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Positron emission tomography/computed tomography in the diagnosis, staging, and prognostic evaluation of natural killer/T-cell lymphoma

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Abstract

Natural killer/T-cell lymphoma (NKTL) is a rare subtype of non-Hodgkin's lymphoma that is associated with Epstein–Barr virus infection. The clinicopathological features of NKTL are unique among lymphomas. NKTL is an aggressive disease with a poor prognosis in the absence of effective treatment. Accurate diagnosis and staging are essential to ensure an appropriate treatment strategy and accurate prognosis of NKTL. ^{18}F-Fluorodexoyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is a valuable technique in the diagnosis, staging, and prognostic evaluation of various types of malignant tumors, including NKTL. PET/CT imaging studies of patients with NKTL have shown that NKTL is ^{18}F-FDG-avid and that PET/CT is superior to conventional methods in detecting cutaneous and extracutaneous lesions. We herein review recent PET/CT studies that have provided considerable insight into the diagnosis, staging, prognostic evaluation, and treatment effectiveness in patients with NKTL.

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Introduction

Natural killer/T-cell lymphoma (NKTL) is an uncommon subtype of non-Hodgkin's lymphoma that is usually associated with Epstein–Barr virus (EBV) infection.[1] Patients with NKTL are mainly located at East Asia, Southeast Asia, and Latin America; conversely, NKTL is relatively unusual in Europe and North America.[2–4] Clinically, NKTL is divided into two types: extranodal nasal type NKTL (ENKTL) and extranasal NKTL. ENKTL is characterized by frequent necrosis, angiocentric growth, and a cytotoxic phenotype and usually affects the nasal cavity, nasopharynx, and upper aerodigestive tract.[5] Extranasal NKTL frequently involves multiple areas including the skin, gastrointestinal tract, testis, and soft tissue.[6] ENKTL is typically associated with a poorer treatment response and prognosis than other types of lymphomas.[7] Chemotherapy in combination with radiotherapy is usually needed to achieve superior outcomes.[8] The cumulative probability of 5-year survival ranges from 37.9% to 49.5%.[9] Accurate diagnosis and staging are essential in the treatment strategy and prognosis of NKTL. However, neither an optimal treatment nor useful prognostic factors have been determined.

^{18}F-Fluorodexoyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has been widely used in the staging, prognosis, and treatment outcomes of various types of malignant tumors, including Hodgkin's lymphoma and various types non-Hodgkin's lymphoma.[10–13] Because of the poorer treatment response and prognosis of ENKTL, accurate diagnosis and staging of NKTL is urgently needed. We herein review recent PET/CT studies that have provided considerable insight into the diagnosis, staging, prognostic evaluation, and treatment effectiveness in patients with NKTL.

Diagnostic utility of PET/CT in patients with NKTL

PET/CT is a valuable tool for assessing extranodal involvement in patients with NKTL.[13–18] In one study, the mean ^{18}F-FDG uptake measured by the maximum standardized uptake value (SUV_{max}) was found to be significantly higher in NKTL.[17] To calculate the SUV_{max}, the region of interest was drawn along the margin of the lesion. The SUV_{max} was obtained using the following formula: SUV_{max} = maximum activity in the region of interest (MBq/g)/[injected dose (MBq)/body weight (g)]).

In 2010, Wu et al.[17] retrospectively analyzed 15 patients with NKTL and assessed the role of 18F-FDG PET/CT in staging. ^{18}F-FDG PET/CT detected nasal or extranasal lymphoma lesions in at least one site in all 15 patients. Of 11 patients with ENKTL, high levels of ^{18}F-FDG uptake were observed in the nasal cavities in 8 patients and in the nasopharynx in 2 patients, and extranasal lesions were found in 7 patients with nasal type

NKTL. In four patients with ENKTL, no obvious ^{18}F-FDG uptake was seen in either the nasal cavity or nasopharynx; however, multiple extranasal lesions were identified.[17] These results suggest that NKTL exhibits high ^{18}F-FDG uptake and that PET/CT is a useful tool in the staging of this disease.

