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Review Article

^{18}F-FDG PET/CT in extranodal natural killer/T-cell lymphoma: a comprehensive evaluation method

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Abstract: Extranodal NK/T-cell lymphoma (ENKTL) is an uncommon subtype of non-Hodgkin's lymphoma that is closely related to Epstein-Barr virus (EBV) infection. ENKTL exhibits distinctive clinicopathological features among lymphomas and has poor overall survival in the absence of effective treatment. The timely and accurate diagnosis of ENKTL is crucial for effective treatment and a positive prognosis. ^{18}F-Fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has emerged as an invaluable diagnostic modality for staging, curative effect evaluation, and prognosis analysis in ENKTL. We herein provide a comprehensive overview of the advances in the application of ^{18}F-FDG PET/CT in patients with ENKTL.

Keywords: ^{18}F-FDG, PET/CT, extranodal natural killer/T-cell lymphoma, ENKTL, diagnosis, staging, prognosis, radiomics

Introduction

Extranodal NK/T-cell lymphoma (ENKTL) is an uncommon subtype of non-Hodgkin's lymphoma categorized under mature T-cell and NK-cell neoplasms by the World Health Organization (WHO) latest classification system [1]. This extremely aggressive malignancy has a poor overall survival in the absence of effective treatment. For patients with stage III/IV ENKTL, chemotherapy stands as the sole treatment option, yet achieving complete remission (CR) rates remain below 20% [2, 3]. Patients with stage I/II ENKTL have the choice of radiation alone or chemoradiotherapy, with a CR ranging from 58% to 78% and a 5-year overall survival of 40% to 59% [4-7]. This underscores the importance of timely and accurate diagnosis for positive prognosis. ^{18}F-Fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has emerged as an invaluable diagnostic modality in various cancers. Integrating measurements of glucose metabolism and anatomical structure imaging of the lesions, ^{18}F-FDG PET/CT is an indispensable imaging tool in the clinical management of lymphomas [8]. It has irreplaceable advantages in evaluating local invasion by the primary tumor, detecting small local recurrence, and identifying distant metastases [9, 10]. For ENKTL, ^{18}F-FDG PET/CT holds promising potential in the staging, evaluating treatment efficacy, and conducting prognostic analysis. In this article, we provide a comprehensive overview of the advances in the application of ^{18}F-FDG PET/CT in patients with ENKTL.

Epidemiological characteristics and clinical manifestation

ENKTL is a malignancy with a unique epidemiological distribution, commonly occurred in Asian and South American populations but exceptionally rare in European origin [11-13]. The incidence rate of ENKTL in the U.S. Whites was six cases per 10 million person-years [14]. Extensive studies have demonstrate that males exhibit a higher incidence rate of ENKTL, with the number of male ENKTL patients being twice that of female patients [15].

ENKTL could be classified into nasal or extranasal types according to the primary site of disease, and Au et al. [16] reported an incidence rate of 68% and 26%, respectively. Nasal ENKTL affects the upper aerodigestive tract

with nasal obstruction, nasal discharge, epistaxis, and necrotic lesions of the nose or palate that are clinically manifested [17]. Extranasal ENKTL can involve various sites, with the intestine being the most commonly affected, accounting for 37% of cases. The skin and testis follow as the next most commonly affected sites at 26% and 17%, respectively, in terms of frequency [16]. The patients with gastrointestinal tract involvement had manifestations including abdominal pain, gastrointestinal tract bleeding and bowel perforation [18]. Most of the patients with skin involvement presented with either cellulitis or skin ulceration [19]. ENKTL can also involve testis and eyes, manifesting as swelling and pain [16]. Laboratory tests revealed anemia, thrombocytopenia, low absolute lymphocyte count and an elevated serum lactate dehydrogenase (LDH) in a subset of ENKTL patients [20]. The estimated 5-year overall survival (OS) rate ranges from 40% to 50%, with prognosis largely dependent on the stage of the disease at the time of diagnosis [21].

Pathology and pathogenesis

Multiple factors have been linked to the pathogenesis of ENKTL. In 1990, the initial report was made regarding the detection of EBV DNA and EBV-determined nuclear antigen 1 (EBNA1) within the lymphoma cells of individuals diagnosed with ENKTL, suggesting the importance of EBV for development of ENKTL [22]. EBV involvement was also confirmed by subsequent studies [23-25]. The development of ENKTL is also influenced by various cytokines, chemokines and microRNAs, which may be produced by EBV-oncogenic proteins in the lymphoma. For example, IL-9 [26], IL-10 [27], soluble intercellular adhesion molecule-1 (sICAM-1) [28], and hepatocyte growth factor (HGF) [29] act as proliferation factors. Meanwhile, interferon-gamma-inducible protein-10 (IP-10) has been found to increase the invasiveness of NNKTL cells [30]. Conversely, downregulation of microRNA (miR)-15a, potentially due to LMP1, reduces antiproliferative signals [31]. Genetic alterations also play an important role in ENKTL pathogenesis. NGS analysis has revealed the mutations located in the tumor suppressors (for example, TP53 mutation and del6q21), JAK-STAT pathway, NF-κB and MAPK signaling pathways [32, 33].

