NK/T Cell Lymphoma: The role of Asparaginase: Chinese Experience

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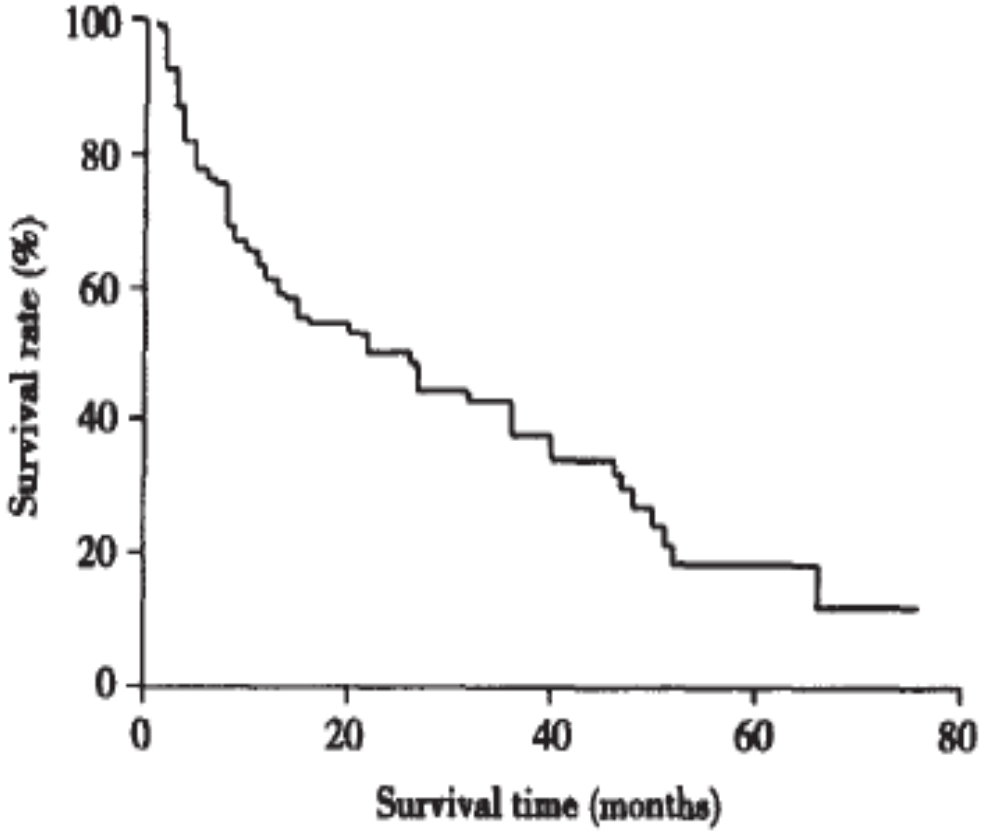
Background

1. NK/TCL is most common subtype T cell lymphoma in China, account for 6% among NHLs
2. No standard chemotherapeutic regimen is available so far.
3. Effectiveness of anthracyclines –based combination is poor.
4. SMILE or AspaMetDex is most frequently administered .
5. Significant adverse events and clinical inconvenience for SMILE or AspaMetDex for monitoring of serum MTX was observed.
6. L-Asparaginase is a major agent in combined chemotherapy for NK/TCL .
7. Optimal chemotherapy remain to be determined.

1. Non-Asparaginae based chemotherapy

CHOP for NK/TCL

- N=81
- CR:41%， RR:66%
- F/U: 17m (1-76 m),
- Median OS: 26 m
- 3-OS: 4 3%
- 5-OS: 17%



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Huang HQ, et al. Prognostic analysis of patients with nasal-type NK/T-cell non-Hodgkin's lymphoma--a report of 93 cases. Chinese journal of cancer. 2005 Dec;24(12):1493-7.

EPOCH for newly diagnosed NK/T, OS

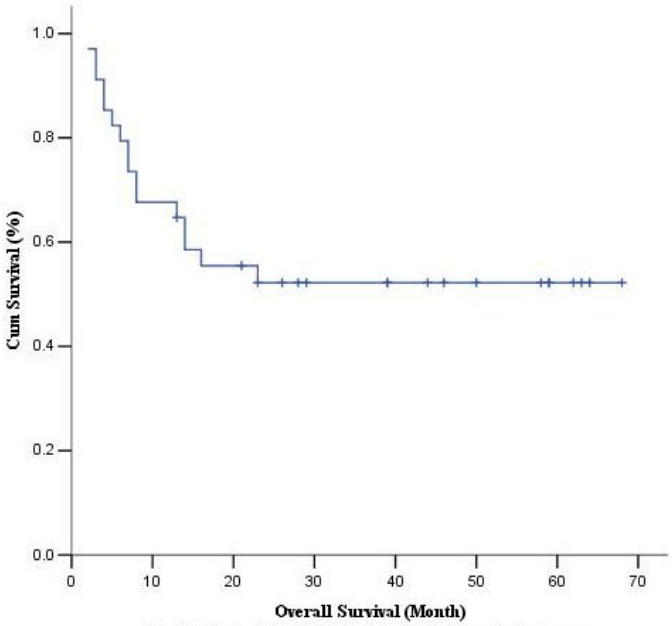


Fig.1 Overall survival curve of the whole group

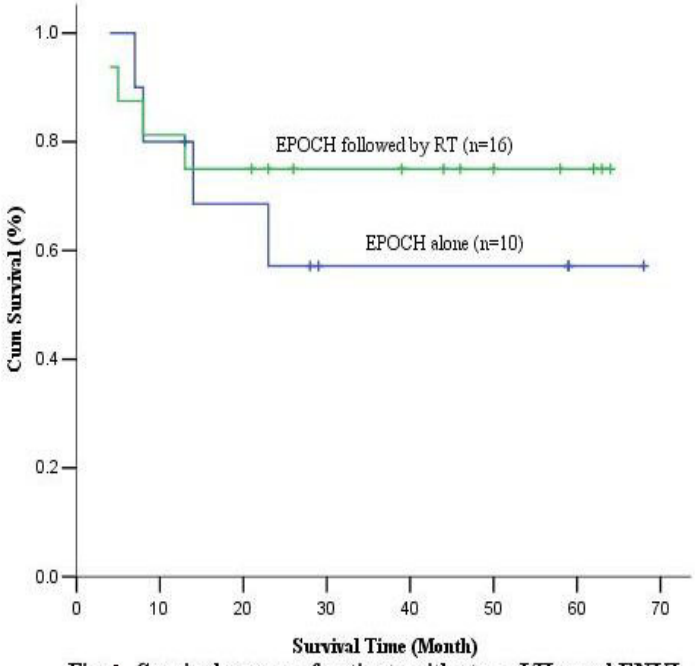


Fig. 2 Survival curves of patients with stage I/II nasal ENKL according to treatment modalities

NCCN guideline

NK/T-CELL TREATMENT REGIMENS
References

SMILE (steroid [dexamethasone/prednisolone], methotrexate, ifosfamide, L-asparaginase and etoposide) followed by involved field RT
Yaemaguchi M, Suzuki R, Kwong YL, et al. Phase I study of dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy for advancd-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia. Cancer Sci 2008;99:1016-1020.

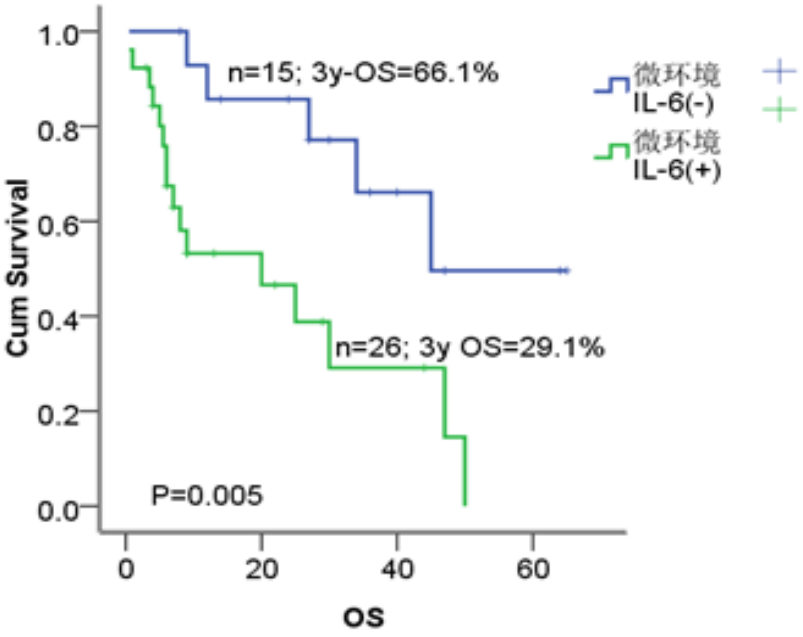
IMEP (ifosfamide, methotrexate, etoposide, prednisolone)- SMILES core regimen
Lee KW, Yun T, Kim DW, et al. First-line ifosfamide, methotrexate, etoposide and prednisolone chemotherapy +/- radiotherapy is active in stage I/II extranodal NK/T-cell lymphoma. Leuk Lymphoma 2006;47:1274-1282.

Dose-adjusted EPOCH
Huang H, Lin Z, Lin X, et al. Long-term outcomes of patients with newly diagnosed NK/T-cell lymphoma treated by EPOCH regimen. ASH Annual Meeting Abstracts. 2009: Abstract 2689.

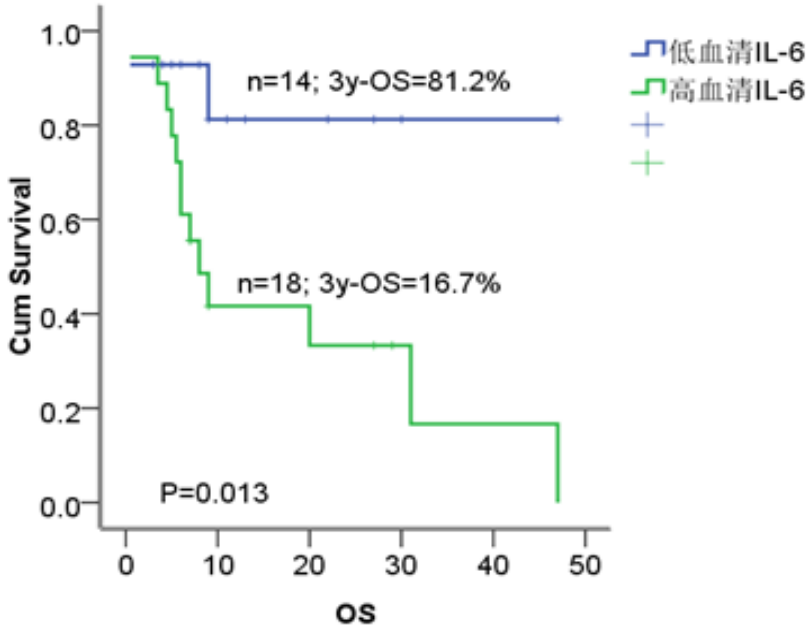
L-asparaginase based regimen
Yong W, Zheng W, Zhu J, et al. L-asparaginase in the treatment of refractory and relapsed extranodal NK/T-cell lymphoma, nasal type. Ann Hematol 2009;88:647-652.

