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Original Article

Role of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with nasal-type natural killer T-cell lymphoma

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Abstract: We assessed the potential of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) imaging in the diagnosis and staging of patients with nasal-type natural killer T-cell lymphoma (NKTCL). Thirty-two consecutive patients with newly diagnosed nasal-type NKTCL, who underwent pretreatment and/or posttreatment ^{18}F-FDG PET/CT, were analyzed in this retrospective study. Among the 22 patients who underwent whole-body ^{18}F-FDG PET/CT before initial treatment, primary lesions were found by PET/CT in two patients, and compared with CT/MRI results; PET/CT found other additional lesions and changed the Ann Arbor stage in five patients. Univariate survival analysis showed that B symptoms ($P < 0.05$), LDH level ($P < 0.01$), and treatment ($P < 0.05$) were significant predictors of overall survival (OS) and progression-free survival (PFS). During subsequent treatment, 18 patients underwent post-treatment ^{18}F-FDG PET/CT, and PET/CT found disease progression in 13 patients, disease control in two, progression-free disease in two, and PET/CT found disease control and disease progression successively in the last patient. ^{18}F-FDG PET/CT may be an effective diagnostic workup and staging tool in nasal-type NKTCL. An ^{18}F-FDG PET/CT scan after treatment could not only predict therapeutic response but also find disease relapse or progression. SUV_{max} had no independent impact on PFS or OS, although this could be related to the small number of subjects included and short follow up time.

Keywords: ^{18}F-fluorodeoxyglucose positron emission tomography, nasal-type natural killer T-cell lymphoma, head and neck, maximum standardized uptake value, prognosis

Introduction

Nasal-type natural killer T-cell lymphoma (NKTCL) is a rare subtype of non-Hodgkin's lymphoma (NHL) in Western countries but is more common in East Asian, Latin and South American populations [1, 2]. NKTCL commonly presents with midline facial destructive disease, shows a strong association with Epstein-Barr virus (EBV), and occurs prototypically within the nasal cavity [3]. The neoplastic cells, derived from natural killer cell and/or cytotoxic T lymphocytes, are involved in the nasal cavity and paranasal sinuses. Lymphoma may extend to adjacent tissues and may disseminate rapidly to various sites (e.g., skin, gastrointestinal tract, testis, and cervical lymph nodes) [4]. Clinically, this lymphoma is characterized by progressive necrotic lesions, mainly in the nasal cavity, and a poor prognosis caused by the rapid progression of the lesion into distinct organs [5]. Pathologically, these tumors are composed of a polymorphous mixture of inflammatory cells, admixed with atypical lymphocytes having hyperchromatic, enlarged, and convoluted nuclei [1]. Immunohistochemical features show that the tumor cells are most frequently $CD2^+$, $CD3^-$, $CD3e^+$, $CD56^+$, and $CD57^-$. NKTCL is an aggressive lymphoma with a poor prognosis, and radiotherapy alone or conventional concurrent chemoradiotherapy is the first-line treatment [6].

Currently, ^{18}F-FDG PET/CT imaging is a tool for assessing metabolic activity and treatment planning for active lesions [7], and has been used widely for the diagnosis, preoperative staging, restaging, prognosis prediction, and detection of unknown primary tumors [8]. PET/CT scans have better sensitivity than conven-

tional staging methods for the detection of malignant lesions, and PET/CT findings altered the original staging category and treatment planning in some cases [9].

Using ^{18}F-FDG PET/CT scans for staging, restaging, and prognosis prediction of patients with NKTCL is not well established. Thus, the purpose of our study was to assess the potential of ^{18}F-FDG PET/CT imaging for the diagnosis and staging of patients with NKTCL and to determine whether the SUV_{max} is a prognostic factor.

Materials and methods

Patients

From May 2010 to December 2016, 32 patients with newly diagnosed nasal-type NKTCL, who underwent pre-treatment and/or post-treatment ^{18}F-FDG PET/CT were enrolled in this retrospective study. Patients were included if they had a pathologically confirmed diagnosis of NKTCL, according to the WHO classification [10]: NK/T-cell-type demonstrated by immunohistochemistry, flow cytometry, or EBV *in situ* hybridization analysis, and primary lesions within the nasal cavity, pharynx, or other head and neck regions. All patients underwent routine staging procedures, including history taking, physical examination, complete blood count, chest radiography, and CT/MRI of the head and neck. Among the 32 patients, there were 22 who underwent whole-body ^{18}F-FDG PET/CT before initial treatment and another 10 patients who underwent post-treatment whole-body ^{18}F-FDG PET/CT. Among the 22 patients who received PET/CT before the initial treatment, eight patients also received post-treatment whole-body ^{18}F-FDG PET/CT. B symptoms were defined as unexplained fever with a body temperature above 38°C, night sweats, and unexplained weight loss of more than 10% of usual body weight in the 6 months before the diagnosis. To evaluate the prognostic value of clinical and PET parameters, OS and PFS were chosen as endpoints. OS was defined as the number of months from the date of diagnosis to the date of death from the disease, or until the date of analysis. PFS was measured as the number of months from the date of diagnosis to the date of first disease progression, or the date of last follow up. Disease progression was defined as progressive disease, relapsed disease, according to the International Working Group response criteria for malignant lymphoma, or death from the disease [11].

The Institutional Review Board (IRB no. 2016-299) of the First Affiliated Hospital, College of Medicine, Zhejiang University (Hangzhou City, China) approved the present study. Written informed consent was obtained from all of the patients before inclusion.