The histological characteristics of ENKTL are marked by diffused lymphoid proliferation, presenting with an angiocentric and angiodestructive growth pattern. Cytologically, the lymphoma cells display a wide spectrum, ranging from small to large cells or a mixture of small and large cells [12]. Necrosis and the presence of inflammatory cells are also observable [26]. The lymphoma cells typically express CD2, cytoplasmic CD3ε, CD56, and cytotoxic markers such as granzyme B, TIA-1, and perforin, while being negative for surface CD3 [20].

Treatment

Anthracycline-containing regimens had proved ineffective in the treatment of ENKTL [34]. Recently, effective non-anthracycline regimens such as DeVIC (dexamethasone, etoposide, ifosfamide, and carboplatin) and VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone) have demonstrated successful outcomes for localized ENKTL through concurrent chemoradiotherapy and sequential chemotherapy followed by radiotherapy [35, 36]. For advanced ENKTL, L-asparaginase-containing regimens such as SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide), DDGP (gemcitabine, pegaspargase, cisplatin, and dexamethasone) and AspaMetDex (L-asparaginase, methotrexate, and dexamethasone) have been proved to improve survival outcomes [37, 38].

Clinical utility of ^{18}F-FDG PET/CT in ENKTL

Diagnostic value

We identified 14 rare ENKTL cases with PET/CT findings based on the literature search on PubMed from 2011 to 2023. The keywords used were “extranodal natural killer/T-cell lymphoma” and “positron emission tomography”. The Basic information and PET/CT findings of all cases are summarized in **Table 1** [39-51]. Existing studies have consistently shown that ENKTL is characterized by intense FDG uptake, making PET/CT highly sensitive in detecting both nasal and extra-nasal lesions (**Figure 1**).

CT and MRI are commonly employed modalities for the clinical diagnosis of nasal ENKTL. CT reveals the extent of the local bone destruction and MRI illustrates the bone marrow or soft tissue involvement [52]. However, detecting small

Table 1. Basic information and ^{18}F-FDG PET/CT findings of patients with ENKTL

No.	References	Gender	Age (y)	Involved sites	^{18}F-FDG PET/CT findings
1	Filizoglu et al. [39]	Female	56	Cutaneous and Subcutaneous	Increased ^{18}F-FDG uptake
2	Huang et al. [40]	Male	37	Left side of vocal cord	Increased ^{18}F-FDG uptake (SUVmax 5.77)
3	Zhang et al. [41]	Male	54	Right upper lip	Increased ^{18}F-FDG uptake (SUVmax 15.3)
4	Tang et al. [42]	Female	28	Vaginal	Increased ^{18}F-FDG uptake (SUVmax 13.76)
5	Gao et al. [43]	Female	50	Vitreoretinal, right breast	Increased ^{18}F-FDG uptake in the right breast
6	Kiratli et al. [44]	Male	57	Conjunctival of the right eye	Increased ^{18}F-FDG uptake anterior to the right eye
7	Charles et al. [45]	Male	39	Right lower eyelid, left calf, right testicular	Increased ^{18}F-FDG uptake
8	Yang et al. [46]	Male	55	Right hemisphere, right maxillary sinus, transverse process and T6 vertebra	Increased ^{18}F-FDG uptake
9	Fei et al. [47]	Female	83	Both lung fields, skin	Increased ^{18}F-FDG uptake (SUVmax 21)
10	Kwon et al. [48]	Male	33	Glottis and supraglottic areas, both anterior chest walls, upper back areas, upper arms, lungs, and perirenal and cervical lymph nodes	Increased ^{18}F-FDG uptake
11	Baek et al. [49]	Male	23	Pancreas, right ventricular	Increased ^{18}F-FDG uptake
12	Moon et al. [50]	Male	60	Left ethmoid sinus, both cervical lymphatic chains and both suprarenal areas	Increased ^{18}F-FDG uptake
13	Moon et al. [50]	Male	46	Nasal cavity, left tonsil, and lymph nodes in left submandibular area	Increased ^{18}F-FDG uptake
14	Liu et al. [51]	Male	30	Left knee joint	Increased ^{18}F-FDG uptake

Note: SUVmax indicates maximum standardized uptake value.

