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Rare subtypes of non-Hodgkin's and Hodgkin's lymphoma

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Diagnosis and treatment of rare NHL variants in children and adolescents

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ESO SIOPE E-learning Session

13. October 2022

Rare pediatric NHL

Definition of „rare“

- all other subtypes than Burkitt‘s lymphoma, DLBCL, LBL or ALCL?
- subtypes comprising <1% of all pediatric NHLs?
- subtypes comprising <5% of all pediatric NHLs?
- subtypes comprising <?% of B-lineage or T-lineage NHL (*i.e.*, PMLBL, PTCL)?
- subtypes of rare histology (*i.e.*, grey zone lymphoma)?
- subtypes confined to certain localisations (*i.e.*, CNS, skin, kidney, etc.)?

Rare pediatric B-NHL

Rare NHL entities

- pediatric-type follicular lymphoma (pFL)
- nodal and extra-nodal marginal zone lymphoma (NMZL, EMZL)
- primary central nervous system lymphoma (PCNSL)
- grey zone lymphoma (GZL)
- peripheral T-cell lymphoma (PTCL)

Pediatric-type FL

Background

- 35% of B-cell NHL in adults – 1% of B-cell NHL in childhood
- mostly occurring in adolescence and young adulthood
- mostly limited disease (lymph nodes, tonsils, testis)
- often high-grade histology & BCL-2-negative and t(14;18)-negative
- very good outcome, but most patients probably treated to aggressively!
- aim: significant & secure reduction of treatment in localized disease

→ retrospective study of EICNHL and i-BFM NHL Committee (n=63)!

Pediatric-type FL – WHO 2022 defintion

Diagnostic criteria	Pediatric-type follicular lymphoma	Large B-cell lymphoma with *IRF4* rearrangement	Reactive follicular hyperplasia (RFH)
Effaced architecture	**at least partially effaced §** „node in node“ feature +/-	at least partly effaced	preserved „naked“ and confluent large germinal centres might be present
Follicular architecture	**pure §**	pure follicular or follicular and diffuse	follicular
Diffuse areas of large cells	**absent §**	present in most cases	absent
Zonation of germinal centres	absent or blurred	absent	preserved at least in the majority of follicles
Starry sky pattern/tingible body macrophages	preserved in part of the cases	absent	present in dark zone
Cytology in follicles	monotonous medium sized cells, atypical centrocytes and centroblasts large nucleoli rare	monotonous large cells with variable cytology mostly centroblasts large nucleoli	variable typical centrocytes and centroblasts
Localization	most head and neck **nodal §**	tonsils payer plaques nodal head and neck (rare)	nodal or extranodal
Immunophenotype	**CD20+ §, BCL6+ §**, CD10+/(-), BCL2-/+, MUM1-/+	CD20+, BCL6+, CD10-/+, BCL2+/-, MUM1++	CD20+, BCL6+, CD10+, BCL2-, MUM1-/+
Clonal *IGH/IGK* rearrange ment	**+ #**	+	-*
Gene translocations *BCL2, BCL6, IGH, MYC, IRF4*	**absent §**	*IRF4*+*** *IGH*+, *BCL6* -/+	absent

§ Essential diagnostic criteria
* Exceptional cases with clonal CD10+ B-cells have been reported in reactive lymphadenitis .
# Prove of clonality is strongly recommended.
*** Exceptional otherwise highly typical cases without proven *IRF4* rearrangement might be accepted.

Pediatric-type FL

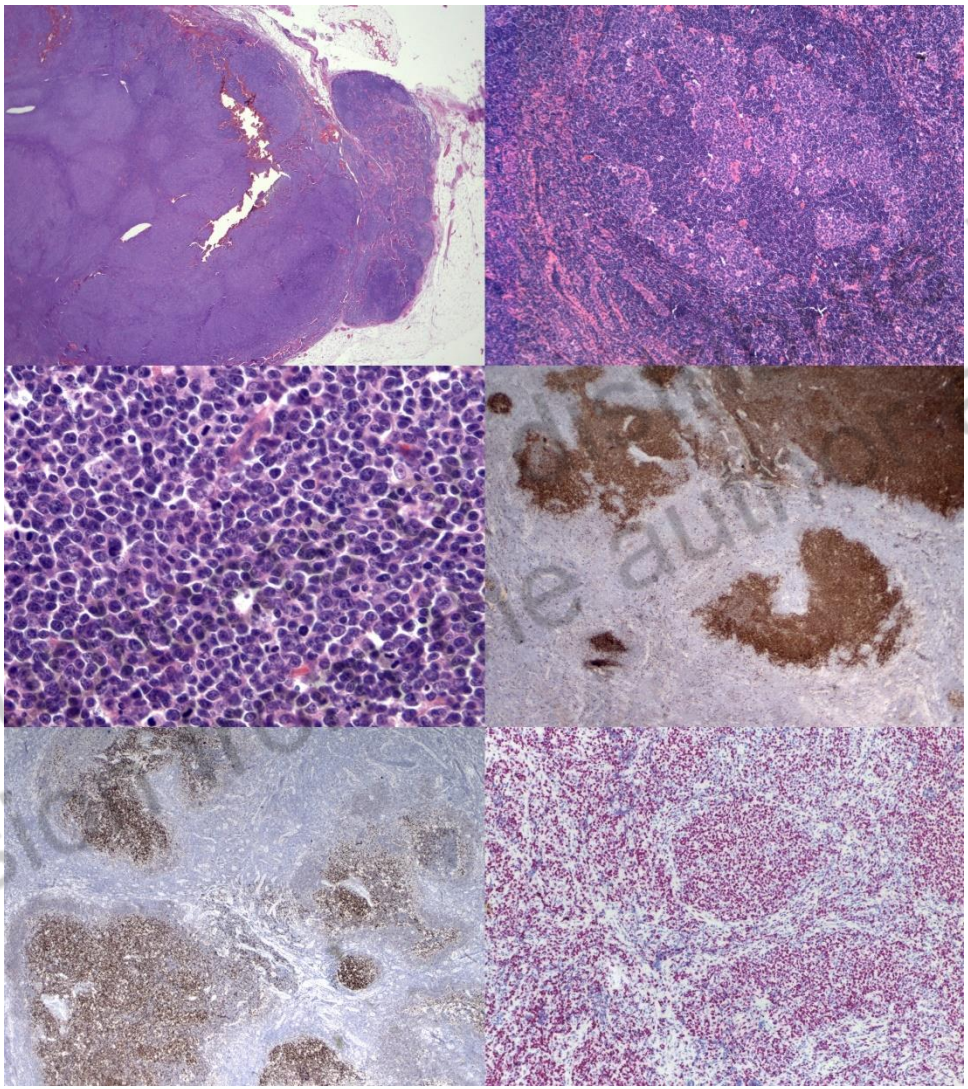


FIGURE 1 Pediatric-type follicular lymphoma: (A) PTFL sparing part of the lymph node (node-in-node pattern); (B) serpiginous outline of some follicles; (C) monotonous population of blastoid cells and a "starry sky" pattern; (D) positivity for CD10 expression in the neoplastic germinal centers; (E) positivity for BCL6 expression; (F) positivity for FOXP1 expression

Pediatric-type FL

Results of the study

- **Gender:**

  male: n=47 (75%) **75%**

  female: n=16 (25%)

  male to female ratio: 3,0

- **Age at diagnosis:**

  median: 13,0 years

  range: 1,4 – 17,1 years

  0 – 10 years: n=18 (28%)

  ≥10 – 15 years: n=25 (40%)

  ≥15 years: n=20 (32%) **72%**

Pediatric-type FL

Results of the study

- **Stage of disease:**

  stage I: n=36 (57%)

  stage II: n=19 (30%) **87%**

  stage III: n=6 (10%)

  stage IV: n=2 (3%)

- **pre-therapeutic LDH level:**

  median: 252 U/l; range: 93 – 550 U/l

  <500 U/l: n=47 (75%) **75%**

  ≥500 U/l: n=5 (8%)

  not available: n=11 (17%)

Pediatric-type FL

Results of the study

- **Sites of involvement:**

peripheral lymph nodes:	n=50 (79%)	**79%**
head and neck (extranodal):	n=1	
tonsils:	n=4	
ENT (tonsils?):	n=4	
mediastinum:	n=0	**0%**
abdomen:	n=9	
bone marrow:	n=2	**1,5%**
CNS:	n=0	**0%**
testis:	n=2	
skin:	n=1	

Pediatric-type FL

Results of the study

- **Resection status:**

incomplete resection / biopsy:	n=26	(41%)
complete resection:	n=32	(51%)
not available:	n=5	(8%)

51%

- **Treatment:**

chemotherapy:	n=44	(70%)
Rituximab only:	n=1	(2%)
Watch and wait:	n=17	(26%)
not available:	n=1	(2%)

72%

- out of 32 patients with complete resection, 17 (53%) patients underwent a watch & wait strategy!

Pediatric-type FL

Results of the study

- **Resection according to stage** (stage I: n=36; stage II: n=19)**:**

  stage I-R: n=30 **83%**

  stage I-NR: n=4

  stage I-n.a.: n=2

  stage II-R: n=2 **11%**

  stage II-NR: n=14

  stage II-n.a.: n=3

- **Radiotherapy:**

  no: n=61 (96%) not available: n=1 (2%)

  yes: n=1 (2%)

Pediatric-type FL

Results of the study

- **Outcome:**

  Relapse: n=1 **after watch and wait**

  Death: n=0

  in CCR: n=63 (100%)

  4-years pEFS: 94%±5%

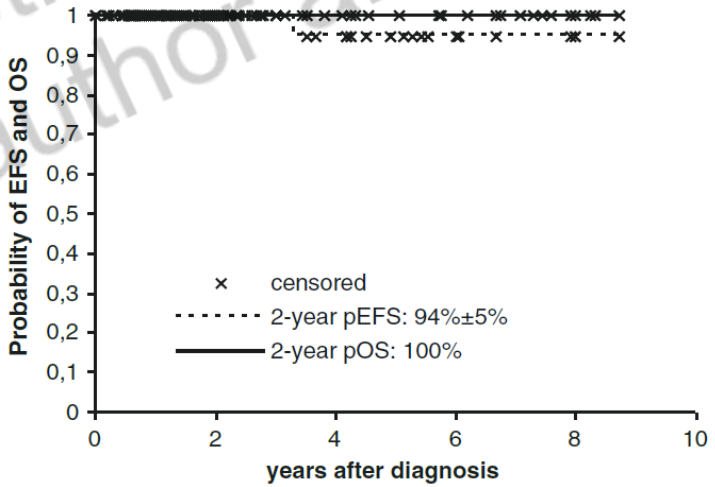


Fig. 1 Two-year event-free and overall survival of the 63 patients with pediatric follicular lymphoma

- **Follow-up:**

  median: 2,2 years

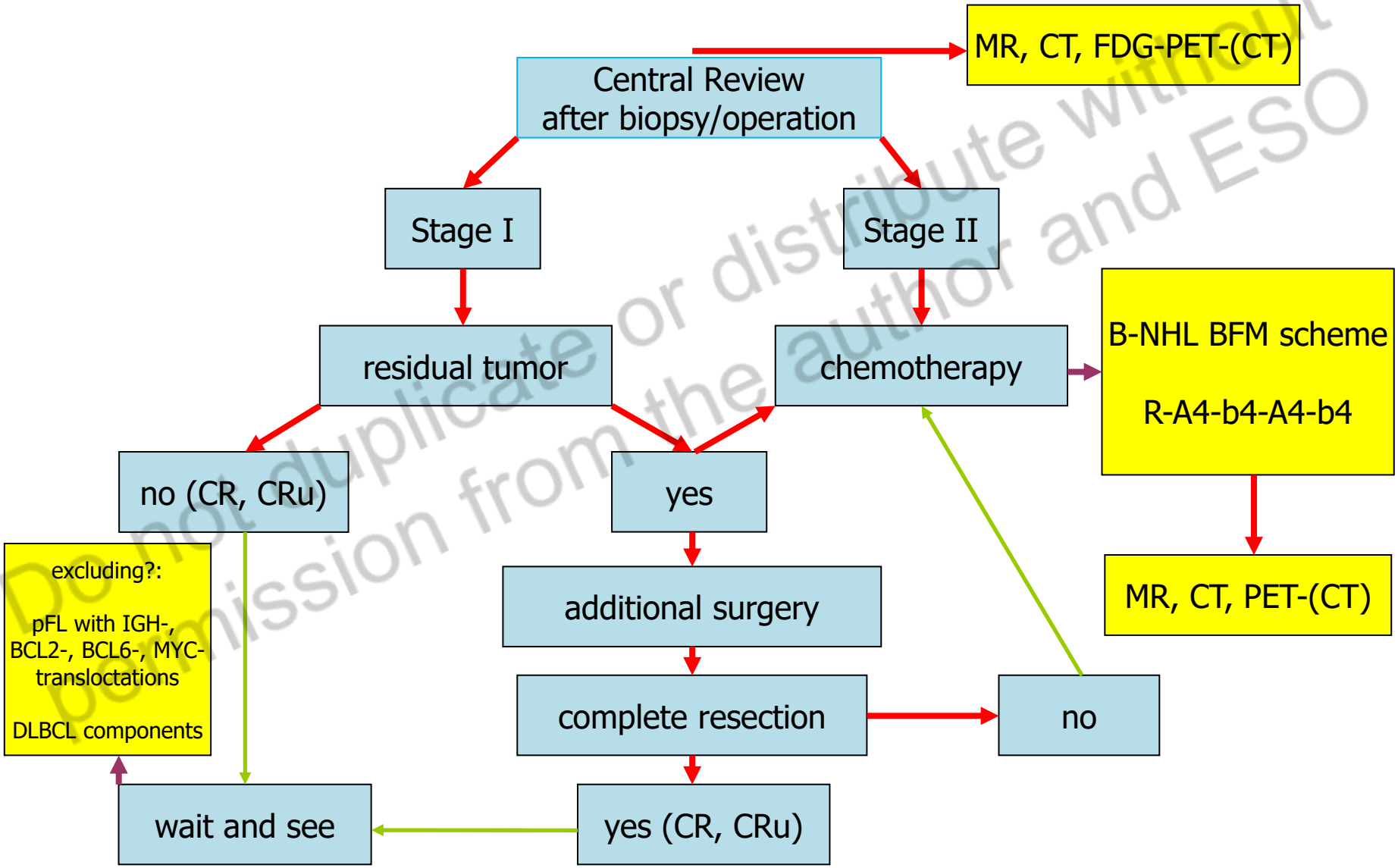
  range: 0,19 – 8,71 years (1 pt. lost to FU)

