Cutaneous B-cell lymphoma : classification, prognostic factors and management recommendations

Senff, N.J.

Chapter 4.

The applicability and prognostic value of the new TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome: results on a large cohort of primary cutaneous B-cell lymphomas and comparison with the system used by the Dutch Cutaneous Lymphoma Group

British Journal of Dermatology 2007; 157(6):1205-11

Nancy J. Senff and Rein Willemze
Department of Dermatology, Leiden University Medical Centre, Leiden, The Netherlands

Summary

Background: Recently, a consensus proposal was published for a TNM classification system for all primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome, meant to document extent of disease in a consistent manner. The applicability and the prognostic significance of this system have not been investigated thus far.

Objectives: To test the applicability and prognostic relevance of the proposed TNM classification system on a cohort of primary cutaneous B-cell lymphomas (CBCL).

Patients/ methods: The study group included 71 primary cutaneous marginal zone lymphomas (PCMZL), 171 primary cutaneous follicle centre lymphomas (PCFCL) and 58 primary cutaneous diffuse large B-cell lymphomas, leg type (PCLBCL, LT). Since only patients with primary cutaneous lymphoma were included (T1-3, N0M0), only T-rating was scored. The results were compared with the scoring as applied by the Dutch Cutaneous Lymphoma Group.

Results: The system was easily applicable to all cases. In PCMZL and PCFCL no correlation was found between T-score and survival (5-year disease-specific survival: T1: 100% and 98%, T2: 94% and 93%, T3: 100% and 88% respectively). In PCLBCL, LT there was an obvious, although statistically not significant, association between increasing T-score and reduced survival (5-year disease-specific survival: T1: 75%, T2: 49%, T3: 0%; p = 0.077). Comparing the TNM system with the Dutch Cutaneous Lymphoma Group system, there was a discrepancy in the classification of 20 cases.

Conclusions: The new TNM- system is a useful tool to document disease extent in patients with CBCL and provides prognostic information in the group of PCLBCL, LT patients.

Keywords: B cell, cutaneous lymphoma, disease extent, prognosis, TNM staging

Introduction

Recently, representatives of the International Society for Cutaneous Lymphomas and the Cutaneous Lymphoma Group of the European Organization for Research and Treatment of Cancer (EORTC) published a consensus proposal for a TNM classification system applicable to all primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome.[1] This proposed TNM system is primarily meant to document extent of disease in a consistent manner, thereby facilitating comparison of studies at different institutes. In the proposed system the T-classification reflects the extent/ distribution of primary cutaneous involvement, the N-classification describes lymph node involvement and the M-classification is used to describe if extracutaneous non-lymph node disease is present. Since, by definition, in all primary cutaneous lymphomas, extracutaneous disease (lymph node or visceral) is absent at the time of diagnosis, the N- and M-scores are only used to document disease extent at the time of relapse or disease progression. A detailed description of the different categories is given in Table 1.

Studies investigating the applicability of this TNM system have not been performed thus far. Moreover, whether this TNM system provides prognostically relevant information for the different types of primary cutaneous lymphoma and thus may serve as an additional guide in the appropriate management of these lymphomas remains to be elucidated.

In the present study we applied the proposed TNM system on a large cohort of 300 primary cutaneous B-cell lymphomas (CBCL), recently reclassified according to the new WHO-EORTC classification.[2;3] This classification distinguishes 3 main types of CBCL: primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous follicle centre lymphoma (PCFCL), both indolent types of CBCL and primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL, LT), which represents a more aggressive type of CBCL. Since these groups have been redefined as compared to the formerly used classifications[4;5], we have summarized the main features of these 3 groups, as found in a recent study[2], in Table 2.

The aims of this retrospective cohort analysis were to test the clinical applicability of the proposed TNM system and to evaluate its prognostic relevance for the group of CBCL. In addition, these results were compared to the scoring of disease extent as used by the Dutch Cutaneous Lymphoma Group.

Methods

Patient selection

The study group is a retrospective cohort of 300 CBCL patients reclassified according to the criteria of the WHO-EORTC classification.[3] In all cases, gender, age at diagnosis, site, size and extent of skin lesions (see below), status at last follow-up and duration of follow-up were recorded as part of a recent study.[2] In addition, in approximately 50% of cases clinical photographs were available for evaluation.

