中国医学科学院肿瘤医院
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Risk-Adapted Therapy in Early-stage Extranodal NK/T-cell Lymphoma

September 2023

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No COIs

Outline

- Brief introduction
- Risk-Adapted Therapy in Non-Antracycline era
- Principles of Radiation Therapy
- Immunotherapy

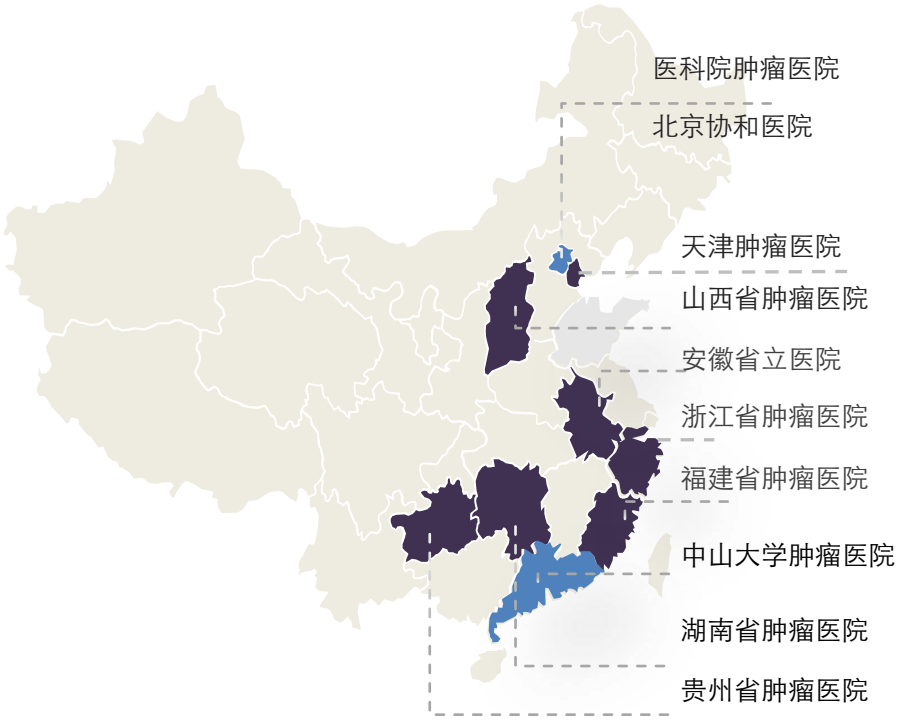
Epidemiological features of Extranodal NK/T-cell lymphoma(ENKTCL)

- Most common subtype of T-/NK- NHL in China
- CD56+/cytoCD3+ malignant NK or T cells
- EBV （Epstein-Barr virus） related
- Predominantly early-staged at diagnosis (~60-80%, stage I-II)
- Originate from nasal cavity in 80% cases