CHOP is still effective for patients with low IL-6

IL-6 in microenvironment



Serum IL-6 level



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2. Asparaginase based chemotherapy

1. L-asparaginase
2. Pegaspargase

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Extranodal NK/T-Cell Lymphoma, nasal type

NCCN Guidelines Inde
NHL Table of Conten
Discussio

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)

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
- SMILE followed by RT 45–50.4 Gy
- VIPD followed by RT 45–50.4 Gy

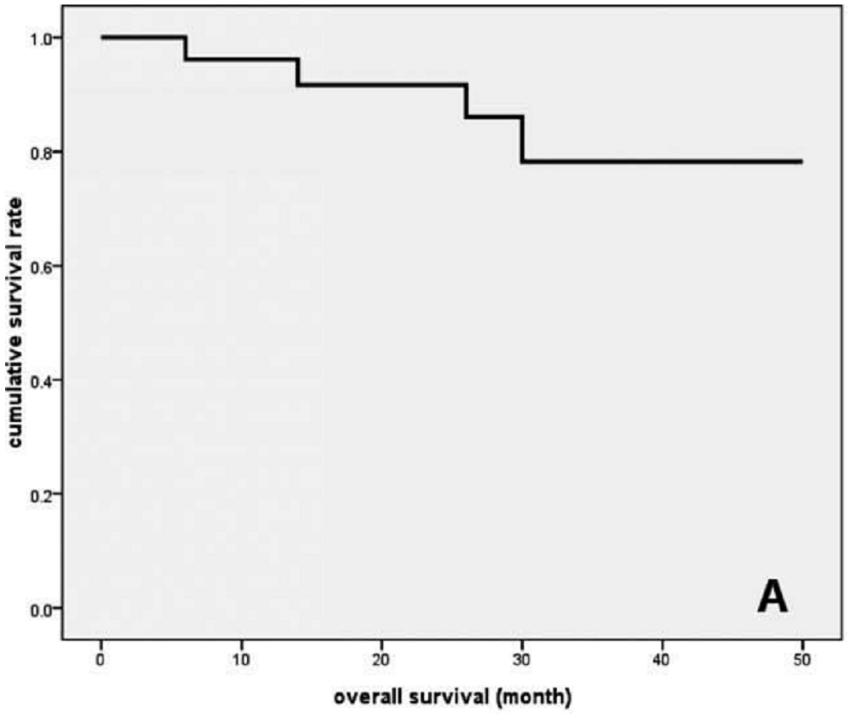
Radiation therapy alone
- Recommended tumor dose is ≥50 Gy
  - Early or up-front RT had an essential role in improved OS and DFS in patients with localized extranodal NK/T-cell lymphoma, nasal-type, in the upper aerodigestive tract.
  - Up-front RT may yield more benefits on survival in patients with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

L-Asparaginase for CHOP refractory diseases

- Yong et al (2003) → Prospective study of 18 patients with disease deemed refractory to CHOP
  - All pts treated with regimen containing L-asparaginase (6000 IU/m2), dexamethasone, and vincristine (1-6 cycles) + XRT
  - Stage II = 38.9% & Stage III/IV = 61.1%
  - Results with a CR 55.6% 5-year OS 55.6%
- Yong et al (2006) → Retrospective study of 46 patients with NK/T-cell lymphoma
  - Initially treated with CHOP to stratify into CHOP-sensitive and CHOP – refractory groups
  - 71.7% FAILED CHOP (SD / PD) → received L-asparaginase-based treatment (n=33) + XRT
- Stage I/II = 58.7% & Stage III/IV = 41.3%
  - 5-year OS = 86.3% (Stage I/II) & 38.3% (Stage III/IV)

Yong W, et al. L-asparaginase in the treatment of refractory and relapsed extranodal NK/T-cell lymphoma, nasal type. Ann Hematol. 2009 Jul;88(7):647-52

First-line GELOX, conventional L-ASP + Gemox, followed by IFRT for stage IE/IIE ENKTCL



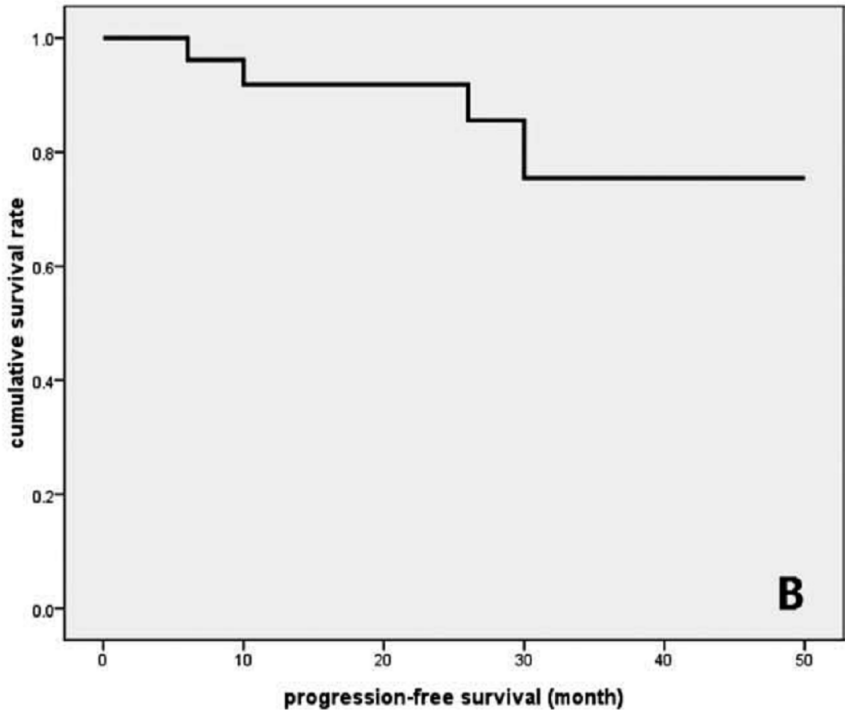


Figure 1. These survival curves indicate (A) 2-year and 3-year overall survival rates of 86% and 78%, respectively; and (B) 2-year and 3-year progression-free survival rates of 86% and 75%, respectively.

GELOX: L-ASP 6000U/m^2 d2,4,6,8 , Gemcitabine 1000mg/m2, d1,8 Oxaliplatin 130mg/m2,d1

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Wang L, et al. First-line combination of gemcitabine, oxaliplatin, and L-asparaginase (GELOX) followed by involved-field radiation therapy for patients with stage IE/IIE extranodal natural killer/T-cell lymphoma. Cancer. 2013 Jan 15;119(2):348-55.

First-line GELOX, conventional L-ASP + Gemox, followed by IFRT for stage IE/IIE ENKTCL

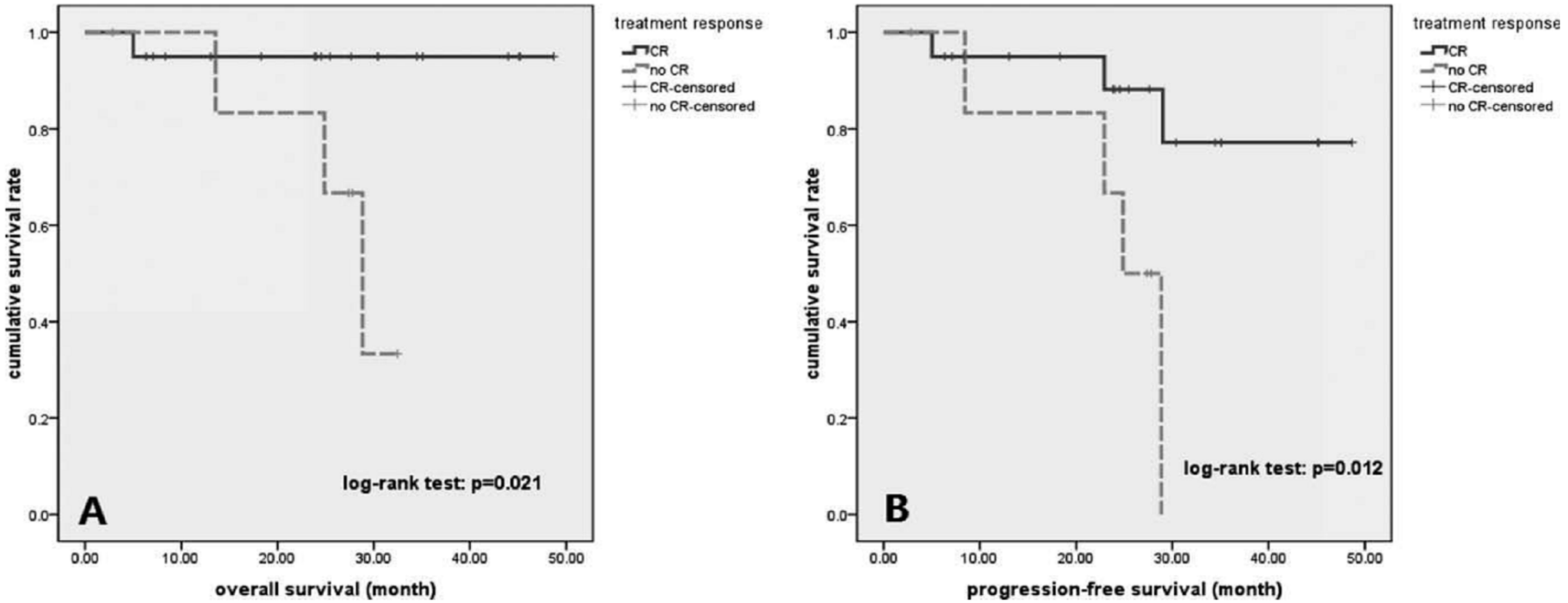

Figure 2. Patients who attained a complete response (CR) at the end of treatment had significantly longer (A) overall survival (P = .021) and (B) and progression-free survival (P = .012) compared with patients who did not attain a CR.

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Wang L, et al. First-line combination of gemcitabine, oxaliplatin, and L-asparaginase (GELOX) followed by involved-field radiation therapy for patients with stage IE/IIE extranodal natural killer/T-cell lymphoma. Cancer. 2013 Jan 15;119(2):348-55.