This group included 71 primary cutaneous marginal zone lymphomas (PCMZL), 171 primary cutaneous follicle centre lymphomas (PCFCL) and 58 primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL, LT).

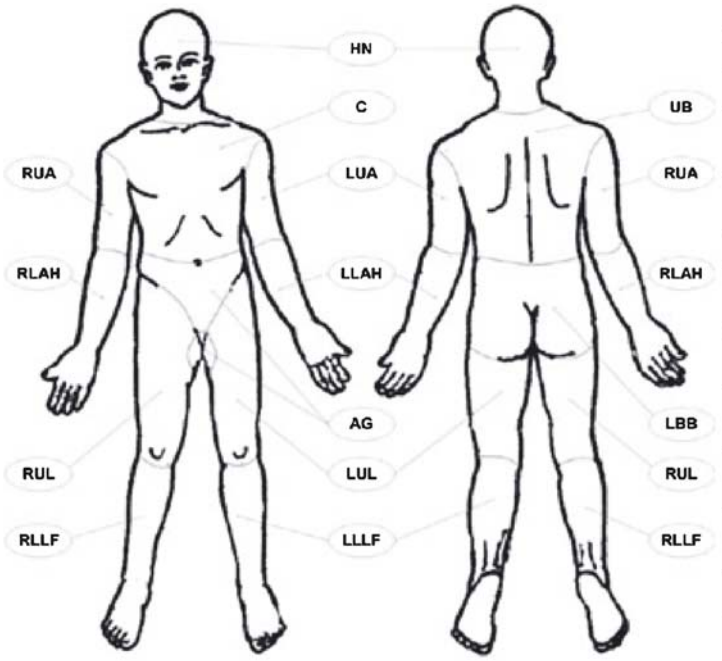
Table 1. Description of different scres in the TNM classification.

Classification		Description
T	**T1**	Solitary skin involvement categories: • **T1a** a solitary lesion $\leq$5 cm diameter • **T1b** a solitary lesion >5 cm diameter
	T2	Regional skin involvement categories: Multiple lesions limited to one body region or two contiguous body regions • **T2a** all disease encompassing in a $\leq$ 15 cm diameter circular area • **T2b** all disease encompassing in a > 15 and $\leq$ 30 cm diameter circular area • **T2c** all disease encompassing in a > 30 cm diameter circular area
	T3	Generalized skin involvement: • **T3a** multiple lesions involving 2 non-contiguous body regions • **T3b** multiple lesions involving $\geq$ 3 body regions
N	**N0**	No clinical or pathologic lymph node involvement
	N1	Involvement of one peripheral lymph node region that drains an area of current or prior skin involvement
	N2	Involvement of two or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement
	N3	Involvement of central lymph nodes
M	**M0**	No evidence of extracutaneous non-lymph node disease
	M1	Extracutaneous non-lymph node disease present

Assessment of disease extent

In all cases extent of skin lesions at the time of diagnosis was scored using the proposed TNM system.[1] Since only patients with primary cutaneous lymphoma were included (T1-3, N0M0), only T-rating was scored (see Table 1 and Figure 1). In case no measurements were recorded in the database of the Dutch Cutaneous Lymphoma Group and clinical photographs were not available, measurements of skin lesions were obtained from patients charts or, in case the patient had undergone radiotherapy, from the files of the radiotherapy department. The results were compared with the scoring of the Dutch Cutaneous Lymphoma Group, used in our previous study.[2] In this Dutch Cutaneous Lymphoma Group system, extent of involved skin is defined as solitary when it concerns a single tumour, as localized when the lesion consists of multiple skin lesions that can be irradiated within one radiation field, and as multifocal for separate lesions in adjacent body regions that can not be irradiated within one radiation field or for lesions involving multiple nonadjacent body regions. In contrast to the TNM system, no further subdivision is made on the basis of the size of the skin lesions or the affected areas.

Figure 1. Body regions as defined in the proposed TNM system for the designation of T-classification. Left and right extremities are assessed as separate body regions.



