

Baseline SUVmax of ¹⁸F-FDG PET-CT indicates prognosis of extranodal natural killer/T-cell lymphoma

Xianwu Xia, MS^{a,b,*}, Yaqi Wang, MD^{b,c,*}, Jianjun Yuan, MS^a, Wenjie Sun, MD, PhD^{b,c}, Jinjin Jiang, PhD^{c,d}, Chang Liu, PhD^{c,d}, Qunling Zhang, MD, PhD^{c,e}, Xuejun Ma, MD, PhD^{b,c,*} 

Abstract

To evaluate the prognostic value of the baseline SUVmax of ¹⁸F-FDG PET-CT in extranodal natural killer/T-cell lymphoma (NKTCL) patients.

From January 2010 to December 2015, 141 extranodal NKTCL patients with staging ¹⁸F-FDG PET-CT scan were divided into two groups based on SUVmax cutoff value obtained from operating characteristic (ROC) curves. All the patients received radiotherapy, chemotherapy or chemoradiation. Survival analysis was performed on the basis of SUVmax.

The median baseline SUVmax of the tumors was 11.67 (range 2.6–34.6). The ROC curves showed that the optimal cutoff of the baseline SUVmax was 9.65. The patients were divided into two groups: low SUV group (SUVmax < 9.65) and high SUV group (SUVmax ≥ 9.65). Patients in high SUV group were more likely to have invasive disease outside the nasal cavity ($P < .001$), poorer ECOG scores ($P = .012$) and higher LDH levels ($P = .034$). The univariate survival analyses indicated that high SUVmax was a poor prognostic factor for overall survival (OS, $P = .038$), progression free survival (PFS, $P = .006$) and distant relapse free survival (DRFS, $P = .001$), but not for local recurrence free survival (LRFs, $P > .05$). These results were consistent with that of the survival analyses using the Kaplan–Meier method. The multivariate survival analyses showed that the baseline SUVmax was no longer a prognostic factor for OS (HR 1.99, 95% CI 0.81–4.88, $P = .135$), but it still indicated worse PFS (HR 2.6, 95% CI 1.24–5.46, $P = .012$) and DRFS (HR 4.58, 95% CI 1.83–11.46, $P = .001$) independent of other variables.

For extranodal NKTCL patients, a higher baseline SUVmax of ¹⁸F-FDG PET-CT was associated with more aggressive clinical features. An SUVmax ≥ 9.65 was an independent poor prognostic factor for DRFS and PFS. Thus, the baseline SUVmax may be a valuable tool to help identify patients with a high risk of disease progression.

Abbreviations: DRFS = distant relapse free survival, ECOG = Eastern Cooperative Oncology Group, FDG = fluorodeoxyglucose, IMRT = intensive modulated radiotherapy, LDH = lactate dehydrogenase, LRFs = local recurrence free survival, NKTCL = natural killer/T-cell lymphoma, OS = overall survival, PET-CT = positron emission tomography-computed tomography, PFS = progression free survival, PINK = prognostic index of natural killer lymphoma, ROC curve = operating characteristic curve, SUVmax = the maximum standardized uptake value.

Keywords: ¹⁸F-FDG PET-CT, extranodal natural killer/T-cell lymphoma, prognosis, SUVmax

1. Introduction

Extranodal natural killer/T-cell lymphoma (NKTCL) is an aggressive type of non-Hodgkin's lymphoma with unique

clinicopathological features. It has an apparent geographic predilection with higher incidence in East Asia and South America than that in western countries.^[1] Most extranodal NKTCL originates from upper aerodigestive tracts, particularly

Editor: Balaji Thas Moorthy.

XX and YW contributed equally to this work.

The authors have no funding information to disclose.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

^a Department of Radiology, Municipal Hospital Affiliated to Medical School of Taizhou University, Taizhou, Zhejiang, ^b Department of Radiation Oncology, Fudan University Shanghai Cancer Center, ^c Department of Oncology, Shanghai Medical College, Fudan University, ^d Department of Nuclear Medicine, Fudan University Shanghai Cancer Center, ^e Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, PR China.

* Correspondence: Xuejun Ma, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, 270 Dong' An Road, Shanghai 200032, PR China (e-mail: chateuma@hotmail.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Xia X, Wang Y, Yuan J, Sun W, Jiang J, Liu C, Zhang Q, Ma X. Baseline SUVmax of ¹⁸F-FDG PET-CT indicates prognosis of extranodal natural killer/T-cell lymphoma. *Medicine* 2020;99:37(e22143).

Received: 7 May 2020 / Received in final form: 25 July 2020 / Accepted: 8 August 2020

<http://dx.doi.org/10.1097/MD.00000000000022143>

nasal and paranasal areas (nasal type), and <20% of the disease spread to various organs and tissues.^[2] There is no standard treatment for extranodal NKTCL. Unlike other peripheral T cell lymphoma, this malignancy is not sensitive to CHOP or CHOP-like chemotherapy but is radiosensitive.^[3] Novel non-anthracycline-based chemotherapy regimens improved the treatment outcome in recent years,^[4–8] but their efficacy still need further investigation in large population. Although early stage extranodal NKTCL patients had achieved good prognosis with radiotherapy or chemoradiation, up to 40% patients experienced systemic relapses. Advanced stage patients had much poorer outcomes.^[9] Thus, it is of vital importance to evaluate and predict patient prognosis accurately. Though various risk factors have been evaluated to predict the prognosis of extranodal NKTCL such as age, disease stage, performance status, B symptom, lactate dehydrogenase (LDH) level, plasma DNA copy of Epstein-Barr virus and primary tumor invasion etc.,^[10–12] but there are few imaging related factors which have been deeply investigated.

