

# Risk-Adapted Therapy for Localized Extranodal NK/T-Cell Lymphoma, Nasal-type

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# Treatment of Early-Stage NK/TCL

- ◆ Role of radiotherapy
- ◆ Role of chemotherapy
- ◆ Optimal combination of radiotherapy and chemotherapy
- ◆ Optimal chemotherapy regimens
- ◆ Optimal RT field and dose

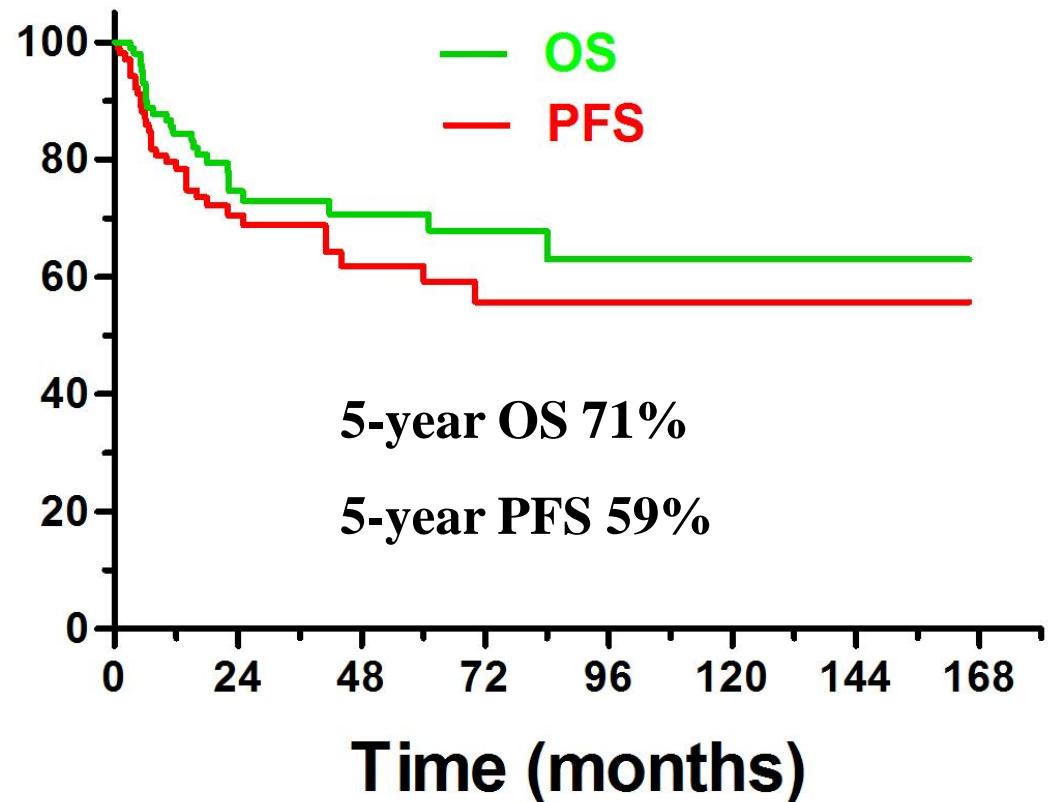
# Treatment of Early-Stage NKTCL

- ◆ Radiotherapy is mainstay of treatment (curable)
  - Primary RT resulted in favorable outcome
  - Radiotherapy is superior to chemotherapy alone
- ◆ Chemotherapy is adjuvant therapy
  - No benefit of adding chemotherapy into radiotherapy for low-risk early-stage NKTCL
  - Radiotherapy followed by chemotherapy prove the most effective therapy for high-risk early stage NKTCL
  - No standard chemotherapy regimens and limited efficacy with new regimens
- ◆ Optimal RT and chemotherapy regimens
  - High locoregional control is associated with improved survival

# Primary Radiotherapy for Early Stage Nasal-NKCL

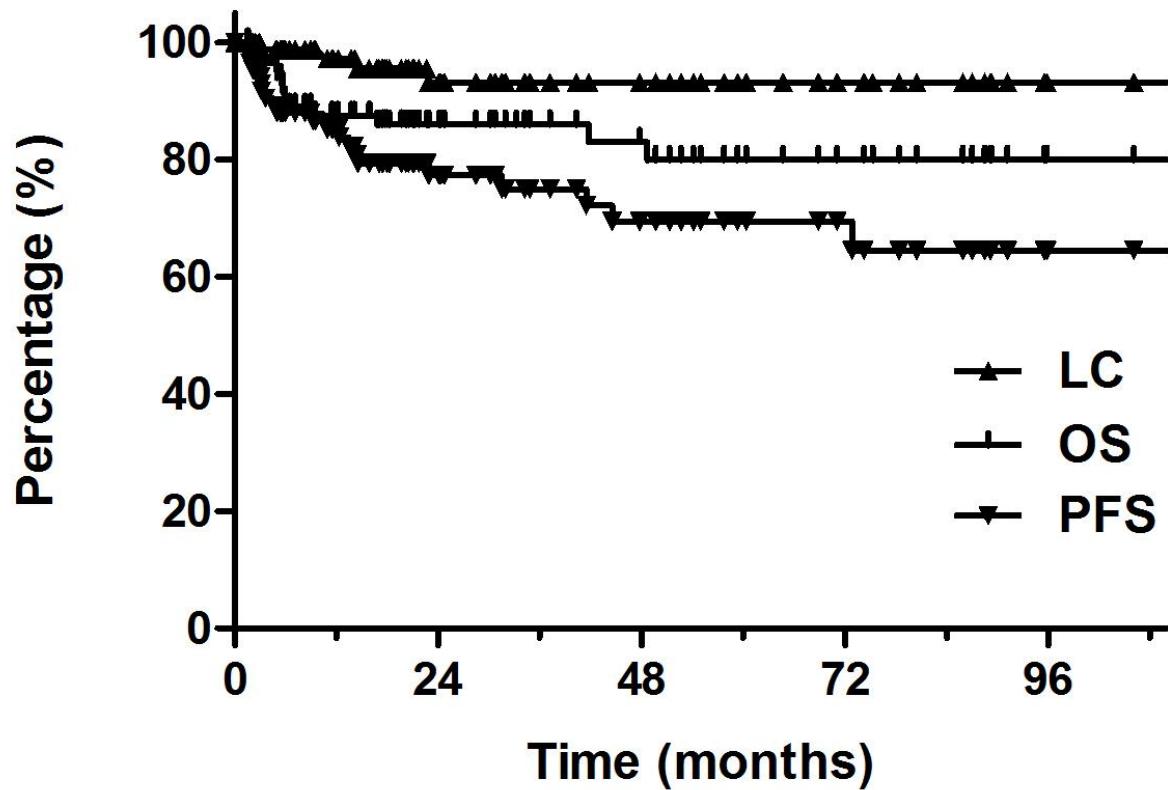
Cancer Hospital of CAMS & PUMC

- ◆ Primary radiotherapy
  - RT alone: 31 cases
  - CMT: 71 cases
  - CT alone: 3 cases
- ◆ 83 stage I, 22 stage II
- ◆ B symptom: 35%
- ◆ Elevated LDH: 50%
- ◆ ECOG 0-1: 83%
- ◆ Paranasal extension: 61%
- ◆ mIPI 0-1: 74%



# Radiotherapy Alone for Stage I UADT-NKTCL

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87 patients  
Extended involved-field  
Median dose: 50 Gy

RT alone	
5-y OS	80%
5-y PFS	69%
5-y LC	93%

# Low CR Rate After Chemotherapy

**CR 5-45%, Most<40%; ORR 51-64%, SD+PD 33-51%**

Author	Time	No	Location	Stage	Regimens of Chemotherapy	Response after ChT (%)			
						CR	PR	S	PD
Cheung	2002	61	Nasal+Nasopharynx	I-II	ProMACE-Cytarabom, CHOP	49		51	(S+PD)
Ribrag	2001	12	UADT	I-II	CHOP, CHOP-like	25	42	0	33
Kim GE	2001	39	UADT	I-II	CHOP, BACOP	5	46	49	(S+PD)
Kim WS	2001	15	Nasal+Nasopharynx	I-II	CHOP	40	20	40	(S+PD)
Kim K	2005	16	UADT	I-II	CHOP, COPBLAM-V	38	19	0	44
Kim SJ	2006	43	UADT	I-II	CEOP-B	44	23	33	(S+PD)
Li YX	2006	40	Nasal Cavity	I-II	CHOP, BACOP	20	40	18	22
Aikemu	2008	22	Nasal Cavity	I	CHOP	23	41	36	(S+PD)
Yang Y	2009	158	UADT	I-II	CHOP, EPOCH	30	30	21	18
Ma X	2009	75	UADT	I-II	CEOP, CEOP + Semustine	24	36	29	11
Nie DH	2010	68	Nasal Cavity	I-II	CHOP, BACOP, EPOCH	21	NA	NA	NA
Wang	2012	110	Nasal Cavity	I-II	2 CHOP	31.8	31.8	26.4	10.0

# Low OS with Chemotherapy Alone for Early Stage NK/TCL

5-year OS: only 12-29%, Median<16 months !

Author	Time	Total No.	Primary site in nasal cavity No. (%)	Stage	No. of ChT	Regimens of chemotherapy	5-y OS (%)	5-y LRC (%)
Li CC	2004	56*	43 (56)	I-II	18	CHOP	15	55
Yang	2009	177	143 (81) UADT	I-II	37	CHOP, EPOCH	18.3	50
Huang	2008	82	66 (80)	I-II	8	CHOP	12.5 (3)	
Au	2009	57	UADT	I-II	23	CHOP	~29	
Yie	2010	85	85 (100)	I-II	20	CHOP	13	
Kim SJ	2006	43	29 (NC+NP, 67)	I-II	26	6 CEOP-B	15.3 (m, Median)	
You	2004	46	46 (100)	I-II	15	CHOP, CEOP	20	
Luo	2010	60	60 (100)	I-II	16	CHOP, BACOP	18.8	
Pongpruttipan	2012	67	42 (63)	I-II	10	Not reported	8 (m, median)	
				I-II	173		12-29	

# High CR Rate After Radiotherapy

**CR: 66-94%, SD+PD: 6-22%**

Author	Time	No	Primary		Stage	RT Dose (Median)	Response after RT (%)		S	PD
			Location				CR	PR		
Cheung	2002	18	Nasal + Nasopharynx		I-II	50 Gy	78			22
Kim GE	2001	104	UADT		I-II	50.4 Gy	69	15		15
Kim GE	2000	92	UADT		I-II	50.4 Gy	66	17		16
Kim K	2005	33	UADT		I-II	50 Gy	94	0	0	6
Koom	2004	102	UADT		I-II	45 Gy	72	14		14
Li YX	2006	65	Nasal Cavity		I-II	50 Gy	83	9	3	5
Aikemu	2008	35	Nasal Cavity		I	50 Gy	74	20		6
Kim K	2005	33	UADT		I-II	50 Gy	94	0	0	6
Ma, et al	2010	23	Nasal Cavity		I-II	50 Gy	70	13	4	13
Luo	2010	24	Nasal Cavity		I-II	45-68 Gy	67	NA	NA	NA
Yang	2015	464	All sites		I-II	50 Gy	93.3			6.7