Pediatric-type FL

Conclusions from the study

- by far the largest cohort of children and adolescents with FL
- associated with male gender and age >10 years
- associated with limited stage of disease and low LDH levels
- mostly peripheral LN involvement; rarely mediastinum, BM and CNS
- in 50% complete resections possible – in 75% chemotherapy
- excellent treatment outcome (also after watch and wait strategy)
- treatment recommendation (in analogy to nodular paragranuloma)?

Pediatric-type FL – Tr. recommendations



Pediatric marginal zone lymphoma (MZL)

Background

- Indolent lymphomas that arise from post-germinal center B-cells
- the WHO classification recognizes three different clinico-pathological entities:
  * splenic marginal zone lymphoma (SMZL)
  * nodal marginal zone lymphoma (NMZL)
  * marginal zone lymphoma of mucosa-associated lymphoid tissue (MZL-MALT)
- male predominance (NMZL m:f = 20:1; EMZL m:f = 5,4:1; Taddesse et al.,2003)
- NMZL: typically: male predominance, asymptomatic lymphadenopathy in the head & neck region, mostly of low-stage.
- EMZL: hypothesis: clonal evolution within the B-cell population in response to an infectious process. Organs: stomach is the most common site involved (H. pylori)
- SMZL: very rare in childhood; most common presentation: splenomegaly, anemia, thrombocytopenia
- Genetic aberrations can be found in some cases (trisomy 3, 18; t(14;18), t(11;18)) - overall the incidence of genetic alterations in MZL in the pediatric and young adult population is low.

Pediatric nodal MZL – WHO 2022 defintion

Essential and desirable diagnostic criteria

Essential:

- Partial effacement of LN architecture by interfollicular proliferation of marginal zone cells with monocytoid and centrocyte-like morphology;
- Monoclonal *IGH* and/or *IGK* genes rearrangements;
- Immunophenotype compatible with marginal zone B-cells (BCL6-, CD43+/-).

Desirable:

- Residual follicles with PTGC-like features;
- Follicular colonization;
- Monotypic light chain restriction;
- Increased PD1+ cells in reactive germinal centres.

Pediatric marginal zone lymphoma (MZL)

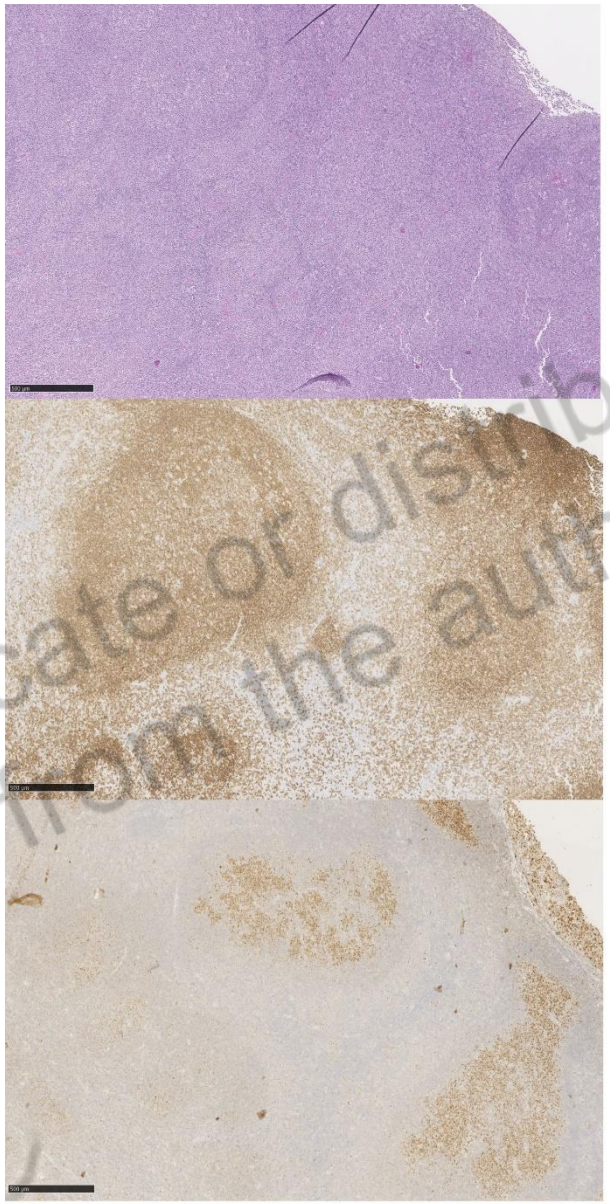


FIGURE 3 Pediatric nodal marginal zone lymphoma: excisional biopsy of a cervical lymph node of a 6-year old boy with isolated lymphadenopathy. (A) The lymph node shows germinal centers with attenuated mantle zones and a prominent pale marginal zone area (hematoxilin and eosin); (B) CD20 stains the germinal centers, mantle, and marginal zone cells; (C) staining for BCL6 indicates colonization of germinal centers by BCL6-negative cells and absence of BCL6 expression in the B-cells of the marginal zone; the scare bars indicate 500 μm

Pediatric marginal zone lymphoma (MZL)

- 4th i-BFM NHL Committee / EICNHL study
- Aim: to collect broad information on the clinical characteristics, treatment and outcome of children and adolescents <18 years with MZL
- diagnosed and treated from 1990 – 2016
- diagnosis reviewed by a reference pathologist

→ 66 patients were identified!

Pediatric MZL: characteristics

	No. of patients (%)
Age	
median	14,2 y
range	2,2-17,9 y
Gender	
male	45 (68)
female	21 (32)
MZL	
NMZL	21 (32)
EMZL	44 (67)
SMZL	1 (1)
St. Jude stage	
I	34 (52)
II	13 (20)
III	12 (18)
IV	4 (6)
n. a.	3 (4)
Serum LDH level	
<500 U/l	53 (80)
≥500 U/l	1 (2)
n. a.	12 (18)
Pre-existing disease	
absent	54 (82)
present	12 (18)

Pediatric MZL: pre-existing diseases

Disease	No. of pts.
Sjögren syndrome	2
Immunodeficiency n. f. sp.:	2
CVID:	2
SCID:	1
STK4 deficiency:	1
Hirsutism, hyperandrogenism:	1
Crigler Najjar syndrome:	1
squamous papilloma:	1
Hodgkin's lymphoma:	1

Pediatric NMZL (n=21)

	No. of patients (%)
Age	
median	14,7 y
range	2,2-17,8 y
Gender	
male	20 (95)
female	1 (5)
Stage	
I	18 (86)
II	0 (0)
III	2 (10)
n. a.	1 (5)
Localisation*	
c / s / n	19 (90)
inguinal	4 (19)
Serum LDH level	
<500 U/l	17 (81)
≥500 U/l	0 (0)
n. a.	4 (19)

	No. of patients (%)
Pre-existing disease	
absent	21 (100)
Therapy**	
Chemotherapy	1 (5)
Radiotherapy	0 (0)
Rituximab	1 (5)
w/w	20 (95)
SCT	0 (0)
Relapse	1 (5)
time to relapse	3,3 months
Death	0 (0)
Follow-up	
median	2,2 y
range	0,1-4,3 y

* 2 patients had lymph nodes involved on both sites of the diaphragm

** 1 patient received chemotherapy and rituximab

Pediatric EMZL (n=44)

	No. of patients (%)
Age	
median	13,1 y
range	4,2-17,5 y
Gender	
male	25 (57)
female	19 (43)
Stage	
I	16 (36)
II	12 (27)
III	10 (23)
IV	4 (9)
n.a.	2 (5)
Localisation*	
LN	8 (18)
ENT	16 (36)
GIT	8 (18)
Skin	9 (20)
CNS/BM	3 (7)
Lungs	4 (9)
other	10 (23)

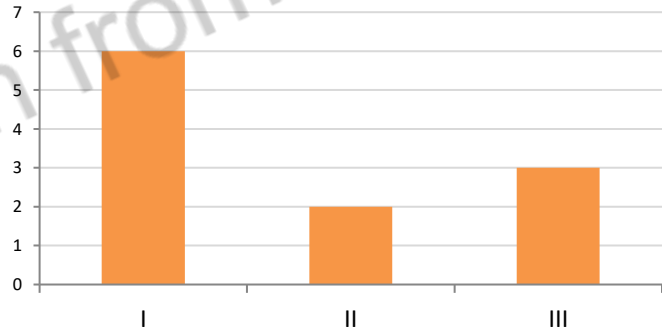
* in 10 patients >1 localisation was involved (2, n=6 / 3, n=4)

	No. of patients (%)
Serum LDH level	
<500 U/l	35 (80)
≥500 U/l	1 (2)
n. a.	8 (18)
Pre-existing disease	
absent	32 (73)
present	12 (27)
Therapy**	
Chemotherapy	21 (48)
Radiotherapy	6 (17)
Rituximab	15 (34)
w/w	12 (27)
SCT	3 (7)
Relapse	
n	10 (23)
median	2,1 y
range	0,7 -4,8 y
Death	2 (4)
Follow-up	
median	3,3 y
range	0,2-12,2 y

** 12 pts. were treated by chemoth.&rituximab (including 1 with RT) and 1 received chemotherapy & SCT

Pediatric MZL: relapse (n=11)

- n=11 (16,7%)
- Median age: 14,7 y (6,8 - 17,2 y)
- male to female: 6 : 5
- 10 EMZL / 1 NMZL
- Stage:

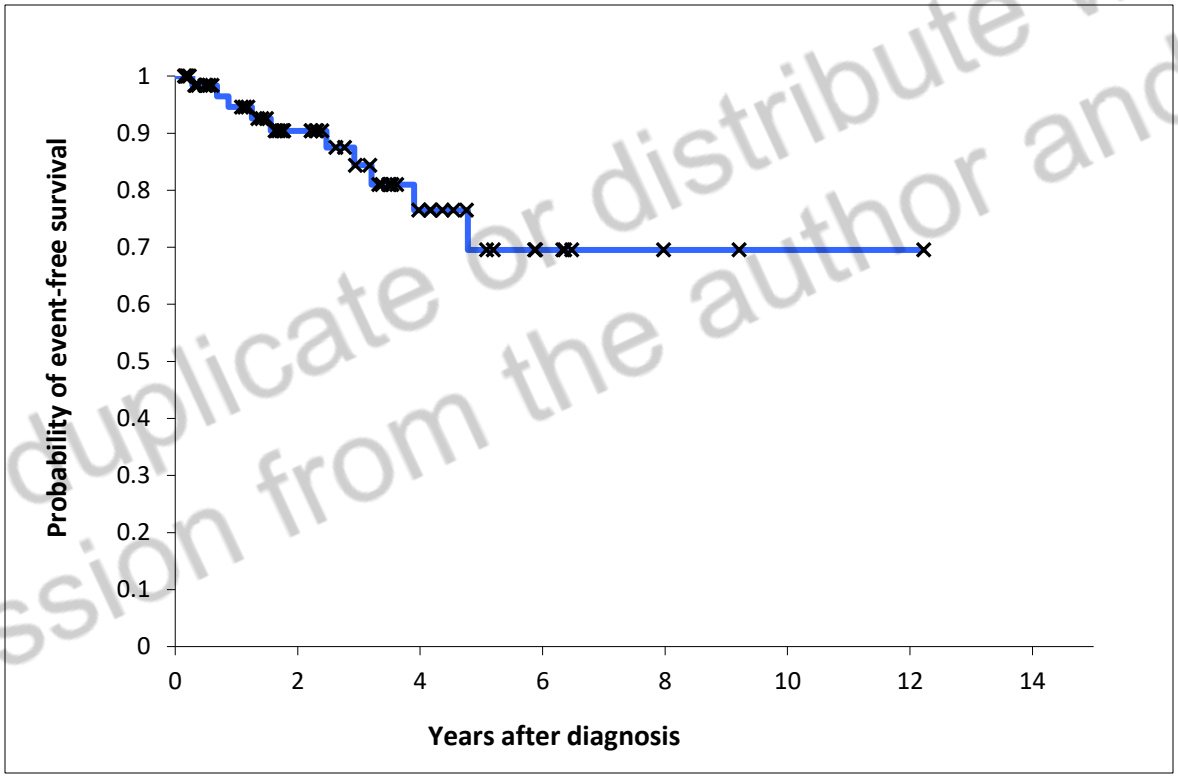


Pediatric MZL: death (n=2)

	No.
Age	11,6 y
range	11,2- 11,9 y
Gender	
male	1
female	1
MZL	
EMZL	2
Stage III	2
Serum LDH level	
n. a.	2
Pre-existing immunodeficiency	
present	2
Therapy*	
Chemotherapy	2
SCT	1
Relapse	1
Time to relapse	4,8 y
OS	
Time to death	3,5 y
range	1,5-5,5 y
Cause	
GvHD & infections	1
therapy-related toxicity (SCT for relapse)	1

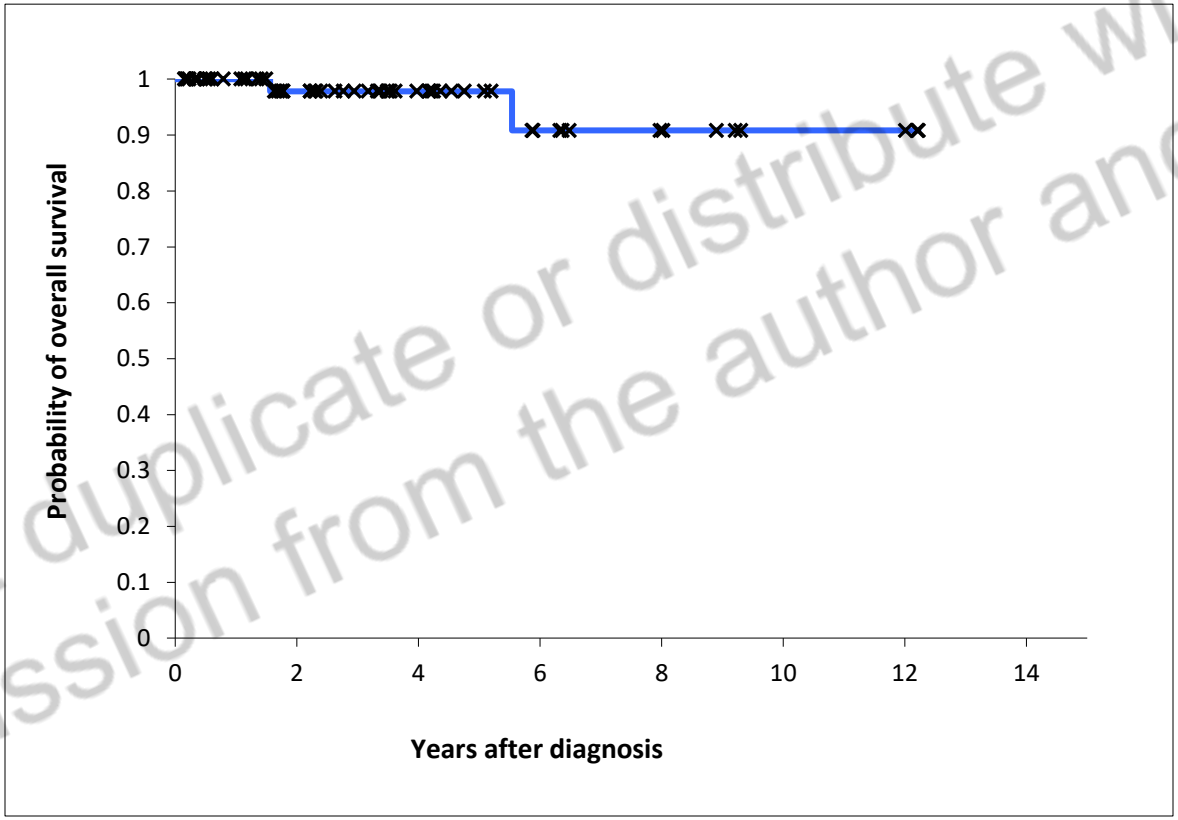
* 1 patient underwent SCT after chemotherapy

pMZL
Event-free survival of all patients



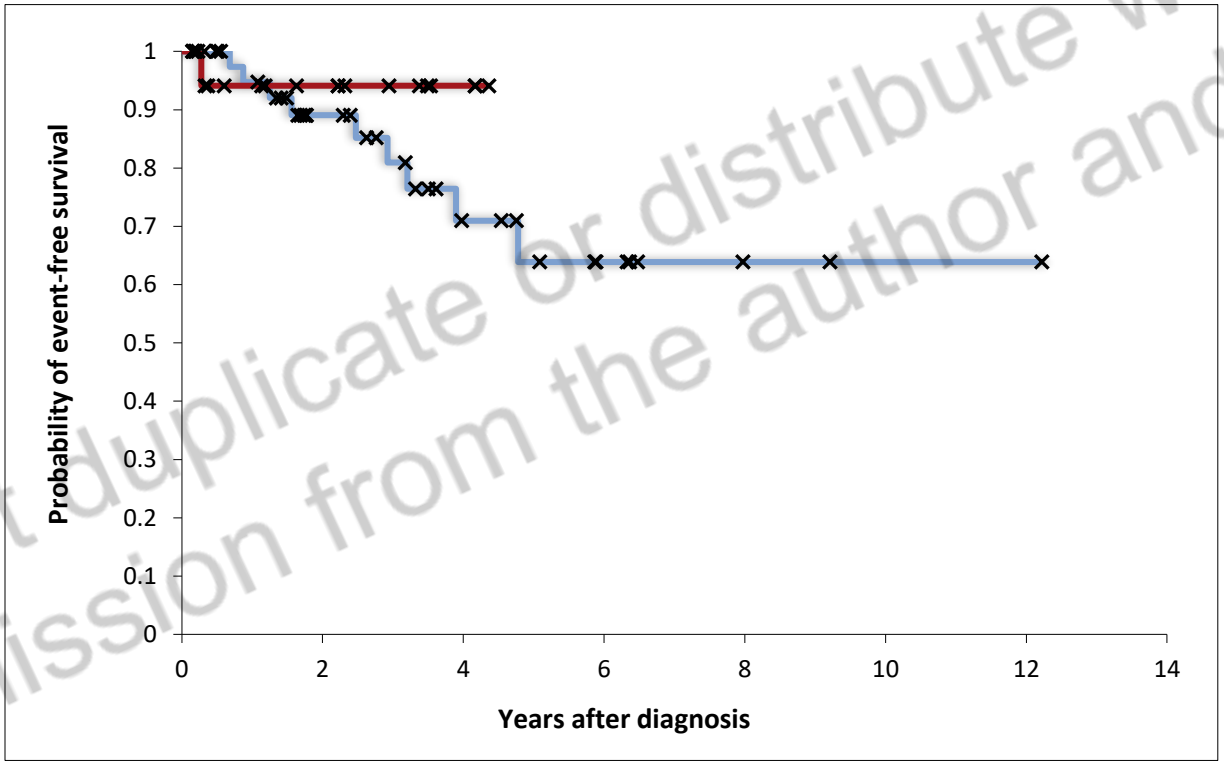
n=66: 5-year event-free survival (EFS): 70%±9%

pMZL
Overall survival of all patients



n=66: 5-year overall survival (OS): 98%±2%

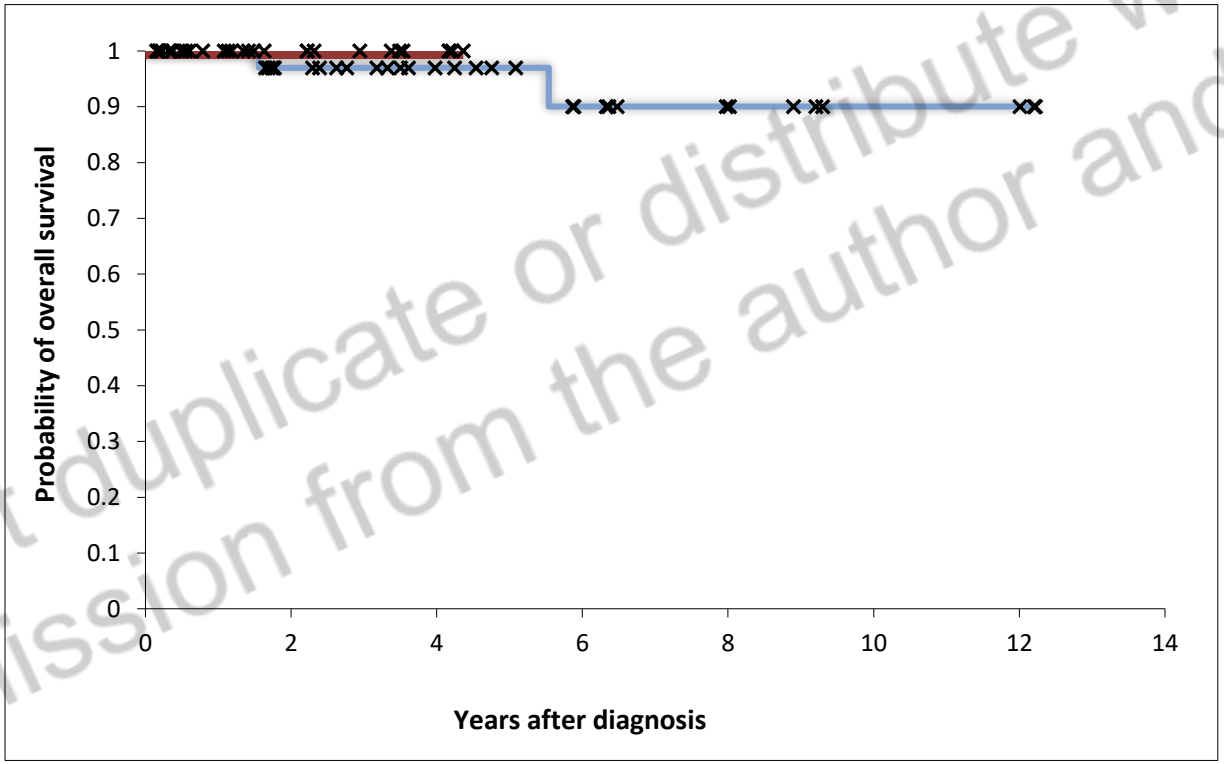
pMZL: EFS according to histology



NMZL: n=21: 5-year event-free survival: 94%±6%

EMZL: n=44: 5-year event-free survival: 64%±11%

pMZL: OS according to histology



NMZL: n=21: 5-year overall survival: 100%

EMZL: n=44: 5-year overall survival: 97%±3%

Pediatric MZL – Conclusions

- by far the largest cohort of children and adolescents with MZL
- associated with male gender and age >10 years
- associated with limited stage of disease and low LDH levels
- EMZL mostly involving ENT, skin, GIT; rarely mediastinum, BM and CNS
- 32/66 underwent a watch & wait strategy; 22/66 chemotherapy
- excellent treatment outcome
  (also after watch-and-wait: 28/32 in CR; in particular for NMZL after W/W)
- treatment recommendation:
  1) NMZL: in analogy to FL
  2) EMZL: therapy of infectious agent?
     W/W in limited, ? in advanced disease

PCNSL – background in children and adolescents

International Primary CNS Lymphoma Collaborative Group (IPCG), between 1978 and 2008: 29 PCNSL patients <21 years, various treatment strategies. 2-year progression free survival 61% and 3-year overall survival 82%; prognostic factors: patient's age and the performance status.
Abla et al. 2011