In 2011, Fujiwara et al.[15] compared the utility of PET/CT with conventional methods (including CT, biopsy, and bone marrow examination) in the staging of ENKTL. Nineteen untreated patients with ENKTL were analyzed, and 116 lesions were detected by conventional methods and PET/CT. In total, 108 lesions (93%) were discovered by PET/CT and only 80 lesions were detected using conventional methods.[15] The number of extranodal lesions detected by conventional methods and PET/CT was 89; 84 (94%) and 51 (61%) lesions were positive as detected by PET/CT and conventional methods, respectively.[15] In a similar study, Liu et al.[16] evaluated the utility of ^{18}F-FDG PET/CT in the diagnosis of cutaneous ENKTL. In total, 39 patients with newly diagnosed ENKTL were included. PET/CT and conventional methods detected 139 lesions, among which 50 were cutaneous and 89 were extracutaneous-positive lesions.[16] ^{18}F-FDG PET/CT detected 48 cutaneous and 88 extracutaneous lesions, while conventional methods detected only 34 cutaneous lesions and 61 extracutaneous lesions that were positive for malignancy.[16]

A similar study was performed in a larger group of patients with ENKTL.[18] In total, 1300 anatomic lesions were assessed with an ^{18}F-FDG PET/CT scan and with conventional methods.[18] Only 59 nodal and 71 extranodal anatomic lesions were truly positive for malignancy. PET/CT detected 58 nodal and 69 extranodal anatomic lesions that were malignant, whereas conventional methods detected only 44 nodal and 61 extranodal anatomic lesions that were malignant.[18] Thus, PET/CT exhibited a significantly better sensitivity and specificity than conventional methods for the detection of malignant lesions. Moreover, PET/CT findings altered the original staging category for 12 patients (21.2%) and affected treatment planning in 23 patients (44.2%).[18] These studies demonstrated that PET/CT is superior to conventional methods in detecting cutaneous and extracutaneous lesions. Zhou et al.[19] assessed the role of FDG-PET/CT in bone marrow involvement in patients with ENKTL and found that the sensitivity and specificity of FDG-PET/CT for identifying bone marrow involvement was 100% and 86%, respectively. They suggested that FDG-PET/CT may be used as a complementary tool in patients with bone marrow involvement not detected by bone marrow biopsy. Thus, PET/CT is a useful tool for staging and treatment planning in patients with NKTL.

PET/CT also has limitations, including false-positive results. Liu et al.[16] reported 2 false-positive lesions of 429 lesions in 39 patients with ENKTL detected by PET/CT. One lesion with high FDG uptake was found in the right abdominal wall skin, but the biopsy revealed herpes zoster. The other lesion was found on the left lower limb, and the biopsy confirmed inflammatory cell infiltration; this lesion disappeared after 1 month.[16] Cheson et al.[20] reported that the false-positive rate of interim PET was 87% and that the positive predictive value was only 32% in patients with diffuse large B-cell lymphoma. They suggested that PET/CT scans should not be performed for at least 3 weeks, preferably 6 to 8 weeks, after completion of therapy because this false-positive result may persist for up to 2 weeks after chemotherapy alone or for 2 to 3 months after radiation therapy or chemoradiotherapy.[20] In another study of patients with cutaneous NKTL, the positive rate of FDG-PET was only 50%.[21] The authors suggested that

there was a limited role of FDG-PET in detection of cutaneous lesions of T/NK cell neoplasms because of the partial volume averaging effect.[21]

Staging and restaging roles of PET/CT in patients with ENKTL

Recent studies have suggested that PET/CT may be more advantageous than a routine work-up in ENKTL staging. ^{18}F-FDG PET/CT may be more effective than conventional methods for detecting nodal and extranodal malignant lesions and for correctly identifying primary sites missed by conventional methods.[15–18,22] Moreover, the original staging may be modified and the treatment strategies may be influenced by PET/CT data.[15–18] However, because limited numbers of patients were included in previous studies, it is difficult to conclude that FDG PET/CT should serve as the standard staging method.[15–18]

Wu et al.[17] found that 18F-FDG PET/CT detected more lesions than did conventional methods (biopsies, regional CT or magnetic resonance imaging, B-ultrasound, chest radiography, and medical examination). 18F-FDG PET/CT imaging of patients with ENKTL changed the stage of disease in six patients: four were upstaged and two were downstaged.[17] Fujiwara et al.[15] compared the utility of PET/CT and that of conventional methods in the staging of ENKTL. The results showed that PET/CT findings altered the stage and treatment strategy in two cases (11%). MacDonald et al.[23] reported that PET/CT improved target volume delineation and aided the staging of and radiotherapy planning in the treatment of ENKTL. Moon et al.[18] reported that PET/CT findings altered the original staging category in 12 patients with ENKTL (21.2%) and affected treatment planning in 23 patients (44.2%). Moreover, PET/CT exhibited significantly better sensitivity than conventional methods for the detection of malignant lesions.[18] Liu et al.[16] found that 18F-FDG PET/CT provided more accurate staging than did conventional methods in patients with cutaneous NKTL. In total, 39 patients with cutaneous NKTL were assessed using an ^{18}F-FDG PET/CT scan and conventional methods, and the results showed that ^{18}F-FDG PET/CT staging was consistent with the final stage determination (biopsy and clinical follow-up) in 94.9% (37/39) of patients, whereas staging by conventional methods was correct in the final stage determination in 74.4% (29/39) of patients.[16] These results indicate that ^{18}F-FDG PET/CT is a valuable modality for staging and treatment planning in patients with ENKTL.