HN	Head & neck
C	Chest
LUA	Left upper arm
LLAH	Left lower arm & hand
AG	Abdominal & genital
LUL	Left upper leg
LLLF	Left lower leg & feet
RUA	Right upper arm
RLAH	Right lower arm & hand
RUL	Right upper leg
RLLF	Right lower leg & feet
UB	Upper back
LBB	Lower back & buttock

Statistical analysis

Statistical calculations were performed using SPSS 12.0.1 (SPSS Inc, Chicago, IL). Disease-specific survival was calculated from the date of diagnosis until death of lymphoma or last follow-up without event. Survival curves were estimated using the method of Kaplan and Meier and statistical comparison between curves was done by log-rank testing.

Results

The median follow-up for the whole group was 56 months (range 2-336 months).
The results of scoring extent of disease by T-score and by the Dutch Cutaneous Lymphoma Group system, as well as the corresponding 5-year disease-specific survival rates, are summarized in Table 3. Because of the clear descriptions of the main T-score groups and the different subgroups (see Table 1), combined with the strictly defined body regions (see Figure 1), this system could be easily applied to all cases.

The study included 71 PCMZL patients (48 males, 23 females) with a median age of 53 years (range 23-87). Using the TNM system most patients were classified as T3 (n = 28; 39%), followed by T2 (n = 25; 35%) and T1 (n = 18; 25%). According to the Dutch Cutaneous Lymphoma Group system 36 patients (51%) had multifocal disease, 17 patients (24%) had localized disease, while 18 patients (25%) had presented with a solitary lesion. Eight cases with multiple separate lesions at adjacent body regions were classified as multifocal according to the Dutch Cutaneous Lymphoma Group system, but as T2 using the TNM system. Representative examples of the different stages are presented in Figure 2.
The five-year disease-specific survival for T1, T2 and T3 were 100%, 94% and 100% respectively, and 100%, 92% and 100% for solitary, localized and multifocal disease according to the Dutch Cutaneous Lymphoma Group system. These results clearly show that extent of disease, either by TNM or Dutch Cutaneous Lymphoma Group system has no prognostic significance in this group.

Table 2. Clinical characteristics of the 3 main groups of primary cutaneous B-cell lymphoma.

	PCMZL	PCFCL	PCLBCL, LT
Median age, years (range)	53 (23-87)	58 (21-89)	78 (42-92)
Male: female ratio	2.1	1.8	0.5
Clinical presentation	solitary or multiple papules, plaques or nodules preferentially on the trunk (55%) or extremities (67%)	solitary or grouped tumours or plaques preferentially on the head (44%) or the trunk (54%) lesions on the leg(s) uncommon (6%)	solitary or multiple nodules and/or tumours most often on the leg(s) (88%) lesions at sites other than the leg(s) uncommon
Relapse rate	57%	30%	69%
Extracutaneous progression	8.5%	10.5%	47%
Prognosis: **5-year DSS** **5-year OS**	 98% 94%	 95% 87%	 50% 37%
Preferred treatment	non-aggressive local treatment or radiotherapy	radiotherapy	multi-agent chemotherapy

Patients with a PCFCL (n = 171; 109 males and 62 females) had a median age of 58 years (range 21-89). Using the TNM system, most patients presented with stage T1 (n = 68; 40%) or T2 (n = 88; 51%). Only 15 patients (9%) were classified as T3 at the time of diagnosis (see Table 3). According to the Dutch Cutaneous Lymphoma Group system 68 patients (40%) had presented with a solitary skin lesion, 76 patients (44%) with localized skin lesions and 27 patients (16%) with multifocal skin lesions. Twelve cases with multiple separate lesions at adjacent body regions were classified as multifocal according to the Dutch Cutaneous Lymphoma Group system, but as T2 using the TNM system. Representative examples of the different stages are presented in Figure 3.
The 5-year disease-specific survival for T1, T2 and T3 was 98%, 93% and 88% and 99%, 95% and 85% for solitary, localized and multifocal according to the Dutch Cutaneous Lymphoma Group system respectively. Although there was a tendency toward reduced survival with increasing T-score, these differences were not significant (p = 0.560). Moreover, no significant differences were found between subgroups within the different T-categories (T1a vs. T1b; T2a vs. T2b vs. T2c; T3a vs. T3b; see Table 3).