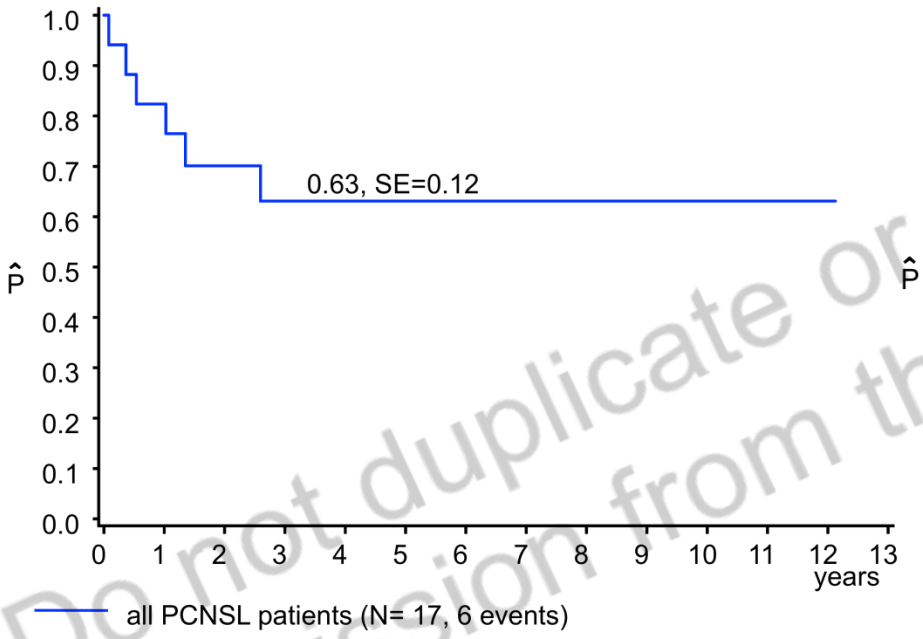
A retrospective chart review at six tertiary care pediatric centers in North America identified 12 PCNSL patients; 8 immunocompetent and 4 immunocompromised. 5-year EFS of 70%±15% for 10 pts. with chemotherapy but no irradiation. 2 chemotherapy patients + cranial irradiation: one relapsed and died while other one alive in CR; Conclusions: pediatric PCNSL pts. achieve long-term remissions with chemotherapy alone without irradiation.
Abla et al. 2006

Retrospective mono-center experience of the Seoul National University Children's Hospital including 6 patients treated with chemotherapy without irradiation and 5-year relapse-free survival in five of the six children.
Yoon et al. 2012

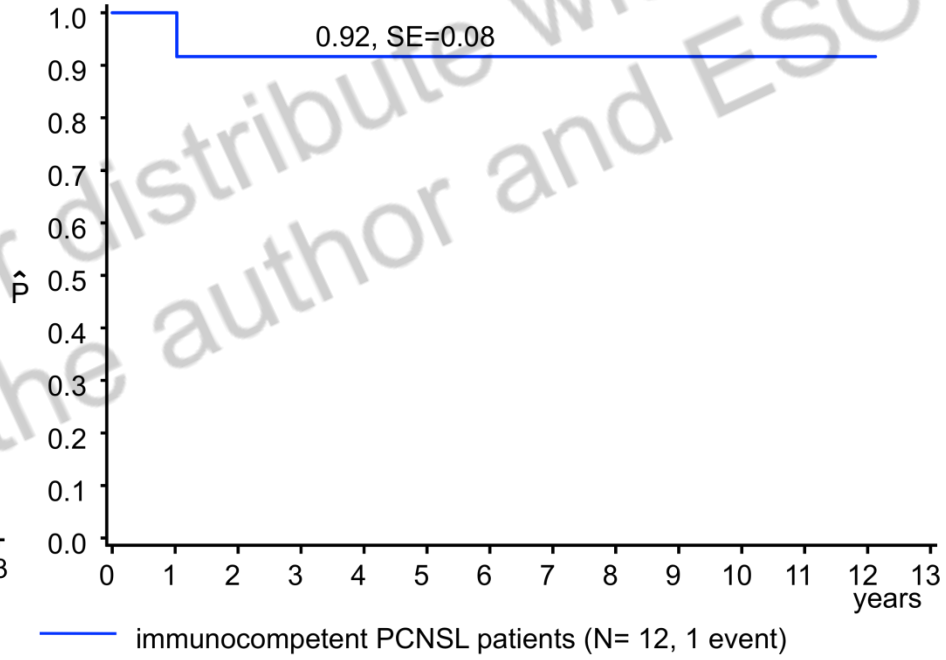
Taking theses cases together with earlier case reports far below hundred cases of PCNSL in children and adolescents were published until today.
Rodriguez et al. 1997; Kai et al. 1998; Zhu et al. 2011; Quadri et al. 2011; Makino et al. 2007; Havlioglu et al. 1995

PCNSL – results of the NHL-BFM SG

pEFS of all PCNSL pts.



pEFS of immunocompetent PCNSL pts.



PCNSL project – definition & objectives

Defintion: any newly diagnosed NHL involving exclusively the brain, the cerebrospinal fluid, the meninges or the spinal cord.

Objectives:

- to characterize initial clinical and laboratory characteristics
- to assess type of therapy
- to assess disease outcome
- to assess disease outcome btw. pts. with or without a pre-existing disorder
- to assess neurological outcome and other late effects

PCNSL – countries contributing

Armenia:	n=1
Belarus:	n=3
Belgium:	n=3
Czech Republic:	n=2
France:	n=9
Greece:	n=1
Hong-Kong:	n=2
Ireland:	n=1
Italy:	n=2
Japan:	n=3
The Netherlands:	n=2
Poland:	n=1
Russia:	n=7
Serbia:	n=1
Slovenia:	n=1
Spain:	n=2
United Kingdom:	n=6
NHL-BFM:	n=21
COG:	n=7
together:	**n=75**

Median follow-up:	5.22 years
Range of follow-up:	0.19 – 25.59 years

PCNSL – i-BFM/EICNHL/COG

Table 1. Initial characteristics and therapy of the 75 PCNSL study patients

Variable	Patients
Patients, n	75
Sex	
Female	29 (39)
Male	46 (61)
Age, y	
Median (range)	12.5 (1.25-18.87)
<10	26 (35)
≥10 to <15	31 (41)
≥15	18 (24)
Preexisting disorder	
Yes	14 (19)
No	56 (75)
Unknown	5 (6)
Lansky score	
<40%	14 (19)
≥40-79%	27 (36)
≥80%	19 (25)
Unknown/not applicable	15 (20)
B symptoms	
Yes	9 (12)
No	59 (79)
Unknown	7 (9)
Cranial nerve palsies	
Yes	33 (44)
No	39 (52)
Unknown	3 (4)
Histopathologic subtype	
DLBCL	37 (49)
Burkitt lymphoma	9 (12)
Mature B-NHL NOS	5 (7)
ALCL	17 (23)
Other NHL	7 (9)
BCP LBL, n	4
EN MZL, n	1
PTCL, n	2
Localization	
Intracranial	70 (93)
Intraspinal only	2 (3)
Leptomeningeal only	3 (4)
No. of lesions	
1	36 (48)
≥2	32 (43)
Unknown/not applicable	7 (9)
Initial LDH level, U/L	
<500	53 (71)
≥500	10 (13)
Unknown	12 (16)

Table 1. (continued)

Variable	Patients
Initial therapy	
Chemo only	31 (41)
Chemo and rituximab	15 (20)
Chemo and RT	24 (32)
Chemo and rituximab and RT	2 (3)
Other	3 (4)
Therapy	
Pediatric NHL-type*	57 (76)
Adult NHL-type†	1 (1)
Miscellaneous‡	17 (23)
Chemotherapeutic drugs, n§	
High-dose methotrexate	68
High-dose cytarabine	55
Anthracyclines	59
Alkylating agents	64
Intrathecal therapies	69
RT	
Yes	26 (35)
No	49 (65)
Stem cell therapy in CR1	
Autologous	3 (4)
Allogeneic	1 (1)
Rituximab in mature B-NHL	17 (32)

PCNSL – i-BFM/EICNHL/COG

Table 2. Disease outcome and long-term side effects of the 75 PCNSL study patients

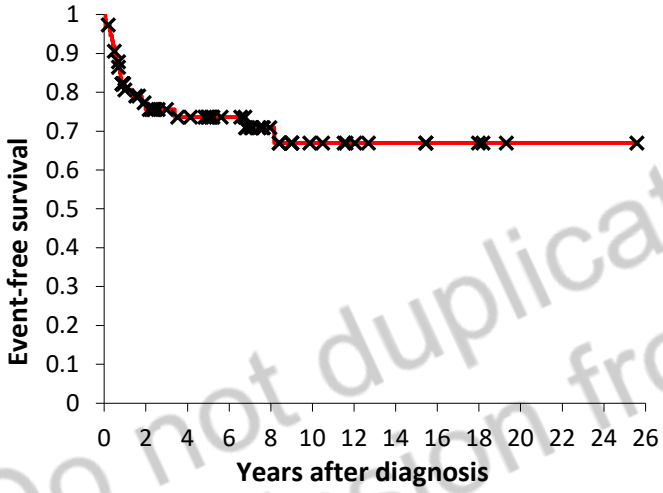
Variable	Patients
Treatment failure	
Median (range) time to, y	0.77 (0.27-6.78)
Relapse*	12 (16)
Progression	2 (3)
Localization of failure, n	
CNS only	8
CNS and other	2
Outside CNS only	2
Unknown	1
Multiple sites n.f.s.	1
Death	12 (16)
Relapse/progression, n	6
Without any therapy, n	1
Therapy-related toxicity, n	4
Unknown, n	1
Second malignancy, n	0
Continuous CR	58 (75)
Follow-up	
Median (range), y	5.22 (0.19-25.29)
In CR1	53 (91)
In CR2	5 (9)
CR not yet achieved at LFU, n	5
Long-term side effects	
Neurological	22 (29)
Endocrine	3 (4)
Cardiac	0 (0)
Other	7 (9)
Osteonecrosis, n	5
Psychosocial, n	1
GVHD, CMV-associated retinitis, n	1

Table 3. Characteristics of the 14 PCNSL patients with preexisting disorders

Type of preexisting disorder	Patients, n	Histology	Event
Immunodeficiency			
HIV infection	2	Burkitt lymphoma/ DLBCL	No/dead: TRM (sepsis)
St. p. heart transplantation	1	DLBCL	Dead: TRM (graft failure)
St. p. kidney transplantation	1	DLBCL	No
St. p. liver transplantation	1	DLBCL	No
SLE	1	DLBCL	Dead (cause unknown)
CLIPPERS	1	DLBCL	No
Colitis ulcerosa	1	DLBCL	Dead: TRM (details NA)
PID n.f.s.	2	DLBCL/DLBCL	No/dead of disease
CVID	1	ALCL	Dead: TRM (pneumonia)
Other disorders			
B-cell precursor LBL	1	DLBCL	No
JMML	1	DLBCL	Relapse
Factor VIII deficiency	1	ALCL	No

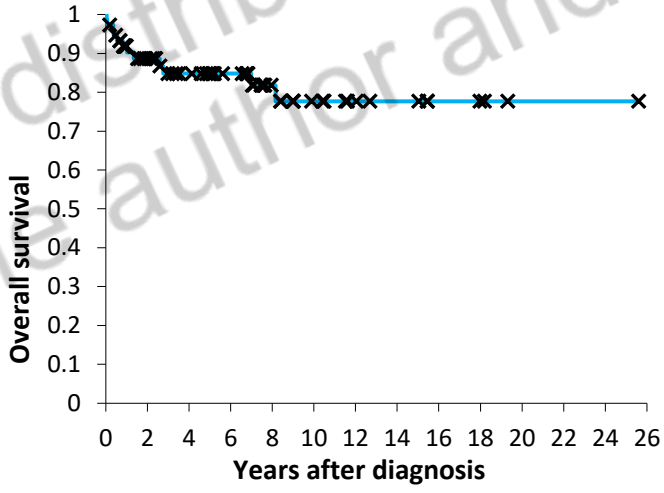
Event-free (EFS) and overall survival (OS) of all pts.