Nowadays, ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) is widely used in the diagnosis, staging, response monitoring, and outcome prediction of various kinds of cancers, especially FDG avid lymphomas, like Hodgkin's lymphoma and diffused large B cell lymphoma.^[13–15] Due to the low incidence of extranodal NKTCL, the number of studies focusing on the clinical value of PET-CT for extranodal NKTCL was relatively small.^[16] Several semiquantitative parameters can be used to measure the radioactivity within a lesion, with the maximum standardized uptake value (SUVmax) being the most widely analyzed. PET-CT parameters have been demonstrated to be a valuable diagnostic and staging tools for extranodal NKTCL.^[17] However, for prognosis prediction, the studies are few, and the conclusions are uncertain. Thus, in this study, we aimed to evaluate the prognostic value of the baseline SUVmax in extranodal NKTCL patients.

2. Patients and methods

2.1. Study cohort

The study was a retrospective cohort study and was approved by the Human Research Ethics Committee of Fudan University Shanghai Cancer Center. From January 2010 to December 2015, patients with pathologically confirmed newly diagnosed extranodal NKTCL at our cancer center were included in our study. Exclusion criteria were:

1. patients who did not receive baseline ¹⁸F-FDG PET-CT examinations,
2. patients who did not have adequate follow-ups,
3. patients who had a previous malignancy and any treatment to that malignancy.

All included patients provided written informed consent to participate in the study.

For all the patients met the inclusion criteria, their baseline clinical features, including sex, age at diagnosis, primary sites, lymph node status, Ann Arbor stage, Eastern Cooperative Oncology Group (ECOG) score, LDH level, B symptoms, and prognostic index of natural killer lymphoma (PINK) score were recorded according to medical histories. The baseline SUVmax measurements were collected from the reports of pre-treatment ¹⁸F-FDG PET-CT examinations. After diagnosis and staging,

patients with limited disease confined within nasal cavity without risk factors were provided with intensive modulated radiotherapy (IMRT) alone. Other stage I and stage II patients were treated with IMRT combined with chemotherapy for 2 to 4 cycles. Patients with advanced stage disease were treated with non-anthracycline-based chemotherapy or combined with stem cell transplant. The IMRT was delivered with total dose of 50 Gy in 25 fractions. The chemotherapy regimens included DICEP regimen (dexamethasone 40 mg d1–4; ifosfamide 1200 mg/m² d1–4; cisplatin 20 mg/m² d1–4; etoposide 60 mg/m² d1–4; pegaspargase 2000 U/m², max 3750 IU d1), DICE regimen (dexamethasone 40 mg d1–4; ifosfamide 1200 mg/m² d1–4; cisplatin 20 mg/m² d1–4; etoposide 60 mg/m² d1–4), and P-GEMOX regimen (pegaspargase 2000 U/m², max 3750 IU d1, gemcitabine 1 g/m² d1, d8, oxaliplatin 85 mg/m² d1). All the chemotherapy was administered every 3 weeks.

After radiotherapy, chemotherapy or chemoradiation, the patients were followed up every 3 months. Overall survival (OS), progression free survival (PFS), distant relapse free survival (DRFS), and local recurrence free survival (LRFS) were obtained after long-term follow-up. Distant relapse was defined as relapse in distant tissues and organs, such as the liver, bone, skin, lung, etc. Local recurrence of early stage patients was defined as relapse in upper aerodigestive tract and cervical lymph nodes.

2.2. PET-CT protocol and image analysis

The ¹⁸F-FDG PET-CT examination was performed on a combined PET-CT scanner (Siemens Biograph 16 HR PET-CT, Germany). After fasting for at least 6 h, ¹⁸F-FDG at a dose of 7.4 MBq/kg was injected intravenously. After resting for ~1 h, whole-body CT and PET scans were performed. The CT scan was acquired first (voltage, 120 kV; current intensity, 40 mA; section thickness, 5 mm; interval, 5 mm) without oral or intravenous contrast agents. Then, the PET scan was acquired using the 3D collection mode and required 2 min/bed position. The brain scan ranged from the roof of the skull to the plane of the mandibles. The body scan ranged from the bottom of the skull to the proximal femur with a total of 6 to 7 bed position. The CT acquisition data were used for attenuation correction, and corrected PET images were reconstructed using the iterative method. Finally, CT images, PET images and PET-CT fusion images in the transverse plane, sagittal plane, and coronal plane were obtained. PET-CT images were read by two physicians specializing in nuclear medicine and diagnoses were made by consensus. Circular regions of interest (ROIs) were drawn on the axial, coronal, or sagittal coregistered PET-CT slices. The SUVmax of the primary lesion within the nasal cavity was calculated and adjusted by body weight using the following standard formula: mean ROI activity (MBq/mL)/(injected dose [MBq]/body weight [kg]).

2.3. Statistical analysis

The disparities of the median SUVmax values in different variable subgroups were compared using *t* tests. After performing the receiver operating characteristic (ROC) curve analysis in terms of the status of distant relapse, the SUVmax cut-off was obtained when the sum of sensitivity and specificity was largest. Then, the patients were divided into two SUVmax groups by the cut-off value. The clinical distribution differences between these two SUVmax groups were compared using the chi-square tests.

Univariate and multivariate Cox proportional hazards regression models were used to perform survival analyses. Kaplan–Meier method was used to draw survival curves and two curves were compared using the log-rank test. Variables with $P < 0.1$ in the univariate analyses or had important clinical significance were included in the multivariate survival analyses. All above analyses were performed by SPSS software (version 22.0, Chicago, IL). And $P < .05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 141 extranodal NKTCL patients met the inclusion criteria. The patients' clinical characteristics and their SUVmax data were shown in Table 1. The primary tumor sites were all located in the aerodigestive tract, with 41.1% (58/141) of them limited in the nasal cavity, 50.4% (71/141) originating from the nasal cavity and invading into adjacent tissues, and 8.5% (12/141) of the primary sites were not within nasal cavity. A total of 67.4% (95/141) of the patients were males, and 32.6% (46/141) were females. Most patients were younger than 60 years old (79.4%, 112/141) and had good performance status (ECOG score 0–1, 88.7%, 125/141). One hundred twenty-seven patients had stage I or II disease, and 14 patients had stage III or IV disease. Positive lymph nodes were observed in 31.9% (45/141) of the patients. B symptoms and elevated LDH levels were found in 39.0% (55/141) and 7.8% (11/141) of the

patients, respectively. One hundred patients (70.9%) had a PINK score of 0, 36 (25.5%) and 5 (3.5%) patients were rated as 1 and 2.

