Mitteldeutsches Kompetenznetz Seltene Erkrankungen

Hyperinsulinism Germany · International

European Reference Network for rare or low prevalence complex diseases

Network Endocrine Conditions (Endo-ERN)

1st webinar of Endo-ERN, MTG3

presenter:

Klaus Mohnike, Otto-von-Guericke-University Magdeburg

moderator:

Indi Banerjee, Royal Manchester Children's Hospital, Manchester

agenda:

1. CHI registries:
    1. HIGlobal CHI registry (patient-driven study)
    2. proposal for clinical registry based on ERDRI-platform
2. Presentation of COACH-working group experience in CHI
3. Regular meetings using CPMS

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CHI registries

1. Congenital Hyperinsulinism International has launched HIGlobal CHI registry in 2018, all centers should invite their patients to participate. Further information: higlobalregistry.org

2. EU launched in 2019 the European RD Registry Infrastructure (ERDRI)-platform for use in clinical registries, epidemiological and research

Principles of ERDRI-platform:

Each ERN-centre's stored patient`s data locally according to hospital rules, e.g. using open source software (RedCap, OSSE etc). At ERDRI-platform no identifiable data (IDAT) and no whole registries hosted. Therefore data-owner will keep data sovereignty with the data owner or custodian.

To allow data sharing format of data elements of the registries are defined in ERDRI.MDR (Metadata Repository). One registry knows what the other one knows.

Further information: https://eu-rd-platform.jrc.ec.europa.eu/erdri

https://eu-rd-platform.jrc.ec.europa.eu/erdri

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European Rare Disease Registry Infrastructure (ERDRI)

European Directory of Registries (ERDRI.dor)

Overview of rare disease registries in Europe including their characteristics

Central Metadata Repository (ERDRI.mdr)

Database containing the data elements used by rare disease registries

EUPID

Pseudonymisation tool

Service offering registries at local level the solution for patient pseudonymisation

European Platform on Rare Disease Registration

Contact

EUROPEAN PLATFORM ON RARE DISEASES REGISTRATION (EU RD Platform)

SET OF COMMON DATA ELEMENTS FOR RARE DISEASES REGISTRATION

GROUP	ELEMENT N°	ELEMENT NAME	ELEMENT DESCRIPTION	CODING	COMMENT
1. Pseudonym	1.1.	Pseudonym	Patient's pseudonym	• String	The JRC is working on providing a pseudonymisation tool to the registries
2. Personal information	2.1.	Date of birth	Patient's date of birth	• Date (dd/mm/yyyy)	
	2.2.	Sex	Patient's sex at birth	• Female • Male • Undetermined • Foetus (Unknown)	
3. Patient Status	3.1.	Patient's status	Patient alive or dead	• Alive • Dead • Lost in follow-up • Opted-out	If dead then answer question 3.2
	3.2.	Date of death	Patient's date of death	• Date (dd/mm/yyyy)	
4. Care pathway	4.1.	First contact with specialised centre	Date of first contact with specialised centre	• Date (dd/mm/yyyy)	
5. Disease history	5.1.	Age at onset	Age at which symptoms/signs first appeared	• Antenatal • At birth • Date (dd/mm/yyyy) • Undetermined	
	5.2.	Age at diagnosis	Age at which diagnosis was made	• Antenatal • At birth • Date (dd/mm/yyyy) • Undetermined	
6 Diagnosis	6.1.	Diagnosis of the rare disease	Diagnosis retained by the specialised centre	Orpha code (strongly recommended – see link) / Alpha code/ ICD-9 code/ ICD-9-CM code / ICD-10 code	http://www.orphadata.org/cgi-bin/inc/product1.inc.php
	6.2.	Genetic diagnosis	Genetic diagnosis retained by the specialised centre	International classification of mutations (HGVS) (strongly recommended – see link) / HGNC / OMIM code	http://www.hgvs.org
	6.3	Undiagnosed case	How the undiagnosed case is	• Phenotype (HPO)	

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Congenital Hyperinsulinism

- genetically heterogeneous disorder
- dysregulated insulin secretion of pancreatic beta cells
- severe hypoglycemia
- Inhibited fatty acid oxidation and low ketones and
- high content of hepatic glycogen