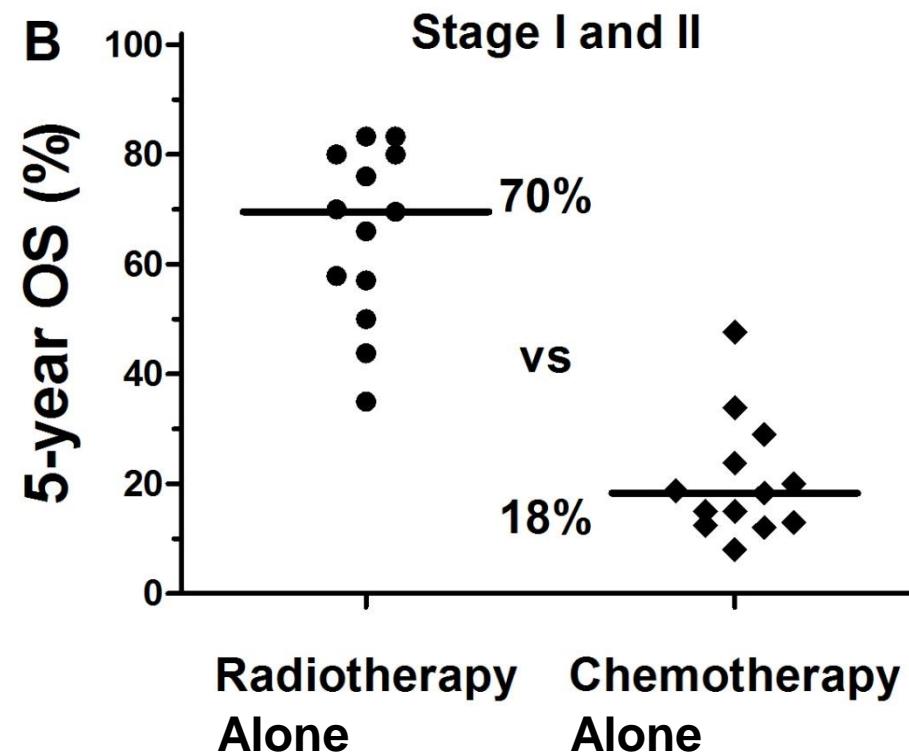
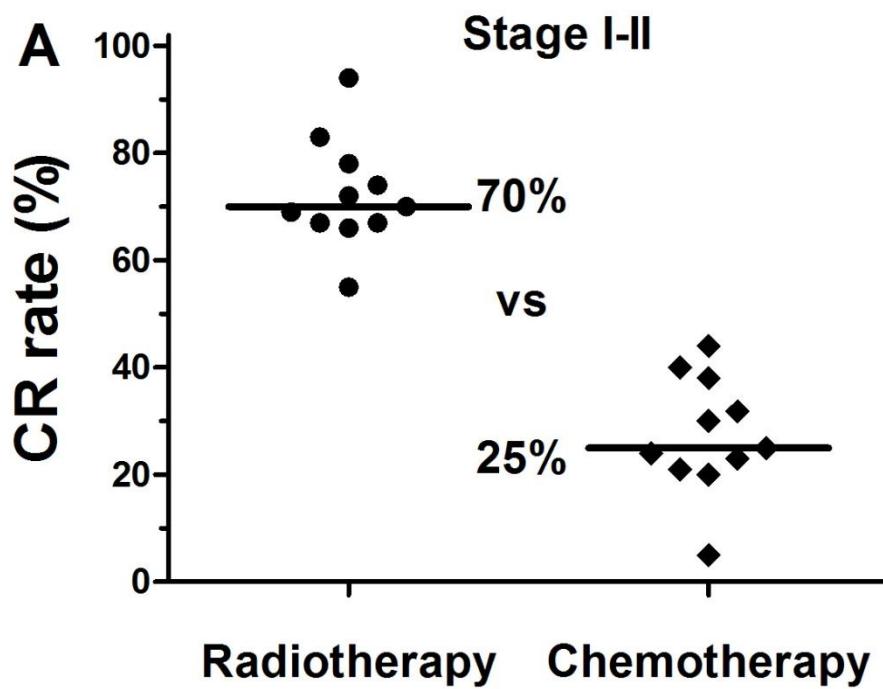
# High OS with Radiotherapy Alone for Early Stage NKCL

5-year OS: 50-84%, except two studies (about 40%)

Author	Time	No. of RT	Nasal Cavity (%)	Stage	5-year OS (%)	No
Li CC	2004	11	43 (56)	I-II	50	
You	2004	6	46 (100)	I-II	83.3	<10 cases
Kim	2005	33	29 (55)	I-II	76	
Ma	2010	23	64 (100)	I-II	57.9	
Li YX	2006	31	105 (100)	I-II	66	
Aikemu	2008	15	57 (100)	I-II	57.1	
Li YX	2011	87	80 (92)	I	80, PFS 69	LCR 93%
Li YX	2012	96	214 (100)	I-II	70, PFS 65	LCR 88%
Yang	2015	253	UADT (99)	I-II	69.6	LCR 90%
Kim	2001	104	74 (52)	I-II	35	Small field, low dose
Isobe	2005	17	28 (80)	I-II	43.8	
676				35 — 84%		

# Comparison of RT and Chemotherapy

Radiotherapy shows much higher initial response and long-term survival than chemotherapy



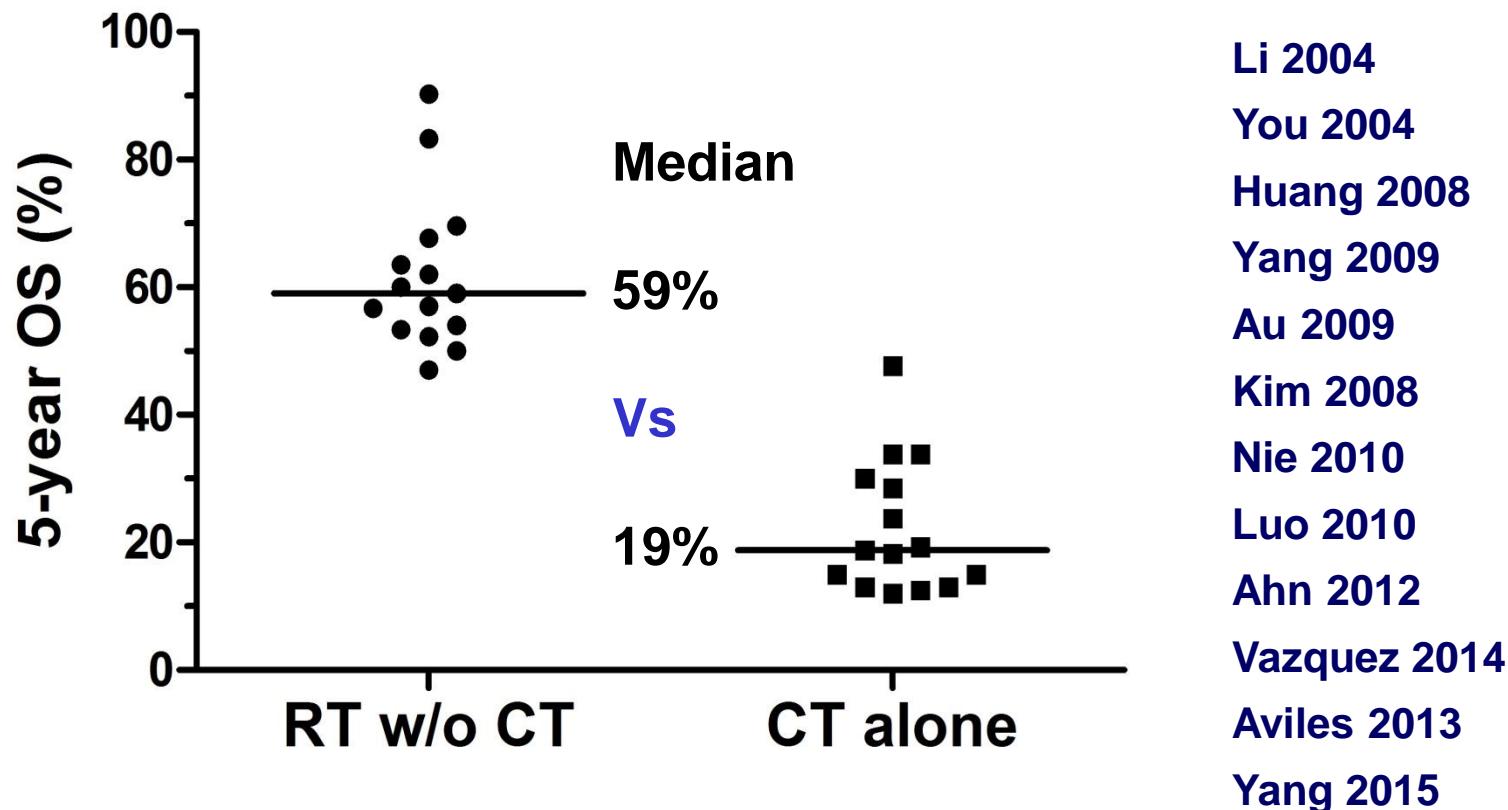
# Radiotherapy is Superior to Chemotherapy

**OS, RT: 50-83%, CT: 12-32%; Difference in OS ≥30%**

Author	Year	No	Primary in Nose, No (%)	Stage	Treatment	5-year OS (%)	P
Li CC et al	2004	56*	43 (56)	I-II	RT alone: 11 RT → CT: 27 CT alone: 18	50 59 15	0.01
You et al	2004	46	46 (100)	I-II	RT alone: 6 CT ± RT: 40	83.3 28.5	0.027
Yang et al	2009	177	143 (81) UADT	I-II	RT ± CT: 140 CT alone: 37	53.4 18.3	<0.01
Huang	2008	82	66 (80)	I-II	RT±CT: 74 CT: 8	62 (3) 12.5	0.000
Au et al	2009	57	UADT	I-II	RT+CT: 34 CT: 23	~58 ~29	0.045
Nie DH	2010	85	Nasal cavity (100)	I-II	RT ± CT: 17 CT + RT: 48 CT alone: 20	54 47 13	0.03 0.049
Lu	2010	60	Nasal cavity (100)	I-II	RT + CT: 37 CT alone: 16	56.7 18.8	<0.05
Vazquez (SEER, USA)	2014	188	Nasal Cavity: 123  Extra Nasal Cavity: 65	I	RT: NA CT alone: NA  RT: NA CT alone: NA	63.5 47.7  52.3 23.8	<0.05  <0.005
Yang	2015	1273	All sites	I-II	RT alone: 253 RT ± CT: 1103 CT alone: 170	69.6 67.7 33.9	<0.001 <0.001
Ahn	2012	20	Skin	I	RT± CT: 10 CT alone: 10	60 (about) 12 (m, Median)	<0.005

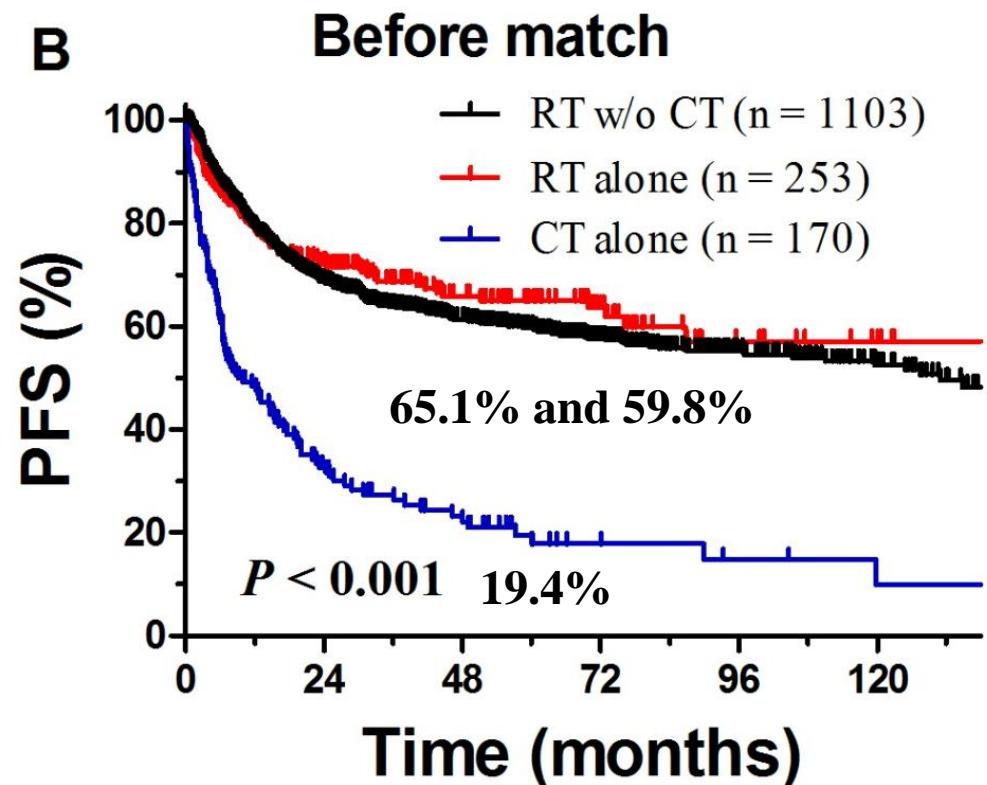
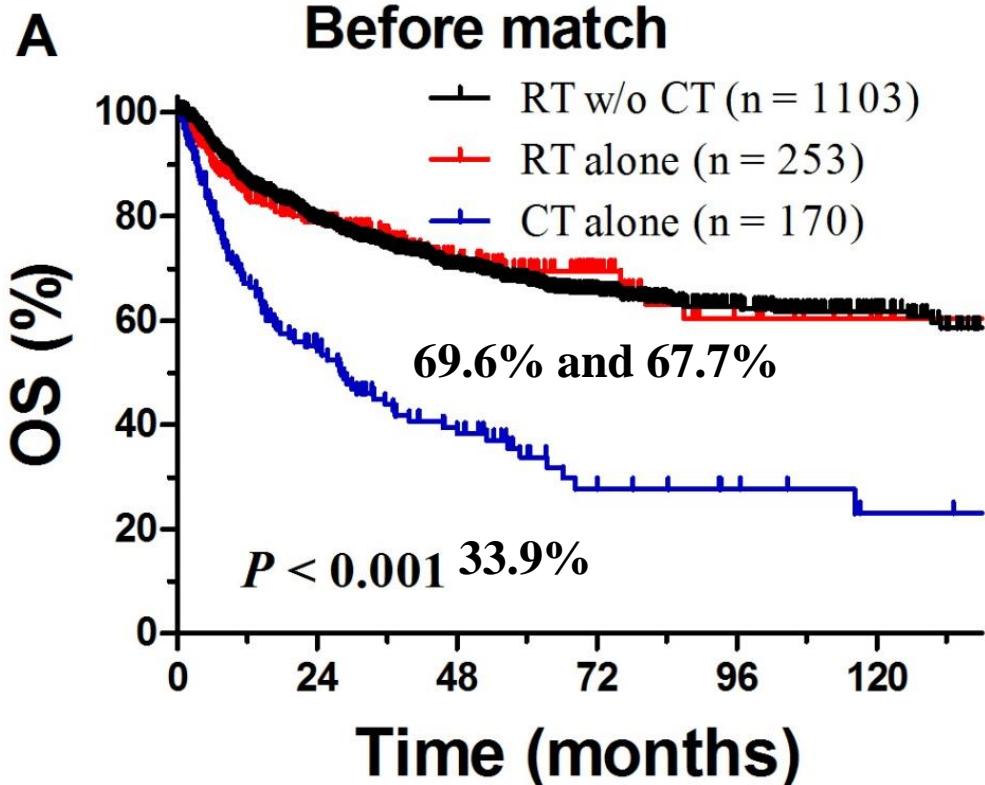
# Radiotherapy is Superior to Chemotherapy in Early Stage NK/TCL in Retrospective Studies