3. Induction of P-Gemox followed by Extensive involved-field radiotherapy for patients with stage I ,II NK/TCL

P-Gemox

Pegaspargase 2000mg/m2 d 1,

Gemcitabine 1000mg/m2, d1,8

Oxaliplatin 130mg/m2, d1 repeated every 3wks

P-Gemox followed by Extensive involved-field radiotherapy for patients with stage I ,II NK/TCL

Clinical characteristics, n=56

Characteristic	Whole cohort% （N）
Gender	
Male	62.5(35)
Female	37.5(21)
Age	
<60 years	80.4(45)
⩾60 years	19.6(11)
ECOG status	
0	78.6(44)
1	21.4(12)
EBV-DNA level	
Normal	58.9(33)
Elevated	41.1(23)
LDH level	
Normal	78.6(44)
Elevated	21.4(12)
Stage	
I_E	60.7(34)
II_E	39.3(22)

Characteristic	Whole cohort% (N)
KPI score	
0	41.1(23)
1	32.1(18)
2	25.0(14)
3	1.8 (1)
IPI score	
0	73.2(41)
1	25.0(14)
2	1.8(1)
Fever	
Present	64.3(36)
Absent	35.7(20)

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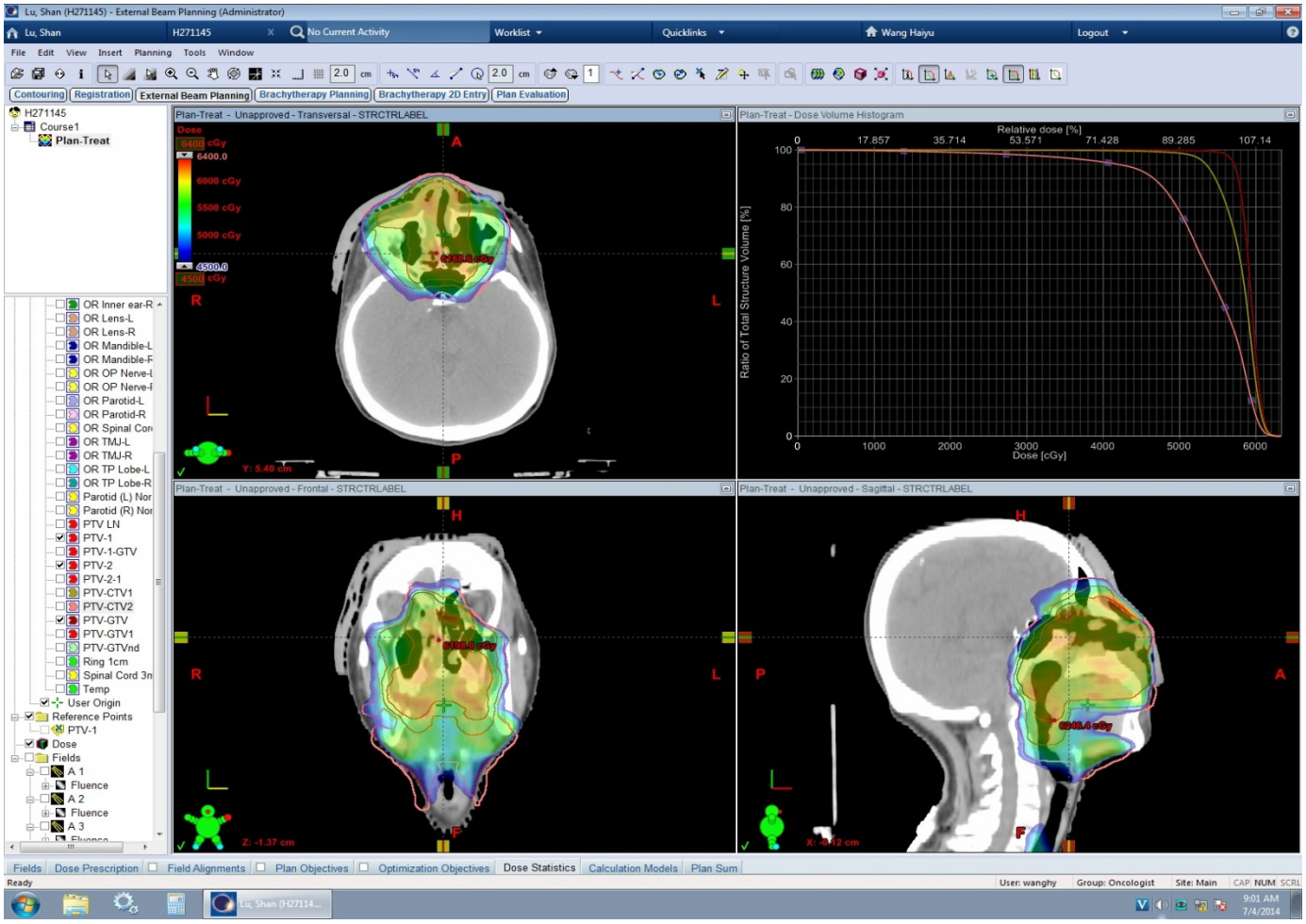
Huang Huiqiang, et al. Data unpublished

Extensive involved-field radiotherapy Radiotherapy for NK/ TCL , SYSUCC



P-Gemox followed by Extensive involved-field radiotherapy for patients with stage I ,II NK/TCL

Objective response

	After induction Chemotherapy (%) (N=56)	After RT (%) (N=56)
Response	89.3(50)	94.6(53)
CR	62.5(35)	89.3(50)
PR	26.8(15)	5.4(3)
SD	7.2(4)	1.8(1)

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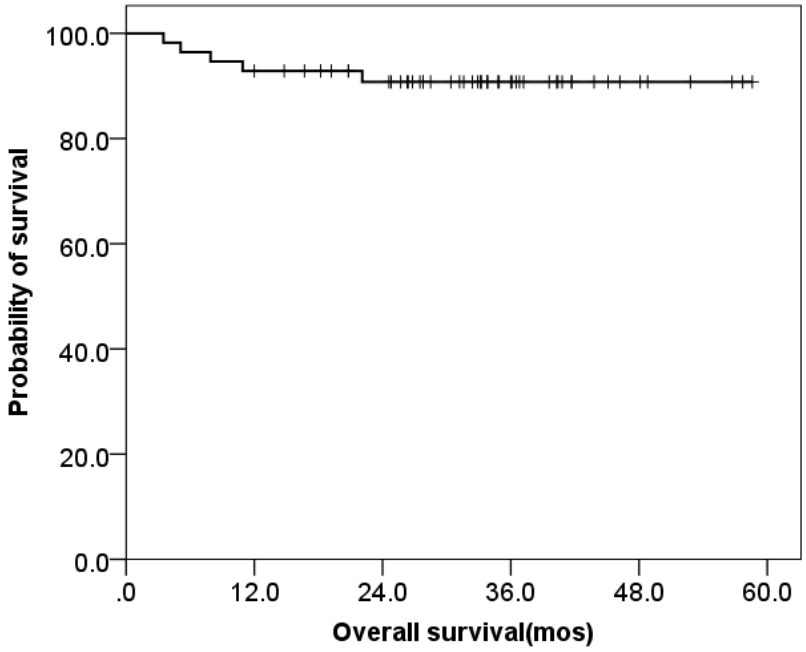
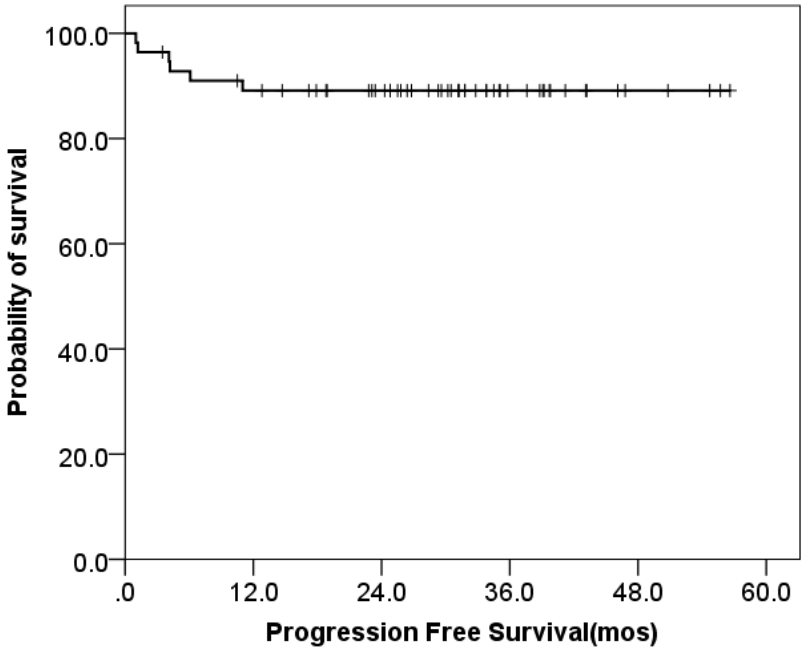
Huang Huiqiang, et al. Data unpublished

P-Gemox followed by Extensive involved-field radiotherapy for patients with stage I ,II NK/TCL