PET/CT scan

Whole-body imaging (from vertex to toe) was performed using a combined PET/CT scanner (Biograph Sensation 16, LSO 39-ring; Siemens Medical, Erlangen, Germany). After at least 4-6 hours of fasting, patients received an intravenous injection of FDG at 5.5-7.4 MBq (0.15-0.20 mCi)/kg of body weight. Patient blood glucose levels were checked before the ^{18}F-FDG injection. Data acquisition for the diagnostic CT was started 60 minutes after FDG administration. Acquisition time was 2 minutes per bed position. The total imaging time for a PET/CT study lasted ~20 minutes. Attenuation correction was based on CT. The PET images were reconstructed iteratively using the ordered subset Syngo Speaking software (Wizard Workstation; Siemens Medical). PET, CT, and fused PET/CT images were generated and reviewed on a computer, while co-registered images were displayed on a workstation.

Data and statistical analysis

The PET/CT scans were interpreted independently by two experienced members of our PET center who were unaware of the histology of the metastatic sites. Any differences in their interpretations were settled with a final unanimous opinion. The standardized uptake value (SUV) was collected from the predominant lesion and calculated based on the attenuation-corrected images, amount of injected ^{18}F-FDG, and body weight:

SUV_{max} = maximum activity in the region of interest (megabecquerels/gram)/[injected dose (megabecquerels)/body weight (grams)].

When multiple lymph nodes were found, only the lymph node with the highest SUV was used. Statistical analysis was performed using SPSS software (ver. 16.0; SPSS Inc., Chicago, IL). The prognostic significance of PET parameters and

Table 1. General characteristics of patients with NKTCL

Characteristic	No. of patients	%
Sex		
Male	21	65.6
Female	11	34.4
Age* (y)	47±15 (range, 19-81)	
≤ 60	26	81.3
> 60	6	18.7
Smoke		
Yes	12	37.5
No	20	62.5
Drink		
Yes	8	25
No	24	75
Primary site of tumor		
Nasal cavity	19	59.4
Nasopharynx	8	25
Paranasal sinus	2	6.2
Tonsil	1	3.1
Soft palate	1	3.1
Gingiva	1	3.1
Symptom		
Nasal obstruction	20	62.5
Fever	13	40.6
Pharyngalgia	8	25
Rhinorrhea	7	21.8
Epistaxis	3	9.3
Mass in nasal cavity	2	6.2
Numbness in nasal cavity	1	3.1
Pain in nasal cavity	1	3.1
Cough	1	3.1
Pharyngeal foreign body sensation	1	3.1
Dysphagia	1	3.1
Cervical mass	1	3.1
Gingival bleeding	1	3.1
Swelling in the eyes	1	3.1
B Symptom		
Yes	13	40.6
No	19	59.4
Involvement of cervical lymph nodes		
Yes	8	25
No	24	75
Ann Arbor stage		
I	15	46.9
II	11	34.4
III	1	3.1
IV	5	15.6
LDH level		
Normal	17	53.1
Elevated	12	37.5

clinical variables (gender, age, IPI score, Ann Arbor stage, LDH level, B symptoms) was assessed by univariate survival analysis.

Results

The cohort consisted of 32 patients: 21 males and 11 females. The male-to-female ratio was up to 1.9:1. The mean age was 47 (range, 19-81) years. The primary site of the tumor was the nasal cavity in 19 (59.4%) patients, and the nasopharynx in 8 (25%) patients. Other rare primary sites of the tumor were the paranasal sinus, tonsils, soft palate, and gingiva. In the 32 cases, nasal obstruction was the most common symptom (62.5%), followed by fever (40.6%), pharyngalgia (25%), rhinorrhea (21.8%), and epistaxis (9.3%). In total, 13 (40.6%) patients had B symptoms, 8 (25%) patients showed involvement of the cervical lymph nodes, 26 (81.3%) patients were in Ann Arbor stage I or II, and 6 (18.7%) were in Ann Arbor stage III or IV. An elevated serum LDH level was observed in 12 (37.5%) patients. In total, 16 (50%) patients had International Prognostic Index (IPI) scores of 0 or 1 (mild risk), and 13 (40.6%) had IPI scores of 2 or 3 (moderate risk). In total, 16 (50%) patients received combined chemotherapy and radiotherapy, 13 (40.6%) received chemotherapy alone, and 3 (9.4%) received radiotherapy alone. There were 3 (9.4%) patients who underwent hematopoietic stem cell transplantation. At the last follow up (September 2015), 17 (53.1%) pa-

Non-available	3	9.4
IPI Score		
0	7	21.9
1	9	28.2
2	10	31.3
3	3	9.3
Non-available	3	9.3
Risk level		
Mild risk	16	50
Moderate risk	13	40.6
Severe risk	0	0
Non-available	3	9.4
Treatment		
Combined chemotherapy and radiotherapy	16	50
Chemotherapy alone	13	40.6
Radiotherapy alone	3	9.4
Stem cell transplantation	3	9.4
Follow-up period of survivors (mo)		
Overall survival (OS)*	18±13 (range, 1-53)	
Progression-free survival (PFS)*	13±11 (range, 1-53)	

*Mean ± SD.

tients were alive, 10 (31.3%) had died of tumor related disease, and 5 (15.6%) were lost to follow up. The mean OS was 18±13 (range, 1-53) months. The mean PFS was 13±11 (range, 1-53) months (**Table 1**).