Figure 1A



PCNSL (n=75): 5-year EFS: 74%±5%

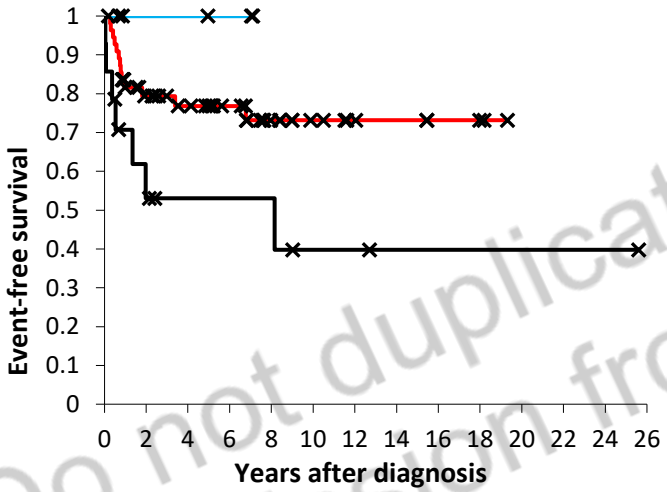
Figure 1B



PCNSL (n=75): 5-year OS: 85%±4%

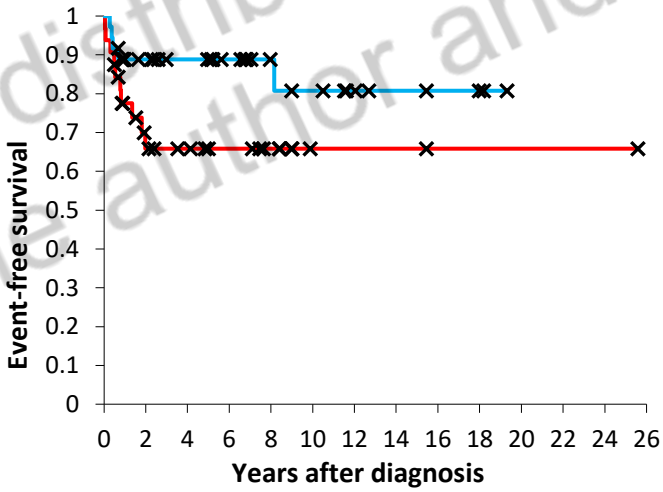
EFS and OS according to pre-existing disorders

Figure 1C



No pre-existing disorder (n=56): 5-year EFS: 77%±6%
Pre-existing disorder (n=14): 5-year EFS: 53%±14%
No information (n=5): 5-year EFS: 100%
p=0.027

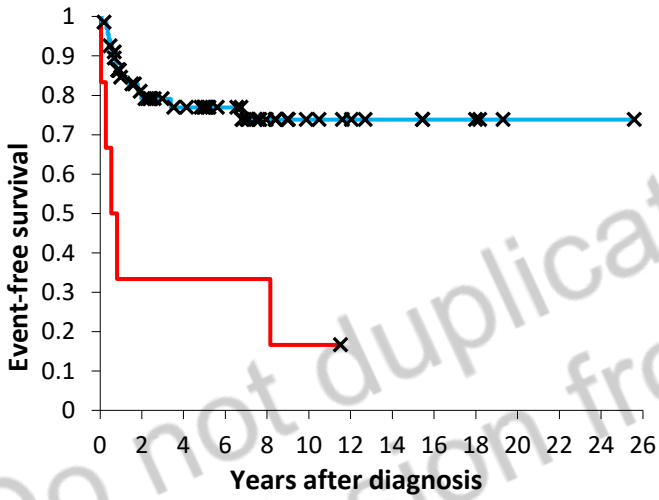
Figure 1D



1 lesion (n=36): 5-year EFS: 89%±5%
≥2 lesions (n=32): 5-year EFS: 66%±9%
p=0.085

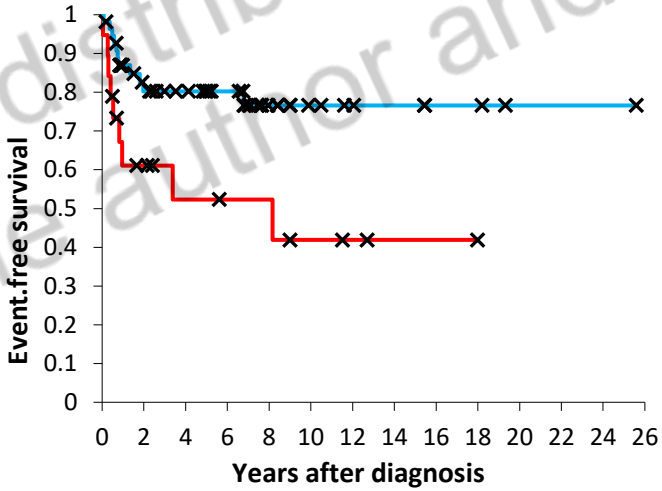
EFS and OS according to type of therapy

Figure 1E



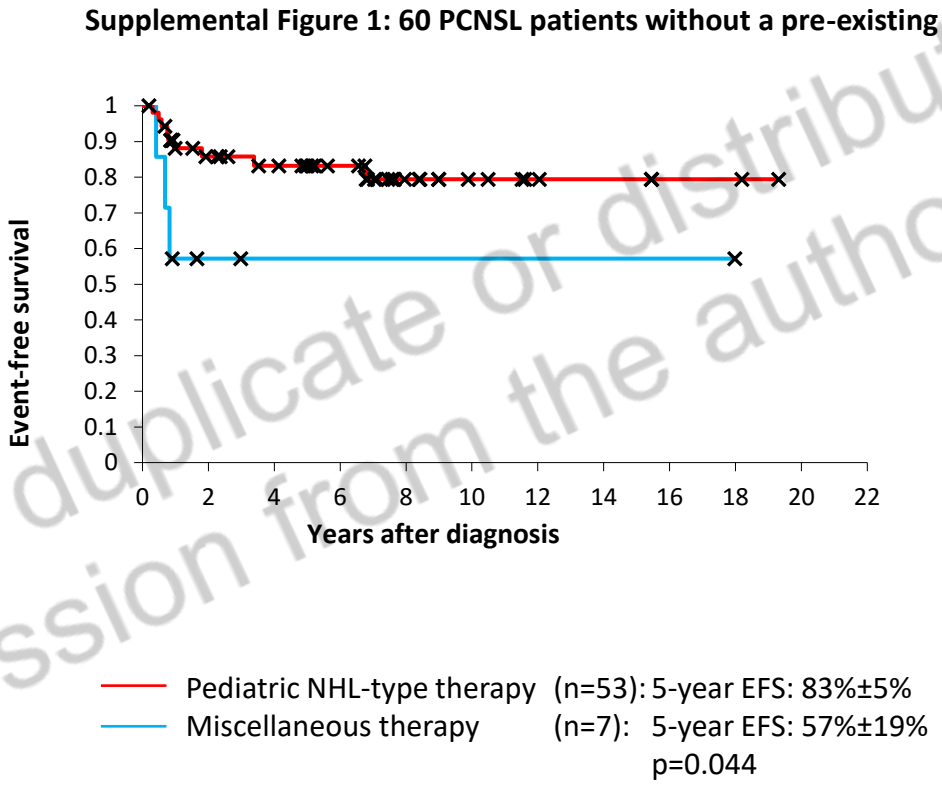
Methotrexate (n=68): 5-year EFS: 77%±5%
No methotrexate (n=6): 5-year EFS: 33%±19%
p=0.0002

Figure 1F



Cytarabine (n=55): 5-year EFS: 80%±6%
No cytarabine (n=19): 5-year EFS: 52%±13%
p=0.012

EFS and OS according to type of therapy



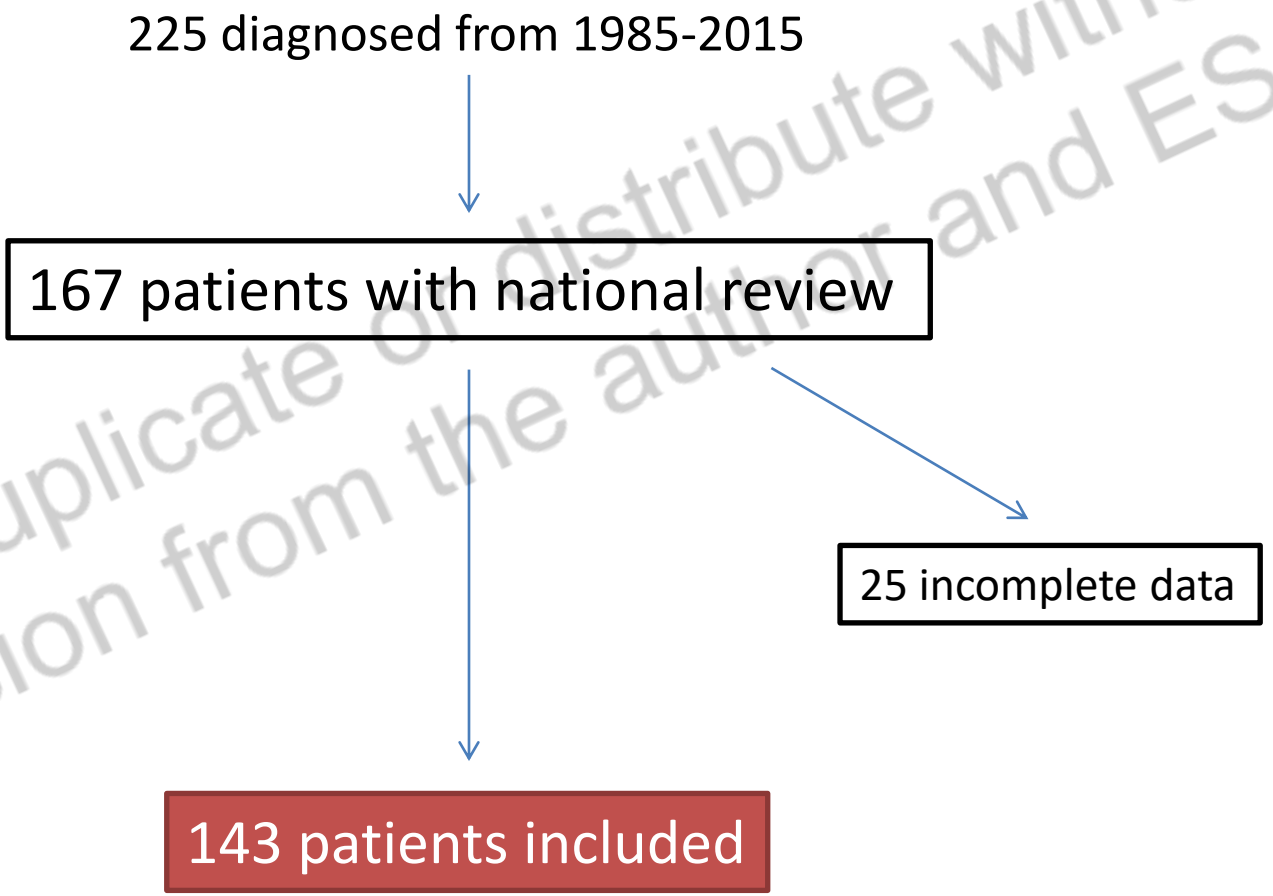
PCNSL – Conclusions

- by far the largest cohort of children and adolescents with PCNSL
- associated with male gender (60%) and age >10 years (66%)
- associated with Lansky <60% (41%) and lack of B-symptoms (78%)
- associated with low LDH levels (74%) and DLBCL histopathology (53%)
- 19% of the patients have a pre-existing disorder
- most pts. are treated with chemotherapy (incl. Rituximab) (63%)
- most pts. are treated with HD-MTX (90%), HD-ARA-C (74%), alkylating agents (87%), doxorubicine (76%) and ith. therapy (93%)
- few pts. have been treated by radiotherapy (32%)

PCNSL – Conclusions

- most pts. are treated with protocols designed for pediatric NHL (81%)
- good outcome, however, patients with pre-existing disorders have a poor prognosis as well as patients not treated with protocols designed for pediatric NHL!
- significant association with neurologic long-term toxicity (31%)