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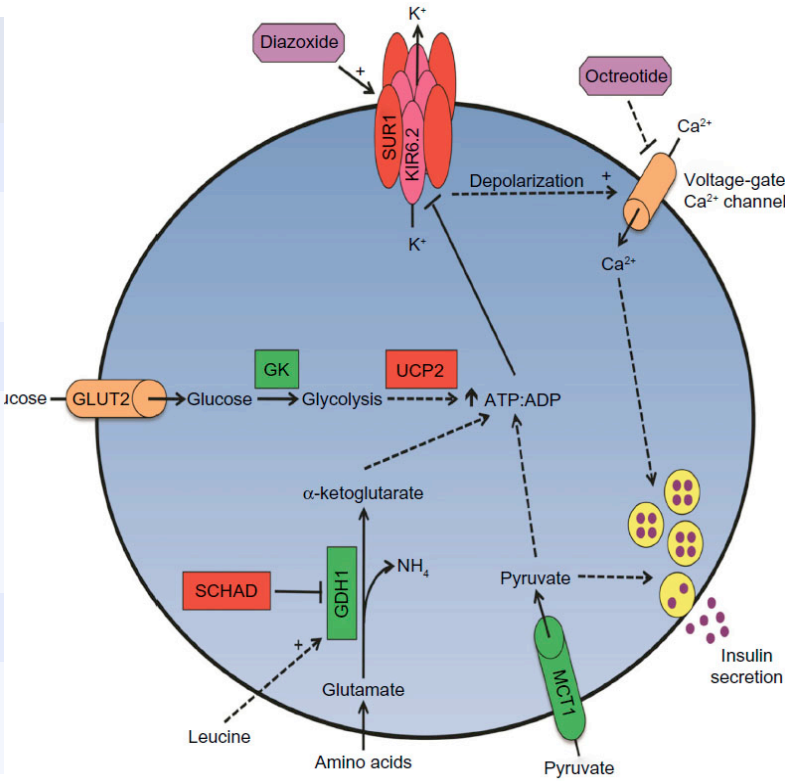
CHI-causes

Gene	Protein	Inheritance	Name of CHI	Diazoxide-responsive
KATP gene				
ABCC8 / KCNJ11	SUR / Kir6.2	AR AD paternal	KATP-HI KATP-HI KATP-HI	Yes/No Usually Yes Usually No
Enzymes / transporters				
GLUD1 GCK HADH UCP2 SLC 16A1	GDH Glucokinase SCHAD UCP2 MCT1	AD/De novo AD/De novo AR AD AD	HI/HA syndrome GCK-HI HADH-HI UCP2-HI EI-HI	Usually Yes Yes/No Yes Yes Yes/No
Transcriptions factors				
HNF4A HNF1A		AD/De novo AD/De novo	HNF4A-HI HNF1A	Yes Yes