Among the 32 patients, 22 underwent whole-body ^{18}F-FDG PET/CT before the initial treatment. All primary lesions were positive in pre-treatment ^{18}F-FDG PET/CT scans (the sensitivity of ^{18}F-FDG PET/CT was 100%, but the specificity could not be calculated). The median SUV_{max} of the primary tumors was 9.25 (range, 3.79-21.22). The mean SUV_{max} of the primary tumors was 10.17±4.74. We used the median SUV_{max} (9.25) as SUV_{max} cutoff values. Univariate survival analysis showed that B symptoms (P = 0.040/P = 0.015), LDH level (P = 0.001/P = 0.003), and treatment (P = 0.021/P = 0.044) were significant predictors of OS and PFS (**Figure 1**). Gender, age, smoking and drinking habits, lymph node involvement, IPI score, and Ann Arbor stage were not significant predictors of OS or PFS (P > 0.05). SUV_{max} category of the primary tumor, using 9.25 as the cut-off valve, showed no statistically significant difference in OS or PFS (P > 0.05).

In our study, two patients first complained of fever but routine examinations did not find lesions or any reason for the fever. They underwent ^{18}F-FDG PET/CT scans and primary lesions were found in the paranasal sinus (Pt. 1) and nasal cavity (Pt. 2), and biopsies confirmed the diagnosis of NKTCL. In total, 20 patients complained about their symptoms and underwent biopsies before receiving PET/CT scans. Compared with CT/MRI results, PET/CT scans found other additional lesions and changed the Ann Arbor stage in five patients. CT found nasosinusitis in Pt. 9, but PET/CT scans found nasopharynx and cervical lymph nodes involved and altered the original staging category. In Pts. 6, 7, 14, and 22, CT/MRI found only local lesions and the patients may have belonged to stage I or II, but PET/CT scans found whole-body disseminated lesions, in the skeleton, liver, spleen, lung, and adrenal glands, so that changed the Ann Arbor stage to stage IV (**Table 2**). The other 10 patients did not undergo whole-body ^{18}F-FDG PET/CT before the initial treatment and they underwent PET/CT scans after a period of treatment instead (**Table 3**). PET/CT findings for all 32 patients were collected and recorded. In total, 18 patients underwent post-treatment ^{18}F-FDG PET/CT scans. PET/CT found disease progression in 13 patients (Pts. 1-3, 5, 23-24, 26-32) (**Figure 2**), disease control in two (Pts. 6-7), progression-free disease in two (Pts. 4, 25) (**Figure 3**), and PET/CT found disease control and disease progression successively in the last patient (Pt. 8).

Discussion

NKTCL is an aggressive lymphoma with a poor prognosis. Because of non-specific clinical features and inadequate experience, the diagnosis and staging of NKTCL are not very clear. Today, ^{18}F-FDG PET/CT imaging is used widely in oncology [12].

As has been reported, NKTCL is intensely FDG-hypermetabolic and high FDG uptake was closely associated with local tumor invasion,