China Lymphoma Collaborative Group (CLCG)-ENKTCL studies

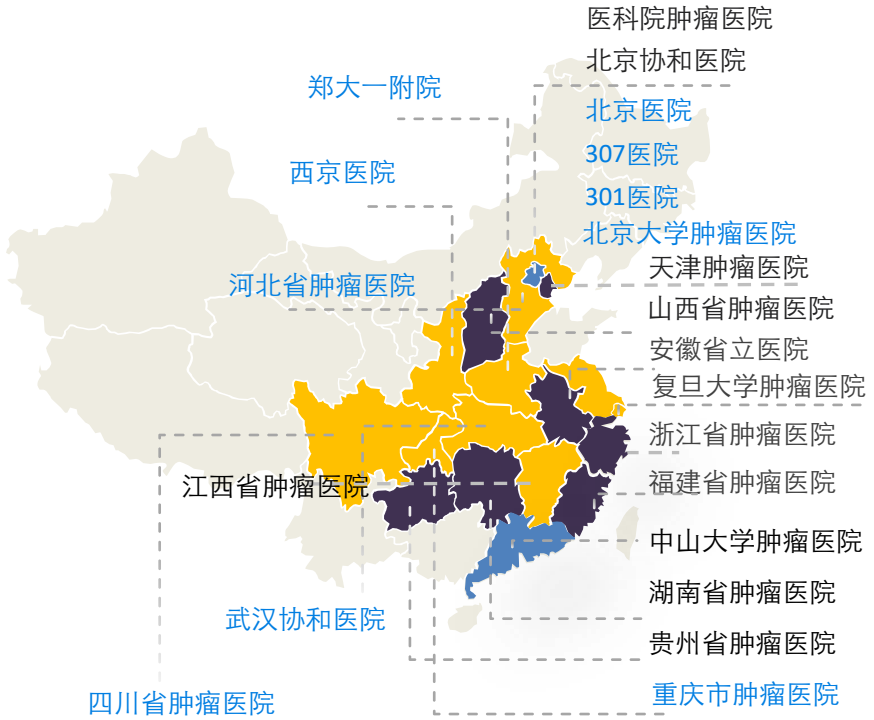
Cohort I （2000-2010） ANT era

N=1383

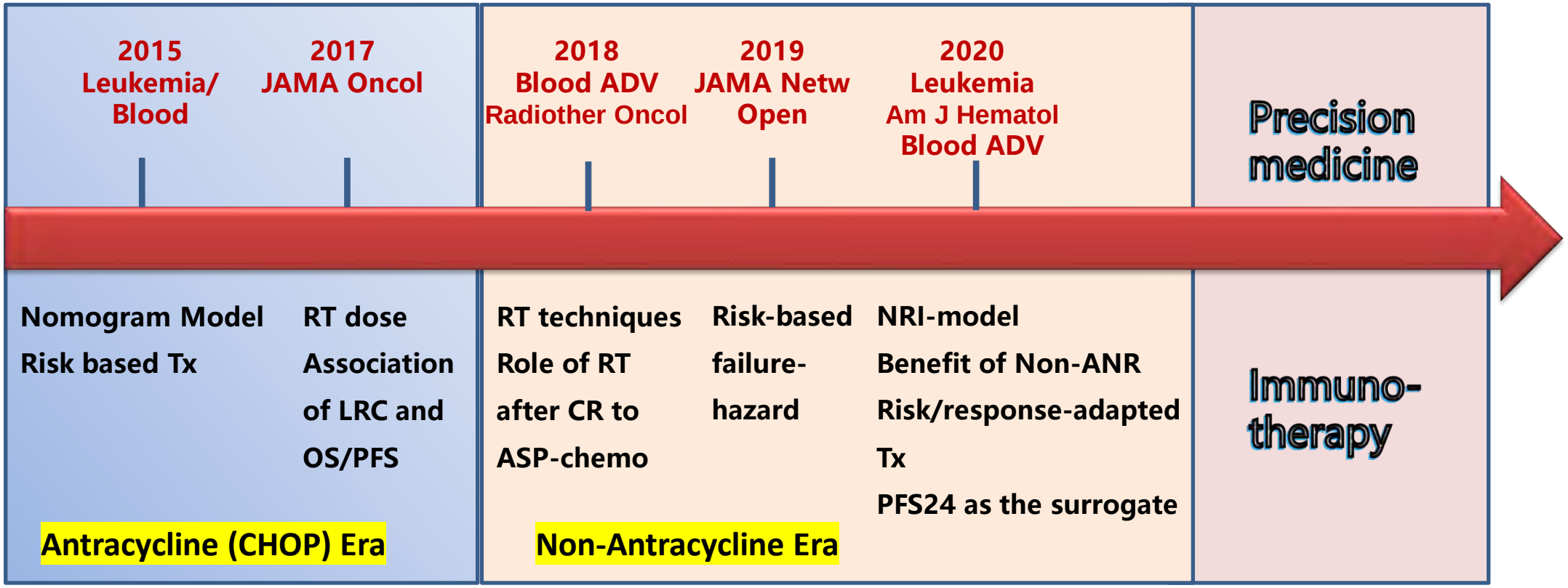


Cohort II （2010-2015） Non-ANT era

N=1663



CLCG multi-center study: Risk-based, response-adapted therapy



Location and heterogeneity of the primary tumor

3 distinct subgroups classified by the anatomic site of origin

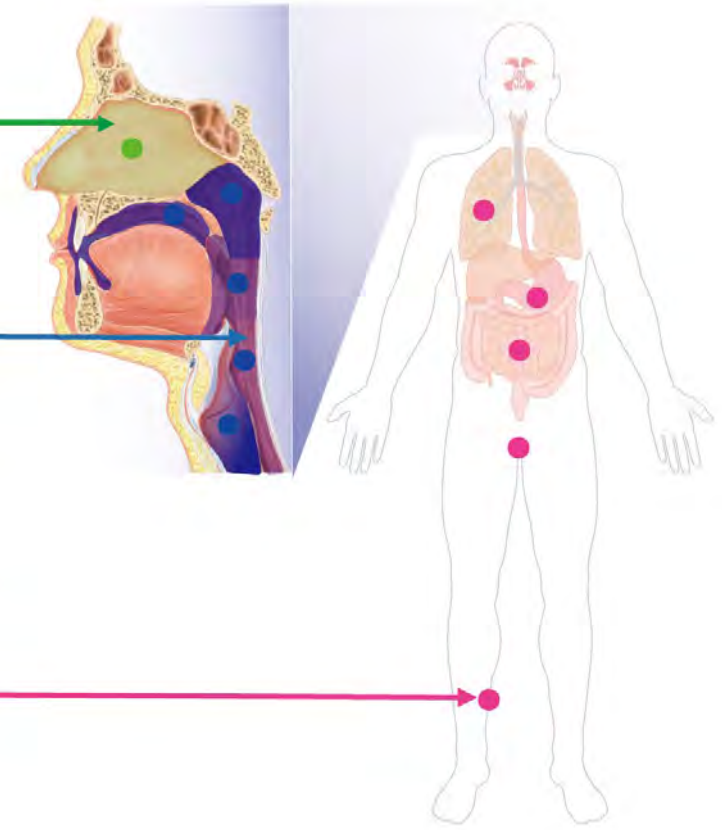
UADT ENKTCL

1 **Nasal-ENKTCL**

2 **Non-nasal-UADT-ENKTCL**
- Nasopharynx
- Oropharynx
- Hypopharynx
- Oral cavity
- Larynx
- Trachea

Extra-UADT ENKTCL

3 **Extra-UADT-ENKTCL**
- Skin and soft tissues
- Gastrointestinal tract
- Lung
- Testis
- Other rare sites

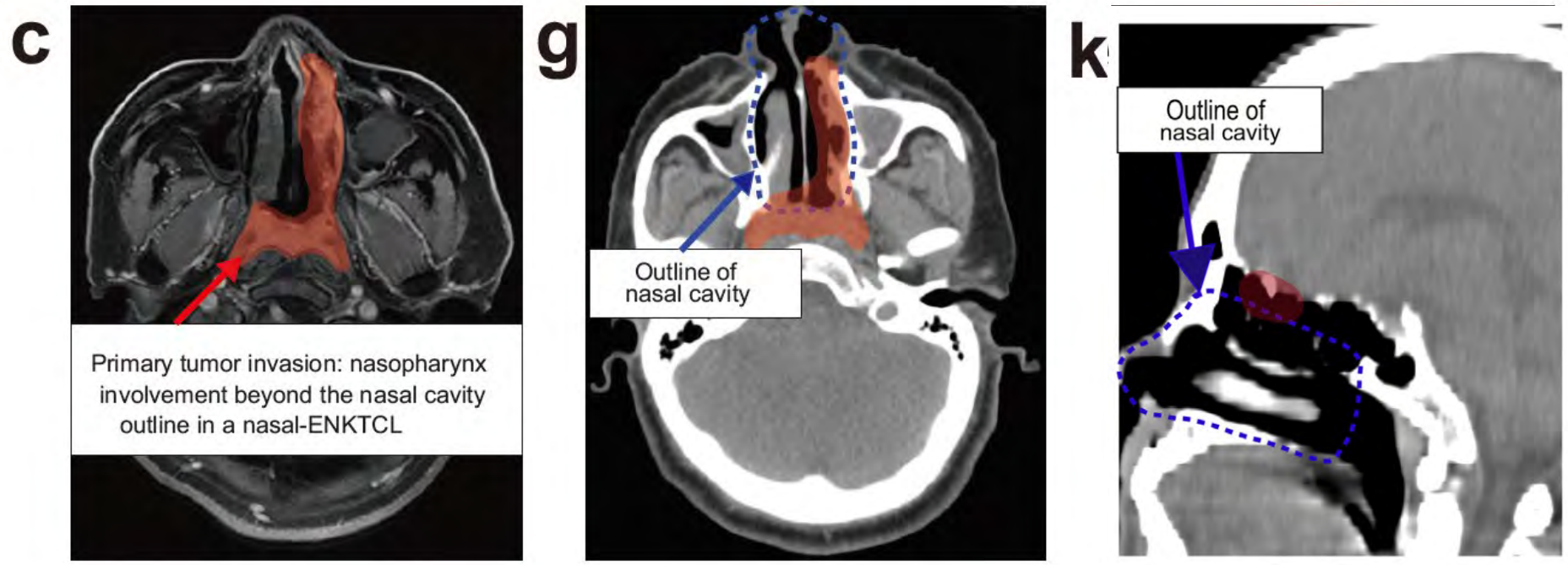


Blood 2008; CCR 2009; JCO 2006; IJROBP 2021

Staging

- A comprehensive evaluation before treatment is critical
- MRI, specifically T1 with contrast, is most useful in assessing primary tumor extension into surrounding normal tissues
- PET/CT is sensitive (sensitivity >95%) in detecting occult distant metastasis
- Direct or fiberoptic examination can find small superficial lesions
- **Primary Tumor Invasion (PTI)** -- important risk factor for early-staged disease

Diagnostic images and example of positive primary tumor invasion in a nasal ENKTCL case



