Extranodal NK/T-Cell Lymphoma, Nasal Type

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Midfacial Granuloma Syndrome

First report: 1897

" Photographs of a case of rapid destrution of the nose and face"

Peter MacBride Scottish Otoraryngologist

Peter McBride

McBride, P. - Journal of Laryngology 12: 64-66, 1897

Synonyms and related names

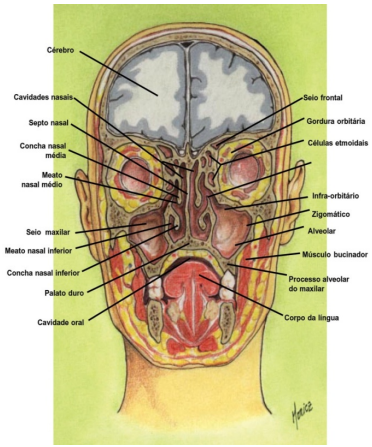
- Lethal Midline Granuloma
- Midfacial Granuloma Syndrome
- Progressive Lethal Granulomatous Ulceration
- Malignat Granuloma
- Malignat Reticulosis
- Polimorphic Reticulosis

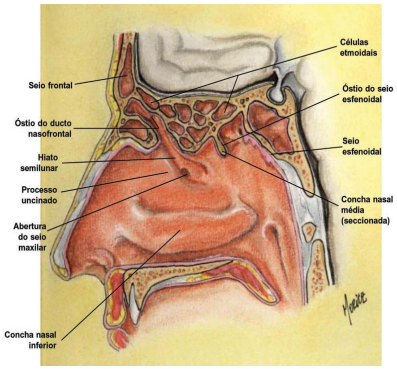
CLÍNICA

- Região médio-facial
- Lesões necróticas, ulceradas,destrutivas e progressivas

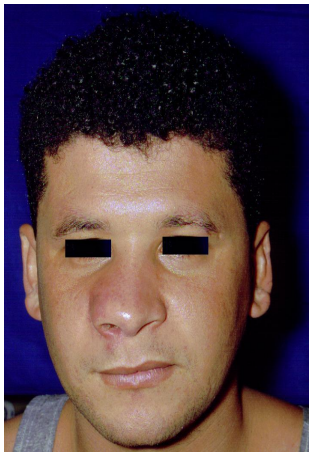
PATOLOGIA

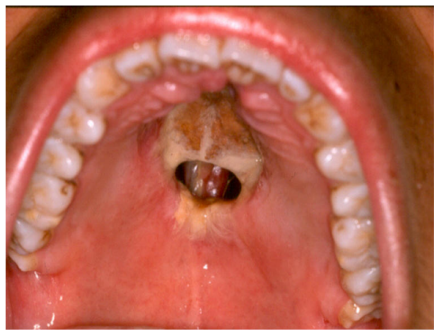
- Necrose
- Material escasso





- Infecções
- Vasculites
- Neoplasias

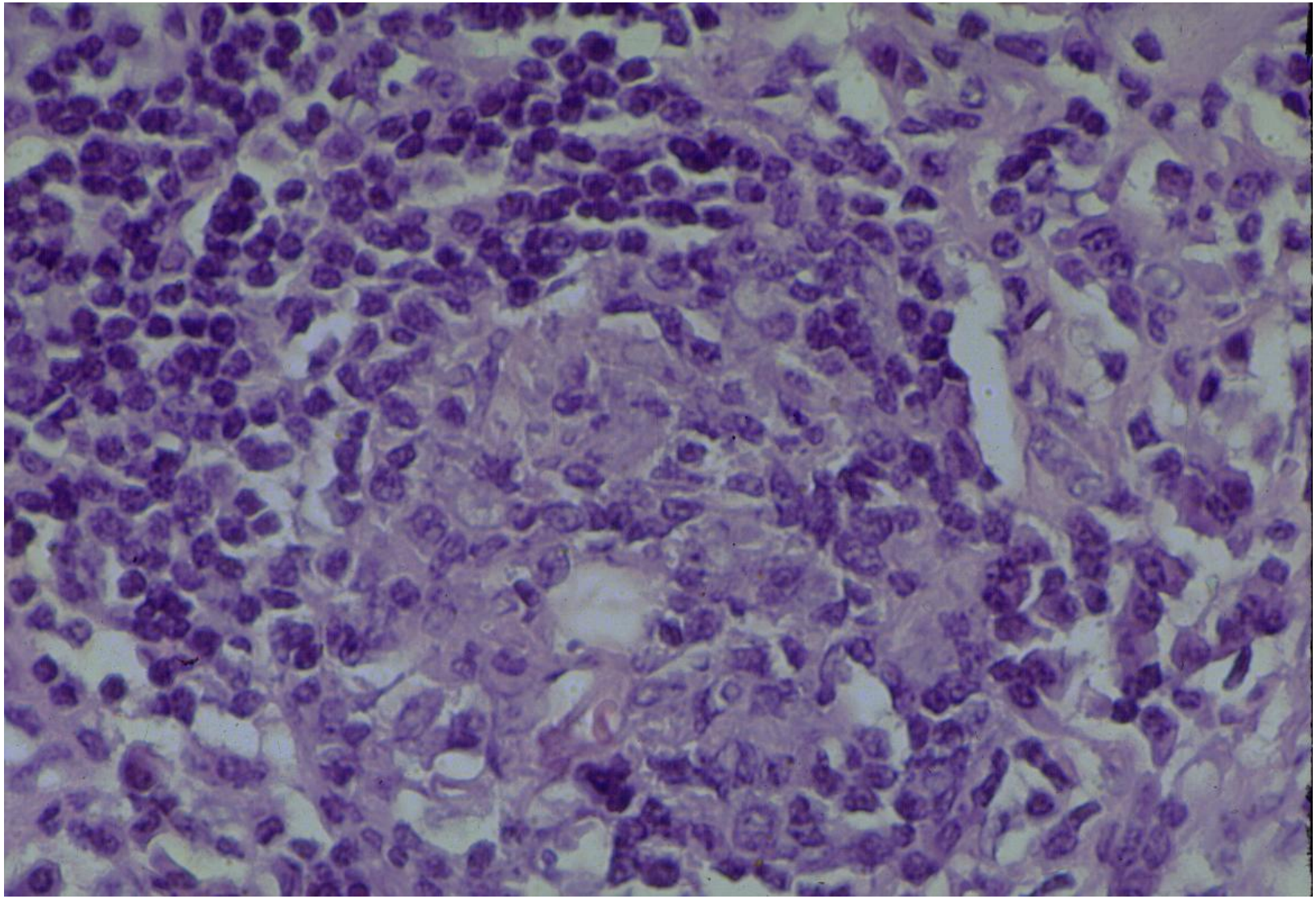




Síndrome do Granuloma Médio-Facial

Angiocentric Lymphoma

REAL Classification– 1994



Workshop of Hong Kong

(International Society of Hematopathology)

Nasal Angiocentric Lymphoma

Phenotypic and Genotypic Aspects♪

- Usually positive: CD2, **CD56**, cCD3, CD45RO, CD43
  EBV (*in situ Hybridization*)
- Usually negative: **sCD3**, CD5, CD57, CD16, βF1, TCRδ
  TCR gene rearrangement
- Occasionally positive: CD7, CD4, CD8, LMP-1

"Nasal NK/T-cell Lymphoma"

Jaffe et al. Am J Surg Pathol 20:103,1996

Pathological Classifications of NK Cell Malignancies

- Rappaport, Kiel and Working Formulation
  - No such entity
- REAL
  - “Angiocentric lymphoma”
  - Angiocentricity is not pathognomonic
- W.H.O
  - Extranodal NK/T-cell Lymphoma, nasal type
    - ✓Nasal
    - ✓Extranasal

Nasal NK/T-cell Lymphoma

- A unique type of mature NK/T-cell lymphoma
- Frequentely associated with EBV
- Distinct extranodal homing pattern
- Unique geographic distribution
  - Oriental Asia (SE Asia, S. China, Japan, Korea)
    - > 5% of all cases of lymphomas
    - > 30% of mature T/NK neoplasms
  - Central and South America

International T-Cell Lymphoma Project

Table 1. Major Lymphoma Subtypes by Geographic Region

Subtype	%		
	North America	Europe	Asia
PTCL-NOS	34.4	34.3	22.4
Angioimmunoblastic	16.0	28.7	17.9
ALCL, ALK positive	16.0	6.4	3.2
ALCL, ALK negative	7.8	9.4	2.6
NKTCL	5.1	4.3	22.4
ATLL	2.0	1.0	25.0
Enteropathy-type	5.8	9.1	1.9
Hepatosplenic	3.0	2.3	0.2
Primary cutaneous ALCL	5.4	0.8	0.7
Subcutaneous panniculitis-like	1.3	0.5	1.3
Unclassifiable T-cell	2.3	3.3	2.4

Vose et al. JCO 26:4124, 2008

"Nasal" NK/T-cell Lymphoma
Clinical Caracteristics

- Male to female ratio: 3
- Median age: fifth decade
- Primary sites: nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx,
- Local extension to orbit and hard palate
- Systemic dissemination is often late and the pattern is similar to that of the primary extranasal NK/T-cell lymphoma
- Marrow (< 10%) and CNS (< 5%) involvement are not common at presentation
  - occult marrow disease diagnosed by ISH for EBER
  - pancytopenia may be due to hemophagocytosis

Pathology of Nasal NK/T-cell Lymphoma

Histology

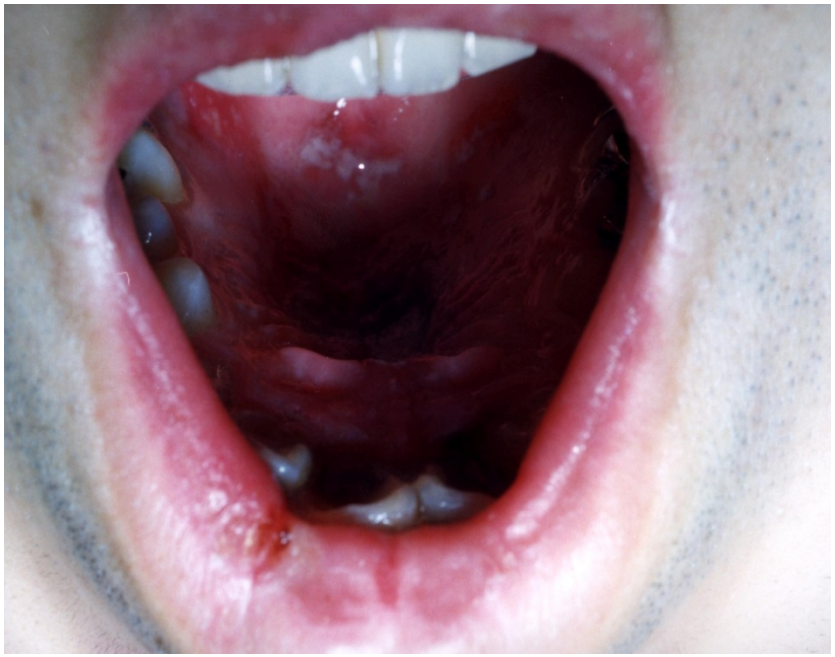
- Pleomorphic cellular infiltrate
- Angiocentricity and Angioinvasion
- Marked tissue necrosis

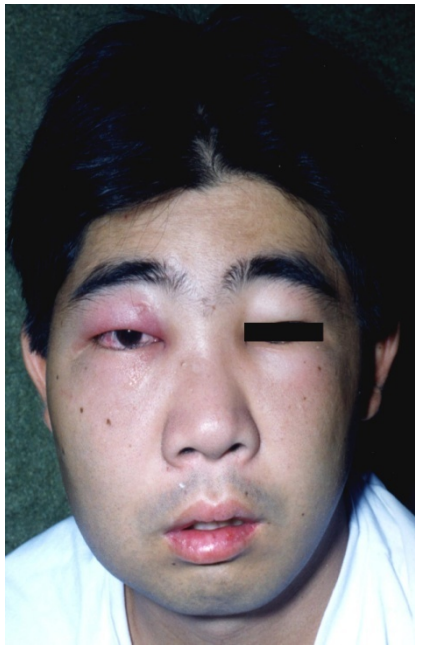
Immunophenotype

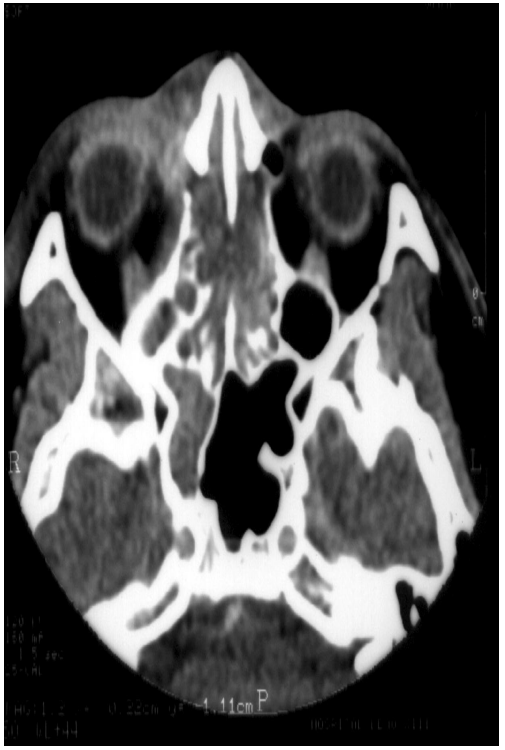
- CD56 positive
- Surface CD3 negative
- Cytoplasmic CD3e positive
- Germ line TCR gene
- Clonal EBV infection

Case 34 (D.T.Y.)

- Periorbitary swelling
- Shift in right nasal flap
- Palate ulceration

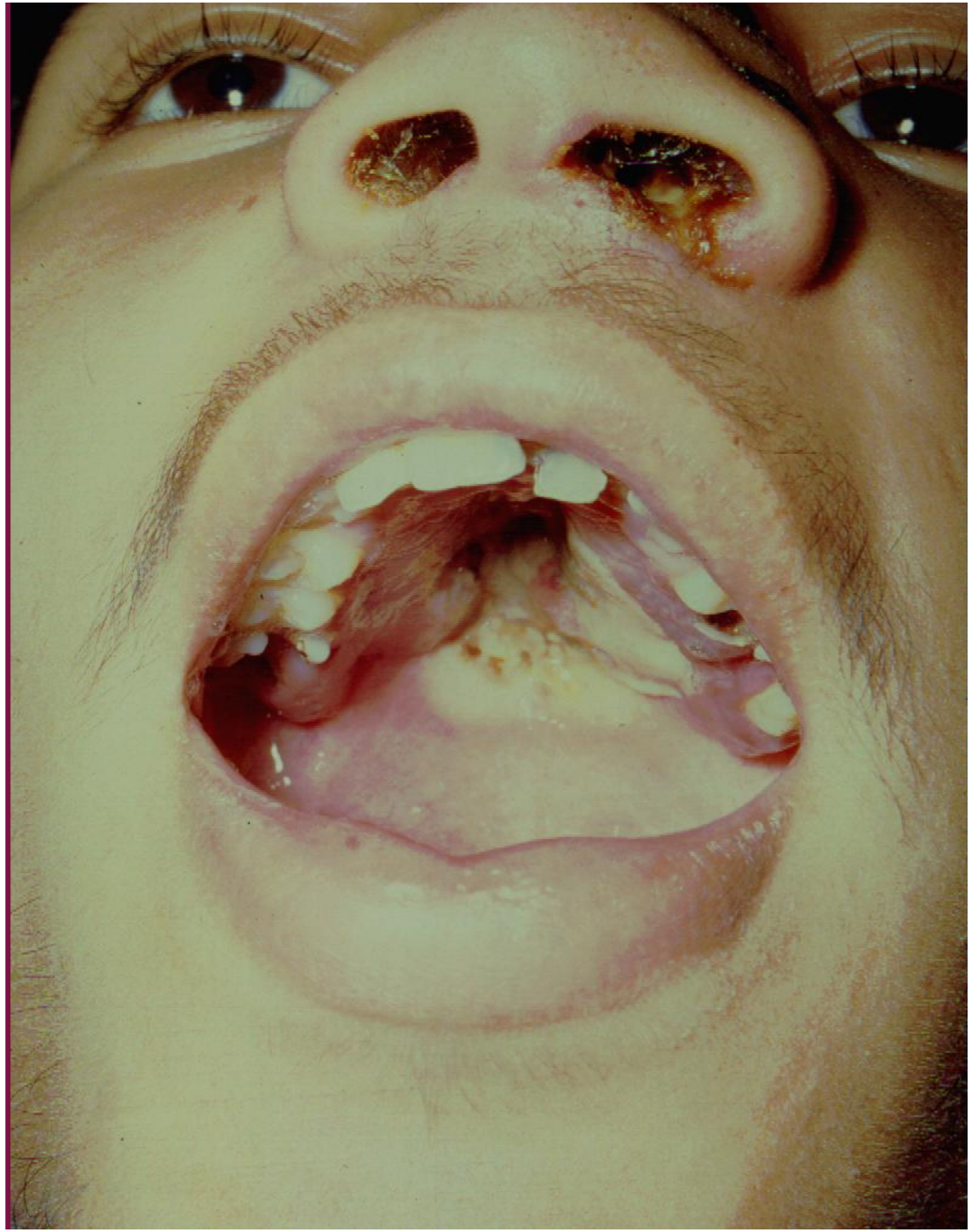


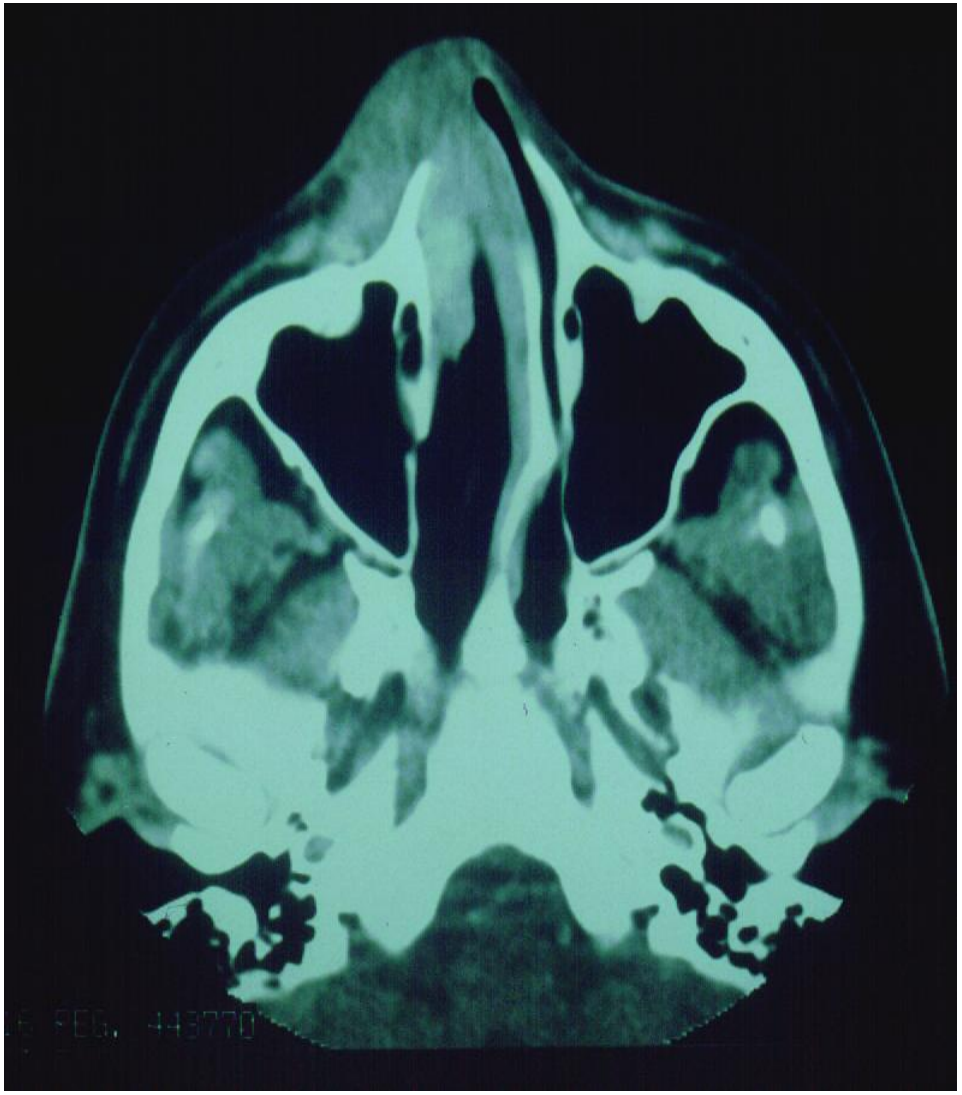


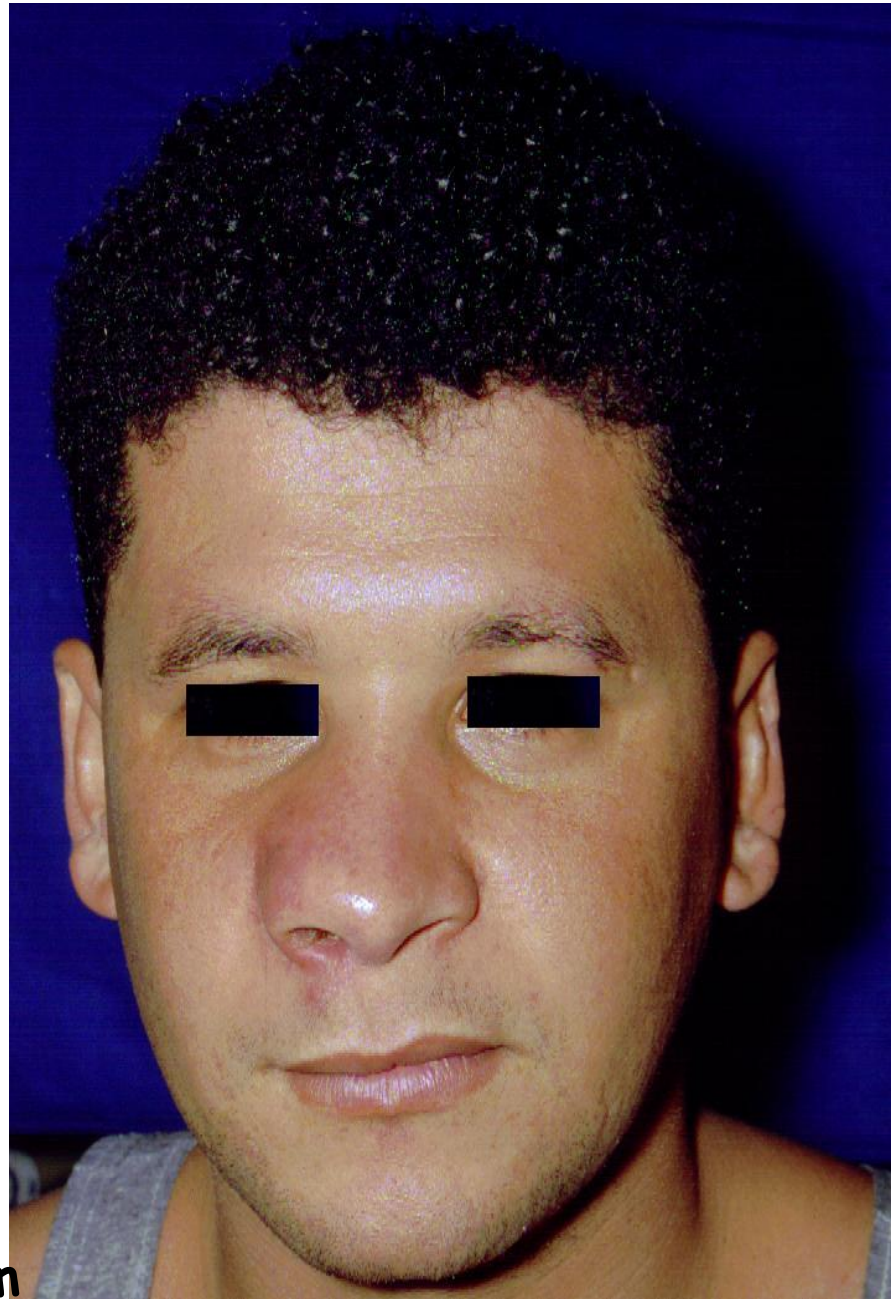


CT with a lesion in nasal cavities, Perforated septum and envolvement of ethmoidal sinuses and orbit

Caso 10 (R.S.)
Lesão na aba do nariz e ulceração do palato

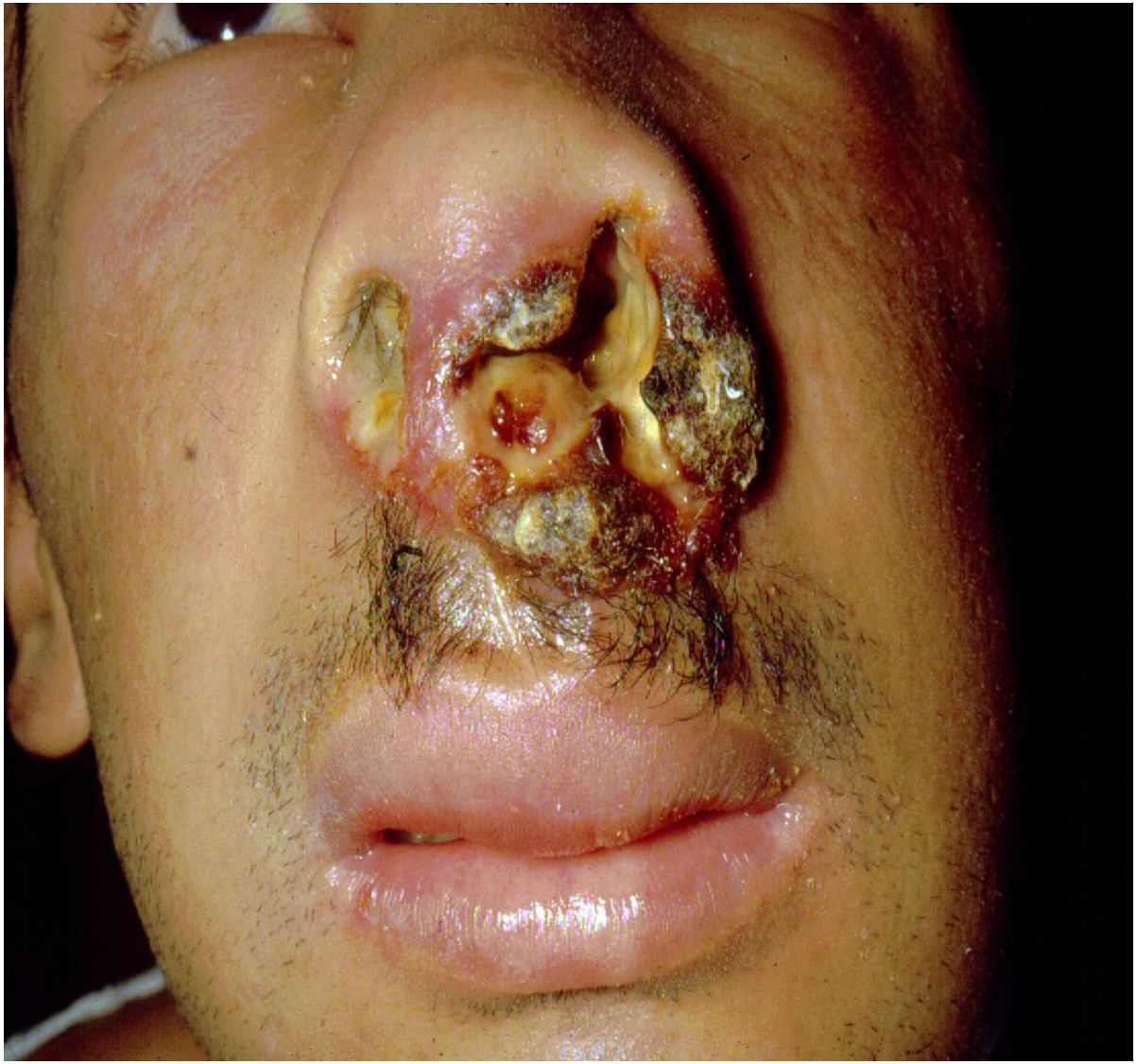


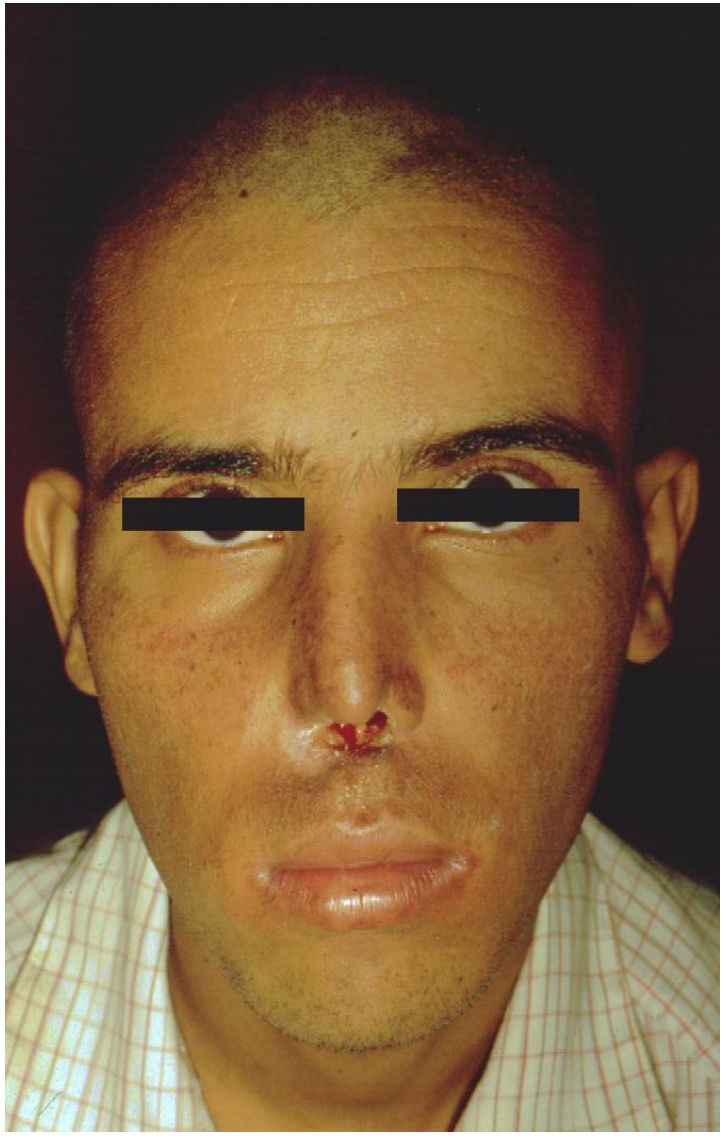




Case 2 (M.F.S.)