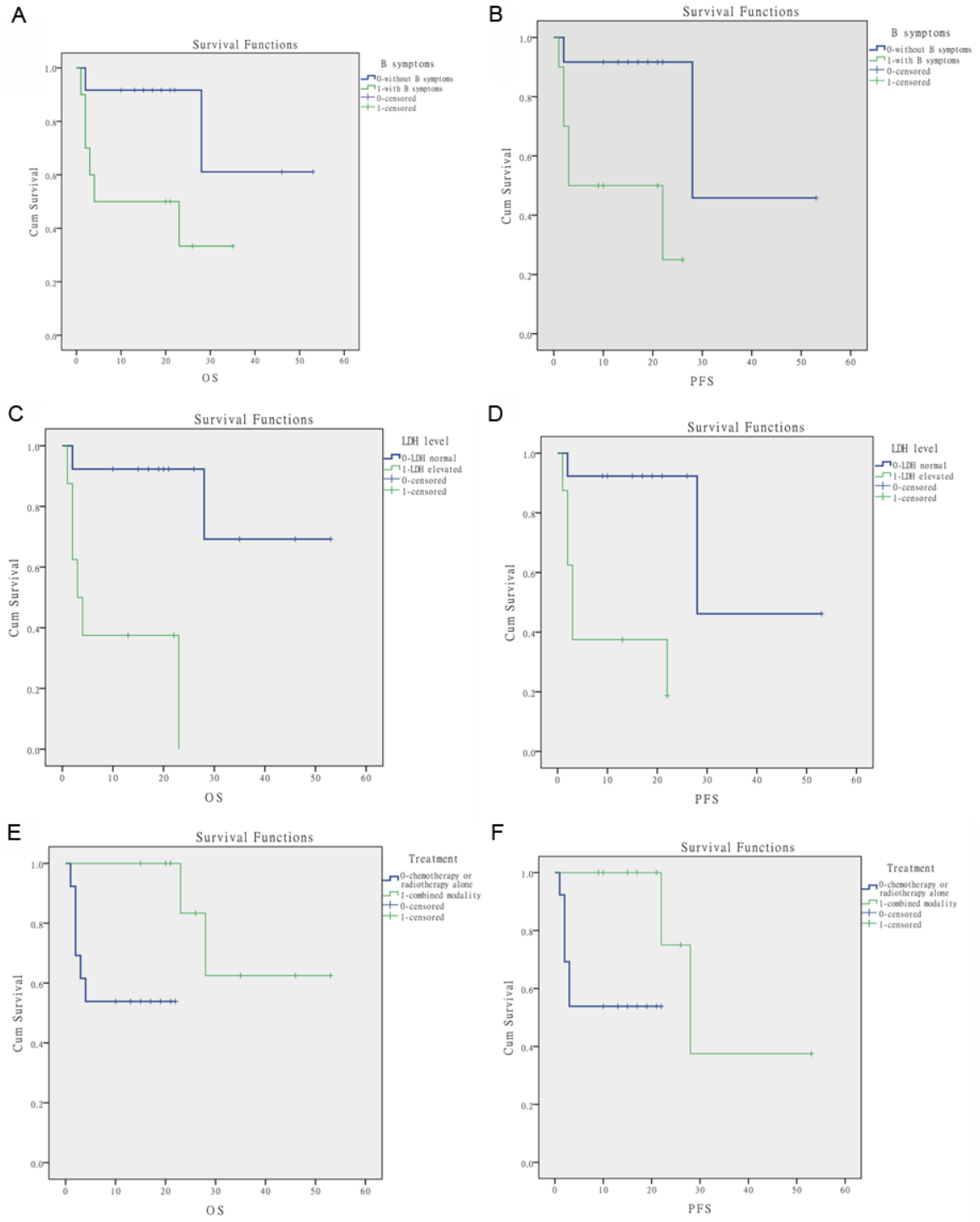

Figure 1. Prognostic factors for OS and PFS. Univariate survival analysis showed that B symptoms ($P < 0.05$, A, B), LDH level ($P < 0.01$, C, D), and treatment ($P < 0.05$, E, F) were significant predictors of OS and PFS.

contributing to unfavorable treatment and survival outcomes in patients with NKTCL [13]. However, our present study showed that only B symptoms, LDH level, and treatment were significant predictors of OS and PFS by univariate analysis. There was no evidence to show that SUV_{max} is predictive of prognosis, which contradicted with previous findings and should be further studied. Soon et al. studied 52 consecutive patients and demonstrated that PET/CT

Table 2. PET/CT before treatments: 22 patients

Pt	Symptom	CT/MRI	PET/CT (SUV_{max})	Ann Arbor stage	Treatment C: Chemotherapy R: Radiotherapy	Prognosis			
						Time*	PET/CT (SUV_{max})	Treatment C: Chemotherapy R: Radiotherapy	Outcome
1	Fever	-	Paranasal sinus (9.89) Subcutaneous nodule (4.29) Nasopharynx (2.99)	IIB	C: CHOP*3	3 M	Nasopharynx (19.72) Paranasal sinus (15.34) Skeleton (8.38) Liver (4.99) Cervical lymph nodes (4.76) Mammary gland (3.93) Spleen (2.55)	C: HyperCVAD-A*1	4 M die
2	Fever	-	Nasal cavity (6.37) Paranasal sinus (5.53)	IB	C: HyperCVAD*1 R: Dt = 5400cGy/27Fr	9 M	Pelvic cavity (6.82) Kidney (3.63) Lung (3.52) Skeleton (3.10) Nasal cavity (2.56)	Chemotherapy	35 M live
						26 M	Lung (6.84) Nasopharynx (3.53) Skeleton (2.50)	NA	
3	Pharyngalgia, fever, cough	-	Nasopharynx (11.35) Cervical lymph nodes (4.82)	IIB	C: ECHOP*5 Hyperpart B*1 ASCT	10 M	Nasal cavity (5.94) Tonsil (5.30) Nasopharynx (3.6)	Radiotherapy	20 M live
						17 M	Skeleton (Elevated#) Nasopharynx (Normal)	NA	
4	Nasal obstruction	-	Nasal cavity (5.26) Subcutaneous nodule (2.65)	IIA	C: SMILE*3 R: Dt = 5400cGy/27Fr	7 M	Normal	-	28 M loss to follow-up
						18 M	Normal	-	
						28 M	Normal	-	
5	Nasal obstruction, rhinorrhea	-	Nasal cavity (8.09)	IA	R: Dt = 5632cGy/26Fr	17 M	Larynx (Elevated#) Cervical lymph nodes (Elevated#)	C: SMILE*3 CHOP + LASP*1 COP + LASP*2 COP + VP16*2 COP + VP16*2	46 M live
6	Pharyngalgia, fever, dysphagia	CT: incrassation of nasopharynx, enlargement of cervical lymph node	Nasopharynx (15.2) Soft palate (7.73) Skeleton (3.05) Spleen (3.0)	IVB**	C: CHOP*4 ECHOP*2 MTX + LASP + DXM*1	11 M	Nasal cavity (6.0) Nasopharynx (Normal) Soft palate (Normal)	Radiotherapy	26 M live
7	Numbness in nasal cavity, rhinorrhea	MRI: papillary epithelioma? nasal polyp? lymphoma?	Nasopharynx (21.22) Lung (6.10) Adrenal gland (7.96) Skeleton (3.19)	IVA**	C: SMILE*4	5 M	Nasopharynx (Normal) Lung (Normal) Adrenal gland (Normal) Skeleton (Normal)	C: CHOP*2 MTX + DXM*4	21 M live