Qi SN, et al. Leuk Lymphoma, 2019

Prognostic model/index for ENKTCL

Models based on baseline clinical factors

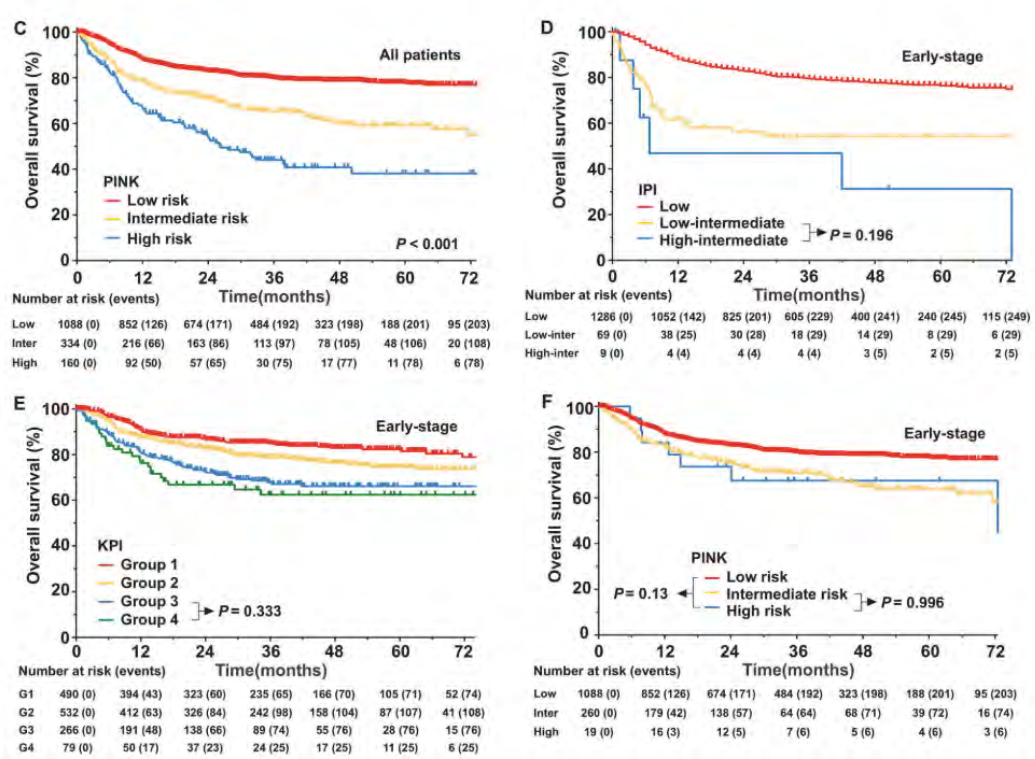
*NRI (CA-stage)	*KPI	PINK(E)	IPI
Age Stage LDH ECOG PS PTI	Stage LDH B symptom regional LN	Age Stage Distant LN Non-nasal type EBV-DNA titre	Age Stage LDH ECOG PS Extranodal site number

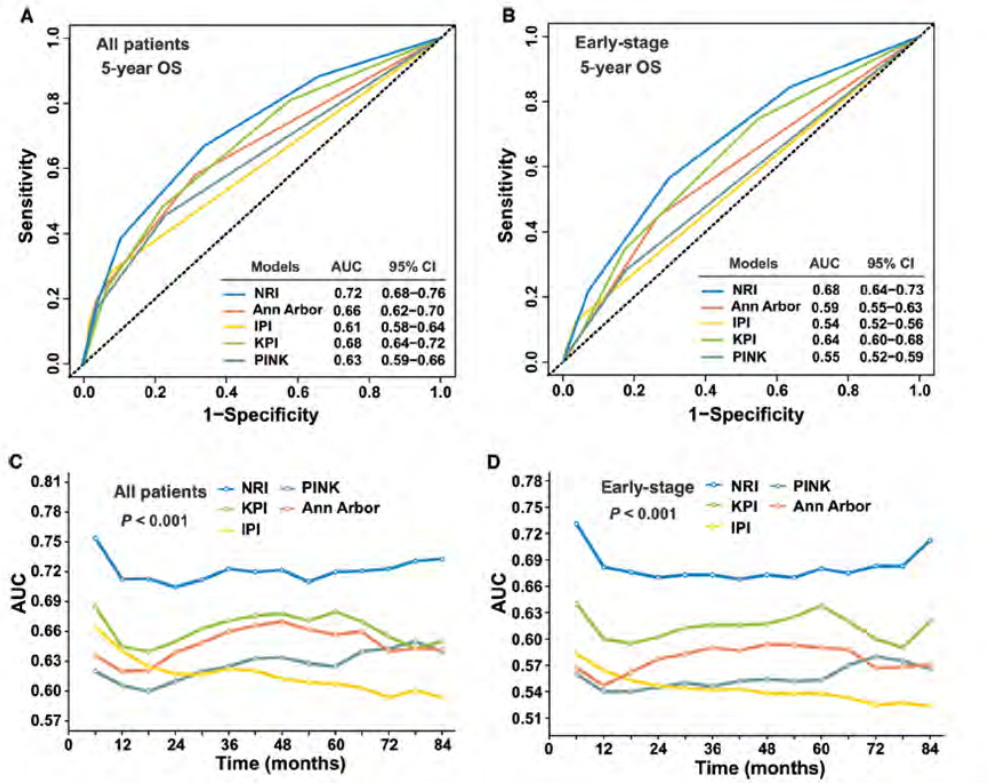
*Developed in the ANT-era

Kim SJ. Lancet Oncol. 2016, 389
Lee J. J Clin Oncol. 2006, 612
Chen SY. Leukemia. 2021, 130

