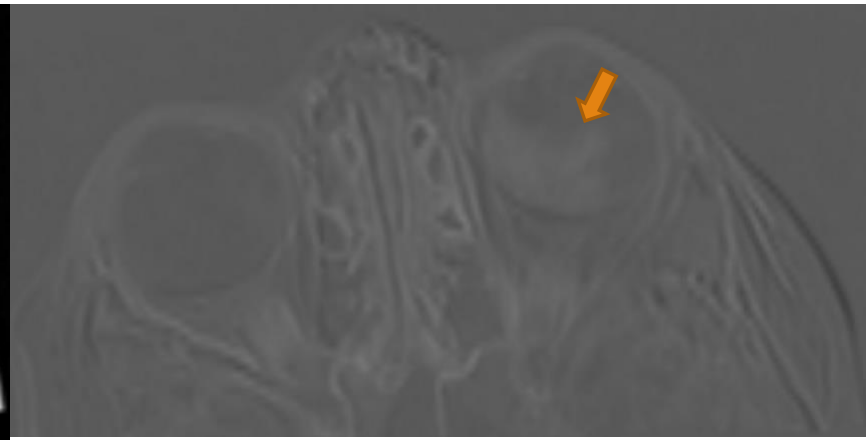
Strong enhancement



Precontrast T1w



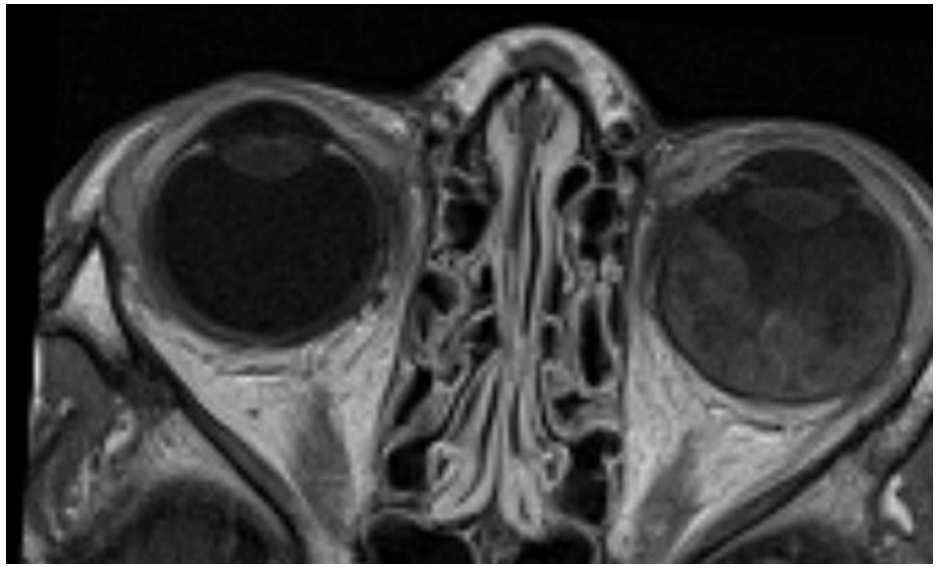
Post contrasteT1w



Substraction

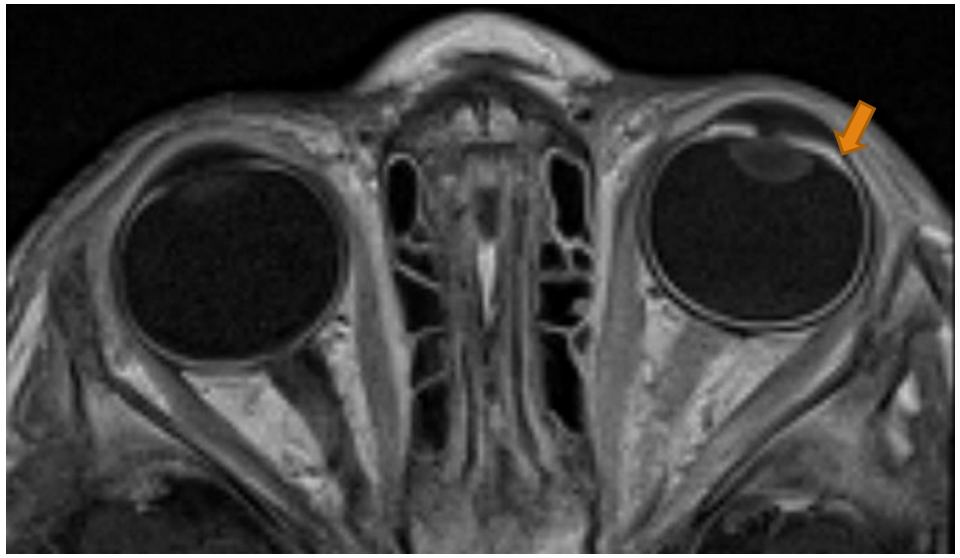
F22 uveite

No



Post contrasteT1w

Yes



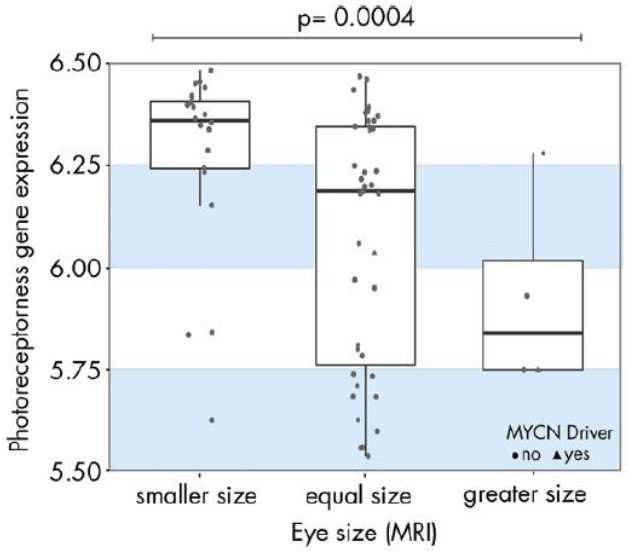
Post contrasteT1w

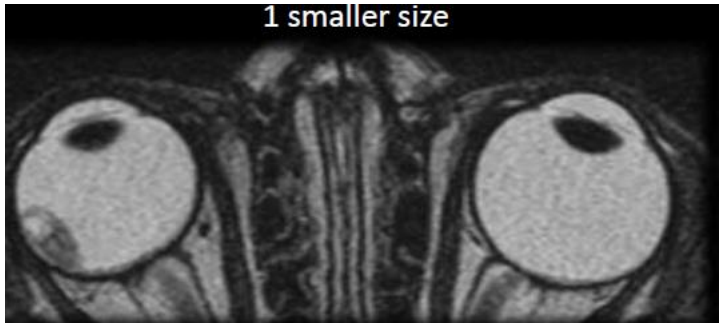
Purpose of the treatment

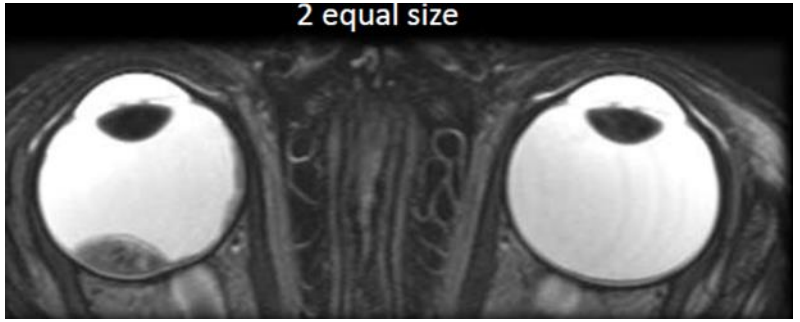
- Save the child's life through early detection
- Treatment of the ocular tumor, and prevention of metastatic spread
- Eye preservation and maximization of visual potential