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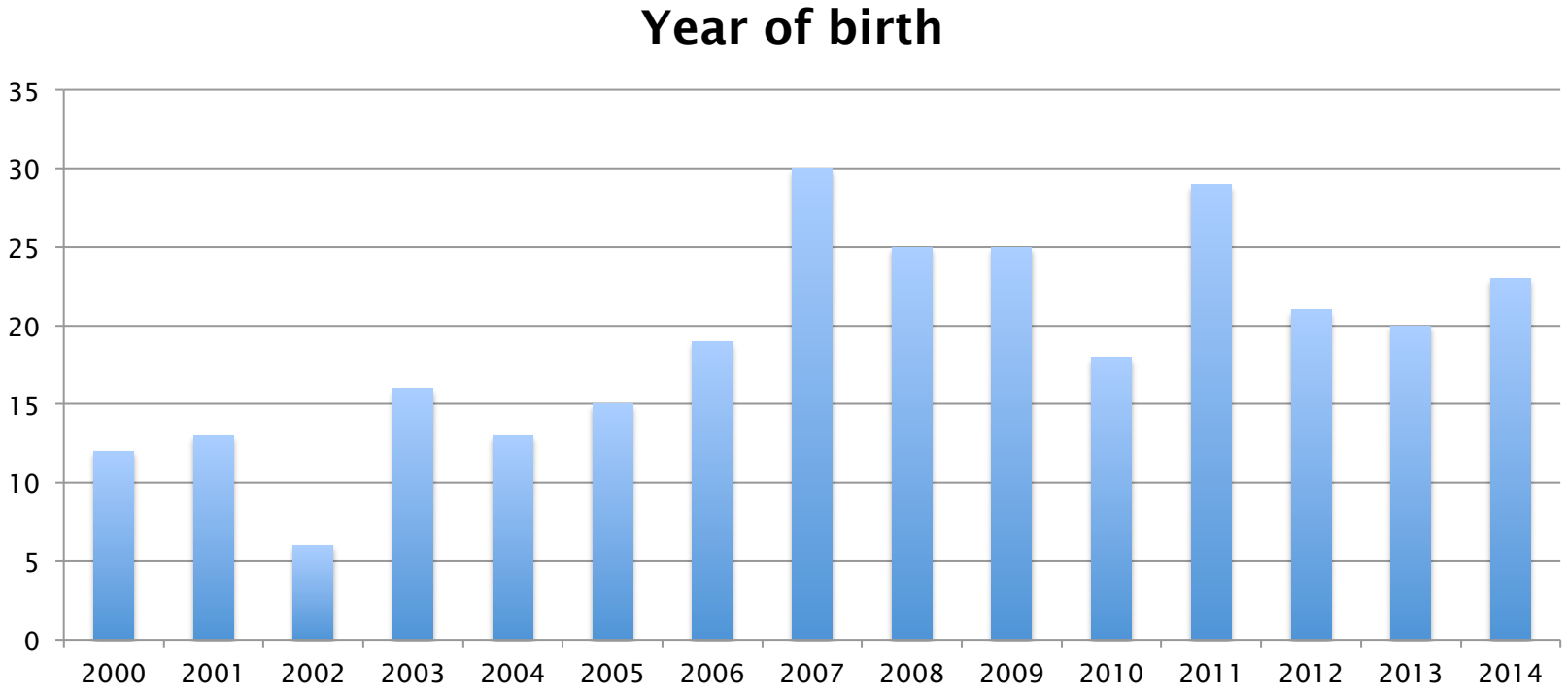
German CHI-registry (as of 2017)

N= 429 patients (Year of birth < 2000: 123)
[18F]F-DOPA-PET-CT: n=208, [18F]F-DOPA-PET-MR: n= 14
surgery reports: n=162
Analysis for SUR-gene mutations: n=217, 10-gene panel 55



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German CHI-registry (n=429): documented genetics (>2001)

investigated samples	gene	positive finding
217	ABCC8	35%
	KCNJ11	6%
55	GCK	5 (10%)
52	GLUD1	4 (10%)
	HADH	4 (10%)
	HNF1A	1 (2%)
	HNF4A	no
	UCP2	1 (2%)
	SLC16A1	no

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Magdeburg cohort: mutations in ABCC8 or KCNJ11

Jahr	Patienten (N)	Mutations-positiv	Heterozygot paternal	Homozygot /compound heterozygot	Heterozygot (dominant)
2013	25	5	5	0	0
2014	20	11	4	3	4
2015	23	10	5	3	2
2016	24	9	5	3	1
2017	28	8	5	2	1
Summe	**120**	**43 (36%)**	**24**	**11**	**8**

Mohnike, K., Wieland, I. et al. (2014): Clinical and genetic evaluation of patients with KATP channel mutations from the German registry for congenital hyperinsulinism. Horm Res Paediatr 81; 156-68