The median baseline SUVmax value was 11.67 (range 2.6–34.6). It was found that SUVmax values were higher in the primary tumors which invaded the tissues next to the nasal cavity than in those limited within the nasal cavity, and SUVmax values were also higher in the tumors originated from sites other than nasal cavity ($P < .001$). In addition, patients with positive lymph nodes ($P = .028$), high ECOG score ($P = .003$), and elevated LDH level ($P = .039$) had higher SUVmax values. However, there were no significant differences of baseline SUVmax among the sex, age, B symptom, Ann Arbor stage, and PINK score subgroups.

3.2. Cutoff value of baseline SUVmax

After performing calculation using the ROC curve (Supplemental Digital Content [Figure S1, <http://links.lww.com/MD/E840>]) in terms of the status of distant relapse, we found that the optimal baseline SUVmax cutoff was 9.65, with a sensitivity of 0.781 and specificity of 0.569 (AUC=0.683, $P = .018$). Thus, the patients were classified into two groups: SUVmax < 9.65 group and SUVmax ≥ 9.65 group. Similar to the findings mentioned above, as shown in Table 1, an SUVmax ≥ 9.65 was more likely to exist in patients with tumors invaded into adjacent tissues of nasal cavity ($P < .001$), poor ECOG scores ($P = .012$) and elevated LDH levels ($P = .034$).

Table 1

The associations between clinical features and SUVmax levels.

| Characteristics, no. (%) | All (N=141) | SUVmax (Mean ± SD) | P- | SUVmax < 9.65 (N=69) | SUVmax ≥ 9.65 (N=72) | P |
|--------------------------|-------------|--------------------|-------|----------------------|----------------------|-------|
| Gender | | | .687 | | | .587 |
| Male | 95 (67.4%) | 11.51 ± 6.89 | | 48 (69.6%) | 47 (65.3%) | |
| Female | 46 (32.6%) | 12.00 ± 6.47 | | 21 (30.4%) | 25 (34.7%) | |
| Age | | | .738 | | | .451 |
| ≤60 | 112 (79.4%) | 11.76 ± 6.77 | | 53 (76.8%) | 59 (81.9%) | |
| > 60 | 29 (20.6%) | 11.29 ± 6.69 | | 16 (23.2%) | 13 (18.1%) | |
| ECOG | | | .003 | | | .012 |
| 0 | 62 (44.0%) | 9.86 ± 5.79 | | 38 (55.1%) | 24 (33.3%) | |
| 1 | 62 (44.0%) | 12.37 ± 7.15 | | 27 (39.1%) | 35 (48.6%) | |
| 2 | 17 (12.1%) | 15.68 ± 6.55 | | 4 (5.8%) | 13 (18.1%) | |
| LDH | | | .039 | | | .034 |
| Normal | 130 (92.2%) | 11.33 ± 6.69 | | 67 (97.1%) | 63 (87.5%) | |
| > ULN | 11 (7.8%) | 15.67 ± 6.24 | | 2 (2.9%) | 9 (12.5%) | |
| Primary site | | | <.001 | | | <.001 |
| Within NC | 58 (41.1%) | 9.34 ± 5.23 | | 38 (55.1%) | 20 (27.8%) | |
| Invading outside of NC | 71 (50.4%) | 13.94 ± 7.02 | | 23 (33.3%) | 48 (66.7%) | |
| Non-NC | 12 (8.5%) | 9.43 ± 7.42 | | 8 (11.6%) | 4 (5.6%) | |
| Lymph node | | | .028 | | | .070 |
| Negative | 96 (68.1%) | 10.72 ± 5.93 | | 52 (75.4%) | 44 (61.1%) | |
| Positive | 45 (31.9%) | 13.68 ± 7.90 | | 17 (24.6%) | 28 (38.9%) | |
| B symptom | | | .063 | | | .090 |
| Negative | 86 (61.0%) | 10.82 ± 6.45 | | 47 (68.1%) | 39 (42.2%) | |
| Positive | 55 (39.0%) | 12.99 ± 7.02 | | 22 (31.9%) | 33 (45.8%) | |
| Ann Arbor stage | | | .119 | | | .108 |
| I/II | 127 (90.1%) | 11.37 ± 6.61 | | 65 (94.2%) | 62 (86.1%) | |
| III/IV | 14 (9.9%) | 14.33 ± 7.51 | | 4 (5.8%) | 10 (13.9%) | |
| PINK score | | | .383 | | | .884 |
| 0 | 100 (70.9%) | 11.50 ± 6.73 | | 50 (72.5%) | 50 (70.9%) | |
| 1 | 36 (25.5%) | 11.56 ± 6.33 | | 17 (24.6%) | 36 (25.5%) | |
| ≥ 2 | 5 (3.5%) | 15.78 ± 9.70 | | 2 (2.9%) | 5 (3.5%) | |

ECOG=Eastern Cooperative Oncology Group, LDH=lactate dehydrogenase, NC=nasal cavity, PINK=prognostic index of natural killer lymphoma, ULN=upper limits of normal.

3.3. Univariate survival analyses in relation to OS, PFS, DRFS, and LRFS

Univariate Cox survival analyses were performed to evaluate the associations between clinical features and survival times (OS, PFS, DRFS, and LRFS in Table 2).

It was found that worse OS was significantly related to higher SUVmax (SUVmax ≥ 9.65, *P* = .038), advanced stages (stage III/IV, *P* = .033) and higher ECOG score (*P* = .001). Poorer PFS was also associated with an SUVmax ≥ 9.65 (*P* = .006), increased LDH level (*P* = .007) and higher ECOG score (*P* = .001). In addition, SUVmax ≥ 9.65 (*P* = .001) and higher ECOG score (*P* = .009) were also prognostic factors of DRFS, which meant a higher risk of developing systemic spread. And patients with advanced stage (stage III/IV, *P* = .016) and higher ECOG score (*P* = .037) were more likely to develop local recurrence and have worse LRFS, but there were no differences of LRFS between the SUVmax < 9.65 and SUVmax ≥ 9.65 groups (*P* = .356).

