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Clinical value of metabolic tumor volume by PET/CT in extranodal natural killer/T cell lymphoma

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ABSTRACT

This study investigated whether metabolic tumor volume (MTV) by PET/CT as indicator of extent of lymphoma burden would be a prognostic factor in stage I_E/II_E extranodal natural killer/T cell lymphoma (ENKTCL). Eighty patients with stage I_E/II_E ENKTCL in the upper aerodigestive tract underwent PET/CT at diagnosis were enrolled and 32 patients received upfront radiotherapy (RTx). MTV was measured on PET/CT images by the extranodal region above SUV, 2.5. Receiver operating curve analyses indicated that an MTV of 35.2 cm^3 was the ideal cut-off to distinguish between low and high MTV groups. Clinical outcomes were compared according to several prognostic factors (age, stage, high performance status [PS], high International Prognostic Index, elevated lactate dehydrogenase [LDH], local tumor invasiveness [LTI], high MTV and up-front RT). High PS, elevated LDH, LTI, high MTV and upfront RT were associated with survivals. In multivariate analysis, high MTV (PFS, HR = 4.170, 95% CI = 1.714–10.147, $p = 0.002$; OS, HR = 4.102, 95% CI = 1.617–10.408, $p = 0.003$) and up-front RT (PFS, HR = 0.410, 95%CI = 0.178–0.946, $p = 0.037$; OS, HR = 0.365, 95% CI = 0.152–0.872, $p = 0.023$) were significant independent prognostic factors. Upfront RTx and extent of tumor burden, as measured by the MTV, had significant prognostic value in patients with ENKTCL.

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1. Introduction

Extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKTCL) is a distinct clinicopathological entity that is very rare in Western populations [1–5] but rather common among Asians and Latin Americans [6–9]. It frequently destroys the facial midline of the upper aerodigestive tract (UAT) and spreads to or relapses at extranodal sites including the skin, gastrointestinal tract, bone marrow, lung, extremities, orbit, adrenal gland, testis, or the central nervous system [10].

Ann Arbor staging, originally developed for Hodgkin's lymphoma, is unclear as a predictor of prognosis in more aggressive subgroups of non-Hodgkin's lymphoma [11,12]. The International Prognostic Index (IPI) has also failed to predict survival in patients with ENKTCL [9,13,14]. Furthermore, poor drug delivery due to tissue necrosis related to angiodestruction and frequent expression of multidrug resistant phenotypes might be important contributing factors. Therefore, front-line use of radiotherapy (RTx) has produced superior survival compared to initial chemotherapy for localized ENKTCL [15].

The extent of ENKTCL is considered a prognostic factor [16,17]. However, measurement of extent is simply based on the tumor-node-metastasis (TNM) staging system of the American Joint Committee (AJC). 18-Fluorine-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) is a promising tool for assessing metabolic activity or treatment planning for active lesions in patients with ENKTCL [18–21].

The objective of this study was to investigate whether metabolic tumor volume (MTV) of involved extranodal lesions is a prognostic factor in stage I_E/II_E UAT-NKTCL.

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Table 1
Baseline characteristics of the patients.

Characteristics	Number of patients (n = 80) (%)
Gender	
Male	47 (58.8)
Female	33 (41.2)
Age (years)	
≥60 years	38 (47.5)
<60 years	42 (52.5)
Primary tumor	
Nasal cavity	63 (78.8)
Nasopharynx	10 (12.5)
Oral cavity/oropharynx	7 (8.7)
Ann Arbor stage	
IE	51 (53.8)
IIE	29 (46.2)
ECOG PS	
0–1	69 (86.3)
≥2	11 (13.7)
B symptoms	
Yes	13 (16.3)
No	67 (83.7)
Local tumor invasiveness	
Yes	25 (31.3)
No	55 (68.7)
Serum LDH level	
High than normal	21 (26.3)
Normal	59 (73.7)
IPI score	
0–1	56 (70.0)
≥2	24 (30.0)
Treatment	
Upfront RTx followed by CTx	32 (40.0)
Only CTx	21 (26.3)
CTx followed by RTx	27 (33.7)

2. Materials and methods

Between 2006 and 2011, 80 patients with Ann Arbor stage I_E and II_E UAT-NKTCL underwent ^{18}F-FDG PET/CT scans at the time of initial diagnosis and were enrolled at six medical centers, including Pusan National University Hospital, Chonnam National University Hospital, Kyungpook National University Hospital, Busan Paik Hospital, Kosin University Gospel Hospital, and Gyeongsang National University Hospital. Patient characteristics are summarized in Table 1. The male to female ratio was 1.42:1. Median age at the time of initial diagnosis was 59 years (range, 23–74 years). The median follow-up time was 35.6 months (range, 10.2–72.5 months). This study was reviewed and approved for chart reviews by our institutional review board.

All pathological specimens were classified based on strict morphological criteria in conjunction with immunophenotypic findings, although Epstein–Barr virus RNA in situ hybridization was performed in only 10 cases. Immunophenotypic procedures were performed on paraffin sections using a routine avidin–biotin–peroxidase complex method using the following antibodies: CD3 (DakoCytomation, Copenhagen, Denmark), CD20 (DakoCytomation), CD45 and CD56 (Monosan, Uden, The Netherlands; DiNonA, Seoul, Korea).