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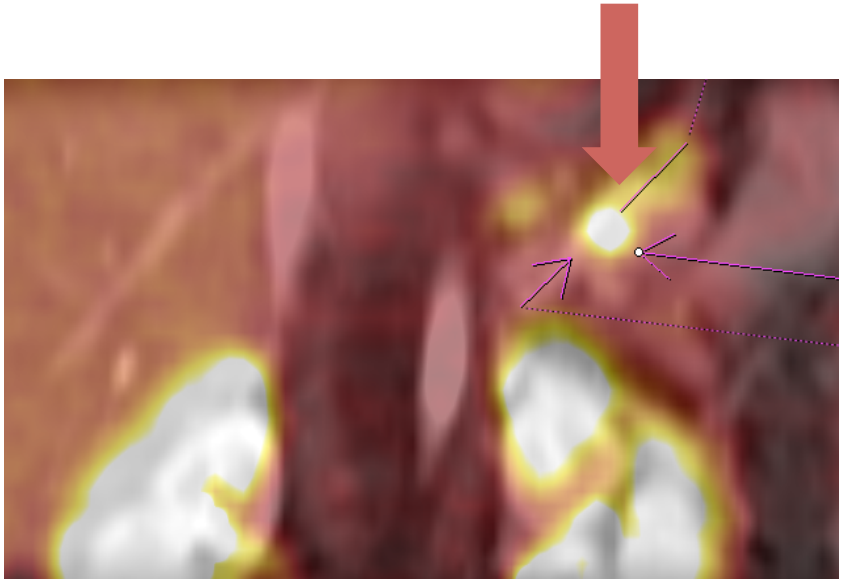
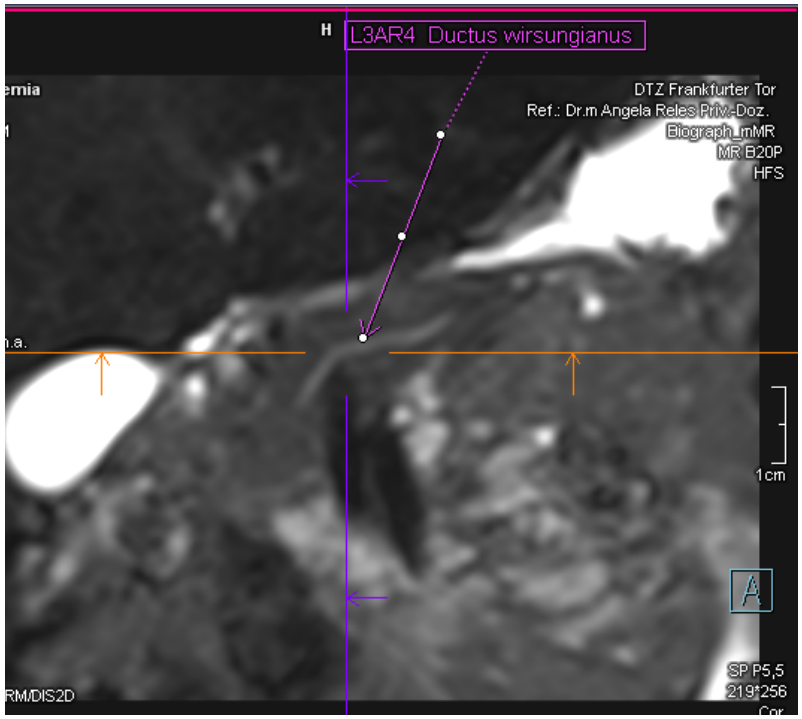
Network Endocrine Conditions (Endo-ERN)