Survival of whole cohort





4-yr OS: 90.7±4.0%

4-yr PFS: 89.1±4.2%

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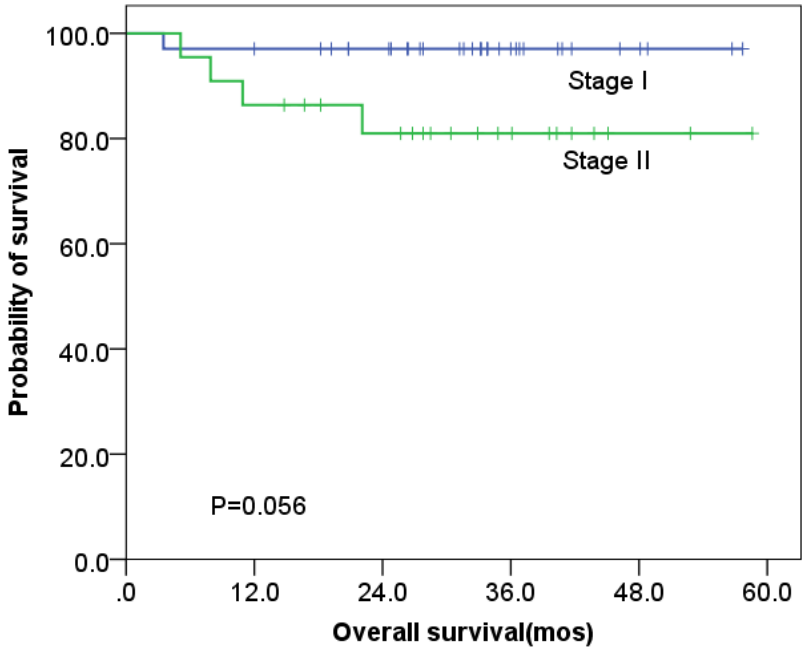
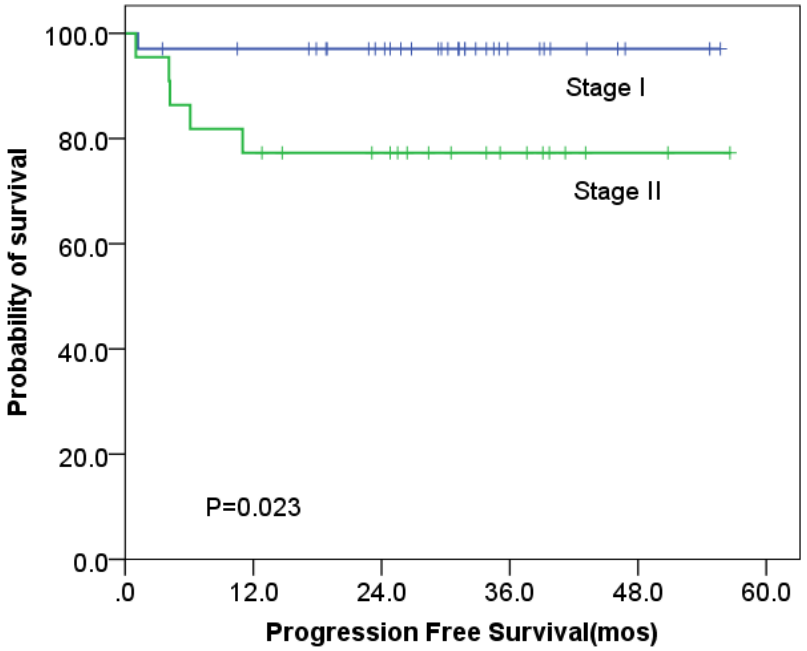
Huang Huiqiang, et al. Data unpublished

P-Gemox followed by Extensive involved-field radiotherapy for patients with stage I ,II NK/TCL

Survival of stage





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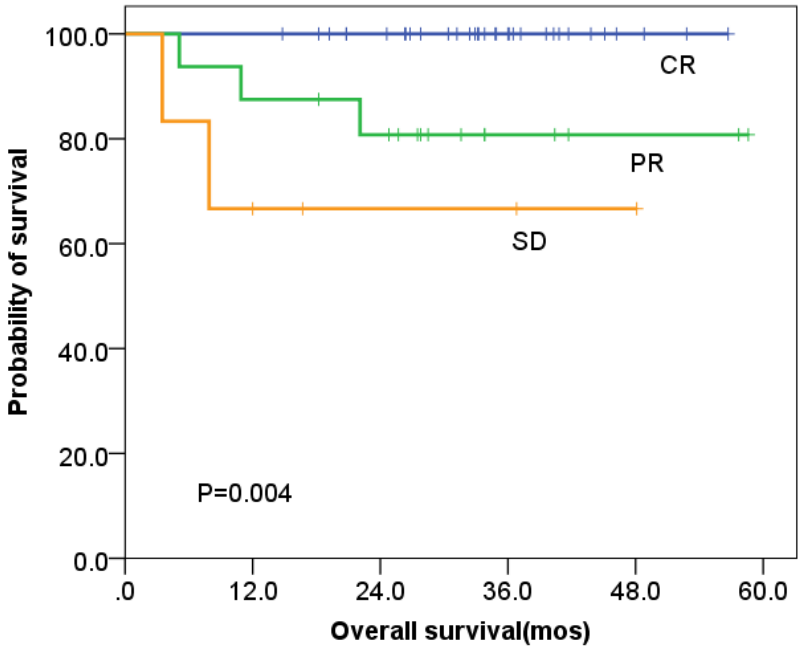
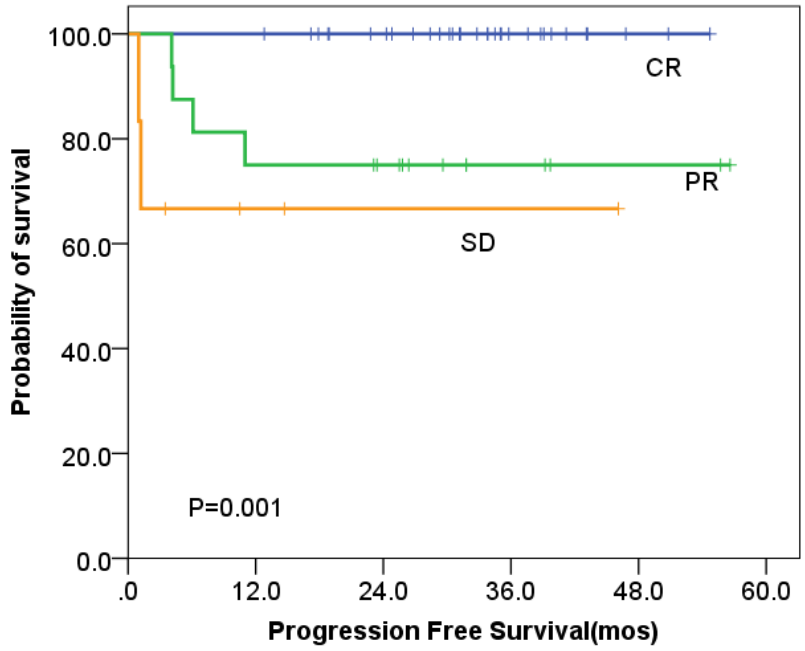
Huang Huiqiang, et al. Data unpublished

P-Gemox followed by Extensive involved-field radiotherapy for patients with stage I ,II NK/TCL

Survival based on response to chemotherapy





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Huang Huiqiang, et al. Data unpublished

P-Gemox followed by Extensive involved-field radiotherapy for patients with stage I ,II NK/TCL

Toxicity

Toxicities	All cases (N)	Grade 1/2 (N)	Grade 3/4 (N)
Neutropenia	80.3 (45)	57.1(32)	23.2(13)
Thrombocytopenia	55.3(31)	35.7(20)	19.6(11)
Anemia	26.8(15)	21.5(12)	5.3(3)
lymphocytoponia	21.4(12)	21.4(12)	0
AST/ALT elevated	32.1(18)	28.6(16)	3.6(2)
Hypoproteinemia	75.0(42)	64.3(36)	10.7(6)
Fbg decrease	44.6(25)	41.0(23)	3.6(2)
APTT prolong	42.8(24)	42.8(24)	0
Hyperglycemia	8.9(5)	8.9(5)	0
Total bilirubin elevated	26.8(15)	26.8(15)	0
Nausea	32.1(18)	28.6(16)	3.6(2)
Anorexia	37.5(21)	37.5(21)	0
Vomiting	26.8(15)	23.2(13)	3.6(2)
Mucositis	21.4(12)	21.4(12)	0

Huang Huiqiang, et al. Data unpublished

4. Longterm outcome of P-GEMOX for patients with advanced or refractory NK/TCL

Longterm outcome of P-GEMOX for patients with advanced or refractory NK/TCL

clinical characteristics， N=61

Characteristic	Whole cohort%（N）
Gender (M/F)	73.3 (44)/26.7 (16)
Newly diagnosed stage III/IV	25.0 (15)
Refractory	43.3(26)
Relapsed	21.7(19)
Age	
<60 years	91.7(55)
⩾60 years	8.3(5)
ECOG status	
0-1	73.3(44)
2	26.7(16)
EBV-DNA level	
Normal	41.7(25)
Elevated	58.3(35)
LDH level	
Normal	58.3(35)
Elevated	41.7(25)
Stage	
I_E	15.0(9)
II_E	16.7(10)
III_E	35.0(21)
IV_E	33.3 (20)

Characteristic	Whole cohort%（N）
KPI score	
0-1	28.3(17)
2	21.7(13)
3	38.3(23)
4	11.7(7)
IPI score	
0-1	48.3(29)
2	31.7(19)
3-4	20.0(12)
Fever	
Present	46.7(28)
Absent	53.3(32)
Pathology	
Nasal type	70.0(42)
Non-nasal type	30.0(18)
Previous number of regimens	8.3(5)
< 2	53.3 (32)
≥ 2	21.7(13)

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Longterm outcome of P-GEMOX for patients with advanced or refractory NK/TCL

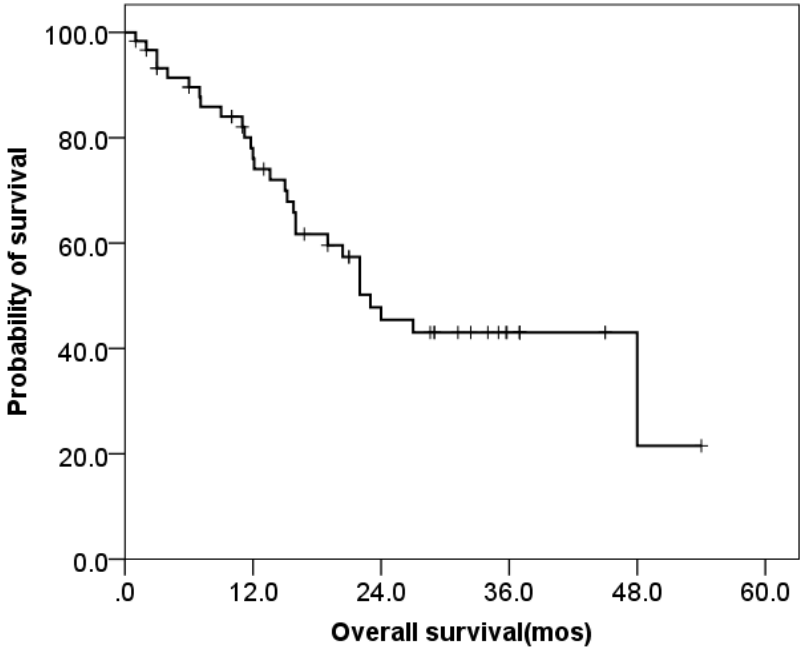
Short-term efficacy

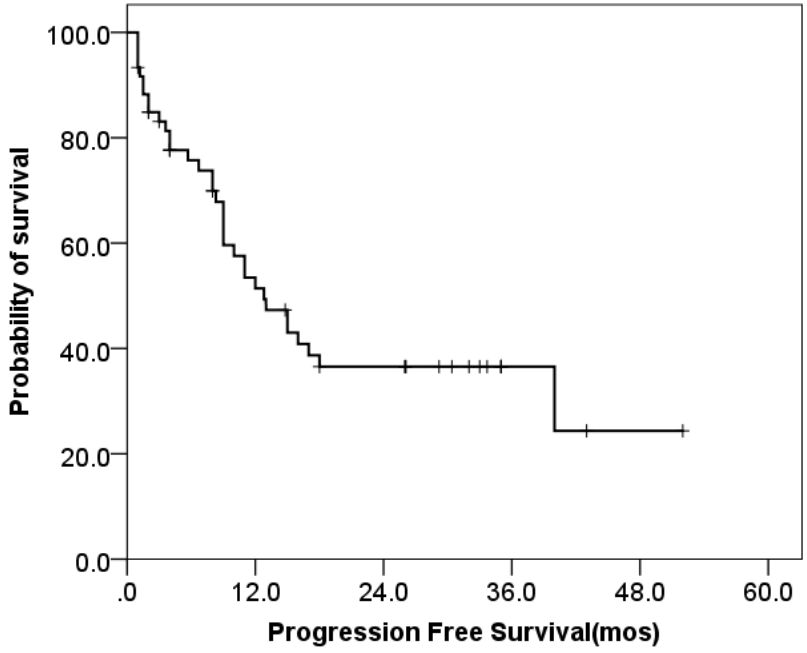
	Newly diagnosed % (N=15)	Refractory/relapsed % (N=45)	Whole cohort % (N=60)
RR	80.0(12)	66.7(30)	70.0(42)
CR	26.7(4)	37.8(17)	35.0(21)
PR	53.3(8)	28.9(13)	35.0(21)
SD	13.3(2)	15.6(7)	15.0(9)