Non-anaplastic peripheral T-cell lymphoma



PTCL – NOS

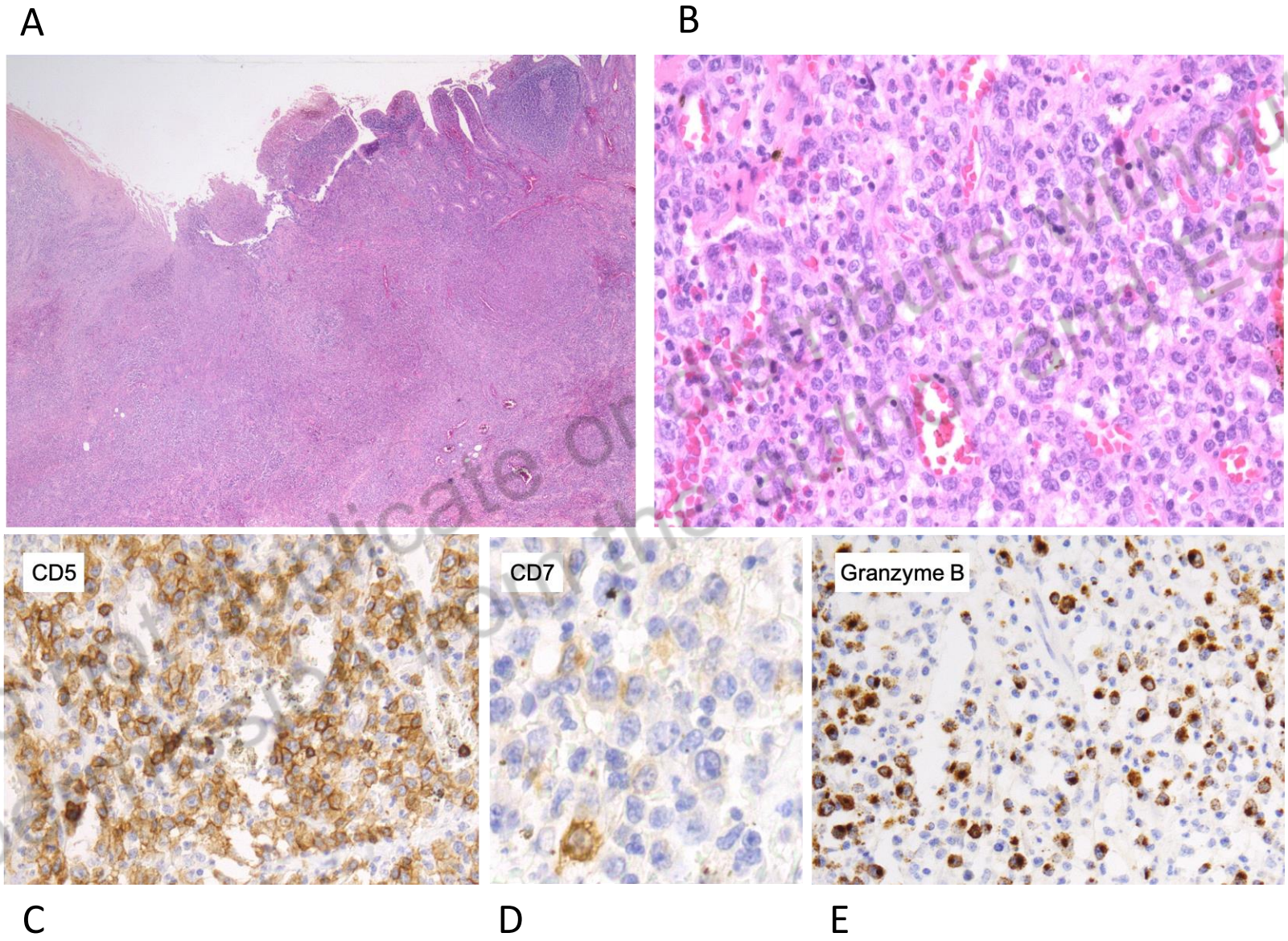


FIGURE 4 Peripheral T-cell lymphoma not otherwise specified: 9-year-old female with a sample of the small intestine with intestinal perforation: the intestinal wall is massively infiltrated by sheets of large and necrotic cells with a cytotoxic T-cell phenotype: hematoxilin and eosin (A, B); CD3-positive, CD5-positive (C); CD7-negative (D); CD8-negative, CD4-negative, CD30-positive, granzyme B–negative (E) and Epstein-Barr encoding region–negative

SPLTCL

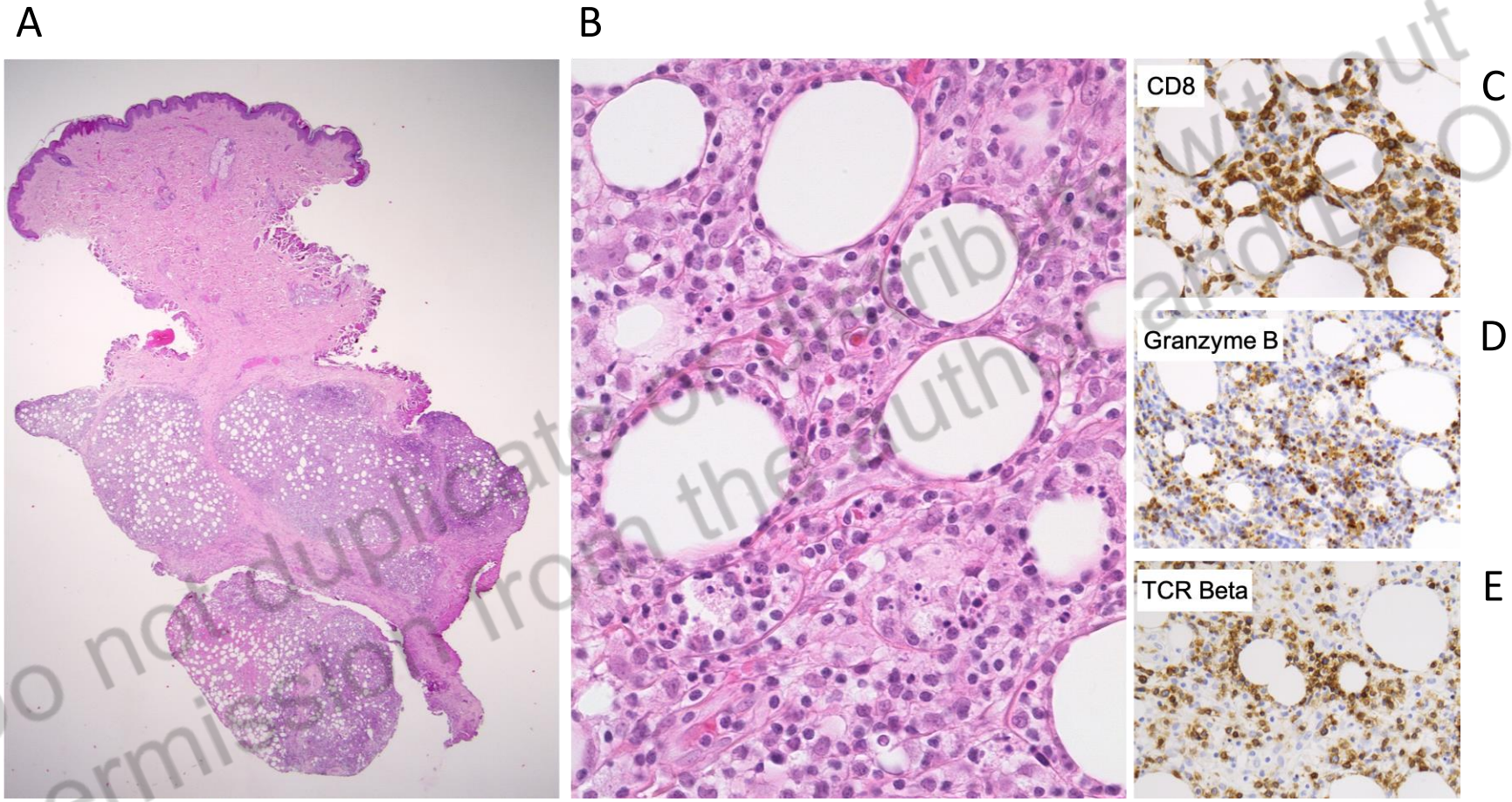
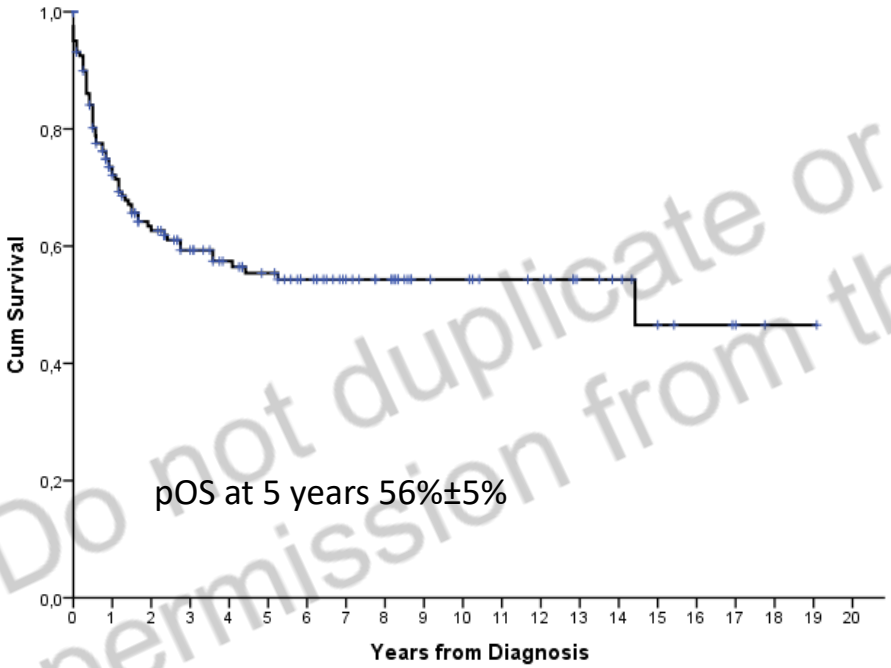


FIGURE 5 Subcutaneous panniculitis-like T-cell lymphoma: tumor sample of a 5-year-old male with numerous features of adipocytic rimming and nuclear debris: hematoxilin and eosin (A, B), which is, predominantly, composed of CD8-positive (C), granzyme B-positive (D), and T-cell receptor (TCR) β-positive (E) cytotoxic T cells

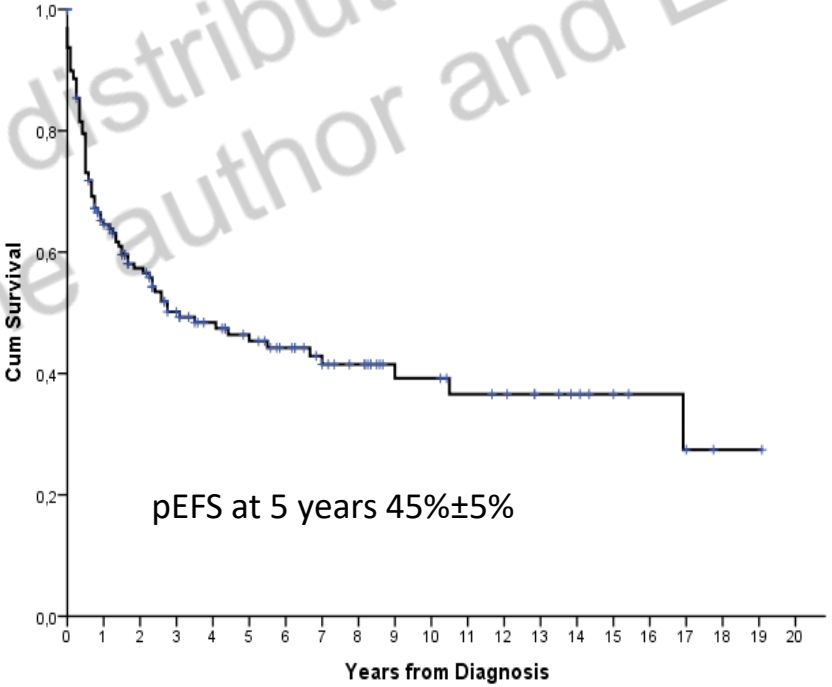
Histopathological sub-entities of PTCL

Classification	No.	Group
PTCL-NOS Angio-immunoblastic PTCL	60 4	nodal group
Hepatosplenic TCL Subcutaneous panniculitis-like TCL Primary cutaneous γδ TCL Extranodal NK/T-cell lymphoma	20 20 1 21	extranodal group
Mycosis fungoides	7	cutaneous group
EBV+/- LPD, peripheral T-cell lymphoma HV-like EBV-related T-cell lymphoma	6/3 1	EBV-related group

PTCL: survival of all 143 pts.

