research article

CT findings predict survival of patients with peripheral T cell lymphoma: a preliminary study

Wenbin Yang, Sen Jiang, Jianbang Lin, Yangkang Li

Department of Radiology, Cancer Hospital, Shantou University Medical College, Guangdong, China

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Correspondence to: Yangkang Li, Department of Radiology, Cancer Hospital, Shantou University Medical College, No7, Raoping Rd, Shantou, Guangdong Province 515041, P. R. China. Phone: +86 0754 8855 5844; Fax: +86 0754 8856 0352; E-mail: liyangkang@yahoo.com

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Background. Peripheral T-cell lymphoma (PTCL) is an uncommon disease with poor clinical outcomes. Radiological reports on the survival of patients with PTCL are scarce. The purpose of this study is to investigate the prognostic value of CT findings to predict clinical outcomes in fifty-one patients with histologically proven PTCL.

Patients and methods. The clinical data and CT images of all patients were retrospectively reviewed. CT features including number of involvement sites, lesion size, shape, margin, density, peritumoral invasion, intratumoral necrosis, lymph node involvement, and degree of contrast enhancement were evaluated. Univariate and multiple logistic regression analysis were used to determine the association between the clinical outcome and radiologic factors.

Results. Multiple site involvement, an ill-defined margin with peritumoral invasion, inhomogeneous density, and intratumoral necrosis were found to be associated with poor outcomes in univariate analysis ($P < 0.05$). An ill-defined margin with peritumoral invasion, was identified as an independent risk sign by further multivariate logistic regression analysis ($P < 0.05$). The area under the ROC curve of this CT feature was 0.745 ($P < 0.05$).

Conclusions. An ill-defined margin with peritumoral invasion was a valuable prognostic factor to predict the worse clinical outcomes in patients with PTCL.

Key words: lymphoma; peripheral T cell lymphoma; computed tomography; prognosis

Introduction

Peripheral T-cell lymphoma (PTCL) is an uncommon disease entity more prevalent in Asia than in Western countries and accounts for 5% to 30% of all non-Hodgkin lymphomas (NHL).[1-3] It is a heterogeneous group of clinically aggressive lymphomas including PTCL-not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T-cell lymphoma (AITL). PTCL is usually associated with poor outcome compared with B-cell lymphomas.[4-7] Thus, PTCL requires prompt diagnosis and vigilant monitoring of progression since it is a life-threatening disease.

The International Prognostic Index (IPI), which was developed for predicting the clinical course of aggressive lymphomas, is commonly used in PTCL. This system is based on age, performance status, lactate dehydrogenase, stage, and extranodal involvement. Establishing the correct diagnosis and accurately evaluating the extent of tumor involvement are important for patients with PTCL because they directly impact the staging and treatment of the tumor. Therefore, accurately describing the characteristics of PTCL (for example, the tumor size and local extension, lymph node metastases, or extranodal involvement, *etc*.) is fundamental in clinical imaging practice.

Computed tomography (CT) is usually used for evaluation of the patient who has lymphoma, because it offers the advantage of obtaining information about both the nodal and extranodal

components of the disease. Hence, it allows for accurate staging of the disease and follow-up of the therapeutic response. Radiologic manifestations about lymphoma have been described in many studies; however, most of them have focused on B-cell lymphoma. Although several reports concerning the imaging characteristics of PTCL have been published[8-10], these studies usually focused on nodal diseases or conducted on this entity only targeting one extranodal site, for example, the head and neck. Furthermore, the prognostic value of the imaging findings was absent in these studies. The purpose of this study was to evaluate the prognostic value of CT findings to predict clinical outcomes in patients with PTCL involving both nodal and extranodal sites.

Patients and methods

Study population and clinical data

This study was conducted in accordance with the declaration of Helsinki and was approved by the Medical Ethics Committee of Cancer Hospital of Shantou University Medical College. The requirement of informed consent was waived, due to the retrospective nature of the study.

Fifty-one patients with pathologically confirmed PTCL were included in our study through a computerized search of the pathology database between October 2005 and July 2015. The histological diagnosis of PTCL was made by pathologists according to the World Health Organization classification, and all of the biopsy specimens were reviewed through immunohistochemical examination. The patient inclusion criteria were as follows: (a) no patient received any treatment; (b) each patient had complete CT data (unenhanced scan and contrast-enhanced scan of head and neck, chest, and abdominopelvic area); (c) visible tumor on CT. Clinical data collected included the patient's age, gender, tumor location, tumor stage, treatment and outcome.