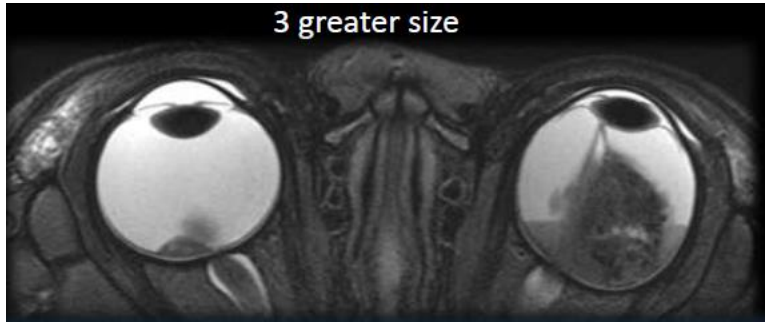
Aerts et al., Arch Pediatr. 2016

Predictive role of MRI findings for genetic characterization





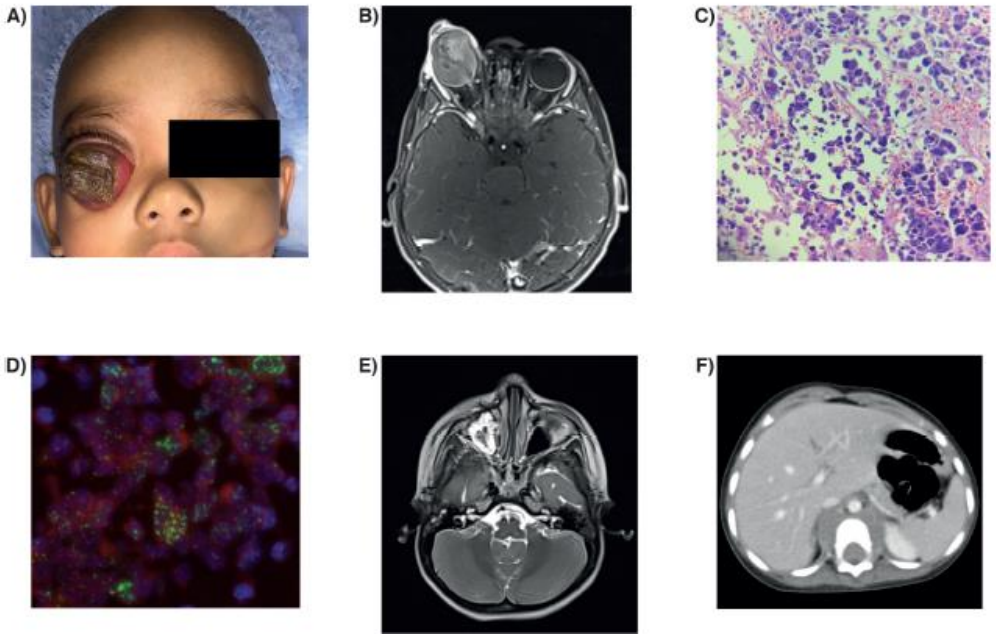




R.W. Jansan et al. ,Radiology 2018
Guide for lesion characterization on MR images in retinoblastoma, P. de Graaf.
I.E. Kooi, et al;, EBioMedicine 2015

Predictive role of MRI findings for genetic characterization

MYCN amplification

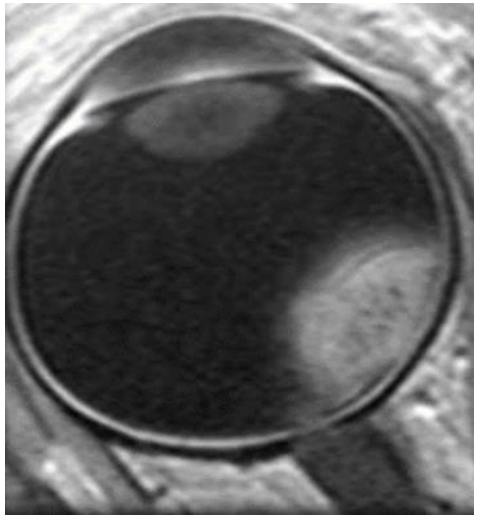


Definition: Number of tumor lesions (tumor seedings excluded).
1=1 lesion, 2=1-5 lesions, 3=5-10 lesions, 4=>10 lesions, 9=indeterminate

R.W. Jansan et al., Radiology 2018
Guide for lesion characterization on MR images in retinoblastoma, P. de Graaf.
S. Zugbi et al., cancers, 2020.

Objective of the study

Determine morphological and radiomic MRI features correlated to genomic subtypes of retinoblastoma



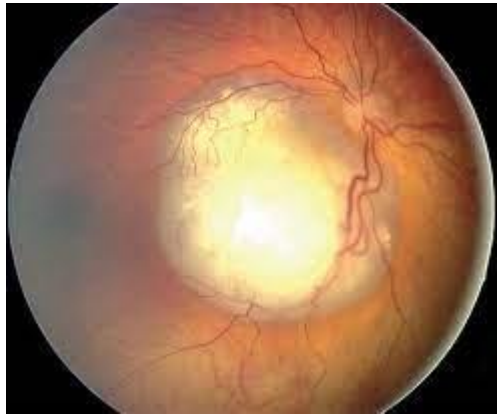
Nioche et al., Cancer Res, 2018

Study

- Retrospective, monocentric, observational
- Conducted between 2004 and 2021
- Focusing on patients with retinoblastoma followed in Curie Institute

Population

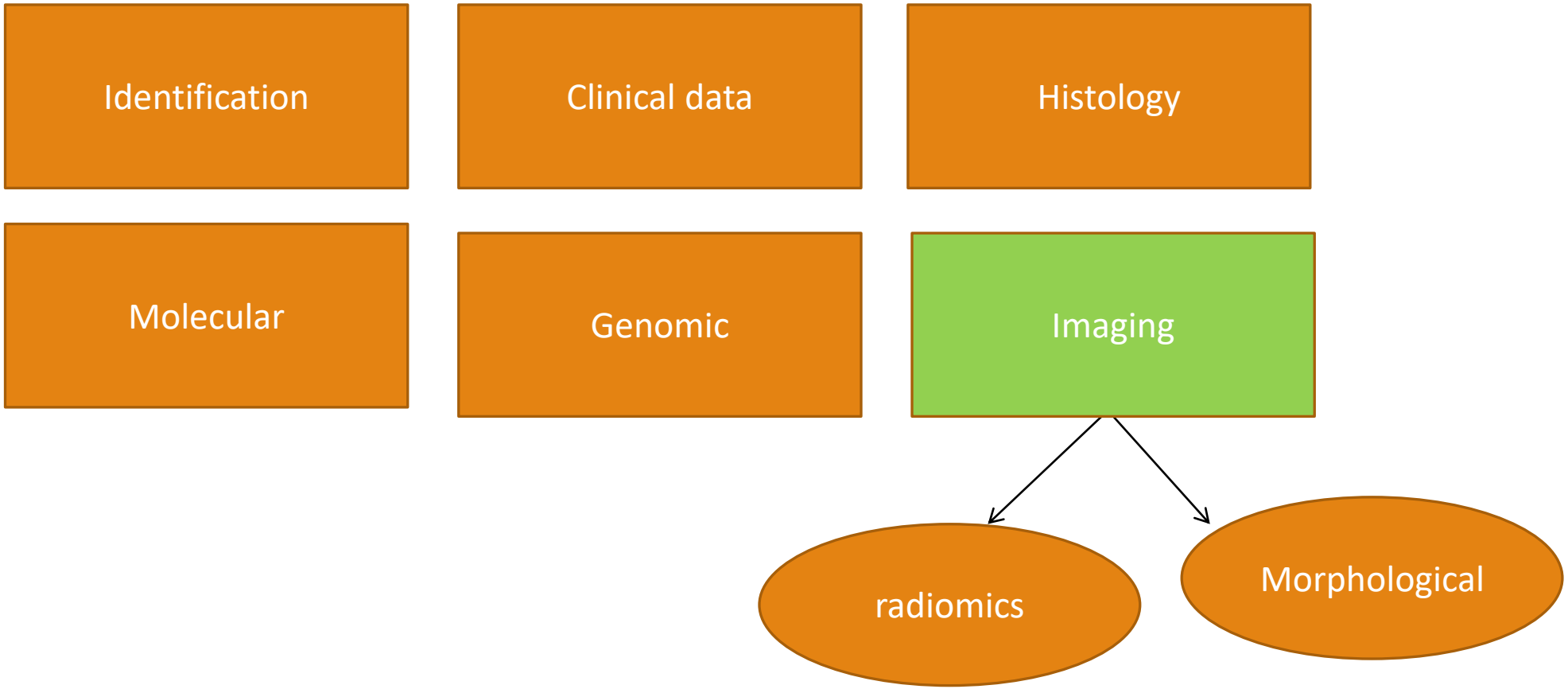
- Patient with a suspected retinoblastoma on the fundus
- Pre treatment MRI (at least T2W)
- With a primary enucleation