Comparison of NRI to other models

Better performance in early stage and entire patient population





Chen SY, Yang Y, Qi SN, et al: *Leukemia*, 2020

Improved OS/PFS with non-ANT chemotherapy

Before PSM

After PSM

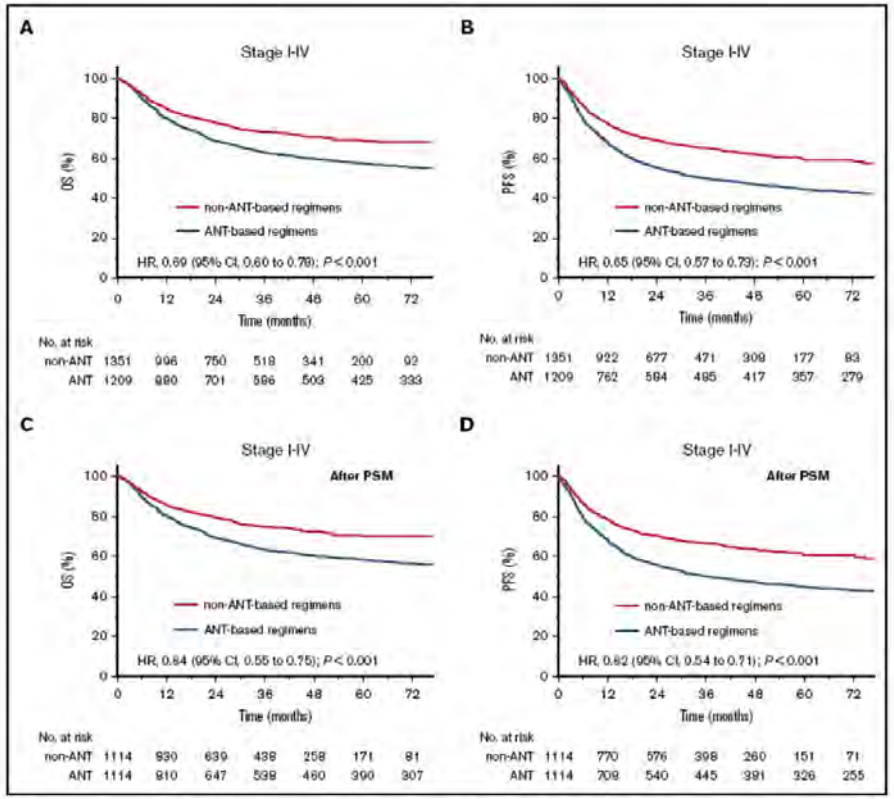


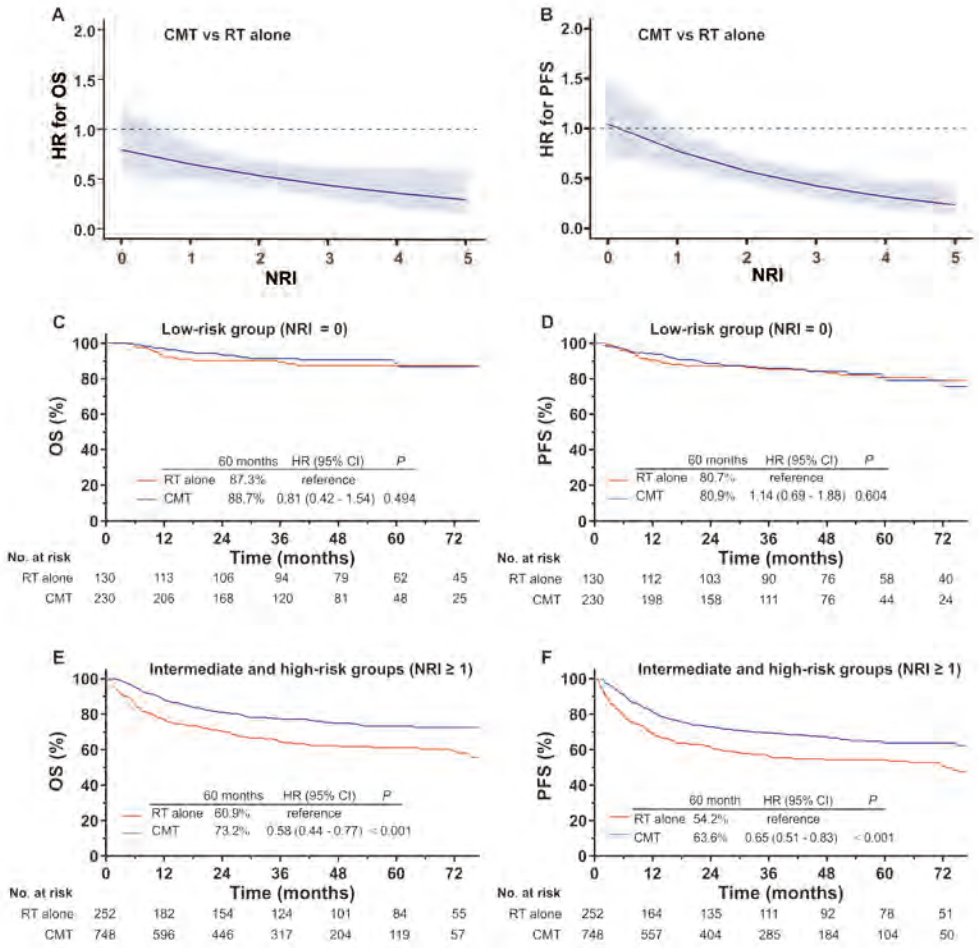
Figure 1. OS and PFS stratified by chemotherapy regimens in the entire cohort. OS (A) and PFS (B) of non-ANT-based regimens vs ANT-based regimens before PSM. OS (C) and PFS (D) of non-ANT-based regimens vs ANT-based regimens after PSM.

5-year OS (HR: 0.6-0.7)

	Before PSM	After PSM
Non-ANT	68.9%	69.9%
ANT	57.5%	59.5%

Qi SN, Yang Y, Song YQ, et al. Blood Adv 4:3141-3153, 2020

NRI-dependent benefit of non-ANT chemotherapy in ES-ENKTCL



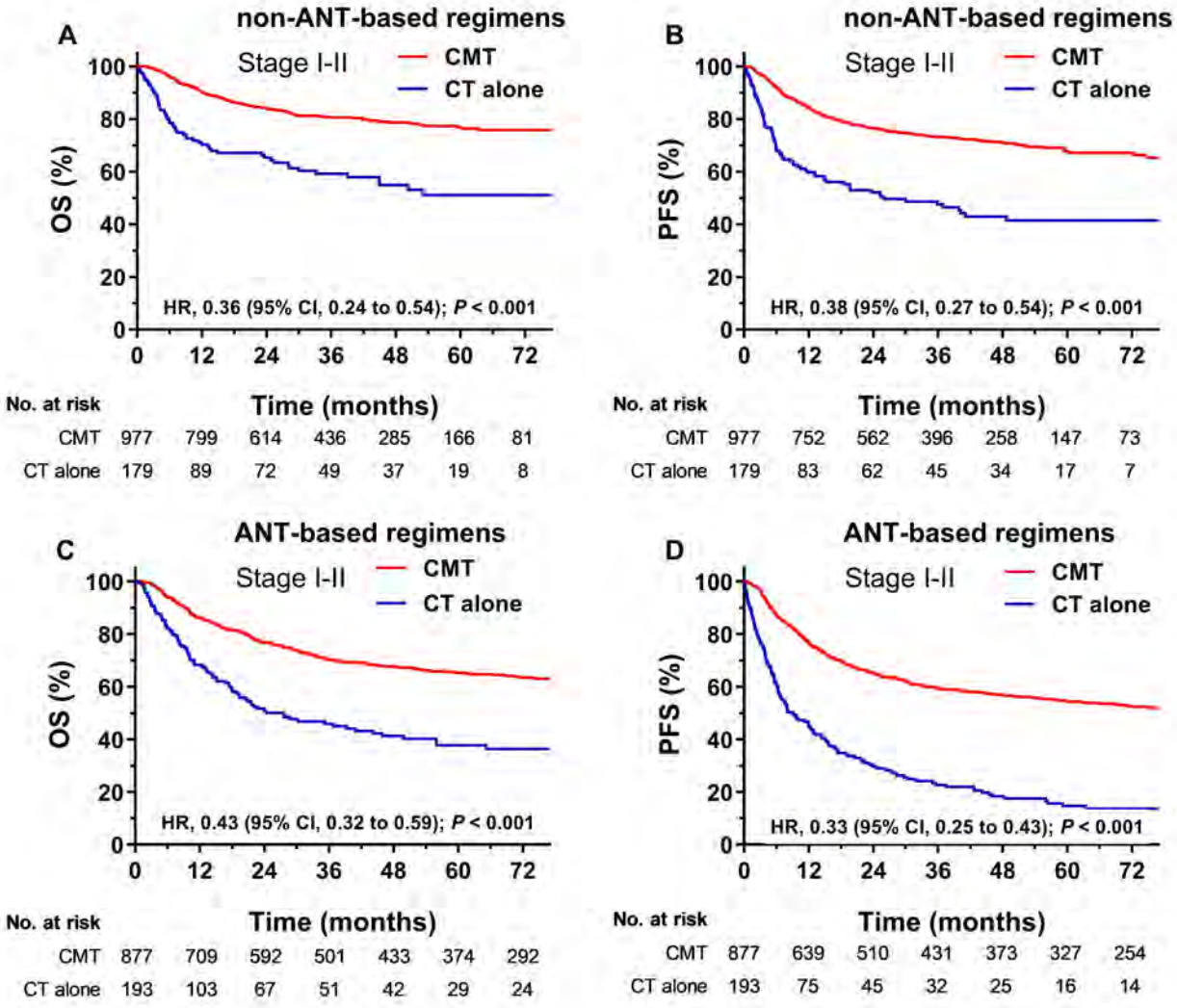
HR for OS/PFS according to CMT versus RT alone at different NRI values