Image analysis

CT examinations of 10 patients were performed on a PQ5000 spiral CT scanner (Picker, New York, NY, USA), 41 patients were examined using a GE Brightspeed Elite 16-detector-row scanner (GE Healthcare, Milwaukee, WI, USA). After a series of unenhanced sections, all patients received intravenous bolus injection of contrast medium (Ultravist 300; Bayer Schering Pharma, Berlin-Wedding, Germany) at a rate of 2.5–3 mL/sec and a volume of 75–90 mL. The section thickness of all images of the single spiral CT was 10 mm. For multidetector CT, contiguous axial images and multiplanar reconstructions (MPR) were performed routinely. The section thickness was 5 mm and reconstruction interval was 1.25 mm.

The qualitative CT findings were reviewed by a consensus between two experienced radiologists (W.B.Y., with 8 years of experience in diagnostic imaging, and S.J., with 12 years of experience in diagnostic imaging). They were aware that the study population had lymphoma, but they were blinded to the pathological type, tumor stage and survival outcome. They evaluated the tumor location, tumor size, margin, shape, density, intratumoral necrosis, peritumoral invasiveness, contrast enhancement pattern, degree of enhancement, and lymph node enlargements. For patients with multiple tumors, the largest tumor was selected as the patient's representative tumor. Tumor size was measured in maximal dimension on the transverse plane. Tumor shape was categorized as round/oval or irregular. Tumor density was categorized as homogenous or heterogeneous on unenhanced CT images with normal muscle as the standard for comparison. The tumor margin was categorized as well-defined or ill-defined. Areas with reduced or missing contrast enhancement were considered to represent intratumoral necrosis. Peritumoral invasiveness was defined as infiltration of surrounding fat, bony invasion or invasion of the skin. The criteria for vascular invasion were vessel occlusion, focal narrowing, or contour deformity, and more than half of the perimeter in contact with the tumor.[11] The degree of enhancement was subjectively assessed and categorized as follows: mild, when the enhancement was similar to that of adjacent muscle; moderate, when the enhancement was higher than that of muscle, but lower than that of blood vessels; and marked, when the enhancement was approaching that of blood vessels. Lymph node enlargements were defined as short axis > 1cm, abnormal round morphology, or central necrosis.

Statistical analysis

To determine the prognostic value of the CT features, the clinical outcomes of patients were simplified into two categories: poor outcome if lesion progression during therapy or recurrence occurred within 24 months after therapy; good outcome if patients survived for more than 24 months with

no evidence of recurrence. Recurrence was defined as local (limited to the primary lesion site), distant (disseminates to distant tissues and organs), or both local and distant.

The radiologic variables included for analysis were categorized as follows: involvement site (single or multiple sites), tumor size (≥ 6.0 cm or < 6.0 cm), shape, lesion margin, density, intratumoral necrosis, peritumoral invasion, lymph node involvement, and degree of contrast enhancement.

The χ^2 test was applied to compare the frequency of the imaging findings between the poor and good outcome groups in patients. When the radiological signs appeared to be significant in the univariate analysis, multivariate analysis was developed to determine the association between clinical outcomes and individual radiologic variables using logistic regression model.

In the multivariate logistic regression model, variables with a *P* value less than 0.05 as determined by each univariate analysis were chosen as the independent variables. Odds ratios (OR) as estimates of relative risk with 95% confidence intervals (CI) were obtained for each risk factor.

The diagnostic performance of each risk factor was established using the area under the receiver operating characteristic (ROC) curve. A two-sided *P* value of less than 0.05 was considered statistically significant. All statistical tests were performed by using SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA).