Data

- Identification
- Clinical data
- Histology
- Molecular
- Genomic
- Imaging

Data


Identification
Clinical data
Histology
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Imaging
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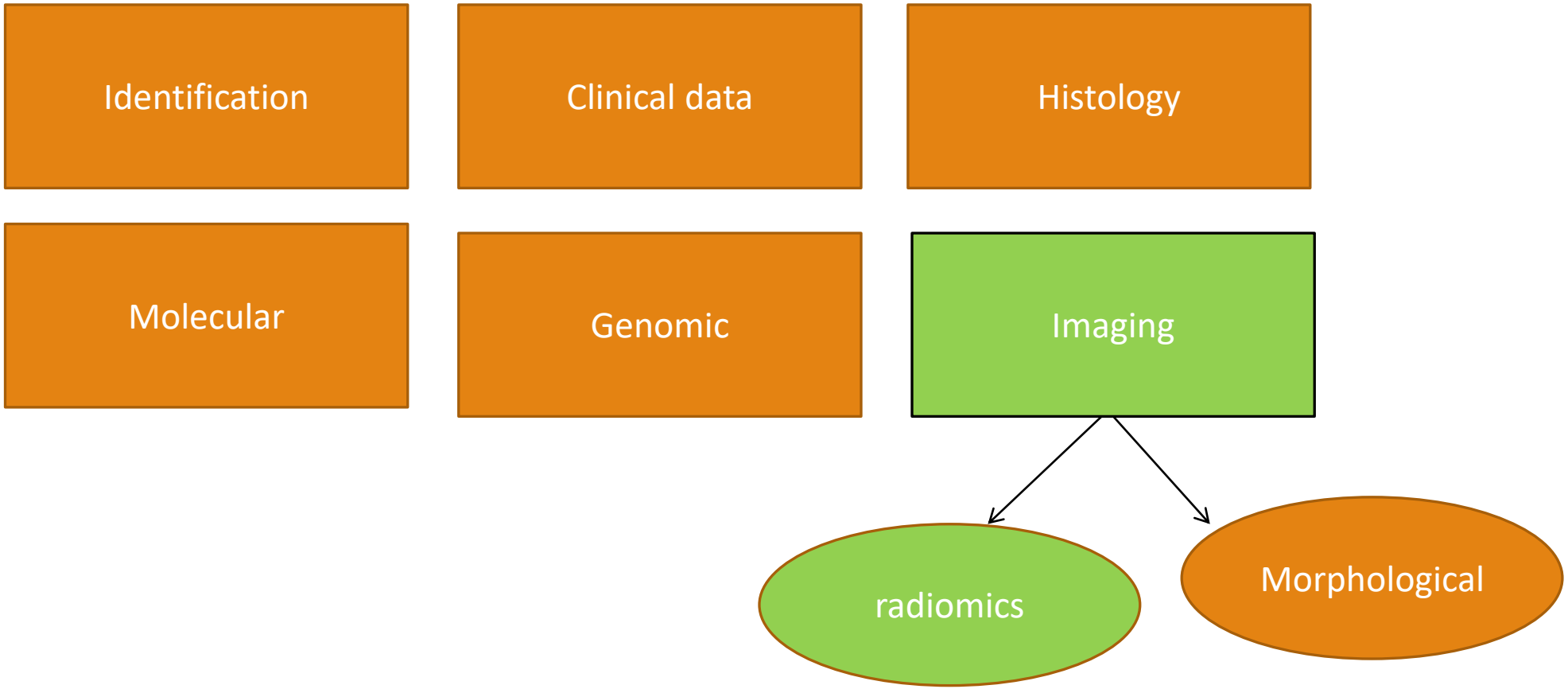
Morphological

Data


Identification
Clinical data
Histology
Molecular
Genomic
Imaging
radiomics
Morphological

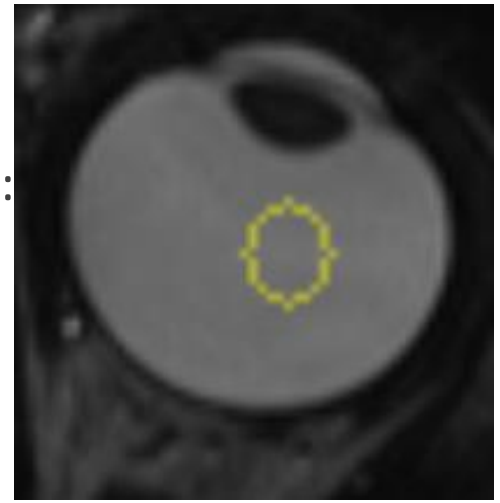
Preprocessing

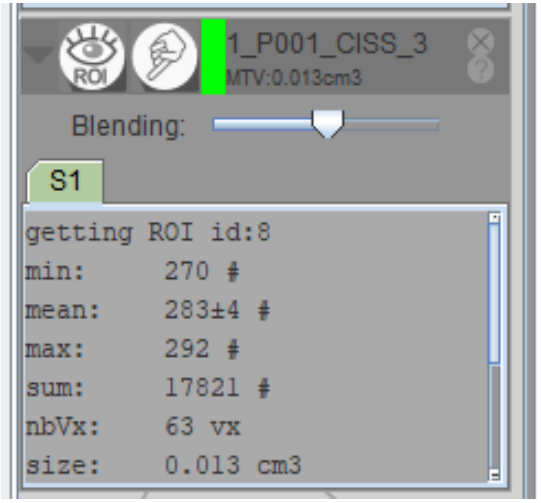
- Process anonymized images: DICOM => NIfTI and json,

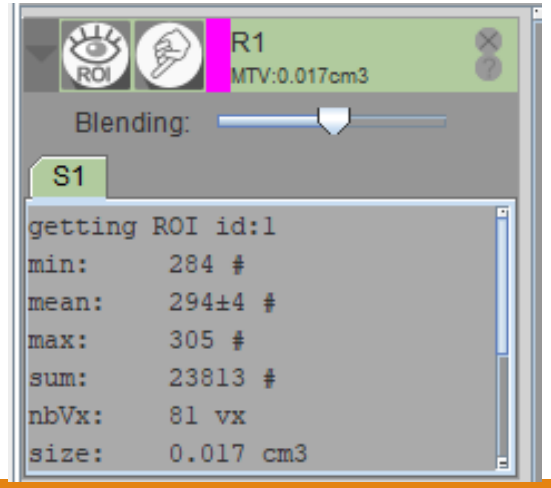
Preprocessing

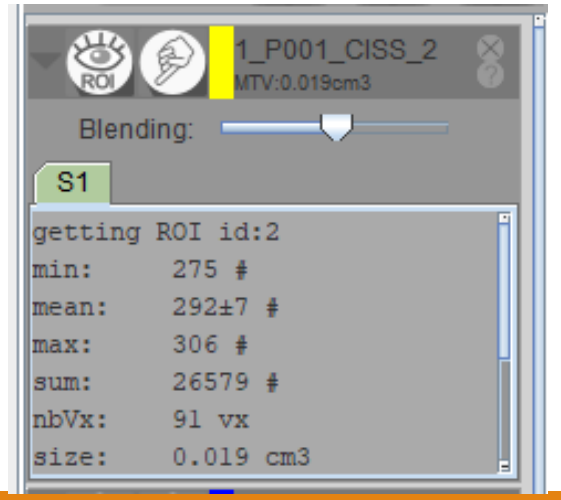
- Intensity normalization (wT2, wT1…):
  - Intense areas,
  - At least 30 vx,
  - Variation under 10%.