These findings from the univariate survival analyses indicated that SUVmax ≥ 9.65 was a poor prognostic factor for OS, PFS, and DRFS, but not for LRFS. The survival curves of the SUVmax < 9.65 and SUVmax ≥ 9.65 groups in terms of OS, PFS, DRFS, and LRFS were shown in Figure 1A–D.

3.4. Multivariate survival analyses of OS, PFS, DRFS, and LRFS

The clinical features that obtained a *P* value < .1 in the univariate Cox survival analyses or those that were considered non-ignorable variables with important clinical significance were included in the multivariate Cox survival analyses. The results were illustrated in Figures 2–5.

After adjusting for the clinical features (ECOG score, LDH level, primary tumor site, lymph node, B symptom, Ann Arbor stage, and PINK score), the SUVmax was not related to OS (HR 1.99, 95% CI 0.81–4.88, *P* = .135), and ECOG score was the only independent prognostic factor for OS. However, for PFS, the SUVmax, LDH level, and ECOG score remained to have prognostic significance independent of other variables. Compared with those with a baseline SUVmax < 9.65, patients with a baseline SUVmax ≥ 9.65 had a higher relative risk of disease progression (PFS) with an adjusted HR of 2.60 (95% CI 1.24–5.46, *P* = .012). For DRFS, the relative risk of distant relapse for patients with an SUVmax ≥ 9.65 was ~4.58 times higher than those with an SUVmax < 9.65 (95% CI 1.83–11.46, *P* = .001). SUVmax was the only independent prognostic factor for DRFS. Unfortunately, no independent prognostic factor was found for LRFS.

Table 2
Univariate survival analyses of prognostic factors in extranodal NKTCL.

| Characteristics | OS | | PFS | | DRFS | | LRFS | |
|------------------------|-------------------|----------|-------------------|----------|-------------------|----------|-------------------|----------|
| | HR (95% CI) | <i>P</i> | HR (95% CI) | <i>P</i> | HR (95% CI) | <i>P</i> | HR (95% CI) | <i>P</i> |
| Gender | | .633 | | .760 | | .962 | | .135 |
| Male | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Female | 1.21 (0.56–2.62) | | 1.11 (0.58–2.11) | | 0.98 (0.47–2.08) | | 2.23 (0.78–6.35) | |
| Age | | .856 | | .655 | | .185 | | .563 |
| ≤60 | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| >60 | 1.08 (0.44–2.68) | | 0.84(0.42–1.77) | | 1.68 (0.78–3.64) | | 0.64 (0.14–2.87) | |
| ECOG | | .001 | | .001 | | .009 | | .037 |
| 0 | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| 1 | 3.23 (1.18–8.90) | .023 | 2.45 (1.17–5.23) | .017 | 2.32 (1.00–5.38) | .050 | 1.69 (0.48–6.01) | .415 |
| 2 | 8.23 (2.69–25.19) | .000 | 5.30 (2.15–13.07) | .000 | 4.91 (1.78–13.57) | .002 | 5.83 (1.45–23.42) | .013 |
| LDH | | .114 | | .007 | | .111 | | .204 |
| Normal | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| >ULN | 2.35 (0.81–6.77) | | 3.30 (1.38–7.86) | | 2.35 (0.82–6.70) | | 2.64 (0.59–11.82) | |
| Primary site | | .141 | | .411 | | .666 | | .161 |
| Within NC | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Invading outside of NC | 2.12 (0.88–5.11) | .095 | 1.33 (0.68–2.60) | .402 | 1.38 (0.65–2.93) | .395 | 1.54 (0.45–5.25) | .492 |
| Non-NC | 3.02 (0.88–10.33) | .078 | 1.95 (0.70–5.43) | .199 | 1.47 (0.41–5.27) | .554 | 4.21 (0.04–18.82) | .060 |
| Lymph node | | .162 | | .677 | | .409 | | .870 |
| Negative | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Positive | 1.71 (0.81–3.61) | | 1.15 (0.60–2.19) | | 1.35 (0.66–2.77) | | 0.91 (0.29–2.90) | |
| B symptom | | .420 | | .248 | | .077 | | .429 |
| Negative | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Positive | 1.36 (0.65–2.85) | | 1.44 (0.78–2.65) | | 1.87 (0.94–3.75) | | 0.63 (0.20–2.00) | |
| Ann Arbor stage | | .033 | | .083 | | .207 | | .016 |
| I/II | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| III/IV | 2.67 (1.08–6.59) | | 2.06 (0.91–4.64) | | 1.85 (0.71–4.81) | | 4.20 (1.31–13.46) | |
| PINK score | | .481 | | .613 | | .372 | | .701 |
| 0 | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| 1 | 1.28 (0.57–2.94) | .563 | 1.34 (0.68–2.65) | .396 | 1.54 (0.72–3.29) | .266 | 1.27 (0.39–4.13) | .687 |
| ≥2 | 2.35 (0.55–10.15) | .251 | 1.58 (0.38–6.66) | .530 | 2.16 (0.51–9.26) | .298 | 2.32 (0.29–18.36) | .424 |
| SUVmax | | .038 | | .006 | | .001 | | .356 |
| <9.65 | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| ≥9.65 | 2.32 (1.05–5.13) | | 2.52 (1.30–4.86) | | 4.17 (1.80–9.65) | | 0.60 (0.20–1.78) | |

DRFS = distant relapse free survival, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, LDH = lactate dehydrogenase, LRFS = local recurrence free survival, NC = nasal cavity, OS = overall survival, PFS = progression free survival, PINK = prognostic index of natural killer lymphoma, ULN = upper limits of normal.