Huang Huiqiang, et al. Data unpublished

Longterm outcome of P-GEMOX for patients with advanced or refractory NK/TCL

Survival of whole cohort





4-yr OS: 43.0±7.3%

4-yr PFS: 36.5±6.9%

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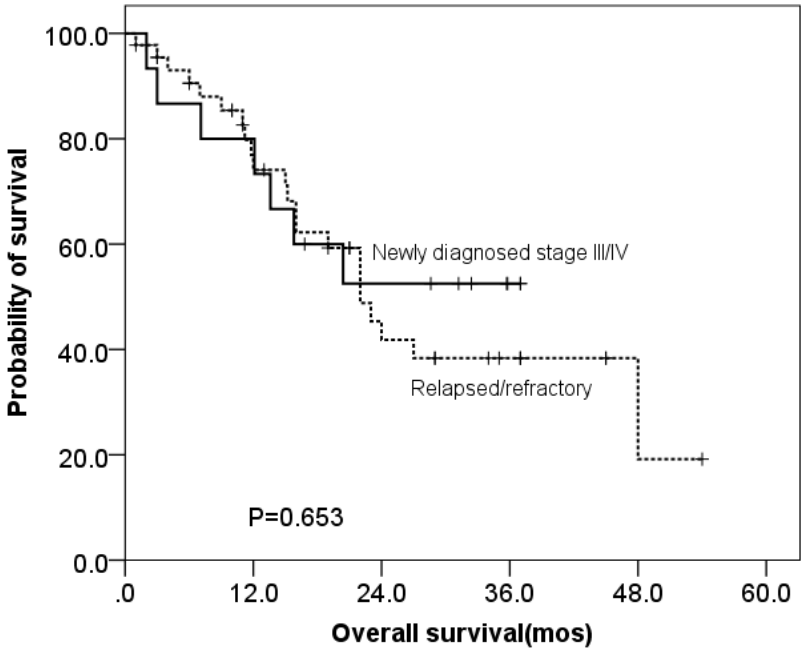
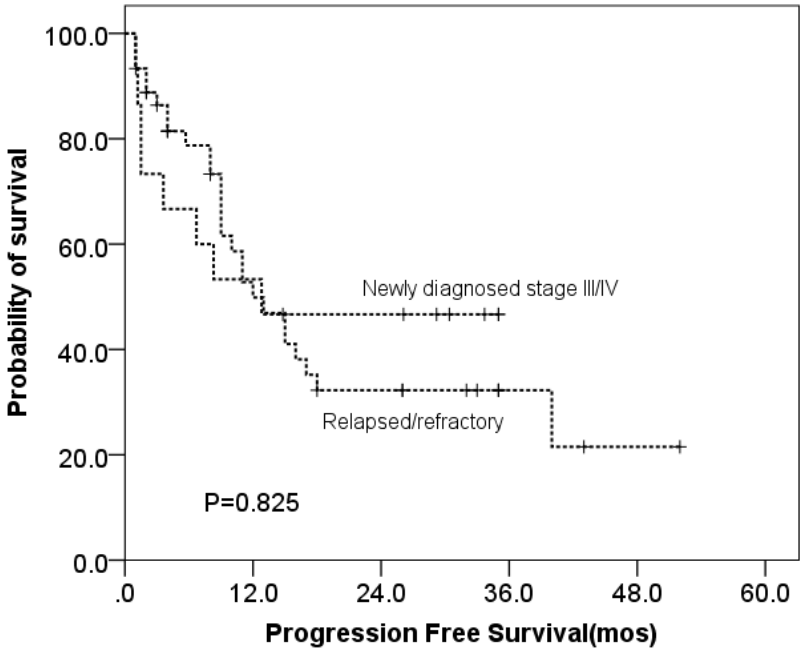
Longterm outcome of P-GEMOX for patients with advanced or refractory NK/TCL

Survival of newly diagnosed stage III/IV and relapsed/refractory NK/TCL





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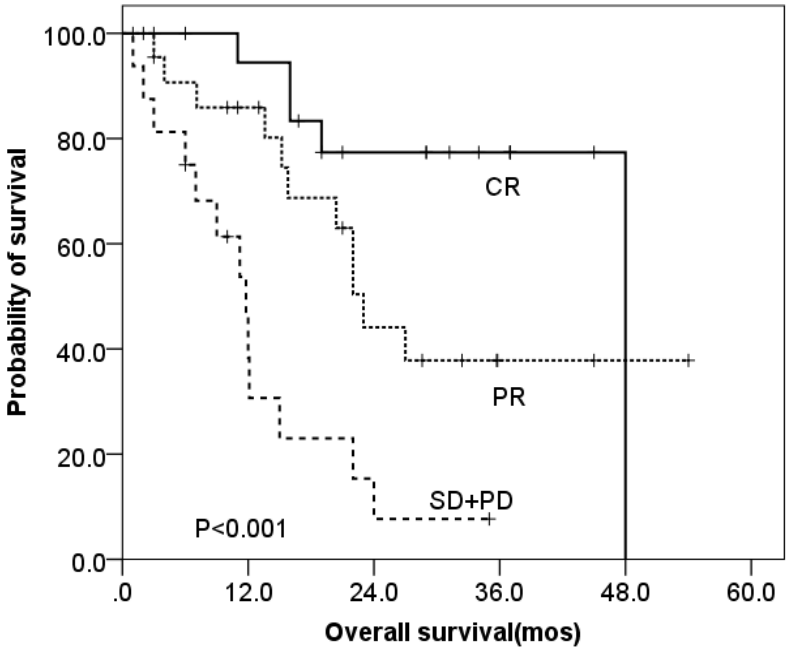
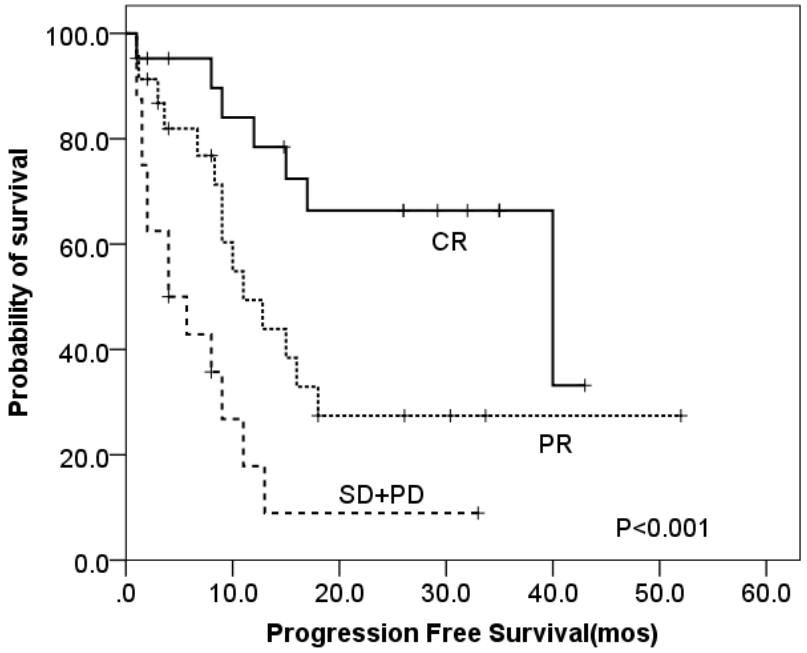
Longterm outcome of P-GEMOX for patients with advanced or refractory NK/TCL

Survival based on response





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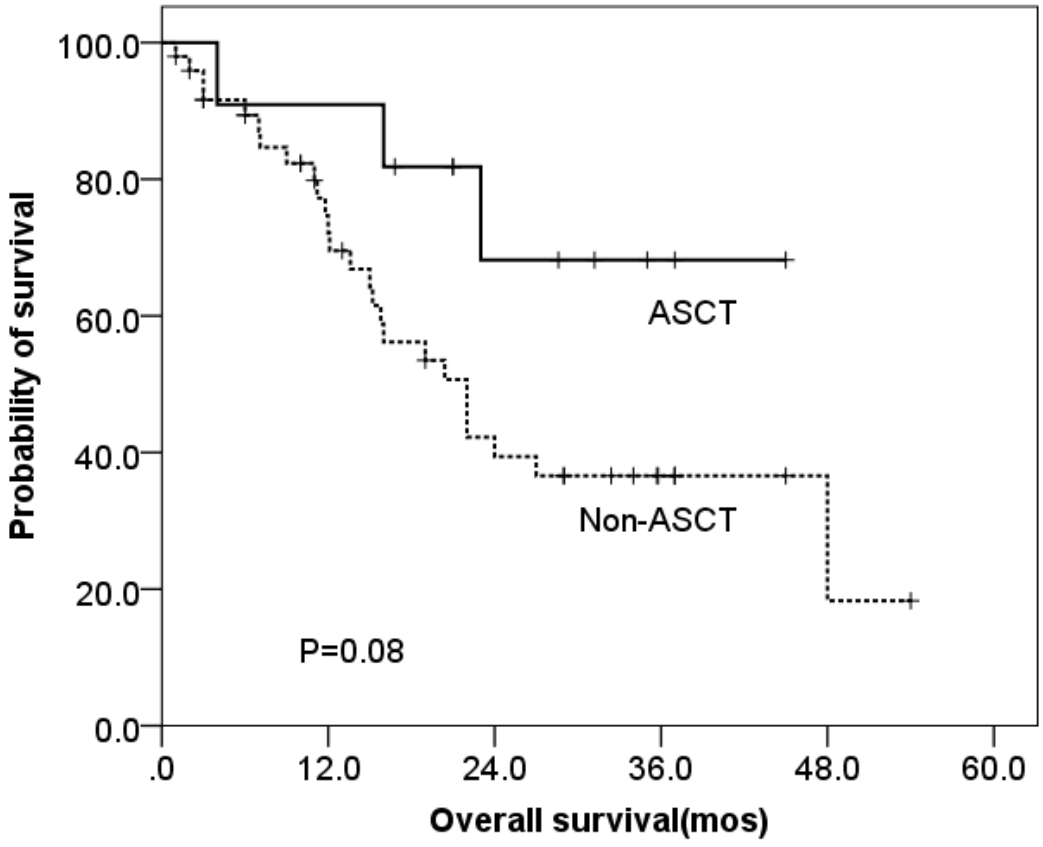
ASCT is beneficial for responders to P-GEMOX for advanced or refractory NK/TCL