CISS







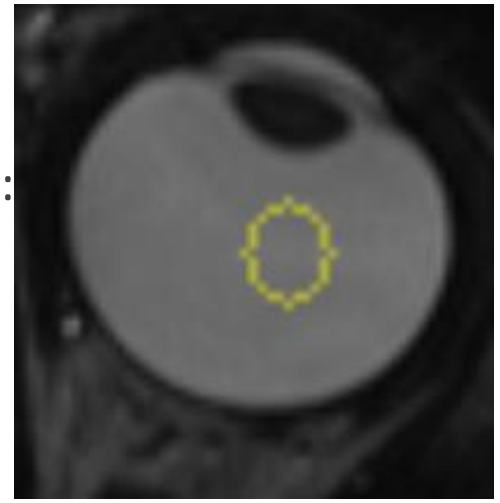


Lacroix et al., Frontiers in oncology,2020.

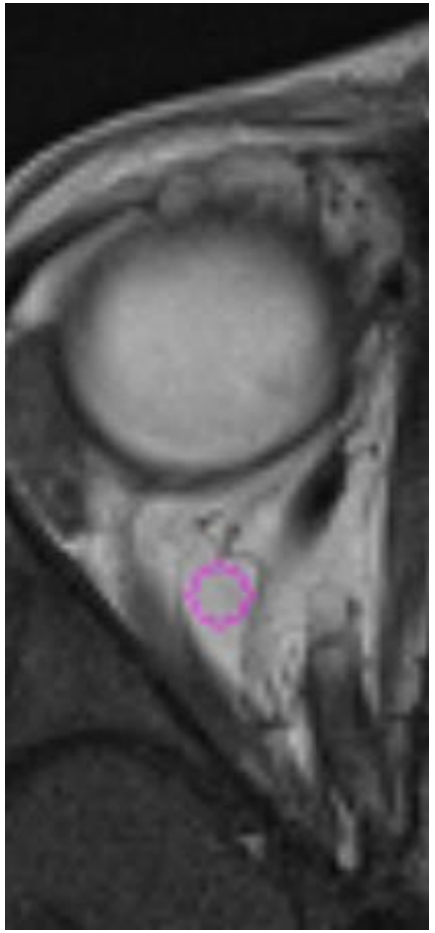
Preprocessing

- Intensity normalization (wT2, wT1…):
  - Intense areas
  - At least 30 vx
  - Variation under 10%

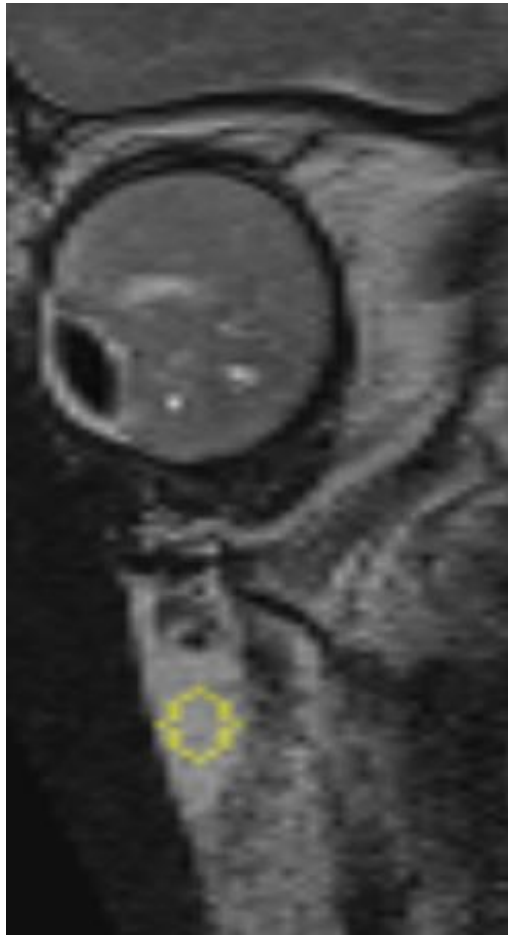
CISS



wT1



wT2



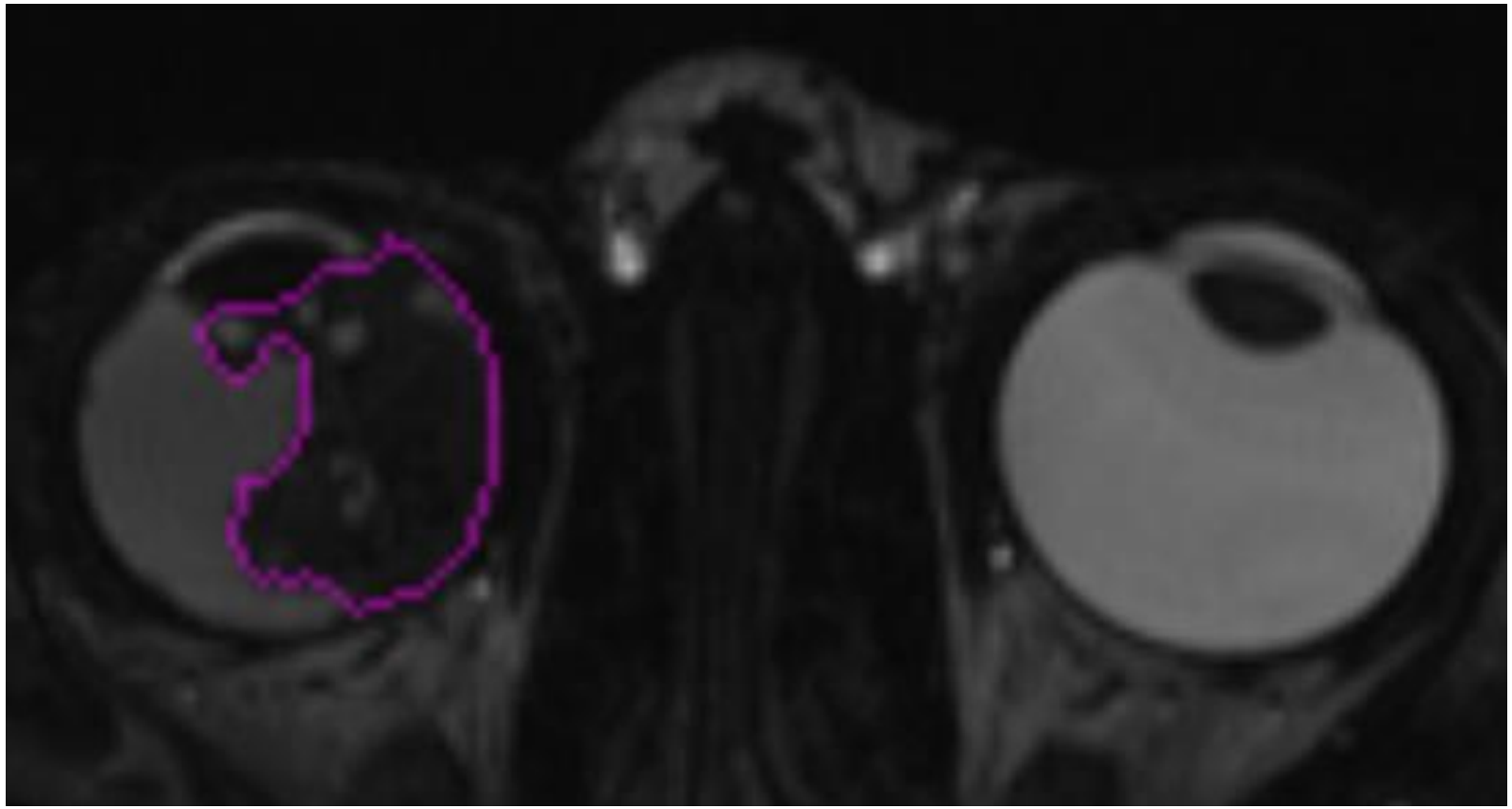
Preprocessing

- Intensity normalization (wT2, wT1…):
  - Purpose: analyze patients in the same frame of reference
  - We determine a region of interest that seems to vary little
  - Application of a linear transformation