Evaluation of NKTL treatment responses with PET/CT

Recent studies have confirmed the beneficial role of PET/CT in monitoring treatment responses in patients with non-Hodgkin's lymphoma, including NKTL, which is FDG-avid. Bai et al.[24] showed that the SUV_{max} predicted the responses to primary treatment in 81 patients with ENKL. A higher SUV_{max} (31.3) predicted treatment failure and was associated with bulky disease, local invasion, and a high Korean Prognostic Index score.

The Deauville score (DS) can also be used to assess treatment responses. The DS is both accurate and reproducible, affording good interobserver agreement.[25] Khong et al.[26] used mid-treatment 18F-FDG PET/CT to prospectively evaluate the responses of patients with ENKTL to the standardized SMILE chemotherapy regimen (prednisolone, methotrexate, ifosfamide, L-asparaginase, and etoposide). ^{18}F-FDG PET/CT was useful for assessing responses during the early to middle phases

of treatment. The study findings suggested that the 5-point DS allows continuous evaluation of treatment responses.[26] Kim et al.[13] found that the post-treatment DS and EBV-DNA status allowed patients with NKTL to be stratified by the risk associated with treatment. All patients were classified into a low- or high-risk group. The low-risk group comprised EBV-DNA-negative patients with a post-treatment DS of 1 or 2, and the high-risk group comprised EBV-DNA-positive patients with a DS of 1 or 2 and EBV-DNA-negative patients with a DS of 3 or 4 at the end of treatment. Continuous treatment was recommended for the high-risk patients, while the low-risk patients underwent follow-up only.[13] A similar study also provided evidence by showing that sophisticated patient selection using PET/CT scanning and whole-blood EBV-DNA might provide additional information in the treatment of ENKTL.[27]

Use of PET/CT to evaluate the prognosis of patients with NKTL

Many factors affect the prognosis of patients with NKTL,[26–33] including advanced-stage disease (stage III or IV), an unfavorable international prognostic index score, a poor Korean Prognostic Index score,[33] bone or skin invasion, an elevated level of circulating EBV-DNA, an elevated lactate dehydrogenase level, a higher body mass index at the time of diagnosis, and the presence of EBV-positive cells in the bone marrow.[34,35] However, reliable prognostic factors for NKTL remain controversial. New prognostic models continue to be developed; these include the prognostic index of natural killer lymphoma (PINK) and the PINK plus EBV-DNA models,[36] featuring PET/CT data including the SUV_{max},[24,28,29] and models such as the whole-body metabolic tumor volume (WBMTV) and the whole-body level of total lesional glycolysis (WBTLG).[30] (The WBMTV was determined from attenuation-corrected PET data using software according to the following procedure. First, a rectangular parallelepiped-shaped volume of interest fully encasing all involved lesions in the axial, coronal, and sagittal FDG PET/CT images was drawn. The boundaries of voxels with an SUV intensity exceeding 3.0 were then produced automatically. Second, normal organs including the brain, heart, stomach, liver, intestines, kidney, ureter, bladder, and brown adipose tissue were manually subtracted from the product of the previous step. Third, false-positive lesions, such as inflammation, infection, or other benign FDG-avid lesions based on histopathological reports or other imaging modalities, were subtracted. Finally, WBTLG was calculated as the summation of individual metabolic tumor volume (MTV) multiplied by its SUV_{mean} of every ENTKL lesion.) Several studies have shown that the SUV and textural features may also predict the prognosis of NKTL.[31,33] However, the SUV_{max} reflects only the most obvious metabolic activity of a tumor in a region of interest and therefore depicts only the maximum metabolic rates of small regions of certain tumors, not the total tumor metabolism. Thus, use of the SUV_{max} alone to predict the prognosis may be quantitatively misleading because FDG uptake may vary according to the individual patient with NKTL, the reference background, and the PET/CT system employed. New models for assessment of the prognosis of NKTL continue to be developed. MTV and total lesional glycolysis (TLG) are easily calculated by new software and reflect the whole metabolic tumor burden. TLG is an ideal metabolic parameter that combines the SUV_{mean} and MTV to combine assessments of tumor volume and metabolism.[30,31] However, several limitations exist: some studies include few patients with ENKTL;

measurement of MTV is not reliable, and reproducibility is low, especially for multiple disseminated lesions; and a standard MTV threshold has not been established.[30,31,37]