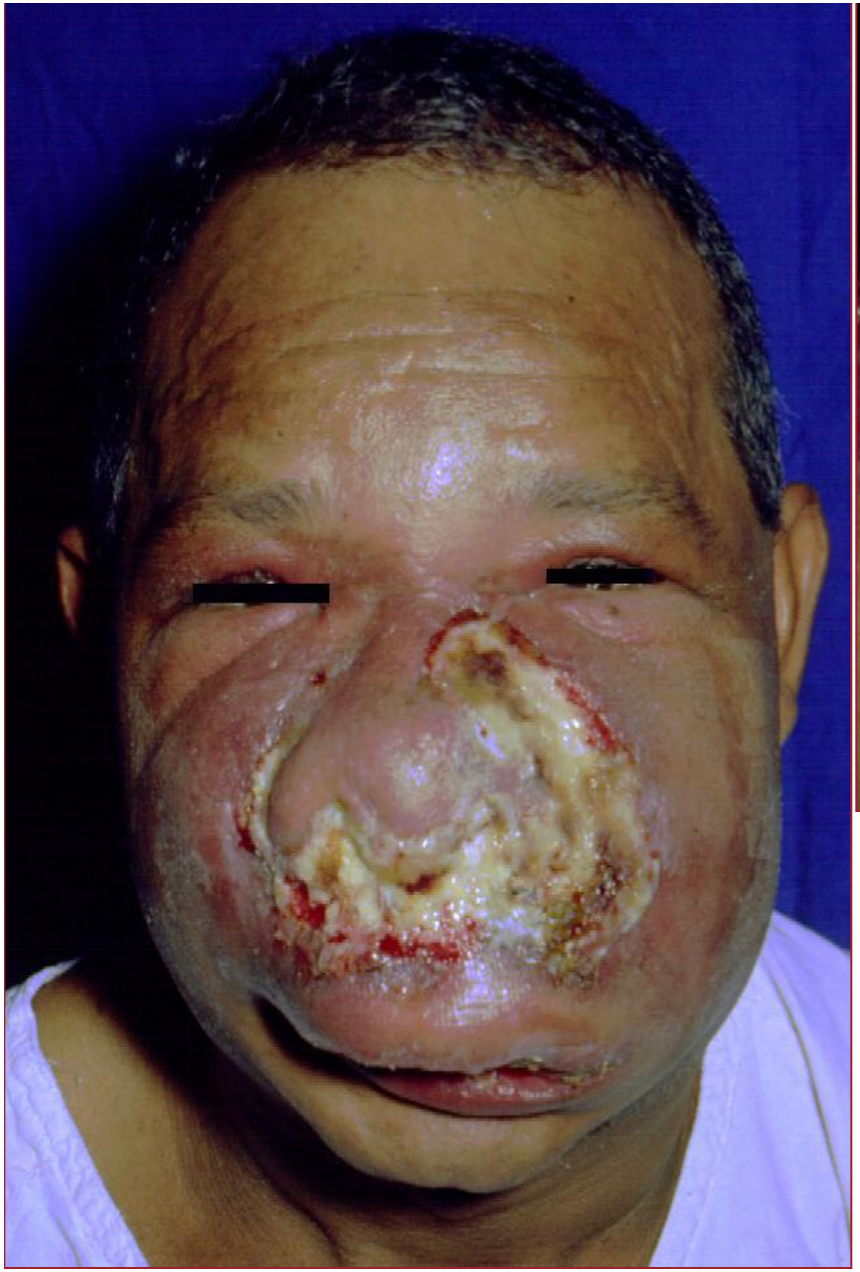
- External nasal deformity
- CT destruction of the nasal septum

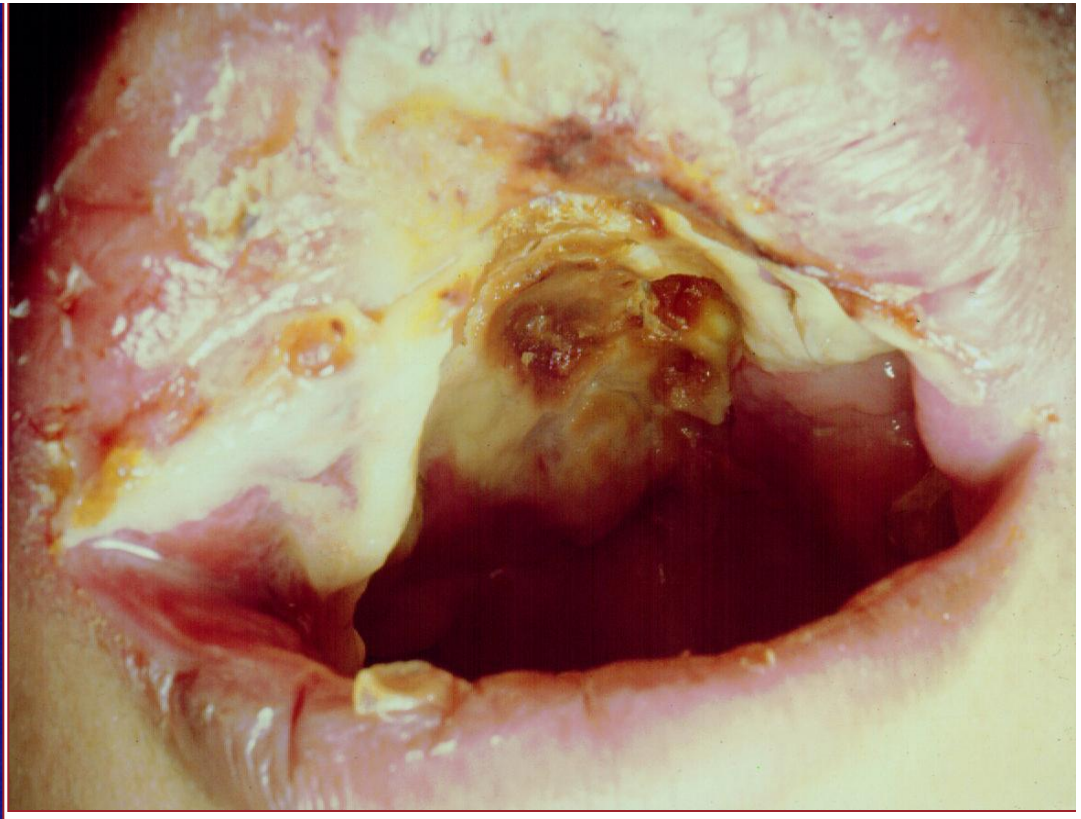




Caso 32 (B.S.G.)

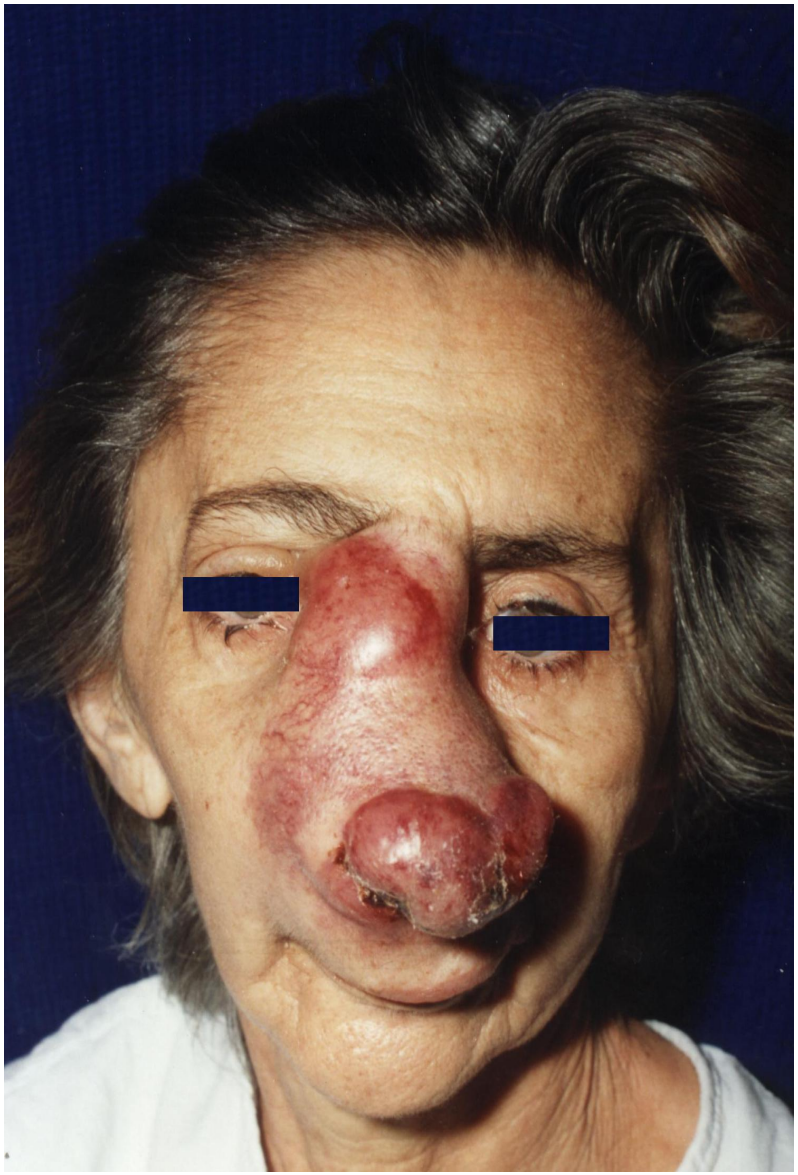
Aspecto do paciente antes e depois do tratamento

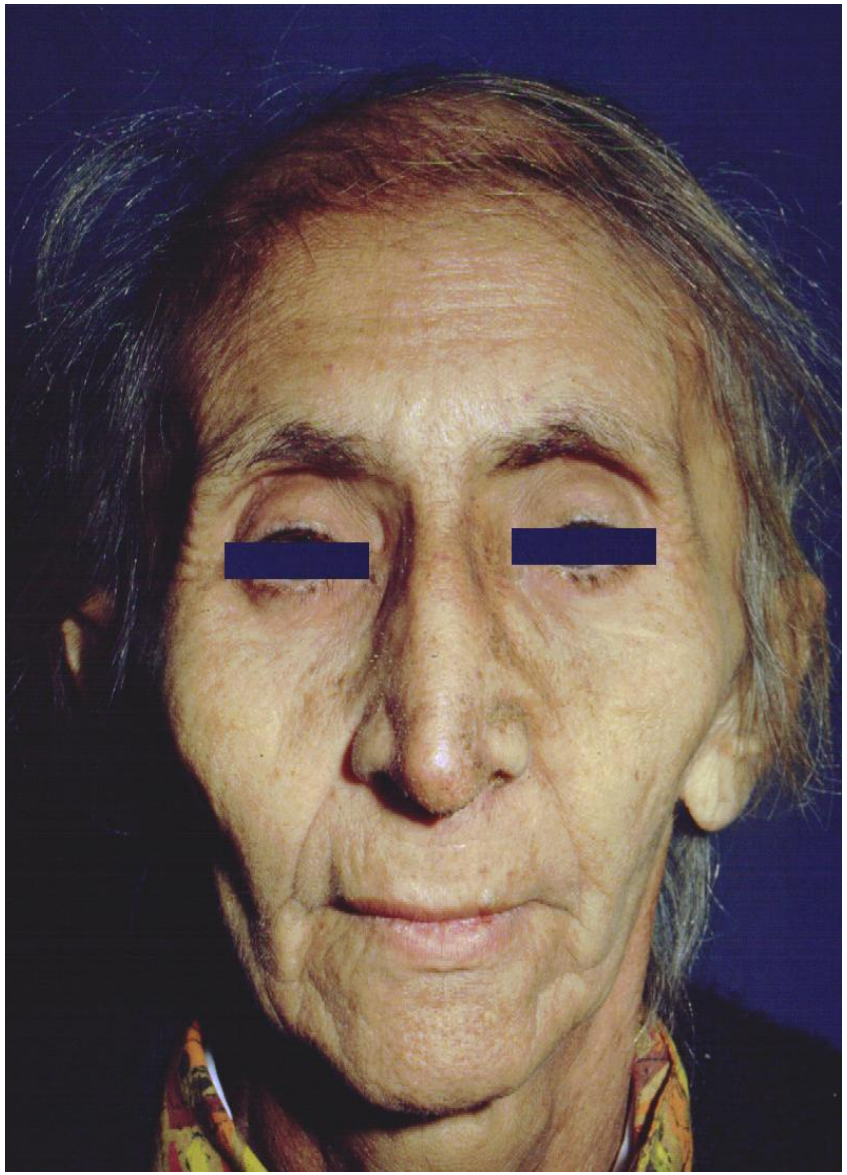




Caso 33 (J.C.B.)

Extensive nasal ulceration
And palate ulceration





Caso 4 (E.G.S.)

Tumoração nasal antes e depois do tratamento

Epstein-Barr Virus and Nasal NK/T-cell Lymphoma

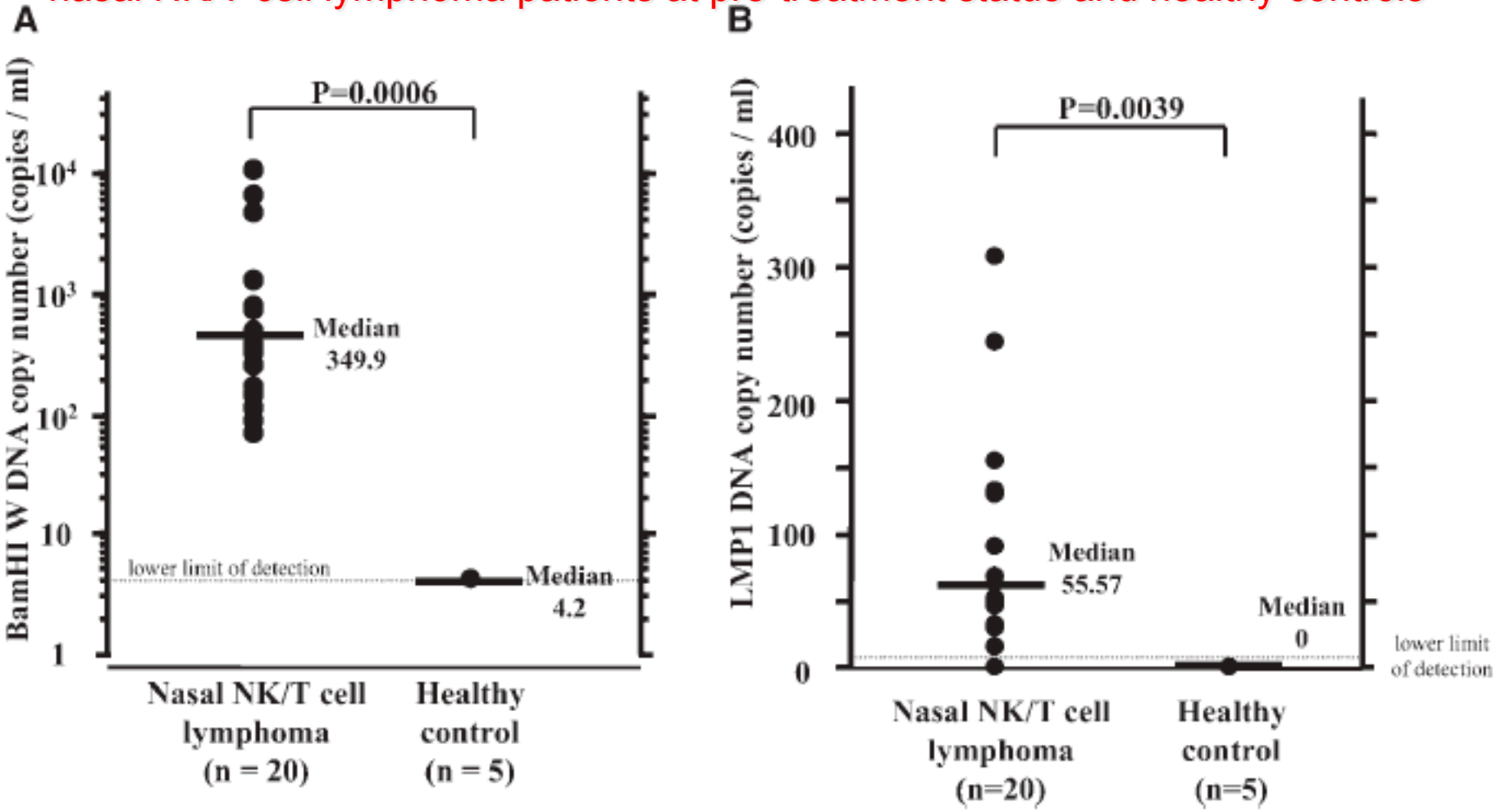
- EBV is integrated into the tumor in clonal episomal form
  - Clonal EBV proliferation
- EBV may play an important etiological role
  - consistent association
  - Latency II – similar to NPC
- Clinical implication
- Diagnostic tool
  ISH staining of EBER as a marker for identifying occult tumor cells (e.g. marrow)
- Prognostic marker: EBV DNA monitoring in peripheral blood
- Possible target treatment

Circulating plasma EBV DNA

- Quantification of circulating plasma EBV DNA by real-time Q-PCR serves as a surrogate tumor marker
  - reflects tumor load
  - prognostic implications
  - monitoring of response
  - detection of relapse

Clinical Usefulness of Serum EBV DNA Levels of BamHI W and LMP1 for Nasal NK/T-Cell Lymphoma

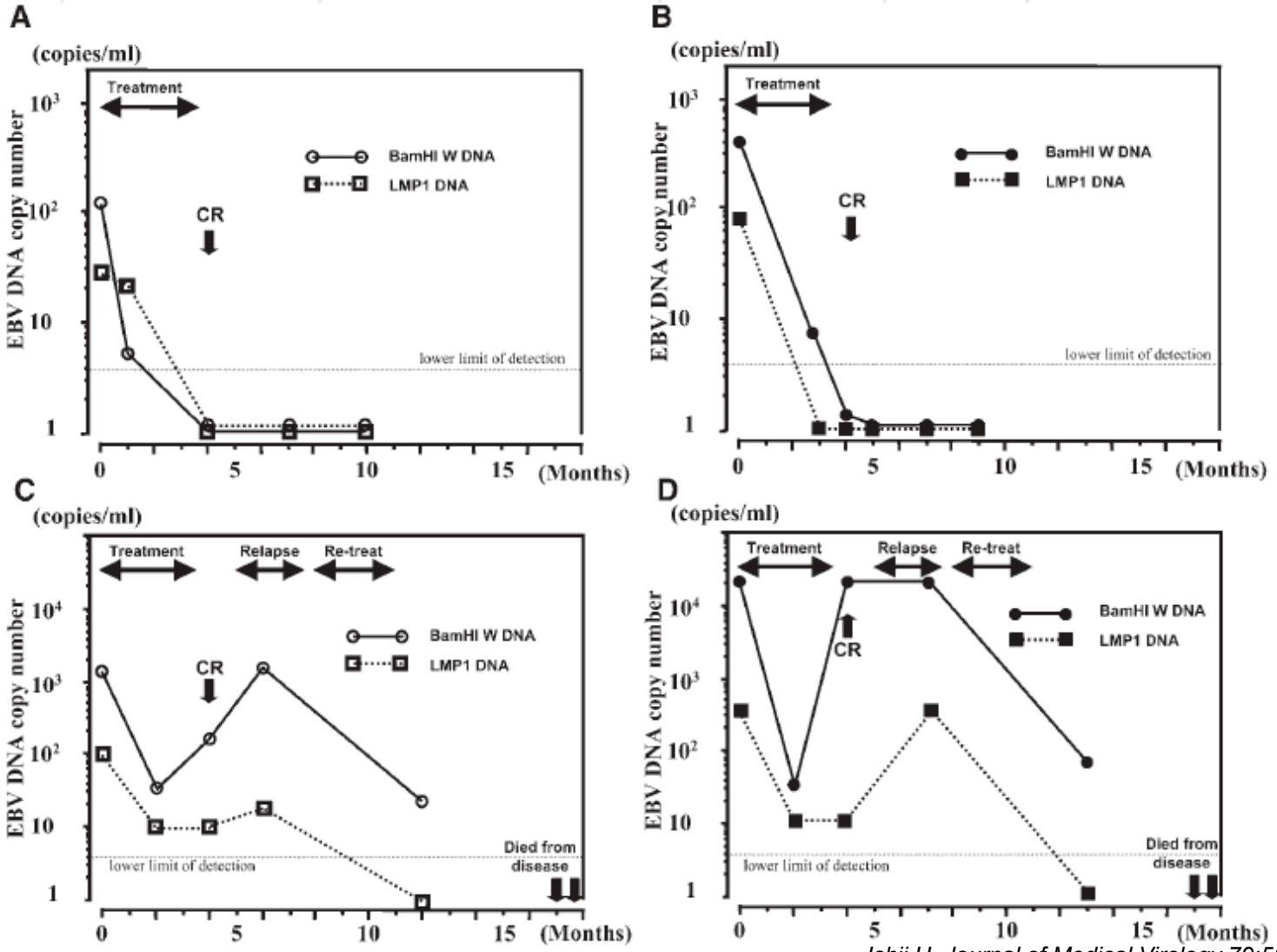
Comparison of serum Bam HI W fragment and LMP1 DNA levels between nasal NK/T-cell lymphoma patients at pre-treatment status and healthy controls



Ishii H,,Journal of Medical Virology 79:562–572 (2007)

Clinical Usefulness of Serum EBV DNA Levels of BamHI W and LMP1 for Nasal NK/T-Cell Lymphoma

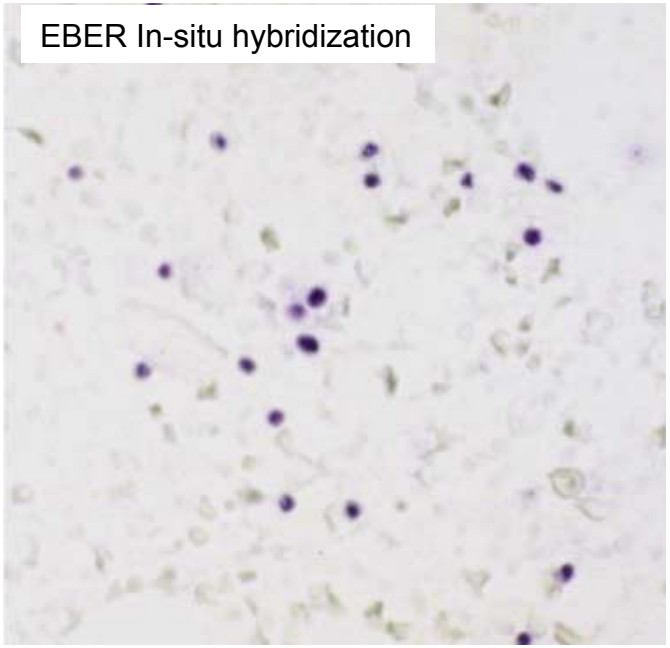
Dynamics of serum EBV DNA levels of patients who kept complete response during follow-up period and patients who experienced tumor relapse after complete response

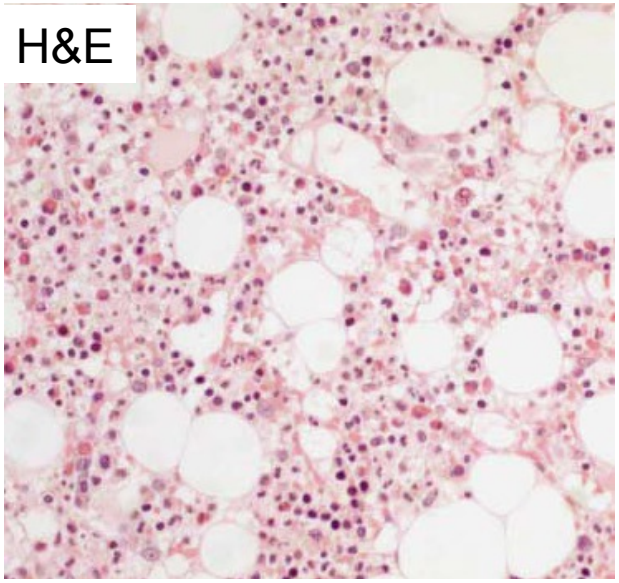


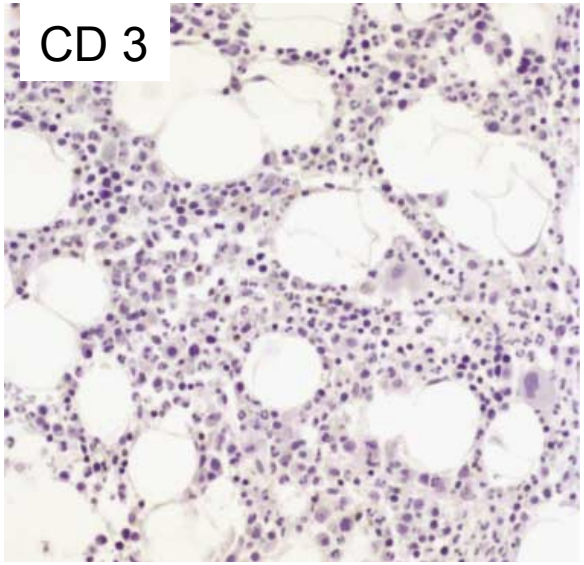
Ishii H,,Journal of Medical Virology 79:562–572 (2007)

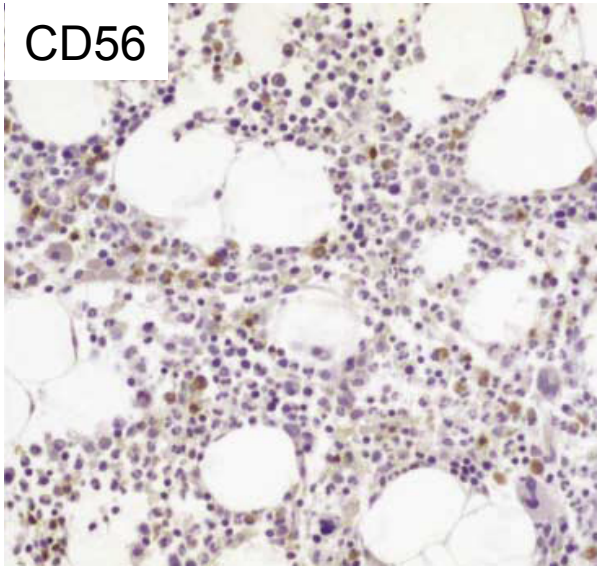
NK/T cell lymphoma in bone marrow is not suspected by H&E stain and immunohistochemical stain with CD 3 and CD56, but detected by EBER in-situ hybridization

Sung et al. J Korean Med Sci 2004; 19: 229-33









Nasal NK/T-cell Lymphoma

- Male to female ratio: 3
- Median age: fifth decade
- Primary sites: nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx, larynx
- Local extension to orbit and hard palate
- Systemic dissemination is often late and the pattern is similar to that of the primary extranodal NK/T-cell lymphoma
- Marrow (< 10%) and CNS (< 5%) involvement are not common at presentation
  - occult marrow disease diagnosed by ISH for EBER
  - pancytopenia may be due to hemophagocytosis.