8	Gingival bleeding	-	Gingiva (13.7)	IA	C: HyperCVAD*2 CHOP + LASP*2 CHOP*2	7 M 16 M	Gingiva (Normal) Oropharynx (Elevated#)	C: CHOP + PregASP*1 C: MTX + DXM + ASP*1	17 M live
9	Pharyngalgia, fever	CT: nasosinusitis	Nasopharynx (9.02) Cervical lymph nodes (6.53)	IIB**	C: CHOP*2 ECHOP*1	-	-	-	2 M die
10	Nasal obstruction	CT: Mass in nasal cavity	Nasal cavity (7.97)	IA	C: ECHOP*1 Radiotherapy	NA	NA	NA	53 M live
11	Epistaxis	-	Nasal cavity (11.83)	IA	Chemotherapy Radiotherapy	NA	NA	NA	15 M live
12	Nasal obstruction	CT: nasosinusitis	Nasal cavity (5.47)	IA	Radiotherapy	NA	NA	NA	13 M live
13	Mass in nasal cavity, fever	-	Nasal cavity (8.15) Cervical lymph nodes (4.47)	IIB	C: CHOP*1 ASCT Radiotherapy	-	-	-	23 M die
14	Nasal obstruction, rhinorrhea	CT: Mass in nasal cavity, nasal polyp? nasosinusitis MRI: Mass in nasal cavity, nasal polyp? Tumor?	Paranasal sinus (14.0) Tonsil (3.92) Skeleton (3.06)	IVA**	C: CHOP*1 CHOP + LASP*2	NA	NA	NA	19 M live
15	Nasal obstruction, swelling in the eyes, fever	-	Nasal cavity (9.48) Skeleton (3.56) Adrenal gland (3.0) Nasopharynx (2.54)	IVB	C: MTX + IFO + VP16 + LASP*1	NA	NA	NA	1 M loss to follow-up
16	Nasal obstruction, epistaxis	CT: Mass in nasal cavity, infection?	Nasal cavity (18.98)	IA	R: Dt = 4000cGy/20Fr	NA	NA	NA	2 M loss to follow-up
17	Nasal obstruction, rhinorrhea, fever	-	Nasopharynx (5.7)	IB	C: MTX + DXM + LASP*1 CHOP*1 DeVIC*1	-	-	-	3 M die
18	Nasal obstruction, rhinorrhea	-	Nasal cavity (9.9)	IA	Radiotherapy	NA	NA	NA	10 M live
19	Nasal obstruction, fever, pharyngalgia	-	Nasopharynx (3.79)	IB	Chemotherapy Radiotherapy	NA	NA	NA	21 M live
20	Nasal obstruction, epistaxis	CT: lesions in nasal cavity, nasopharynx, paranasal sinus, parapharyngeal space	Nasal cavity, paranasal sinus, Nasopharynx (16.4)	IIA	C: OP*1 CHOP*1 GDP + L*3 GDP*2	NA	NA	NA	22 M live
21	Pain in nasal cavity, nasal obstruction	-	Nasal cavity (4.4) Tonsil (4.57) Thyroid gland (3.79) Pelvic cavity (7.43)	IIIA	C: SMILE*4 SMIE + Velcade*2	NA	NA	NA	15 M live
22	Nasal obstruction, pharyngalgia, fever	CT: mass in nasal cavity, nasosinusitis, enlargement of cervical lymph node	Nasal cavity (7.67) Nasopharynx (5.52) Liver (4.27) Inguinal lymph nodes (2.77) Skeleton (Elevated#)	IVB**	C: HyperCVAD*2	-	-	-	2 M die

Time*: The interval time from disease diagnosed to the time underwent PET/CT scan. Elevated#: The local lesion SUV ingestion was greater than normal ingestion, but the exact number was missing. Ann Arbor stage**: In Pts. 6, 7, 9, 14, and 22, compared with CT/MRI results, PET/CT scans found other additional lesions and changed the Ann Arbor stage.