Preoperative Localization by [18F]F-DOPA-PET/MRI

1. Fokuslokalisation



2. OP-kritische Strukturen
- Pankreasgang
- Gefässe



3. Strahlensicherheit
- [18F]F-DOPA: 0,08 mCi/kg
- MRT: 0
- CT: 100 mrem

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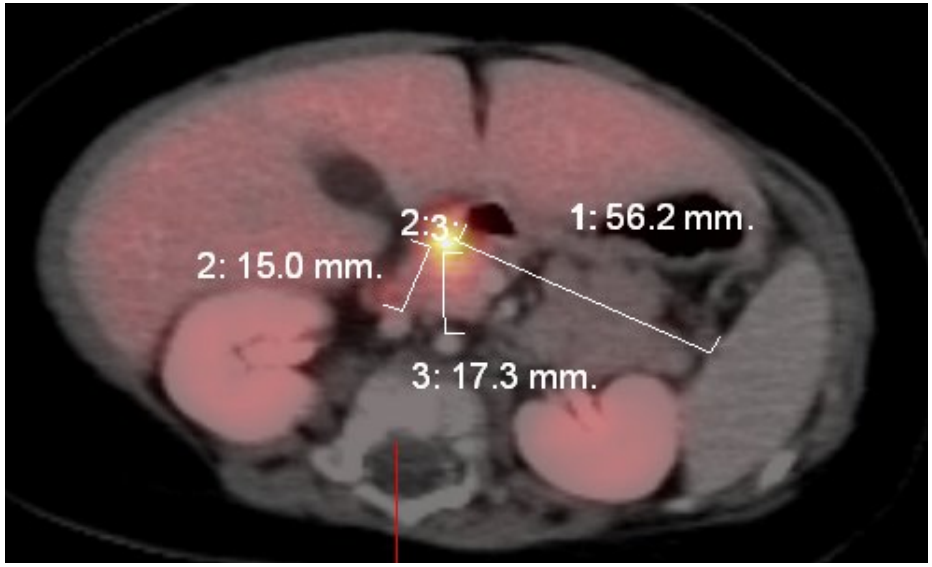
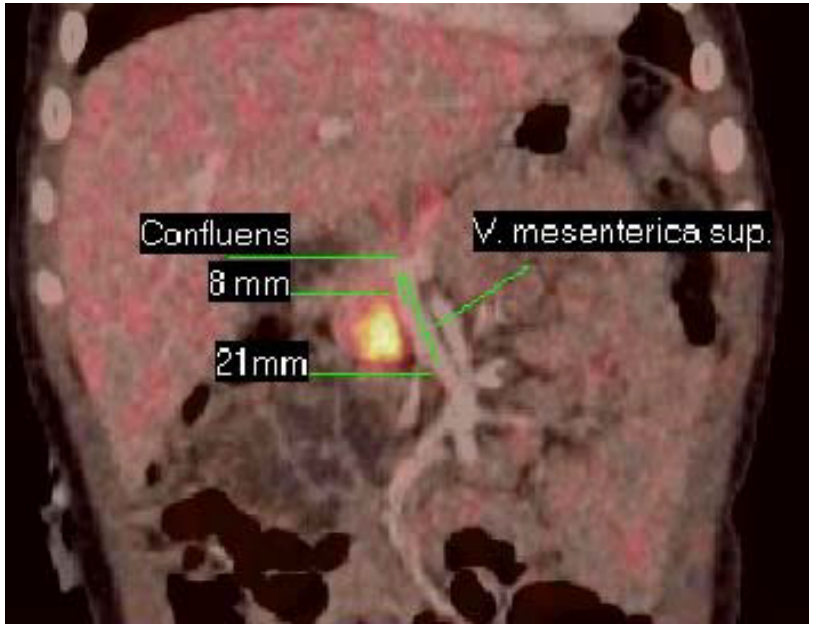
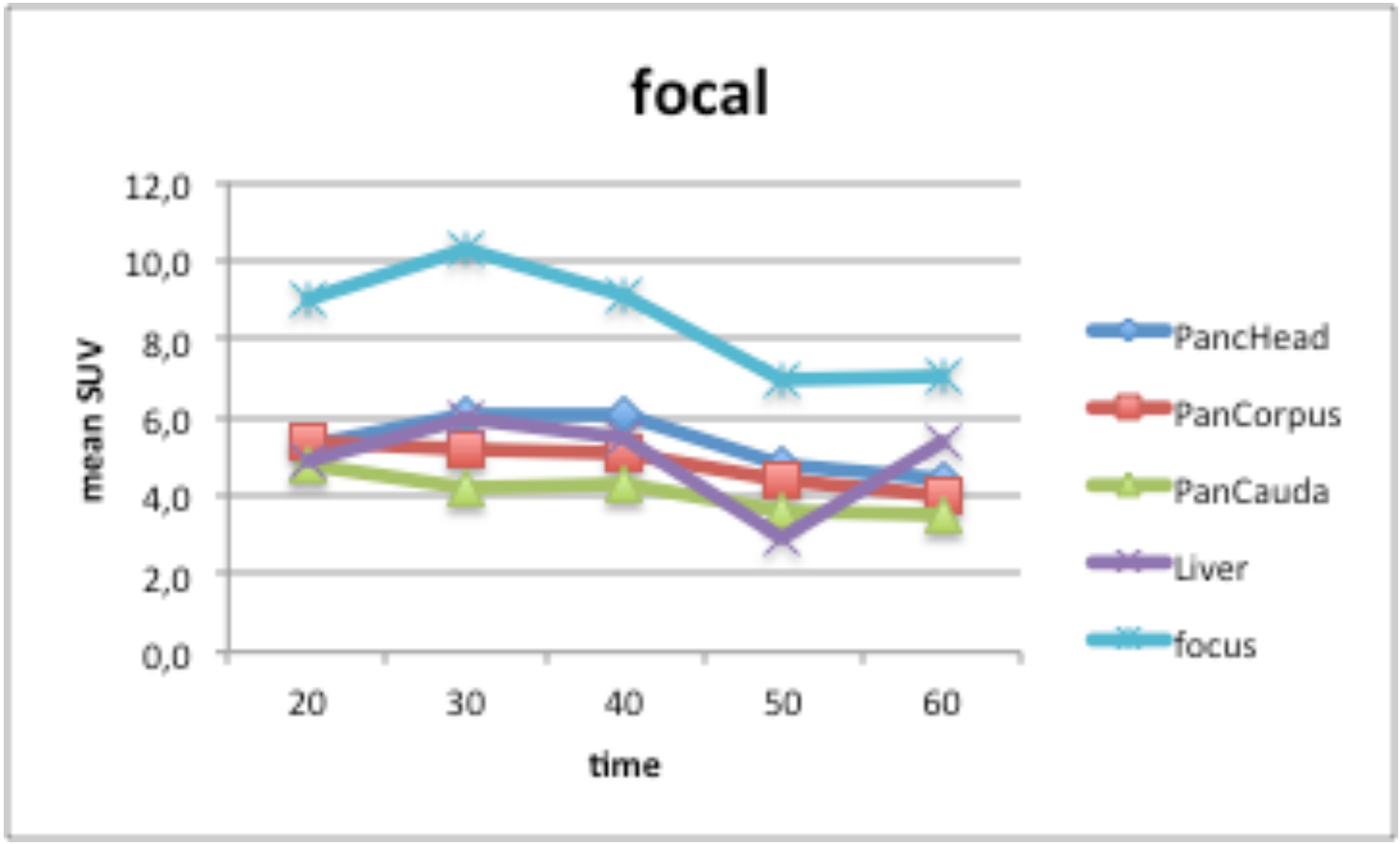
Localization (n= 208)