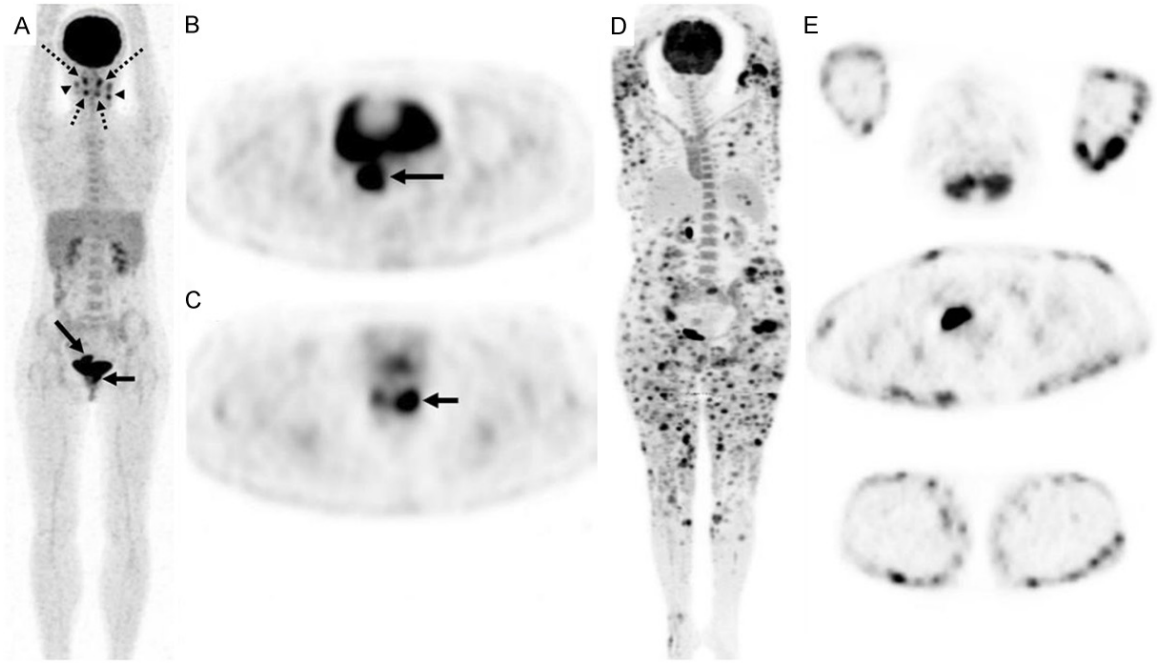

Figure 1. ^{18}F-FDG PET/CT at initial diagnosis. A 28-year-old woman who was diagnosed with ENKTL by biopsy. The ^{18}F-FDG PET/CT maximum intensity projection image (A) demonstrates two lesions (long arrow and short arrow) in the pelvic region with increased metabolic uptake. The symmetrical uptakes in the tonsils (long dotted arrows), sublingual glands (short dotted arrows), and lymph nodes (arrowheads) are considered benign. The axial PET im-

ages (B and C) reveal increased metabolic uptake in the right vaginal wall (long arrows; SUVmax 13.76) and in the left vaginal wall (short arrows; SUVmax 10.73). A 56-year-old woman who was diagnosed with ENKTL. ^{18}F-FDG PET/CT maximum intensity projection image (D) and axial PET image (E) demonstrated wide spread lesions all over the body with increased metabolic uptake, especially in the shoulders, gluteal region, and thigh. (A-C) are cited from Tang et al. [42] with permission from Wolters Kluwer Health, Inc., while (D and E) are cited from Filizoglu et al. [39].

local recurrence, lymph node involvement and distant metastases can pose a challenge for these modalities. In contrast, by combining the detection of metabolic activity and detailed anatomical images of the lesion, PET/CT can provide a more comprehensive picture of the extent and location of nodal, extranodal lesions [50, 51, 53-55].

A study conducted by Fujiwara et al. [53] showed that PET/CT outperformed conventional methods (contrast-enhanced CT, biopsies from primary sites, and bone marrow examinations) in the identification of nodal lesions (100% vs. 93%), extranodal lesions (94% vs. 61%) and cutaneous lesions (100% vs. 65%). Similarly, Moon et al. [50] revealed that PET/CT displayed increased sensitivity in detecting malignant lesions in both nodal and extranodal sites when compared with conventional methods. A meta-analysis conducted by Zhou et al. [54] investigated the usefulness of PET/CT in diagnosing ENKTL, the pooled sensitivity for six studies with patient-based data were 95%. Liu et al. [51] found that PET/CT detected 96% cutaneous lesions and 99.9% extracutaneous lesions, while conventional methods only detected 68% cutaneous lesions and 68.5% extracutaneous lesions. Guo et al. [55] have also reported similar results to the aforementioned studies. They compare the effectiveness of PET/CT and MRI in the local detection of malignancies in 36 patients with histologically proven early-stage ENKTL. PET/CT demonstrated a sensitivity of 100%, whereas MRI had a sensitivity of only 81.4%. These studies collectively highlight the superior ability of PET/CT in detecting lesions that are often missed by conventional methods, underscoring its value in the initial diagnosis of ENKTL.