Table 3. PET/CT after treatments: 10 patients

Pt	Symptom	CT/MRI	Ann Arbor stage	Prognosis				
				Treatment C: Chemotherapy R: Radiotherapy	Time*	PET/CT (SUV_{max})	Treatment C: Chemotherapy R: Radiotherapy	Outcome
23	Mass in nasal cavity	-	IA	C: CHOP*2 R: Dt = 5000cGy/25Fr	23 M	Nasopharynx (9.5) Skeleton (4.4) Nasal cavity (3.8)	C: SMILE*3 Velcade + SMILE*1 HSCT	32 M live
24	Rhinorrhea	-	IA	C: CHOP + L-ASP*4 Radiotherapy	9 M	Cervical lymph nodes (3.01) Nasal cavity (Normal)	NA	28 M live
25	Nasal obstruction, rhinorrhea	-	IA	C: CHOP*2 LOAP*2 Ara-C + CHOP*1 Radiotherapy	6 M	Nasal cavity (Normal)	NA	6 M loss to follow-up
26	Nasal obstruction	CT: nasal polyp? enlargement of cervical lymph nodes	IIA	C: DICE*4 CHOP*1 CHOP + LASP*8 MINE*4 R: DT = 5000cGy/25Fr	22 M	Hilar lymph nodes (16.74) Cervical lymph nodes (6.73)	C: CHOP*1 HyperCVAD-A*2 MTX + DXM*1	30 M die
27	Pharyngalgia, nasal obstruction, fever	CT: tumor in nasopharynx and cervical lymph node?	IIB	C: CHOP*4	6 M	Cervical lymph nodes (15.84) Nasopharynx (9.04)	NA C: GDP*4	6 M loss to follow-up
28	Nasal obstruction, pharyngalgia, fever	CT: mass in nasal cavity	IIB	C: DTIC*5 R: Dt = 5000cGy/25Fr	13 M	Cervical lymph nodes (Elevated#)	R: Dt = 3780cGy/21Fr	22 M die
		B ultrasound: no cervical lymph node enlargement			22 M	Spleen (7.7) Skeleton (5.4) Liver (4.7) Gastric wall (4.6) Nasal cavity (Normal)	C: ECHOP*1	
29	Pharyngalgia, fever	MRI: tumor in tonsil and parotid gland?	IB	C: ECHOP*3	3 M	Nasal cavity (13.36) Parotid gland (10.31)	C: CHOP + LASP*2	8 M die
30	Pharyngeal foreign body sensation, nasal obstruction	MRI: lymphoma in soft palate and oropharynx?	IIA	C: HyperCVDA + L-ASP*5	6 M	Oropharynx (3.17) Larynx (2.68)	Patient refuse to accept treatment	29 M live
					22 M	Nasal cavity (16.51) Tonsil (5.54) Nasopharynx (4.15)	C: MTX + DXM + LASP*1 SMILE*1	
31	Nasal obstruction, cervical mass	MRI: mass in nasopharynx	IIA	Radiotherapy	1 M	Spleen (Elevated#) Skeleton (Elevated#)	C: ECHOP*1	2 M die
32	Nasal obstruction	-	IA	C: CHOP*6 R: Dt = 5000cGy/25Fr	11 M	Nasal cavity (Elevated#) Paranasal sinus (Elevated#) Cervical lymph nodes (Elevated#) Hilar lymph nodes (Elevated#)	C: MINE*2 ECHOP*1 GDP*2	25 M die
					25 M	Nasal cavity (Elevated#) Paranasal sinus (Elevated#)	C: GDP*2 HyperCVAD*1 R: Dt = 4800cGy/24Fr	

Time*: The interval time from disease diagnosed to the time underwent PET/CT scan. Elevated#: The local lesion SUV ingestion was greater than normal ingestion, but the exact number was missing.

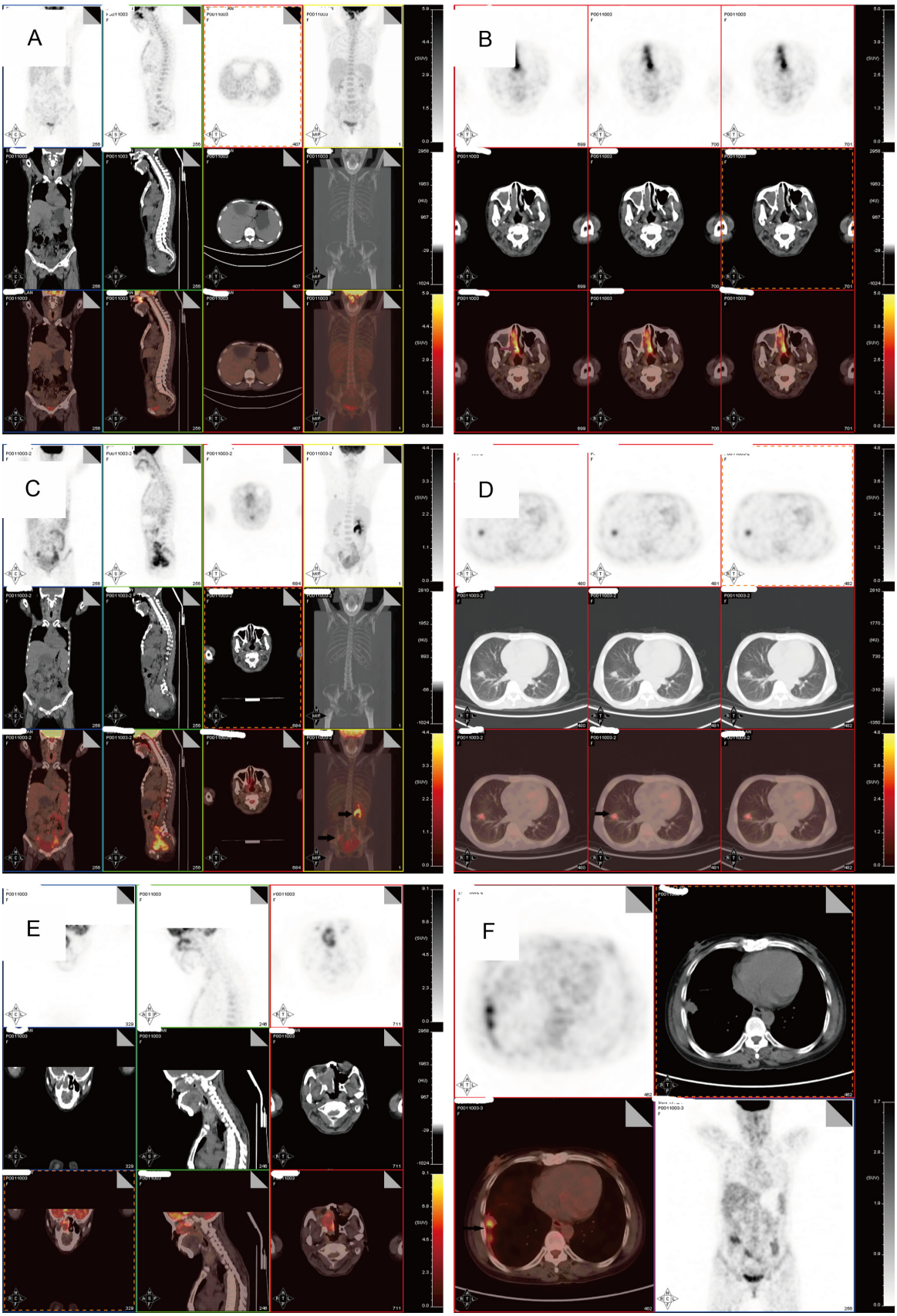

Figure 2. Images demonstrating tumor ^{18}F-FDG PET uptake and tumor invasiveness of Pt.2. Pretreatment PET/CT (A, B) showed lesions only in the nasal cavity and paranasal sinus. PET/CT after 9 months of chemoradiotherapy (C,