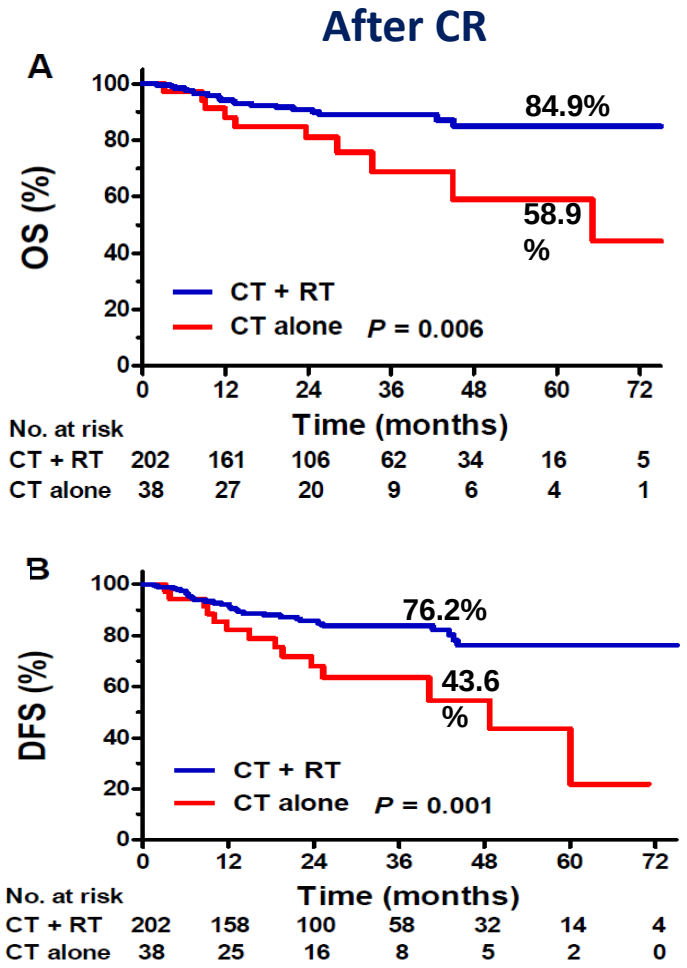
Adding CT into RT confer no survival benefit in low-risk group

CMT improved survival compared with RT alone in patients with risk factors

Qi SN, Yang Y, Zhang YJ, et al. Am J Hematol, 2020

Radiotherapy: backbone of curative treatment in ES-ENKTCL





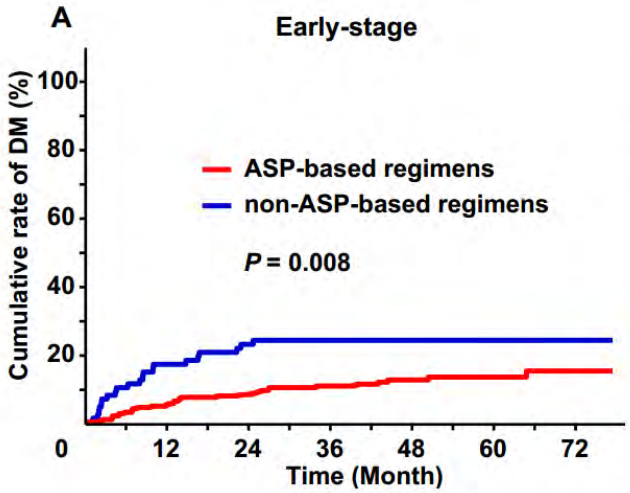
Qi SN, et al. Blood Adv, 4:3141-53, 2020

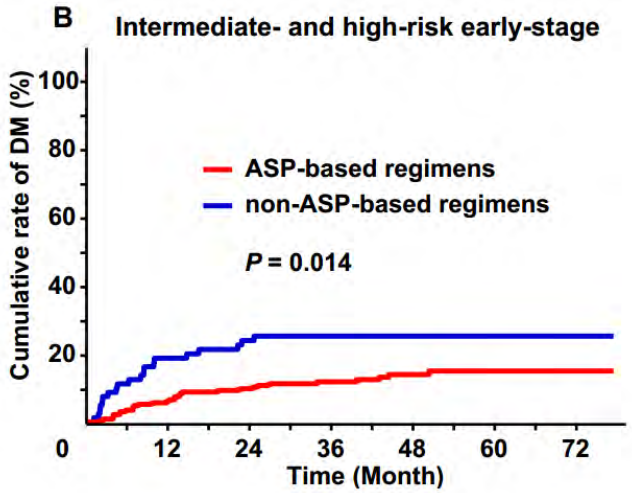
Deng XW, et al. Radiother Oncol, 2018

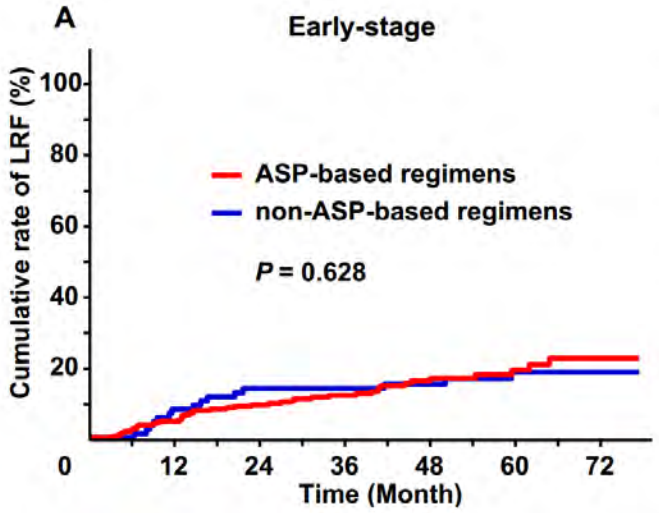
Chemotherapy regimens on NCCN guideline

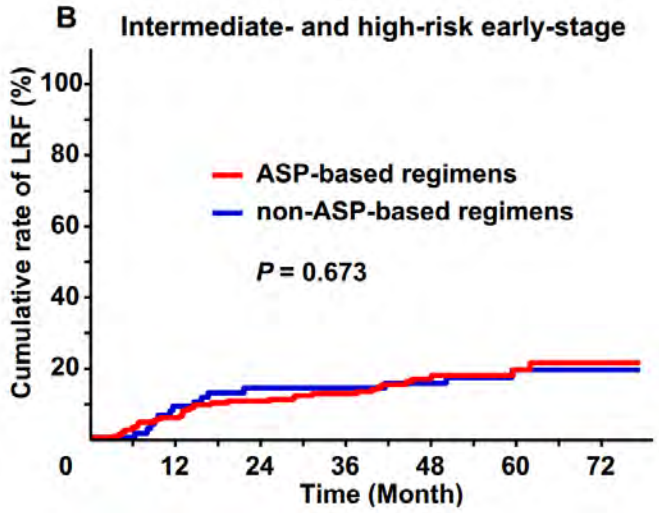
Asparaginase-based	Non–asparaginase-based (platinum)
Modifed-SMILE	DeVIC (concurrent chemoradiation)
P-GEMOX	VIPD (concurrent chemoradiation)
DDGP	DHAP (second line)
AspaMetDex	ESHAP (second line)
	GDP (second line)
	GemOx (second line)
	ICE (second line)