"Nasal" NK/T-cell Lymphoma
Clinical Caracteristics

- Male to female ratio: 3
- Median age: fifth decade
- Primary sites: nasal cavity, nasopharynx, paranasal sinuses, tonsils, hypopharynx,
- Local extension to orbit and hard palate
- Systemic dissemination is often late and the pattern is similar to that of the primary extranasal NK/T-cell lymphoma
- Marrow (< 10%) and CNS (< 5%) involvement are not common at presentation
  - occult marrow disease diagnosed by ISH for EBER
  - pancytopenia may be due to hemophagocytosis

Nasal NK/T-cell Lymphoma
Clinical Symptoms

- Mass lesion: facial swelling
- Nasal obstruction
- Nasal bleeding
- Hoarseness of voice
- Dysphagia
- Proptosis
- Impaired ocular movement
- Halitosis
- Airway obstruction
- Dysphonia

"Extranasal" NK/T-cell Lymphoma
Clinical Caracteristics

- Male to female ratio: 2.3
- Median age: fifth decade
- Common sites:

  skin, gastrointestinal tract, salivary gland, spleen, testis, muscle, genital tract
- Isolated lymph node involvement is rare
- Early systemic dissemination
- Nasal NK/T-cell lymphoma also involves similar anatomical sites
  - CD56 facilitates cellular adhesion
  - Homing pattern
  - Examine the nasal cavity

"Extranasal" NK/T-cell Lymphoma
Clinical Caracteristics

- Male to female ratio: 2.3
- Median age: fifth decade
- Common sites:

  skin, gastrointestinal tract, salivary gland, spleen, testis, muscle, genital tract
- Isolated lymph node involvement is rare
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- Nasal NK/T-cell lymphoma also involves similar anatomical sites

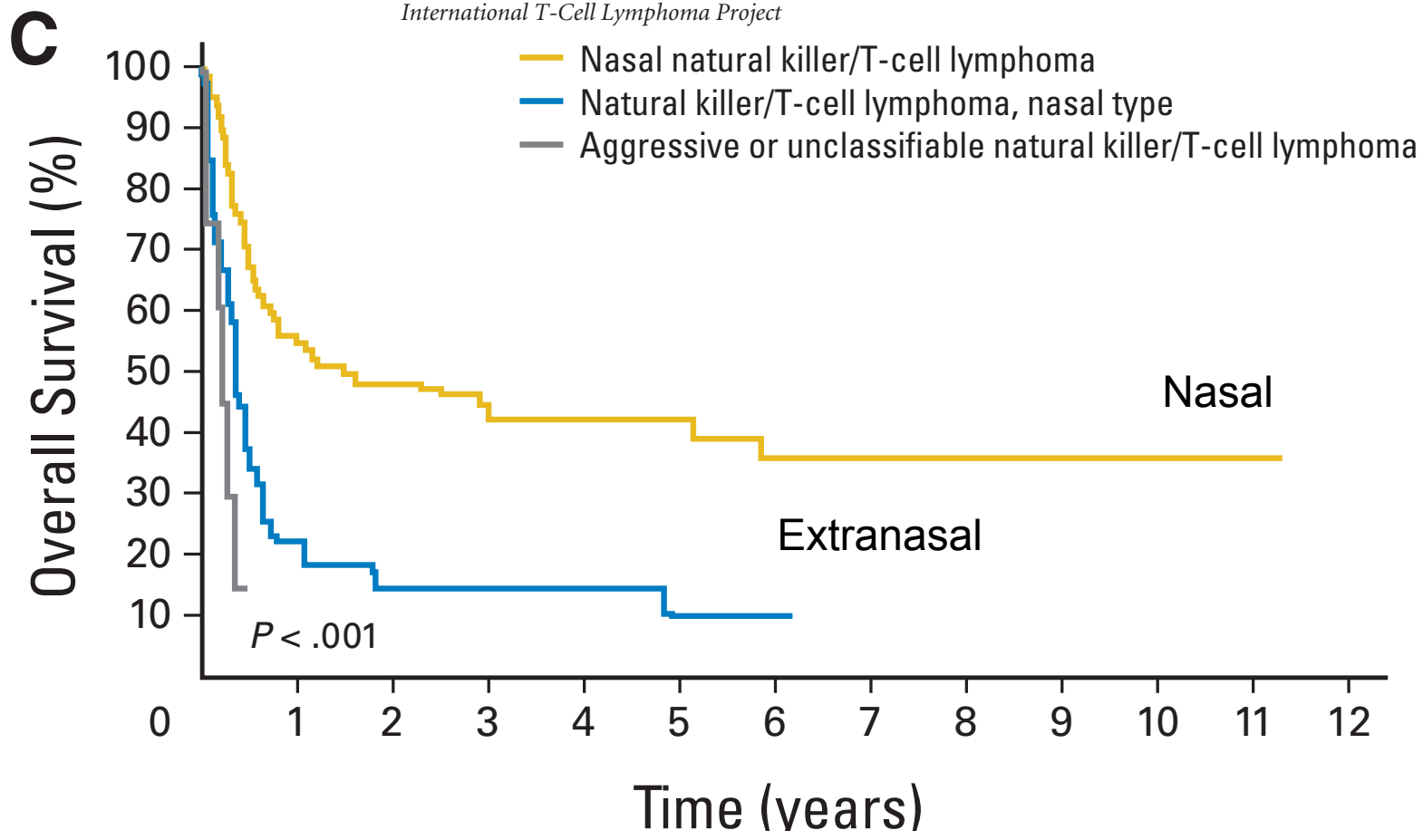
VOLUME 26 · NUMBER 25 · SEPTEMBER 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study: Pathology Findings and Clinical Outcomes

International T-Cell Lymphoma Project



Korean Prognostic Model

Table 2. Survival and Relative Risk of Death According to Risk Group As Defined by the New Prognostic Index

Risk Group	No. of Factors*	No. of Patients	%	% 5-Year OS	SE	RR	95% CI
Group 1	0	60	27	80.9	5.5	1.0	N/A
Group 2	1	68	31	64.2	6.5	1.8	0.9 to 3.5
Group 3	2	44	20	34.4	9.5	4.1	2.0 to 8.3
Group 4	3 or 4	47	22	6.6	4.3	13.6	7.0 to 26.6

Abbreviations: OS, overall survival; RR, relative risk; N/A, not applicable.
*Factors: the presence of "B" symptoms, Ann Arbor stage ≥ III, LDH > 1× upper normal limit, and regional lymph nodes (N1-N3, not M1) involvement according to the TNM staging system.

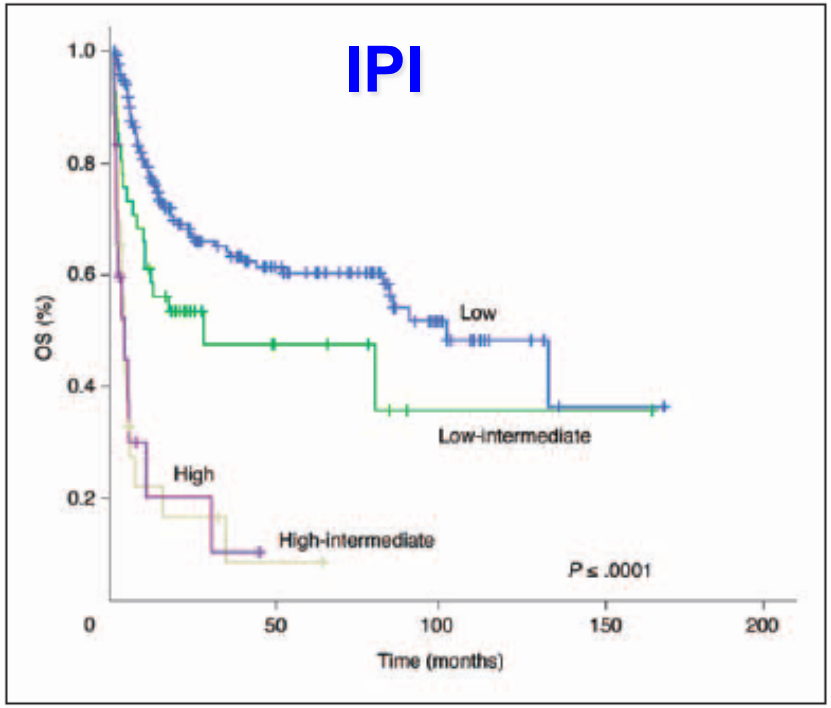


Fig 4. Survival according to IPI. Low risk, n = 148 (69%); low-intermediate risk, n = 34 (16%); high-intermediate risk, n = 19 (9%); high risk, n = 14 (7%). OS, overall survival.

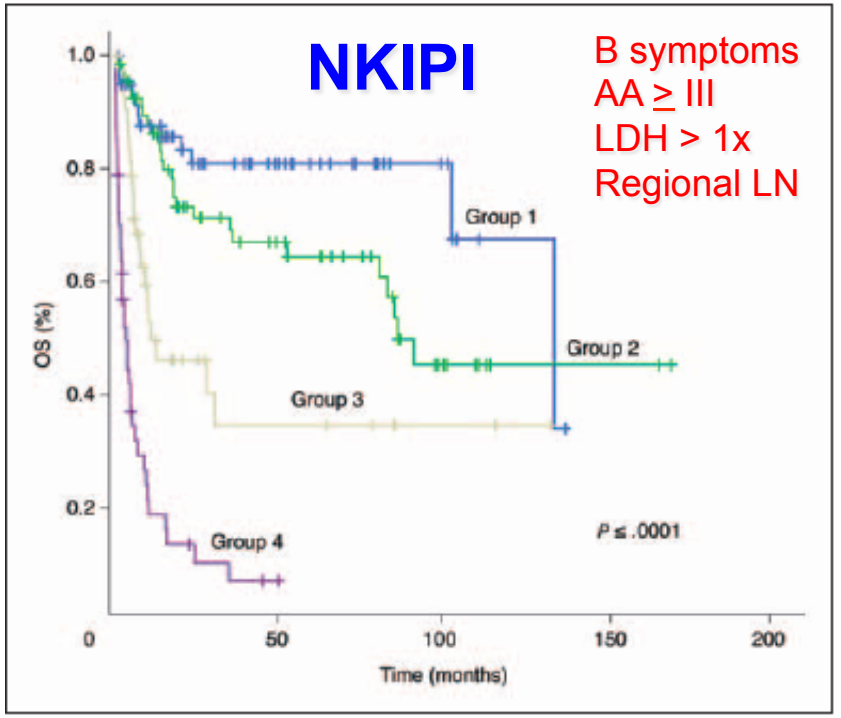


Fig 3. Survival according to the new prognostic index. Group 1, n = 60 (27%); group 2, n = 68 (31%); group 3, n = 44 (20%); group 4, n = 47 (22%). OS, overall survival.

Lee et al. JCO 2006, 24:612

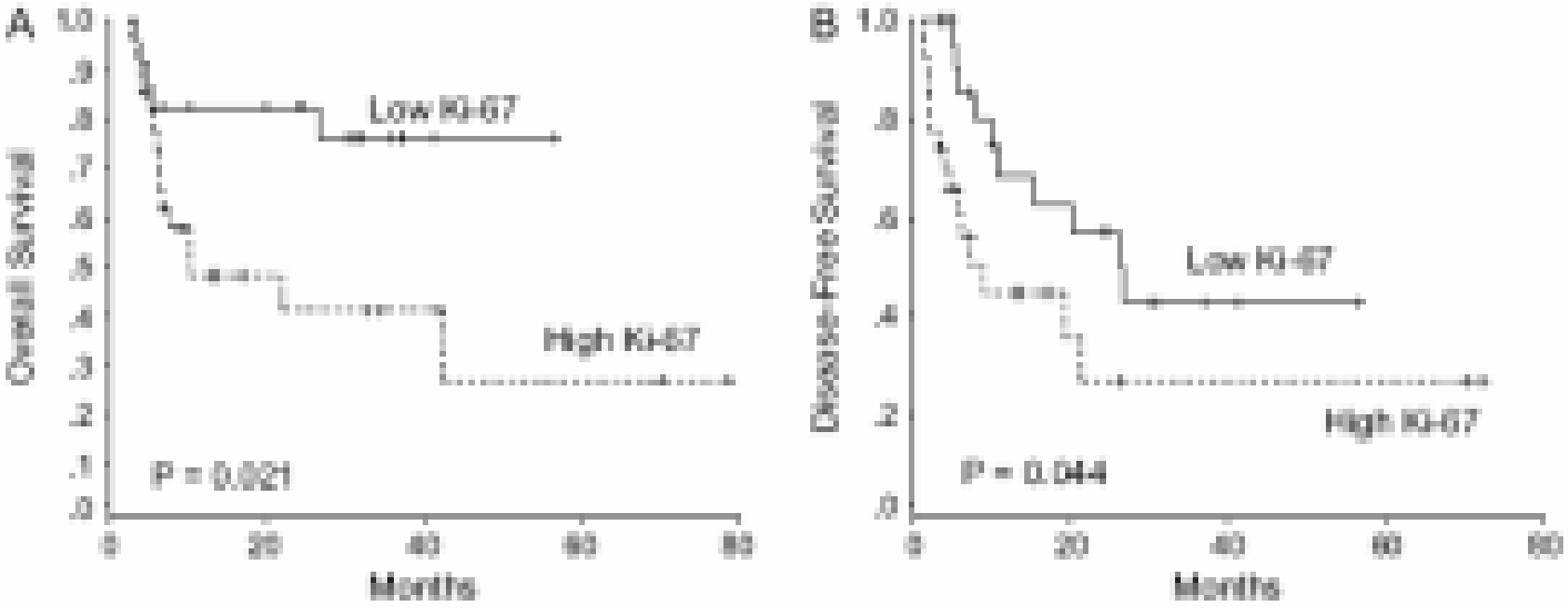
original article

Annals of Oncology 18: 1382–1387, 2007
doi:10.1093/annonc/mdm183

Ki-67 expression is predictive of prognosis in patients with stage I/II extranodal NK/T-cell lymphoma, nasal type

S. J. Kim[1], B. S. Kim[1]*, C. W. Choi[1], J. Choi[2], I. Kim[2], Y.-H. Lee[3] & J. S. Kim[1]

low (< 65%) versus high Ki-67 (≥ 65%).



NK/T CELL LYMPHOMA PROGNOSTIC INDEX[a]

ALL PATIENTS

Serum LDH > 1 x normal
B symptoms
Lymph nodes, N1 to N3, not M1
Ann Arbor Stage III

	Number of risk factors
Low	0
Low intermediate	1
High intermediate	2
High	3 or 4

[a] Lee J, Suh C, Park YH, et al. Extranodal natural killer T-cell lymphoma, nasal-type: A prognostic model from a retrospective multicenter study. J Clin Oncol. 2006;24:612-618.

Management of Localized Nasal Disease

- **Radiotherapy** is most important for local control
- Doses ranging from 30-60 Gy has been used but higher dose of 50-55 Gy is recomended
- Careful planning with the assistance of CT or even better MRI is recommended
- Overall response 60-100%
- Better than chemotherapy alone
- Relapse 50% and long term survival 40-60%
  - Mostly locorregional recurrence
  - Systemic relapse 25-30%
- **Combined chemotherapy and radiotherapy recommended**
  - Optimal sequence and timing?
  - Early radiotherapy recommended?
  - Concorrent chemotehrapy and radiotherapy (+ cisplatin?)
  - Watch out for progression during therapy
  - Close monitoring of response: endoscopy, biopsy, CT/MRI

Treatment

- There is a lack of consensus on treatment of ENKTL
- There is no therapy considered standard

Combined Treatment
Optimal sequence ?

Summary of the Literature

Reference	Phenotype	Treatment	No.	LFR	5-yr OAS (%)
Itami et al., 1991[14]	NK or T-cell	CT → RT or RT	9	6/9	NR
Aviles et al., 2000[16]	NK or T-cell	RT → CT	108	NR	86 (8 yrs)
Kim et al., 2001[17]	NK cell	CT → RT	17	NR	59 (3 yrs)
Yamaguchi et al., 2001[18]	NK cell	RT → CT or CT → RT	12	7/12	39
Ribrag et al., 2001[19]	NK or T-cell	RT → CT or CT → RT or RT	20	NR	NR
Cheung et al., 2002[20]	NK cell	CT → RT	79	31.1%	37.1
Chim et al., 2004[21]	NK cell	CT → RT	67	35/67	42.5 (10 yrs)
You et al., 2004[22]	NK cell	CT → RT	46	NR	36.5
Current study	NK or T-cell	CT → RT or RT	35	34.8%	47.3

LFR: local failure rate; OAS: overall survival; NK: natural killer; CT: chemotherapy; RT: radiotherapy; NR: not reported.

Radiotherapy

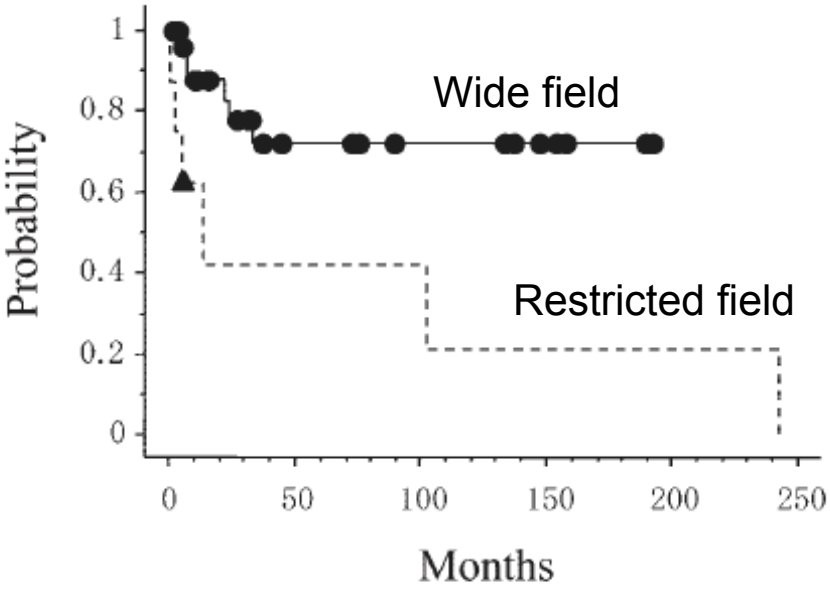


FIGURE 2. This graph illustrates the local control probability as a function of radiotherapy (RT) field. Solid line: an RT field that encompassed all sinuses, the nasopharynx, and macroscopic lesions; dashed line: an RT field that included macroscopic lesions with a margin.

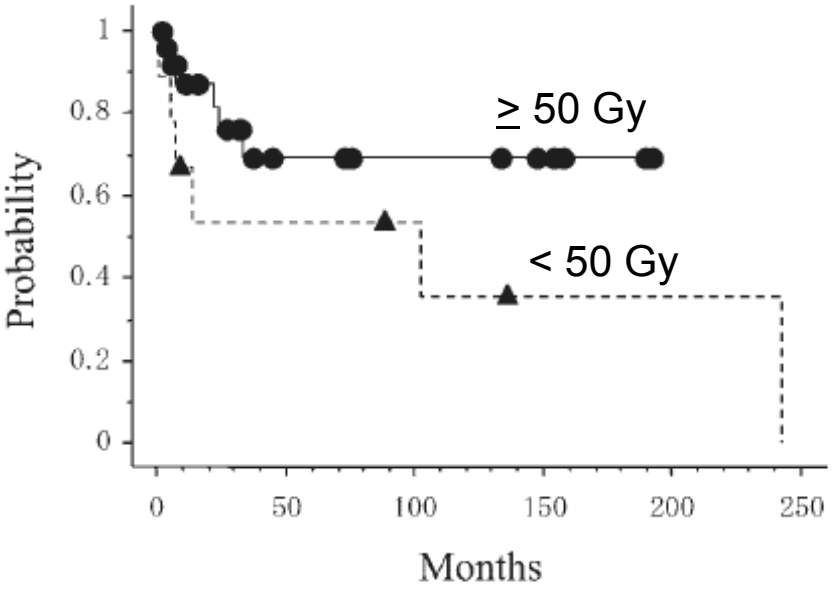


FIGURE 3. This graph illustrates the local control probability as a function of radiotherapy dose. Solid line: doses ≥ 50 grays (Gy); dashed line; doses < 50 Gy.

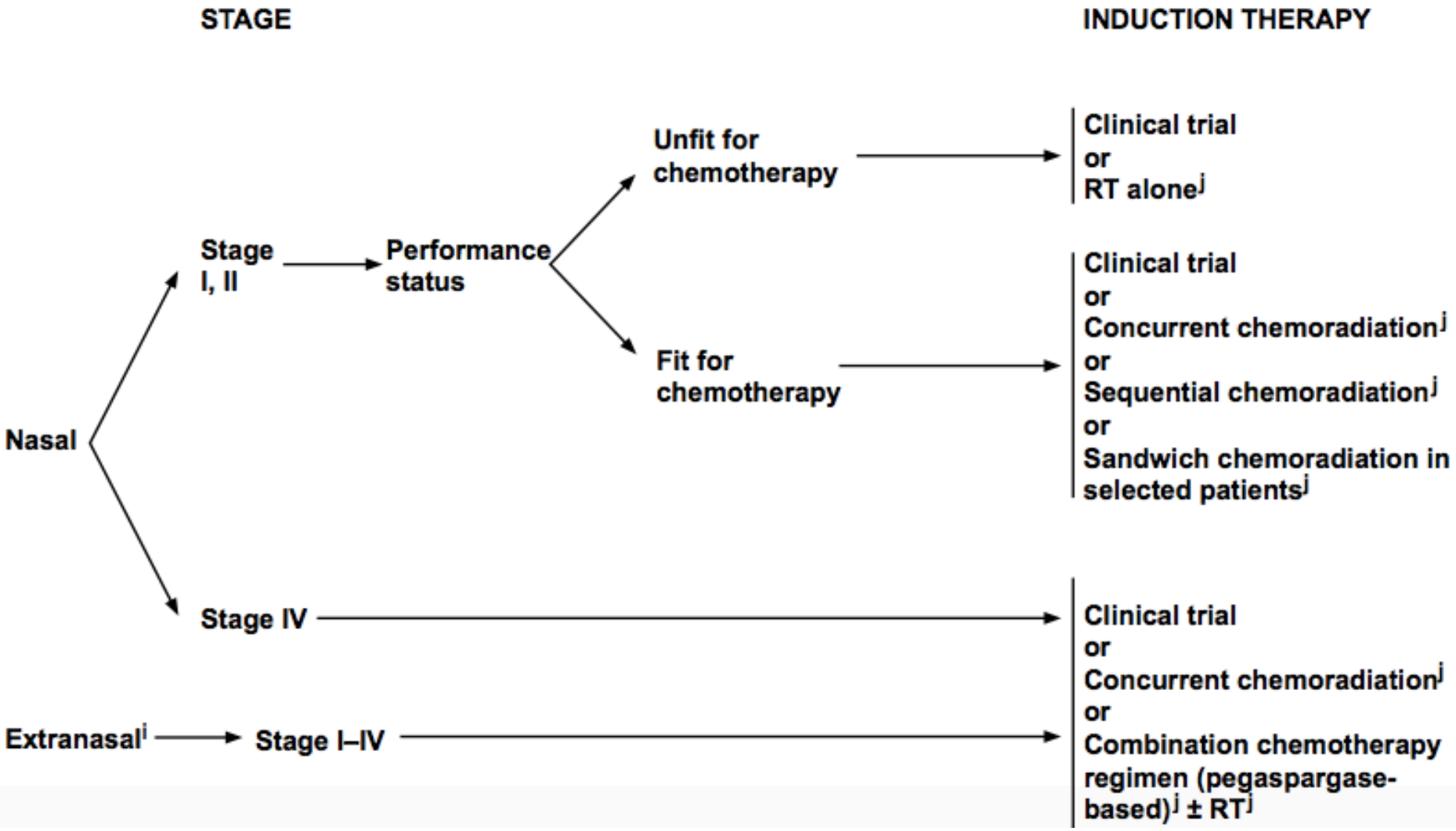
Management of Localized Nasal Disease

Radiotherapy

- **Is most important for local control**
  - Doses ranging from 30-36 Gy has been used but higher dose of 50-55 Gy is recomended
  - Overall response 60-100%
  - Better than chemotherapy alone
  - Relapse 50%
    - Mostly locorregional recurrence
    - Systemic relapse 25-30%

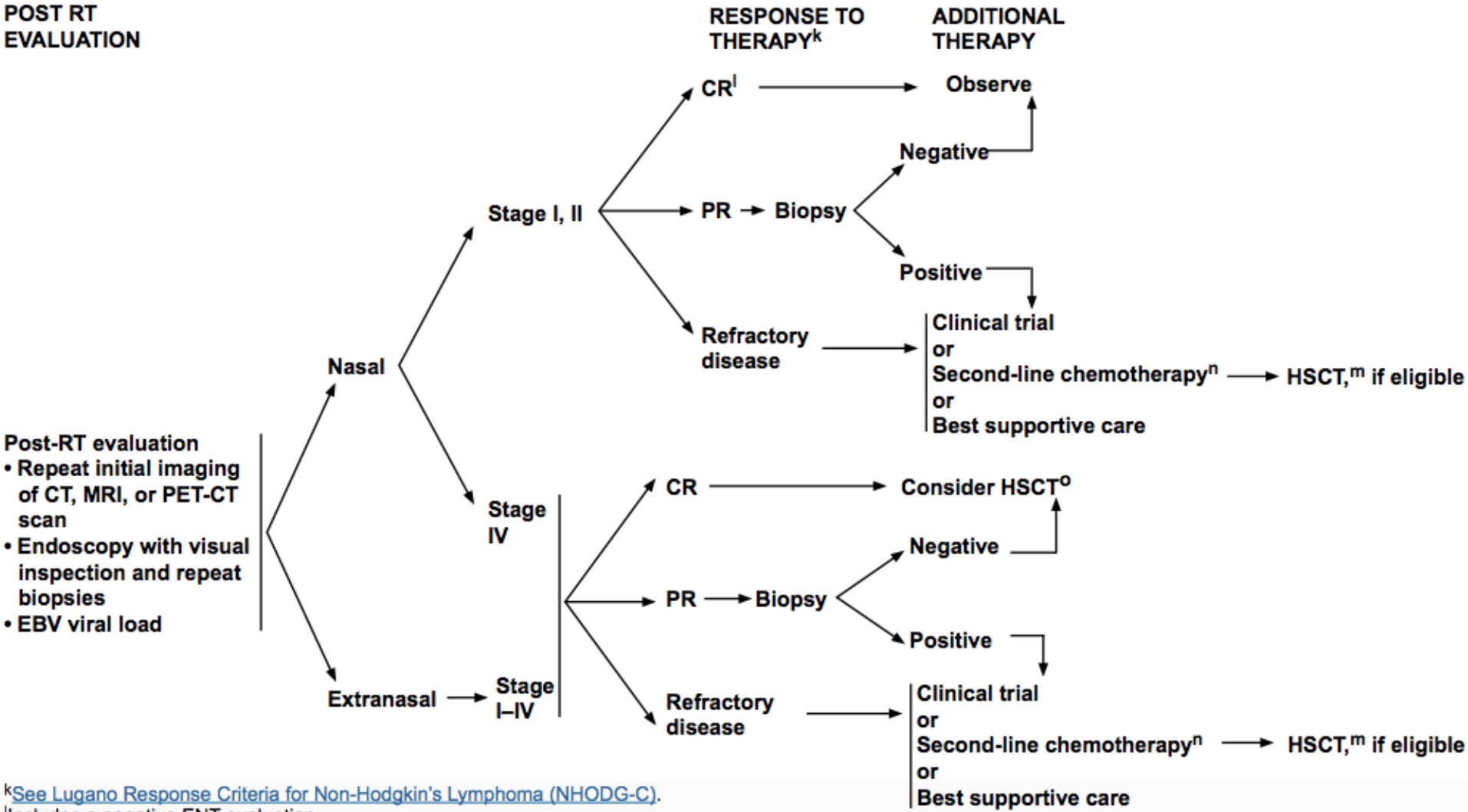
National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Extranodal NK/T-Cell Lymphoma, nasal type



Extranodal NK/T-Cell Lymphoma, nasal type

NHL Table of Contents
Discussion



[k] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[l] Includes a negative ENT evaluation.

SUGGESTED TREATMENT REGIMENS[a]

(in alphabetical order)

Combination chemotherapy regimen (pegaspargase-based)
- **AspaMetDex (pegaspargase, methotrexate, and dexamethasone) (Reported as a second-line regimen)**
- **SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase, and etoposide) x 4–6 cycles for advanced stage**
- **GELOX (gemcitabine, pegaspargase, and oxaliplatin)**

Concurrent chemoradiation therapy (CCRT)
- **CCRT (radiation 50 Gy and 3 courses of DeVIC [dexamethasone, etoposide, ifosfamide, and carboplatin])**
- **CCRT (radiation 40–52.8 Gy and cisplatin) followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)**

Sequential chemoradiation
- **For Stage I, II, SMILE followed by RT 45–50.4 Gy x 2–4 cycles**

Sandwich chemoradiation[b]
- **GELOX x 2 cycles followed by RT 56 Gy followed by GELOX x 2–4 cycles**

Radiation therapy alone
- **Recommended tumor dose is ≥50 Gy**
  - **Early or up-front RT had an essential role in improved OS and DFS in patients with localized extranodal NK/T-cell lymphoma, nasal-type, in the upper aerodigestive tract.**
  - **Up-front RT may yield more benefits on survival in patients with stage I disease.**

Management of Localized Nasal Disease

- **Radiotherapy** is most important for local control
  - Doses ranging from 30-36 Gy has been used but higher dose of 50-55 Gy is recomended
  - Overall response 60-100%
  - Better than chemotherapy alone
  - Relapse 50%
    - Mostly locorregional recurrence
    - Systemic relapse 25-30%

- **Combined chemotherapy and radiotherapy recommended**
  - Optimal sequence and timing?
  - Early radiotherapy recommended?

- **Hematopoietic Stem Cell Transplantation**
  - 3 previously published series
  - Seems to confer a survival benefit in RC as consolidation

Suzuki et al. Biol Blood Marrow Transplant 14: 1356, 2008

Management of Localized Nasal Disease

Combined chemotherapy and radiotherapy

Rational

- Relapse 50%
- Mostly locorregional recurrence
- Systemic relapse 25-30%

Questions

- What is the best chemotherapy?
- Optimal sequence and timing?
- Early radiotherapy recommended?

Chemotherapy

- Anthracyclines containing regimens such as CHOP are commonly used
  - anthracyclines not essential?