TABLE 1. Clinical characteristics of 51 patients with PTCL

Characteristics	Number of cases	Percentage(%)
Gender		
Male	32	62.7
Female	19	37.3
Age(y)	47.8 ± 19.1 (range, 9–83)	
Histology		
PTCL-NOS	27	52.9
ALCL ALK+	8	13.7
ALCL ALK-	7	15.7
AITL	9	17.6
Ann Arbor stage		
I-II	21	41.2
III- IV	30	58.8
Clinical outcome		
Progression or relapse within 24 months	27	52.9
No evidence of relapse within 24 months	24	47.1

ALCL ALK+ = anaplastic large cell lymphoma anaplastic lymphoma kinase positive; ALCL ALK- = ALCL anaplastic lymphoma kinase negative; AITL = angioimmunoblastic T-cell lymphoma; PTCL-NOS = PTCL-not otherwise specified

Results

Clinical findings

As shown in Table 1, the median age of the patients at diagnosis was 47.8 years (ranged 9 to 83 years), and 35 of 51 patients (68.6%) were below 60 years old. The male to female ratio was 1.7:1. Thirty (58.8%) patients presented with advanced Ann Arbor stage. According to the histology, there were 27 PTCL-NOS, 15 ALCL (8 anaplastic lymphoma kinase [ALK] positive and 7 ALK negative), and 9 AITL. All the patients received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based chemotherapy. 11 patients also accepted radiotherapy. Follow-up period ranged from 10 to 115 months (mean, 45.9 ± 24.6 months). The lesion showed progression during therapy in 8 patients. Lesion relapse within 24 months after therapy was found in 19 patients, including local relapse in 7, systemic dissemination in 10, and local relapse with dissemination in 2. These 27 patients were categorized as the poor outcome group. 24 patients survived without any evidence of relapse at least 24 months after therapy, and were classified as the good outcome group.

CT characteristics

Nodal disease was found in 32 cases (62.7%). Extranodal involvement was found in 39 cases (76.5%). The extranodal involvement sites included nasal cavity, paranasal sinus, periorbital area, Waldeyer's ring, parotid gland, lung, liver, spleen, adrenal gland, gastrointestinal tract, breast and musculoskeletal tissue. The size of the tumors ranged from 1.5 to 14.0 cm (mean, 6.0 cm). The shape was depicted as oval (n = 17) or irregular (n = 34). The density was described as homogeneous (n = 28) and heterogeneous (n = 23). A well-defined margin was seen in 29 cases. An ill-defined margin with peritumoral invasion was seen in 22 cases. Intratumoral necrosis was seen in 14 cases. On unenhanced CT images, the density of the solid component of all tumors was 31–58 HU (mean, 45 HU) which was similar to that of muscle. After contrast medium administration, mild or moderate enhancement was detected in 21 and 30 cases, re-

TABLE 2. CT findings of 51 patients with PTCL

Characteristics	Number of cases	Percentage(%)
Involvement site		
Single	27	52.9
Multiple	24	47.1
Tumor size(cm)	6.0 ± 2.4 (range, 1.5–14.0)	
Tumor margin		
Well-defined	29	56.9
Ill-defined with peritumoral invasion	22	43.1
Tumor shape		
Round/oval	17	33.3
Irregular	34	66.7
Tumor density		
Homogenous	28	54.9
Heterogeneous	23	45.1
Intratumoral necrosis		
Present	14	27.5
Absent	37	72.5
Enhancement degree		
Mild	21	41.2
Moderate	30	58.8
Lymph node involvement		
Present	32	62.7
Absent	19	37.3

spectively. CT findings of all cases are summarized in Table 2. CT findings of one patient with good clinical outcomes are depicted in Figure 1. CT findings of three patients with poor clinical outcomes are depicted in Figures 2–4.

Prognostic analysis

The statistical results of univariate analysis are summarized in Table 3. In univariate analysis, four CT features, including multiple site involvement, an ill-defined margin with peritumoral invasion, intratumoral necrosis, and inhomogeneous density were associated with poor clinical outcomes ($P < 0.05$). Multivariate analysis showed that only one feature, an ill-defined margin with peritumoral invasion, remained a significantly independent predictor of poor clinical outcomes ($P < 0.05$). Further ROC curve analysis showed that the area under the curve of this significant CT feature was 0.745 ($P < 0.05$), which suggests that the multivariate logistic regression model is a reasonable predictor of clinical outcome (Table 4).