$$Is(v) = [I(v) - F]/\sigma$$

Preprocessing → Manual segmentation by two observers

- Orbital structures
- Slice thickness <2.5 mm
- T2w



380 enuclations between 2004 and 2021

380 enuclations between 2004 and 2021

↓

167 Redcap reports

380 enuclations between 2004 and 2021

↓

167 Redcap reports

↓

139 contributive MRI

380 enuclations between 2004 and 2021

↓

167 Redcap reports

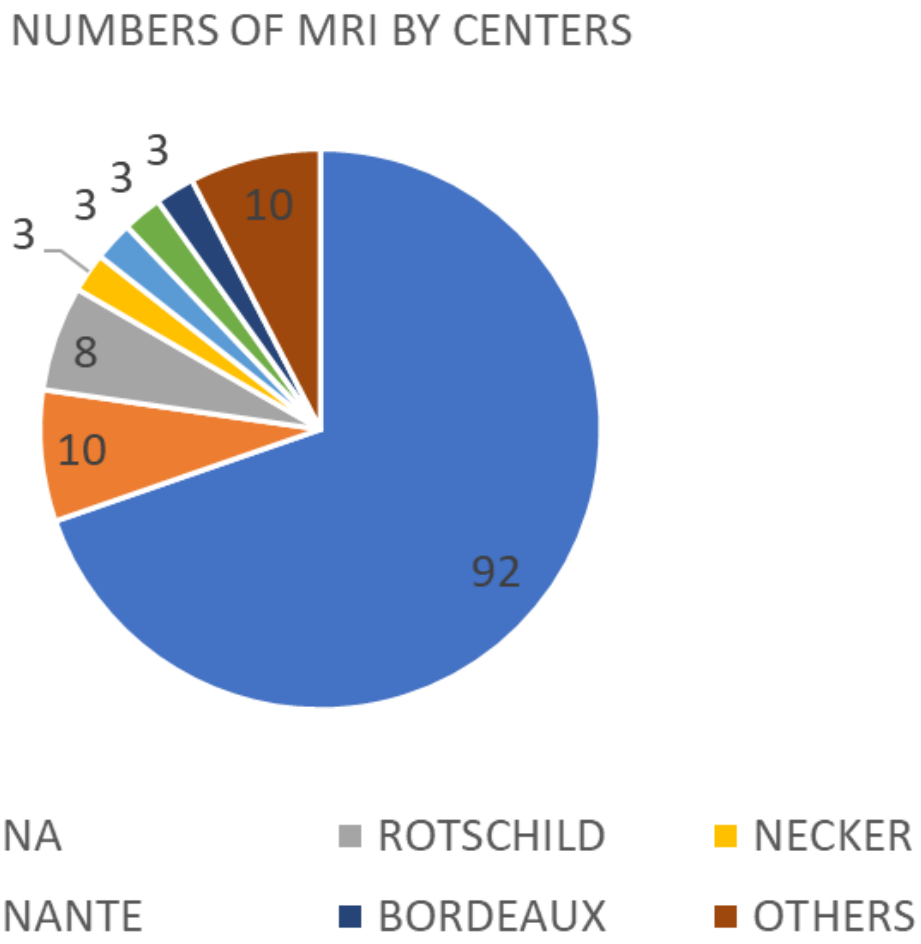
↓

139 contributive MRI

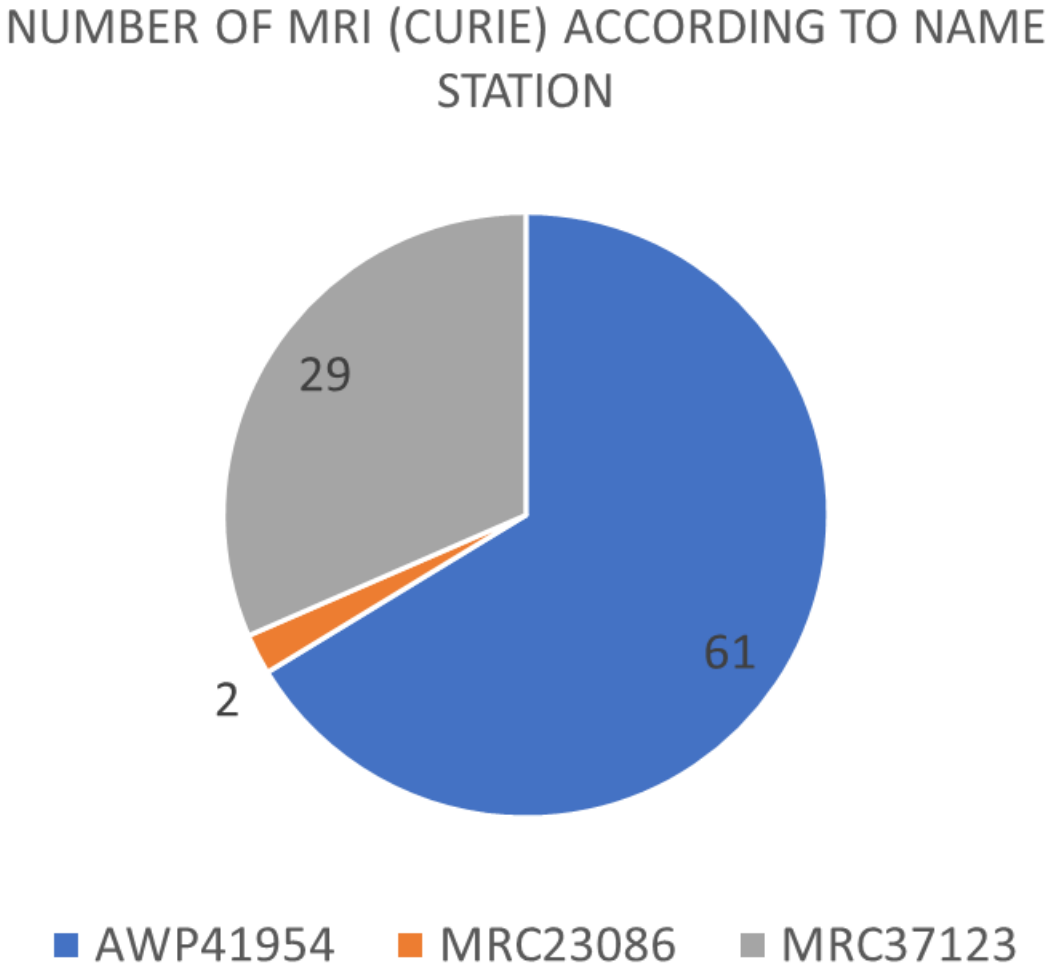