CT scans of the head and neck area were performed in each patient for an accurate evaluation of primary lesions. The other staging evaluation included a complete history and physical examination, chest X-ray, and laboratory studies, including a complete blood count and liver function tests. Chest and abdominal CT scans were performed to exclude advanced stage disease (stage III/IV). Local tumor invasiveness (LTI) was defined as bony invasion or perforation or invasion of skin as described by Kim et al. [22]. The extent of bone involvement was defined according to the CT scan and physical findings.

2.1. Treatment

Thirty-two patients (40.0%) received upfront RTx followed by chemotherapy (CTx), whereas 21 patients (26.3%) received only CTx and 27 patients (33.7%) received CTx followed by RTx. A variety of CTx regimens were used. Doxorubicin containing regimens were used in 36 patients: cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) in 21 patients; CHOP plus etoposide in 13 patients; and CHOP plus alemtuzumab in two patients. The other regimen included methotrexate, etoposide, ifosfamide, and prednisone in 43 patients.

Radiation was delivered to the primary site only in patients with Ann Arbor stage I_E and the primary site with ipsilateral neck and supraclavicular fossa in patients with Stage II_E disease. The total radiation dose in patients who received RTx was 36.0–60.0 Gy (median, 45.0 Gy). The response to treatment was assessed by a physical examination and a CT scan performed within 6 weeks after completion of the treatment schedule. Tumor response was assessed using standard response criteria [23].

2.2. Measurement of MTV by PET/CT

^{18}FDG-PET images were evaluated for extranodal regions of focally increased tracer uptake in patients with UAT-NKTCL. Dual-modality PET/CT tomography was performed on a biograph instrument (Siemens Medical Solution, Hoffman Estates, IL, USA), based on dual-slice helical CT and full-ring PET tomography. A volume of tissue, containing a standard uptake value of greater than or equal to 2.5, as a contouring border for the FDG tracer uptake target lesions, was considered to represent the pathological lesion according to article by Freudenberg et al. [24]. Other clinical data were also referred to the contouring border [25,26]. The CT images were used for correlation of PET attenuation. Corrected emission data images were reconstructed after Fourier transformation with AWOSEM software (2 iterations, 8 subsets, 5 mm Gaussian filter). The measurements were performed by a nuclear medicine expert. The CT images were acquired with 130 mAs, 130 kV, and a slice width (or 5 min and table feed) of 8 mm per rotation. Intravenous or oral contrast agents were used in all patients, and a standardized breathing protocol was applied.

2.3. Statistical analyses

Receiver operating characteristic (ROC) curves were calculated to estimate the accuracy for predicting the ideal MTV cut-off value. Estimation of sensitivity and specificity was based on the MTV cut-off value. Progression-free survival (PFS) was calculated from the date of diagnosis to documented disease progression; observations were censored either on the date the patient was last known to be alive or on the date of death for patients dying as a result of causes unrelated to lymphoma or treatment. Overall survival (OS) was calculated from the date of diagnosis until either death as a result of any cause or the date last known to be alive. PFS and OS were estimated by the Kaplan–Meier method, and the difference was compared using the log-rank test. Statistical analysis was carried out with SPSS software for Macintosh version 15.0 (SPSS Inc., Chicago, IL, USA). A probability value <0.05 was considered statistically significant.

3. Results

3.1. Patient clinical characteristics

The clinical characteristics of the 80 patients with ENKTCL of the head and neck are summarized in Table 1. Thirty-eight patients were >60 years of age. The primary site of the tumor was the nasal cavity in 63 patients, nasopharynx in 10 patients, and the oral cavity/oropharynx in seven patients. Fifty-one patients were in Ann Arbor stage I_E (53.8%), and 29 patients were in stage II_E (45.2%). Thirteen patients (16.3%) had B symptoms and 11 patients (13.7%) had Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade >2. Twenty-five patients (31.3%) had LTI. Twenty-one patients (26.3%) had elevated lactate dehydrogenase (LDH) levels above the upper normal limit, and 24 patients (30.0%) were classified with a high International Prognostic Index (IPI) score (≥2). Thirty-two patients (40.0%) underwent upfront RTx followed by CTx, whereas 48 patients (60.0%) received CTx only or CTx followed by RTx. The complete response (CR) rate and overall response (OR) rate for stage I_E were 64.7% (n = 33) and 92.1% (n = 47), whereas the CR rate and OR rate for stage II_E were 65.5% (n = 19) and 79.3% (n = 23) (Table 1).

3.2. MTV ROC curve analysis and the survival pattern

ROC curve analysis was used to determine the accuracy of the ideal cut-off value for distinguishing the high MTV group from the low MTV group. The estimated area under the ROC curve of MTV was 0.795. Various MTV cut-off values were used to obtain a reasonable balance of sensitivity and specificity. A value of 35.2 cm^3 provided sensitivity of 90.2% and specificity of 52.2% (Fig. 1). The patients were separated into two MTV groups such as low (<35.2 cm^3) and high MTV groups (≥35.2 cm^3).