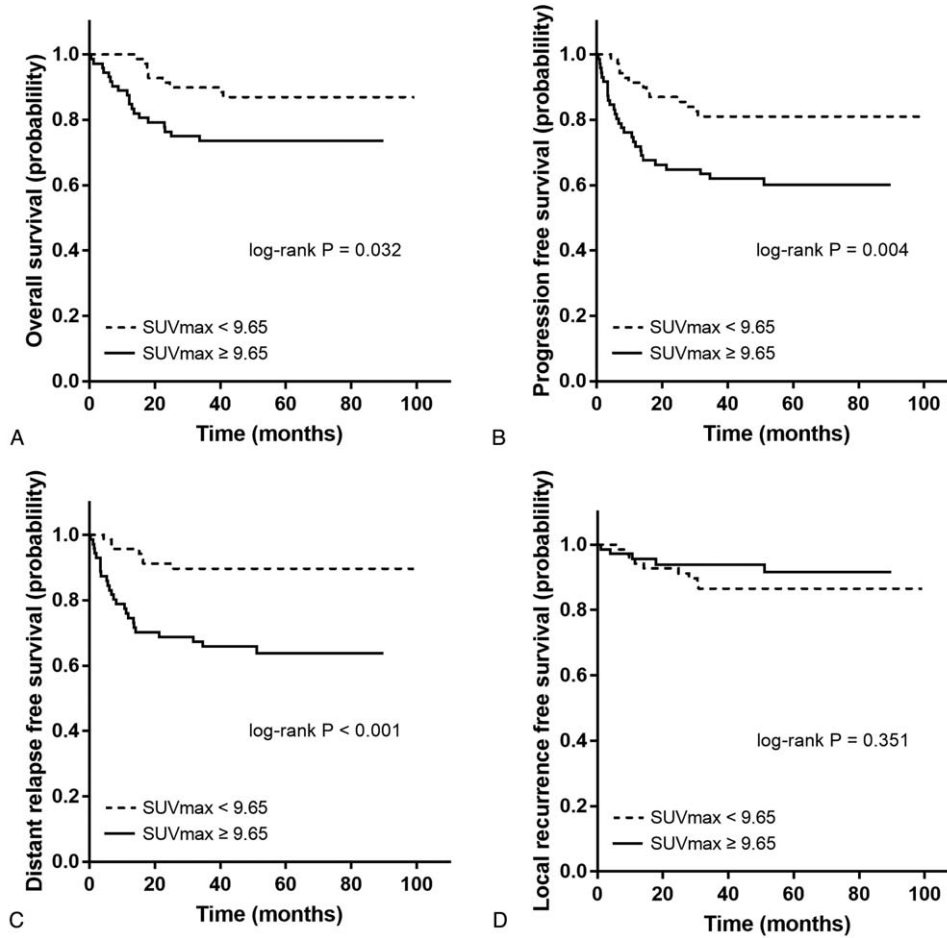


Figure 1. Kaplan–Meier plots of overall survival (A), progression free survival (B), distant relapse free survival (C) and local recurrence free survival (D) in extranodal NK/TCL patients stratified by lower and higher baseline SUVmax groups.

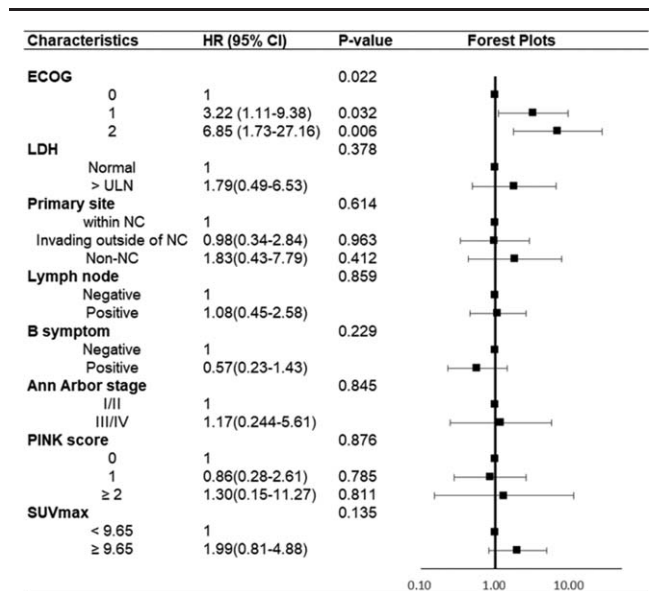


Figure 2. Multivariate survival analyses and forest plots in terms of overall survival in extranodal NK/TCL patients.

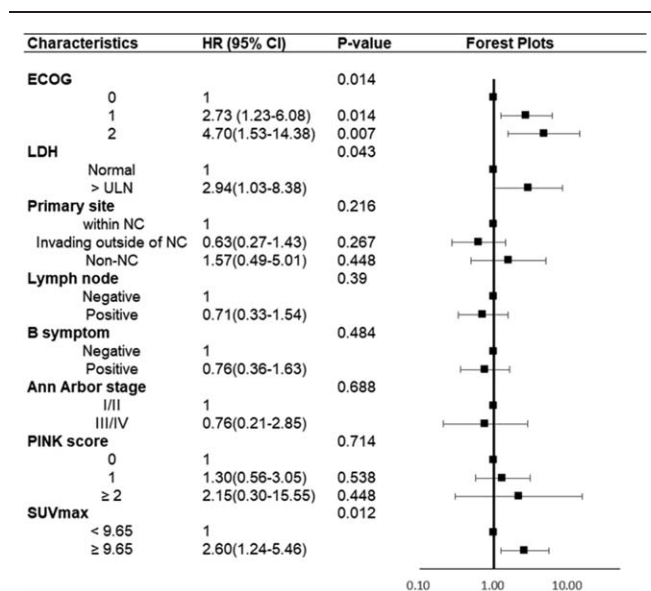


Figure 3. Multivariate survival analyses and forest plots in terms of progression free survival in extranodal NK/TCL patients.