↓

89 primary enucleations

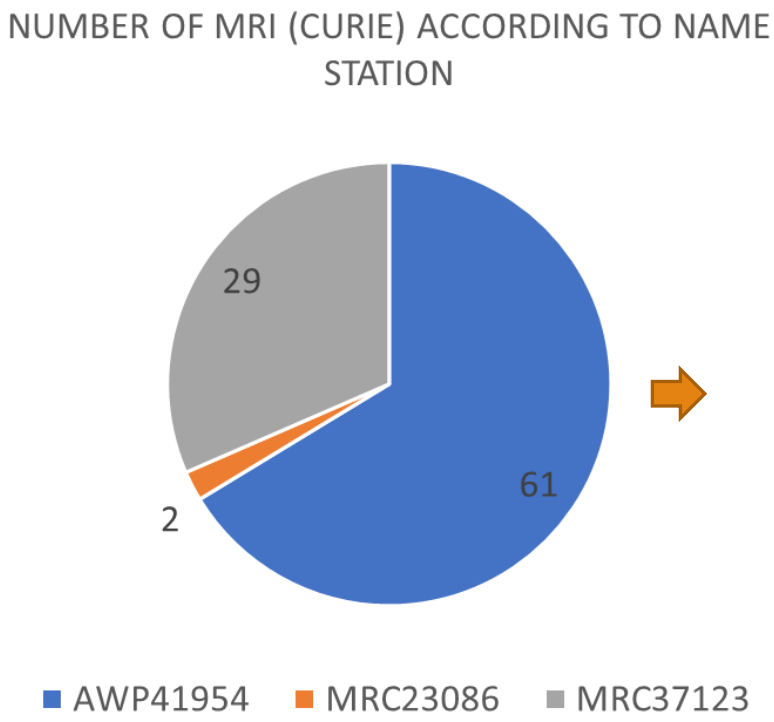
139 contributive MRI



92 MRI AT CURIE INSTITUTE



92 MRI AT CURIE INSTITUTE



61 AWP41954:

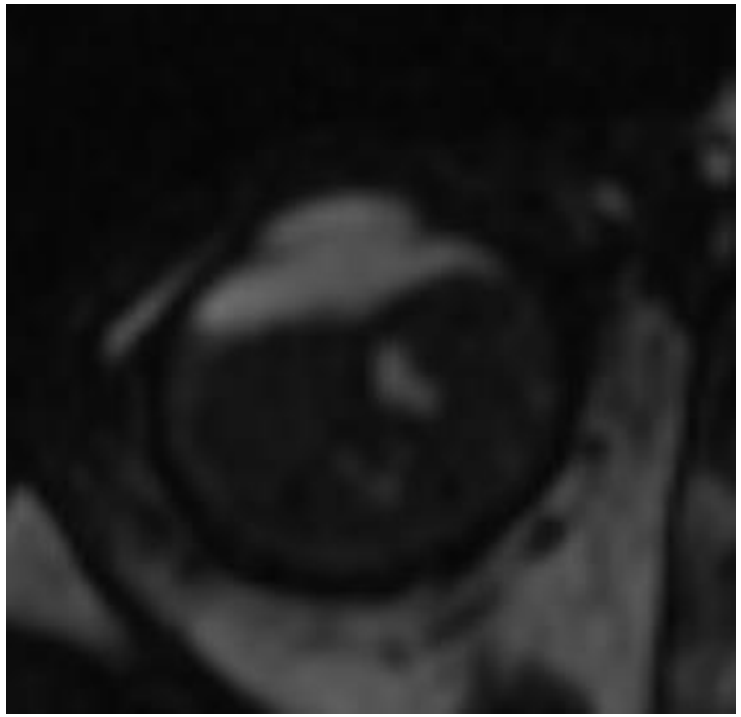
- 3 wT2 with a slice thickness of 2 mm.
- 58 CISS with a slice thickness between 0.65 mm and 0.8 mm.

Identification	Clinical data	Histology
Molecular	Genomic	Imaging

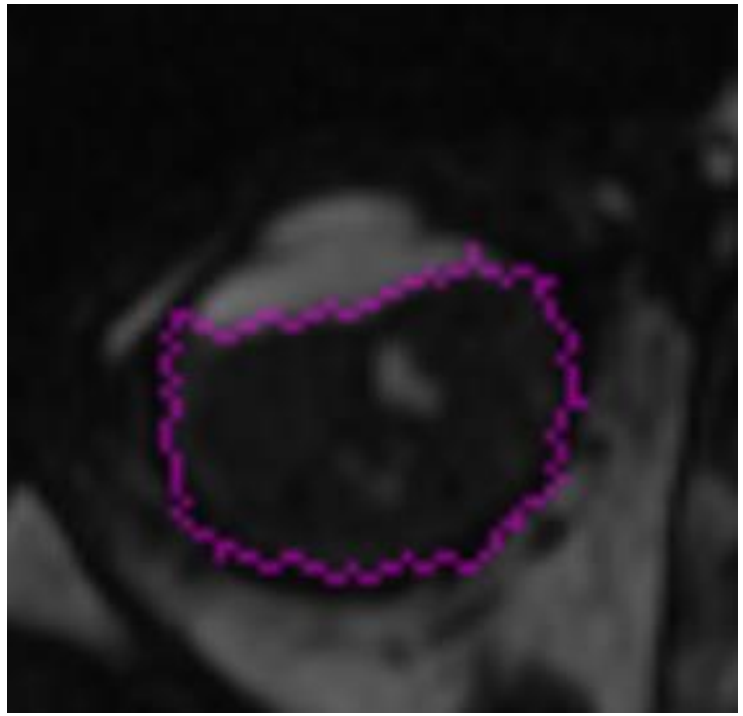
- Consensus of readers for segmentation and morphological aspects