Discussion

In the present study, an ill-defined margin with peripheral tissue invasion was identified to be an independent risk factor for clinical outcome of patients with PTCL. This CT sign is considered more indicative of squamous cell carcinomas than of NHL, if there is no history of previous treatment or recent infection. For squamous cell carcinoma, an ill-defined margin with peripheral tissue invasion increases the risk of local failure, distant metastases, and decreased survival.[10,12] To our knowledge, there are only a few reports on the prognostic significance of ill-defined margin and local tumor invasion in NHL, perhaps because they have been considered uncommon findings in malignant lymphoma. Zhou *et al.*[13] reported that the lesion margin was an independent risk factor for clinical outcome

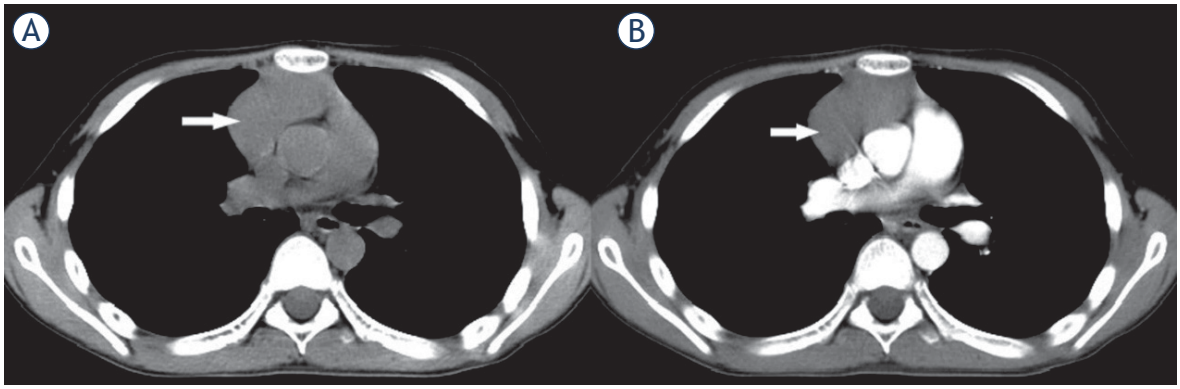

FIGURE 1. A 13-year-old boy with PTCL in the anterior mediastinum. **(A)** Axial non-contrast CT image shows an oval, well-defined mass with homogeneous density in the anterior mediastinum (white arrow). **(B)** Contrast-enhanced CT image shows the tumor with homogeneously mild enhancement (white arrow). Tumor recurrence was not noted during the 36-month follow-up period.

in 59 patients with head and neck NHL. Kim *et al.*[14] also reported that local tumor invasion as assessed by CT or MR imaging was a more important prognostic factor than IPI in predicting a low probability of complete remission and lower overall and disease-free survival in extranodal lymphoma. The result of our study was in agreement with previous literatures.

For malignant solid tumors, direct invasion may result in the infiltration of tumor cells to surrounding tissues and neighboring organs. Although a lymphoma is not really considered as a solid tumor, it does form a mass. For aggressive lymphoma subtypes, peritumoral/extracapsular infiltration often occurs. In the present study, the local invasion of PTCL, affected the fat, bone, skin or vessel nearby the tumor and gave the tumor an ill-defined margin on CT images. Of primary importance in the prognosis of patients with PTCL is the sequence of events leading to the development of tumor cell invasion. In previous studies, extensive deregulation of genes that control functions typically damaged in malignant cells, such as matrix remodeling, cell adhesion, transcription regulation, proliferation, and apoptosis, was found in T-cell or B-cell lymphomas.[15-19] The complexity of these tumors is represented by 25 to 30 up-regulated cancer genes and several down-regulated tumor suppressors that provide a growth advantage and enhance the ability to invade and disseminate. This might explain the mechanisms of local invasion and distant dissemination of PTCL in our study. The course of tumor invasion entails a series of stages that lead to dissemination and the formation of secondary tumors in distant organs and is, largely, responsible for the mortality and morbidity of PTCL.

TABLE 3. Univariate analyses of CT findings

Factor	Category	Number of good vs poor outcomes	*P* value
Involvement site			0.016*
	Single	17:10	
	Multiple	7:17	
Tumor size			0.328
	< 6.0cm	14:13	
	≥ 6.0cm	10:14	
Ill-defined margin with peritumoral invasion			< 0.001*
	Present	4:18	
	Absent	20:9	
Tumor shape			0.617
	Round/oval	8:9	
	Irregular	16:18	
Inhomogenous density			0.001*
	Present	5:18	
	Absent	19:9	
Intratumoral necrosis			0.025*
	Present	3:11	
	Absent	21:16	
Enhancement degree			0.586
	Mild	10:11	
	Moderate	14:16	
Lymph node involvement			0.069
	Present	12:20	
	Absent	12:7	