Improved DMFS with ASP-based regimen









Zheng Xuan, ESMO open, 2021: 83

PRINCIPLES OF RADIATION THERAPY

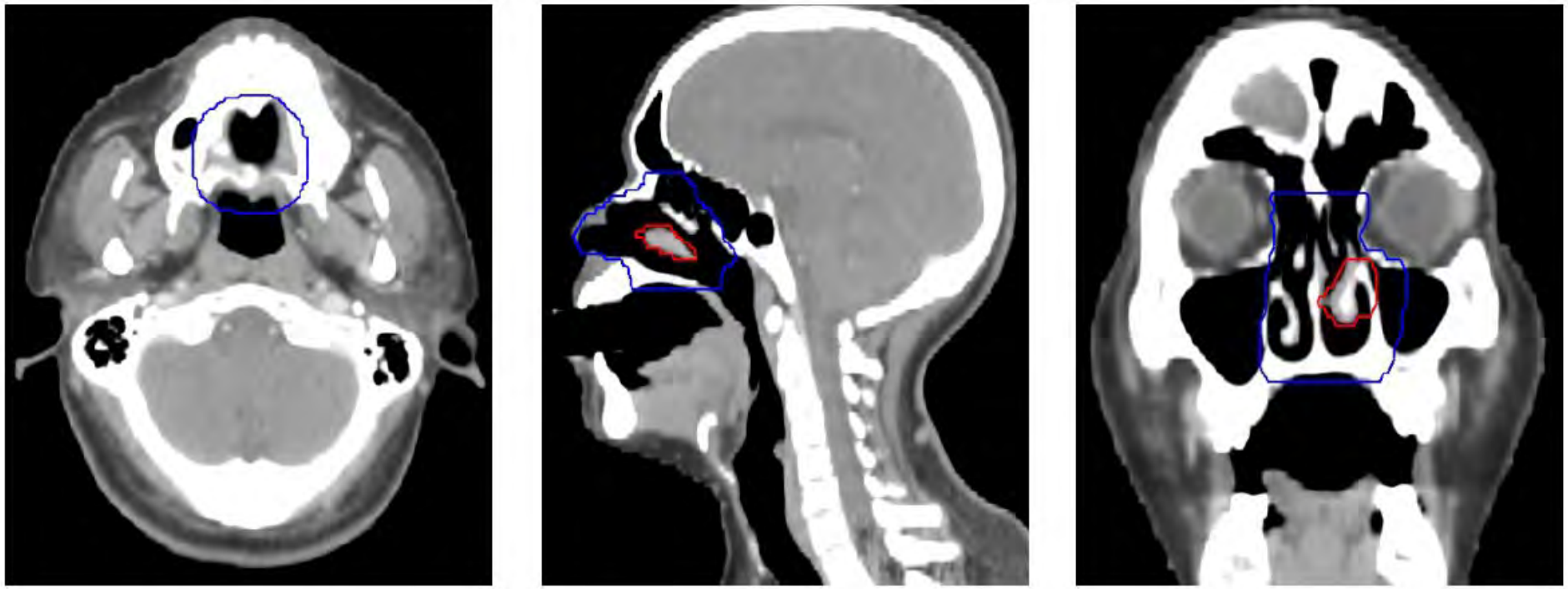
CTV definitions

Target volumes	Disease involvement
Nasal-ENKTCL	
CTV-primary tumor	
(Pre-chemotherapy or pre-surgery) GTV with a 5 mm margin and high-risk regions of primary tumor invasion. Entire nasal cavity, ipsilateral medial maxillary wall (*lateral*), anterior ethmoid sinuses (*superior*), hard palate (*inferior*), posterior nasal aperture (*posterior*) (Fig. 3).	Primary disease confined to the nasal cavity (unilateral or bilateral) without primary tumor invasion.
The CTV expands further to fully cover the disease extension as follows.	Primary disease extends into adjacent structures or organs.
● To include the whole nasopharynx (Fig. 4).	If primary nasal disease is close to the posterior nasal aperture or invades the nasopharynx.
● To include the posterior ethmoid sinuses.	If the anterior ethmoid sinuses are involved or posterior ethmoid sinuses are involved.
● To include the whole maxillary sinus (Fig. 4).	If the maxillary sinus (often medial maxillary wall) is involved.
● To include the involved facial subcutaneous soft tissue with a bolus of 0.5–1 cm.	If the primary tumor involves the subcutaneous soft tissue or facial skin.
● To include the (pre-chemotherapy or pre-surgery) orbital-GTV with a 3 mm margin. Normal structures in the orbital cavity that were clearly uninvolved, though previously displaced by the GTV, should be excluded from the CTV according to clinical judgment after induction chemotherapy.	If the orbit is involved.

CTV definitions

Target volumes	Disease involvement
Non-nasal-UADT-ENKTCL	
CTV-primary tumor	
(Pre-chemotherapy or pre-surgery) GTV with a 5 mm margin.	
Whole Waldeyer's ring (nasopharynx, tonsils, tongue base, and oropharynx), posterior nasal aperture, and adjacent organs or structures involved (Fig. 5-6).	Primary disease in the Waldeyer's ring (single or multisite involvement).
The entire structure and adjacent soft tissues involved with at least 2 cm margin.	Primary disease in the oral cavity, larynx or hypopharynx.
CTV-lymph node	
Prophylactic irradiation of the neck can be considered (Fig. 5).	No lymph node involvement.
The bilateral cervical lymph nodes (Fig. 6).	If the cervical nodes are positive.
Extra-UADT-ENKTCL	
CTV-primary tumor	
Cutaneous and soft tissues with a margin of at least ≥2 cm, and adjacent organs or structures involved.	Primary disease in cutaneous and soft tissues.
The entire stomach and adjacent soft tissues if involved.	Primary disease in the stomach.
CTV-lymph node	
Prophylactic irradiation of regional lymph nodes is not necessary.	No lymph node involvement.
The regional lymph nodes.	If the regional lymph nodes are positive.