Patients with PCLBCL, LT (n = 58; 20 males, 38 females) had a median age of 78 years (range 42-92). In this group the numbers according to the T-score corresponded entirely with the numbers in the extent categories as used by the Dutch Cutaneous Lymphoma Group: T1/ solitary 24% (n = 14), T2/ localized 57% (n = 33) and T3/ multifocal 19% (n = 11) (see Figure 4). Although statistically not significant (p = 0.077) an obvious correlation was seen between extent and survival (5-year disease-specific survival of 75%, 49% and 0% respectively). Moreover, the classification into subgroups within the main T-scores provided additional prognostic value. For instance, patients in the T2 group showed a decreased survival with increasing size of the affected areas (5-year disease-specific survival for involved area of ≤ 15 cm, 15-30 cm or > 30 cm is 67%, 48% and 0% respectively; see Table 3).

Discussion

This study investigates the applicability and prognostic significance of the newly proposed TNM system and describes for the first time how this system is applied to a large group of primary cutaneous lymphomas.
Our results show that the TNM system can easily be applied to the three commonest groups of CBCL. In both indolent entities, PCMZL and PCFCL, the system does not appear to have prognostic significance, but in PCLBCL, LT, the group with an intermediate prognosis, increasing T-score seems to be associated with worse survival. In addition, subdivision based on the size of the skin lesion or the affected body area, or in case of T3 classification, the amount of involved body regions, provided additional prognostic information in this group of PCLBCL, LT.

Table 3. Scoring of disease extent in 300 CBCL according to the TNM-system and the Dutch Cutaneous Lymphoma Group -system.

	PCMZL (n = 71)				PCFCL (n = 171)				PCLBCL, LT (n = 58)			
	TNM no. of patients (%)	**5-yr DSS**	**DCLG** no. of patients (%)	**5-yr DSS**	**TNM** no. of patients (%)	**5-yr DSS**	**DCLG** no. of patients (%)	**5-yr DSS**	**TNM** no. of patients (%)	**5-yr DSS**	**DCLG** no. of patients (%)	**5-yr DSS**
T1	**18 (25%)**	**100%**	**Solitary**		**68 (40%)**	**98%**	**Solitary**		**14 (24%)**	**75%**	**Solitary**	
T1a	15 (21%)	100%	18 (25%)	100%	53 (31%)	98%	68 (40%)	99%	8 (14%)	86%	14 (24%)	75%
T1b	3 (4%)	100%			15 (9%)	100%			6 (10%)	56%		
T2	**25 (35%)**	**94%**	**Localized**		**88 (51%)**	**93%**	**Localized**		**33 (57%)**	**49%**	**Localized**	
T2a	7 (10%)	75%	17 (24%)	92%	44 (26%)	91%	76 (44%)	95%	18 (31%)	67%	33 (57%)	47%
T2b	7 (10%)	100%			27 (16%)	96%			9 (16%)	48%		
T2c	11 (15%)	100%			17 (10%)	92%			6 (10%)	0%		
T3	**28 (39%)**	**100%**	**Multifocal**		**15 (9%)**	**88%**	**Multifocal**		**11 (19%)**	**0%**	**Multifocal**	
T3a	3 (4%)	100%	36 (51%)	100%	4 (2%)	100%	27 (16%)	85%	5 (9%)	20%	11 (19%)	0%
T3b	25 (35%)	100%			11 (6%)	83%			6 (10%)	0%		

Consistently, in two recent studies on PCLBCL, LT, patients presenting with a solitary tumour had a better prognosis than patients presenting with multiple tumours on one or both legs.[6;7] However, in a study of 40 PCLBCL, LT by Kodama et al[8] no difference in survival was found between patients with solitary or multiple tumours. Zinzani et al reported a significantly higher overall survival for PCMZL/ PCFCL patients with a single skin lesion compared to those with regional/ disseminated disease.[7] Since the authors do not describe this relation for PCMZL and PCFCL separately, comparison with the results of the present study is impossible.

Comparing the TNM-system with the Dutch Cutaneous Lymphoma Group system, there was a discrepancy in the classification of 20 cases (8 PCMZL and 12 PCFCL) with multiple separate lesions at two contiguous body regions (see Figure 2B). Since there is no anatomical or biological relation between such separate lesions, in the Dutch Cutaneous Lymphoma Group such lesions are classified as multifocal or generalized disease, and not as regional disease. However, since the T3 category in the TNM system is defined as involvement of 2 non-contiguous body regions or 3 or more body regions, such cases are not classified as T3, but as T2, which denotes regional skin involvement. Classification of such cases as T2 is of minor clinical importance in PCMZL and PCFCL, since both groups represent indolent types of CBCL, which can be treated with non-aggressive therapies, irrespective of the extent of skin lesions. However, in other types of lymphoma, classifying separate lesions at adjacent body sites as T2 might have important therapeutic consequences.