*$P < 0.05$

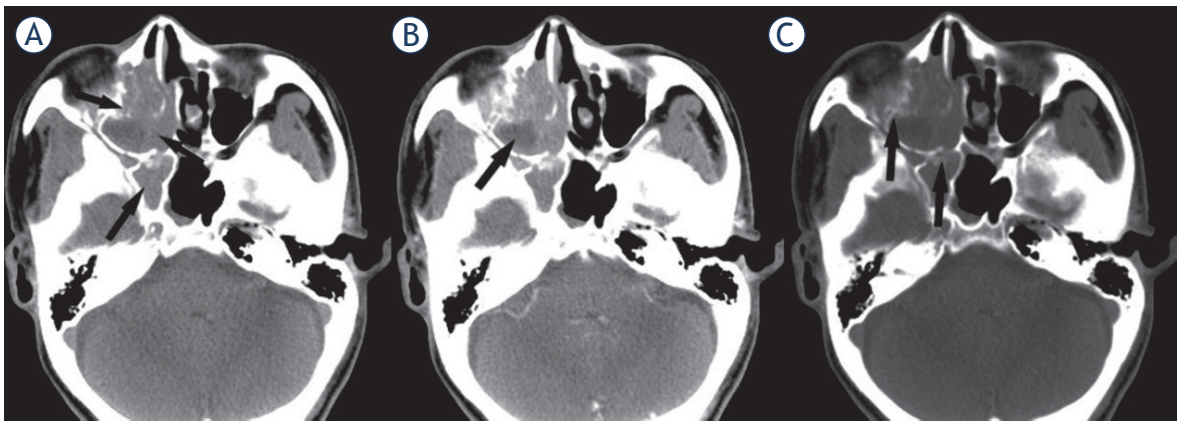

FIGURE 2. A 54-year-old man with PTCL in the sinonasal cavity. **(A)** Axial non-contrast CT image shows an ill-defined, irregular mass with inhomogeneous density in the right nasal cavity, maxillary and sphenoid sinus (black arrows). **(B)** Contrast-enhanced CT image shows the tumor with heterogeneously moderate enhancement. Intratumoral necrosis is seen in the mass (black arrow). **(C)** Bony destruction is detected on non-contrast CT image. The tumor relapsed 11 months after therapy.

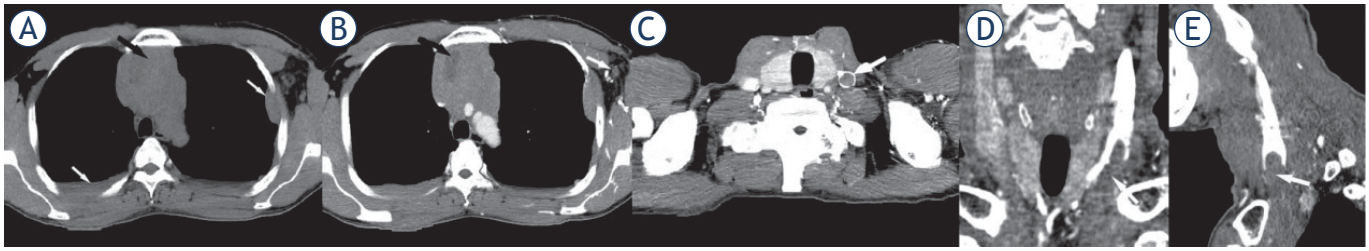

FIGURE 3. A 47-year-old man with PTCL in the anterior mediastinum. **(A)** Axial non-contrast CT image shows an ill-defined, irregular mass with inhomogeneous density in the anterior mediastinum (black arrow). Multiple pleural metastases are detected (white arrows). **(B)** Contrast-enhanced CT image shows the tumor with heterogeneously mild enhancement. Intratumoral necrosis is seen in the mass (black arrow). Lymphadenopathy is seen in the left axillary fossa (white arrows). **(C, D, E)** The left internal jugular vein is invaded by the tumor and vessel occlusion is detected on contrast-enhanced CT image and MPR images (white arrows). Tumor progression was found during therapy. This patient deceased at 3 months after therapy.