- No evidence that the more intensive regimens like ProMACE-CytaBOM are better

- Early experience with L-asparaginase containing regimens is encouraging
  - **SMILE**: steroid, methotrexate, ifosfamide, L-asparaginase and etoposide
  - International Phase II Study (Kasuo Oshimi)

Int J Clin Oncol (2009) 14:181–190
DOI 10.1007/s10147-009-0882-7

REVIEW ARTICLE

Yasuaki Harabuchi · Miki Takahara · Kan Kishibe
Shigetaka Morlai · Toshihiro Nagato · Hideyuki Ishii

Nasal natural killer (NK)/T-cell lymphoma: clinical, histological, virological, and genetic features

Table 3. Regimen for arterial infusion chemotherapy (MPVIC-P)

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Radiation	1.8 Gy × 15				1.8 Gy × 15									
MPVIC-P														
Etoposide (100 mg/m^2)	↓		↓		↓		↓				↓		↓	
Ifosfamide (1500 mg/m^2)	↓		↓		↓		↓				↓		↓	
Carboplatin (100 mg/m^2)		↓		↓		↓		↓				↓		↓
Methotrexate (260 mg/m^2)		↓						↓				↓		
Peplomycin (7 mg/m^2)				↓				↓						↓
Prednisolone (75 mg × 3)	↓	↓	↓	↓	↓	↓	↓	↓			↓	↓	↓	↓
	1 Course				2 Courses						3 Courses			

- Ifosfamide, carboplatin, methotrexate, and peplomycin do not have sensitivity against multidrug resistance genes (MDRs)
- Etoposide is known to be effective for virus-associated hemophagocytic syndrome
- One course took 4 weeks, and three courses was the total number given in treatment
- Radiation with 1.8 Gy per day was applied collaterally, and a 1-week interval was made at week 4
- The radiation field included the root of the nose and buccal region, with the central focus on the nose
- In some patients, course 3 was done as consolidation chemotherapy after 2–3 months

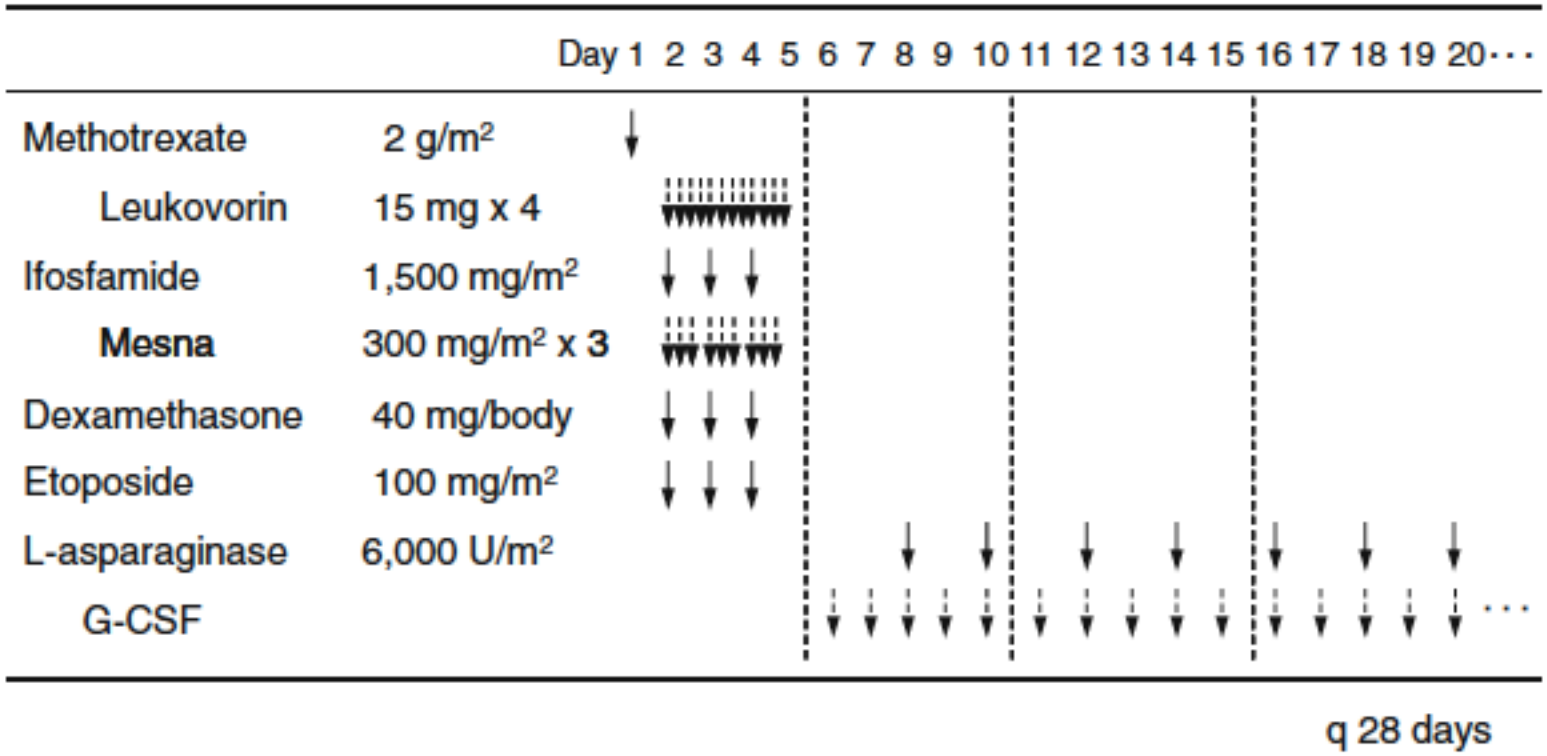
Chemotherapy

- Anthracyclines containing regimens such as CHOP are commonly used
  - anthracyclines not essential?

- No evidence that the more intensive regimens like ProMACE-CytaBOM are better

- Early experience with L-asparaginase containing regimens is encouraging
  - **SMILE**: steroid, methotrexate, ifosfamide, L-asparaginase and etoposide
  - International Phase II Study (Kasuo Oshimi)

Smile


Day 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20···
Methotrexate 2 g/m²
Leukovorin 15 mg x 4
Ifosfamide 1,500 mg/m²
Mesna 300 mg/m² x 3
Dexamethasone 40 mg/body
Etoposide 100 mg/m²
L-asparaginase 6,000 U/m²
G-CSF
···
q 28 days

Treatment outcome of early-stage NK/T-cell lymphoma using combined RT and CT in selected studies

Treatment	No. patients	ORR, %	CR, %	OS	PFS	Reference
RT → CHOP	172	93.3	82.2	3 y: ~80%	NA	1
RT → L-asparaginase/gem-based CT	37	93.3	82.2	3 y: ~80%	NA	
CHOP → RT	523	61.3	25.1	3 y: ~70%	NA	
L-asparaginase/gem-based CT → RT	118	77.9	31.6	3 y: ~70%	NA	
SMILE + sandwich RT	29	86	69	NA	NA	7
LVP + sandwich RT	26	92	42	2 y: 89%	2 y: 81%	8
GELOX + sandwich RT	27	93	56	2 y: 86%	2 y: 86%	9

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CR, complete response rate after initial RT or CT; GELOX, gemcitabine, L-asparaginase, and oxaliplatin; gem, gemcitabine; LVP, L-asparaginase, vincristine, and prednisolone; ORR: overall response rate after initial RT or CT; OS, overall survival; PFS, progression-free survival; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide.

Blood, 2015

Table 1. Novel chemotherapeutic regimens for NK/T-cell lymphomas

Regimen	Protocol	Reference
AspaMetDex	*Escherichia coli* L-asparaginase: 6000 U/m^2 IM, days 2, 4, 6, and 8 Methotrexate: 3000 mg/m^2 IV, day 1 Dexamethasone: 40 mg orally, days 1-4	16
2/3DeVIC	Dexamethasone: 40 mg IV, days 1-3 Etoposide: 67 mg/m^2 IV, days 1-3 Ifosfamide: 1000 mg/m^2 IV, days 1-3 Carboplatin: 200 mg/m^2 IV, day 1	56
VIPD	Etoposide: 100 mg/m^2 IV, days 1-3 Ifosfamide: 1200 mg/m^2 IV, days 1-3 Cisplatin: 33 mg/m^2 IV, days 1-3 Dexamethasone: 40 mg IV or orally, days 1-4	57
LVP	L-asparaginase: 6000 IU/m^2 IV, days 1-5 Vincristine: 1.4/m^2 IV, day 1 Prednisolone: 100 mg orally, days 1-5	59
GELOX	Gemcitabine: 1000 mg/m^2 IV, days 1 and 8 *E. coli* L-asparaginase: 6000 units/m^2 IM, days 1-7 Oxaliplatin: 130 mg/m^2 IV, day 1	60
SMILE	Dexamethasone: 40 mg IV or orally, days 2-4 Methotrexate: 2000 mg/m^2 IV, day 1 Ifosfamide: 1500 mg/m^2 IV, days 2-4 *E. coli* L-asparaginase: 6000 U/m^2 IV, days 8, 10, 12, 14, 16, 18, and 20 Etoposide: 100 mg/m^2 IV, days 2-4	62

Tse T, Kwong Y, Blood 2013; 121: 4997

Advances in Malignant lymphomas:
The case of extranodal
and T-cell lymphomas

Santiago de Chile
April 5-6, 2016

Auditorio Dr. Lucas Sierra
Hospital del Salvador
Av. Providencia 364

Analysis of data of patients registered up to March 15, 2016 diagnosed with NKTCL (N=154)

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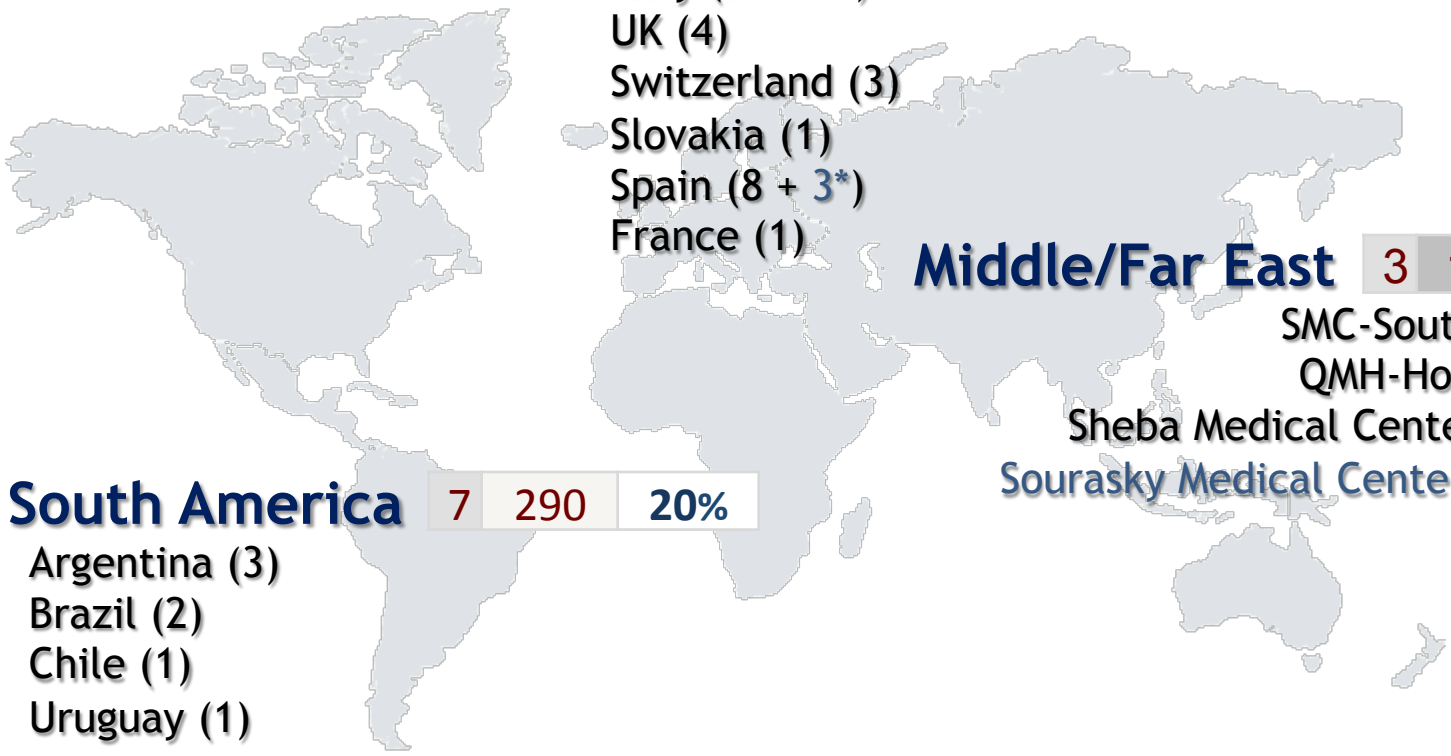
NKTCL

Carlos S. Chiattone, MD, PhD
Santa Casa Medical School
Sao Paulo - Brazil

Institutions & Patients

as of March 15, 2016	Inst	Pts	%
Recruiting	74	1499	100
Active, Not Yet Recruiting	5	-	-

* active, not yet recruiting



USA

8 | 328 | 22%

MSKCC
MDACC
UNMC
Stanford
CCF
FHCRC
WUStL
Yale

Europe

56 | 649 | 45%

Italy (39 + 1*)
UK (4)
Switzerland (3)
Slovakia (1)
Spain (8 + 3*)
France (1)

Middle/Far East

3 | 182 | 13%

SMC-South Korea
QMH-Hong Kong
Sheba Medical Center-Israel
Sourasky Medical Center-Israel*

South America

7 | 290 | 20%

Argentina (3)
Brazil (2)
Chile (1)
Uruguay (1)

data as of March 15, 2016

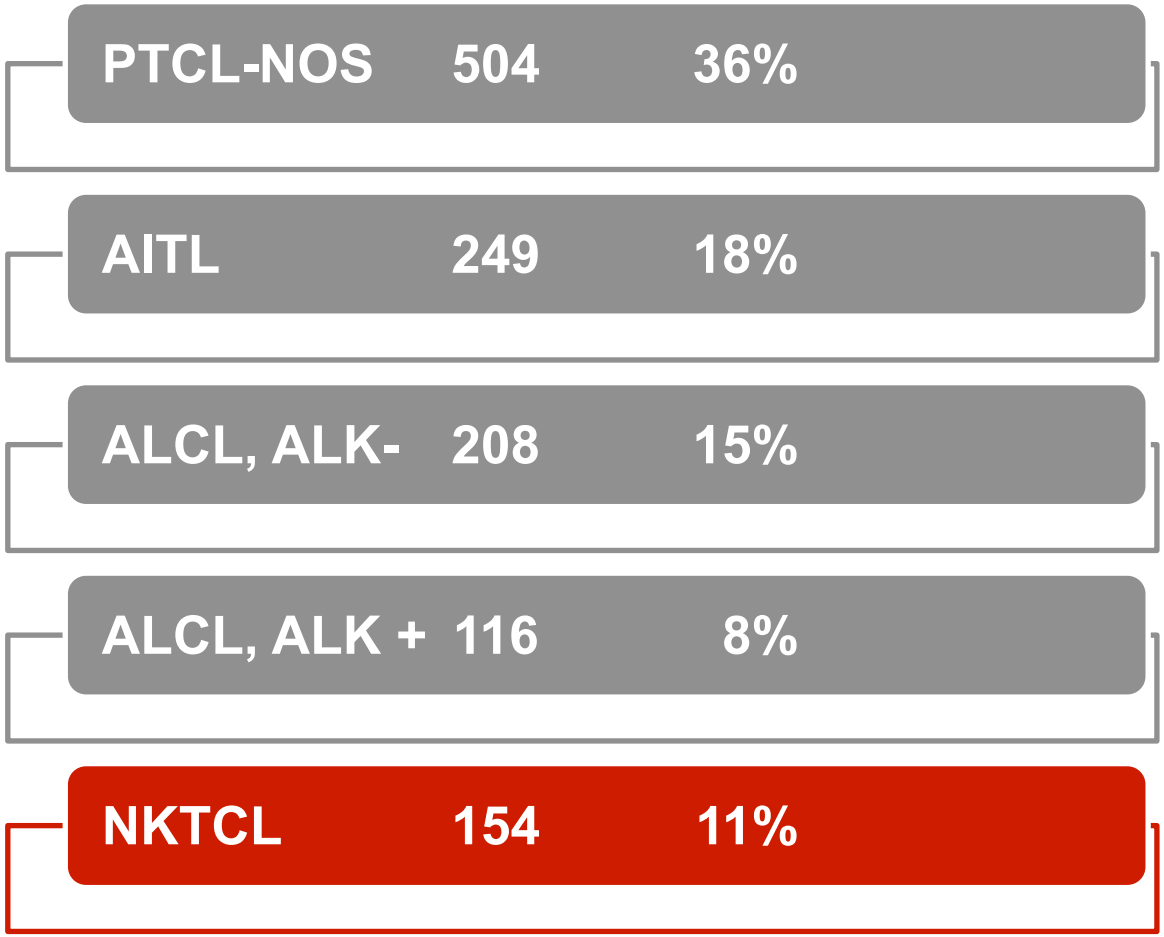
- 1,499 cases with PTCL or NK/T cell lymphoma

  (110 excluded so far; 1,389 analyzed))
- Newly diagnosed 2006-2016
- 74 sites globally
- Expert Hematopathology review
- Correlation with clinical outcomes

Histotype distribution

according to LOCAL/CENTRAL DIAGNOSIS

if review not possible or not yet done local diagnosis is reported



Histotype distribution

according to LOCAL/CENTRAL DIAGNOSIS

if review not possible or not yet done local diagnosis is reported

Enteropathy type	62	5%
Hepatosplenic	26	2%
Subcutaneous pann-like	20	1%
Peripheral γδ	13	1%
Unclassifiable T-cell	37	3%

Advances in Malignant lymphomas:
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and T-cell lymphomas

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Analysis of data of patients registered up to March 15, 2016 diagnosed with NKTCL (N=154)

NKTCL by geographic area and by South American Countries (N=154)

[% by ROW]

Subtype	South America (N=26)		USA (N=26)		Europe (N=49)		Asia (N=53)	
	N	**%**	N	%	N	%	N	%
Nasal [n=36)	9	**25**	4	**11**	16	**44**	7	**19**
Nasal type [n=106]	17	**16**	21	**20**	26	**24**	42	**40**
Unclassifiable NK [12]	-	**-**	1	**8**	7	**58**	4	**33**

Subtype	South America (N=26)		Chile (N=141)	Brazil (N=64)	Argentina (N=38)	Uruguay (N=18)
	N	**%**	%	%	%	%
Nasal [n=36)	9	**100**	**33**	**33**	**11**	**22**
Nasal type [n=106]	17	**100**	**41**	**53**	**6**	**0**
Unclassifiable NK [12]	-	**-**	-	-	-	-

Type of NKTCL in each geographic area (N=154)

[% by COLUMN]

Subtype	South America (N=26)		USA (N=26)		Europe (N=49)		Asia (N=53)	
	N	**%**	N	**%**	N	**%**	N	**%**
Nasal [n=36)	9	**35**	4	**15**	16	**33**	7	**13**
Nasal type [n=106]	17	**65**	21	**81**	26	**53**	42	**79**
Unclassifiable NK [12]	-	**-**	1	**4**	7	**14**	4	**7**

Subtype	South America (N=26)		USA (N=26)		Europe (N=49)		Asia (N=53)	
	N	**%**	N	**%**	N	**%**	N	**%**
Nasal [n=88)	17	**65**	12	**46**	23	**47**	36	**68**
Extranasal [n=39]	8	**31**	4	**15**	15	**31**	12	**23**
Unknown [n=27]	1	**4**	10	**38**	11	**22**	5	**9**

Type of NKTCL in each geographic area (N=154)

[% by COLUMN]

	South America (N=26)		USA (N=26)		Europe (N=49)		Asia (N=53)	
Subtype	N	%	N	%	N	%	N	%
Nasal [n=88)	17	65	12	46	23	47	36	68
Extranasal [n=39]	8	31	4	15	15	31	12	23
Unknown [n=27]	1	4	10	38	11	22	5	9

Patients characteristics (%): Nasal (N=88) Extranasal (N=39) [1]

	South America		USA		Europe		Asia	
N	17	8	12	4	23	15	36	12
Subtype	Nasal	Extra	Nasal	Extra	Nasal	Extra	Nasal	Extra
Median age (yrs, range)	50 21-82	50 28-70	57 29-87	51 24-68	57 31-90	52 29-69	52 18-80	46 18-75
Age ≥60 yrs	29	37	42	50	43	27	28	17
Gender (Male)	53	62	67	50	65	60	72	58
ECOG >1	25	37	-	50	9	31	3	25
B-symptoms	50	62	8	75	29	61	18	42
Discomfort disease-related	37	37	42	-	57	31	82	42
IPI LOW-LOW/INT	100	29	78	50	90	64	97	42
0-2								
PIT LOW-LOW/INT	82	60	78	100	94	64	94	83
0-1								
IPI INT/HIGH-HIGH	-	71	22	50	9	36	3	58
3-5								
PIT INT/HIGH-HIGH	18	40	22	-	6	36	6	17
2-4								

Patients characteristics (%): Nasal (N=88) Extranasal (N=39) [2]

	South America		USA		Europe		Asia	
N	17	8	12	4	23	15	36	12
Subtype	Nasal	Extra	Nasal	Extra	Nasal	Extra	Nasal	Extra
Stage III-IV	-	50	-	100	13	71	-	92
Nodal only disease	-	12	-	-	4	7	-	-
Bulky disease ≥ 10 cm	-	12	-	-	-	7	-	-
≥ 5 cm	-	25	-	25	-	7	3	-
NSE >1	35	75	25	75	30	64	6	83
BM involvement	-	-	-	-	-	15	-	33
LDH > ULN	10	57	37	25	33	50	31	58
HB ≤ 11 g/Dl	15	25	-	25	9	33	11	58
Platelets ≤ 150K/mm^3	7	37	9	-	9	17	8	17
Lymphocytes ≤ 1000/mm^3	8	43	36	50	48	42	17	25
Monocytes > 800/mm^3	27	17	18	-	5	18	29	25
B2-micro> ULN [N=49/20]	25	100	N.D.	100	43	75	63	70
CRP > ULN [N=44/22]	50	100	N.D.	100	50	37	54	89

Treatment details (%): Nasal (N=76) Extranasal (N=36)

	South America		USA		Europe		Asia	
N	14	8	11	3	18	13	33	12
Subtype	Nasal	Extra	Nasal	Extra	Nasal	Extra	Nasal	Extra
Tx with curative intent	100	75	100	100	100	100	97	100
Induction therapy								
No Tx/Best supportive care	-	25	-	-	-	-	3	-
RT alone	7	-	18	-	11	-	-	-
CHT alone	21	50	-	33	39	61	3	75
CHT/RT combined	71	25	82	67	50	38	94	25
Type of induction CHT								
Anthracycline	92	67	-	33	75	46	6	25
Etoposide	8	17	89	67	19	8	75	75
Anthracycline + Etoposide	-	-	-	-	-	15	-	-
Other	-	17	11	-	6	31	19	-
Transplant use								
as consolidation in 1st line	-	12	9	67	6	23	9	17
as salvage treatment	-	-	-	-	-	31	15	8

Response to initial Therapy (%): Nasal (N=76) Extranasal (N=36)

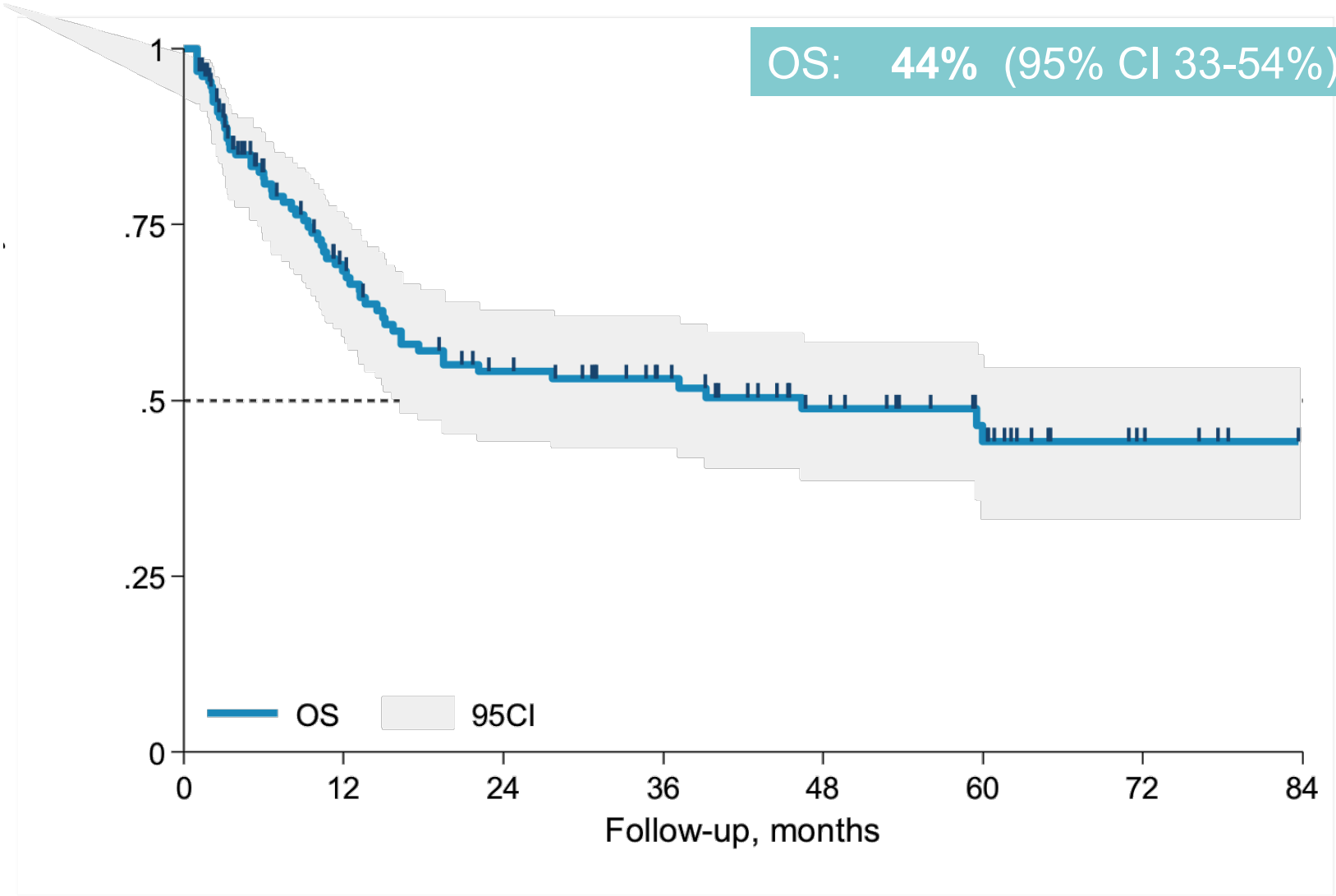
	South America		USA		Europe		Asia	
N	58	8	21	3	65	13	7	12
Subtype	Nasal	Extra	Nasal	Extra	Nasal	Extra	Nasal	Extra
CR/CRu	50	25	91	67	67	38	88	42
PR	7	25	9	-	6	8	-	-
NR/PD	43	58	-	12	17	33	6	46
Not Evaluable	-	12-	-	-	11	8	3	-
No Tx/Best supportive care	-	25	-	-	-	-	3	-
Evaluable patients N	14	5	11	3	16	12	31	12
CR/CRu	50	40	91	67	75	42	93	42
PR	7	40	9	-	6	8	-	-
NR/PD	43	20	-	33	19	50	6	58

Main Patients characteristics & Treatment by South American Country (%): Nasal (N=17) Extranasal (N=8)

	All S.A. 17 8		Chile 6 4		Brazil 7 4		Argentina 2 -		Uruguay 2 -	
	Nas	Ext	Nas	Ext	Nas	Ext	Nas	Ext	Nas	Ext
Median age (yrs)	50	50	45	48	51	51	47	-	58	-
Age ≥60 yrs	29	37	17	25	29	50	50	-	50	-
Sex (Male)	53	62	67	75	57	50	-	-	50	-
ECOG >1	25	37	33	75	14	-	-	-	50	-
B-symptoms	50	62	50	75	57	50	100	-	-	-
Stage III-IV	-	50	-	50	-	50	-	-	-	-
NES >1	35	75	50	50	29	100	50	-	-	-
Therapy with curative intent	100	75	100	50	100	100	100	-	100	-
Chemotherapy +/- RT	92	75	100	50	83	100	100	-	100	-
Anthracycline	92	67	100	100	100	50	50		100	
Etoposide	8	17	-	-	-	25	50		-	
	-	-	-	-	-	-	-		-	
Both				-	-	-			-	
HDT consolidation/salvage	-/-	12/-	-/-	-/-	-/-	25/-	-/-	-/-	-/-	-/-

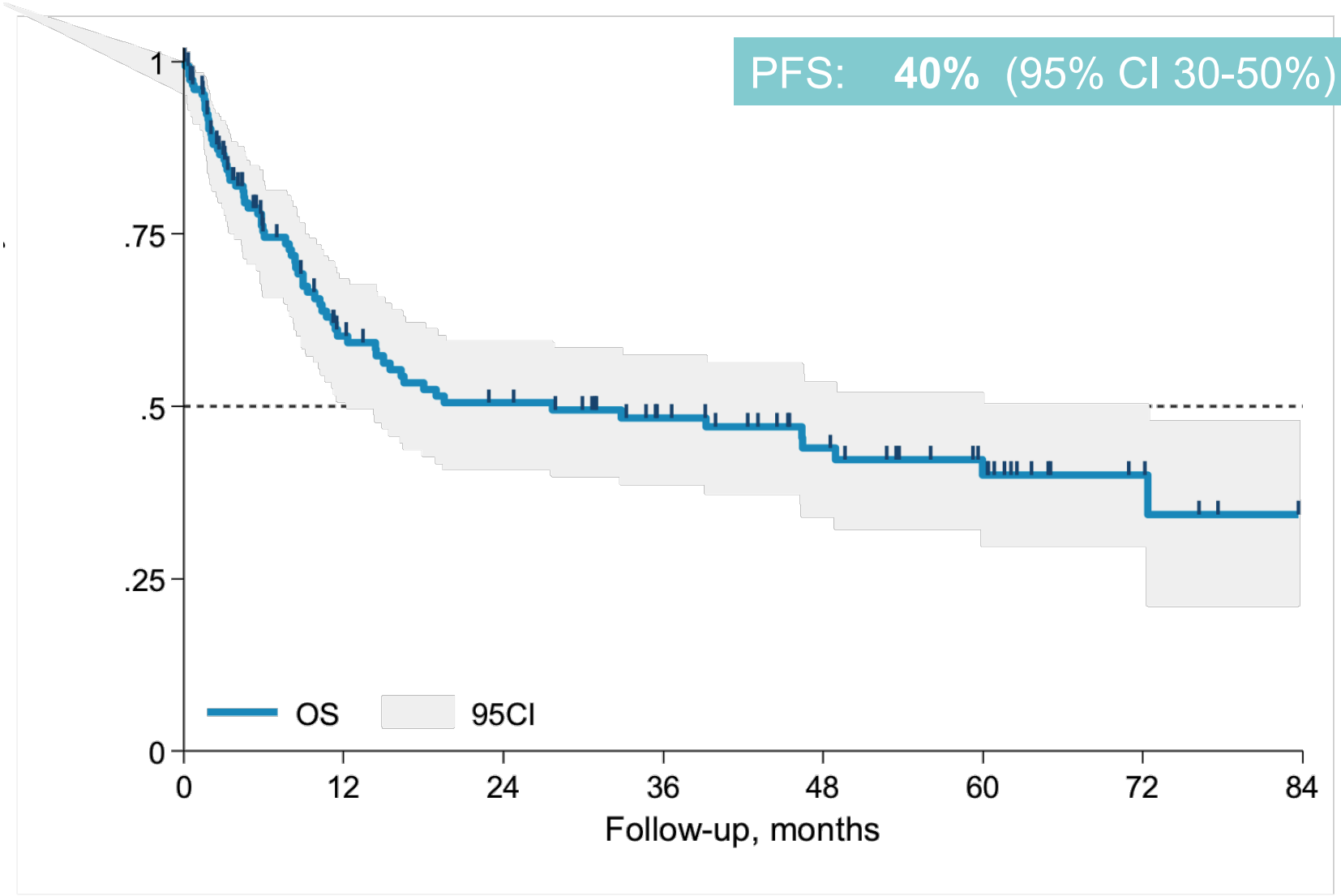
Overall Survival NKTCL, All (N=154)