Staging utility

Conventional imaging examinations such as CT, MRI, and ultrasound primarily discern observable structural or size alterations induced by tumors within tissues or organs. Their ability to identify small or early localized lesions is constrained, and imaging range is also limited. This frequently leads to a discrepancy between clinical staging and the actual disease status, thereby diminishing the guiding efficacy of clinical staging for treatment and prognosis. In contrast, PET/CT, through the capture of ^{18}F-FDG uptake in lesions, exhibits heightened sensitivity compared to conventional imaging examinations. This is particularly notable in the detection of occult lesions without apparent density and morphological changes, as well as those too diminutive for facile detection. Conclusively, PET/CT has irreplaceable advantages in evaluating both local invasion by the primary tumor and distant metastases, which may influence the staging of ENKTL (**Figure 2**) [42].

In a study, PET/CT was found to detect more nodal and extranodal lesions compared to conventional methods, which led to upstaging of 2 patients (11%) [53]. This suggests that PET/CT may be a more sensitive imaging modality for ENKTL staging compared to traditional methods. Similarly, Wu et al. [56] evaluated the staging utility of PET/CT in 13 newly diagnosed patients and 2 recurrent patients. The results showed that PET/CT accurately staged the patients, with 2 patients being down-staged, and 4 patients being upstaged based on the PET/CT findings. The impact of PET/CT on ENKTL staging is further highlighted by a study conducted by Moon et al. [50], which found that PET/CT findings led to a change of stage in 21.2% (12 patients) of cases and a modification of treatment strategy in 44.2% (23 patients) of cases. Furthermore, a meta-analysis reported a pooled sensitivity of 98% and specificity of 99% of PET/CT staging in ENKTL, indicating that PET/CT can detect the presence or absence of the disease with a high level of accuracy [54]. This is significant, as accurate staging is critical in determining the most appropriate treatment strategy for patients with ENKTL. In a study conducted by Liu et al. [51], the concordance between PET/CT staging and the final stage in ENKTL patients was investigated. PET/CT staging exhibited a higher concordance rate of 94.9% (37/39) compared