Kopf: 31 %, Kopf/ Corpus: 9 %
Corpus: 24 %, Corpus/ Cauda: 4 %
Cauda: 31 %






focal
12,0
10,0
8,0
6,0
4,0
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50
60
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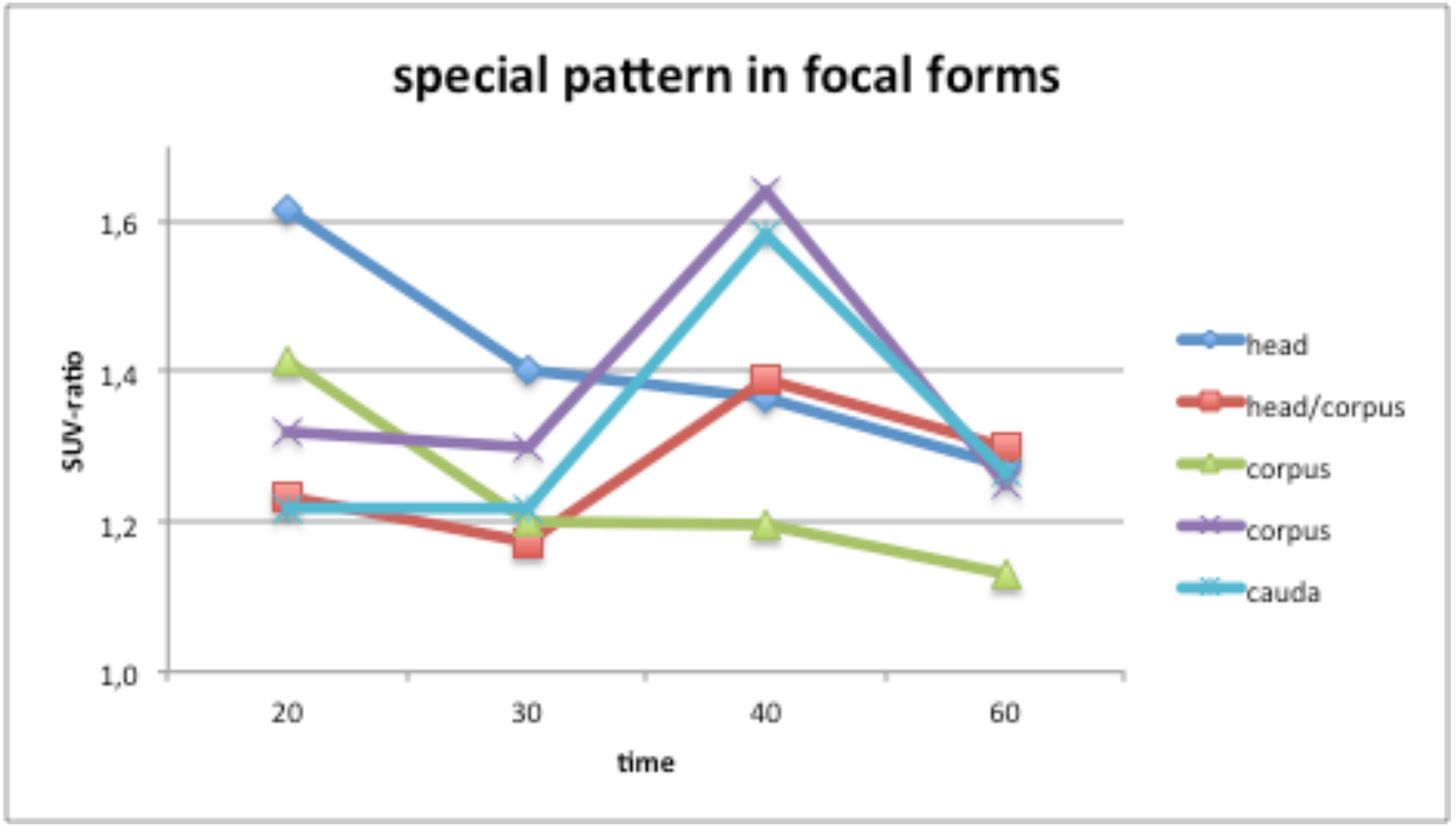
PancHead
PanCorpus
PanCauda
Liver
focus


special pattern in focal forms
SUV-ratio
1,6
1,4
1,2
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20
30
40
60
time
head
head/corpus
corpus
corpus
cauda