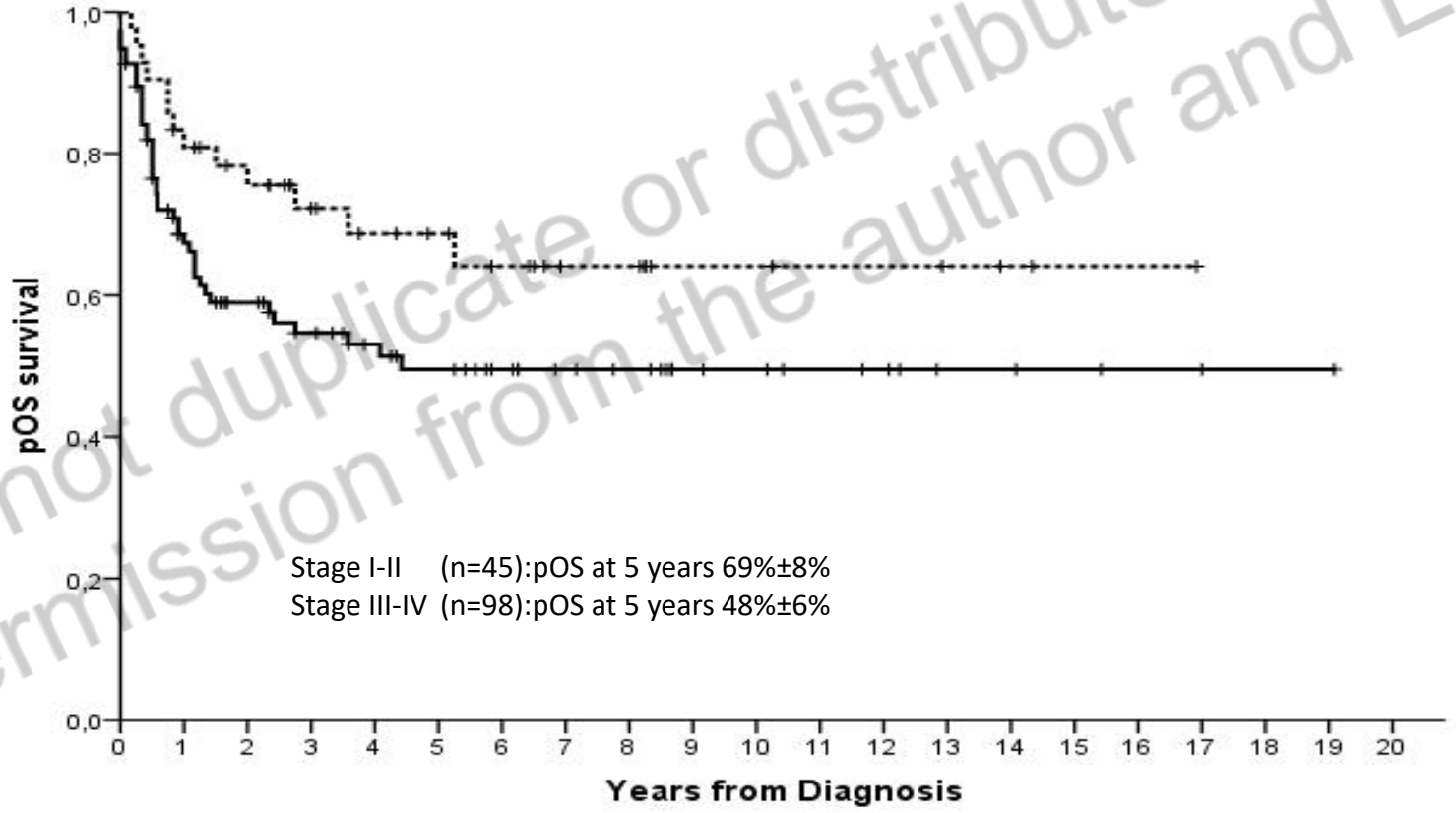


pOS at 5 years 56%±5%



pEFS at 5 years 45%±5%

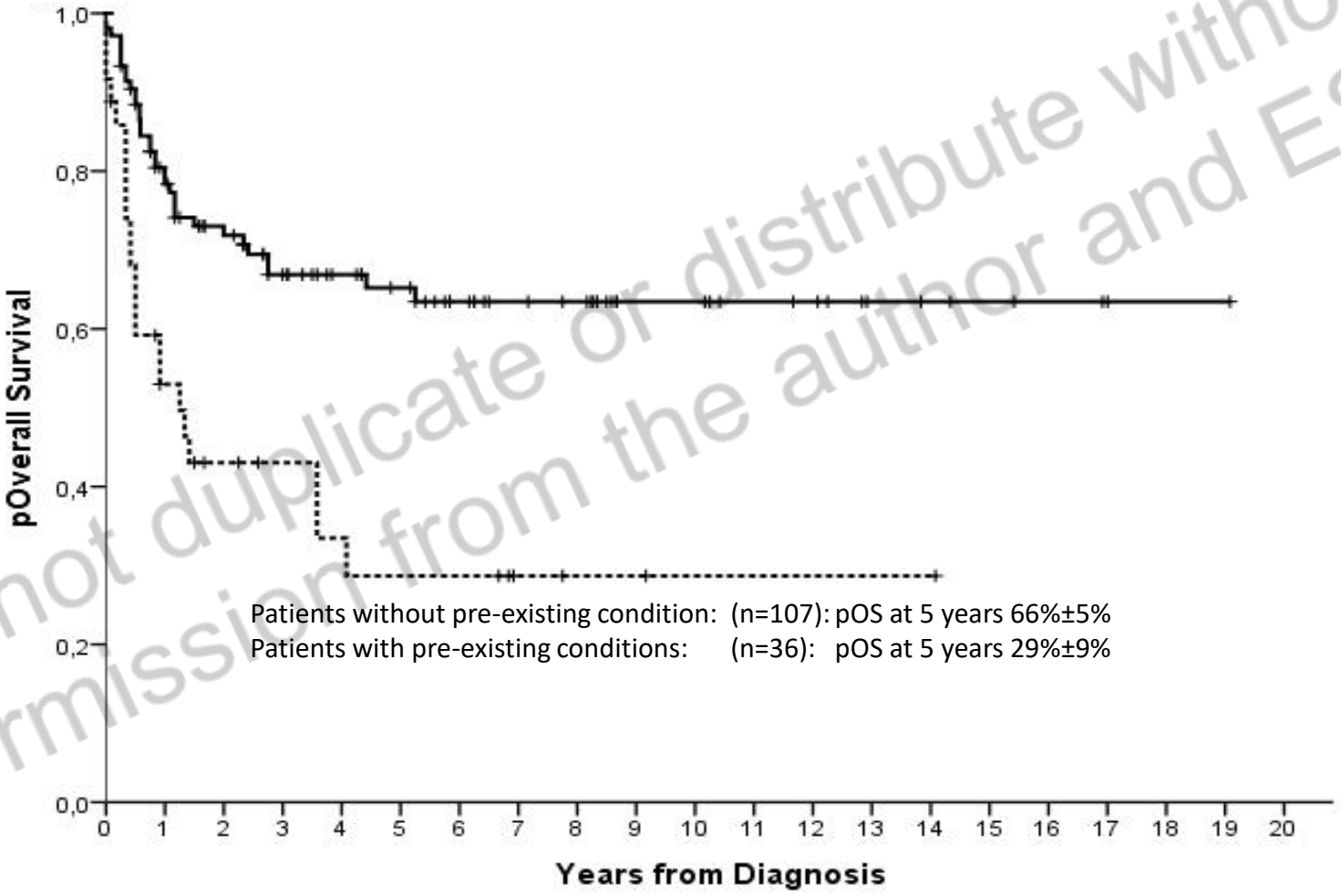
Survival of pts. according to stage



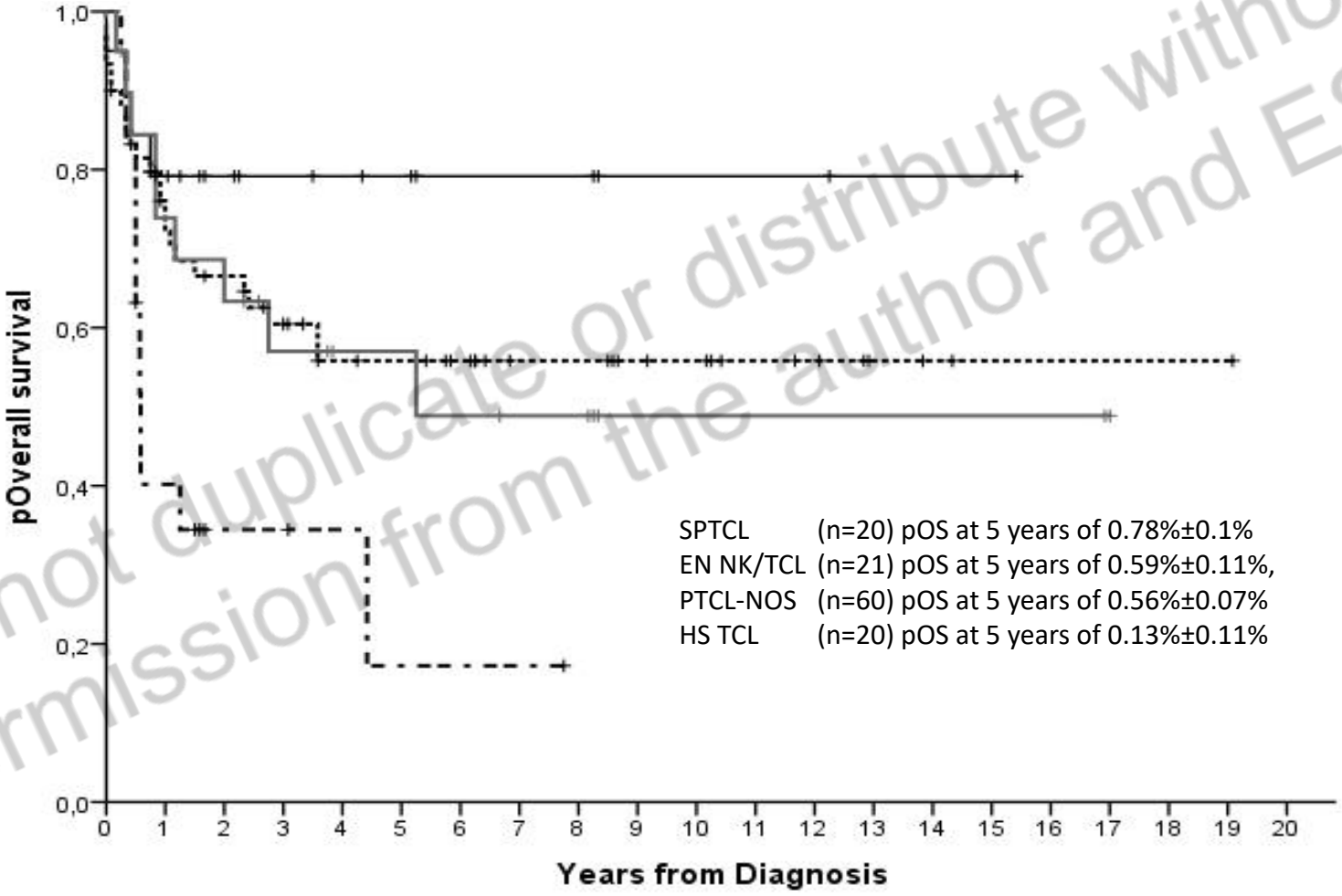
PTCL and pre-existing conditions

	Autoimmune /IS therapy	PID	PTCL as SMN	NBS	Syndrome	Previous Tx	Hepatitis
EBV-pos. LPD PTCL	0	0	0	0	0	1	0
EBV-neg. LPD	0	0	0	0	0	3	0
Extranodal T/NK cell NHL	0	2	0	0	2	0	0
HSTL	4	1	1	1	0	2	0
HV like EBV	0	1	0	0	0	0	0
PTCL NOS	2	3	1	6	1	2	0
SPTCL	0	1	0	0	1	0	1