OS of patients with ASCT or not



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Longterm outcome of P-GEMOX for patients with advanced or refractory NK/TCL

Toxicities

Toxicities	All cases (%)	Grade 1/2 (%)	Grade 3/4 (%)
Neutropenia	51(85.0)	32(53.3)	19(31.6)
Thrombocytopenia	22(36.7)	15(25.0)	7(11.7)
Anemia	43(71.6)	18(66.7)	3(5.0)
lymphocytoponia	14(23.3)	12(20.0)	2(3.3)
AST/ALT elevated	26(43.3)	22(36.7)	4(6.7)
Hypoproteinemia	53(88.3)	48(84.9)	8(13.3)
Fbg decrease	41(68.3)	39(65.0)	2(3.3)
APTT prolong	16(26.7)	16(26.7)	0
Hyperglycemia	7(11.6)	7(11.6)	0
Total bilirubin elevated	9(15.0)	9(15.0)	0
Nausea	21(35.0)	21(35.0)	0
Anorexia	32 (53.3)	32 (53.3)	0
Vomiting	19(31.6)	19(31.6)	0
Allergic reactions	1(1.7)	1(1.7)	0
herpes zoster	3(5.0)	3(5.0)	0

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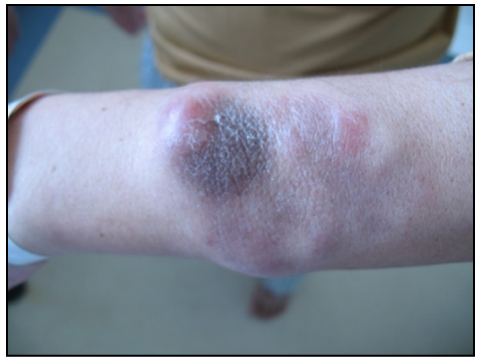
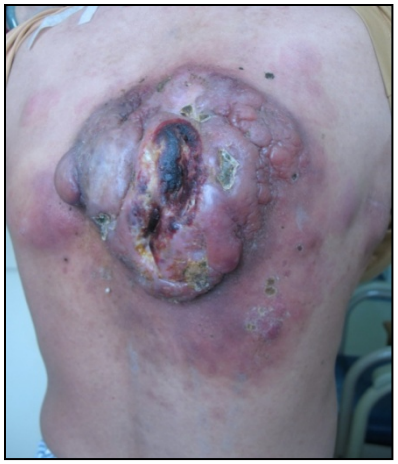
Huang Huiqiang, et al. Data unpublished

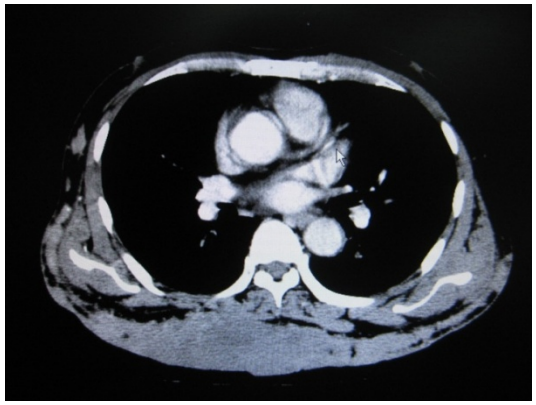
Pegaspargase + Gemox : Promising!

FSX ,Male ,49y, rNKTCL

2011-12-16
Baseline







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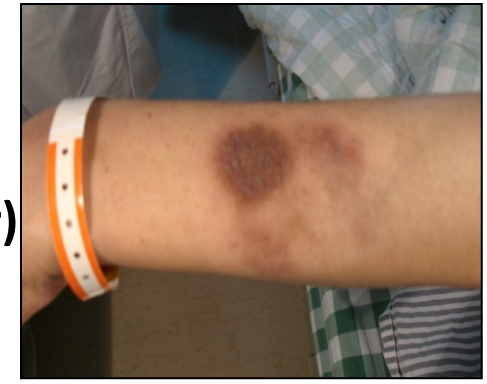
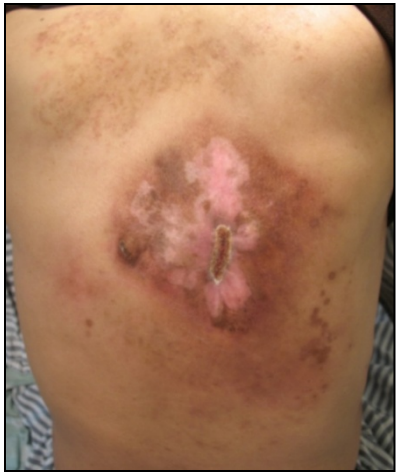
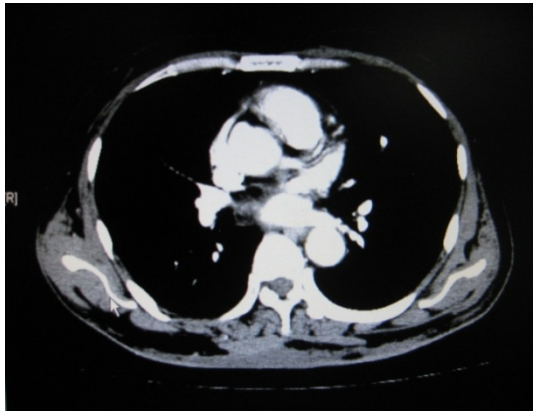
(2 cycles after)







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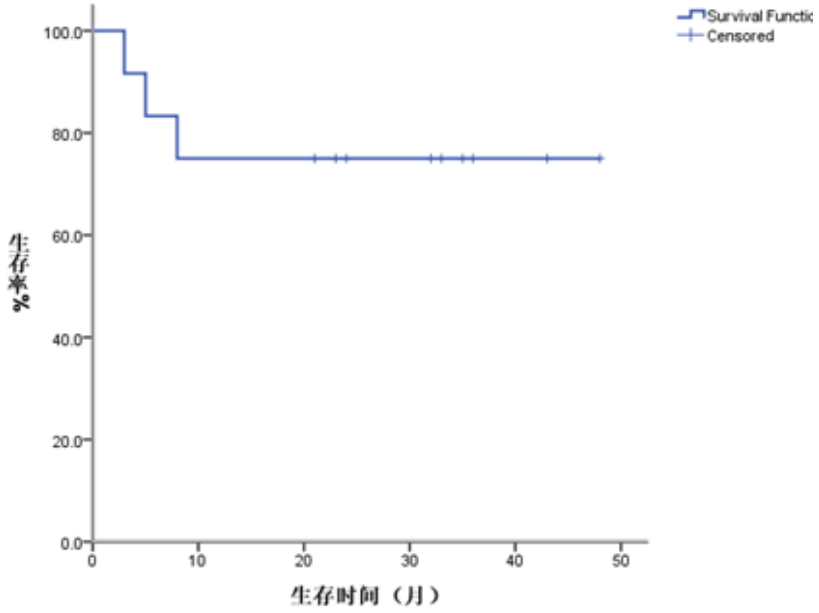
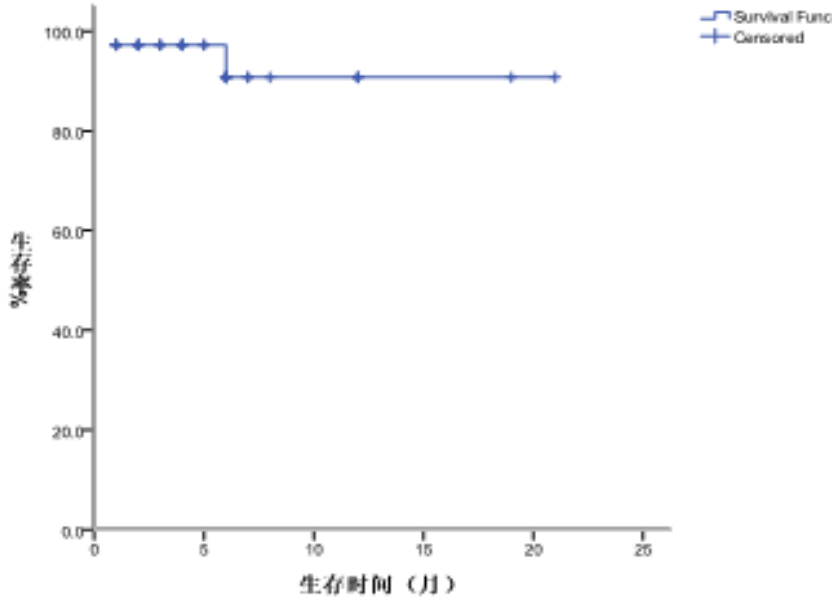
Huang Huiqiang, et al. Data unpublished