Representative slices of target delineation



- GTV (red line) and CTV (blue line)

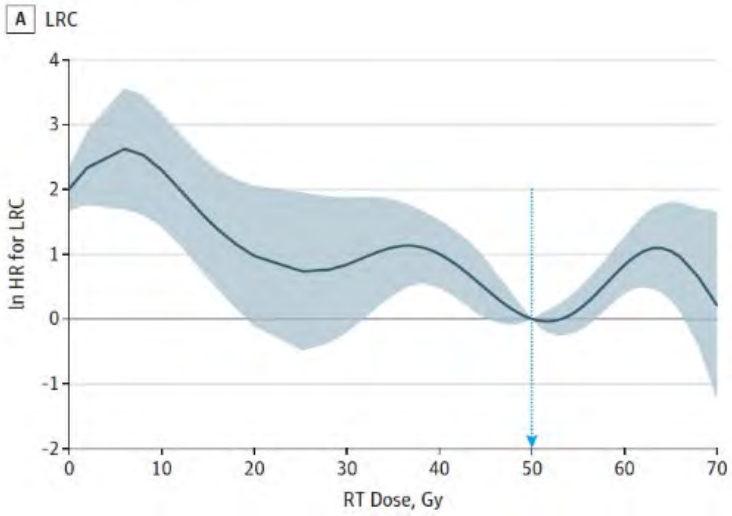
Radiation dose and organs constraints

- Radical radiation dose required to maximize tumor control: 50Gy/2Gy/25f
- A boost of 5 to 10 Gy is recommended for suspicious residual disease
- Organ at risk constraints:
  - the brainstem ≤50 Gy
  - the spinal cord ≤40 Gy
  - the optic nerve and chiasm ≤50 Gy
  - the retina ≤45 Gy, the cornea ≤50 Gy
  - the lens ≤10 Gy

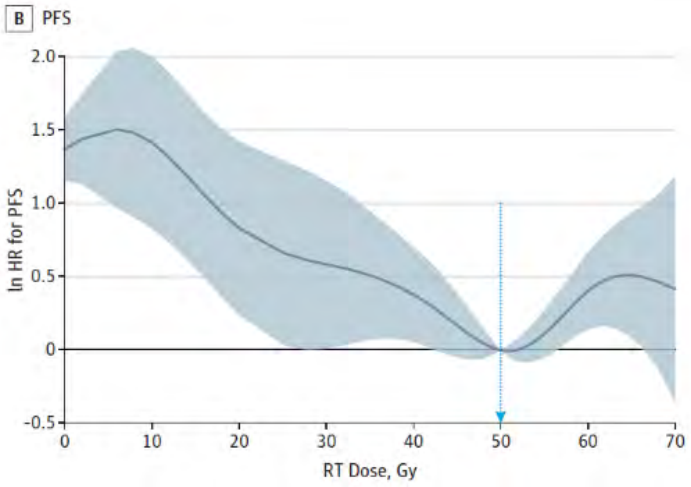
Relationships between RT dose and LRC/survival

CLCG-NKT-cohort 1 (N=1383)