In conclusion, our results show that the proposed TNM system provides the clinician with a useful tool to document the disease extent in patients with CBCL in a consistent manner. In cases of PCLBCL, LT it also provides prognostic information. The applicability of the definitions for T2c and T3a/b should be evaluated in cohorts of other types of primary cutaneous lymphomas, because this might have undesirable therapeutic consequences.

Figure 2. Examples of different T-scores in primary cutaneous marginal zone lymphoma. A: T2a; Dutch Cutaneous Lymphoma Group: localized, B: T2c; Dutch Cutaneous Lymphoma Group: multifocal.

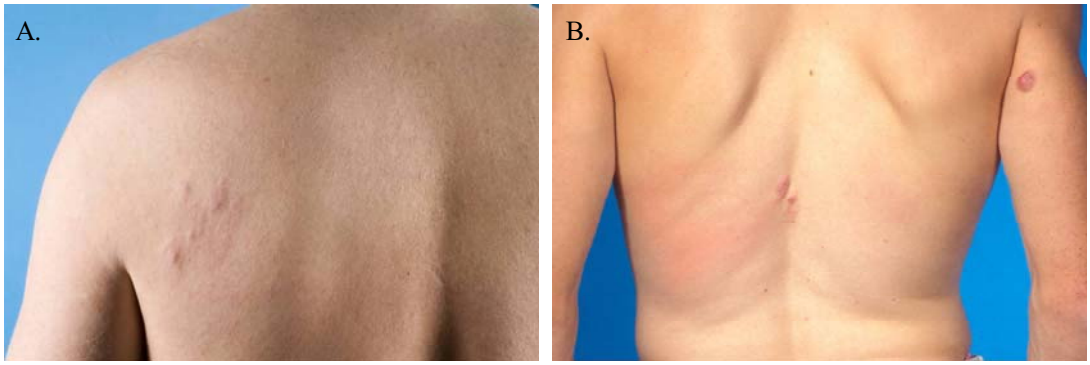


Figure 3. Examples of different T-scores in primary cutaneous follicle centre lymphoma. A: T1b; Dutch Cutaneous Lymphoma Group: solitary, B: T2b; Dutch Cutaneous Lymphoma Group : localized, C and D: T3b; Dutch Cutaneous Lymphoma Group : multifocal.