As early as 2008, Suh et al.[28] evaluated whether the pretreatment 18F-FDG uptake was a predictor of survival in patients with ENKTL. Multivariate analysis revealed that only the SUV_{max} of the primary site independently predicted disease-specific survival.[28] However, their study had certain limitations, including a short follow-up time, a retrospective design, and a small number of patients. Bai et al.[24] also found that the pretreatment SUV_{max} is predictive of the prognosis in patients with newly diagnosed ENKTL. Jiang et al.[29] prospectively investigated the prognostic utility of pretreatment ^{18}F-FDG uptake and interim and post-therapy PET/CT data in 33 patients with ENKTL. The multivariate analysis revealed that the SUV_{max} of the primary tumor and post-therapy PET/CT data were prognostic in terms of both progression-free survival (PFS) and overall survival (OS). However, the interim PET/CT data were not significantly predictive of survival.[29]

Kim et al.[30] were the first to explore whether the SUV_{max}, WBMTV, and WBTLG of pretreatment FDG PET/CT images were predictive of the prognosis of patients with ENKTL. The WBMTV and WBTLG were higher in patients with than without progressive disease. The WBMTV and WBTLG of patients who died were higher than those of survivors. The multivariate analysis revealed that an SUV_{max} of >8.1, WBMTV of >14.4 cm^3, and WBTLG of >52.7 cm^3 were significantly prognostic in terms of PFS. Of these factors, a WBMTV of >14.4 cm^3 was the best prognostic factor in terms of OS.[30]

Song et al.[31] explored whether the MTV as determined by PET/CT (a measure of the lymphoma burden) was prognostic in 80 patients with I_E/II_E stage NKTL. The 3-year PFS and OS of patients with high MTVs were lower than those of patients with low MTVs when a value of 35.2 cm^3 was used as the MTV cut-off. The multivariate analysis revealed that a good disease status and upfront radiotherapy were independently predictive of both PFS and OS.[31] The addition of radiotherapy to chemotherapy was suggested to benefit patients with high tumor burdens.[31] Liang et al.[38] suggested that the SUV_{max} reflects the highest metabolic rate at only a single lymphoma site and was thus not representative of the metabolic rates at all lymphoma sites. Although the WBMTV and WBTLG may better reflect the metabolic status of all lymphoma sites, this is still disputed. Therefore, the cited authors introduced three new models using the SUVs of different sites. The $WB1SUV_{max}$ model gives the sum of the whole-body SUV_{max} values of 11 nodal and 10 extranodal lesions. The $WB2SUV_{max}$ model gives the sum of the whole-body SUV_{max} values of 3 nodal (neck, axillary, and inguinal and spleen) and 10 extranodal lesions. The $WB3SUV_{max}$ model gives the sum of the whole-body SUV_{max} values of 3 nodal (superior diaphragm, inferior diaphragm, and spleen) and 10 extranodal lesions. Receiver operating characteristic curves revealed that the optimal cut-off values for the $WB1SUV_{max}$, $WB2SUV_{max}$, and $WB3SUV_{max}$ models were 15.8 (sensitivity, 92%; specificity, 67%; area under the curve [AUC], 0.811; $p < 0.001$), 12.7 (sensitivity, 96%; specificity, 57%; AUC, 0.785; $p < 0.001$), and 15.8 (sensitivity, 88%; specificity, 70%; AUC, 0.793; $p < 0.001$), respectively. The $WB1SUV_{max}$, $WB2SUV_{max}$, and $WB3SUV_{max}$ models were all significantly better than the SUV_{max} model. The $WB3SUV_{max}$ model was selected for further prognostic investigation. The multivariate analysis showed

that the WB3SUV$_{max}$ value was an independent prognostic factor.[38]