D) showed tumor invasion into the pelvic cavity and lung, indicating disease progression. PET/CT after 26 months chemoradiotherapy (E, F) showed lesions mainly in lung and nasopharynx.

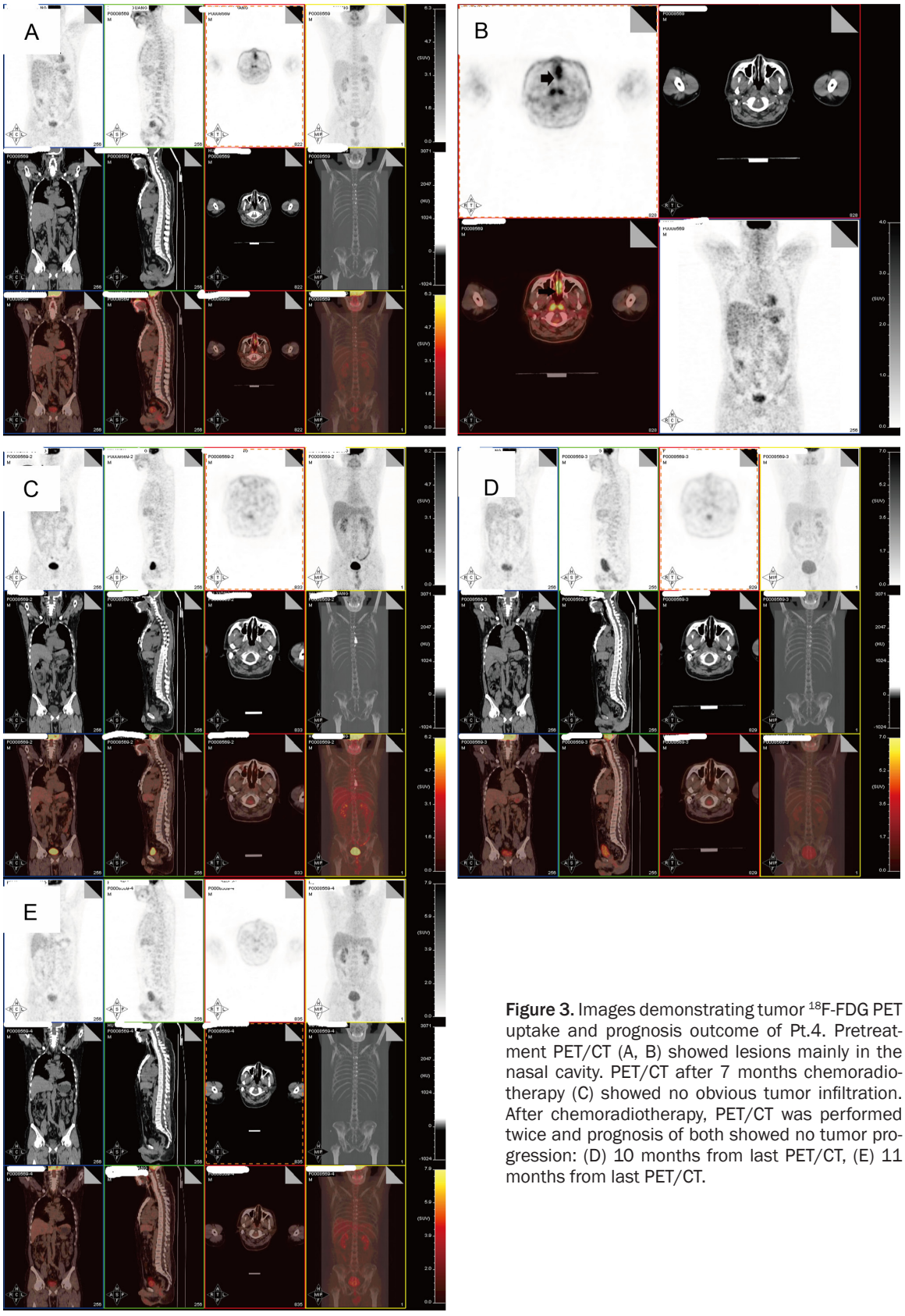

Figure 3. Images demonstrating tumor ^{18}F-FDG PET uptake and prognosis outcome of Pt.4. Pretreatment PET/CT (A, B) showed lesions mainly in the nasal cavity. PET/CT after 7 months chemoradiotherapy (C) showed no obvious tumor infiltration. After chemoradiotherapy, PET/CT was performed twice and prognosis of both showed no tumor progression: (D) 10 months from last PET/CT, (E) 11 months from last PET/CT.