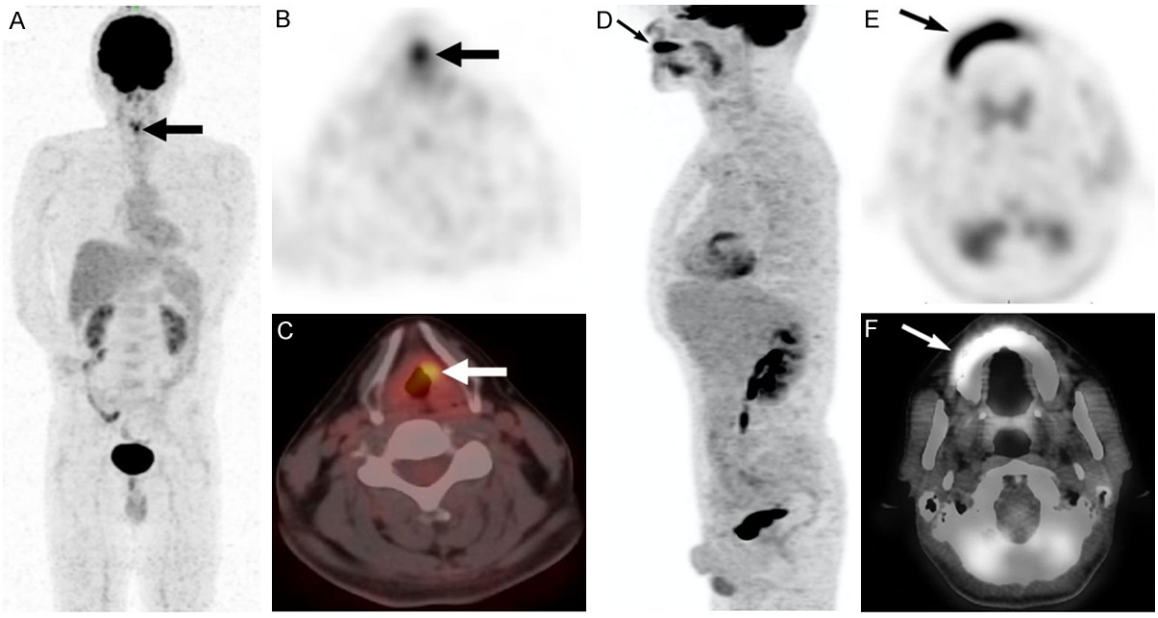

Figure 2. ^{18}F-FDG PET/CT in initial staging. A 37-year-old man with a newly diagnosed ENKTL, was referred for initial staging with ^{18}F-FDG PET/CT. (A-C) The maximum intensity projection image (A) revealed increased metabolic uptake in the larynx lesion (thick arrow). The axial PET (B) and fusion (C) images showed increased FDG uptake in the left vocal cord (thick arrows; SUVmax 5.77). No other abnormal uptake was seen on the PET/CT images. A 54-year-old man was diagnosed with ENKTL by biopsy. ^{18}F-FDG PET/CT was then performed for staging. (D-F) The maximum intensity projection (D) image demonstrated increased metabolic uptake in the upper lip (thin arrow). The axial PET (E) and fused PET/CT (F) images revealed high FDG accumulation (thin arrows; SUVmax 15.3) in the upper lip. No other abnormal tracer distribution was seen in rest of the body. (A-C) are cited from Huang et al. [40] with permission from Wolters Kluwer Health, Inc., while (D-F) are cited from Zhang et al. [41].

to conventional methods, which had a concordance rate of only 74.4% (29/39). These findings support the use of PET/CT as a highly accurate staging tool for ENKTL and demonstrated that PET/CT may provide better diagnostic information than conventional methods.

Bone marrow biopsies (BMB) are commonly employed in the initial staging of lymphoma to evaluate bone marrow infiltration (BMI) [57]. According to a study by Fujiwara et al. [53], out of 7 ENKTL patients with BMI, 3 patients (43%) had a discordant result between PET/CT and BMB. PET/CT showed negative results for BMI (PET-CT/BM-), while BMB indicated positive results (BMB/BM+). This highlights the limitations of PET/CT in detecting BMI and the importance of using other diagnostic tools, such as BMB, for accurate diagnosis and staging. In another study, PET/CT detected BMI in 46.2% (12/26) of BMB/BM+ advanced-stage patients. However, 10 PET-CT/BM+ patients showed negative BMB results [58]. When patients exhibit localized bone marrow lesions outside the bone marrow biopsy site, it might yield false-negative results, potentially diminishing the sensitivity of PET/CT. Zhou et al. [59] reported twelve BMI cases detected by PET/CT, with seven patients having discordant results (PET-CT/BM+ but BMB/BM-). In a study involved 101 newly diagnosed ENKTL patients conducted by Wang et al. [60], PET/CT identified 11 BMI-positive cases, while BMB only detected 4. According to Wang, BMB did not change the staging results determined by PET/CT and other procedures, indicating its limited impact on disease staging and treatment selection in newly diagnosed ENKTL [59, 60]. These studies suggest that combining PET/CT with targeted BMB assessment could potentially lead to improved diagnostic accuracy for BMI evaluation, especially in advanced patients. However, for early-stage patients, Adams et al. [61] and Wang et al. [60] reported 100% specificity of PET/CT in detecting BMI. Therefore, in patients with PET/CT staging limited to stages I-II, based on the strong specificity of PET/CT, BMI assessment through BMB may be omitted.

Treatment response evaluation

In order to accurately assess minimal residual disease status and develop an effective personalized treatment regimen, Deauville score (DS) has been used as an evaluation indicator for ENKTL [62]. The DS describe metabolic activity in the lesion by referencing the activity of mediastinal blood pool and liver as background standards, ensuring consistency and accuracy in the interpretation of PET/CT imaging results. In a study conducted by Khong et al. [63], the accuracy and reliability of PET/CT in evaluating the response of ENKTL patients to SMILE therapy were investigated. Results showed that both interim and post-treatment DS were independent predictors of both OS and progression-free survival (PFS). The findings of Xu's prospective study [64] were consistent with Khong's study despite using the different treatment regimen. In a retrospective study, it was found that positive interim and post-treatment PET/CT results (DS > 3) had good correlation with poor OS and PFS [65]. According to a meta-analysis conducted by Wang et al. [66], the DS on both interim and post-treatment PET/CT were significant predictors of both PFS and OS, with combined hazard ratios (HR) of 5.15 and 5.80 for interim PET/CT, and 3.65 and 3.32 for post-treatment PET/CT, respectively. Similarly, Qin et al. [67] reported that the DS on interim PET/CT scan was found to independently predict both PFS and OS. The findings of these studies suggested that DS on PET/CT could provide early feedback on a patient's response to treatment. This allows for timely adjustments in therapy, optimizing patient outcomes and minimizing unnecessary interventions.