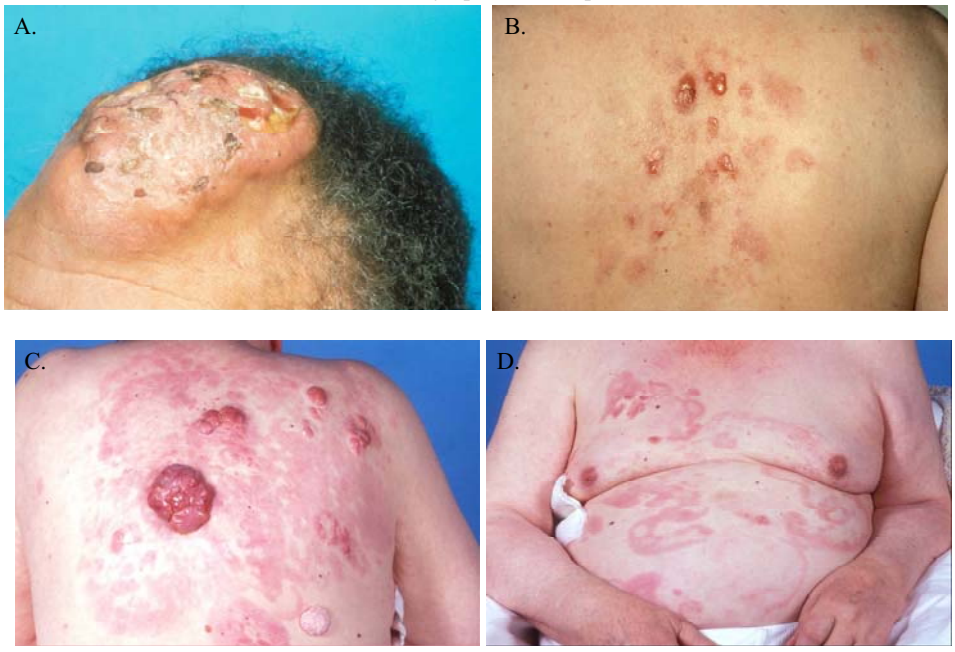
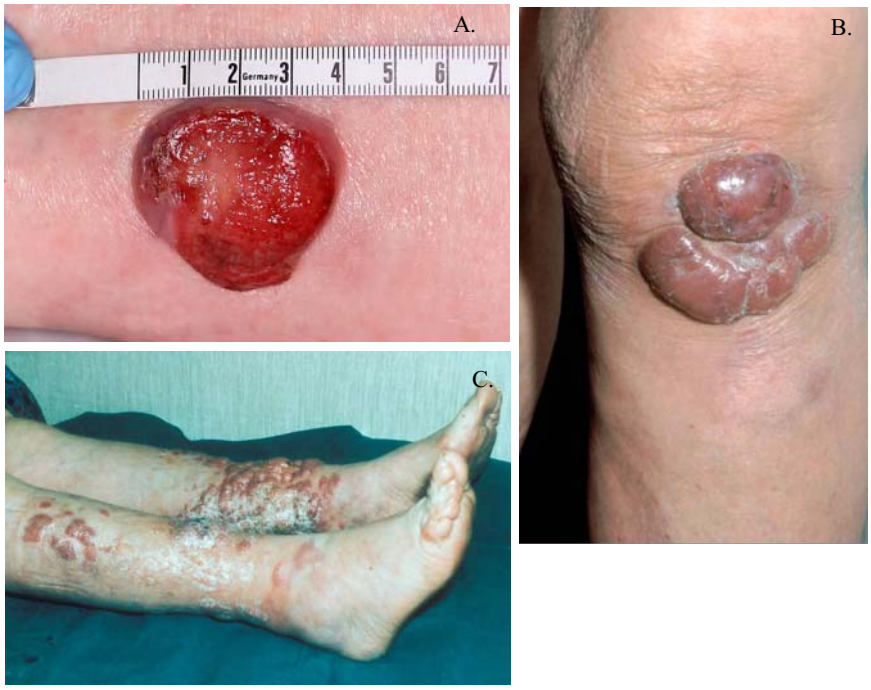


Figure 4. Examples of different T-scores in primary cutaneous diffuse large B-cell lymphoma, leg type. A: T1a; Dutch Cutaneous Lymphoma Group : solitary, B: T2a; Dutch Cutaneous Lymphoma Group: localized, C: T3a; Dutch Cutaneous Lymphoma Group: multifocal



References

1. Kim YH, Willemze R, Pimpinelli N et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood 2007;110:479-484.

2. Senff NJ, Hoefnagel JJ, Jansen PM et al. Reclassification of 300 primary cutaneous B-Cell lymphomas according to the new WHO-EORTC classification for cutaneous lymphomas: comparison with previous classifications and identification of prognostic markers. J.Clin.Oncol. 2007;25:1581-1587.

3. Willemze R, Jaffe ES, Burg G et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-3785.

4. Jaffe ES, Harris NL, Stein H, Vardiman JW. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Hematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001.

5. Willemze R, Kerl H, Sterry W et al. EORTC classification for primary cutaneous lymphomas: a proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer. Blood 1997;90:354-371.

6. Grange F, Bekkenk MW, Wechsler J et al. Prognostic factors in primary cutaneous large B-cell lymphomas: a European multicenter study. J.Clin.Oncol. 2001;19:3602-3610.

7. Zinzani PL, Quaglino P, Pimpinelli N et al. Prognostic factors in primary cutaneous B-cell lymphoma: the Italian Study Group for Cutaneous Lymphomas. J.Clin.Oncol. 2006;24:1376-1382.

8. Kodama K, Massone C, Chott A et al. Primary cutaneous large B-cell lymphomas: clinicopathologic features, classification, and prognostic factors in a large series of patients. Blood 2005;106:2491-2497.