- Consensus of readers for segmentation and morphological aspects

Reader 1

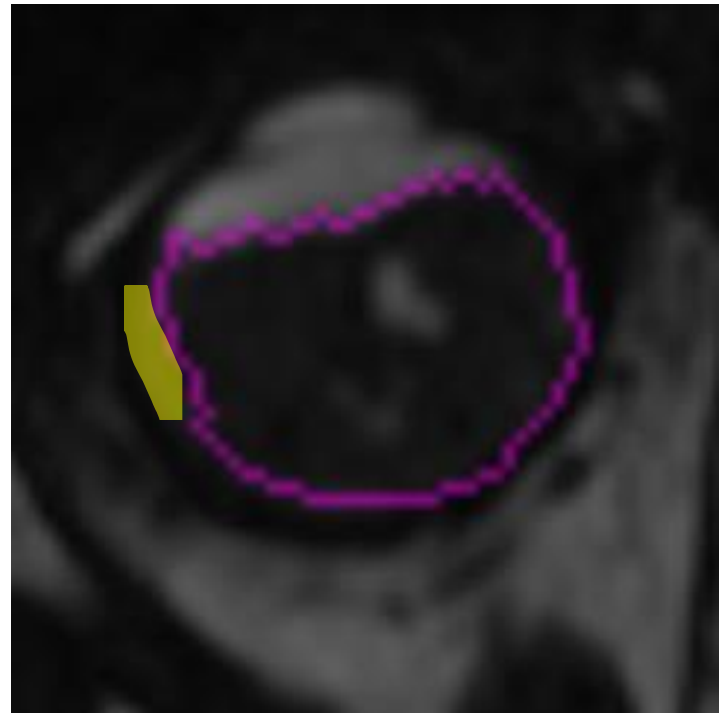


CISS



CISS

Reader 2

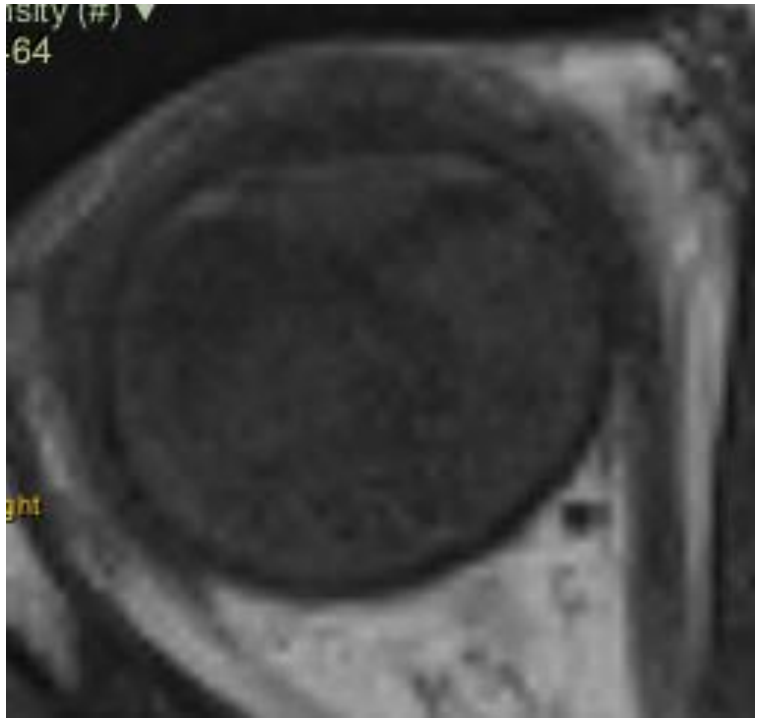


CISS

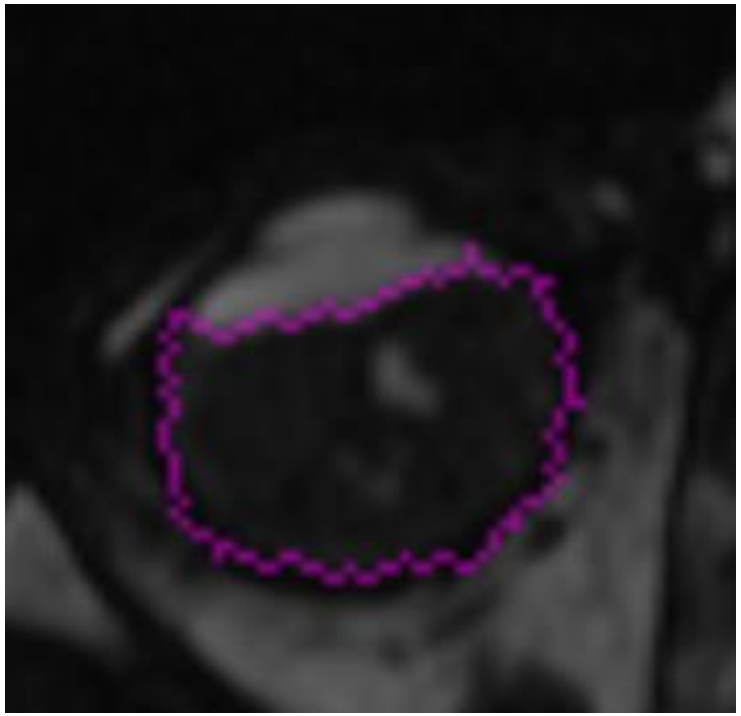
- Consensus of readers for segmentation and morphological aspects

Reader 1

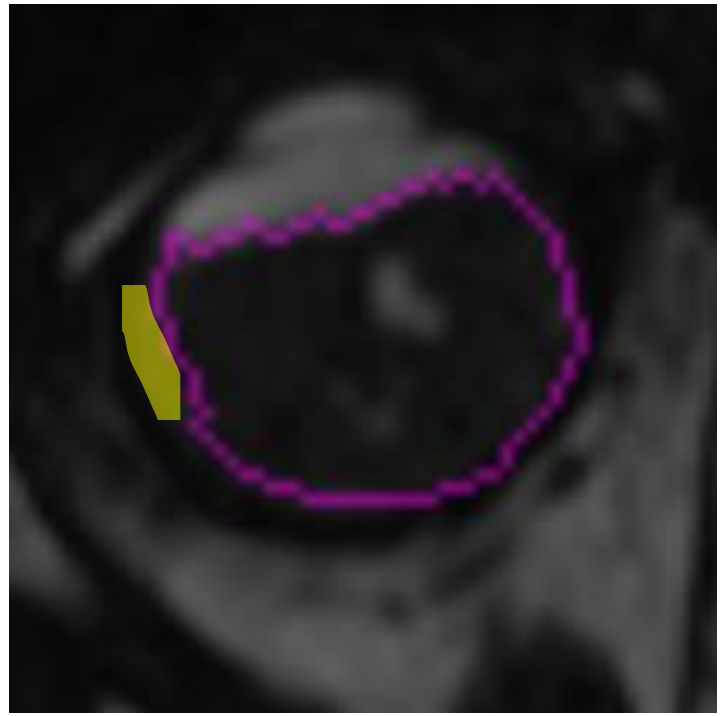
Reader 2



Pre contrast T1w

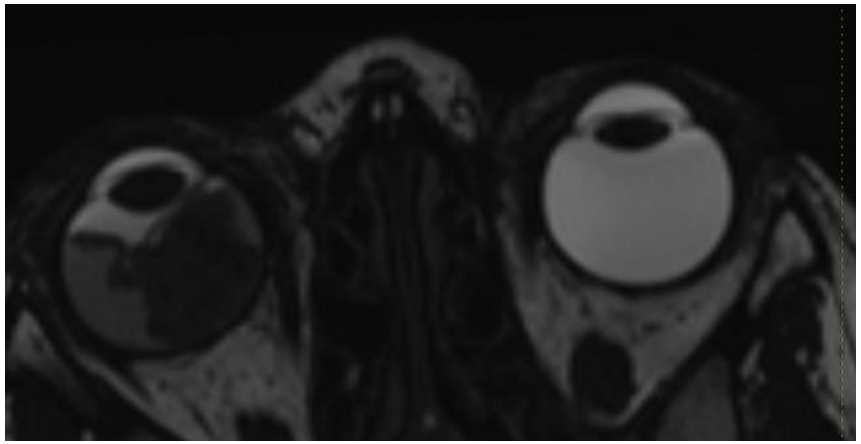


CISS

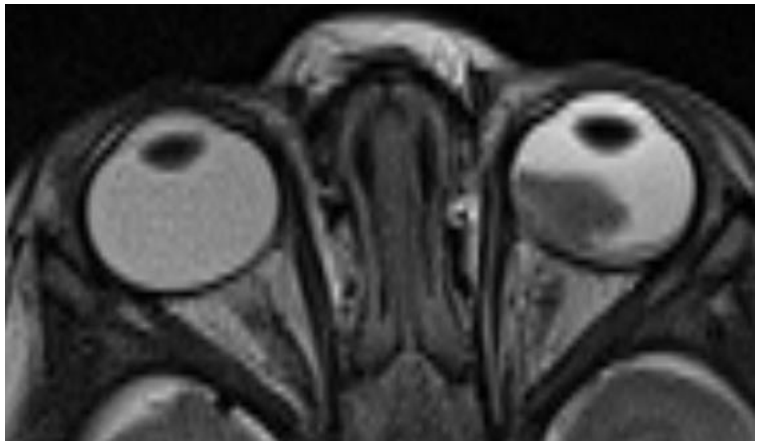


CISS

- Consensus of readers for segmentation and morphological aspects
- Consensus about sequences