To further explore whether DS on PET/CT can accurately differentiate patients with high or low risk of treatment failure in ENKTL, Kim et al. [62] proposed the risk classification system that categorized patients into three groups (low-risk, high-risk, and treatment failure) based on their post-treatment DS and EBV DNA assessment. This model showed a significant association with PFS, suggesting that post-treatment DS and EBV DNA could provide earlier indicator of treatment failure. Similarly, Lim et al. [68] reported that OS and PFS were significantly different between favorable risk group and unfavorable risk group classified according to pretransplant DS and EBV DNA detection. This finding may provide an insight that pretransplant risk classification based on DS and EBV DNA help identify the ENKTL patients who can benefit more from autologous stem cell transplantation.

However, Jiang et al. [69] yielded an inconsistent conclusion that the value of interim PET/CT in predicting treatment response is restricted, which may be due to their use of the International Harmonization Project (IHP) criteria to interpret interim PET/CT, instead of using DS. In another study, they reported that DS better predicted treatment outcomes than IHP criteria and SUV-based assessment on Interim PET/CT. In addition, given its rarity, there is still a lack of consensus on a standardized treatment strategy for ENKTL. Chen et al. [70] utilized presently acknowledged chemotherapy regimens in their study, mainly the VDLP regimen. The findings indicated that while the DS on interim PET/CT served as an independent predictor of PFS but not OS, the maximum standardized uptake value (SUVmax) independently predicted both PFS and OS. As a result, the conclusion was drawn that SUVmax may have greater value in treatment response evaluation than DS. Thus, more research is required to ascertain the clinical significance of using DS on interim PET/CT to evaluate treatment response of ENKTL patients. It is also important to investigate whether modifying treatment based on interim PET/CT results would improve patient survival.

Prognosis evaluation

Numerous studies have reported that many prognostic factors are associated with outcomes in ENKTL. Lee et al. [71] proposed a prognostic model known as the Korean Prognostic Index (KPI) specifically for ENKTL, which identified several factors that indicated a poor prognosis. These factors included the presence of "B" symptoms, which consist of fever with a temperature exceeding 38°C, inexplicable weight loss of over 10% of baseline value, and night sweats. Other factors that are indicative of a poor prognosis include advanced disease stage, elevated serum LDH level, and regional lymph nodes involvement. Considering the prognosis of ENKTL patients improves

Table 2. Results of baseline ^{18}F-FDG PET/CT parameters and radiomics features in predicting prognosis

References	Number of cases	PET/CT parameters and radiomics features correlated with prognosis	Prognostic parameters predicted
Suh et al. [73]	18	SUVmax (cut-off: 5.5)	Disease-specific survival (P = 0.023)
Bai et al. [74]	81	SUVmax (cut-off: 15)	OS (P = 0.020)
Kim et al. [75]	20	SUVmax (cut-off: 8.1)	PFS (HR 6.18, P = 0.036)
		WBMTV (cut-off: 14.4 cm^3)	OS (HR 8.37, P = 0.048) and PFS (HR 5.96, P = 0.016)
		WBTLG (cut-off: 52.7)	PFS (HR 4.74, P = 0.035)
Chang et al. [65]	52	SUVmax (cut-off: 15.1)	OS (P = 0.017)
		WBMTV (cut-off: 11.2 cm^3)	OS (P = 0.018) and PFS (P < 0.001)
		WBTLG (cut-off: 46.4)	OS (P = 0.041) and PFS (P = 0.017)
Song et al. [76]	80	MTV (cut-off: 35.2 cm)	OS (HR 4.102, P = 0.003) and PFS (HR 4.170, P = 0.002)
Wang et al. [66]	535	SUVmax	OS (HR 4.78, P < 0.0001) and PFS (HR 2.78, P = 0.0007)
		MTV	OS (HR 3.20, P = 0.002) and PFS (HR 3.61, P < 0.0001)
		TLG	OS (HR 7.76, P = 0.006) and PFS (HR 5.62, P = 0.001)
Li et al. [77]	171	SUVmax	OS and PFS
Ko et al. [79]	17	PET textural features (dissimilarity and low-intensity short-zone emphasis)	PFS
Wang et al. [80]	110	41 radiomics features; SUVmax, MTV, and TLG	OS and PFS
Guo et al. [81]	167	128 deep learning features	PFS

Note: SUVmax indicates maximum standardized uptake value; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; WBMTV, whole-body metabolic tumor volume; WBTLG, whole-body total lesion glycolysis; MTV, metabolic tumor volume; TLG, total lesion glycolysis; KPI, Korean Prognostic Index.

with development of non-anthracycline-based chemotherapy and optimal combination of radiotherapy, Kim et al. [72] developed two prognostic indices for ENKTL: natural killer lymphoma (PINK) and PINK-E, which takes into account the presence of EBV DNA.