Survival of pts. according pre-existing conditions

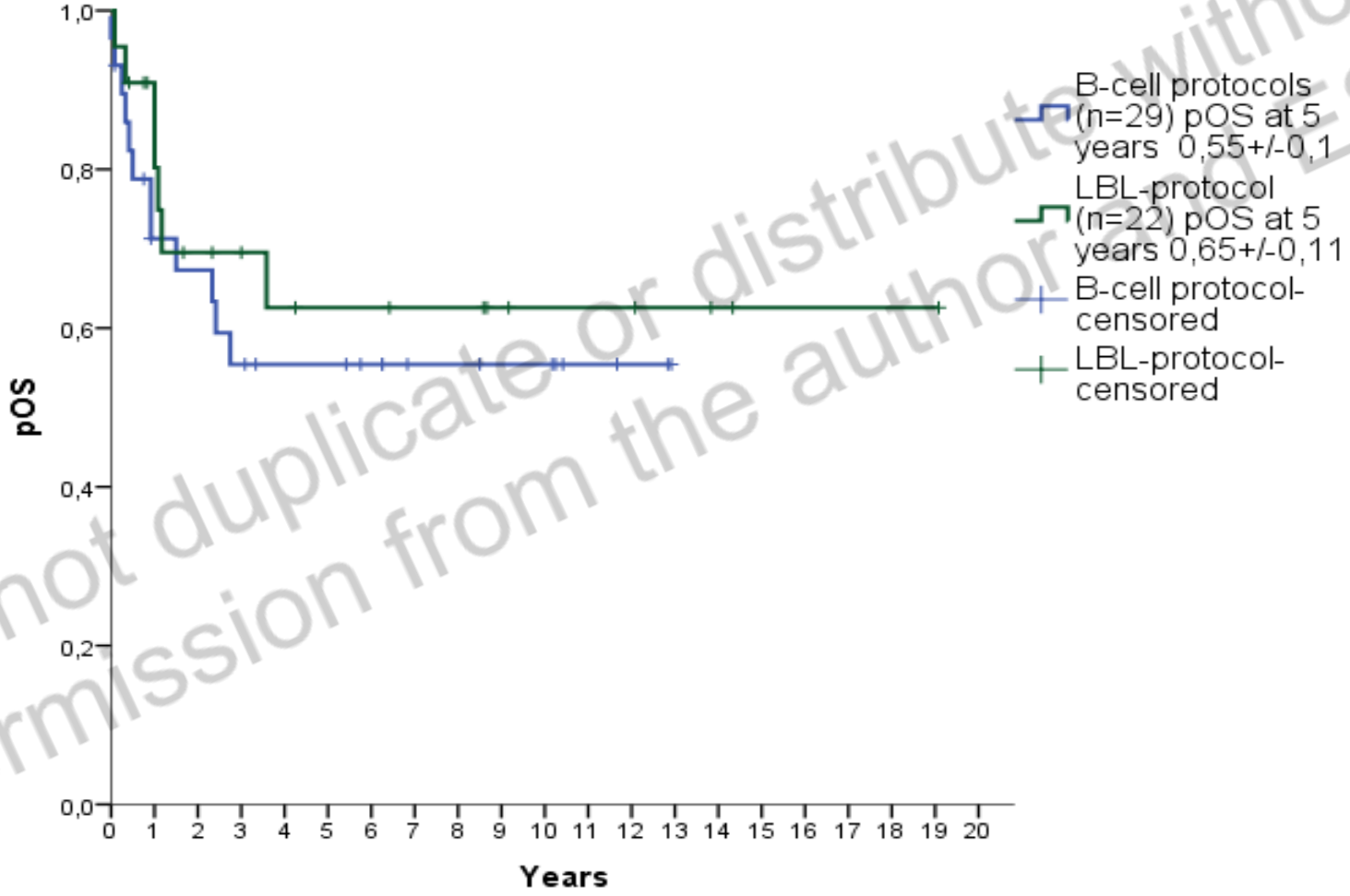


Survival of pts. according to the subtype of PTCL



SPTCL (n=20) pOS at 5 years of 0.78%±0.1%
EN NK/TCL (n=21) pOS at 5 years of 0.59%±0.11%,
PTCL-NOS (n=60) pOS at 5 years of 0.56%±0.07%
HS TCL (n=20) pOS at 5 years of 0.13%±0.11%

Survival of pts. with PTCL NOS according to therapy



PTCL – Conclusions

- largest cohort of patients of children and adolescents with PTCL
- overall moderate outcome with EFS and OS rates around 50% which, however, was subtype-dependent, but overall worse than in other ped. NHL
- pts. with SPLTCL had the best while pts. with HS TCL had the worst outcome – pts. with PTCL NOS and EN NK/TCL were in-between
- 25% of the patients had pre-existing disorders. They had a worse outcome as compared to pts. with PTCL and no pre-existing diseases.
- subtype-directed treatment recommendations are necessary. While SPLTCL may benefit from B-NHL therapy, there was no difference in outcome between B- and T-NHL therapy in PTCL NOS

Rare NHL – Conclusions

TABLE 2 Key clinical and outcome features for PTFL, MZL, and pediatric nonanaplastic PTCL

NHL subtype	No. of patients[a]	5-y EFS	5-y OS	Gender M/F	Median age	Stage I-II/III-IV/NR	Presentation	Preexisting disorder
PTFL	63[b]	94 ± 5%[c]	100%[c]	47/16	13.0	55/8	LNs of head and neck	0
pMZL	66	70 ± 9%	98 ± 2%	45/21	14.2	45/18/3		12 (18%)
pnMZL	21 (32%)	94 ± 6%	100%	20/1	14.7	18/2/1	LNs of head and neck	0
eMZL	44 (67%)	64 ± 11%	97 ± 3%	25/19	13.2	27/15/2	MALT, skin	12 (100%)
sMZL	1 (1%)	Alive	Alive	0/1	NA	0/1	Spleen	0
Pediatric PTCL	143[d]	45 ± 5%	56 ± 5%	87/56	11.1	46/97		36 (25%)
PTCL-NOS	60 (42%)	47 ± 7%	56 ± 7%	36/24	10.4	14/46	LNs, extranodal sites, effusions	15 (42%)
HSTCL	20 (14%)	NA	13 ± 12%	12/8	14.7	0/20	Liver, spleen, BM	9 (25%)
SPTCL	20 (14%)	74 ± 12%	78 ± 1	12/8	8.0	10/10	Subcutaneous nodules	3 (8%)
AILT	4 (3%)	NA	NA	3/1	12.5	0/4	LNs, liver, spleen, BM, skin	0

Abbreviations: AILT, angioimmunoblastic T-cell lymphoma; BM, bone marrow; EFS, event-free survival; eMZL, extranodal marginal zone lymphoma; F, female; HSTCL, hepatosplenic T-cell lymphoma; LNs, lymph nodes; M, male; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; NA, not applicable; No., number;NR, not reported; OS, overall survival; pnMZL, pediatric nodal marginal zone lymphoma; PTCL, peripheral T-cell lymphoma; PTCL-NOS, PTCL not otherwise specified; PTFL, pediatric-type follicular lymphoma; sMZL, splenic marginal zone lymphoma; SPTCL, subcutaneous panniculitis-like T-cell lymphoma; y, years.

[a]Total number of cases in the EICNHL/i-BFM study.

[b]Diagnosis of these cases did not use the 2016 *WHO definition*.

[c]Two-year event-free and overall survival.

[d]Thirty-nine of the 143 patients (27%) are not included in this analysis, as they were other subtypes of nonanaplastic PTCL.

Rare NHL – Conclusions

TABLE 3 Treatment recommendations/considerations for PTFL, MZL, and pediatric nonanaplastic PTCL

	Treatment recommendation/considerations for primary disease
Pediatric-type follicular lymphoma	
Localized disease—complete resection	Watch and wait
Localized disease—incomplete resection	Secondary operation[a], or low-dose chemo- and immunotherapy[b]
Advanced/disseminated disease	Low-dose chemo- and immunotherapy[b]
Marginal zone lymphoma	
Localized disease—complete resection	Watch and wait
Localized disease—incomplete resection	Watch-and-wait or secondary operation[a] or low-dose chemo- and immunotherapy[b]
Advanced/disseminated disease	Low-dose chemo- and immunotherapy[b]
Nonanaplastic peripheral T-cell lymphoma	
PTCL not otherwise specified	Block-like ALCL-derived polychemotherapy (2nd choice: ALL-type therapy)
Hepatosplenic TCL	Block-like mature B-NHL- or ALCL-derived polychemotherapy followed by allo-HSCT in CR1
Subcutaneous panniculitis-like TCL	Block-like ALCL-derived polychemotherapy (2nd choice: ALL-type therapy)
Angioimmunoblastic TCL	Block-like mature B-NHL- or ALCL-derived polychemotherapy followed by auto- or allo-HSCT in CR1

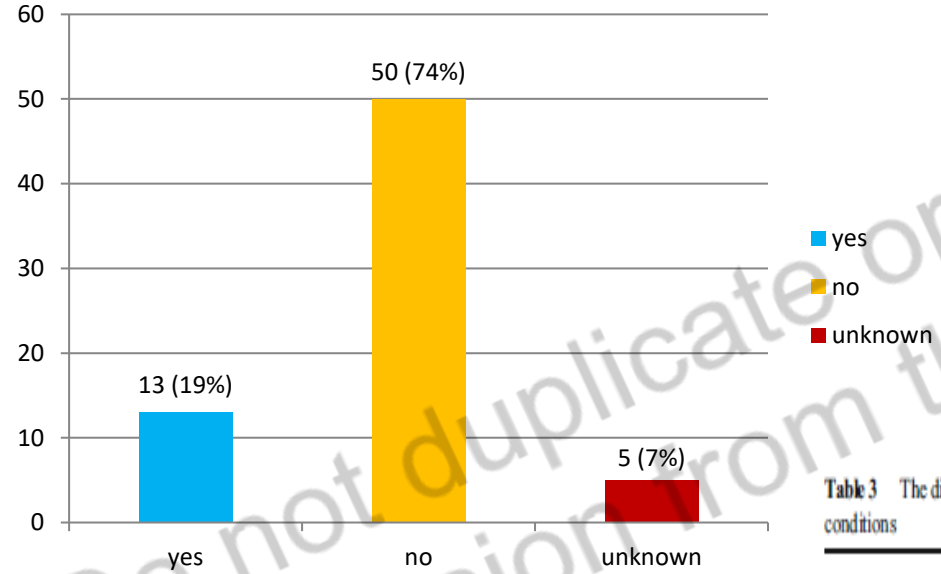
Abbreviations: ALL, acute lymphoblastic leukemia; ALCL, anaplastic large cell lymphoma; allo, allogeneic; auto, autologous; B-NHL, B-cell non-Hodgkin lymphoma; CR1, first complete remission; HSCT, hematopoietic stem cell transplantation; PTCL, peripheral T-cell lymphoma; TCL, T-cell lymphoma.

[a]Only if the operation can be performed easily and safely, and most importantly, without any mutilation.

[b]Anthracycline-free but rituximab-containing mature B-NHL courses, R-COP, or R-CVP.

Rare NHL – Conclusions

Pre-existing disorders in PCNSL (13/68)



HIV infection:	n=2
PID n. f. sp.:	n=2
CVID:	n=1
JMML + allo-SCT:	n=1
BCP-LBL:	n=1
CLIPPERS:	n=1
Colitis ulcerosa:	n=1
SLE:	n=1
St. p. NTX:	n=1
St. p. HTX:	n=1
St. p. LTX:	n=1

Pre-existing disorders in MZL (12/66)

Sjögren syndrome	2
Immunodeficiency n. f. sp.:	2
CVID:	2
SCID:	1
STK4 deficiency:	1
Hirsutism, hyperandrogenism:	1
Crigler Najjar syndrome:	1
squamous papilloma:	1
Hodgkin's lymphoma:	1

Pre-existing disorders in PTCL (36/143)

Table 3 The distribution of histopathological subgroups and type of pre-existing disease or malignancy in the 36 patients with PTCL and pre-existing conditions

	Autoimmune/IS therapy	PID	PTCL as SMN	Nijmegen	Syndrome	Previous Tx	Hepatitis
EBV-pos LPD	0	0	0	0	0	1	0
EBV-neg LPD	0	0	0	0	0	3	0
EN NK/TCL	0	2	0	0	2	0	0
HS TCL	4	1	1	1	0	2	0
HV like EBV	0	1	0	0	0	0	0
PTCL NOS	2	3	1	6	1	2	0
SP TCL	0	1	0	0	1	0	1

INTERNATIONAL BFM STUDY GROUP

ACTIVITY OF THE RARE NHL COMMUNITY

ACTIVITY OF THE RARE NHL COMMUNITY

a) I-BFM NHL – EICNHL study on follicular lymphoma (***Annals of Hematology***, 2013)
b) I-BFM NHL – EICNHL study on peripheral T-cell lymphoma (***Annals of Hematology***, 2016)
c) I-BFM NHL – EICNHL study on NHL in patients with pre-existing disorders (***Haematologica***, 2016)
d) I-BFM NHL – EICNHL study on marginal zone lymphoma (***Pediatric Blood and Cancer***, 2018)
e) I-BFM NHL – EICNHL position paper on malignancies in inborn errors of immunity and DNA repair disorders (***Frontiers in Immunology***, 2018)
f) Textbook on NHL in childhood and adolescence (***Springer***, 2019)
g) I-BFM NHL – EICNHL- COG study on PCNSL (***Blood Advances***, 2019)
h) I-BFM NHL – EICNHL study on SML after primary NHL therapy (***Leukemia***, 2020)
i) I-BFM NHL – I-BFM SCT – EICNHL study on HSCT in r/r mature B-NHL and LBL (***Cancers***, 2021)
j) I-BFM NHL – EICNHL consensus paper in rare NHL (***Pediatric Blood and Cancer***, 2020)

k) I-BFM-NHL – EICNHL study on primary isolated CNS PTLD (***BJH,*** 2021)
l) I-BFM-NHL – EICNHL review on Leukemia and Lymphoma in AT patients (***Cancers***, 2022)
m) I-BFM-NHL – EINCHL study on B-cell precursor lymphoblastic lymphoma (LBL) (***Cancers***, 2022)
n) I-BFM-NHL – EINCHL – COG study on C-MYC-IGH+ B-cell precursor neoplasms (***Haematologica***, 2022)