OS, RT: 47-90%, CT: 12-47.7%; Difference in OS $\geq$ 30%



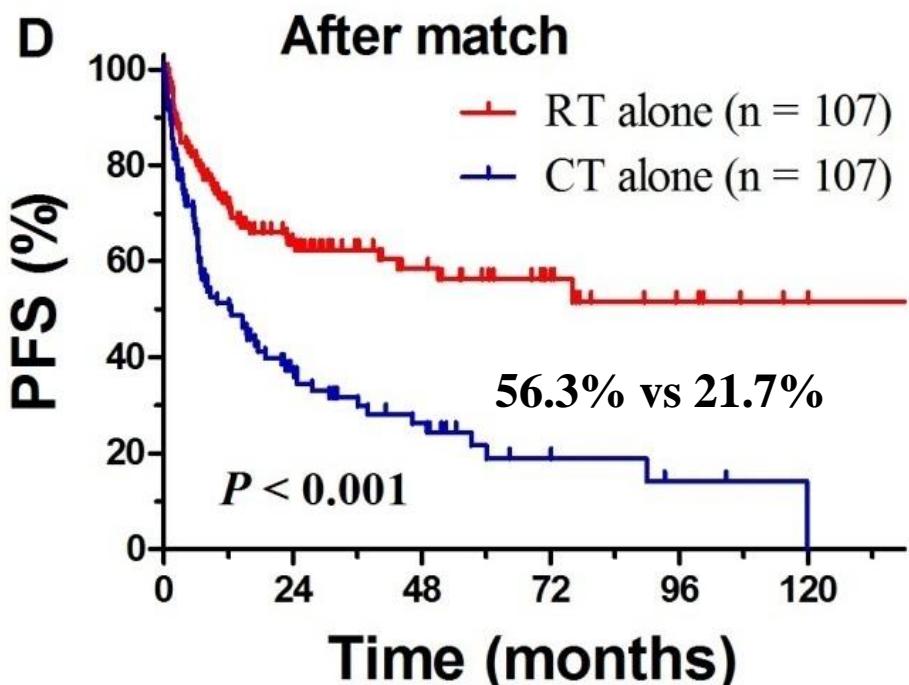
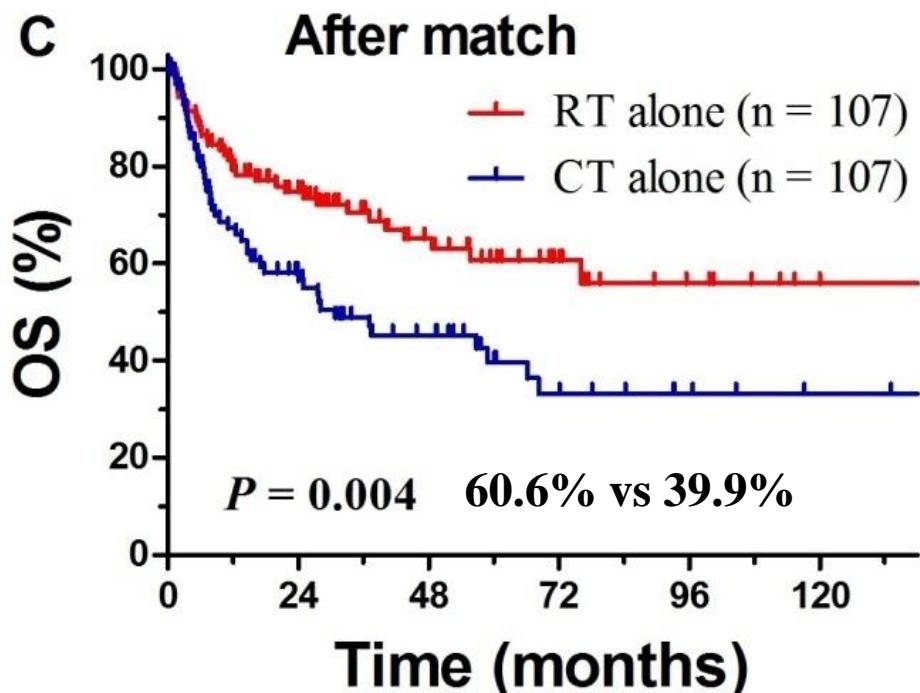
# RT vs Chemotherapy Alone in Early-Stage NKTCL from Multicenter Study

## Before PSM Analysis



# RT Alone vs Chemotherapy Alone in Early-Stage NKCL from Multicenter Study

After Propensity Score Matched (PSM) Analysis  
Comparable clinical features between groups



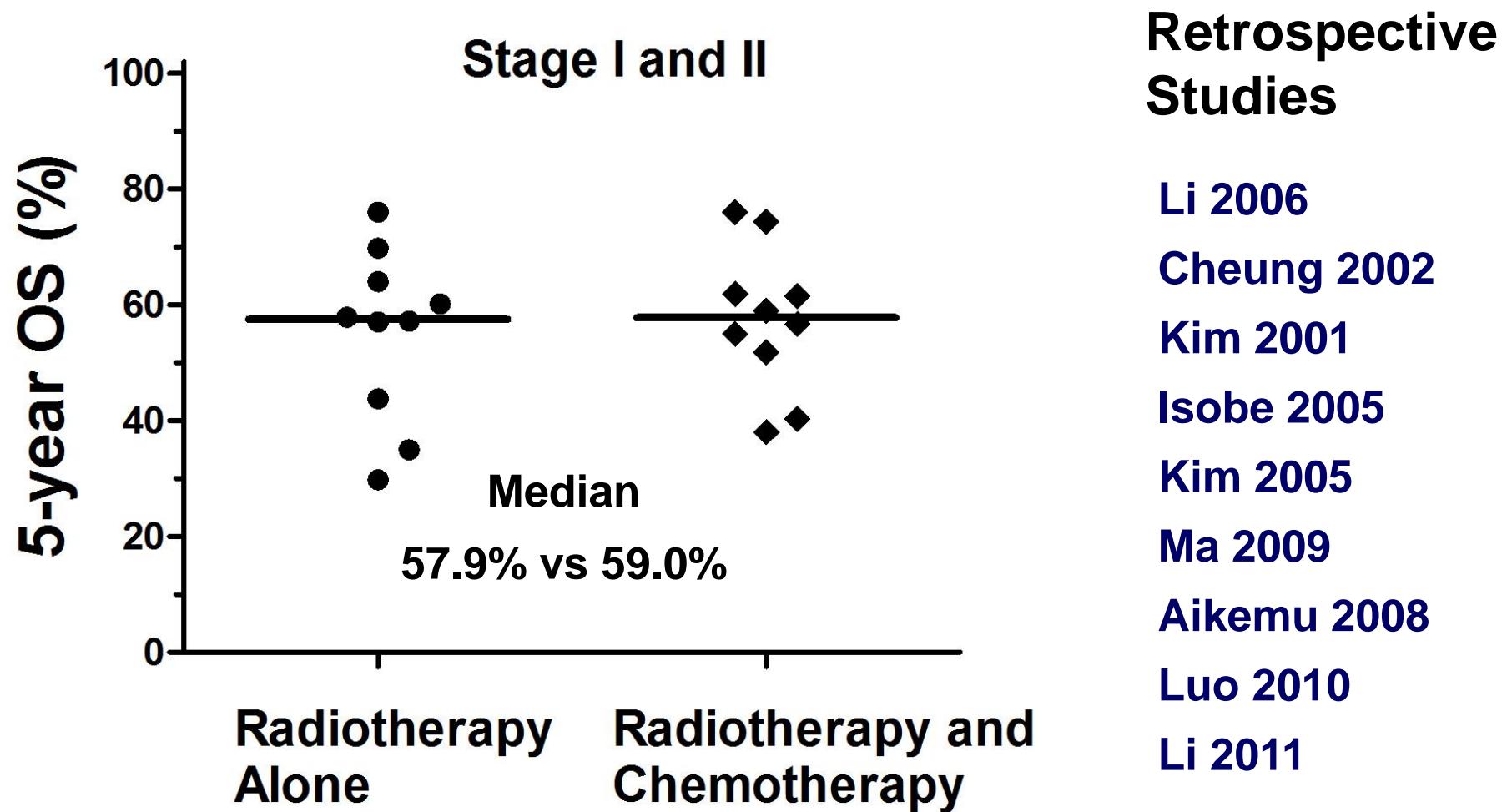
Yong Y, et al. Blood, 126:1424-32, 2015

# Adjuvant Chemotherapy for Early-Stage NK/TCL

**Radiotherapy can cure the majority of early-stage disease (70%), and chemotherapy play an adjuvant role in the treatment of early-stage disease**

- ◆ Adding chemotherapy to radiotherapy did not provide benefit in most studies
  - CMT and RT alone resulted in similar OS
  - RT alone achieved similar outcome for low-risk group
- ◆ Adding chemotherapy to radiotherapy improved OS for high-risk early stage NK/TCL
  - RT consolidated by chemotherapy proved the most effective therapy for high-risk group