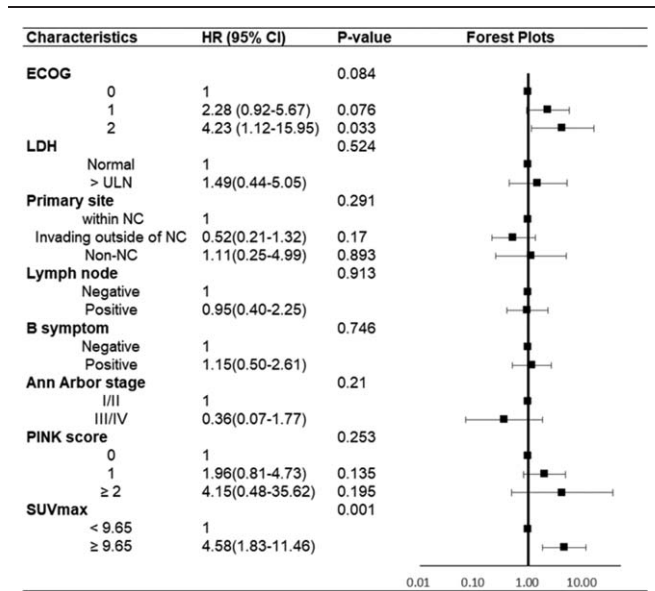


Figure 4. Multivariate survival analyses and forest plots in terms of distant relapse free survival in extranodal NKTCL patients.

The above results of the multivariate survival analyses indicated that SUVmax ≥ 9.65 was a poor prognostic predictor for PFS and DRFS independent from other factors, but not for OS and LFRS.

4. Discussion

¹⁸F-FDG is a glucose analogue with high uptake rate in cancer cells, and this high uptake can distinguish malignant cells from normal cells. During the past decade, many studies have shown that ¹⁸F-FDG PET-CT has a central role in the diagnosis, staging, and response evaluation of malignant lymphoma, such as Hodgkin’s lymphoma (HL), follicular lymphoma (FL), and

diffuse large B-cell lymphoma (DLBCL).^[13–15] For extranodal NKTCL, it was reported that high ¹⁸F-FDG uptake is closely related to local tumor invasion.^[18] Zhou et al^[17] reviewed 135 extranodal NKTCL patients from 6 studies and concluded that ¹⁸F-FDG-PET-CT had high sensitivity and specificity in the diagnosis and staging of extranodal NKTCL.

For extranodal NKTCL, several studies have shown that the baseline SUVmax can be a predictor of the prognosis. Kim et al^[19] retrospectively analyzed 20 stage I to IV extranodal NKTCL patients and found that a high SUVmax (cutoff=8.1) was significantly related to poor PFS, but not OS. Bai et al^[20] also retrospectively analyzed 81 stage I to IV extranodal NKTCL patients and found that a higher SUVmax (cutoff=15) was associated with poorer response to primary therapy, and inferior OS. It should be noted that the patients in the above two studies received anthracycline-containing regimen, which was proved not effective chemotherapy. Nowadays, non-anthracycline-containing regimen were widely used in extranodal NKTCL patients,^[3–8] including patients in our study. For these patients, the prognostic value of SUVmax was also verified by several researches. Chang et al^[21] analyzed 52 stage I to IV extranodal NKTCL patients and found that baseline SUVmax > 15.1 was a poor predictor for OS independent of other clinical features but not for PFS.

There are few researches focusing on the particular nasal type patients. Jiang et al^[22] studied 33 stage I to IV extranodal NKTCL nasal type patients and demonstrated that the baseline SUVmax (cutoff = 10.0) could independently predict PFS and OS. Pak et al^[23] enrolled another 36 stage I to IV extranodal NKTCL nasal type patients from five centers and found a higher baseline SUVmax (cutoff = 12.8) was associated with a poorer OS. The patients in the above two studies all received non-anthracycline-containing regimen with or without radiation, which was similar to our study. However, the sample size of these studies was relatively small.

In the present study, we also focused on the patients with extranodal NKTCL, nasal type, with up to date the largest sample size (n=141). All patients received chemotherapy with non-anthracycline-containing regimen and radiation (50 Gy/25 Fx). We found that the optimal cutoff of baseline SUVmax was 9.65. A higher SUVmax (≥9.65) was related to more aggressive clinical features, including primary tumors that invaded outside of the nasal cavity, poor ECOG score, and elevated LDH level, which were consistent with the findings by Suh et al^[18] and Bai et al.^[20] As expected, we also demonstrated the poor prognostic value of higher SUVmax (≥9.65). After adjusting for other clinical features, the multivariate survival analyses indicated that an SUVmax ≥ 9.65 was an independent poor prognostic factor for PFS and DRFS, which indicated a higher risk of distant relapse, however, not local recurrence. This is the first study to focus on the associations between SUVmax and the risk of local recurrence and distant relapse, respectively. Thus, we suggested that the patients with higher baseline SUVmax values need more aggressive systematic chemotherapy to control distant spread after diagnosis. It is recommended that patients who had localized disease within nasal cavity without risk factor can receive radiotherapy alone, but if these patients have high baseline SUVmax, radiotherapy alone may not be appropriate.

It is interesting that the cutoff values of the present and previous studies varied a lot, ranging from 8 to 16. This disparity may be due to the inconsistency of the PET-CT scanning systems, examination protocols, calculation methods, and

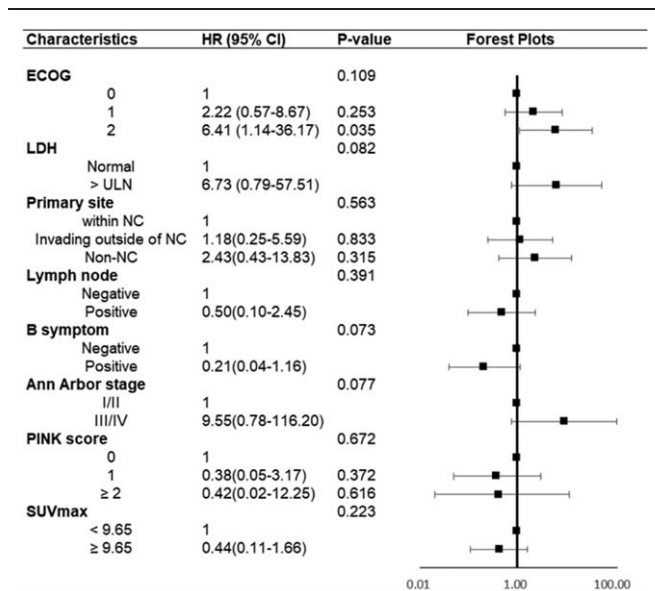


Figure 5. Multivariate survival analyses and forest plots in terms of local recurrence free survival in extranodal NKTCL patients.

patient enrollment criteria, which made the results from different centers incomparable and limited its value in clinical practice. Thus, it's of importance to establish standard criteria for all hospitals to perform PET-CT examination and data analyses.