OS: **44%** (95% CI 33-54%) at 5 yr

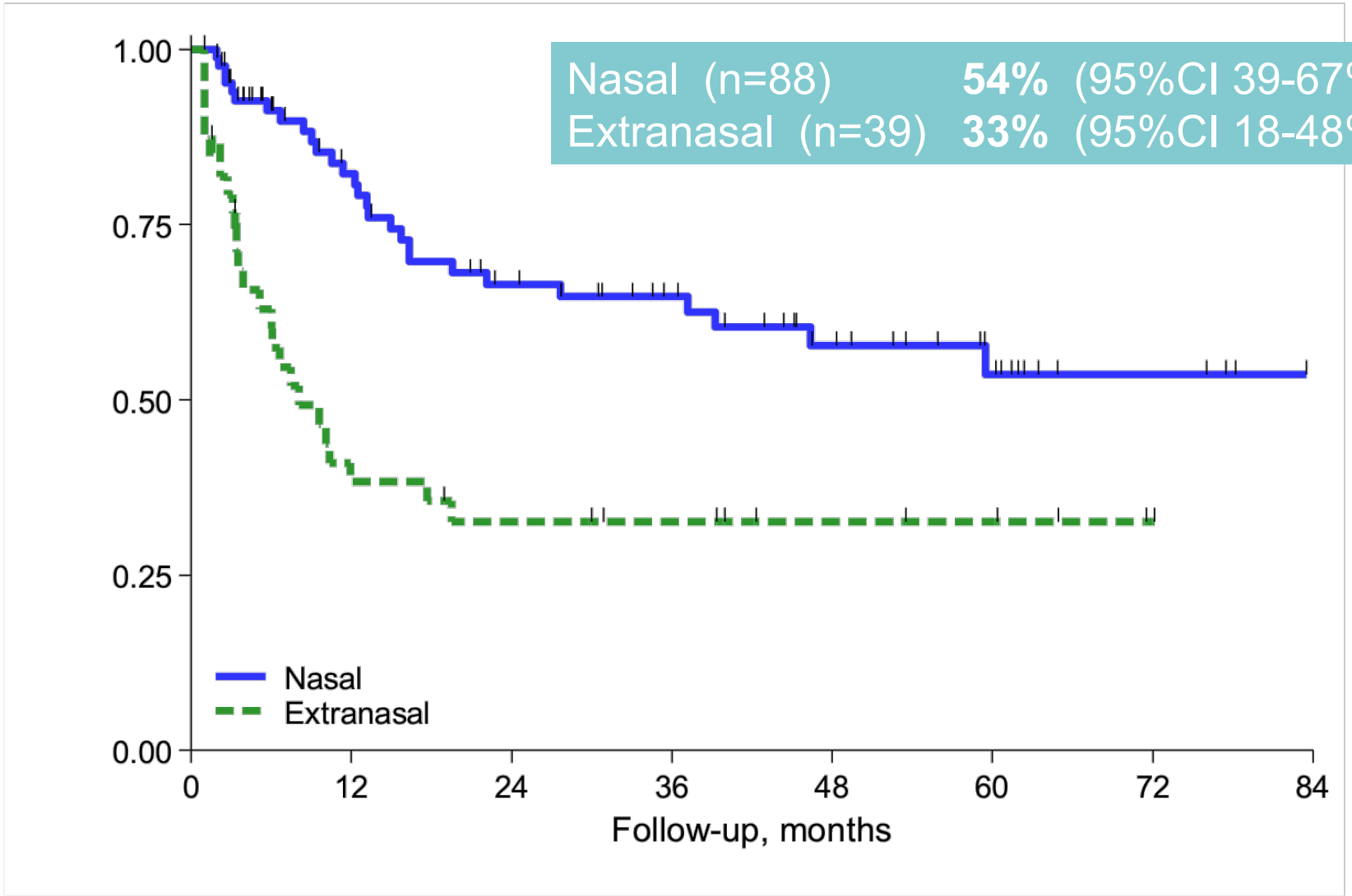


Progression-free Survival NKTCL, All (N=154)

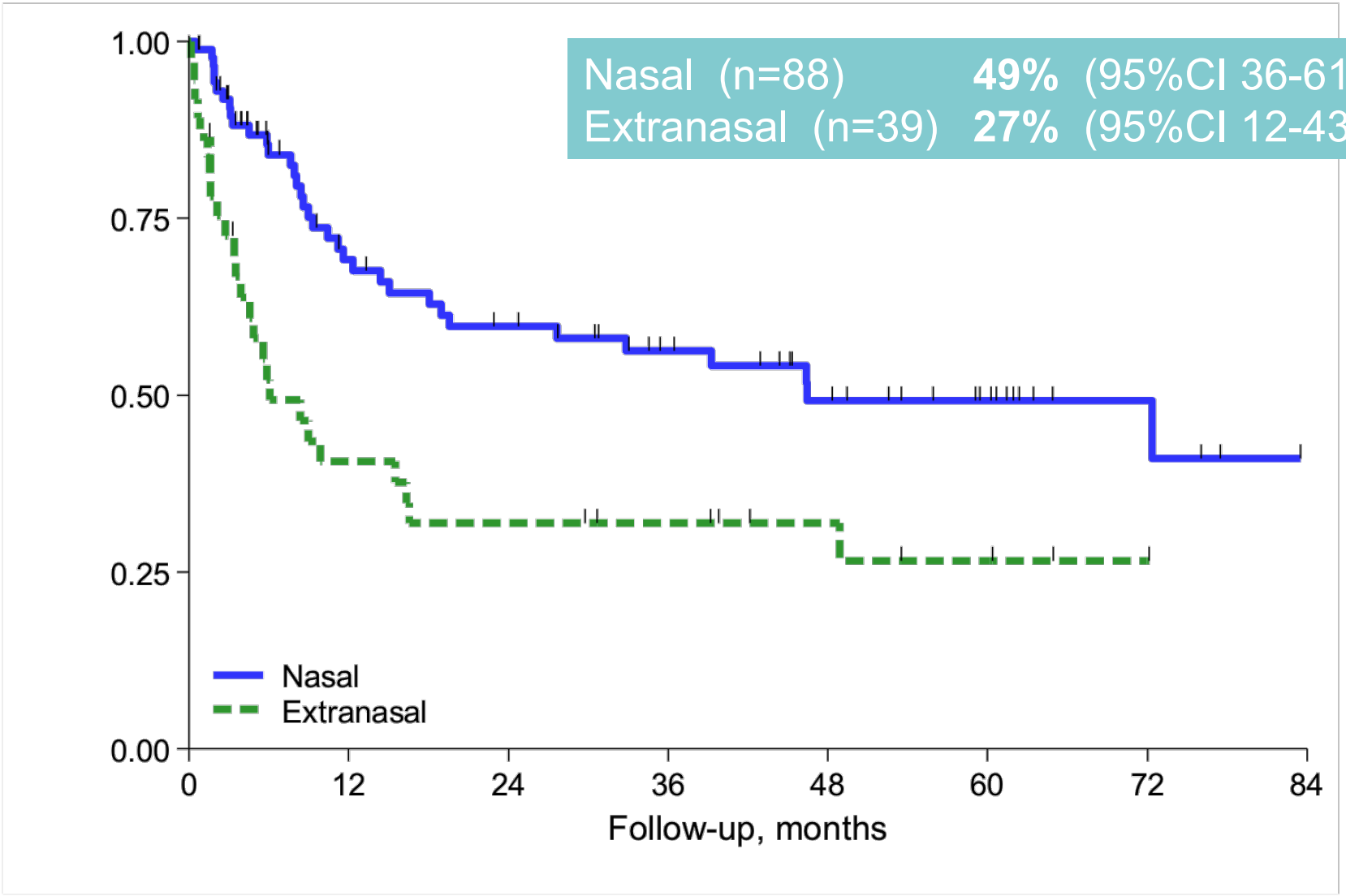
PFS: **40%** (95% CI 30-50%) at 5 yr



Overall Survival by type of disease (N=127)



PFS by type of disease (N=127)



Nasal (n=88)	**49%** (95%CI 36-61%)	at 5 yr
Extranasal (n=39)	**27%** (95%CI 12-43%)	at 5 yr

Extranodal NK/T-cell Lymphoma
Take Home Messages

- Diagnosis highly dependent on clinical aspects
- Frequent dissemination to other extranodal regions
- Necrosis in almost all cases, with or without angioinvasion
- NK Phenotype (few cases T-cell cytotoxic ?)
- Presence of EBV virtualy in all cases
- RT is important treatment component for localized disease
- Asparaginase was incorporated in CT regimens

Acknowledgments

- Monica Bellei (International T-Cell Project)
- Flávia Parra (T-Cell Project Brazil)
- Prof. Massimo Federico (International T-Cell Project)

Int J Hematol (2010) 92:690–696
DOI 10.1007/s12185-010-0720-8

Treatment of localized extranodal NK/T cell lymphoma, nasal type

Seok Jin Kim · Won Seog Kim

Table 1 Treatment outcome of chemotherapy followed by radiotherapy in stage I/IIE ENKTL of the upper aerodigestive tract

Authors (references)	No. (stage I/II)	Treatment	CR (%)	OS (%)
Kim et al. [6]	17 (17)	CHOP (4 cycles) + RT (median 45 Gy)	10 (58)	3 years 59
Kim et al. [7]	59 (41)	CHOP or COPBLAM-V ± RT	18 (44)	2 years 44[a]
Kim et al. [9]	43 (43)	CEOP-B (4–6 cycles) ± RT (44–60 Gy)	19 (44)	3 years 48
Lee et al. [10]	17 (17)	DI-CHOP (2 cycles) + RT (44 Gy) + CHOP (4 cycles)	13 (76)	3 years 56
Wang et al. [8]	25 (25)	CHOP (6 cycles) + RT (median 45 Gy)	11 (44)	2 years 78
	28 (28)	CHOP + semustine (6 cycles) + RT (median 45 Gy)	15 (53)	2 years 56

Table 2 Comparison of initial response and survival of stage I/IIE ENKTL of the upper aerodigestive tract: radiotherapy versus chemotherapy

Authors (references)	No.	Treatment strategy	Initial treatment	CR	OR	5-year OS (%)
Kim et al. [12]	104	RT	RT (median 50.4 Gy)	69%	85%	38
	39	CT/RT	CHOP, BACOP or m-BACOP (1–6 cycles)	5%	51%	35
Cheung et al. [13]	18	RT	RT (median 50 Gy)	77%	77%	29
	61	CT/RT	CHOP, CEOP or ProMACE (3–6 cycles)	NR	49%[a]	40
You et al. [14]	6	RT	RT (54–60 Gy)	NR	100%	83[b]
	40	CT ± RT	CHOP/CEOP, m-BACOD or ProMACE cytaBOM (3–6 cycles)	NR	55%[b]	28
Kim et al. [15]	33	RT	RT (median 50 Gy)	52%	94%	76
	20	CT/RT	CHOP or COPBLAM-V (4–6 cycles)	38%	57%	59
Li et al. [16]	31	RT	RT (median 50 Gy)	97%	NR	66
	34	RT/CT	RT (median 50 Gy)	71%	NR	77
	37	CT/RT	CHOP, CHOP-bleo or COBVP-16	19%	NR	74
Huang et al. [17]	9	RT	RT (median dose 50 Gy)	100%	NR	62[c]
	65	RT/CT	CHOP (1–3 cycles) followed by RT[c]	87%	NR	12
	8	CT	CHOP	25%	NR	

Table 3 Prospective trials with concurrent chemoradiotherapy for stage I/IIE ENKTL

Authors (references)	No.	Treatment	Stage IE/IIE	NKIPI group[a]	CR (%)	OR (%)	Local/ systemic relapse	Main toxicity	OS
Yamaguchi et al. [27]	27	Concurrent radiotherapy with chemotherapy (RT-two-thirds DeVIC) RT: 50 Gy for stage IE, 50.4 Gy for stage IIE CT: 3 courses of two-thirds DeVIC[b]	18/9	17/10	77	81	4%/33%	Mucositis	2 years 78%
Kim et al. [28]	30	Concurrent chemoradiotherapy plus chemotherapy CCRT: RT (median 40 Gy) with weekly cisplatin 30 mg/m^2 CT: 3 courses of VIPD[c]	15/15	21/9	80	83	7%/7%	Leucopenia	3 years 86%

Chemotherapy: SMILE for lymphoma

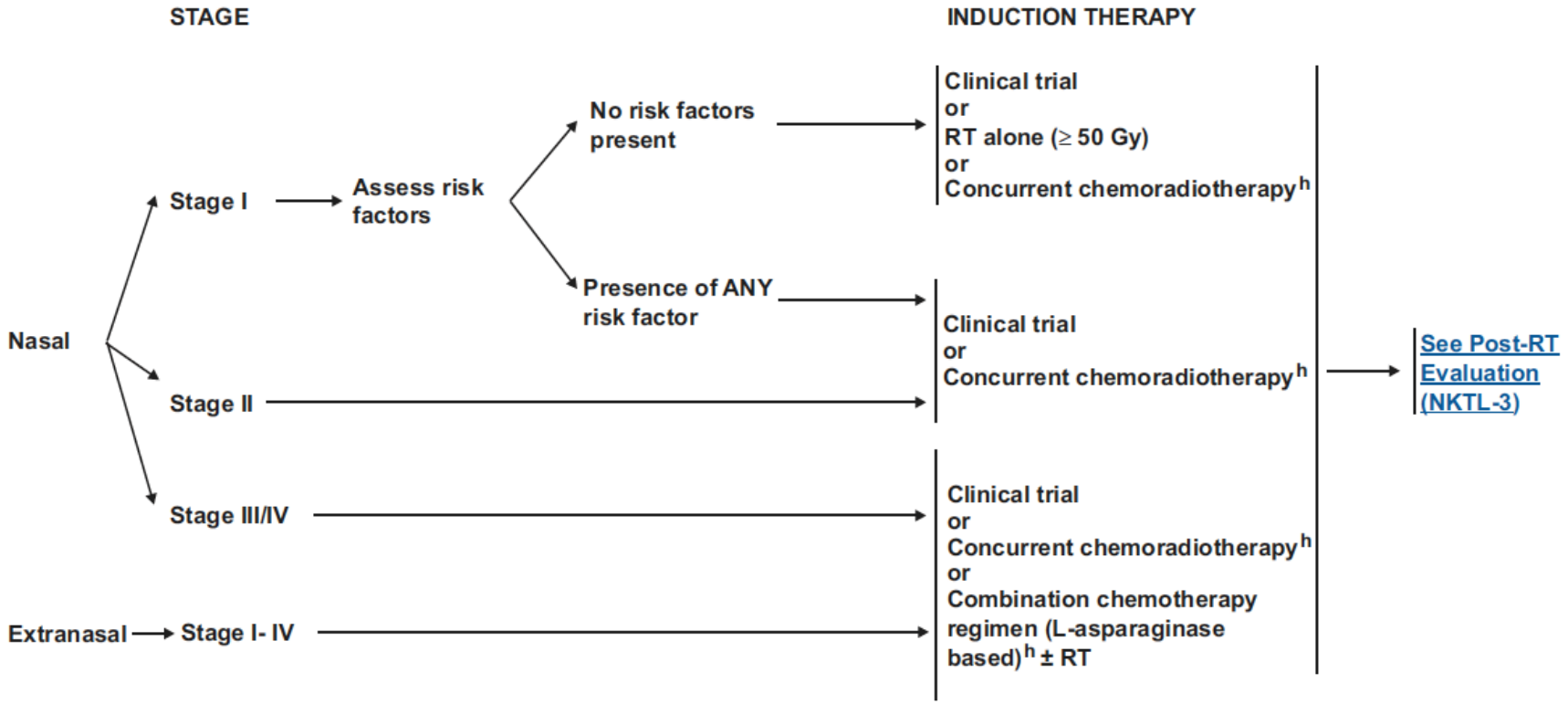
Methotrexate (2Gm/m^2) into 500 ml NS infusion over 6 hr on **Day 1.**
Ifosfamide (1500mg/m^2) + **Mesna** (900mg/m^2) into 1000 ml NS over 6 hr from **Day 2 to Day 4.**
Etoposide (VP-16) (100mg/m^2) into 500ml NS over 2 hr from **Day 2 to Day4.**
Folinic acid (45mg/dose) *p.o. Q6H x 4 doses from **Day 2 to Day 4.**
(24hr exactly after MTX completion)
Dexamethasone (40mg/day) *p.o. daily from **Day 2 to Day 4.**
L-asparaginase (6,000U/m^2) into 250mlNS over 2 hr on **D8, D10, D12, D14, D16, D18 & D20**

Day	Date	Route/Drug	Dose	Administration (solution/duration)	Clinician's Signature	Pharmacist's Signature	Drug given by
D1.	_____	IV Methotrexate	___Gm	_____	_____	_____	_____
D2.	_____	IV Ifosfamide +	___mg	_____	_____	_____	_____
		IV Mesna	___mg	_____	_____	_____	_____
		IV VP-16	___mg	_____	_____	_____	_____
		PO Folinic acid	45 mg				
		PO Dexamethasone	40 mg				
D3.	_____	IV Ifosfamide +	___mg	_____	_____	_____	_____
		IV Mesna	___mg	_____	_____	_____	_____
		IV VP-16	___mg	_____	_____	_____	_____
		PO Folinic acid	45 mg				
		PO Dexamethasone	40 mg				
D4.	_____	IV Ifosfamide +	___mg	_____	_____	_____	_____
		IV Mesna	___mg	_____	_____	_____	_____
		IV VP-16	___mg	_____	_____	_____	_____
		PO Folinic acid	45 mg				
		PO Dexamethasone	40 mg				
D8.	_____	IV L-asparaginase	___U	_____	_____	_____	_____
D10.	_____	IV L-asparaginase	___U	_____	_____	_____	_____
D12.	_____	IV L-asparaginase	___U	_____	_____	_____	_____
D14.	_____	IV L-asparaginase	___U	_____	_____	_____	_____
D16.	_____	IV L-asparaginase	___U	_____	_____	_____	_____
D18.	_____	IV L-asparaginase	___U	_____	_____	_____	_____
D20.	_____	IV L-asparaginase	___U	_____	_____	_____	_____

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Extranodal NK/T-cell Lymphoma, nasal type

NCCN Guidelines Index
NHL Table of Contents
Discussion



Nasal
Stage I
No Risk Factors: clinical trial or RT alone (> 50Gy) or Chemoradiotherapy
Presence Risk Factors: clinical trial or Chemoradiotherapy
Stage II: clinical trial or Chemoradiotherapy
Stage III/IV: clinical trial, Chemotherapy, Combination CT (L-asparaginase) + RT

Hematopoietic Stem Cell Transplantation

- **Auto-transplant for CR1**
  - Marrow often not involved
  - 68-80% overall survival
  - Highly selected cases were included
  - Benefit only high risk patients?

- **Allo-transplant**
  - Advantage of graft versus lymphoma effect
  - 2-year survival of 40-50% reported
  - High treatment related mortality 25-60%
  - Choice of patients

Suzuki et al. Biol Blood Marrow Transplant 14: 1356, 2008

Extranodal NK/T cell Lymphoma, Nasal Type

Nasal

Stage I

- **No Risk Factors**:
  clinical trial or RT alone (> 50Gy) or Chemoradiotherapy
- **Presence Risk Factors:**
  clinical trial or Chemoradiotherapy

Stage II

clinical trial or Chemoradiotherapy

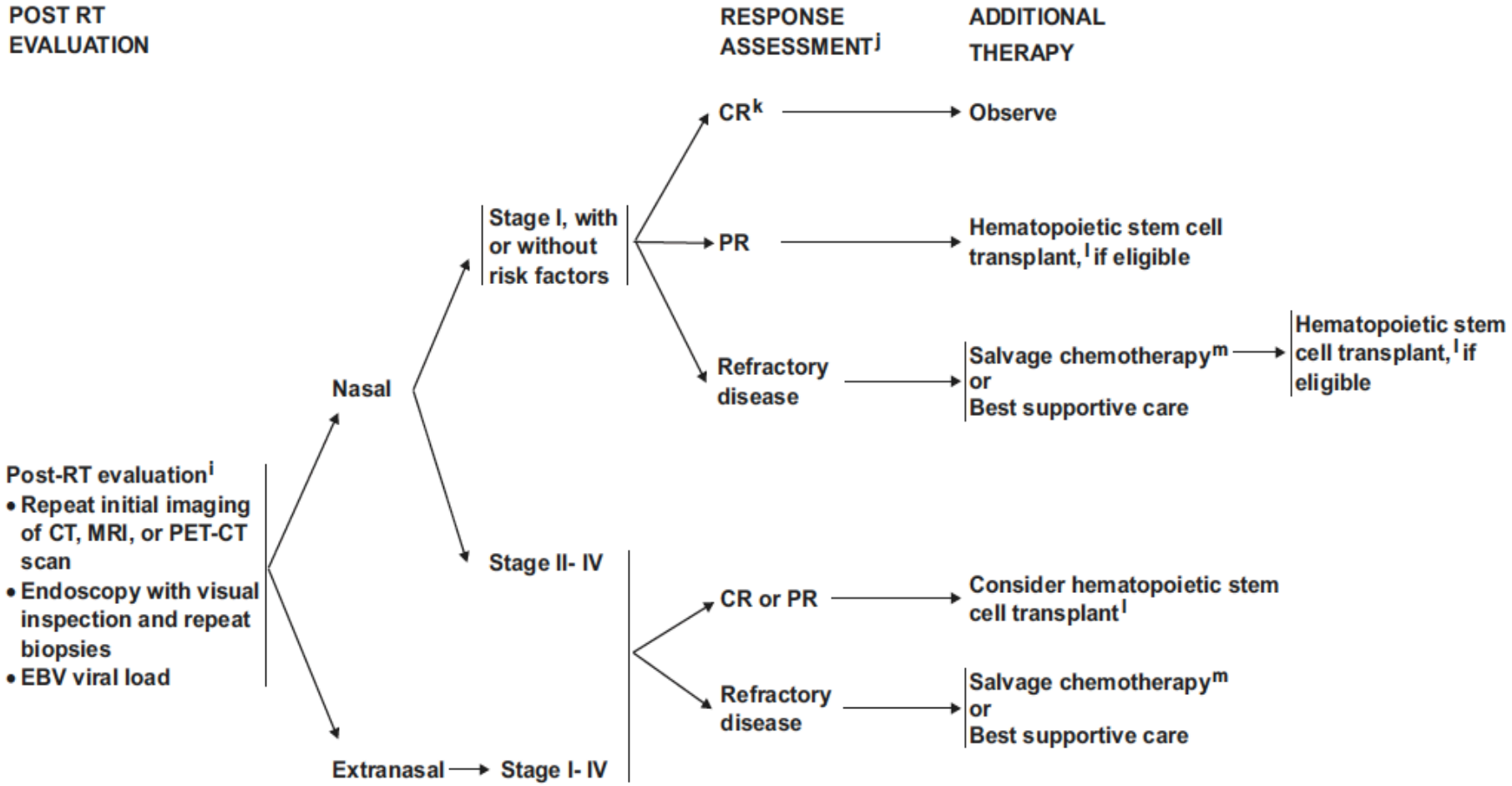
Stage III/IV

clinical trial, Chemoradiotherapy,
combination CT (L-asparaginase) + RT

Extranasal

Stage I-IV

clinical trial, Chemoradiotherapy,
combination CT (L-asparaginase) + RT


POST RT EVALUATION
RESPONSE ASSESSMENT[j]
ADDITIONAL THERAPY
Post-RT evaluation[i]
• Repeat initial imaging of CT, MRI, or PET-CT scan
• Endoscopy with visual inspection and repeat biopsies
• EBV viral load
Nasal
Stage I, with or without risk factors
CR[k]
Observe
PR
Hematopoietic stem cell transplant,[l] if eligible
Refractory disease
Salvage chemotherapy[m] or Best supportive care
Hematopoietic stem cell transplant,[l] if eligible
Stage II- IV
CR or PR
Consider hematopoietic stem cell transplant[l]
Refractory disease
Salvage chemotherapy[m] or Best supportive care
Extranasal
Stage I- IV

SUGGESTED TREATMENT REGIMENS[a]

Combination chemotherapy regimen (L-asparaginase based)

- **SMILE (steroid [dexamethasone], methotrexate, ifosfamide, L-asparaginase, and etoposide)**

Concurrent chemoradiotherapy (CCRT)

- **CCRT (radiation 50 Gy and 3 courses of DeVIC [dexamethasone, etoposide, ifosfamide, and carboplatin])**

- **CCRT (radiation 40 to 52.8 Gy and cisplatin) followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)**

Radiotherapy alone (or in sequence with chemotherapy)

- **Early or up-front RT had an essential role in improved OS and DFS in patients with localized extranodal NK/T-cell lymphoma, nasal-type, in the upper aerodigestive tract. The recommended tumor dose was ≥ 50 Gy. Up-front RT may yield more benefits on survival in patients with stage I disease.**

SUGGESTED TREATMENT REGIMENS

References

Combination chemotherapy regimen (L-asparaginase based)

Jaccard A GN, Coppo P, Morschhauser F, et al. A prospective phase II trial of an L-asparaginase containing regimen in patients with refractory or relapsing extra nodal NK/T-cell lymphoma. ASH Annual Meeting Abstracts. 2008;112:79.

Yamaguchi M KY, Maeda Y, Hashimoto C, et al and The NK-Cell Tumor Study Group Phase II study of SMILE chemotherapy for newly-diagnosed stage IV, relapsed or refractory extranodal NK/T-cell lymphoma, nasal type: NKTSG study. J Clin Oncol (Meeting Abstract). 2010;28:8044.

Concurrent chemoradiotherapy

Yamaguchi M TK, Oguchi M, Isobe Y, et al, Japan Clinical Oncology Group Lymphoma Study Group (JCOG-LSG) Phase I/II study of concurrent chemoradiotherapy for localized nasal NK/T-cell lymphoma: Final results of JCOG0211. J Clin Oncol (Meeting Abstract). 2009;27:8549.

Kim SJ, Kim K, Kim BS, et al. Phase II trial of concurrent radiation and weekly cisplatin followed by VIPD chemotherapy in newly diagnosed, stage IE to IIE, nasal, extranodal NK/T-cell lymphoma: Consortium for Improving Survival of Lymphoma study. J Clin Oncol 2009;27:6027-6032.

Radiotherapy alone

Huang MJ, Jiang Y, Liu WP, et al. Early or up-front radiotherapy improved survival of localized extranodal NK/T-cell lymphoma, nasal-type in the upper aerodigestive tract. Int J Radiat Oncol Biol Phys 2008;70:166-174.