CISS ≈

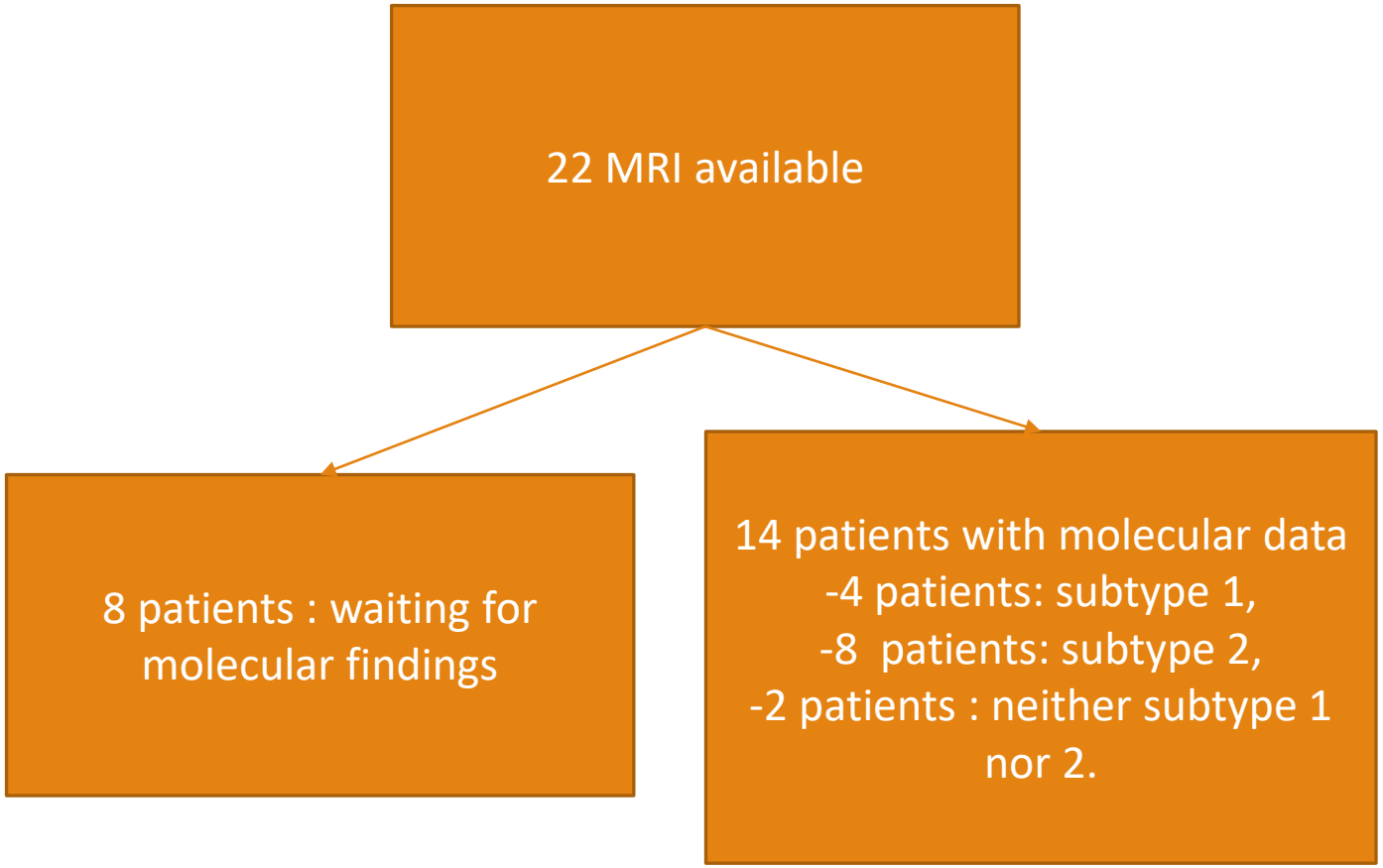


wT2

- Consensus of readers for segmentation and morphological aspects
- Consensus about sequences : CISS ≈ wT2?
- Teamwork with other specialists

- Consensus of readers for segmentation and morphological aspects
- Consensus about sequences : CISS ≈ wT2?
- Teamwork with other specialists
- Waiting for the results of molecular analysis to estimated the size of the groups

Size of groups?

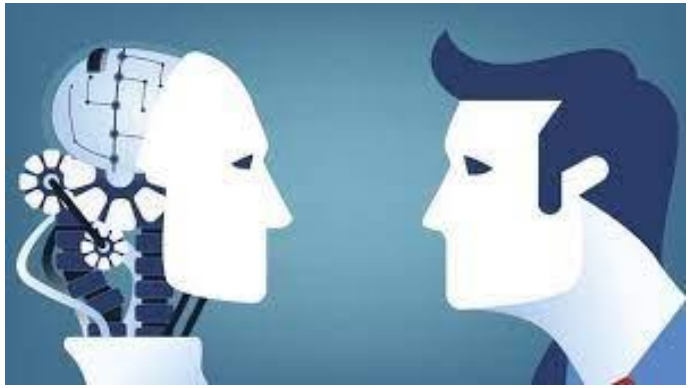


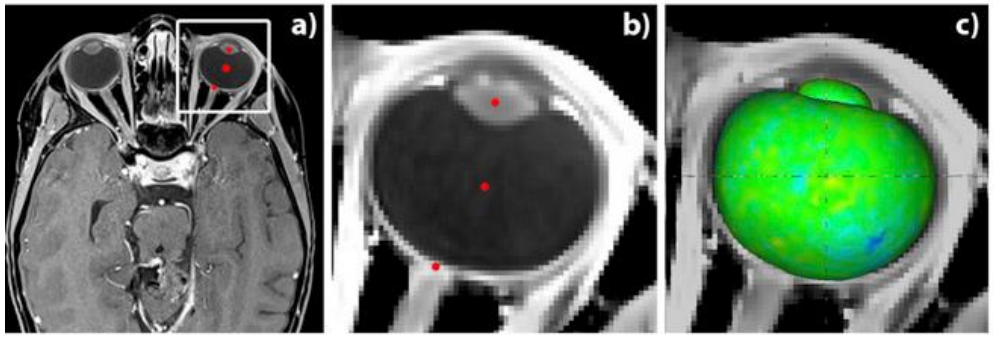
Outemzabet, Rapport de stage dans le cadre du M2 AMI2B de l'Université Paris-Saclay, 2021

- Consensus of readers for segmentation and morphological aspects
- Consensus about sequences : CISS ≈ wT2
- Teamwork with other specialists
- Waiting for the results of molecular analysis to estimated the size of the groups
- ComBat

Orlhac F et al., J Nucl Med. 2022

Prospects: supervised machine learning analysis.

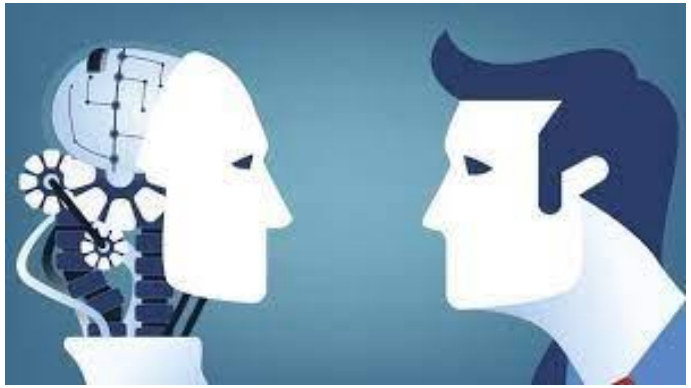


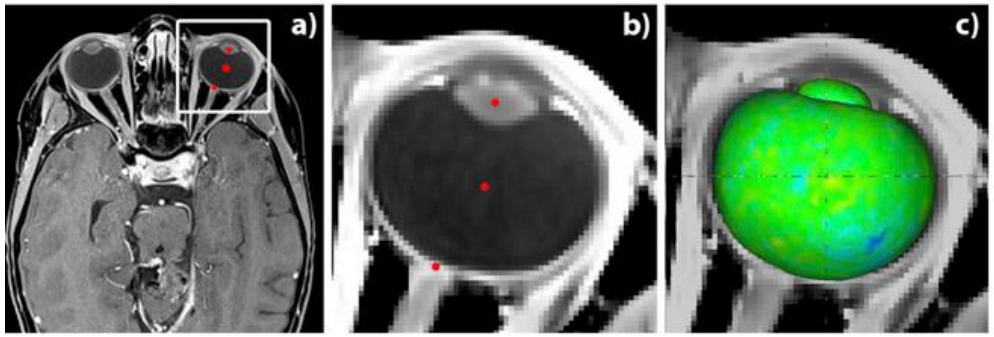


- Training set: 24 eyes on 3T MRI
- Manual annotation
- Leave-one-out cross Validation

Ciller et al.,International Journal Radiation Oncology, 2015

Prospects: supervised machine learning analysis.



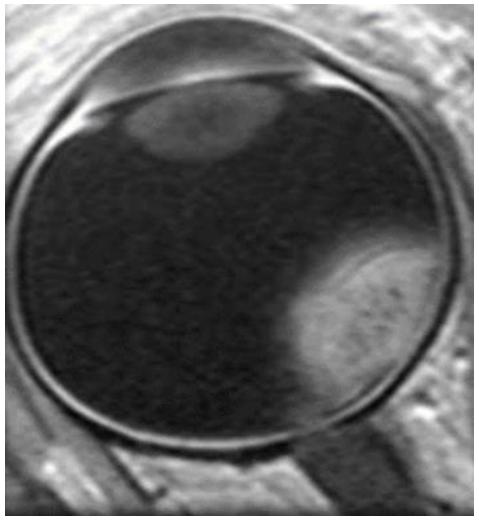


- Dice similarity coefficient of 94.90 ± 2.12% for the sclera and the cornea
- 94.72 ± 1.89% for the vitreous humor
- 85.16 ± 4.91% for the lens

Ciller et al.,International Journal Radiation Oncology, 2015

Work in progress!

Acquisition	≃ 150
Segmentation	Choice of sequences, type of segmentation....
Preprocessing	Anonymization, normalization, Combat…
Extraction	Form parameters, first order, second order
Sélection	Selection of parameters
Classification	Supervised
Validation	Multicenter approach...



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Thank you for your attention