Previous studies have identified a serial of traditional clinical unfavorable prognostic factors, such as presence of B symptoms, local tumor invasion, advanced stage, poor performance status, elevated serum LDH level, higher prognostic scores (IPI/KPI/PINK), etc.^[10,24,25] We also included these clinical features into the univariate and multivariate survival analyses, and finally verified similar independent prognostic value of ECOG score (for PFS and OS) and LDH level (for PFS) in our cohort. The prognostic value of Ann Arbor stage only remained in univariate survival analyses (for OS and LRFS). The negative prognostic results of other viable such as local tumor invasion and PINK score were probably due to the inadequate sample size and asymmetric distribution among subgroups.

Furthermore, it's worth noting that other ¹⁸F-FDG PET-CT parameters besides baseline SUVmax of the primary lesion, such as the metabolic tumor volume (MTV), total lesion glycolysis (TLG), and Deauville score (DS), are emerging as promising prognostic factors. SUVmax represents the highest uptake of the primary lesion, which only reflects the most serious spot, and ignores the range of the lesion. MTV includes the tumor areas with uptake higher than a certain threshold. And TLG is usually calculated as SUVmean × MTV. In other word, MTV draws an outline and obtained a volume, and TLG combines the mean uptake and volume together. Both MTV and TLG were demonstrated as significant predictive factors for PFS or OS in previous studies.^[23,26] In addition, the DS on the five-point scale is developed according to the Deauville criteria, comparing the ¹⁸F-FDG uptake of the tumor with that of the mediastinum and liver.^[27] It was reported that interim and post-therapy DS might represent residual disease and could predict unfavorable PFS and OS, which probably helped to stratify the risk of those patients.^[28–30]

We noted that the above studies had no standard consensus on patient enrollment processes, treatment regimens, PET-CT parameter interpretation and cutoff value calculation. Thus, their results should be interpreted with caution and need to be verified in larger-scale studies. However, it cannot be denied that these parameters have promising prognostic values for extranodal NKTCL patients. In 2018, Wang et al^[16] reviewed and meta-analyzed a total of 535 extranodal NKTCL patients from 9 trials. For baseline PET-CT, the SUVmax, MTV, and TLG were found significantly related to PFS (HRs: 2.78, 3.61, 5.62) and OS (HRs: 4.78, 3.20, 7.76). For interim and post-therapy PET-CT, DS was demonstrated to be a significant predictor of PFS (HRs: 5.15, 3.65) and OS (HRs: 5.80, 3.32). Thus, except for the clinical features, such as age, B symptom, ECOG score, LDH level, stage, PINK score, etc, these PET-CT-derived parameters also contributed to the prognostic prediction for extranodal NKTCL patients, potentially help construct a more accurately prognostic prediction model.

Of course, there were some limitations in our study. First, we only investigated the prognostic value of the baseline SUVmax. The prognostic value of other parameters, such as the whole-body SUVmax, MTV, TLG, and DS, need to be investigated in our cohort in the future. Second, because PET scan is not covered by Medicare reimbursement in China, we did not perform interim and post-treatment PET-CT scans to evaluate treatment efficacy, thus, the prognostic value of interim/post-treatment PET-CT

parameters and the changes compared with baseline PET-CT parameters were unclear.

In conclusion, for extranodal NKTCL patients, the baseline SUVmax of ¹⁸F-FDG PET-CT was associated with aggressive features, and a high SUVmax (≥ 9.65) was an independently poor prognostic factor of DRFS and PFS. Baseline SUVmax is a valuable tool to help identify patients with a high risk of disease progression and may help guide the treatment strategy. Moreover, larger scale prospective research and investigation of other new PET-CT-derived parameters are needed in the future.

Acknowledgments

We would like to thank American Journal Experts (<https://www.aje.com>) for assisting with language editing.

Author contributions

Conceptualization: Xianwu Xia, Xuejun Ma.

Data curation: Yaqi Wang, Jianjun Yuan.

Formal analysis: Yaqi Wang.

Investigation: Xianwu Xia, Wenjie Sun.

Methodology: Yaqi Wang, Jinjin Jiang.

Project administration: Xianwu Xia.

Resources: Wenjie Sun, Qunling Zhang, Xuejun Ma.

Software: Yaqi Wang.

Supervision: Chang Liu, Qunling Zhang, Xuejun Ma.

Validation: Chang Liu.

Visualization: Jinjin Jiang, Yaqi Wang.

Writing – original draft: Xianwu Xia, Yaqi Wang.

Writing – review & editing: Yaqi Wang, Xuejun Ma.