TABLE 4. Multivariate analyses of CT findings

Factor	Odd ratio	95% CI	*P* value
Involvement site	3.499	0.766–15.987	0.106
Ill-defined margin with peritumoral invasion	7.749	1.567–38.315	0.012*
Inhomogenous density	2.356	0.324–17.116	0.397
Intratumoral necrosis	3.157	0.253–39.370	0.372

*$P < 0.05$

Concentrating research efforts on identifying and understanding the mechanisms concerned in peritumoral invasion may lead to limiting tumor progression and, as a result, to a reduction in mortality for PTCL patients. In our opinion, when PTCL manifests as an ill-defined margin and peritumoral invasion, no matter the nodal disease or the extranodal lesion, patients are significantly more likely to experience poor outcomes than those with a well-defined lesion without local tumor invasion. And it may suggest the high aggressiveness of the disease, and more aggressive therapy is warranted for such circumstances.

A severely inhomogeneous tumor pattern on CT images was found to be associated with a high malignancy grade in NHL. This CT pattern was also compatible with a poor prognosis in patients treated with chemotherapy.[10,20] In this study, inhomogeneous density was another radiological sign that was associated with poor survival outcome in univariate analysis. This result was similar to those of previous studies. Although inhomogeneous density can be noted in other diseases, such as epithelial tumor, soft tissue neoplasia or infection, nearly a half of the patients (about 45%) with PTCL in our study showed this radiological characteristic. Inhomogeneous density may correspond to asymmetric tumor cell density, intralesional hemorrhage, necrosis or cystic change. This heterogeneity of tumor parenchyma always leads to heterogeneous density on CT images. Intratumoral hemorrhage and cystic change are seldom seen in

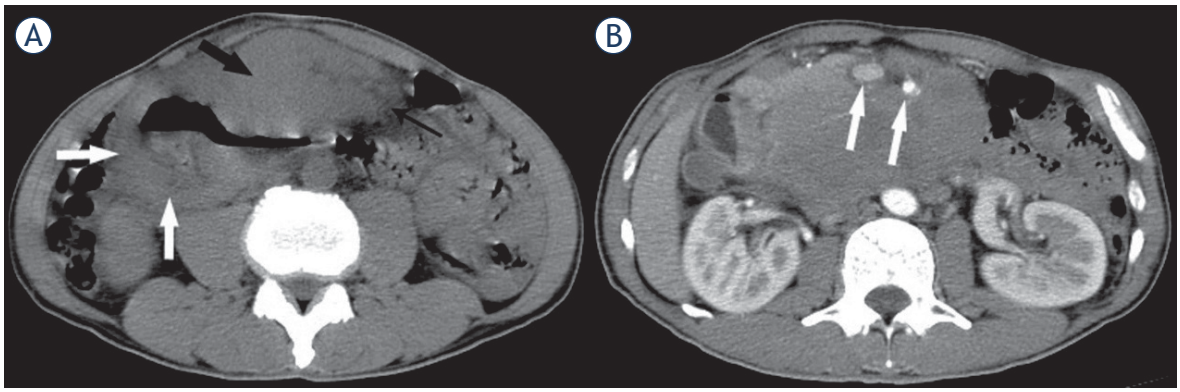

FIGURE 4. A 61-year-old man with PTCL in the deudenum. **(A)** Axial non-contrast CT image shows the thickening of the duodenal wall (white arrows).The lesion grows in an expansive centripetal fashion (black arrow) with an ill-defined margin and invasion of adjacent fatty tissue (thin black arrow). **(B)** Contrast-enhanced CT image shows the tumor with heterogeneously mild enhancement. Superior mesenteric artery and vein are encased by the tumor (white arrows). Tumor progression was found during therapy. This patient deceased at 5 months after therapy.

untreated lymphoma. In our opinion, asymmetric tumor cell density and uneven distribution of blood vessel density in PTCL may contribute to inhomogeneous density on CT images, though the corresponding radiological-pathological studies are absent in our study. A previous study showed that tumor cells of T-cell lymphoma grown under an inhomogeneous cell density, especially under a high cell density environment, become better adapted to survival. They are not only superior in their tumorigenic potential, but are also resistant to the antitumor action of multiple anticancer drugs.[21] Increased intratumoral vascularity has also been described as a negative prognostic factor in diffuse large B-cell lymphoma (DLBCL) treated with rituximab plus chemotherapy.[22]