FDG parameters from PET/CT also provide valuable information in patients with ENKTL (**Table 2**). Suh et al. [73] conducted a study on ENKTL patients with the head and neck involvement and found that only the SUVmax was identified as an independent factor determining disease-specific survival in the multivariate analysis. However, due to the retrospective design, limited patient population and relatively short follow-up, this conclusion may be subject to inaccuracies. Bai et al. [74] reported that SUVmax on baseline PET/CT is a predictive factor for prognosis in newly diagnosed ENKTL. Patients with SUVmax > 15 were associated with local invasion, high score of Korean Prognostic Index, resistance to primary treatment, poor OS and poor PFS.

Kim et al. [75] firstly evaluated the prognostic value of pretreatment whole-body metabolic tumor volume (WBMTV) and whole-body total lesion glycolysis (WBTLG) measured on ^{18}F-FDG PET/CT in ENKTL patients. The findings indicate that a high WBMTV serves as a dependable indicator of OS and PFS. Additionally, the study revealed that increased SUVmax and WBTLG were also statistically significant predictors of PFS. These results are consistent with those of a study by Chang et al. [65], which also found that WBTLG and SUVmax were significant prognostic indicators in patients with ENKTL. A prospective study conducted by Song et al. [76] suggested that a higher metabolic tumor volume (MTV), which indicates the lymphoma burden, was associated with worse survival outcomes in ENKTL patients. Wang et al. [66] analyzed baseline PET/CT data from nine trials comprising 535 ENKTL patients and found that SUVmax, MTV, and total lesion glycolysis (TLG) were significantly associated with OS and PFS. In addition, TLG displayed a tendency to outperform SUVmax and MTV in predicting survival

outcomes based on baseline PET/CT results. To better estimate OS and PFS and optimize an individualized surveillance strategy for patients with ENKTL, Li et al. [77] developed nomograms using pretreatment SUVmax and clinical parameters (stage, LDH, β2-microglobulin and hemoglobin). The calibration plots revealed a high degree of concordance between predicted and observed probabilities for OS, suggesting the nomograms possess considerable potential as effective personalized prognostic tools in ENKTL patients.

These studies demonstrated that SUVmax, MTV, TLG, WBMTV and WBTLG on baseline PET/CT may be essential predictors of PFS and OS in patients diagnosed with ENKTL. As a result, prognostic assessments that collectively considered multiple PET/CT parameters were deemed necessary for the optimal management of ENKTL patients.

Utility of PET/CT-based radiomics in ENKTL

PET/CT-derived semiquantitative parameters, such as SUV, MTV and TLG, have been widely utilized in research on diagnosis, prognosis and treatment outcome prediction of ENKTL. However, these parameters only provide basic imaging features and can miss tumor heterogeneity.

Radiomics is a promising method that employs sophisticated computer algorithms to extract large amount of tumor features that may be concealed in clinical images, unveiling tumor characteristics across various imaging modalities [78]. This modality could provide a profound understanding of tumor heterogeneity and potentially enhancing clinical decision-making for patients with ENKTL (**Table 2**).

Ko et al. [79] extracted the textural features and identified dissimilarity and low-intensity short-zone emphasis of pretreatment ^{18}F-FDG PET images as significant predictors of PFS. Incorporating these predictors into prognostic assessments may improve individualized prognostic stratification and enhance prognostic accuracy for ENKTL patients.

In the study conducted by Wang et al. [80], they analyzed pretreatment PET images of 110 ENKTL patients and extracted a total of 41 radiomic features. The radiomic features were selected using interobserver repeatability and LASSO Cox regression algorithms. Alongside the radiomic features, conventional metabolic parameters such as SUVmax, MTV, and TLG were also extracted to design two models: a radiomics-based model and a metabolism-based model. These models were presented in the form of nomograms. The study revealed that while radiomic features could be used to predict the outcomes of patients with ENKTL, the metabolism-based model performed better. However, this research solely employed PET for extracting radiological features. Integrating PET and CT images can broaden the feature repertoire, potentially revealing additional predictive radiological characteristics.

Recently, the artificial intelligence (AI) has shown potential in building high-performance predictive models combined with PET/CT-based radiomics. Using AI, Guo et al. [81] extracted 128 deep learning features from PET/CT images within the training set. They further proposed a novel biomarker named prediction similarity index (PSI). The PSI is calculated as the positive to negative predicted probability ratio. According to their findings, PSI independently predicted PFS in both weakly supervised deep learning method (WSDL) and conventional deep learning method (**Figure 3**). Given its capability to make use of incomplete follow-up data, the WSDL holds promise as a valuable tool for enhancing survival prediction in ENKTL.