Int J Hematol (2010) 92:697–701
DOI 10.1007/s12185-010-0726-2

Treatment of advanced extranodal NK/T cell lymphoma, nasal-type and aggressive NK-cell leukemia

Ritsuro Suzuki

Table 1 Treatment outcome of advanced NK-cell malignancy

Diagnosis	Stage	Status	Design	*N*	Treatment	CR rate (%)	Survival	Year
NL (T/B)	III/IV	Fresh	R	33	CHOP, etc.	30	5-year OS 8%	1995
ENKL	III/IV	Fresh	R	9	CHOP, etc.	–	5-year OS 12%	1998
NL (T/B)	III/IV	Fresh	R	14	CHOP, etc.	–	5-year OS 30%	1998
ENKL		R/R/D	R	33	LVD	52	5-year OS 55%	2003
ANKL	IV	Fresh	R	22	Anthracycline, etc.	19	2-year OS 5%	2004
ENKL		R/R/D	PCT	6	SMILE	50	–	2008
ENKL		R/R/D	R	15	L-asp ± MTX, etc.	47	3-year OS 33%	2009
ENKL		R/R/D	PCT	18	LMD	56	–	2009
ENKL	IV	Fresh	R	47	CHOP, etc.	18	5-year OS 10%	2010
ENKL		R/R/D	PCT	39	SMILE	38	–	2010

Smile

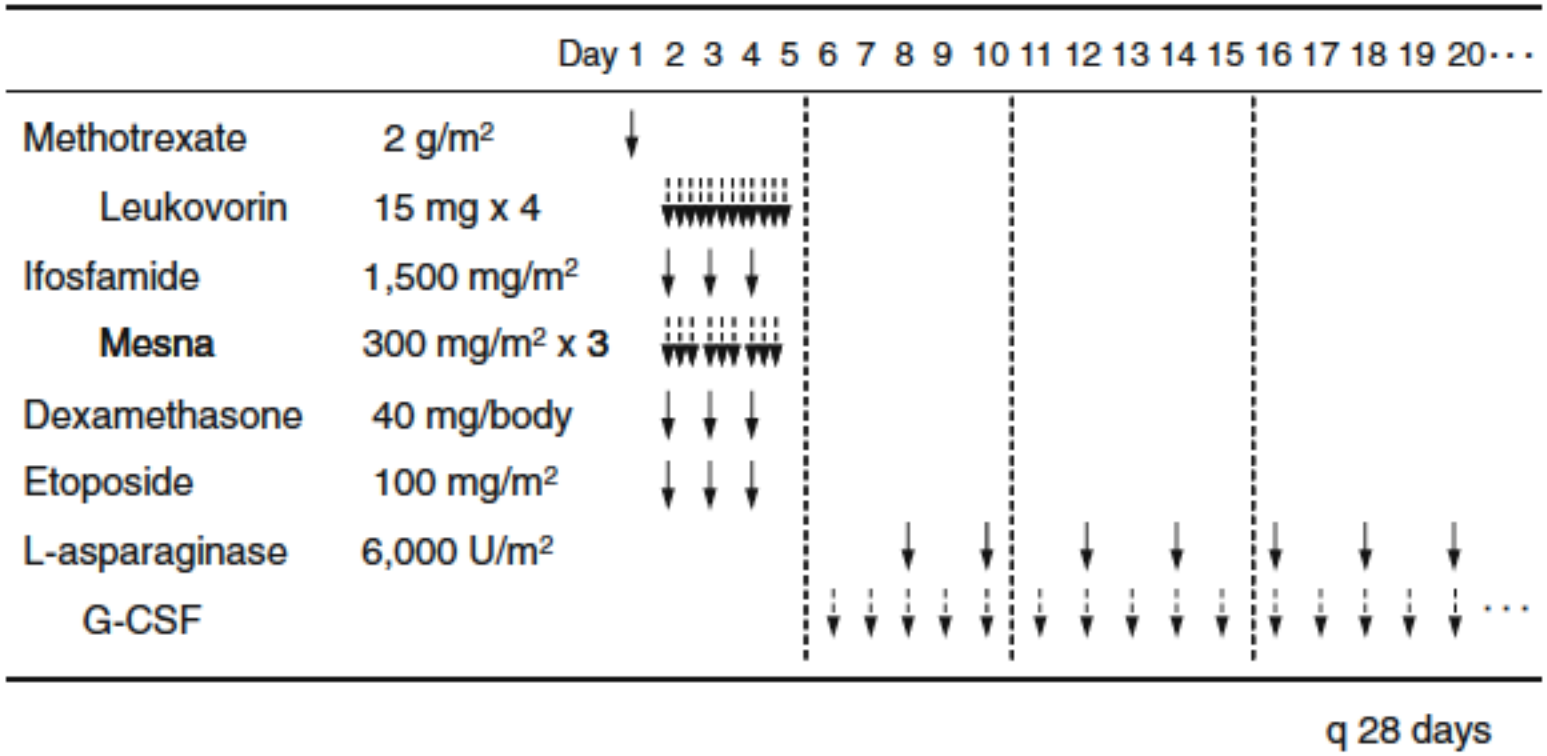

Day 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20···
Methotrexate 2 g/m²
Leukovorin 15 mg x 4
Ifosfamide 1,500 mg/m²
Mesna 300 mg/m² x 3
Dexamethasone 40 mg/body
Etoposide 100 mg/m²
L-asparaginase 6,000 U/m²
G-CSF
···
q 28 days

Table 3 Recommended treatment strategy of ENKL and ANKL

Status	Recommendation
Localized ENKL	Concurrent chemoradiotherapy
Advanced ENKL	
65 years old or younger with sufficient organ function[a]	SMILE
Older than 65 years or mild organ damage with severe organ dysfunction[b]	Dose-reduced SMILE (2/3 to 3/4 dose) L-asparaginase + dexamethasone → SMILE
ANKL	
In good condition	SMILE (dose should be adjusted)
In poor condition[b]	L-asparaginase + dexamethasone → SMILE
Relapsed/refractory ENKL	
65 years old or younger with sufficient organ function[a]	SMILE
Older than 65 years or mild organ damage	Dose-reduced SMILE (2/3 to 3/4 dose)

Extranodal Natural Killer/T-Cell Lymphoma, Nasal Type

The Significance of Radiotherapeutic Parameters

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Takashi Uno, M.D.[1]
Jun-ichi Tamaru, M.D.[2]
Hiroyuki Kawakami, M.D.[1]
Naoyuki Ueno, M.D.[1]
Hisashi Wakita, M.D.[3]
Jun-ichi Okada, M.D.[4]
Jun Itami, M.D.[5]
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[5] Department of Radiation Therapy and Oncology, International Medical Center of Japan, Tokyo, Japan.

Cancer 2006;106:609–15.

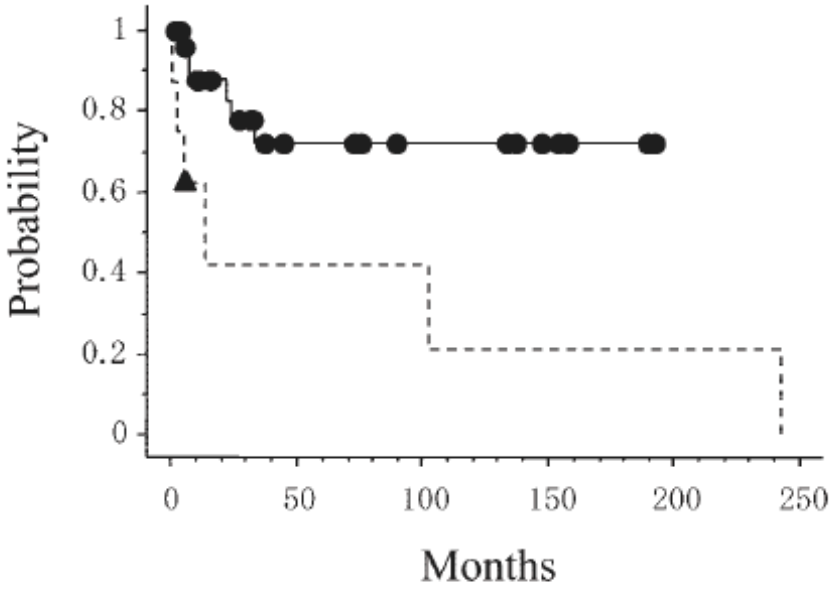


FIGURE 2. This graph illustrates the local control probability as a function of radiotherapy (RT) field. Solid line: an RT field that encompassed all sinuses, the nasopharynx, and macroscopic lesions; dashed line: an RT field that included macroscopic lesions with a margin.

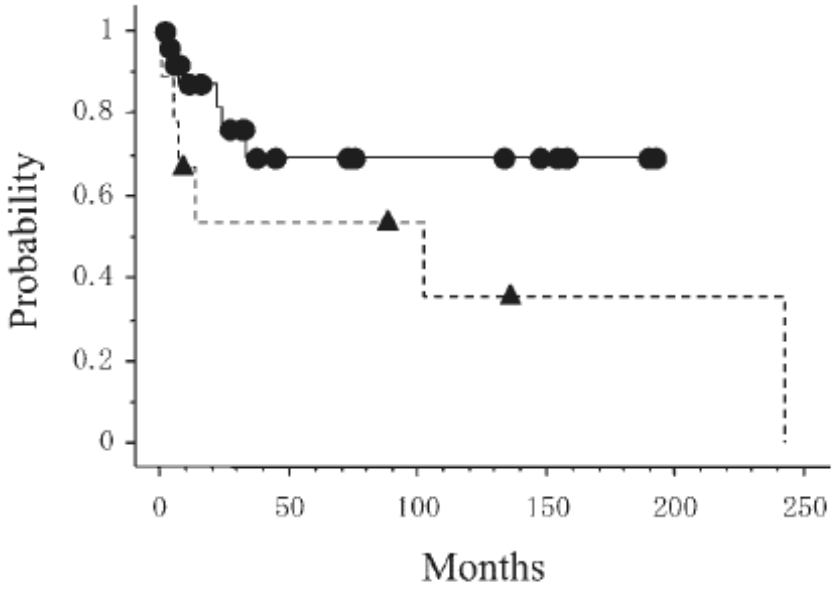
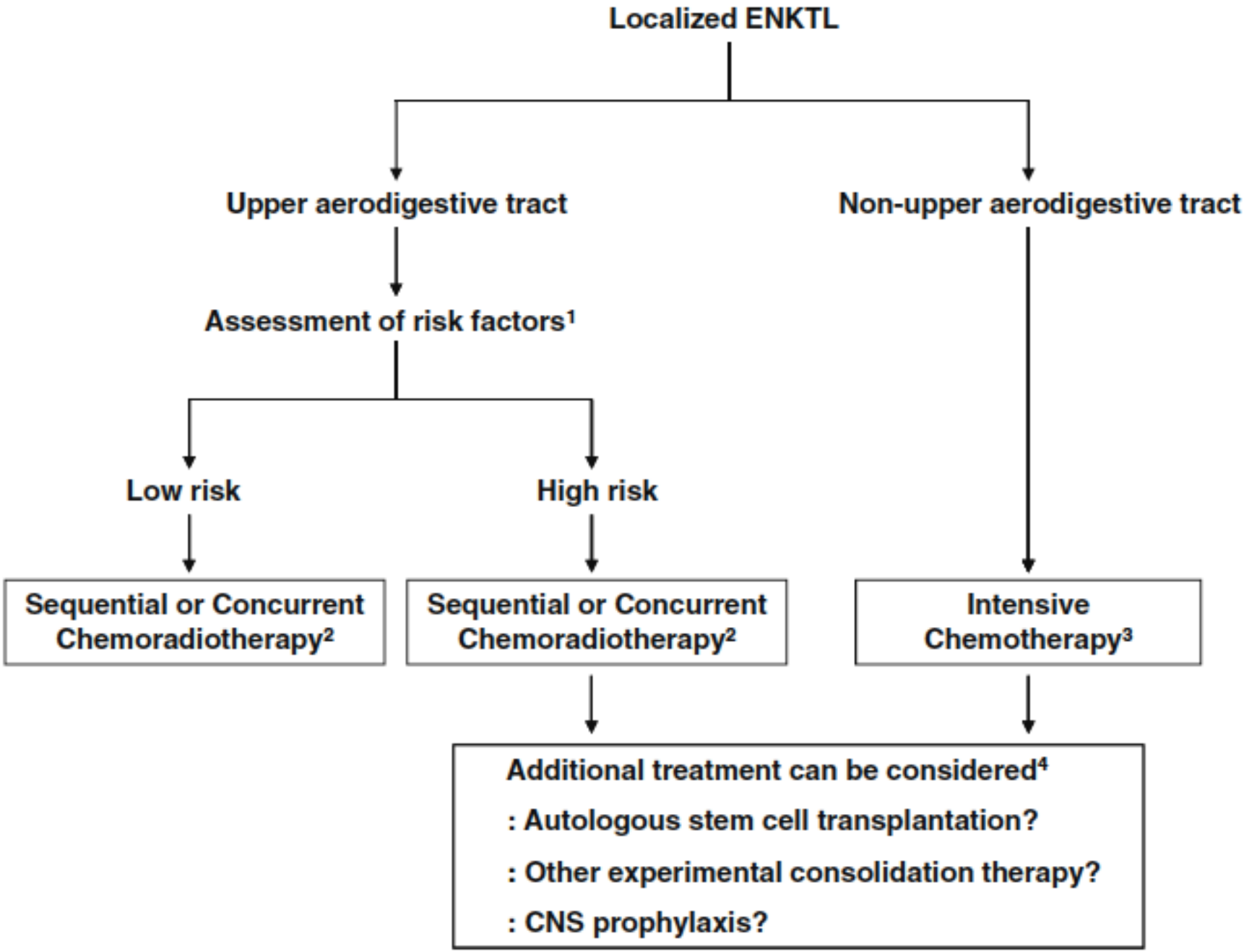


FIGURE 3. This graph illustrates the local control probability as a function of radiotherapy dose. Solid line: doses $\geq$ 50 grays (Gy); dashed line; doses $<$ 50 Gy.

Summary of the Literature

Reference	Phenotype	Treatment	No.	LFR	5-yr OAS (%)
Itami et al., 1991[14]	NK or T-cell	CT → RT or RT	9	6/9	NR
Aviles et al., 2000[16]	NK or T-cell	RT → CT	108	NR	86 (8 yrs)
Kim et al., 2001[17]	NK cell	CT → RT	17	NR	59 (3 yrs)
Yamaguchi et al., 2001[18]	NK cell	RT → CT or CT → RT	12	7/12	39
Ribrag et al., 2001[19]	NK or T-cell	RT → CT or CT → RT or RT	20	NR	NR
Cheung et al., 2002[20]	NK cell	CT → RT	79	31.1%	37.1
Chim et al., 2004[21]	NK cell	CT → RT	67	35/67	42.5 (10 yrs)
You et al., 2004[22]	NK cell	CT → RT	46	NR	36.5
Current study	NK or T-cell	CT → RT or RT	35	34.8%	47.3

LFR: local failure rate; OAS: overall survival; NK: natural killer; CT: chemotherapy; RT: radiotherapy; NR: not reported.


Localized ENKTL
Upper aerodigestive tract
Non-upper aerodigestive tract
Assessment of risk factors[1]
Low risk
High risk
Sequential or Concurrent Chemoradiotherapy[2]
Sequential or Concurrent Chemoradiotherapy[2]
Intensive Chemotherapy[3]
Additional treatment can be considered[4]
: Autologous stem cell transplantation?
: Other experimental consolidation therapy?
: CNS prophylaxis?

Monitoring of response after therapy

- **Clinical assessment with repeated endoscopy and biopsy**
  - Randon biopsy
  - CD56 staining
  - ISH for EBER
- **CT/MRI scanning**
- **Serial peripheral blood monitoring**
  - Plasma EBV DNA (q PCR)
  - Detection of methylated tumor suppressor genes
  - Measuring circulating Fas-ligand?

Monitoring of response after therapy

- **Clinical assessment with repeated endoscopy and biopsy**
  - Randon biopsy
  - CD56 staining
  - ISH for EBER
- **CT/MRI scanning**

What are the outcomes with CHOP-like regimes in aggressive T-cell lymphoma

- Meta-analysis: 31 studies with 2919 pts, excluded ALCL
- Estimated 5-year OS for non-ALCL pts was 37.3% (95% CI 35.1-39.6)

Linfoma T/NK	5-year OS
Nasal-type NK/T-cell	48 %
AILT	36.5 %
PTCL-NOS	34 %
Enteroropathy-type	21 %
Panniculitis-like	~ 50 %
Hepatosplenic	0 -10 %

Abonyabis et al. Blood 2007; abst 3452

Localized Extra-nasal Disease

- Limited data
- Treatment options:
  - Chemotherapy
  - Radiotherapy
  - Surgery
- Disappointing clinical outcome
  - Median survival of 20 months only

Advanced Disease

- Combination therapy is the main treatment
- Disappointing clinical outcome also
- CHOP like regimen: 20% response rate
- High expression of MDR gene
- L-asparaginase containing regimens
  - SMILE regimen
  - Effective as salvage
    - ✓CHOP refractory cases: 50-60% response
    - ✓60% long term survival
  - Being tested for first line therapy

Annals of Oncology Advance Access published October 22, 2009

original article

Annals of Oncology
doi:10.1093/annonc/mdp412

When do we need central nervous system prophylaxis in patients with extranodal NK/T-cell lymphoma, nasal type?

S. J. Kim[1], S. Y. Oh[2], J. Y. Hong[1], M. H. Chang[1], D. H. Lee[3], J. Huh[4], Y. H. Ko[5], Y. C. Ahn[6], H.-J. Kim[2], C. Suh[3], K. Kim[1] & W. S. Kim[1]*

[1]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; [2]Department of Internal Medicine, Dong-A University College of Medicine, Busan; Departments of [3]Oncology and [4]Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul; Departments of [5]Pathology and [6]Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Received 4 February 2009; revised 3 June 2009 & 15 July 2009; accepted 17 July 2009

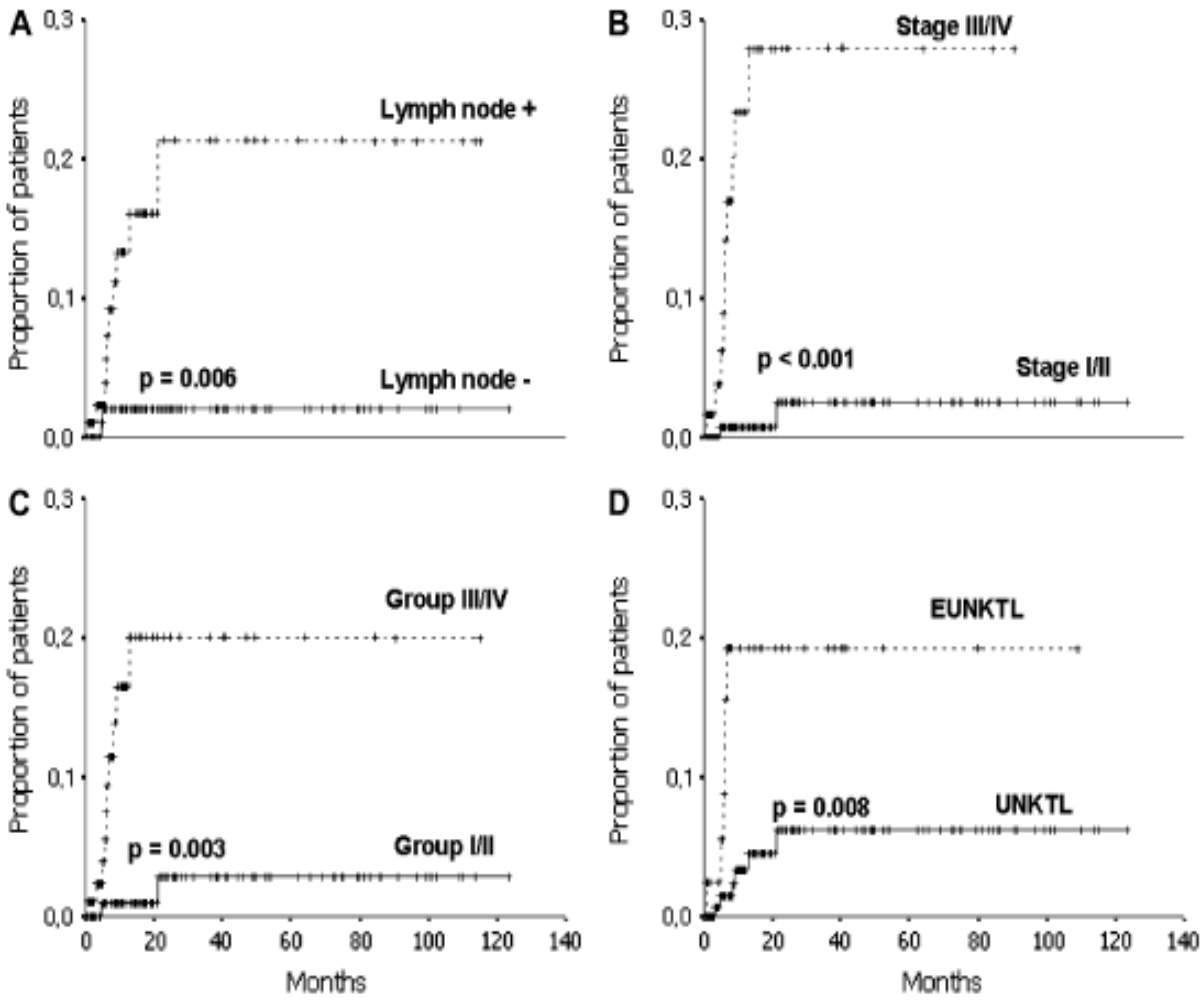


Figure 1. Cumulative risk for central nervous system diseases in patients with extranodal natural killer/T-cell lymphoma, nasal type, according to the involvement of lymph nodes (A), Ann Arbor stage (B), NKPI risk group (C) and the anatomic site of involvement (D).

PF: B symp, st III or IV, LDH , LN inv
G III: 2 RF; G IV; 3 or 4 RF
Lee et al. JCO 2006; 24:612

UNKTL: upper aerodigestive tract
EUNKTL: extra upper aerodigestive tract

Hematopoietic Stem Cell Transplantation

- **Auto-transplant for CR1**
  - Marrow often not involved
  - 68-80% overall survival
  - Highly selected cases were included
  - Benefit only high risk patients?

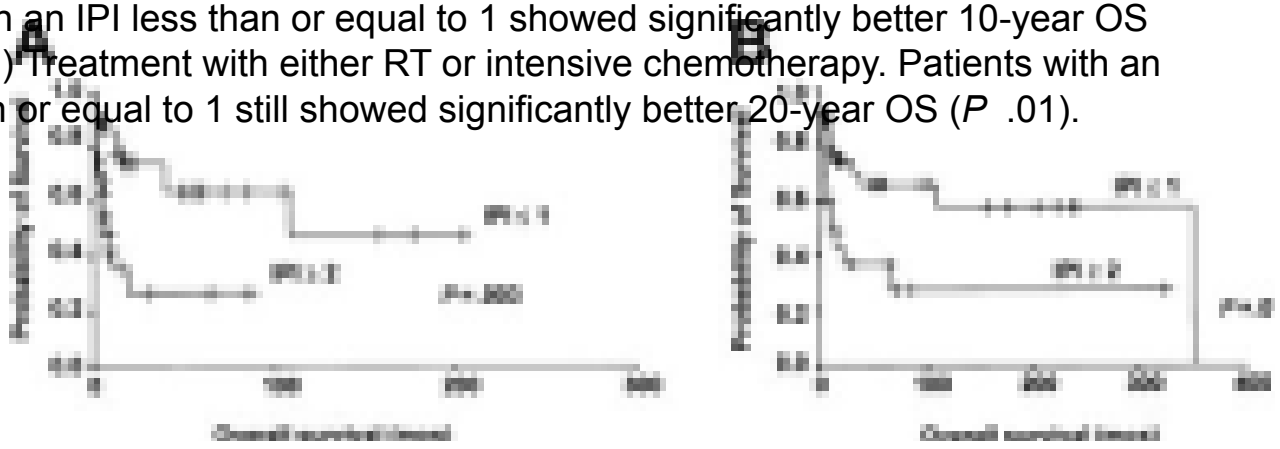
- **Allo-transplant**
  - Advantage of graft versus lymphoma effect
  - 2-year survival of 40-50% reported
  - High treatment related mortality 25-60%
  - Choice of patients

Suzuki et al. Biol Blood Marrow Transplant 14: 1356, 2008

Primary nasal natural killer cell lymphoma: long-term treatment outcome
and relationship with the International Prognostic Index
Chor-Sang Chim, Shing-Yan Ma, Wing-Yan Au, Carolyn Choy, Albert K. W. Lie, Raymond Liang, Chun-Chung Yau, and Yok-Lam Kwong

BLOOD, 1 JANUARY 2004 VOLUME 103, NUMBER 1

Figure 3. Prognostic impact of IPI. (A) Treatment with intensive chemotherapy. Patients with an IPI less than or equal to 1 showed significantly better 10-year OS (*P* .003). (B) Treatment with either RT or intensive chemotherapy. Patients with an IPI less than or equal to 1 still showed significantly better 20-year OS (*P* .01).



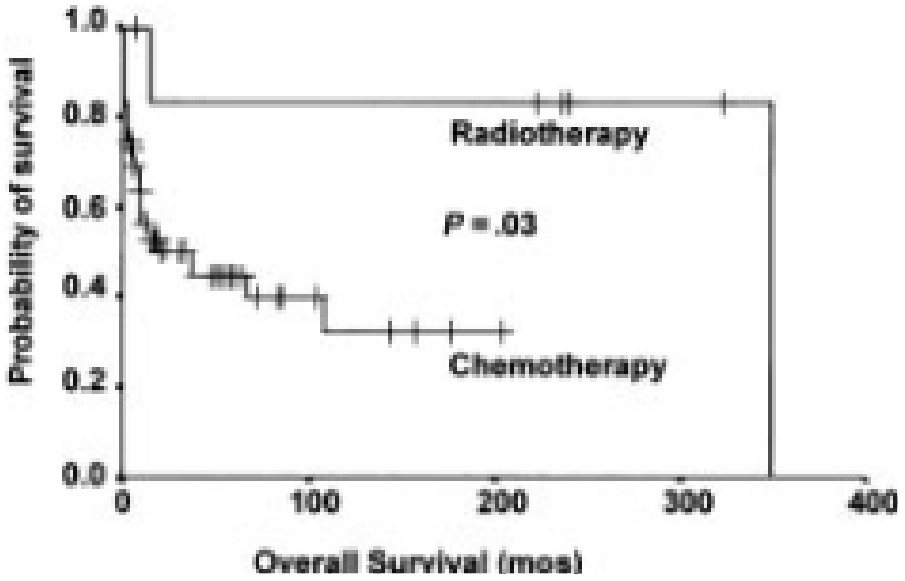


Figure 2. OS of patients showing a significance difference (*P* .03) in favor of RT.

Nasal NK/T - Cell Lymphoma

Contribution to the study of the clinical, histological, phenotypic, genotypic aspects and association with Epstein-Barr vírus

Retrospective Study of 40 cases

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Department of Hematology and Oncology
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Sao Paulo - Brazil

Patient characteristics (N=40)

Median age (years), range	42.5 (17-78)	
Sex M:F	2.3 : 1	
Ethnic group	White	18 (45%)
	African descent	16 (40%)
	Asiatic	6 (15%)
PS (ECOG ≥ 2)	20 (50%)	
B symptom (+)	25 (62.5%)	
Stage I / II	33/38 (86.8%)	
IPI		
Low	6 (15%)	
Low-Intermediate	8 (20%)	
High-Intermediate	13 (32.5%)	
High	13 (32.5%)	
LDH (high)	26 (65%)	
Hematophagocytic syndrome	1 (2.5%)	

Patient characteristics (N=40)

Presentation	
- Nasal obstrution	27/40 (67.5%)
- Palatal ulcer/edema	18/40 (45%)
Localization	
- Nasal cavity	38/40 (95%)
- Pararanasal Sinuses	30/40 (52.5%)
- Palatal lesion	20/40 (50%)
EBV ISH (+)	36/40 (90%)
T-cell origem (TCR gene rearrangement)	2/36 (5.5%)
Immunohistochemical studies	
- CD20	0/40 (0%)
- CD2	40/40 (100%)
- cCD3	39/39 (100%)
- CD56	37/40 (92.5%)
- Granzime B	29/40 (72.5%)
- TIA-1	39/40 (97.5%)

Table 7. **Frequency of primary local in 40 patients with Nasal NK/T cell Lymphoma (Santa Casa de São Paulo)**

Affected Local	*Number of occurrence*	*%*
Cavidade nasal	38	95,0
Seio etmoidal	21	52,5
Seio maxilar	20	50,0
Palato	20	50,0
Nasofaringe	13	32,5
Aba do nariz	11	27,5
Órbita	11	27,5
Seio esfenoidal	9	22,5
Seio frontal	6	15,0
Orofaringe	3	7,5
Fossa pterigopalatina	2	5,0
Tonsila palatina	1	2,5
Língua	1	2,5
Fossa craniana anterior	1	2,5
Linfonodo submandibular	1	2,5

Table 3. Distribution of 40 patients with **Nasal NK/T cell Lymphoma**, according to birth place (Santa Casa de São Paulo)

Birth Place	Number of Patients	%
São Paulo	18	45,0
Bahia	5	12,5
Minas Gerais	5	12,5
Pernambuco	3	7,5
Ceará	2	5,0
Chile	1	2,5
Goiás	1	2,5
Japan	1	2,5
Maranhão	1	2,5
Pará	1	2,5
Rondônia	1	2,5
Santa Catarina	1	2,5
Total	40	100,0

Tabela 5. Número de biópsias e data (ano) do diagnóstico de 40 pacientes com LCTNKN (Santa Casa de São Paulo)

Número de biópsias	*Data do diagnóstico*		*Total*
	Antes de 1990	*Depois de 1990*	
1	-	12	12
2	1	14	15
3	4	4	8
4	2	-	2
5	-	3	3
Total	7	33	40

Data diag.	$\overline{X}$ No.biópsias
< 1990	3,14
≥ 1990	2,03

p = 0,004

Tabela 6. Freqüência de sinais e sintomas de 40 pacientes com LCTNKN (Santa Casa de São Paulo)

Sinais e Sintomas	*Número de ocorrências*	*%*
Obstrução nasal	27	67,5
úlcera/edema do palato	18	45,0
Odor fétido	14	35,0
Rinorréia	9	22,5
Edema peri-orbitário	8	20,0
Abaulamento nasal	7	17,5
úlcera nasal externa	6	15,0
Sinusite recorrente	6	15,0
Dor na face	5	12,5
Epistaxe	3	7,5
Edema da face	3	7,5
Edema nasal	2	5,0
Anosmia	2	5,0
Tumoração nasal externa	1	2,5
Abaulamento do palato	1	2,5
Abaulamento da face	1	2,5
Lesão vegetante na língua	1	2,5
Otalgia	1	2,5
Otorréia	1	2,5
Hipoacusia	1	2,5
Paral. nervo facial periférico	1	2,5
Nódulo submandibular	1	2,5

Tabela 7. Freqüência da localização primária em 40 pacientes com LCTNKN (Santa Casa de São Paulo)

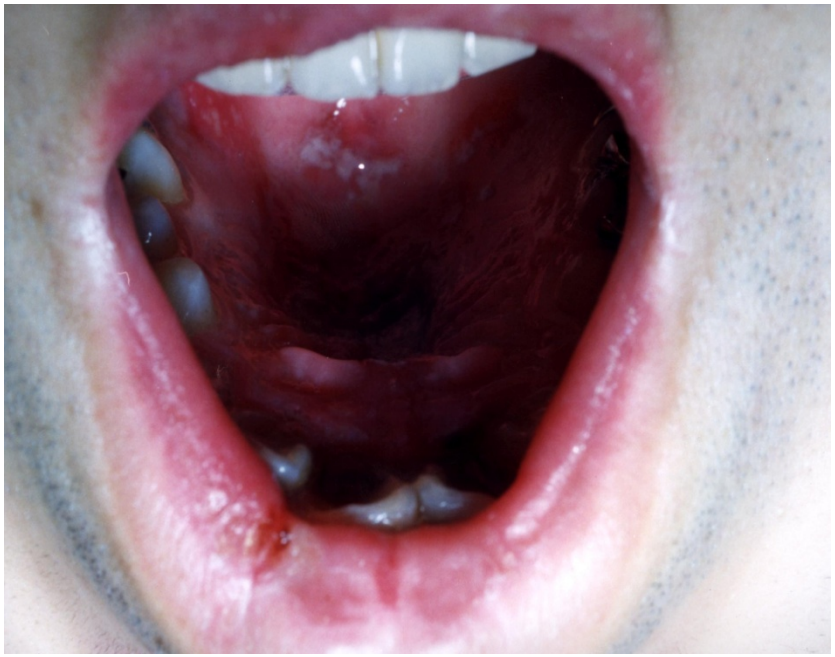
Estrutura comprometida	*Número de ocorrências*	*%*
Cavidade nasal	38	95,0
Seio etmoidal	21	52,5
Seio maxilar	20	50,0
Palato	20	50,0
Nasofaringe	13	32,5
Aba do nariz	11	27,5
Órbita	11	27,5
Seio esfenoidal	9	22,5
Seio frontal	6	15,0
Orofaringe	3	7,5
Fossa pterigopalatina	2	5,0
Tonsila palatina	1	2,5
Língua	1	2,5
Fossa craniana anterior	1	2,5
Linfonodo submandibular	1	2,5

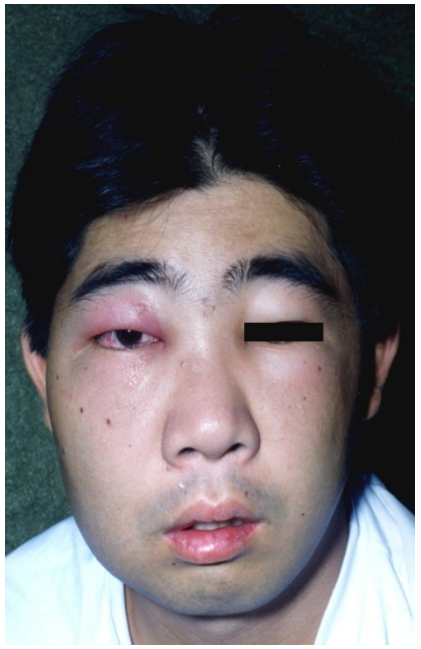
Table 8. Distribution of 40 patients with Nasal NK/T - cell Lymphoma, according to stage (Santa Casa de São Paulo)

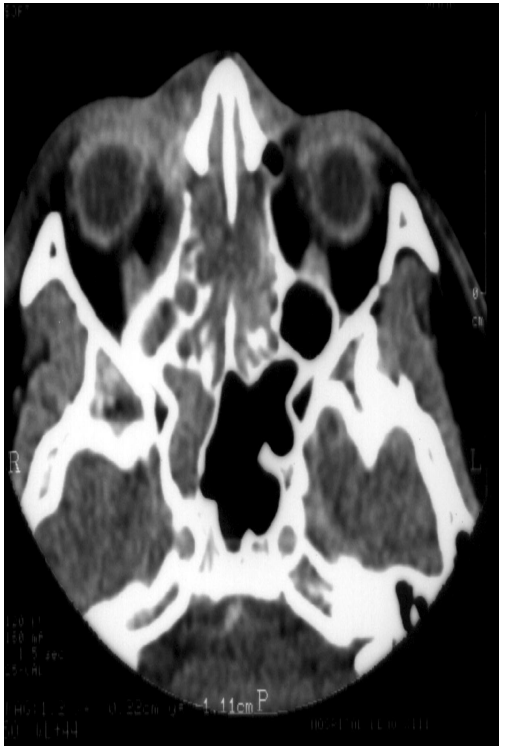
Stage	*Number of Patients*	*%*
IE	32	80,0
IV	5	12,5
IIE	1	2,5
Unknown	2	5,0
Total	40	100,0

Case 34 (D.T.Y.)