References

- [1] Au WY, Ma SY, Chim CS, et al. Clinicopathologic features and treatment outcome of mature T-cell and natural killer-cell lymphomas diagnosed according to the World Health Organization classification scheme: a single center experience of 10 years. *Ann Oncol* 2005;16:206–14.
- [2] Tse E, Kwong YL. The diagnosis and management of NK/T-cell lymphomas. *J Hematol Oncol* 2017;10:85.
- [3] Li YX, Yao B, Jin J, et al. Radiotherapy as primary treatment for stage IE and IIE nasal natural killer/T-cell lymphoma. *J Clin Oncol* 2006;24:181–9.
- [4] 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;27:6027–32.
- [5] Kim SJ, Yang DH, Kim JS, et al. Concurrent chemoradiotherapy followed by L-asparaginase-containing chemotherapy, VIDL, for localized nasal extranodal NK/T cell lymphoma: CISL08-01 phase II study. *Ann Hematol* 2014;93:1895–901.
- [6] Kwong YL, Kim WS, Lim ST, et al. SMILE for natural killer/T-cell lymphoma: analysis of safety and efficacy from the Asia Lymphoma Study Group. *Blood* 2012;120:2973–80.
- [7] Yamaguchi M, Kwong YL, Kim WS, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group study. *J Clin Oncol* 2011;29:4410–6.
- [8] Yamaguchi M, Tobinai K, Oguchi M, et al. Phase I/II study of concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: Japan Clinical Oncology Group Study JCOG0211. *J Clin Oncol* 2009;27:5594–600.
- [9] Lee J, Kim WS, Park YH, et al. Nasal-type NK/T cell lymphoma: clinical features and treatment outcome. *Br J Cancer* 2005;92:1226–30.
- [10] 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;24:612–8.

- [11] Kwong YL, Pang AW, Leung AY, et al. Quantification of circulating Epstein-Barr virus DNA in NK/T-cell lymphoma treated with the SMILE protocol: diagnostic and prognostic significance. *Leukemia* 2014;28:865–70.
- [12] Yang Y, Zhu Y, Cao JZ, et al. Risk-adapted therapy for early-stage extranodal nasal-type NK/T-cell lymphoma: analysis from a multicenter study. *Blood* 2015;126:1424–32. quiz 517.
- [13] Biggi A, Gallamini A, Chauvie S, et al. International validation study for interim PET in ABVD-treated, advanced-stage hodgkin lymphoma: interpretation criteria and concordance rate among reviewers. *J Nucl Med* 2013;54:683–90.
- [14] Luminari S, Biasoli I, Arcaini L, et al. The use of FDG-PET in the initial staging of 142 patients with follicular lymphoma: a retrospective study from the FOLL05 randomized trial of the Fondazione Italiana Linfomi. *Ann Oncol* 2013;24:2108–12.
- [15] Safar V, Dupuis J, Itti E, et al. Interim [18F]fluorodeoxyglucose positron emission tomography scan in diffuse large B-cell lymphoma treated with anthracycline-based chemotherapy plus rituximab. *J Clin Oncol* 2012;30:184–90.
- [16] Wang H, Shen G, Jiang C, et al. Prognostic value of baseline, interim and end-of-treatment 18F-FDG PET/CT parameters in extranodal natural killer/T-cell lymphoma: A meta-analysis. *PLoS One* 2018;13:e0194435.
- [17] Zhou X, Lu K, Geng L, et al. Utility of PET/CT in the diagnosis and staging of extranodal natural killer/T-cell lymphoma: a systematic review and meta-analysis. *Medicine (Baltimore)* 2014;93:e258.
- [18] Suh C, Kang YK, Roh JL, et al. Prognostic value of tumor 18F-FDG uptake in patients with untreated extranodal natural killer/T-cell lymphomas of the head and neck. *J Nucl Med* 2008;49:1783–9.
- [19] Kim CY, Hong CM, Kim DH, et al. Prognostic value of whole-body metabolic tumour volume and total lesion glycolysis measured on (1)(8) F-FDG PET/CT in patients with extranodal NK/T-cell lymphoma. *Eur J Nucl Med Mol Imaging* 2013;40:1321–9.
- [20] Bai B, Huang HQ, Cai QC, et al. Predictive value of pretreatment positron emission tomography/computed tomography in patients with newly diagnosed extranodal natural killer/T-cell lymphoma. *Med Oncol* 2013;30:339.
- [21] Chang Y, Fu X, Sun Z, et al. Utility of baseline, interim and end-of-treatment (18)F-FDG PET/CT in extranodal natural killer/T-cell lymphoma patients treated with L-asparaginase/pegaspargase. *Sci Rep* 2017;7:41057.
- [22] Jiang C, Zhang X, Jiang M, et al. Assessment of the prognostic capacity of pretreatment, interim, and post-therapy (18)F-FDG PET/CT in extranodal natural killer/T-cell lymphoma, nasal type. *Ann Nucl Med* 2015;29:442–51.
- [23] Pak K, Kim BS, Kim K, et al. Prognostic significance of standardized uptake value on F18-FDG PET/CT in patients with extranodal nasal type NK/T cell lymphoma: a multicenter, retrospective analysis. *Am J Otolaryngol* 2018;39:1–5.
- [24] Chim CS, Ma SY, Au WY, et al. Primary nasal natural killer cell lymphoma: long-term treatment outcome and relationship with the International Prognostic Index. *Blood* 2004;103:216–21.
- [25] Lee J, Park YH, Kim WS, et al. Extranodal nasal type NK/T-cell lymphoma: elucidating clinical prognostic factors for risk-based stratification of therapy. *Eur J Cancer* 2005;41:1402–8.
- [26] Song MK, Chung JS, Shin HJ, et al. Clinical value of metabolic tumor volume by PET/CT in extranodal natural killer/T cell lymphoma. *Leuk Res* 2013;37:58–63.
- [27] Barrington SF, Qian W, Somer EJ, et al. Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. *Eur J Nucl Med Mol Imaging* 2010;37:1824–33.
- [28] Jiang C, Su M, Kosik RO, et al. The Deauville 5-point scale improves the prognostic value of interim FDG PET/CT in extranodal natural killer/T-cell lymphoma. *Clin Nucl Med* 2015;40:767–73.
- [29] Jiang C, Liu J, Li L, et al. Predictive approaches for post-therapy PET/CT in patients with extranodal natural killer/T-cell lymphoma: a retrospective study. *Nucl Med Commun* 2017;38:937–47.
- [30] Kim SJ, Choi JY, Hyun SH, et al. Risk stratification on the basis of Deauville score on PET-CT and the presence of Epstein-Barr virus DNA after completion of primary treatment for extranodal natural killer/T-cell lymphoma, nasal type: a multicentre, retrospective analysis. *Lancet Haematol* 2015;2:e66–74.