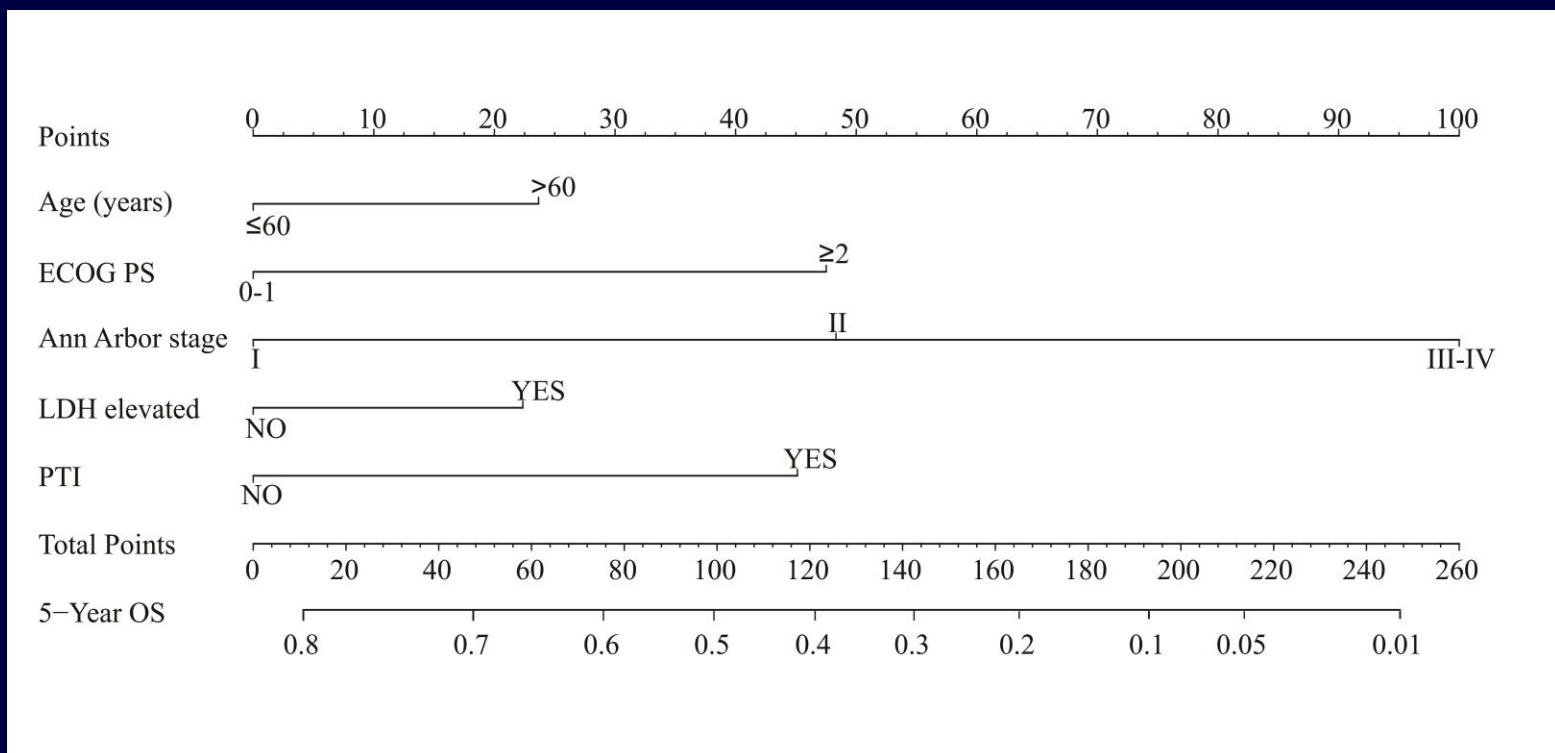
# No Survival Benefit of Adding Chemotherapy to Radiotherapy in Early-Stage NK/TCL



# Independent Prognostic Factors for NKTC

Nomogram individually predicts OS: 1383 patients from multicenter study

- ◆ Age
- ◆ ECOG PS
- ◆ Stage
- ◆ LDH
- ◆ PTI

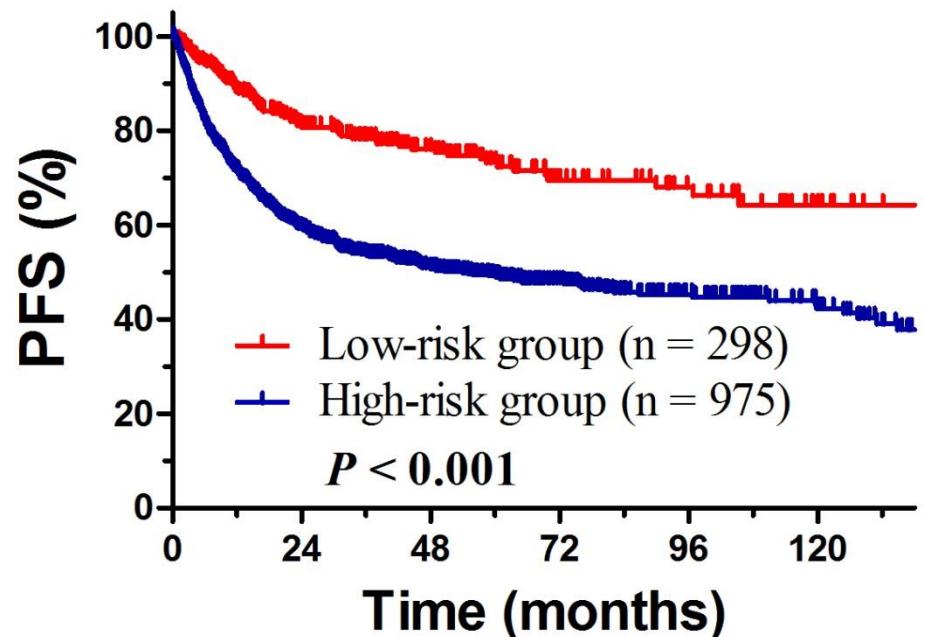
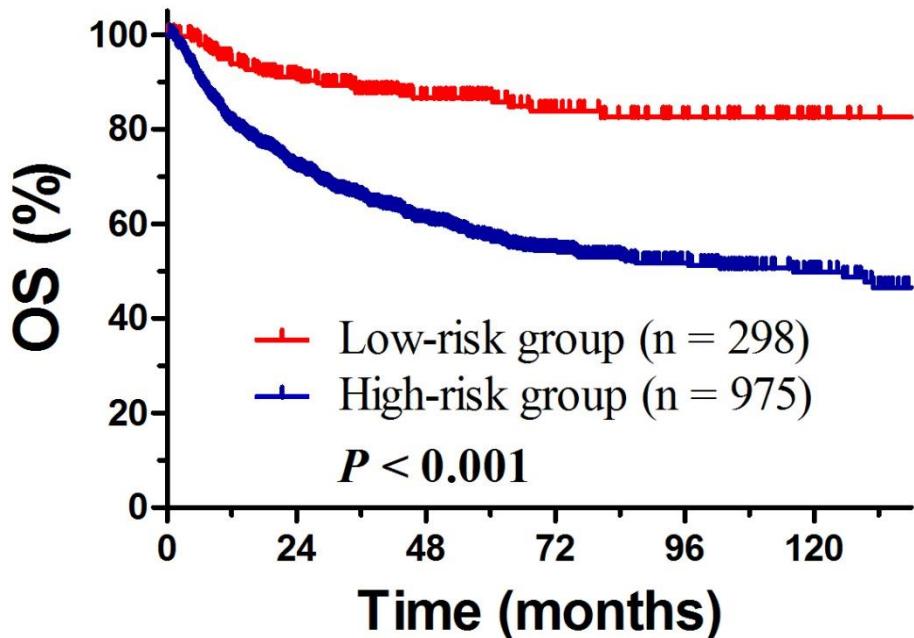


# Low-Risk and High-Risk Early-Stage NKTCL

--Multicenter Study

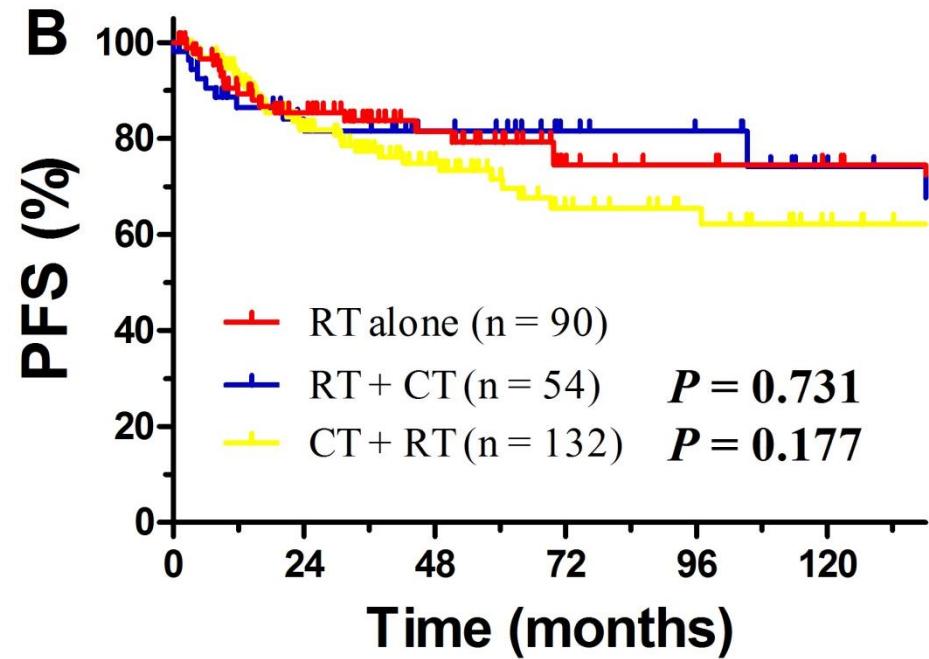
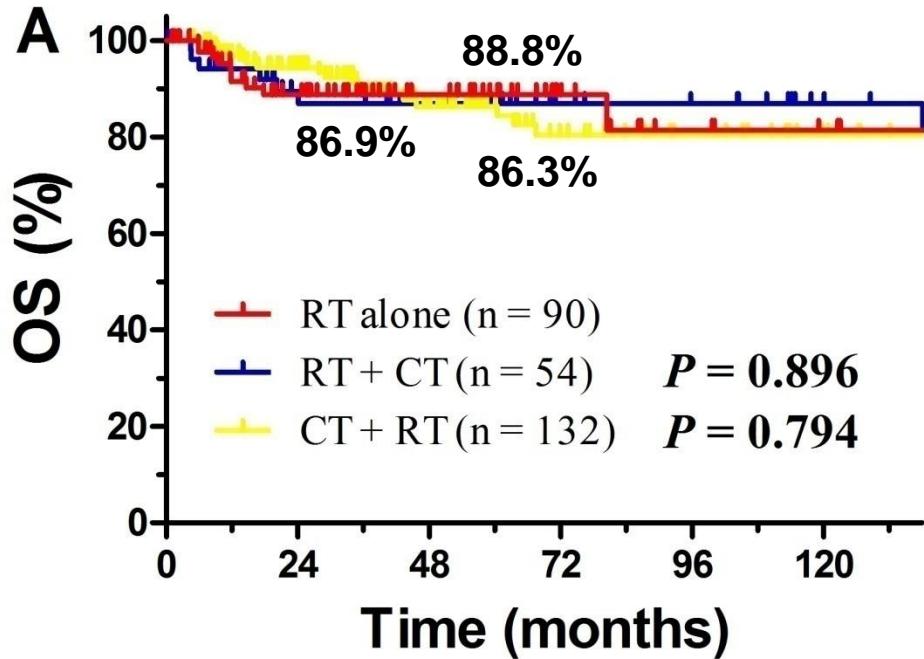
**Low-Risk: No risk factor; High-Risk: Any risk factor**