- Periorbitary swelling
- Shift in right nasal flap
- Palate ulceration

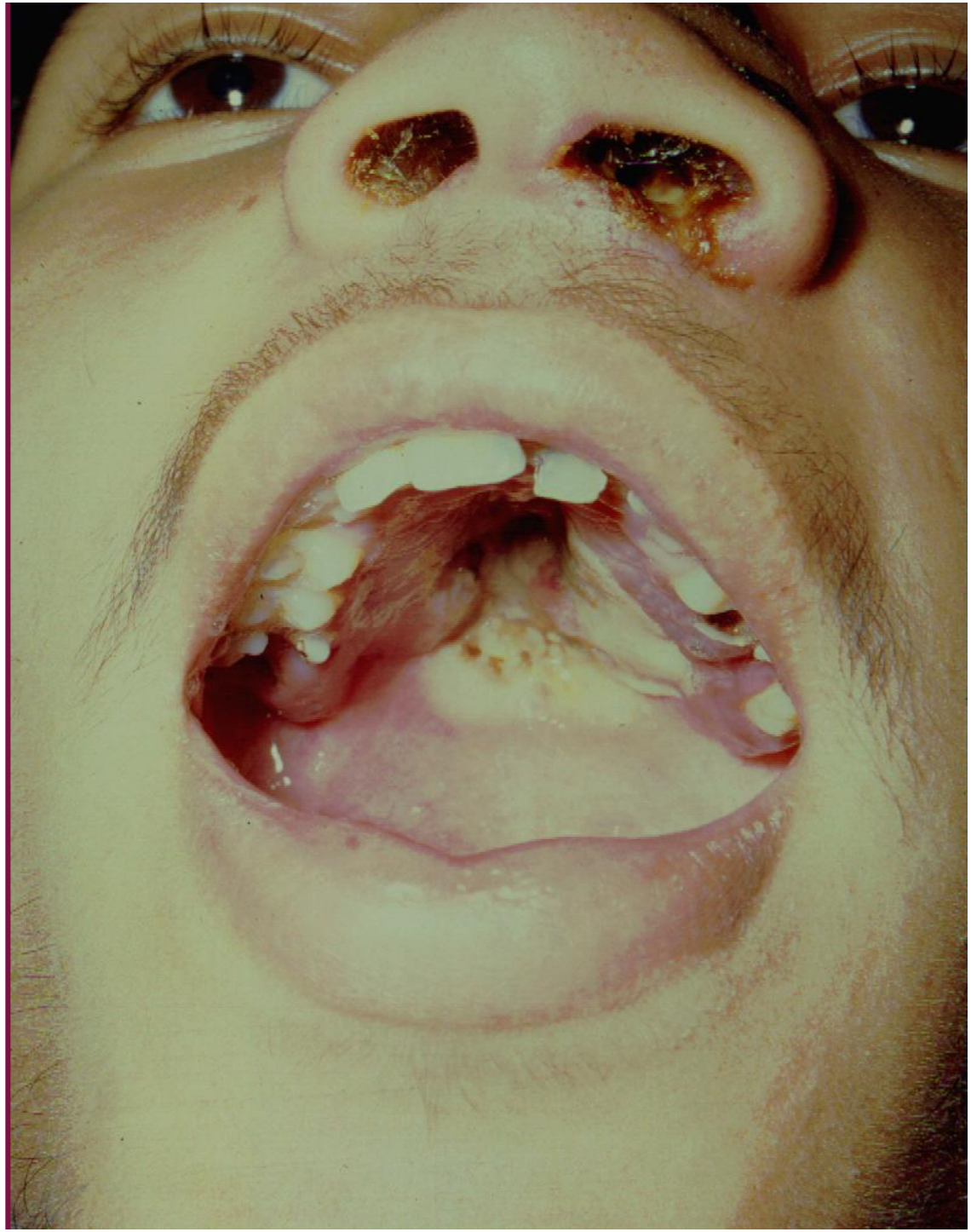


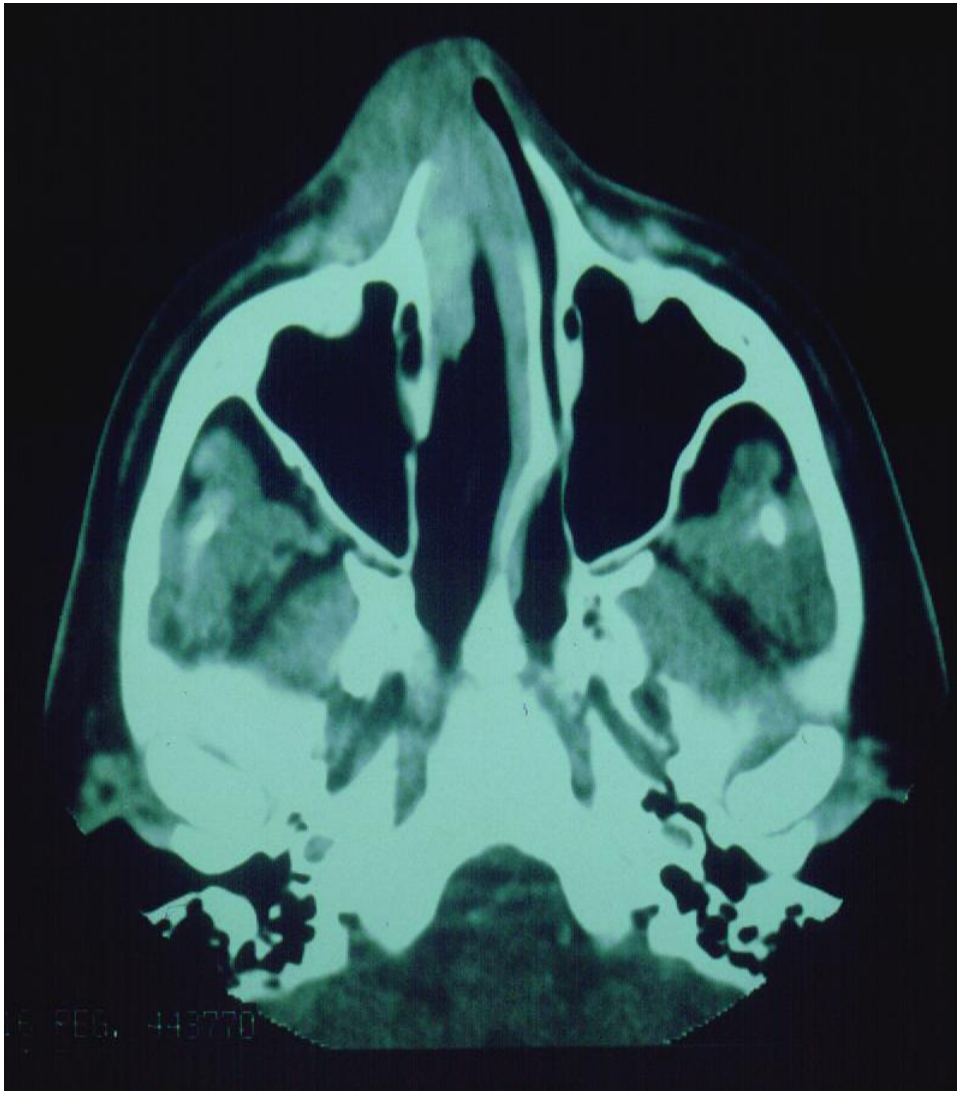


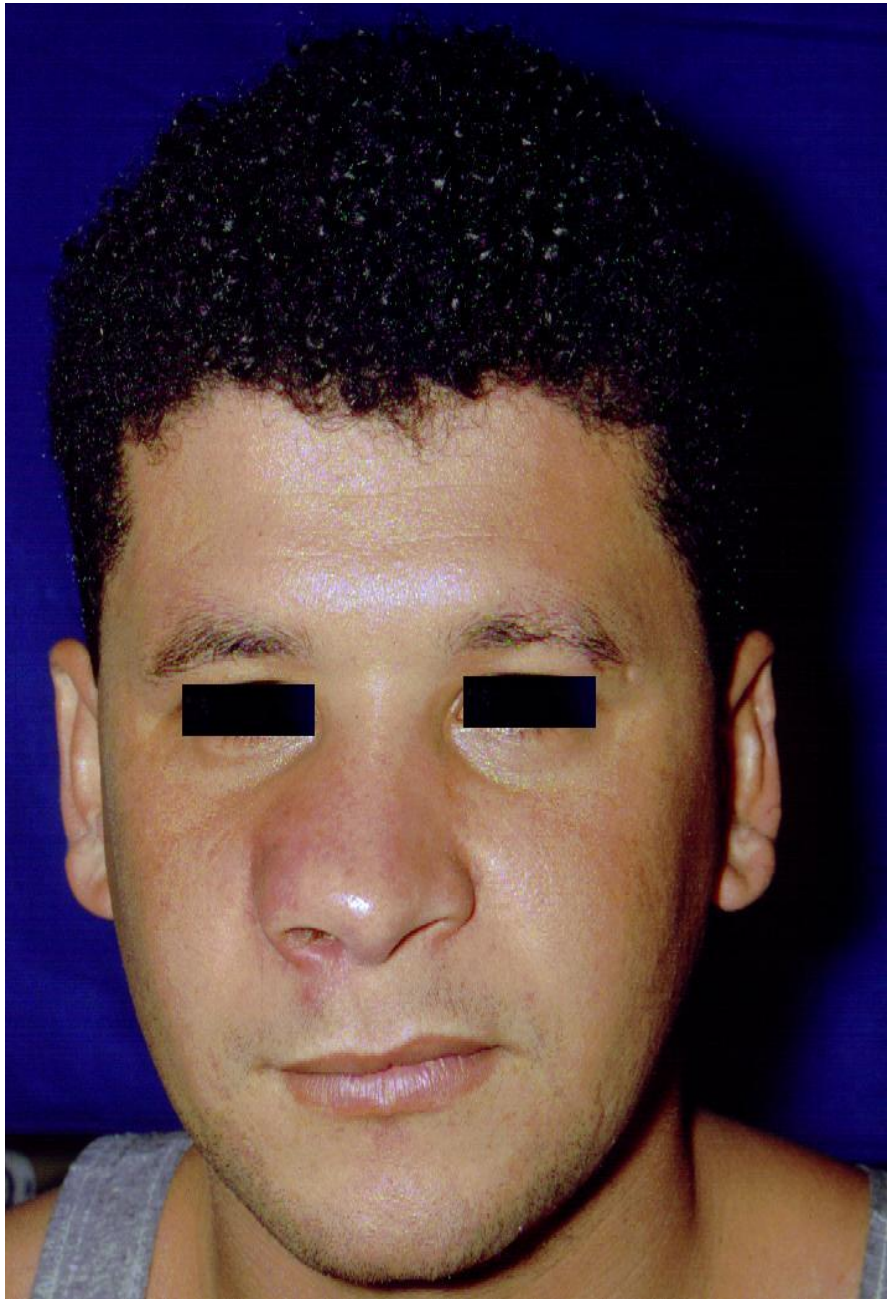


CT with a lesion in nasal cavities, Perforated septum and envolvement of ethmoidal sinuses and orbit

Caso 10 (R.S.)
Lesão na aba do nariz e ulceração do palato

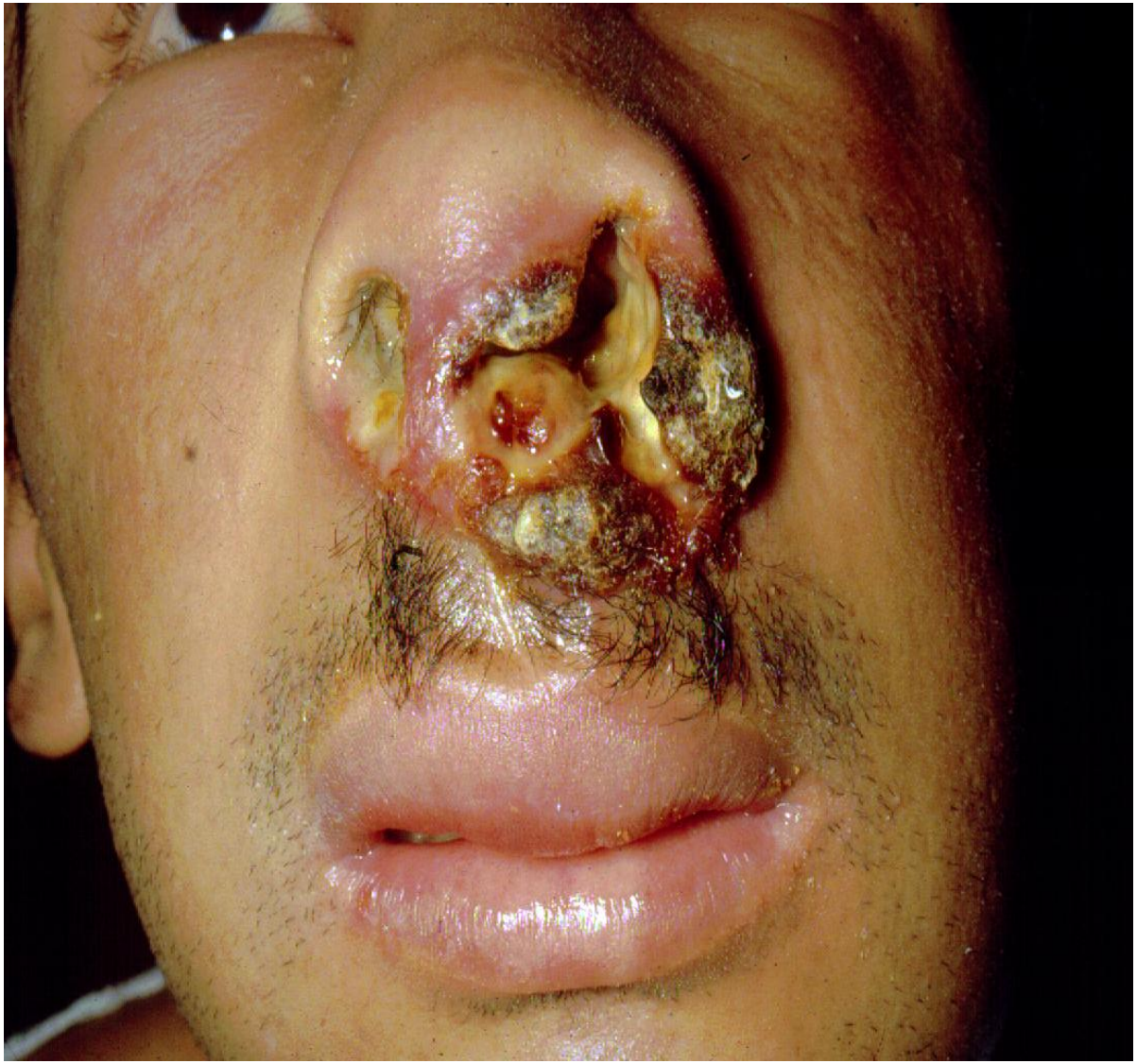


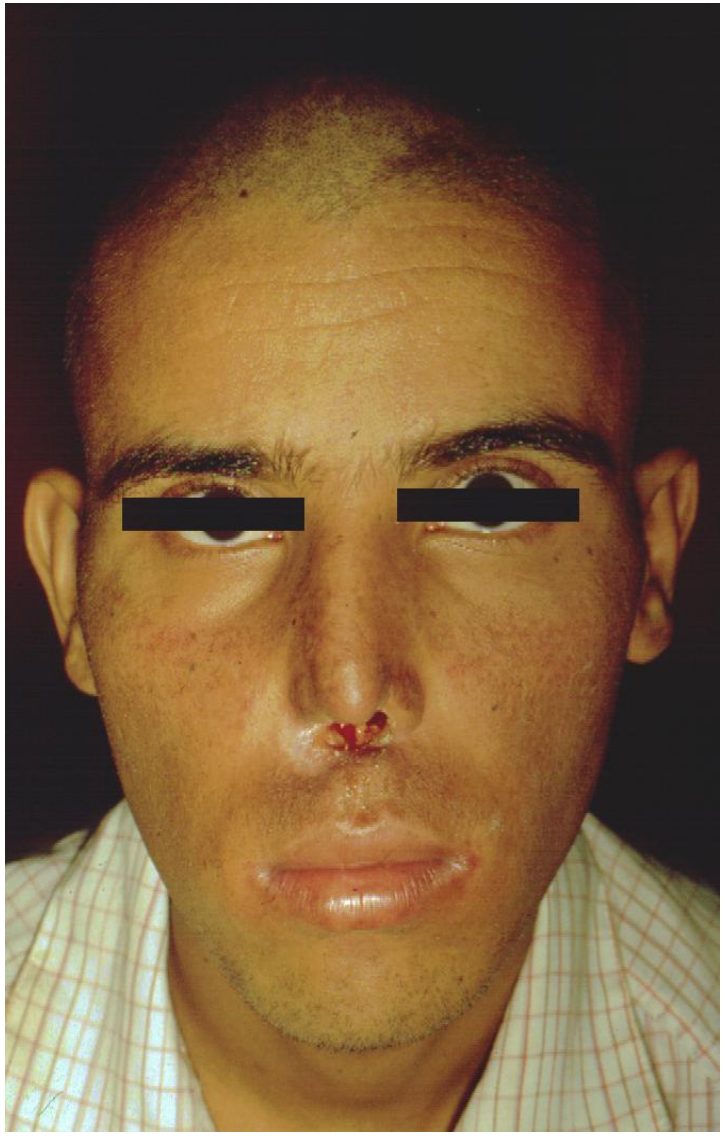




Caso 2 (M.F.S.)

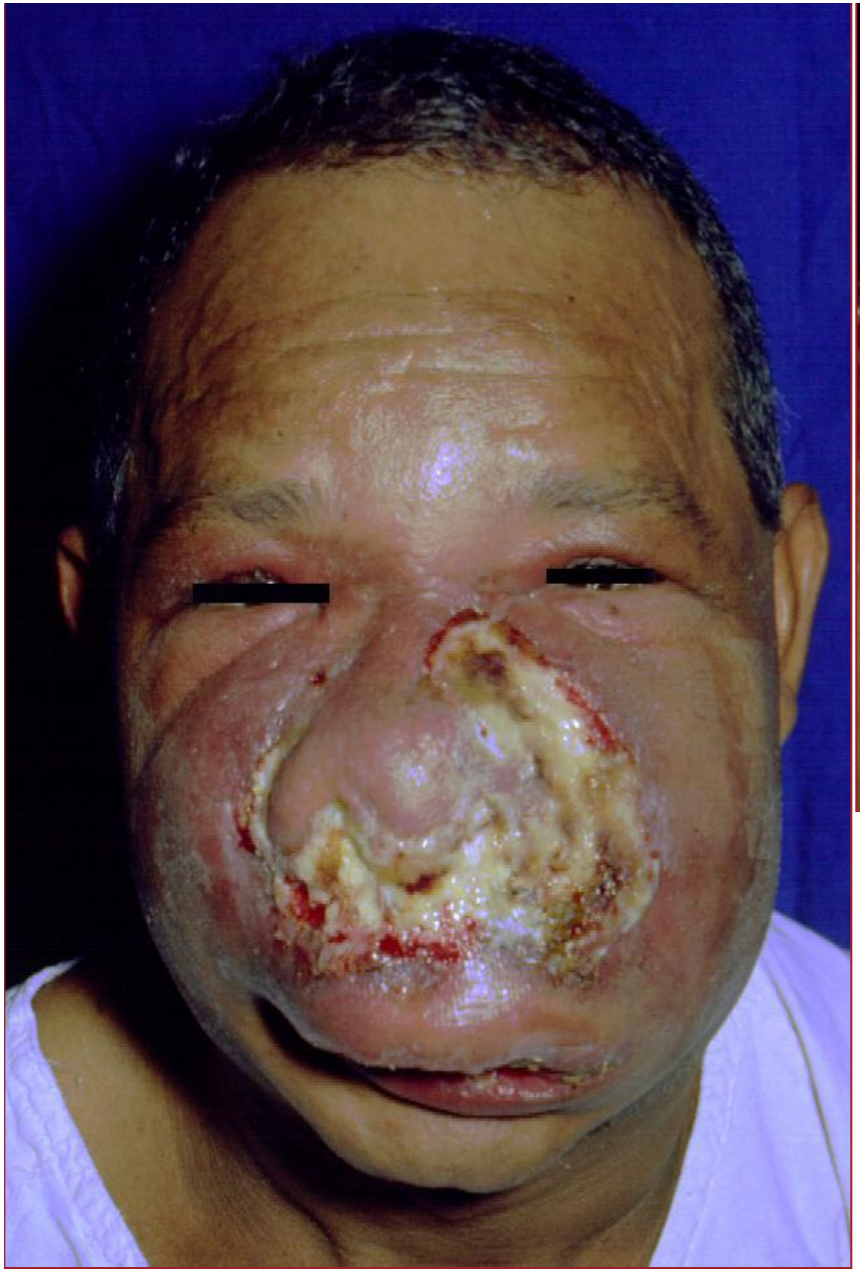
- Abaulamento nasal
- TC lesão na cavidade nasal com extensão para aba do nariz e destruição do septo

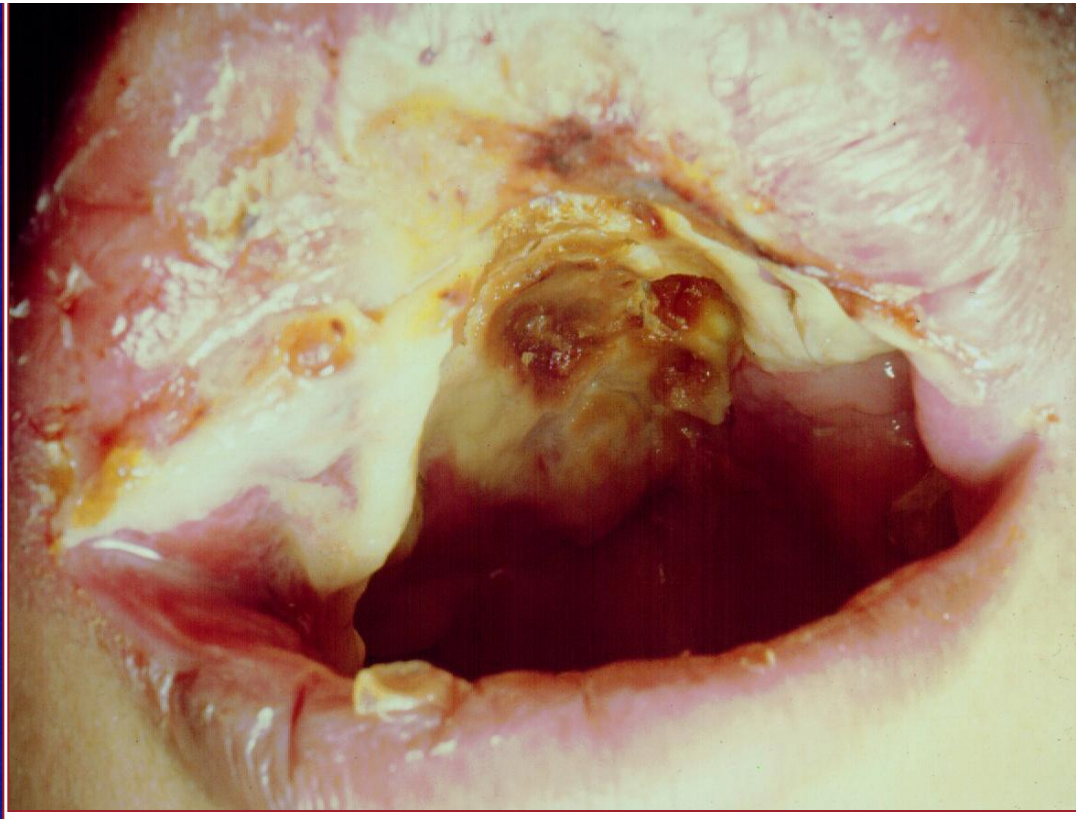




Caso 32 (B.S.G.)