scans had better sensitivity than conventional staging methods (physical examination, CT with intravenous contrast, biopsies from primary sites, and bone marrow examinations) for the detection of malignant lesions. Moreover, PET/CT findings altered the original staging category for 12 (21.2%) patients and affected treatment planning in 23 cases [9]. Compared to their results, they did not mention the role of PET/CT in the follow up. Our present work not only provides information about the role of PET/CT in altering original staging category, but also adds some useful information about what PET/CT does in the follow up. Previously, we reported a case of laryngeal NKTCL and found that PET/CT had better sensitivity than other conventional methods and may play an important role in the diagnosis, staging, and follow up of nasal-type NKTCL [14]. MacDonald et al. reported three cases with early-stage extranodal natural killer/T-cell lymphoma. PET/CT changed the stage and target volume requiring treatment in two patients. A third patient was unable to tolerate an MRI, but could undergo PET/CT; it improved the accuracy of the target volume [15]. Tse et al. also believed that an accurate histopathological diagnosis and precise staging using PET/CT scan were essential in the management of patients with NKTCL [16]. In our study, 22 patients with NKTCL underwent pre-treatment PET/CT scans. Two patients first complained about fever but routine examinations found no lesion. PET/CT scans then found primary lesions in the paranasal sinus and nasal cavity, and biopsies confirmed the diagnosis of NKTCL. Also, compared with CT/MRI results, PET/CT scans found other additional lesions and changed the Ann Arbor stage and treatment plan in five patients. Thus, we suggest that ^{18}F-FDG PET/CT may be an effective diagnostic workup and staging tool in nasal-type NKTCL, and it could change the Ann Arbor stage leading to better treatment planning for patients with NKTCL.

In our series, ^{18}F-FDG PET/CT may not only provide an effective diagnostic workup and staging tool for nasal-type NKTCL but may also detect the effect of treatments and disease progression. In the present study, 18 patients underwent post-treatment ^{18}F-FDG PET/CT scans. PET/CT found disease progression in 13 patients, disease control in two, progression-free disease in two, and in the last patient, PET/CT found disease control and disease progression, successively. In a prospective study, Khong et al. [17] found an early mid-treatment ^{18}F-FDG PET scan after two or three cycles of chemotherapy to be useful in the prediction of SMILE therapy responses in NKTCL patients. An early mid-treatment assessment was also helpful in evaluating the effectiveness of the given treatment, and for excluding the possibility of disease progression, potentially allowing response adapted treatment strategies for which therapy can be tailored to the individual's response.

The prognosis of NKTCL is variable. In our series, univariate analysis showed that B symptoms ($P < 0.05$), LDH level ($P < 0.01$), and treatment ($P < 0.05$) were significant predictors of OS and PFS. Unfavorable prognostic factors in NKTCL include advanced-stage disease (stage III or IV), unfavorable IPI, bone or skin invasion, an elevated circulating EBV DNA level, and the presence of EBV-positive cells in bone marrow [4]. As Bai et al. reported [12], 81 patients with newly diagnosed NKTCL were reviewed to investigate the prognostic role of pretreatment SUV_{max} on PET/CT. They found that patients with high SUV_{max} were associated with bulky disease ($P < 0.001$), local invasion ($P < 0.05$), high Korean Prognostic Index score (KPI, $P < 0.05$), resistance to primary treatment ($P < 0.05$), poor OS ($P < 0.001$), and unfavorable PFS ($P < 0.001$). Multivariate analyses revealed the following independent prognostic factors for OS: age > 60 years ($P = 0.001$), stage III-IV ($P < 0.05$), $SUV_{max} > 15$ ($P < 0.05$), and bulky disease (> 5 cm; $P < 0.01$). They suggested that in using the SUV_{max}, patients in most subgroups stratified by the KPI or the IPI were further discriminated in OS with a statistically significant difference, and pretreatment SUV_{max} was predictive of prognosis in patients with newly diagnosed NKTCL, and that SUV_{max} may provide additional prognostic information beyond IPI and KPI. Ma et al. [1] analyzed 64 patients with early-stage NKTCL, and multivariate analysis showed that Eastern Cooperative Oncology Group performance status score ≥ 2, local tumor invasion out of the nasal cavity, and lower complete remission rates in the initial treatment were significant unfavorable independent prognostic factors. Cheung et al. [18] believed that good performance status was a significant favorable factor for disease-free survival (DFS; $P = 0.011$), whereas good perfor-

mance status and Ann Arbor stage IE disease were shown to be significant favorable factors for OS (P = 0.001 and 0.013, respectively).

Our study has some limitations. First, the small sample size with only 32 patients being newly diagnosed nasal-type NKTCL, from May 2010 to December 2014, who underwent pre-treatment and/or post-treatment ^{18}F-FDG PET/CT were enrolled in our retrospective study. Second, there are some missing values in LDH levels and IPI scores. Thus, the univariate survival analysis may not be exact. Third, the follow up periods of some patients were not long enough to reflect prognosis conditions exactly. Also, because of some loss to follow up, overall survival and progression-free survival may not be exact. Despite these limitations, we believe this study provides important information about the role of ^{18}F-FDG PET/CT in patients with NKTCL.

In conclusion, our results suggest that ^{18}F-FDG PET/CT may be an effective diagnostic workup and staging tool in nasal-type NKTCL. An ^{18}F-FDG PET/CT scan after treatment could not only predict therapeutic response but also find disease relapse or progression. SUV_{max} had no independent impact on PFS or OS, even though it might be related to a small number of subjects included and short follow up time.

Disclosure of conflict of interest

None.

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