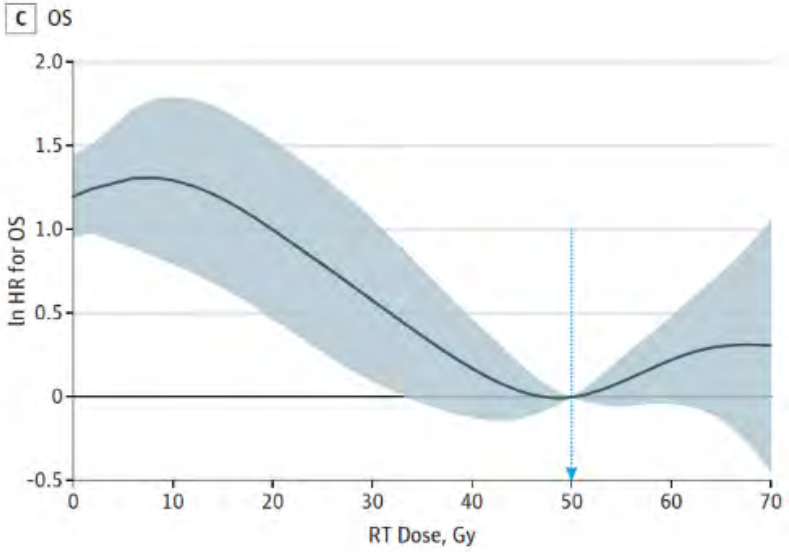
Local-regional relapse hazard



Relapse/progression hazard

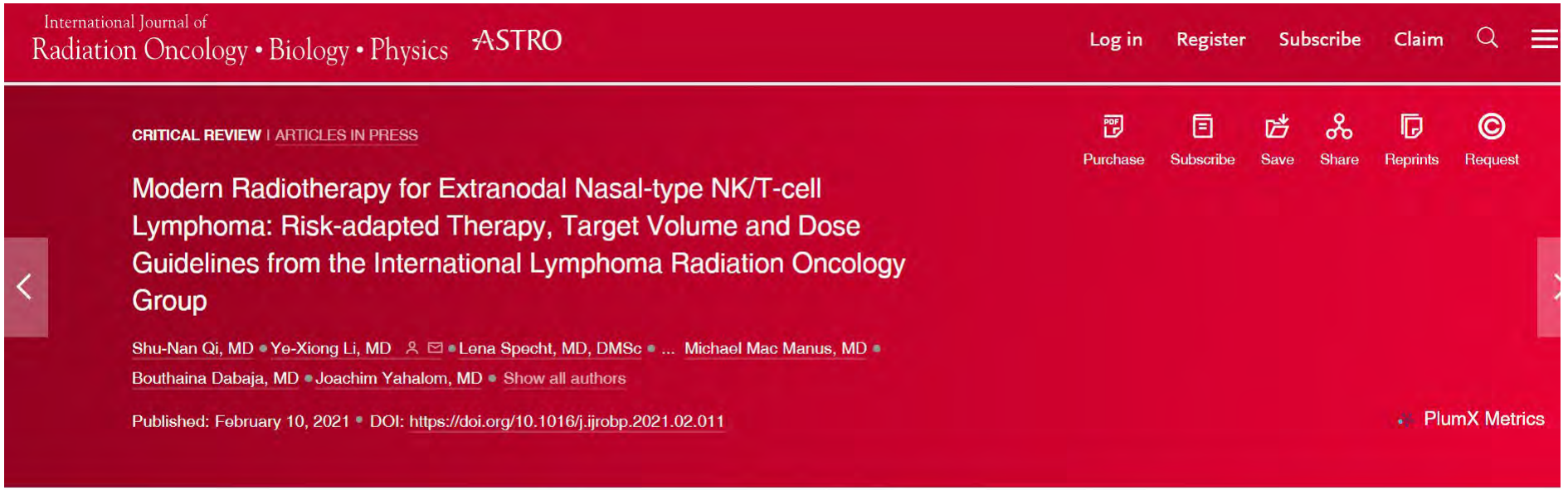


Mortality hazard



Yang Y, et al. JAMA Oncol, 3:83-91, 2017

ENKTCL ILROG-guideline



DOI: http://doi.org/10.1016/j.ijrobp.2021.02.011

IMMUNE CHECKPOINT INHIBITOR

Immune checkpoint studies in R/R ENKTCL

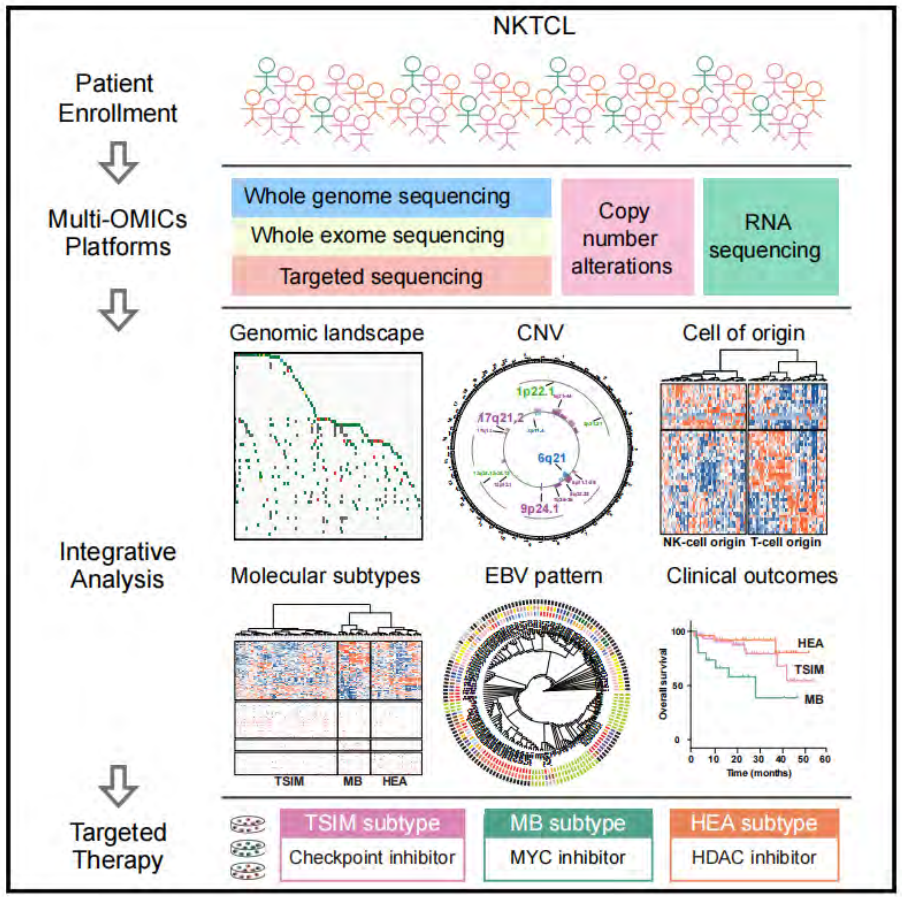
Author	ICI	Number	ORR (%)	CR (%)
Kwong	PD-1 (Pembrolizumab)	7	100	71.4 (n=5)
Kim	PD-1 (Pembrolizumab)	14	42.9	35.7 (n=5)
Cho	PD-1 (Pembrolizumab)	11	36.4	27.3 (n=3)
Li	PD-1 (Pembrolizumab)	7	57.1	28.6 (n=2)
Lai	PD-1 (Pembrolizumab)	1	100	100 (n=1)
Chan	PD-1 (Nivolumab)	3	66.7	66.7 (n=2)
Liu	PD-1 (Nivolumab)	5	60	0
Lim	PD-1 (Pembrolizumab)	19	47.4	36.8 (n=7)
Tao	PD-1 (Sintilimab)	28	68	7.1 (n=2)
Kim	PD-L1 (Avelumab)	21	38	24 (n=5)
Huang	PD-L1 (Sugemalimab)	80	44.9	35.9

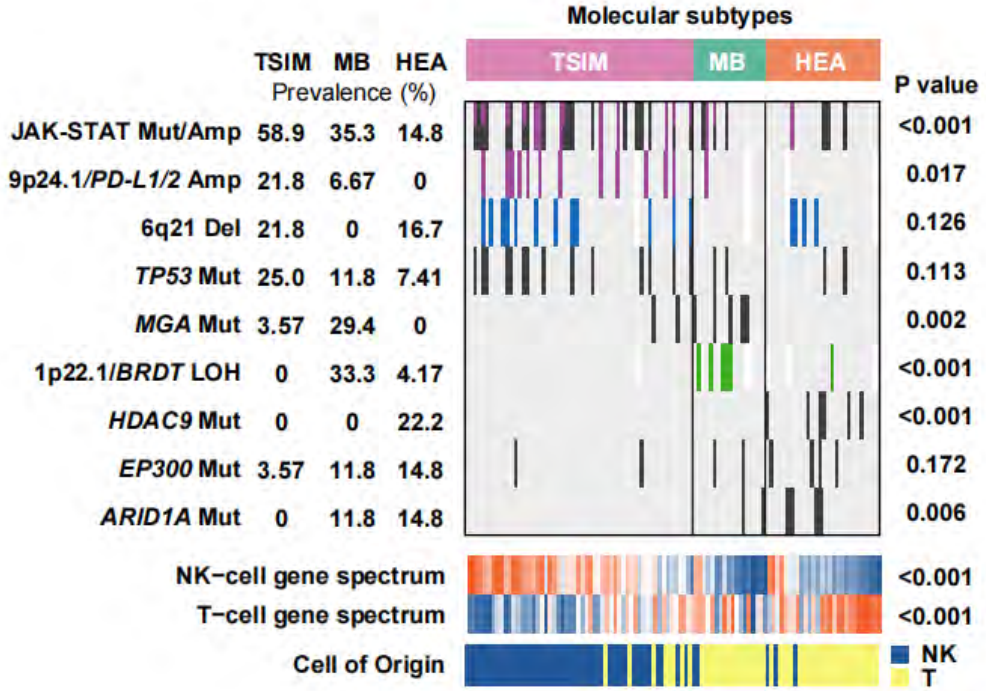
Ongoing ICI trials in untreated ENKTCL

NCT number	Immune checkpoint and drug	Clinical setting	Phase	Patient Number
04417166	PD-1 (Pembrolizumab)	Stage I-II, not eligible to chemotherapy	2	30
03728972	PD-1 (Pembrolizumab)	Untreated	2	19
04338282	PD-1 (Toripalimab)	Plasma EBV-DNA positive after first-line Peg-A-based regimens	2	20
04127227	PD-1 (sintilimab) + P-GemOx	Newly diagnosed advanced ENKTL	2	63
04676789	PD-1 (sintilimab) + Peg-ASP	Untreated stage I-II	2	30
04414969	Anti-PD-1 antibody+Peg-Asparaginase+Chidamide	Untreated stage I/II with high risk	2	35
CLCG-2101	PD-1 (Tislelizumab)	Untreated stage I/II - low risk	2	30
CLCG-2102	PD-1 (Tislelizumab) + PGEMOX	Untreated stage I/II - high risk	2	54
04365036	PD-1 (Toripalimab) + PGEMOX	Newly diagnosed early stage NKTCL	3	207

Genomic and Transcriptomic Characterization

Overexpression of PD-L1/2 in TSIM subtype may potentiate the therapeutic activity of ICI





TSIM N=56 cases, based on mutations in JAK-STAT pathway and TP53, as well as amp9p24.1/JAK2 locus, p17q21.2/STAT3/5B/5A locus, amp9p24.1/PD-L1/2 locus, and del6q21

Xiong J. Cancer Cell. 2020;37(3):403

Summary

- **Risk-adapted therapy strategy for ENKTCL**

Stage	NRI Risk factor	Risk group	Treatment	5y OS (%)
I	0	Low	RT±chemotherapy	~90
I/II	1	Intermediate-low	RT+ASP-based chemotherapy; or Brief chemotherapy (≤3 cycles) with non-ANT regimens followed by radiotherapy; or Concurrent chemo-radiotherapy followed by non-ANT chemotherapy	~80
	2	Intermediate-high		~70
	≥3	High		55
III/IV	3	High	Clinical trial; or Asparaginase-based chemotherapy with or without radiotherapy	10-40
	≥4	Very high		

- **ICI showed efficacy in selected cases (TSIM)**

THANK YOU !