**Risk factor: Age >60, Elevated LDH, II, ECOG $\geq$ 2, PTI**



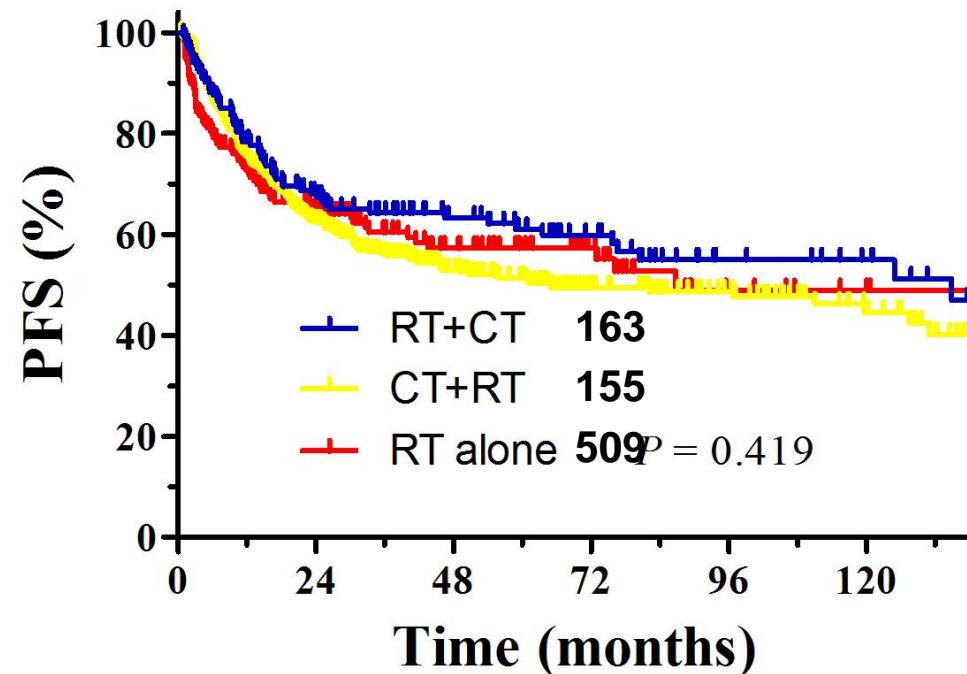
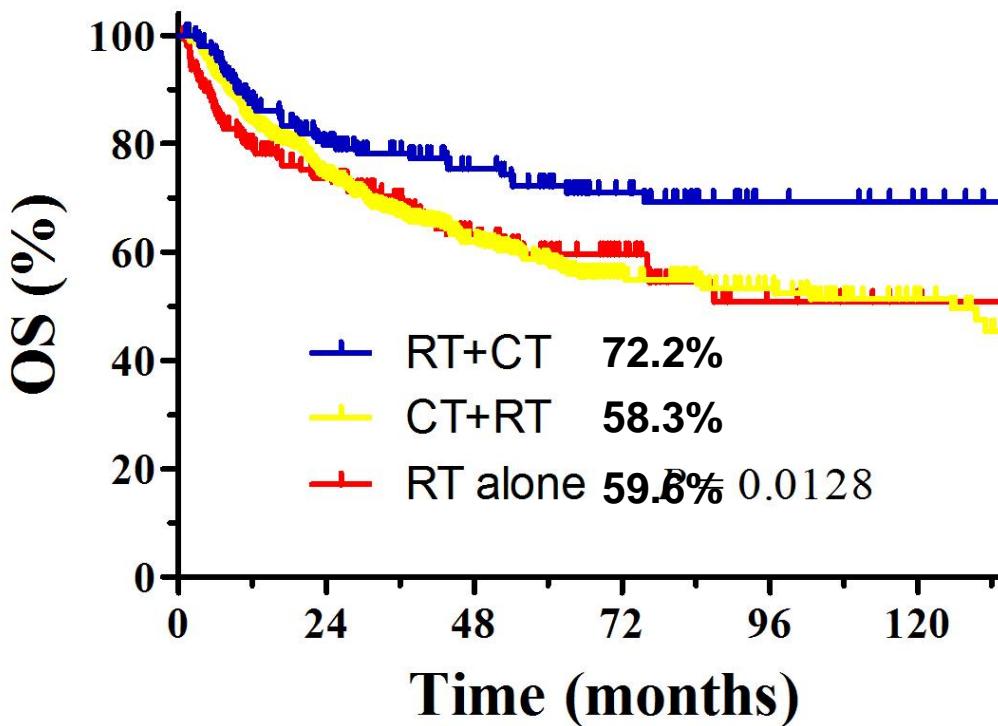
# RT alone Achieved Favorable Outcome in Low-Risk Early-stage NKTCL

Multicenter study in China



# RT followed by Chemotherapy is Most Effective Therapy in High-Risk Early-Stage NKTCL

Optimal Sequence: RT consolidated by chemotherapy provided better OS than RT alone or Chemotherapy followed by RT

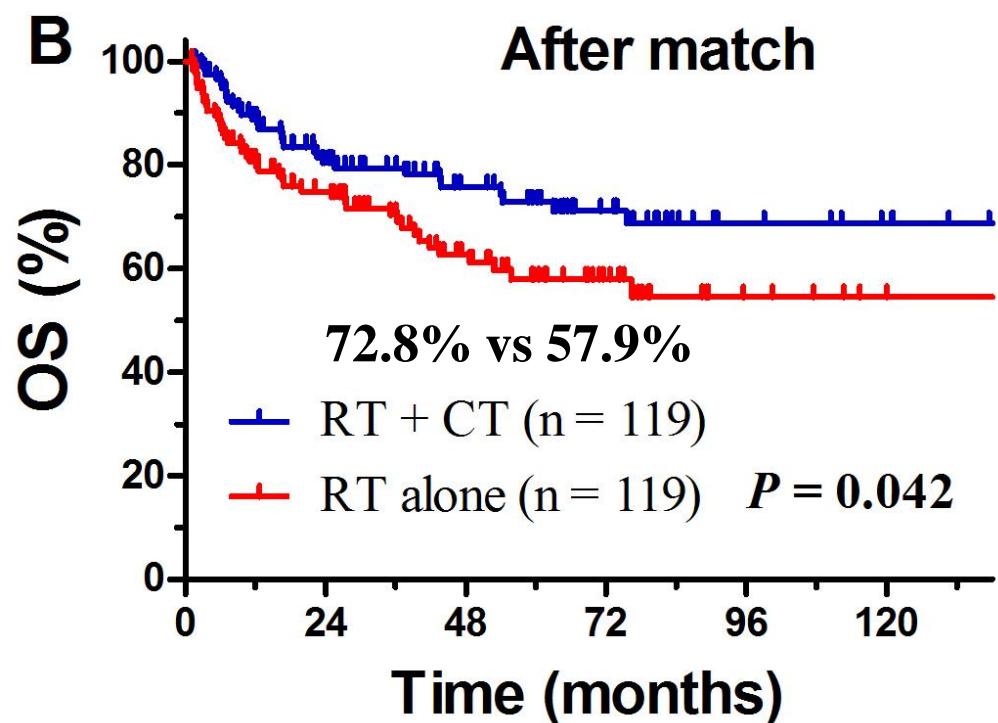
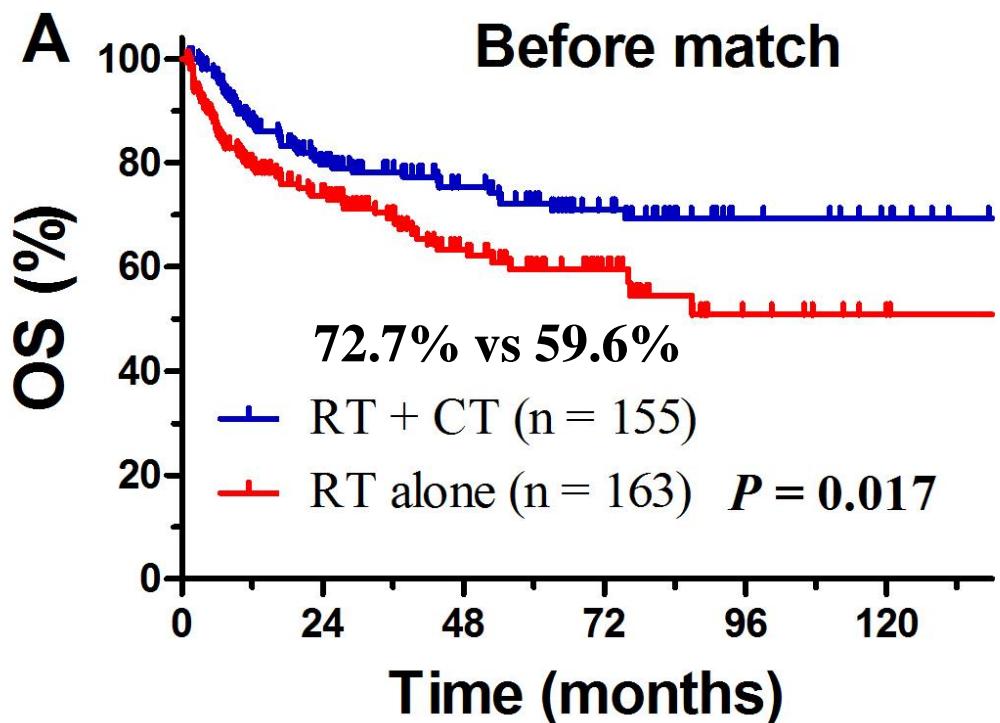


Multicenter study in China

Yong Y, et al. Blood, 126:1424-32, 2015

# RT followed by Chemotherapy is Better Than RT Alone in High-Risk Early-Stage NKTCL

## Before and After Propensity Score Matched (PSM) Analysis

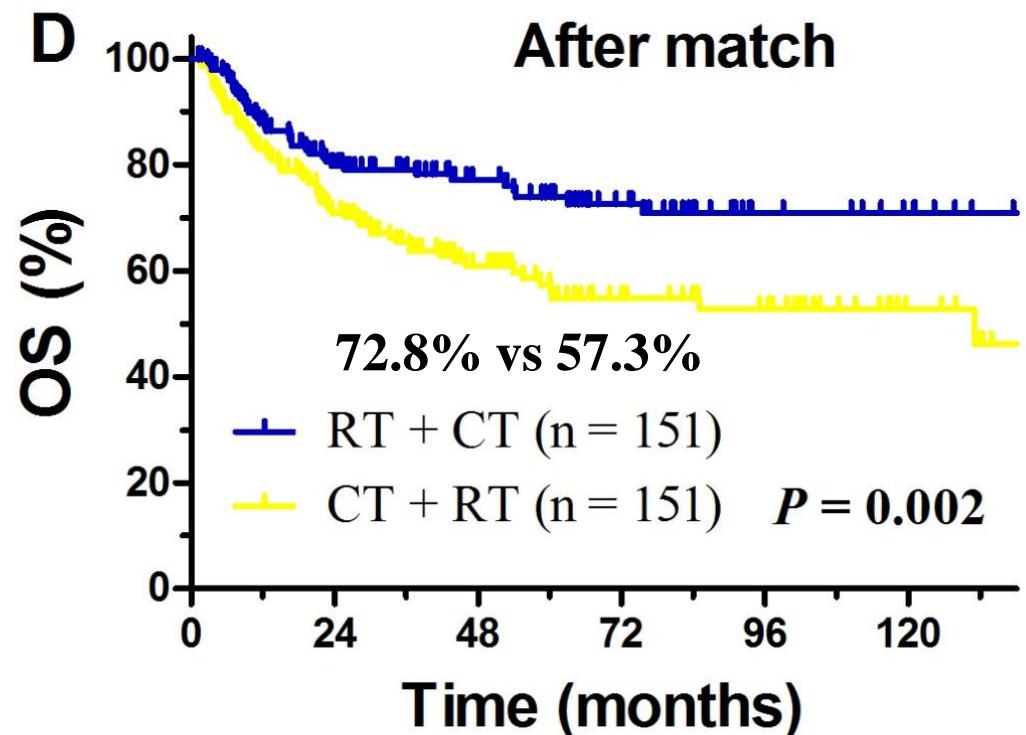
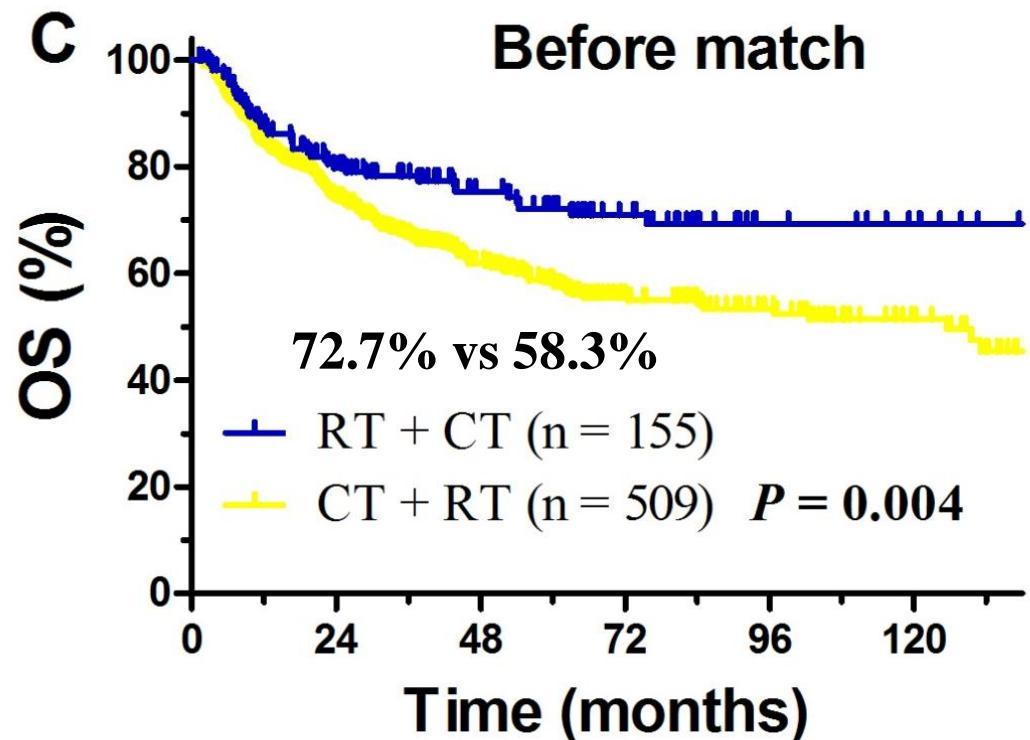