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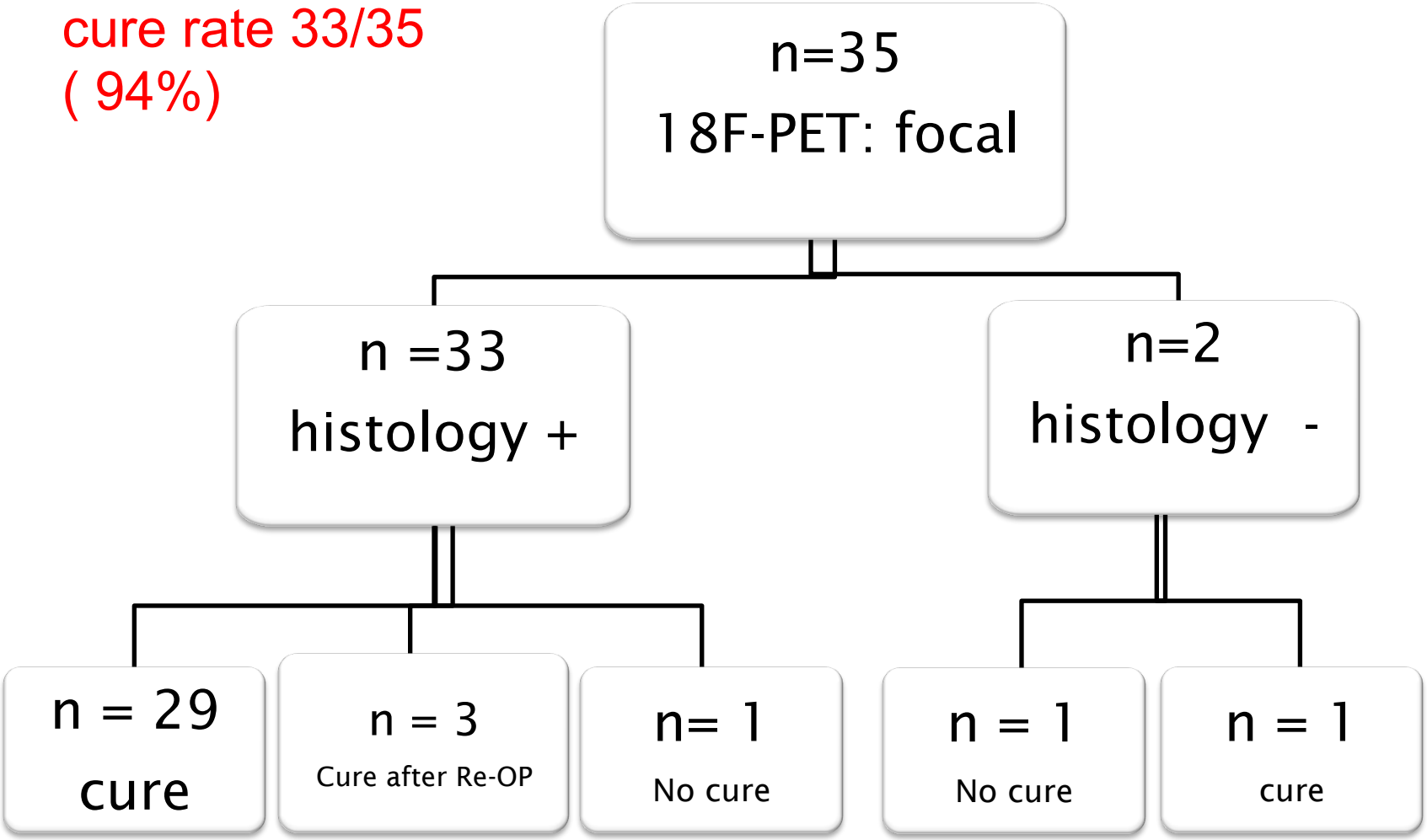
cure rate 33/35
(94%)



pUPD and expression of focal CHI

Patient. No.	Exon	Mutation		Observed freq.* [Ref.]	Age at surgery (months)	mRNA expression	LOH	Paternal UPD11p15
		Nucleotide	Protein					
ABCC8								
1	1	c.50T>C	p.V17A	2* [11]	10	monoallelic mutant	++	++
2	10	c.1530G>T	p.K510N	1 [11]	10	monoallelic mutant	++	++
3	12	c.1792C>T	p.(R598*)	Multiple [CM050968]	7	no (NMD)	++	++
4	22	c.2560-?_2697+?	p.(D854_W899del46)	2 [CG107114]	8	monoallelic r.2560_2697del	ROH	n.d.
5	34	c.4162_4164delTTC	p.F1388del	Multiple [CD962164]	9	monoallelic mutant	++	++
6	35	c.4241C>T	p.P1414L	Multiple [CM068331]	6	monoallelic mutant	++	++
7	35	c.4259C>T	p.S1420L	1 [Barthlen et al, submitted]	2	monallelic mutant	+	+
KCNJ11								
8	1	c.286G>A	p.A96T	1* [11]	2	mutant/wt 75%/25%	+	+
9	1	c.612C>A	p.D204E	2 [CM083531]	2	monoallelic mutant	++	++
10	1	c.844G>A	p.E282K	3 [CM071810]	17	monoallelic mutant	++	++
11	1	c.901C>G	p.R301G	Multiple [CM088147]	6	monoallelic mutant	(+)	+

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Discussion

Members of MTG3 should use the CPMS-tool for discussion of CHI patients. Data management is safe, consent forms should be adapted according to hospital rules

- proposal a fixed date of MTG3 for CPMS
- next case is already enrolled: therapy in GLUD1-mutation
- Use of exendin for localisation during surgery (Case K. Raile)

- regular webinar every 2nd month
- Lab. Exeter performs gene panel in CHI with negative investigated patients for ABCC8/KCNJ11