Comparison of L-ASP and peg-ASP based chemotherapy for relapsed NKTCL

PFS



L-ASP



PEG-ASP

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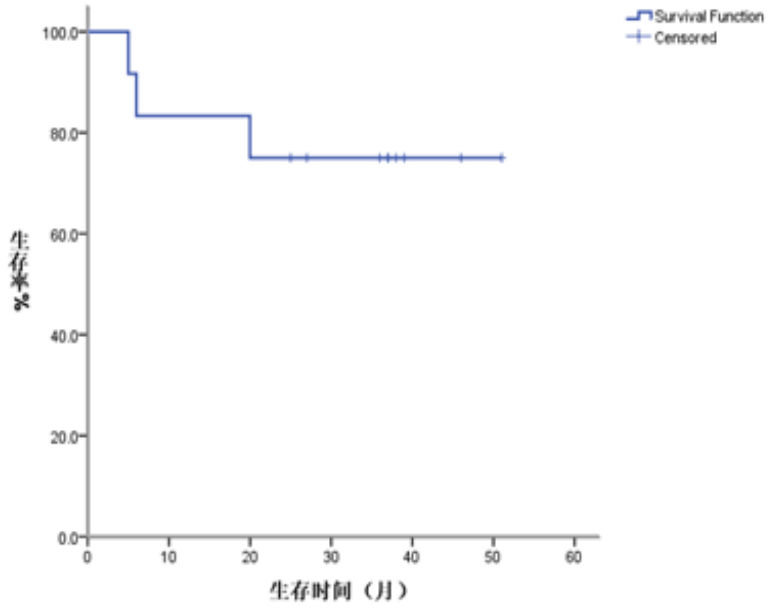
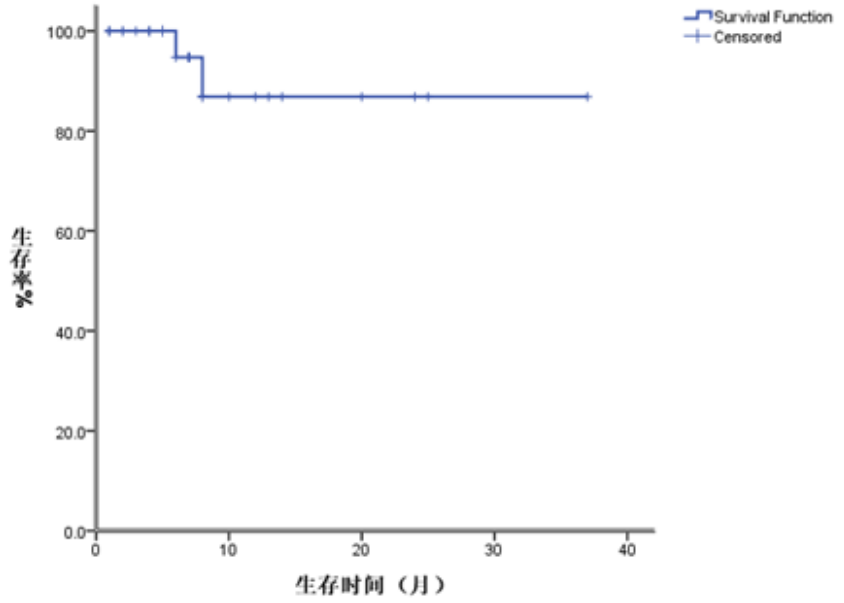
Comparison of L-ASP and peg-ASP based chemotherapy for relapsed NKTCL

OS



L-ASP



PEG-ASP

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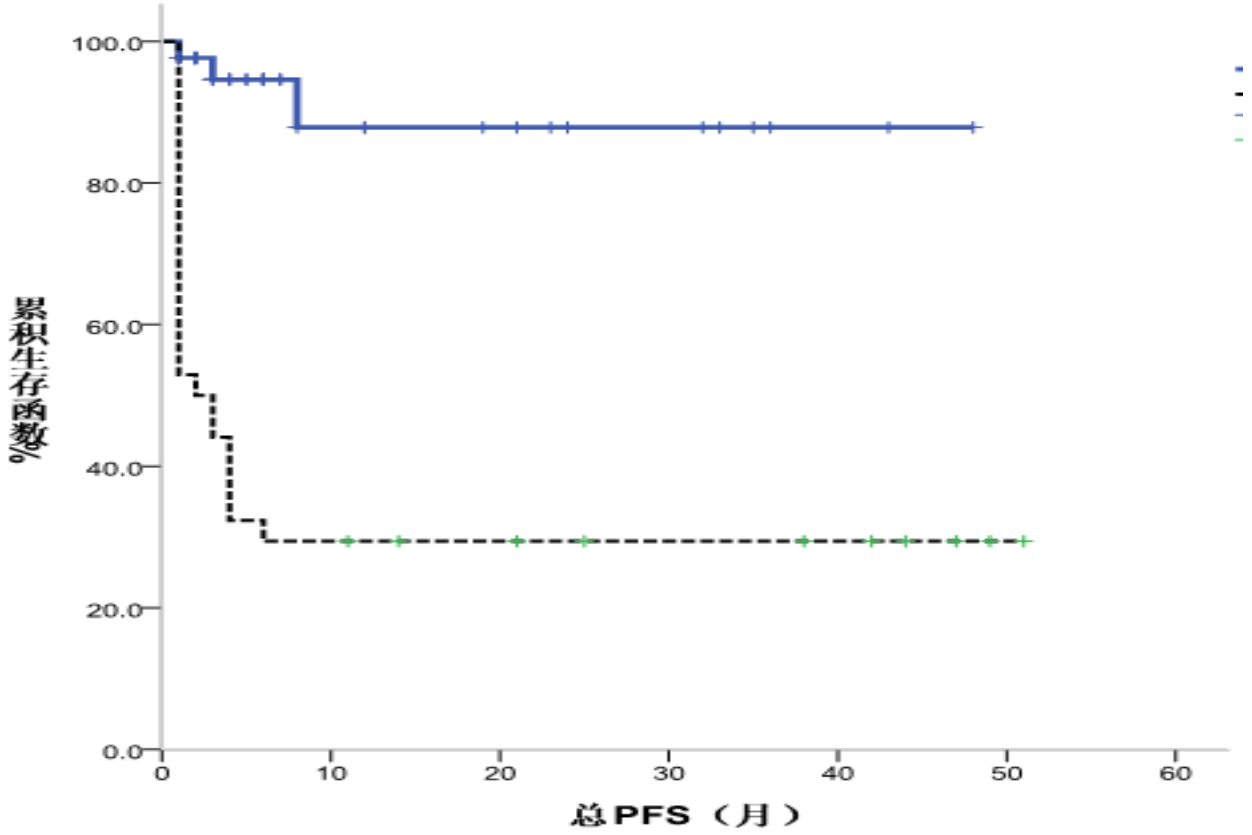
EPOCH vs P-Gemox in NKTCL

OS



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5. Comparison of asparaginase- and non-asparaginase-containing chemotherapies for patients with NK/T-cell lymphoma： Single institution experience， SYSUCC

Huang Huiqiang, et al. Data unpublished

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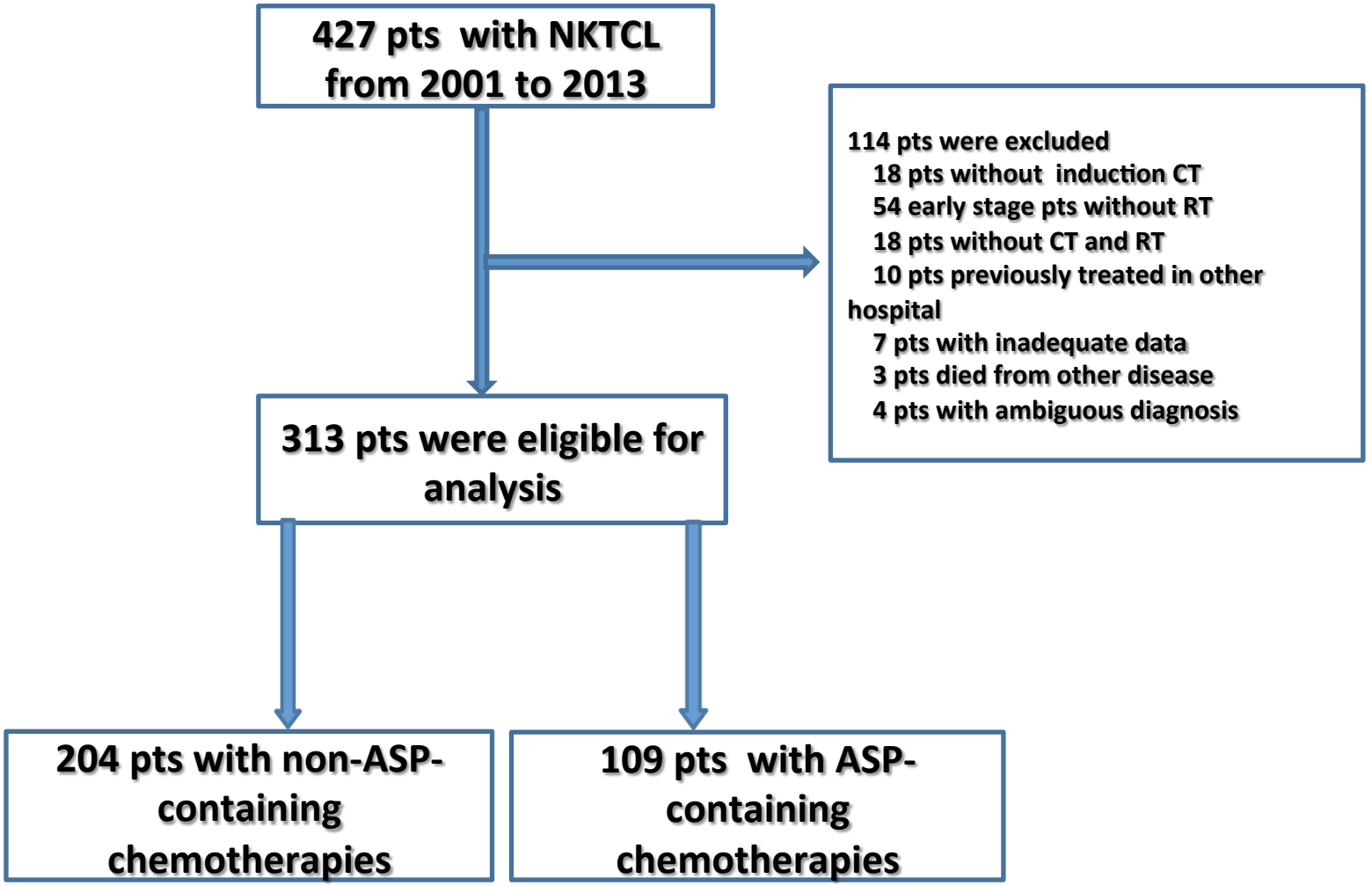
Comparison of asparaginase- and non-asparaginase-containing chemotherapies for NKTCL



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Huang Huiqiang, et al. Data unpublished

Comparison of asparaginase- and non-asparaginase-containing chemotherapies for NKTCL

Group	Regimen	N
ASP-containing CT	ASP-Gemox	81
	Other ASP-containing regimens	25
Non-ASP-containing CT	EPOCH	40
	CHOP (CHOP-like)	48
	Other regimens	12