Multicenter study in China

Yong Y, et al. Blood, 126:1424-32, 2015

# RT followed by Chemotherapy is Better Than CT Followed by RT in High-Risk Group

Before and After Propensity Score Matched (PSM) Analysis

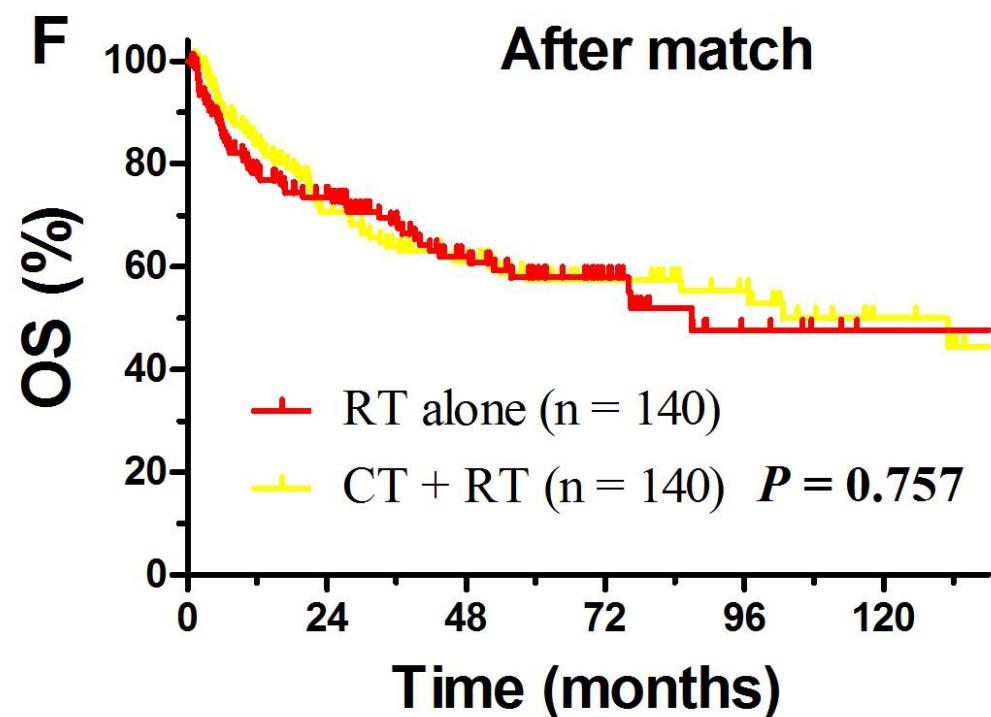
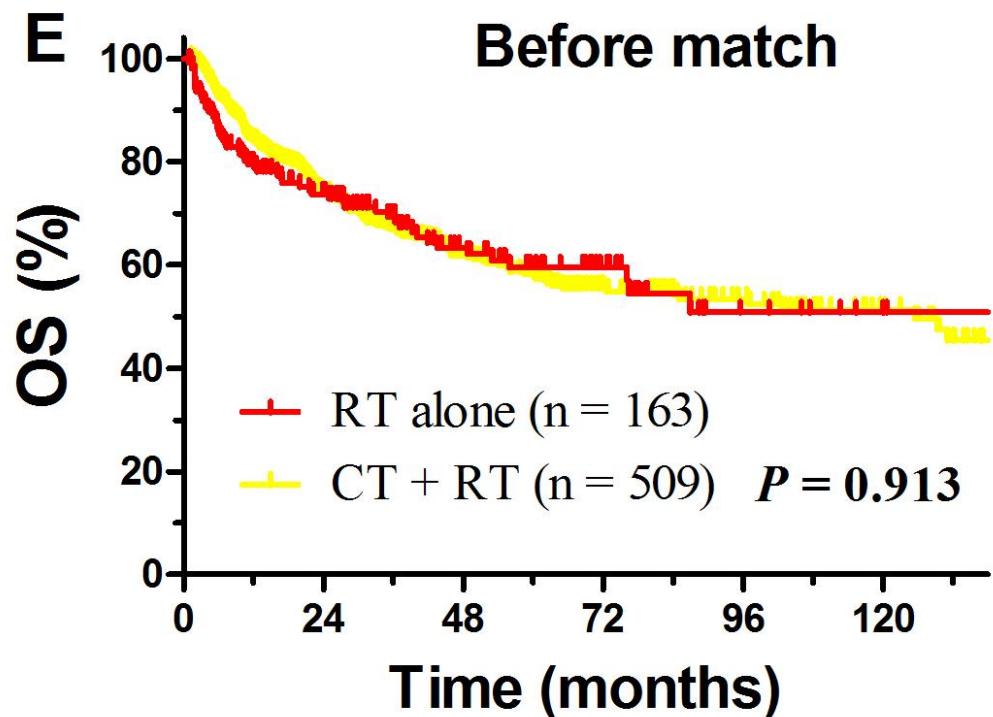


Multicenter study in China

Yong Y, et al. Blood, 126:1424-32, 2015

# RT Alone is Comparable to CT Followed by RT in High-Risk Group

Before and After Propensity Score Matched (PSM) Analysis



Multicenter study in China

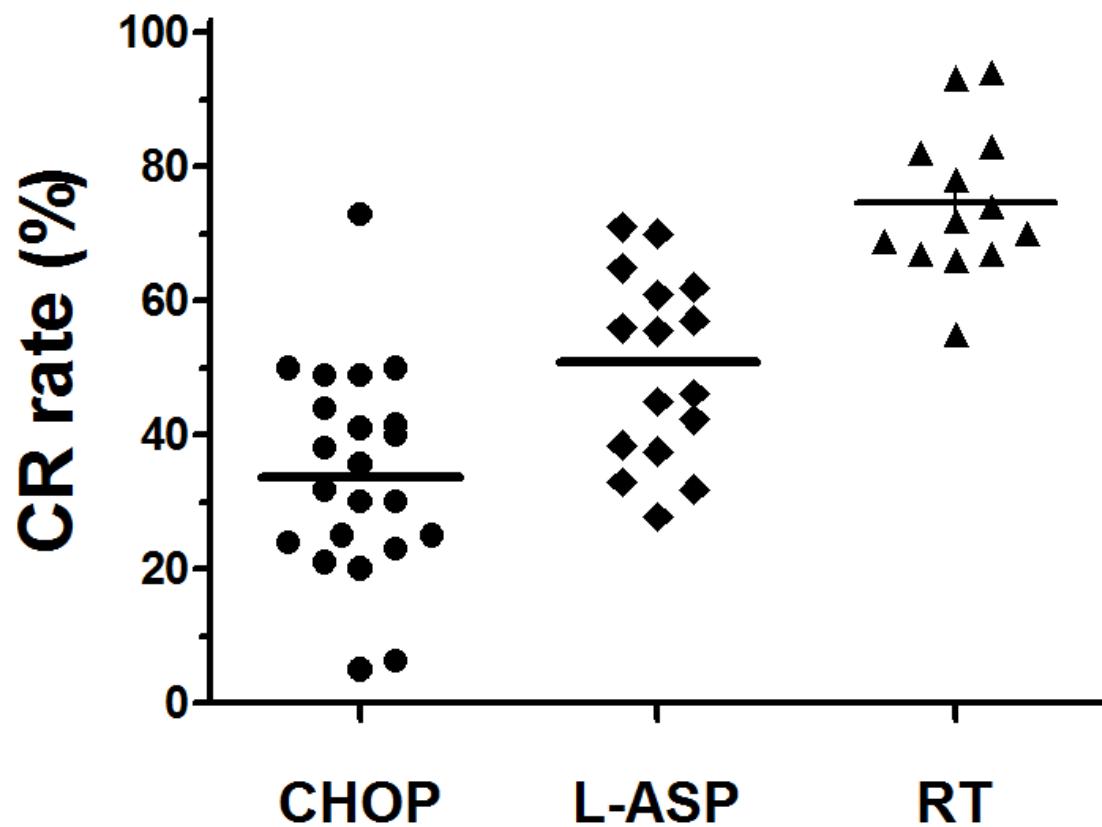
Yong Y, et al. Blood, 126:1424-32, 2015

# Optimal Chemotherapy Regimens

- ◆ **Consensus: asparaginase or gemcitabine**
  - Standard regimens: No (no phase III trial)
- ◆ **Role of new regimen chemotherapy**
  - Improve initial response
  - Very low survival for advanced stage disease
  - limited role when adding to RT in early stage disease

# Comparison of Initial Response

Median:	33.7%	50.9%	72.0%
Mean:	34.2%	50.0%	74.7%



**CR rate of L-asparaginase based regimens is higher than doxorubicin-based regimen, but lower than radiotherapy**

# Novel chemotherapy for advanced stage NK/TCL

—Median OS 5-36 m, PFS 5-15 m, short follow-up

Author	No.	Eligibility	Stage	Chemotherapy		CR (%)		5-y OS (%)	5-y PFS (%)
				regimens	RT	CT (%)	CT+RT		
Kim 2015	70	New diagn.	III 4, IV 66	L-IMEP: 22	0	65	—	36.6 m	10.1 m
				IMEP: 48		21.7	—		
Ji 2014	21	New diag.	II 1, III/IV 20	GLIDE (HSCT 4)	0	57.1	—	56 (3)	35.8 (3)
Kim 2015	27	New diag.	IV 27	SMILE* (HSCT 11)	0	33	—	10.6 m*	5.1 m
Bi 2015	73	New diag.	III 11, IV 62	L-ASP: 23	17 (27)	31.9	—	38.3 (2)	25.4 (2)
				Non-L-ASP: 46					
Ding 2015	13	Relapse or refractory	III 8, IV 5	MEDA	8 (62)	46.2	61.5	69.2 (1)	61.5 (1)
Wang 2015	18	New diag.	III 3, IV 15	LVDP	18 (100)	<27.8	27.8	33.3 (2)	33.3 (2)
								23.0 m	10.5 m

\*5 patients died of SMILE chemotherapy

# Novel chemotherapy for early and advanced stage NK/TCL

## —L-Asp regimens: 5-year OS 50-67%

Author	No.	Eligibility	Stage	Chemotherapy	RT	CR (%)		5-y OS	5-y PFS
						No.(%)	CT (%)	CT+RT	
Yong 2003	18	refractory	I/II 7, III/IV 11	L-ASP	18 (100)	—	55.6	55.6	NR
Yong 2009	45	Relapse or refractory	I/II 33, III/IV 12	LVD	41 (91)	—	55.6	66.9	NA
Jaccard, 2011	19	Relapse or refractory	I/II 12, III/IV 7	AspaMetDex (HSCT 5)	1 (5)	61	NA	12.2 m	12.2 m
Yamaguchi 2011	38	Relapse or refractory advanced	I/II 11, III/IV 27	SMILE* (HSCT 21)	NR	45	NA	55 (1)	53 (1)
Kwong 2012	87	New diag 43 Relap/refr44	I/II 38, III/IV 49	SMILE (HSCT 24)	19 (22)	56	66	50*	64
Lin 2013	38	New diag	I/II 31, III/IV 7	CHOP-L	31 (82)	71.1	81.6	80.1 (2)	81 (2)
Guo 2014	55	New diag	I/II 45, III/IV 10	GOLD	45 (82)	62	—	74 (3)	57 (3)
Zhou 2014	17	Relapse or refractory	I/II 8, III/IV 9	DDGP	4 (24)	38.5	52.9	82.4 (1)	64.7 (1)
Wang 2015	98	New diag	I/II 77, III/IV 21	GELOX, P-GEMOX	77 (79)	—	64	65.3 (3)	57.0 (3)

\*5 patients died of SMILE chemotherapy

# Concurrent Chemoradiotherapy for early stage NK/TCL

—New regimens: 2-5 year OS 60-88%, PFS 40-90%

Author	Time	No.	Location	Stage	Regimens	RT (Gy)	CR (%)	OS (%)	PFS (%)
Yamaguchi	2009	33	Nose	I-II	DeVIC	EF中位50	81	73 (5)	67
Kim (Korea)	2009	30	Nose	I-II	VIDP	中位40	80	86 (3)	85
Tsai	2014	33	UADT	I-II	DEP-CRT, VIDP	50.4	63	66 (5)	60
Ke	2014	32	UADT	I-II	GDP	IMRT中位 56	84.4	87.5 (3)	84.4
Lee (Korea)	2014	27	UADT	I-II	VIDP or SMILE	44-54	70	59 (3)	41
Kim (Korea)	2014	30	UADT	I-II	VIDL	40-44	87	60 (5)	73
Michot	2015	13	UADT	I-II	ESHAP	44-54	92.3	72 (2)	90
Oh	2015	62	UADT	I-II	VIDP/VIDL/ MIDLE	40	96.5	83.1 (3)	77.1