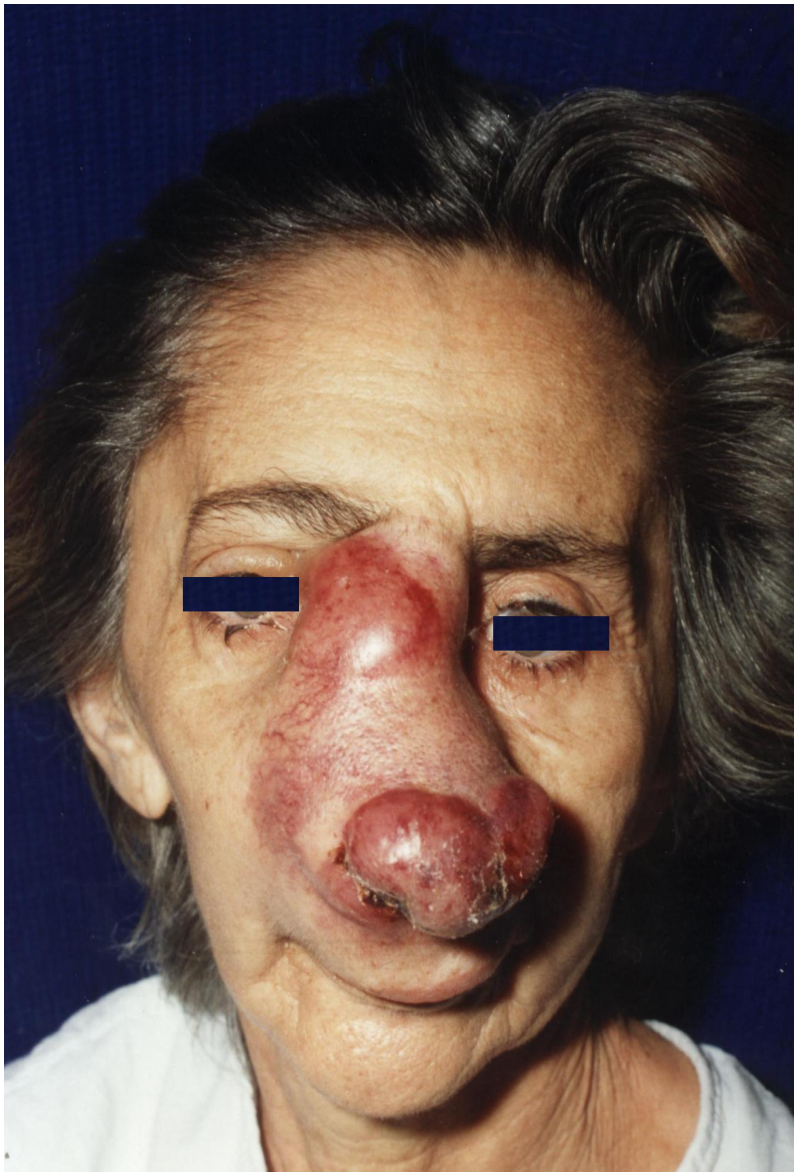
Aspecto do paciente antes e depois do tratamento

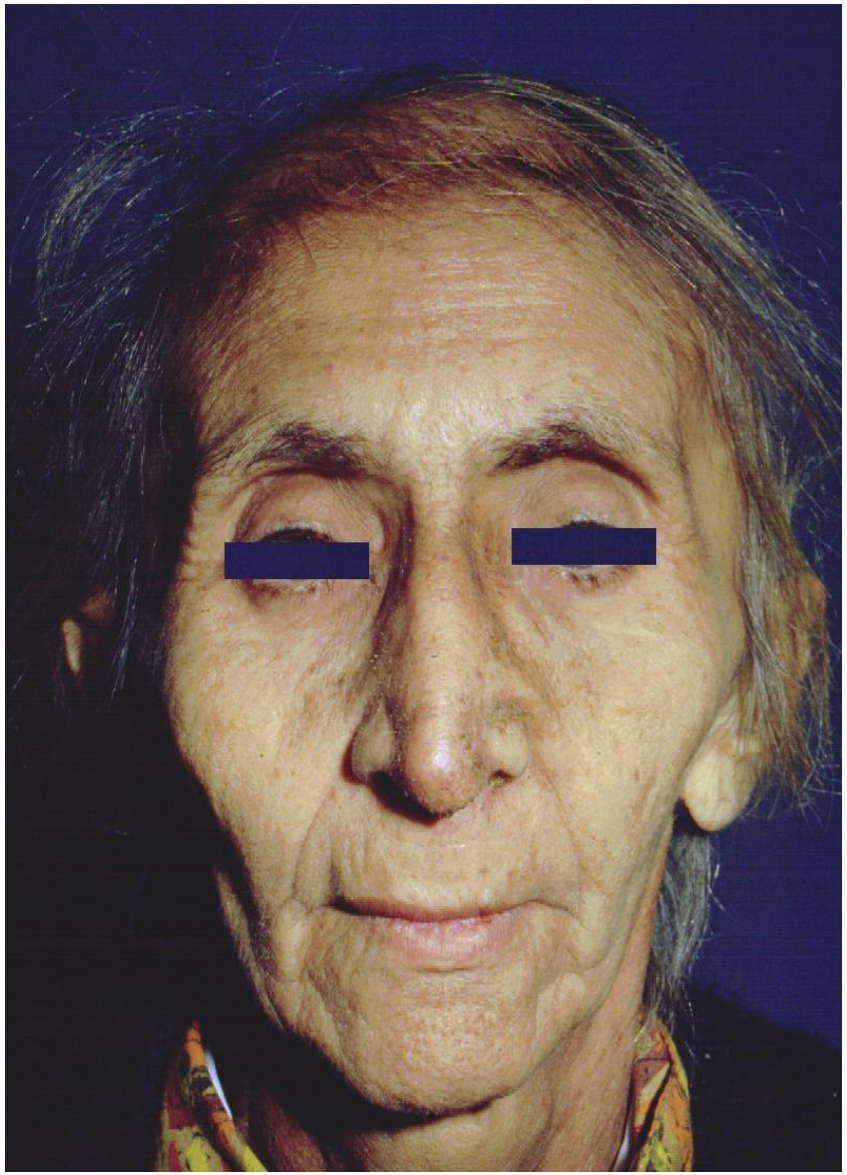




Caso 33 (J.C.B.)

Extensa ulceração nasal externa e úlcera do palato



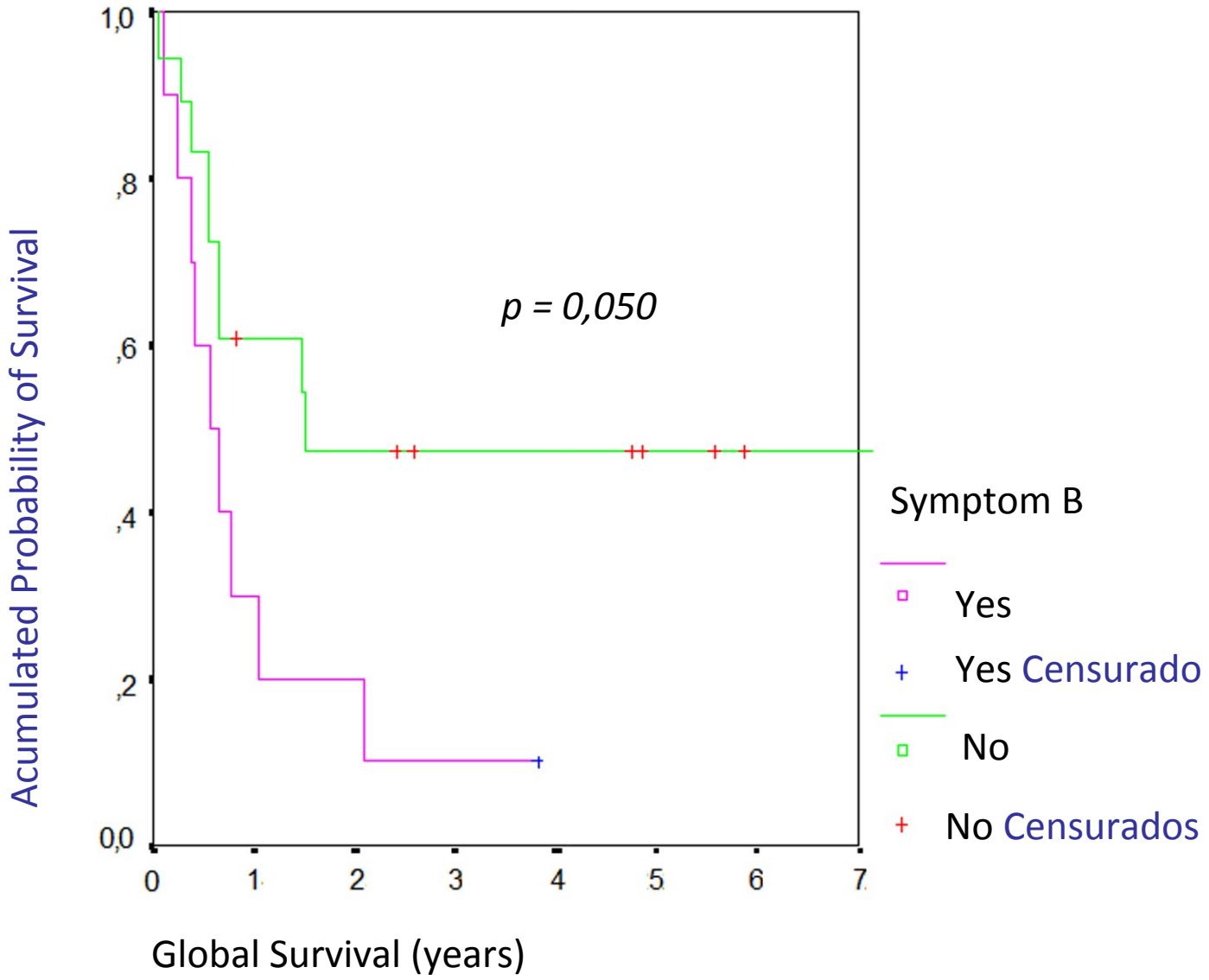


Caso 4 (E.G.S.)

Tumoração nasal antes e depois do tratamento

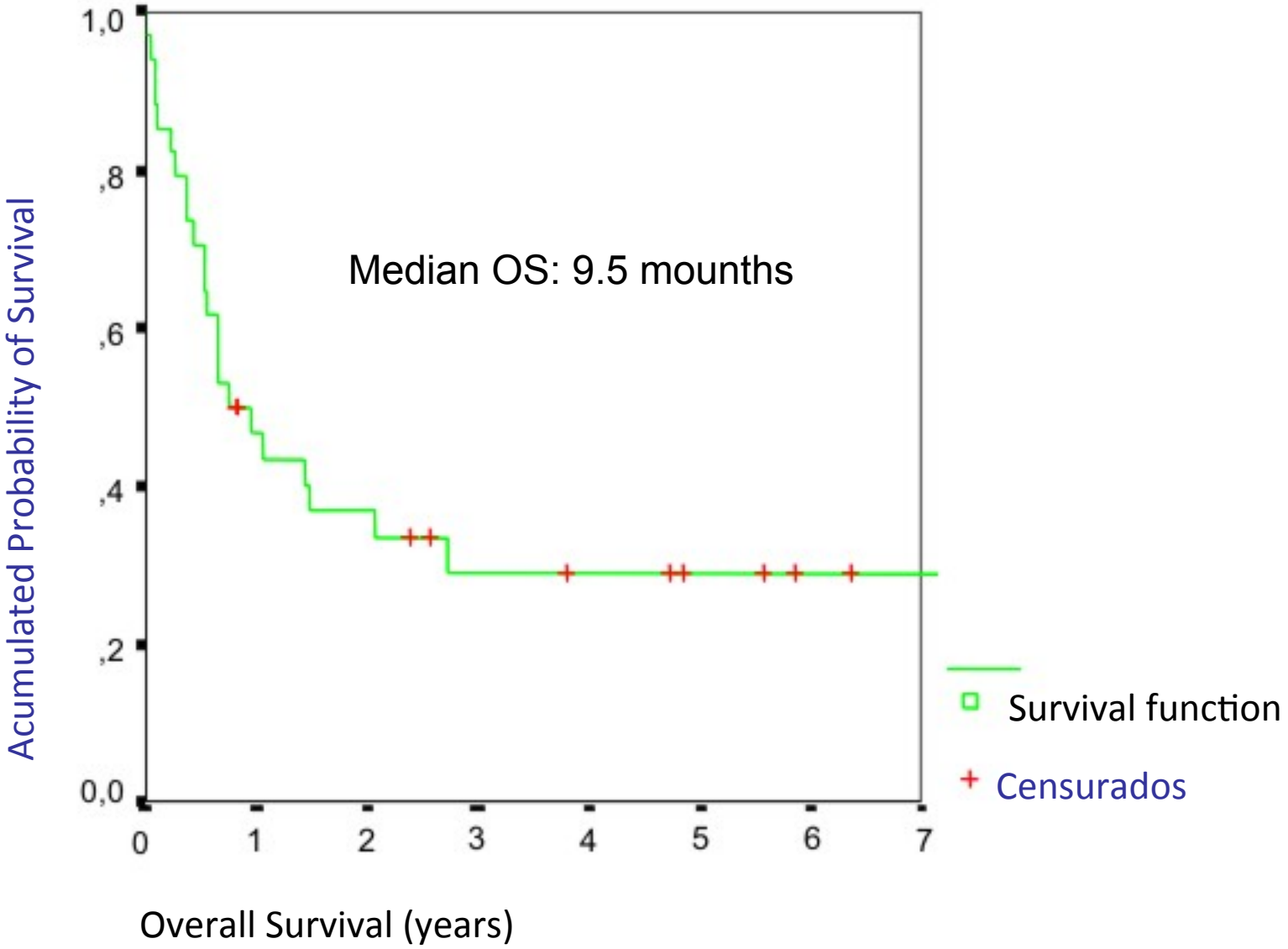
Causes of death in 23 patients with TNKCNL

• **Infection**	**15(65,2%)**
- Sepsis	7(30,4%)
- Bronchopneumonia	6(26,0%)
- Fungal Infection	2(8,7%)
• **Lymphoma**	**6(26,0%)**
• **Other**	**2(8,6%)**



Graph 1. Overall Survival of patients with Nasal NK/T cell Lymphoma, according to stage IEA and IEB (Santa Casa de São Paulo)

Overall Survival (34 cases)



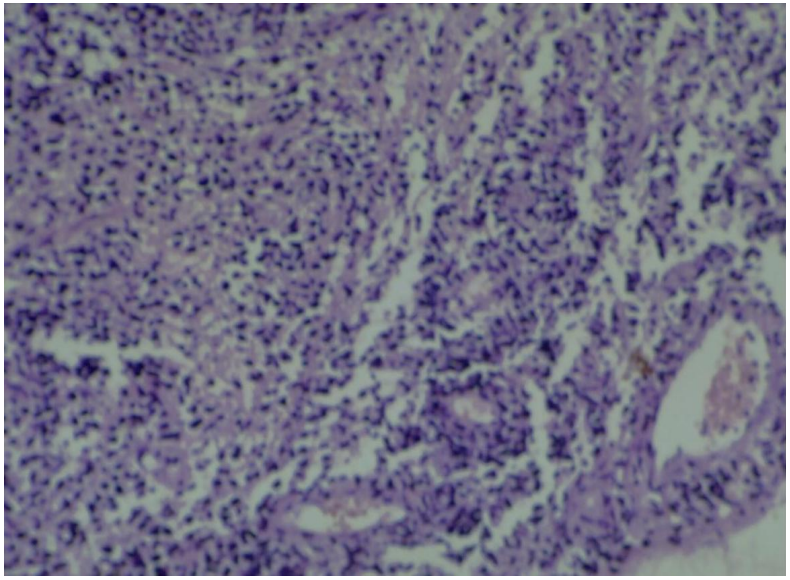


Fig. A: HE, 16 x. Mucosa de vias aéreas superiores. Observar proliferação linfocitária predominantemente perivascular.

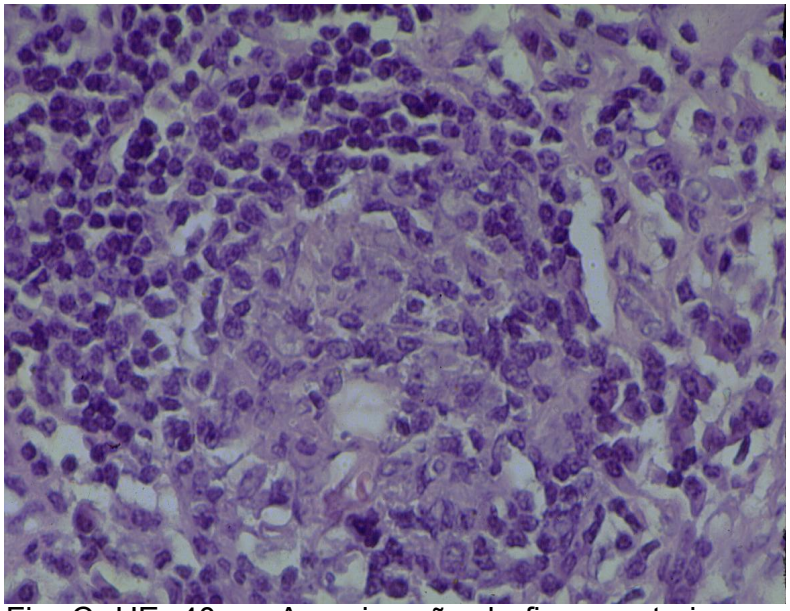


Fig. C: HE, 40 x: Aproximação da figura anterior mostrando angio-invasão pelos linfócitos neoplásicos.

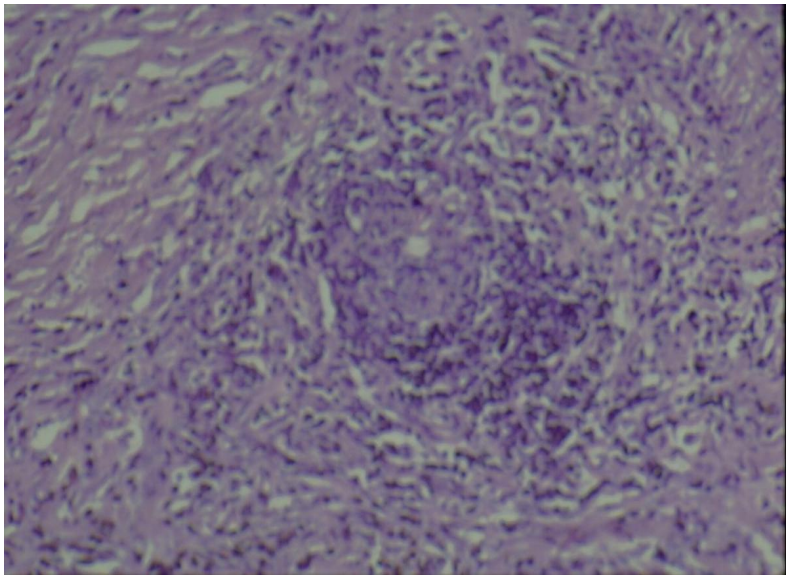


Fig. B: HE, 16x: Observar angiocentrismo de linfócitos neoplásicos.

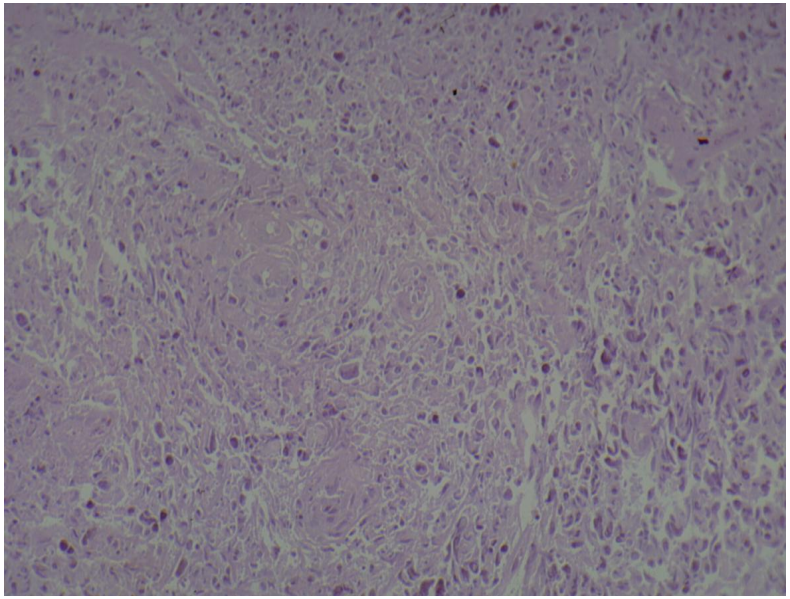


Fig. D: HE, 16 x: áreas neoplásicas com predomínio de necrose de coagulação.

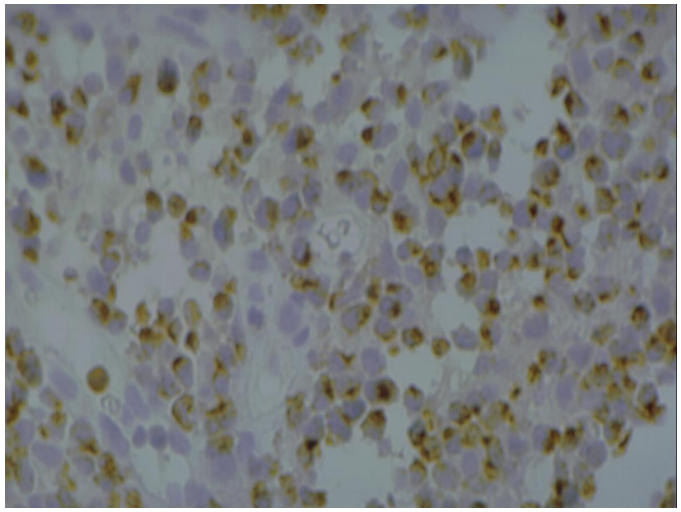


Fig. O, TIA-1, 40x : Demonstração de grânulos citotóxicos no citoplasma de células neoplásicas com anticorpos **anti-TIA-1**.

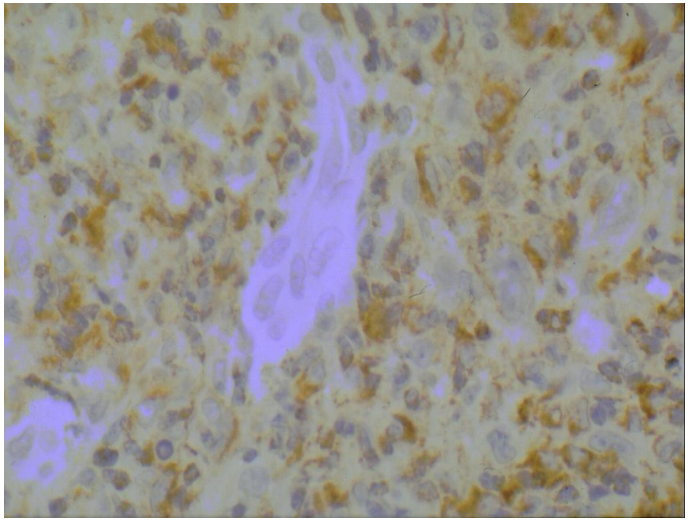


Fig. Q, 40x. Demonstração de células citotóxicas por anticorpos **anti-grazima**, granulação citoplasmática .

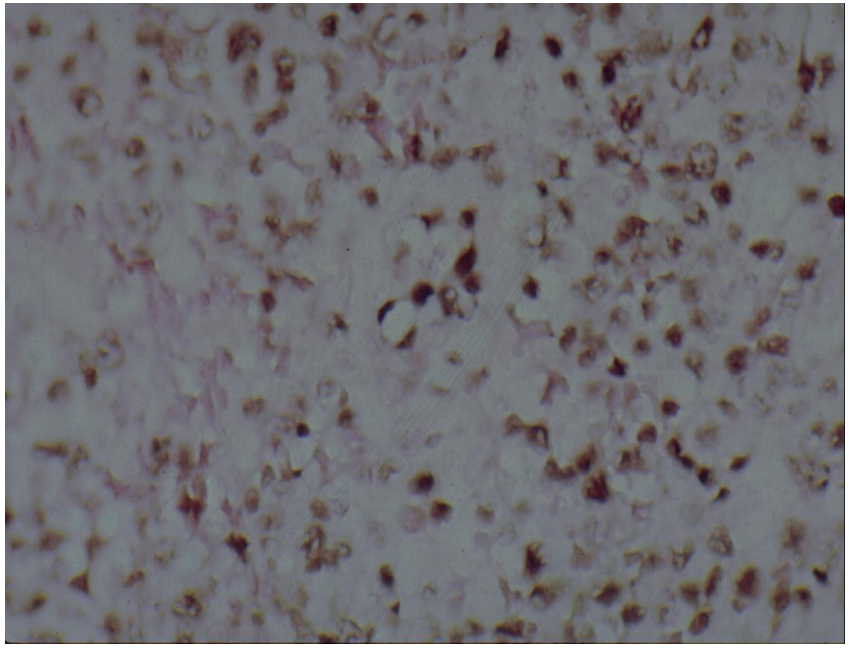


Fig. T, 40x: **Hibridização "in situ"** para RNA do vírus Epstein-Barr, em linfócitos neolpásicos

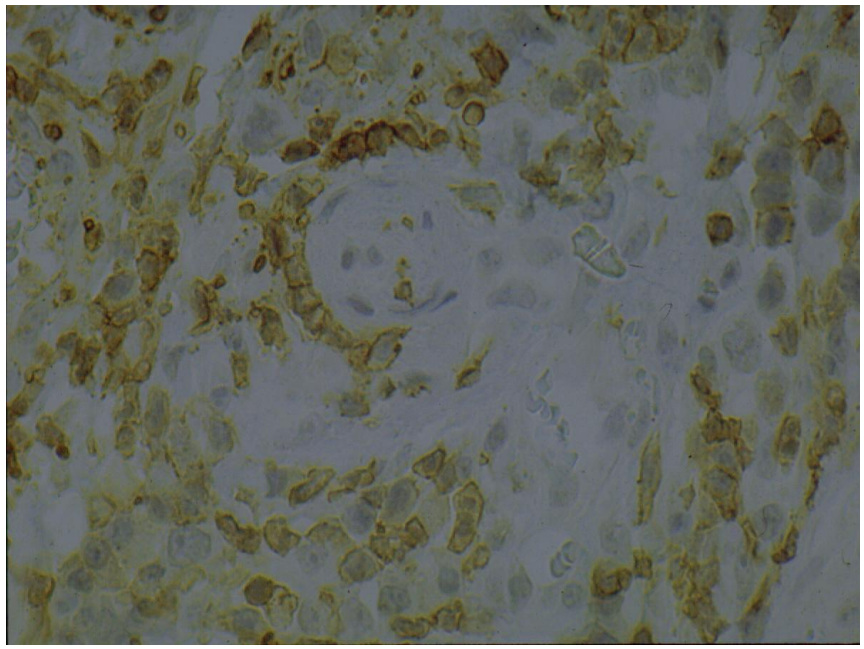


Fig. L, **CD56**, 40X:Grupo de células linfóides neoplásicas grandes com imunofenotipo de célula NK. Observar a disposição angiocêntrica.

Table 5. Number of biopsies and year of the diagnosis of 40 patients with NTNKCL (Santa Casa de São Paulo)

Number of biopsies	*Year of diagnosis*		*Total*
	Before 1990	*After 1990*	
1	-	12	12
2	1	14	15
3	4	4	8
4	2	-	2
5	-	3	3
Total	7	33	40

Date diag.	$\bar{X}$ No.biopsies
< 1990	3.14
$\geq$ 1990	2.03

p = 0.004

In Situ Hybridization for EBER

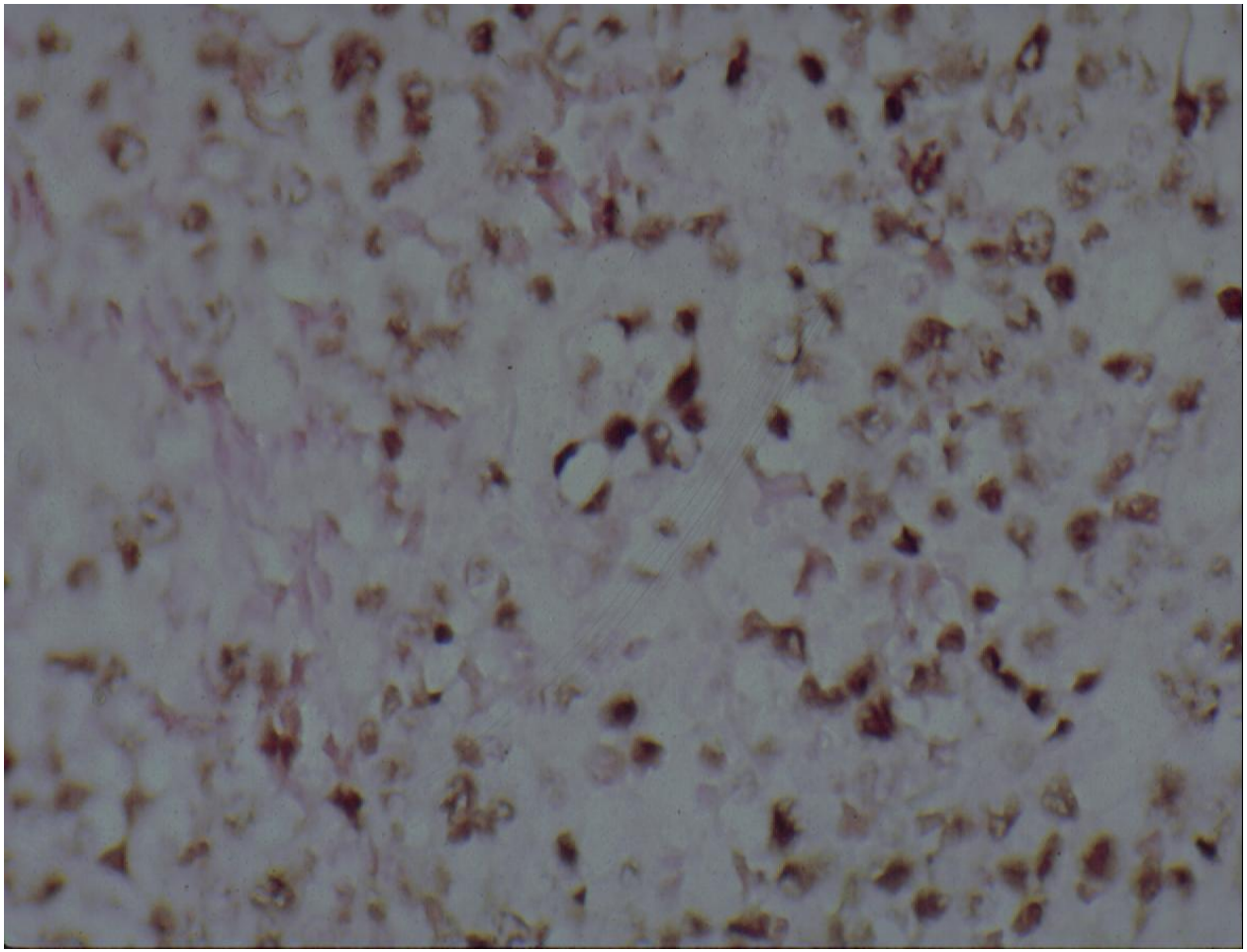


Fig. T, 40x: ISH for EBER in nasal lymphoma

Extranodal NK/T-cell Lymphoma
Clinical, histological and phenotypic aspects

- Diagnosis highly dependent on clinical aspects
- Unusual involvement of LN, even in the relapse
- Frequent dissemination to other extranodal regions
- Low incidence of hematophagocytic syndrome !
- Necrosis in almost all cases, with or without angioinvasion
- Phenotype NK, few cases T-cell cytotoxic
- Presence of EBV

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Sao Paulo – Brazil

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Santa Casa Medical School
Sao Paulo - Brazil

Extranodal NK/T cell Lymphoma, nasal type

- Unique epidemiologic caracteristics
- Genetics and molecular mechanisms poorly understood
- Cases with the same presentation but:

  EBV negative or T-cell origem
- Rare disease in Western countries
- Lack of studies comparing cases from different parts of the world

There is room for international comparative study

- Proposal for a comparative study of clinical and biological caracteristics in:

- Asia (Hong Kong)
- Europe (Italy)
- South America (Brazil)