In conclusion, the use of radiomics and AI has shown potential in predicting the outcomes of ENKTL patients. These advanced methods may provide a more comprehensive understanding of tumor heterogeneity and could help clinicians in developing more accurate predictions and better treatment strategies for ENKTL patients. Further research is needed to fully explore the potential of these techniques and integrate them into clinical practice.

Conclusion

ENKTL is a malignancy with a highly aggressive nature and a generally unfavorable prognosis when effective treatment is lacking. In patients with ENKTL, ^{18}F-FDG PET/CT has become a crucial modality for diagnosis, staging, assessment of treatment response, and prognosis

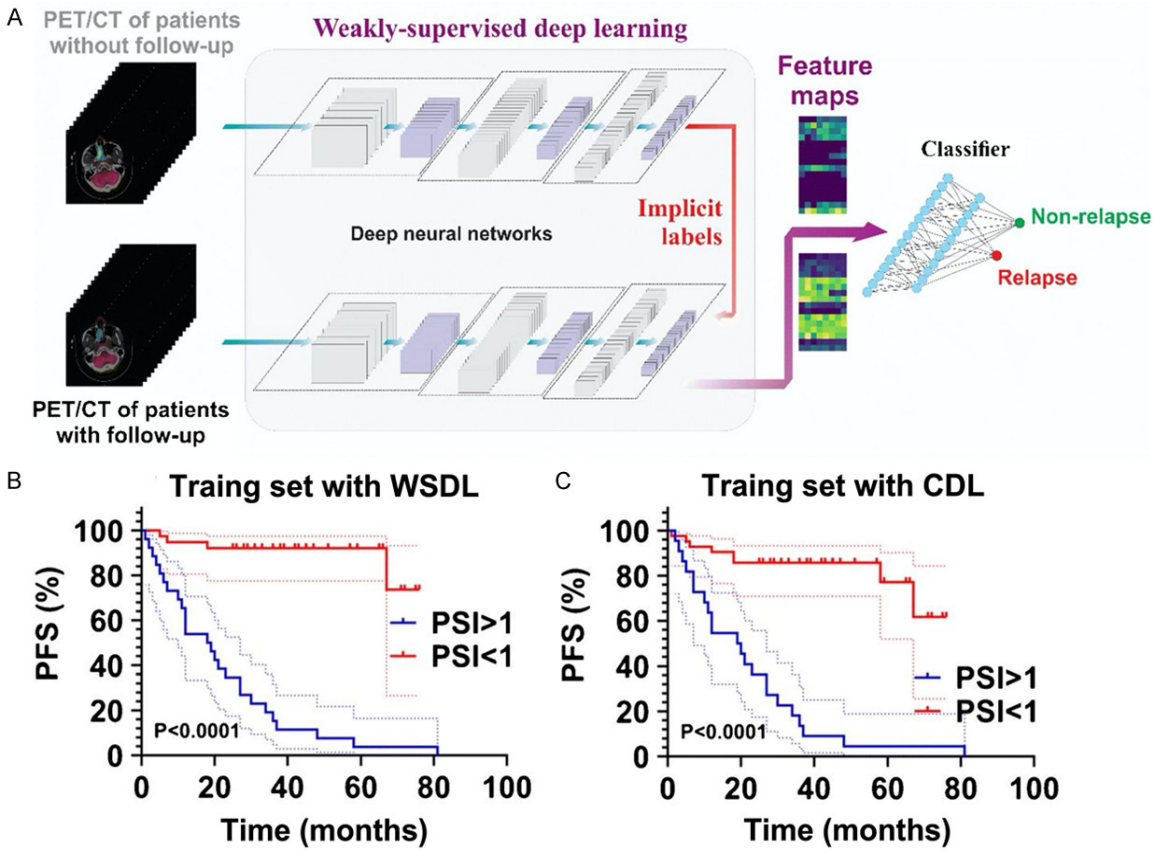

Figure 3. The illustration of the concept of the weakly supervised deep learning method (A) and Kaplan-Meier estimates of PFS in the training sets of patients with high and low PSI (B and C). (A-C) are cited from Guo et al. [81] with permission from Springer. PFS, progression-free survival; PSI, prediction similarity index; WSDL, weakly supervised deep learning; CDL, conventional deep learning.

evaluation. However, the value of DS on interim PET/CT in ENKTL is still unclear and requires further investigation. A model that incorporates multiple PET/CT parameters to predict individualized outcomes in ENKTL patients is needed. ^{18}F-FDG PET/CT-based radiomics holds great promise as a tool for constructing high-performance predictive models.

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Written informed consent was obtained from the patient.

Disclosure of conflict of interest

None.

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