# Sequential chemoradiotherapy for early stage NKTC

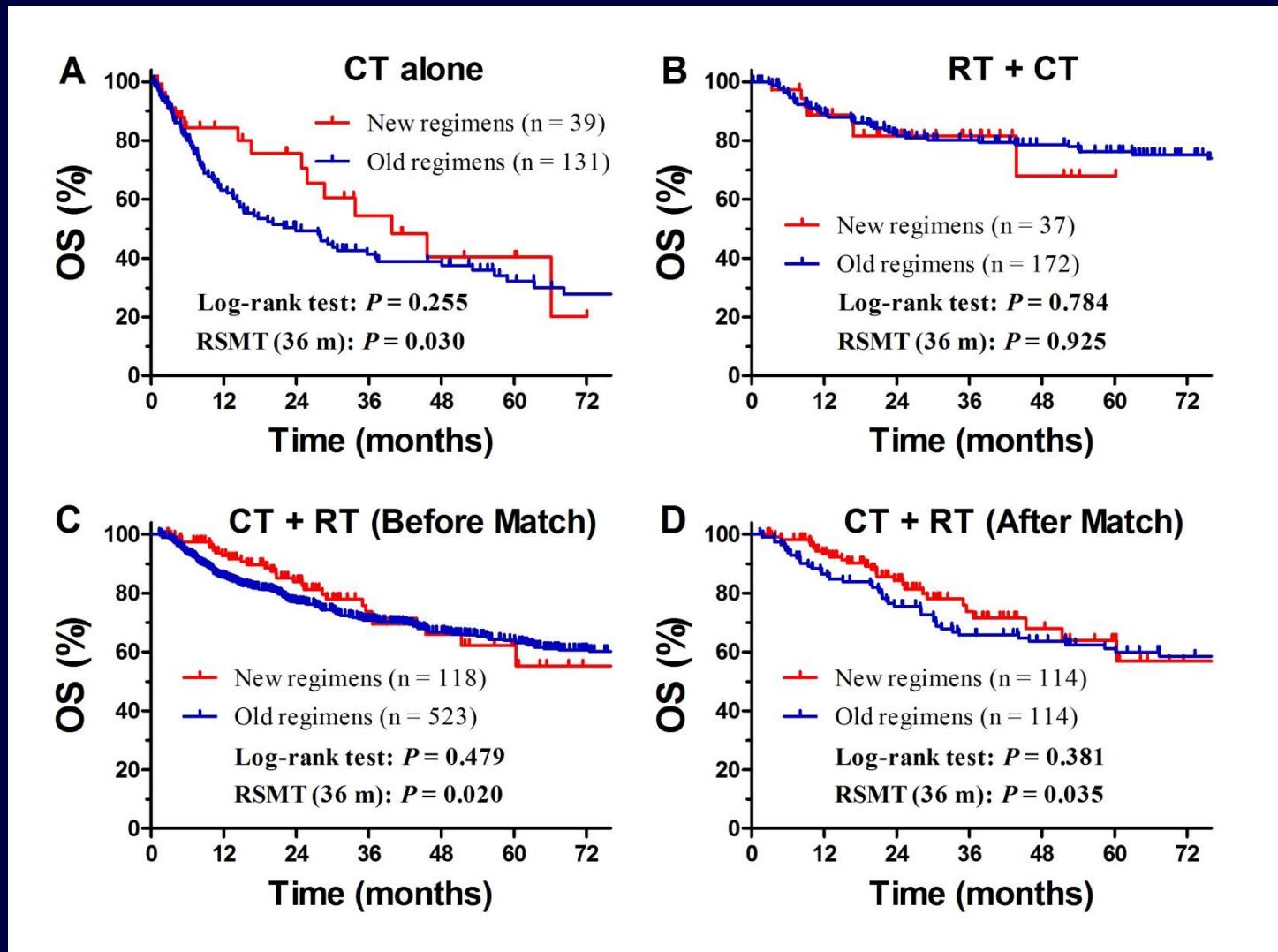
## —Novel regimens, 2-5 years OS 50-89%, PFS 46-80%

Author	Time	No.	Stage	chemo regimen	RT dose (Gy)	CR (%)		OS (%)	PFS (%)
						化疗	CT+RT		
Kim	2014	44	I-II	IMEP/RT		73	78	66 (3)	65
Jiang	2012	26	I-II	LVP/RT	56	42.3	80.8	88.5 (2)	80.6
Wang	2013	27	I-II	GELOX/RT	56	55.6	66.7	86 (2)	86
Liang*	2014	227	I-II	GELOX/RT: 38		68.4	92.6	87 (3)	72
				EPOCH/RT: 54	56	42.6	89.2	54 (3)	50
				CHOP/RT: 135		31.8	80.6	54 (3)	43
Wang*	2015	93	I-II	GELOX/RT: 40	56	70.0	80	78.9 (5)	79.0
				EPOCH/RT: 53	(40-60)	41.5	66	50.4 (5)	46.5
Zang	2015	64	I-II	CHOP-L/SMILE早RT	56	—	80	84.2 (3)	74.3
				CHOP-L/SMILE晚RT		—	50	57.6 (3)	55.9

\*Data from the same institution

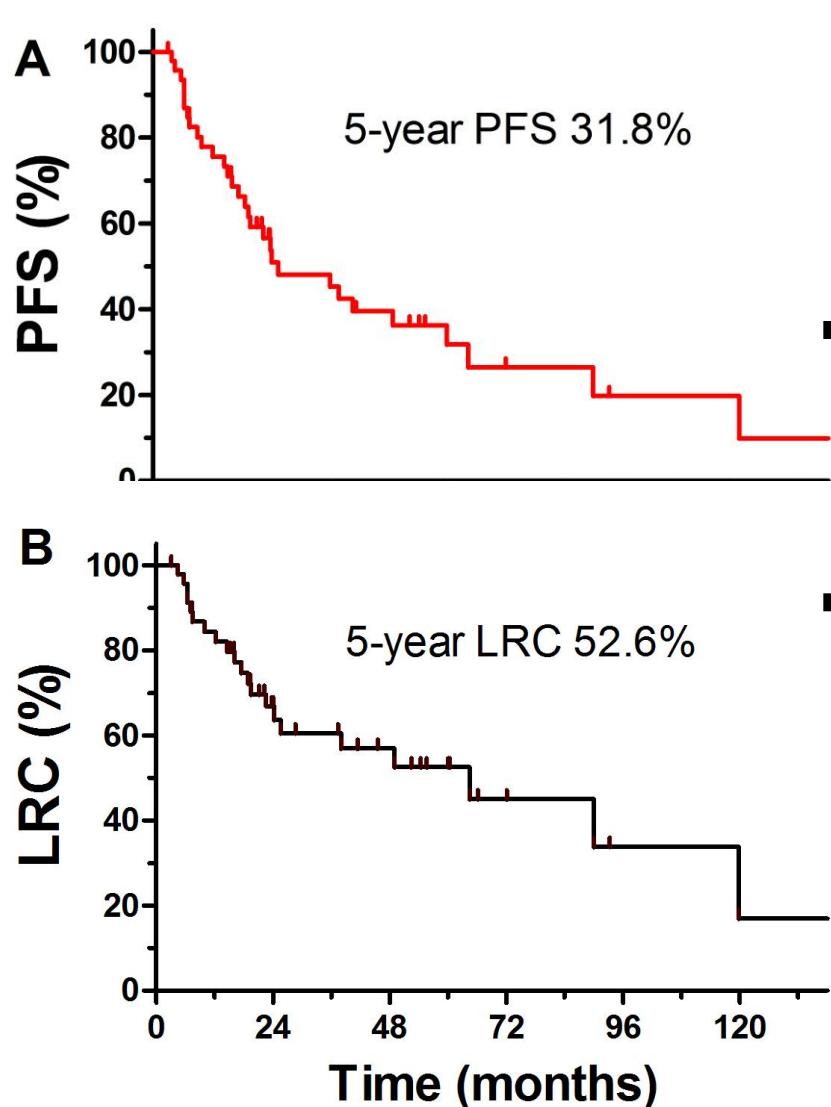
# New Regimen Chemotherapy in Early Stage NK/TCL

## Multicenter study in China



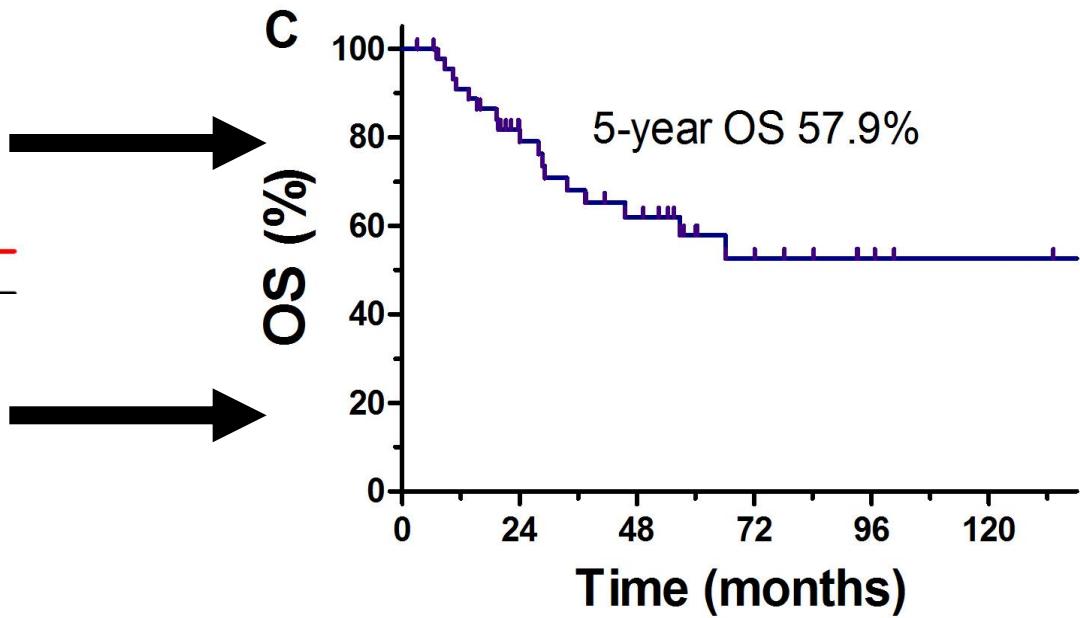
# High Relapse in CR Patients After CT in Localized NKCL

Indicating secondary refractory to chemotherapy



10 pts: L-ASP

37 pts: CHOP



RT can be omitted? No.