Huang Huiqiang, et al. Data unpublished

Comparison of asparaginase- and non-asparaginase-containing chemotherapies for NKTCL

Comparison of reponse

Regimen	CR (%)	PR (%)	SD (%)	PD (%)	Total
ASP-containing CT	**62 (58.5)**	33 (31.1)	3 (2.8)	8 (7.5)	106
Non-ASP-containing CT	**35 (35.0）**	31 (31.0)	14 (14.0)	20 (20.0)	100
Total	97 (47.1%)	64 (31.1)	17 (8.3)	28 (13.6)	206

CR , 58.5% vs. 35.0%, $P < 0.001$

ORR, 89.6% vs. 66.0%%, $P < 0.001$

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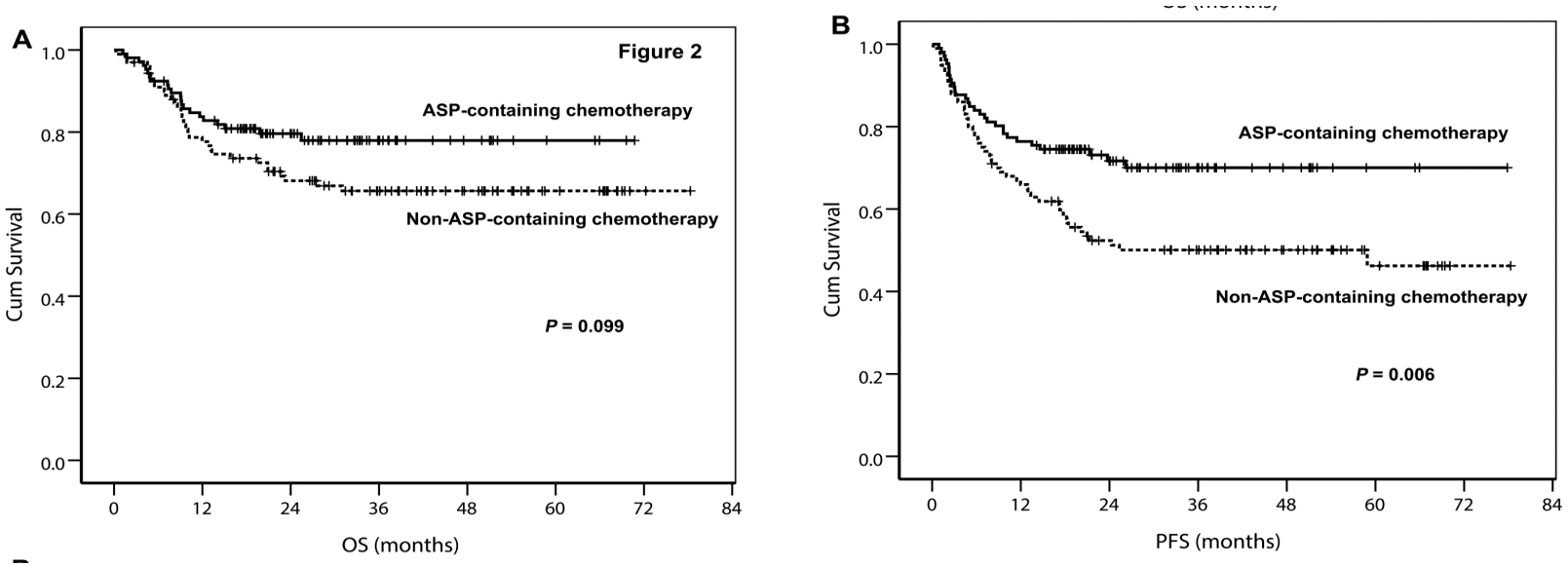
Comparison of asparaginase- and non-asparaginase-containing chemotherapies for NKTCL

Comparison of long-term efficacy



3-y OS, 77% vs 66%, P=0.099

3-y PFS, 70% vs 50%, P=0.006

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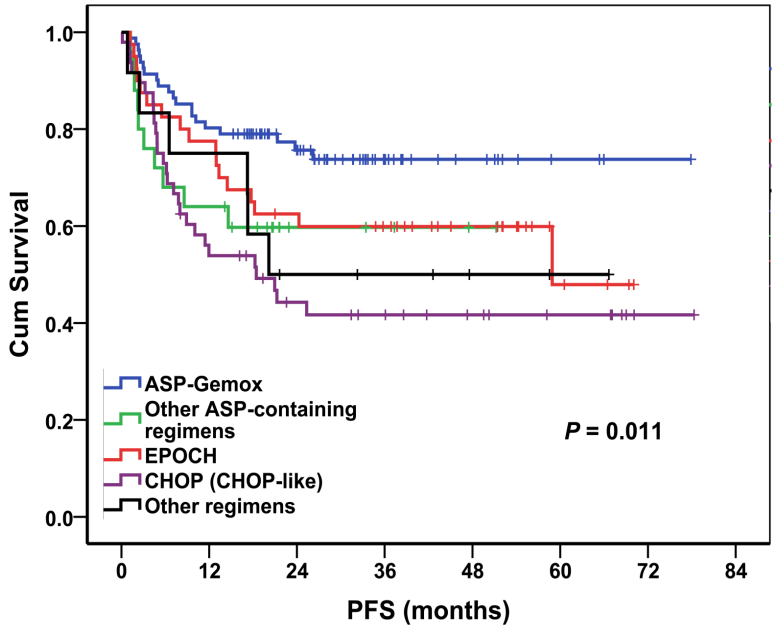
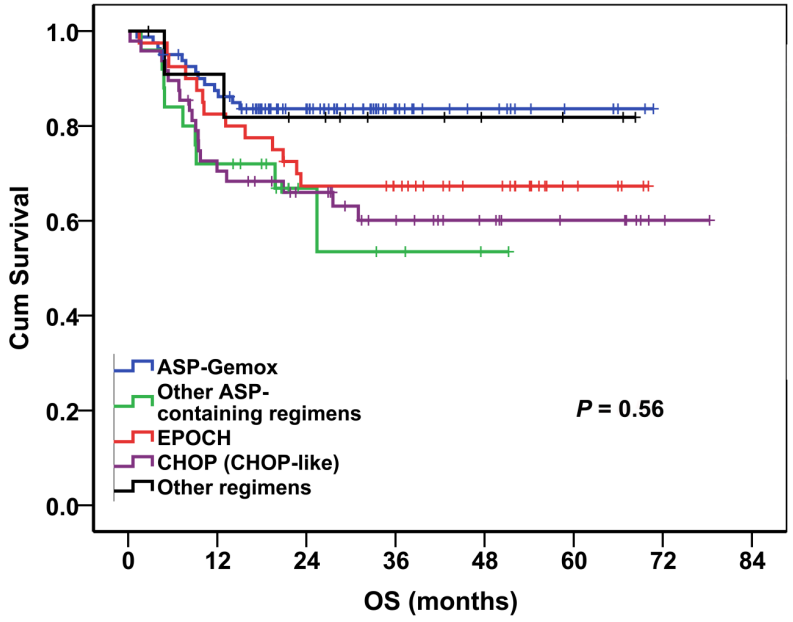
Comparison of asparaginase- and non-asparaginase-containing chemotherapies for NKTCL

Comparison in PFS and OS





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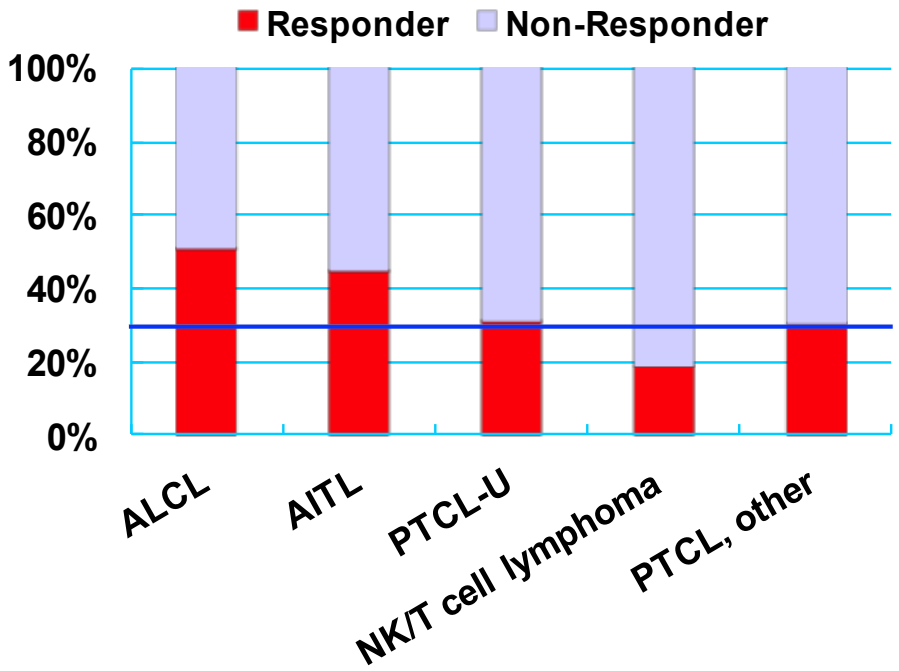
Future: Chidamide, a new HDAC inhibitor, for NK/TCL

Pathological subtypes of pts enrolled

Pathological subtype	FAS, N=79
PTCL-unspecified (PTCL-U)	23 (29%)
NK/T cell lymphoma, nasal type	16 (20%)
Anaplastic large-cell lymphoma (ALCL)	16 (20%)
Angioimmunoblastic T-cell lymphoma (AITL)	9 (11%)
Enteropathy-associated T-cell lymphoma (ESTL)	2 (3%)
Transformed mycosis fungoides	1 (1%)
PTCL, other	10 (12.7%)



Response rate in different subtypes (>10% of pts enrolled)

- 20% of patients enrolled were extra-nasal NK/T, a predominant form seen in East Asia population often with worst outcome
- The response rates to Chidamide for ALCL, AITL, PTCL-U were all ≧30%, and NK/T cell lymphoma showed relative lower response.
- Parameters of prior systemic regimens, gender, age, weight did not seem to be different to the drug response.

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Conclusion

1. L-Asparaginase is the most important agent in combined chemotherapy .
2. L-asparaginase based chemotherapy is most effective on NK/TCL ,better than non-L –asparaginase regimen.
3. P-Gemox is a effective ,less toxic and simplified regimen for NK/TCL especially for stage I/II NK/TCL， yield 4 year OS of 90%.
4. Effectiveness of P-Gemox for advanced or refractory NK/TCL is till unsatisfied and consolidation of ASCT after response is effective and imperative.
5. Further investigation to clarify optimal L-asparaginase based combination for NK/TCL is warranted.

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6. **All my patients !**

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