Although intratumoral necrosis was not a common feature of NHL, it was found in nearly 27.5% of patients (14/51) in our study. Three previous studies have investigated the prognostic implications of tumor necrosis at CT or MRI in lymphoma.[23-25] Hopper *et al.*[23] investigated chest CT scans of 76 patients with newly diagnosed Hodgkin lymphoma with mediastinal involvement. Their results showed that the presence of mediastinal necrotic lymph nodes appears to have little prognostic significance in patients with Hodgkin lymphoma. Saito *et al.*[24] evaluated CT and MRI scans of 60 patients with different non-Hodgkin lymphoma subtypes for the presence of necrosis in lymph nodes. They found that lymph node necrosis had no significant influence on patients' disease-free survival, but may have a prognostic significance in patients with non-Hodgkin lymphomas. Adams *et al.*[25] studied CT scans of 51 patients with DLBCL for the tumor necrosis in lymph nodes as well as extranodal sites. The findings of their study also indicate the prognostic potential of tumor necrosis at CT in newly diagnosed DLBCL. The result of our study was similar to those of Saito *et al.* and Adams *et al.* Univariate analysis showed that intratumoral necrosis was associated with poor clinical outcomes. This may indicate that the underlying PTCL has an aggressive tumor growth. Although intratumoral necrosis was not an independent risk factor by multivariate analysis, it may have a prognostic significance in patients with PTCL.

The results of our study showed that PTCL is likely to involve multiple regions and manifest as a generalized disease. Lee *et al.*[8] also found that the most common radiologic feature of PTCL was systemic dissemination, including various organ involvement and generalized lymphadenopathy. In addition, in their series of 581 patients with intestinal non-Hodgkin lymphoma, Kim *et al.*[26] identified that B-cell lymphoma mainly presented as localized disease while T-cell lymphoma involved multiple sites. Three subtypes of T-cell lymphoma including PTCL-NOS, EATL and NK/T lymphoma had a relatively lower response rate and a higher recurrence rate. Although multiple site involvement was not an independent risk factor to predict patients' prognosis in our study, it was associated with poor clinical outcome in univariate analysis. Again, this may suggest that this characteristic is an indicative sign of the aggressive clinical course of PTCL.

In diagnosis, staging, monitoring of treatment and prediction of prognosis in patients with lymphoma, ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET/CT) has proved to be a more effective modality than diagnostic CT.[27-30] Jung *et al.*[31] investigated the prognostic accuracy of interim PET/CT in PTCL and derived cutoffs for standardized uptake value (SUV) and metabolic tumor volume (MTV) assessments that were significantly predictive for survival. Cottereau *et al.*[32] also reported that higher MTV predicted a poor survival in patients with PTCL. However, in China the limited number of hybrid PET/CT scanners and major financial restrictions also prevent widespread use of this expensive modality. Furthermore, intravenous contrast material administration is usually absent in FDG PET/CT studies and blood vessel invasion by lymphoma may not be clearly depicted. Small disease missed by PET/CT because of the absence of FDG uptake and non-pathological FDG accumulation can also be properly identified by contrast-enhanced CT.

Our study has several limitations, the first of which is its retrospective nature. Second, a detailed pathological study was absent to be correlated to the imaging findings. Therefore, further investigation on large cases with a detailed radiological-pathological correlation study is needed. Third, different CT equipment and techniques were used. CT examinations of 10 patients were performed on a single spiral CT with a section thickness of 10 mm. Compared with the smaller section thickness, it may affect the quality of the CT images and decrease the probability that more tissue of a given lesion will be captured. Fourth, different histological subtypes of PTCL were involved, and each subtype may have different clinical features and treatment response. However, this problem is simply unavoidable due to the limitations of a retrospective study and the rarity of PTCL, and should not have significantly affected the imaging characteristics studied.

In conclusion, multiple site involvement, an ill-defined margin with peritumoral invasion, inhomogeneous density, and intratumoral necrosis are relatively significant CT features of PTCL. An ill-defined margin with peritumoral invasion indicates a high risk of unfavorable survival outcome for PTCL. Nevertheless, the interaction between the different clinical and radiologic parameters is complex, and the imaging-based criteria for the assessment of treatment success and outcome is still the subject of ongoing investigations. To reliably evaluate the survival of patients with PTCL, it is important that the imaging examinations be performed according to unified technology and are interpreted according to standardized rules.

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