Unpublished data from multicenter study

# Optimal RT Field and Dose

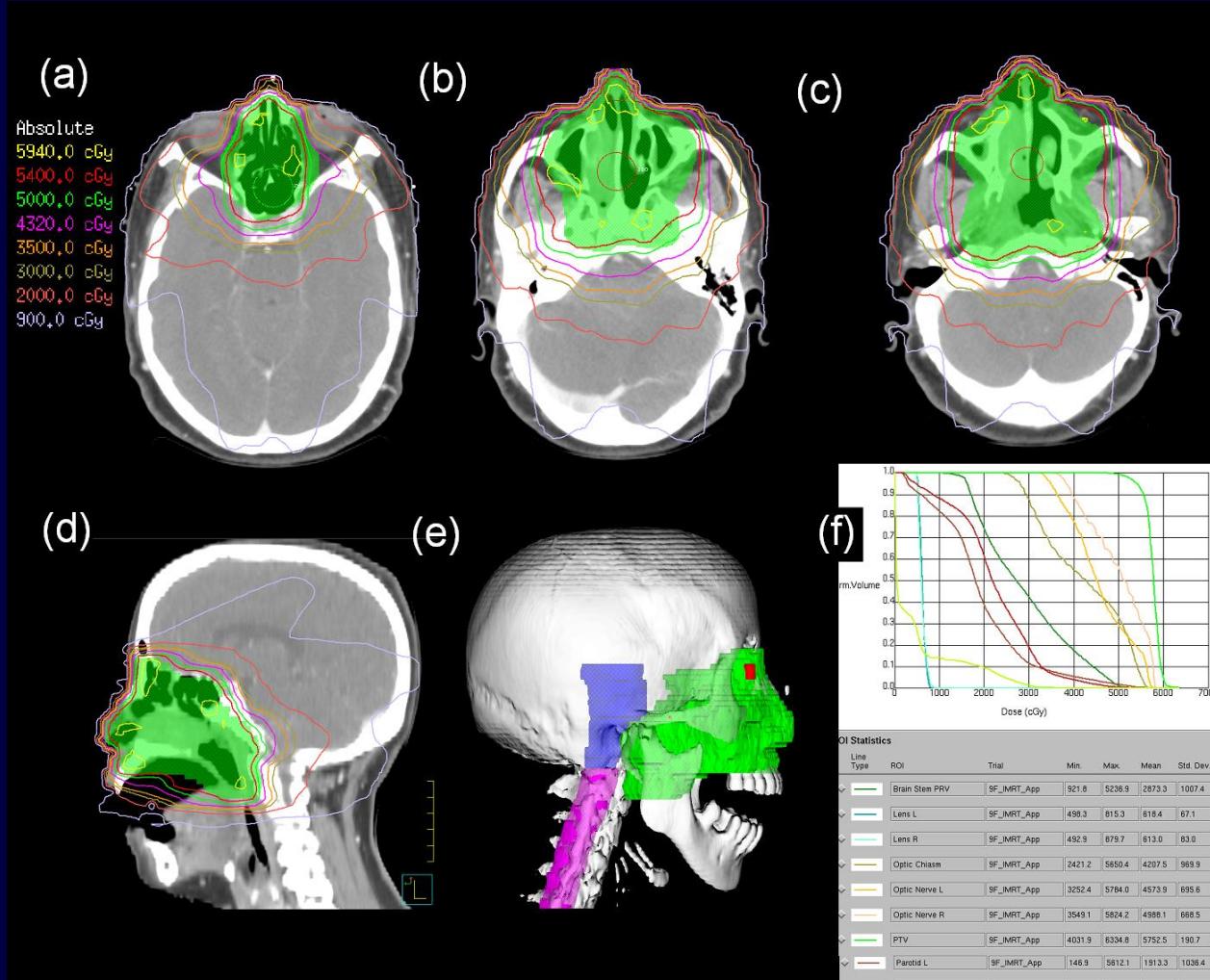
## ◆ RT Field (CTV)

- Extended Involved Field: Nasal Primary
- Extended Field: Extra-nasal UADT

## ◆ RT Dose

- Radical Dose: 50 Gy
- Boost Dose: 5-10 Gy to residual disease

# CTV Definition for Nasal NKCL



Limited stage I

Location of Tumor

Bilateral nasal cavity

nasopharynx

CTV (Extended involved-field)

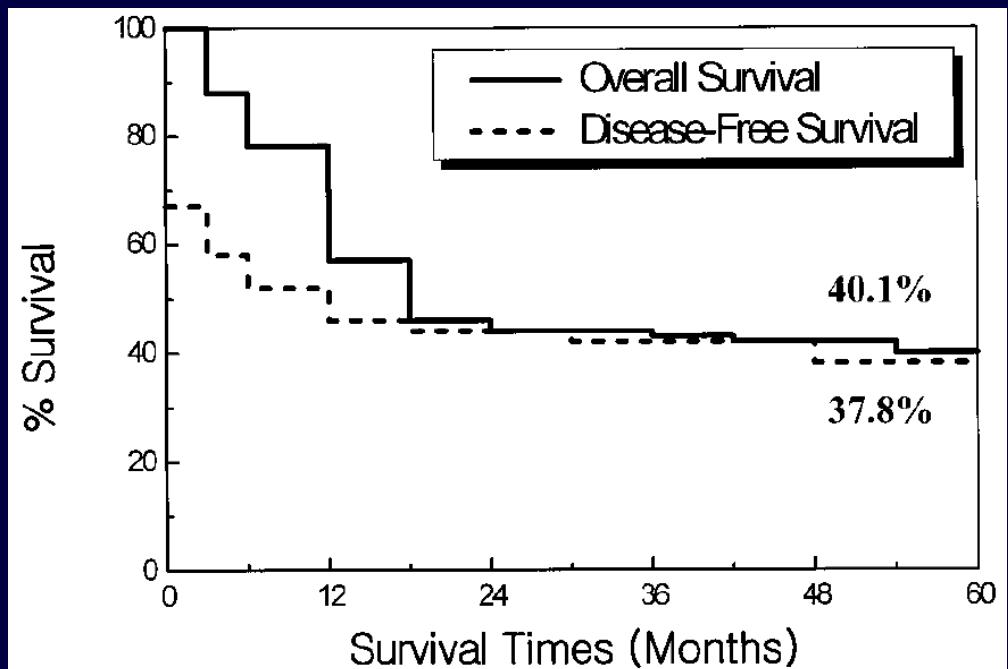
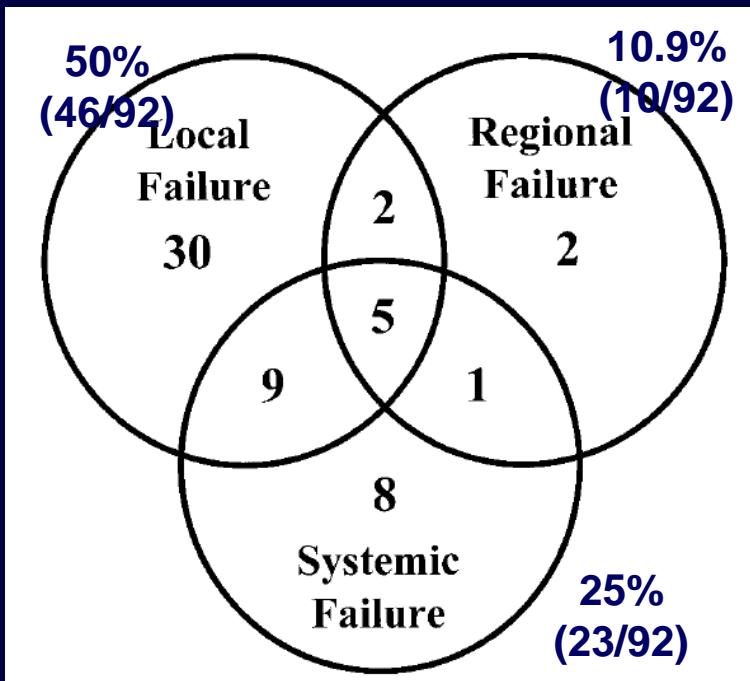
- ◆ Entire nasal cavity
- ◆ Bilateral maxillary sinus
- ◆ Bilateral anterior ethmoid sinus
- ◆ Nasopharynx

Wang H, et al. IJROBP, 2012

Yahalom, et al. IJROBP, 2015

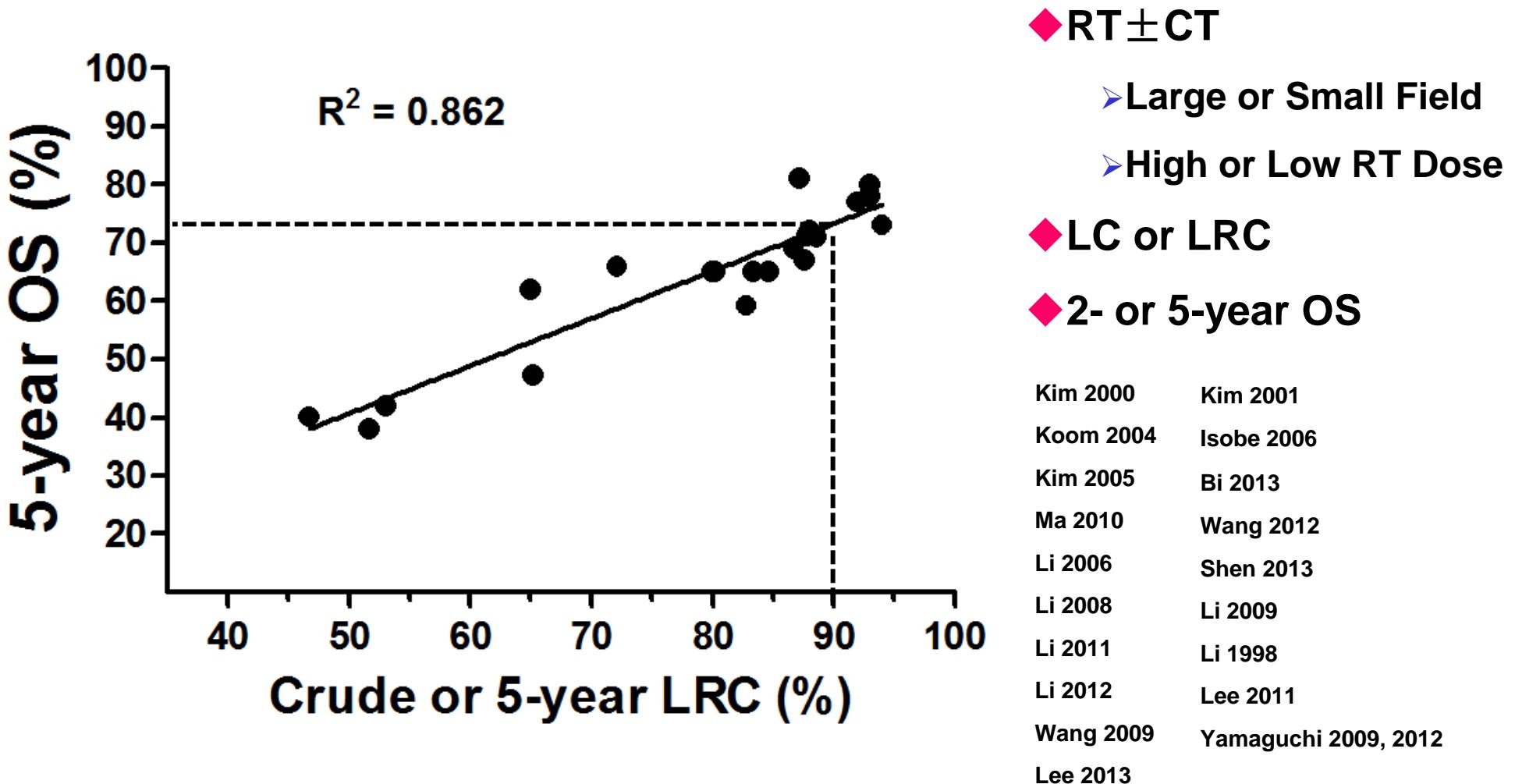
# High Locoregional Failure Associated with Low OS in Early Stage I-II NKTCL Treated with Radiotherapy

- ◆ Median RT dose: 45 Gy
- ◆ RT field: Lesion + Margin



- ◆ 41 patients had local recurrence at or around the primary lesion
- ◆ 5 outside of the radiation field

# Locoregional Control Associated with OS in Early-Stage NKTC Treated with RT



# Why Can RT Cure Early-stage NKTCL

- ◆ Majority (70-90%) of patients presented with early-stage NKTCL
- ◆ Radiotherapy achieved CR: >70%, LRC: 90%, 5-year OS: 60-90%
- ◆ Chemotherapy is adjuvant therapy due to the low efficacy
  - CR: 30-50%, 5-year OS: 30% for early-stage NKTCL
  - Adding chemotherapy to RT improves survival for high-risk group
  - Limited improvement of efficacy with new regimens: Median OS of 24 months for advanced-stage NKTCL without RT
- ◆ Radiotherapy can not be safely omitted in early-stage NKTCL
- ◆ More accurate staging with PET-CT and biomarker are needed

# Treatment suggestion of NK/TCL

**Risk factor: >60 years, II, elevated LDH, ECOG ≥2, PTI\***

Stage	Risk factor	Definition	Treatment	5-year OS
I	No	Low-risk	Radiotherapy alone	85-92%
	≥1	High-risk	Radiotherapy followed by chemotherapy	60-70%
II	any	High-risk	Radiotherapy followed by chemotherapy	60-70%
III-IV	any	Advanced stage	Clinical Trial or primary chemotherapy (RT to primary tumor)	0-30%

\*PTI, primary tumor invasion (any adjacent organs or structures)

Li YX et al. JCO, 24:181, 2006  
LI YX et al. Blood, 2008, 2009

Yang Y, et al. Leukemia, 2015  
Yang Y, et al. Blood, 2015