Some authors have found that the DS may be prognostic of NKTL. Khong et al.[26] used mid-treatment DS cut-offs of 1 to 3 (compared with 4 to 5) when performing receiver operating characteristic analysis of OS. The DS was the only predictor of both OS and PFS and was thus more powerful than other measures.[26] Kim et al.[13] used the following 5-point DS scale to assess 102 patients with NKTL after completion of planned treatment: 1 (absence of lesion uptake), 2 (low lesion uptake or uptake equivalent to that of the mediastinum), 3 (high lesion uptake by the mediastinum but low or equivalent uptake by the liver), 4 (moderately high liver uptake), and 5 (markedly high uptake in the liver with development of new lesions). A post-treatment DS of 3 or 4 and EBV-DNA positivity were independently prognostic. The results suggested that the DS is easily calculated, reproducible, and associated with good interobserver agreement when used to assess the prognosis of NKTL.[13] Lim et al.[27] assessed the prognostic utility of the pretransplant DS (using the above-mentioned 5-point scale) in 27 patients with ENKTL who underwent autologous stem cell transplantation followed by PET/CT combined with assessment of whole-body EBV-DNA positivity. A DS cut-off of 1 to 2 was used to evaluate survival. Two groups of patients were created according to their pretransplantation DS and EBV-DNA data: a favorable risk group (DS of 1 or 2 and EBV-DNA negativity) and an unfavorable risk group (DS of 3–5 and EBV-DNA negativity, DS of 1 or 2 and EBV-DNA positivity, or DS 3–5 and EBV-DNA positivity). The estimated 3-year OS and PFS rates were 67% and 44%, respectively, in the first group, but only 39% and 15%, respectively, in the second group.[27] The multivariate analysis revealed that the DS and EBV-DNA positivity were the only independent prognostic factors.[27] The prospective study by Jiang et al.[32] yielded similar results. The cited authors explored the prognostic utility of 3 different models in 60 patients with ENKTL: the International Harmonization Project (IHP) model, the Deauville 5-point scale, and SUV-based assessment. The IHP model was not predictive of either PFS or OS. It was suggested that FDG is not a specific tracer and can be absorbed by inflammatory cells and yield false-positive results on interim PET/CT. All FDG uptake ranges (very low uptake, significant residual uptake but less than pretreatment uptake, no change in uptake, and uptake progression) were associated with high false-positive rates. Univariate analyses revealed that the interim PET/CT outcomes based on the DS and change in SUV$_{max}$ were predictors of survival. The multivariate analysis showed that the DS was prognostic of PFS and OS and that the change in SUV$_{max}$ was the only significant predictor of OS.[32] In an another study, the authors assessed the ability to predict prognosis using the IHP criteria, Deauville 5-point scale, and change in SUV$_{max}$ in 59 patients with ENKTL. They found that the Deauville 5-point scale was more valuable for predicting prognosis than was the IHP or change in SUV$_{max}$ in patients with ENKTL.[39] However, Khong et al.[26] found that the change in SUV$_{max}$ was not significantly prognostic of PFS or OS. Differences in the therapies employed in the two studies may partly explain the conflicting results.

Ko et al. found that the following textural features were associated with PFS: contrast, dissimilarity, high-intensity short-zone emphasis, high-intensity zone emphasis (HIZE), low-intensity short-zone emphasis (LISZE), busyness, coarseness, black/white symmetry, and run-length variability.[31] The univariate analysis showed that the extent of cancer, contrast, dissimilarity, HIZE, LISZE, coarseness, and

black/white symmetry were predictive of PFS. The multivariate analysis revealed that dissimilarity and LISZE were the principal predictors of PFS. However, neither SUV_{max}, WBMTV, nor WBTLG predicted the prognosis of NKTL.[31] The differences among these studies may be attributed to differences in the sample size, type of NKTLs evaluated, SUV threshold, or SUV_{max} cut-off. All of the studies reviewed above were limited by small sample sizes and single-center designs; prospective multicenter studies are needed.

A recent meta-analysis of the prognostic value of PET/CT suggested that multiple parameters of PET/CT were more valuable than a single parameter for assessment of the prognosis of patients with ENKTL.[37]

Conclusions

^{18}F-FDG PET/CT may play pivotal roles in the diagnosis, staging, restaging, and evaluation of treatment outcomes in patients with NKTL. The combination of many parameters with the SUV_{max} of PET/CT may be more valuable for prognostic evaluation in these patients.

Author contributions

JJD and SHZ designed the review and wrote the manuscript. YLC reviewed some of the literature. KZ reviewed some of the literature and revised the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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