Applicability and Prognostic Value of the New TNM Classification System in 135 Patients With Primary Cutaneous Anaplastic Large Cell Lymphoma

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Objectives: To test the applicability and prognostic value of the new TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome in patients with primary cutaneous anaplastic large cell lymphoma (C-ALCL) and to evaluate the prognostic significance of other clinical variables, in particular the site of presentation.

Design: Retrospective cohort analysis.

Setting: Dutch Cutaneous Lymphoma Group database.

Patients: One hundred thirty-five patients with C-ALCL.

Main Outcome Measures: Clinical variables, including T category and site of presentation.

Results: Eighty patients (59.3%) presented with T1 disease, 37 (27.4%) with T2 disease, and 18 (13.3%) with T3 disease. Median follow-up was 56 months (range, 11-288 months). Five-year disease-specific survival (DSS) was 93% for T1 disease, 93% for T2 disease, and 77% for T3 disease (P=.19). Patients with skin lesions on a leg had reduced 5-year DSS compared with lesions on other sites (82% for leg vs 95% for head and neck, 96% for trunk, and 95% for arm; P=.23). Patients with leg involvement (n=32) had significantly worse 5-year DSS than did patients without leg involvement (n=103; 76% vs 96%; P=.03 after adjustment for T category).

Conclusions: The new TNM system can be applied well to patients with C-ALCL and may provide prognostic information, in particular when combined with site of presentation. Patients with T2 or T3 disease with skin lesions on the leg may have reduced survival and require close surveillance during follow-up.

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Primary cutaneous anaplastic large cell lymphoma (C-ALCL) is a non-Hodgkin lymphoma of T-cell origin that presents in the skin without evidence of extracutaneous disease at the time of diagnosis. It is characterized by large cells with an anaplastic, pleomorphic, or immunoblastic cytomorphologic presentation and by expression of the CD30 antigen by more than 75% of the tumor cells. Patients with C-ALCL show overlapping clinical, histologic, and immunophenotypical features with lymphomatoid papulosis that together form a spectrum of disease collectively designed as primary cutaneous CD30-positive lymphoproliferative disorders. Distinction between C-ALCL and lymphomatoid papulosis is based on a combination of clinical, histologic, and immunophenotypical criteria. Primary C-ALCL is regarded as an indolent type of cutaneous T-cell lymphoma, as illustrated by several large studies showing 10-year disease-specific survival (DSS) of approximately 90% and 10-year overall survival of approximately 75%. Risk factors that predict an unfavorable course, occurring in few patients with C-ALCL, are largely unknown. However, several studies have suggested that ages older than 60 years, absence of spontaneous remission, and presentation with multifocal skin lesions may correlate with reduced survival. Moreover, extensive single-limb involvement and localization on the head and neck have been associated with a less favorable prognosis.

Recently, a new TNM classification system has been developed for primary cutaneous lymphomas other than mycosis fungoides (MF) and Sézary syndrome (SS). This classification system is primarily meant to document the extent of disease in a consistent manner, facilitating comparison of studies at different institutions (Table 1). Recent studies have started to evaluate the clinical usefulness of this TNM system. Studies of large groups of cutaneous B-cell lymphomas confirmed its applicability and suggested that this system has prognostic significance in primary cutaneous diffuse large B-cell lymphomas, leg type, but not in primary cutaneous follicle center lymphomas and primary cutaneous marginal zone lymphomas. However, studies in cutaneous T-cell lymphoma other than MF and SS have not been published thus far.

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The aim of the present study is to test the applicability and prognostic value of this TNM classification system for C-ALCL. In addition, the prognostic significance of other clinical variables, in particular the site of presentation, was evaluated.

### STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 16.0 (SPSS Inc, Chicago, Illinois). Rates of DSS and overall survival were calculated from date of diagnosis until death from lymphoma and death from any cause, respectively, or from last follow-up without an event. Survival curves were estimated using the Kaplan-Meier technique, and comparison between curves was performed using the log-rank test. Prognostic factors were evaluated by means of univariate and multivariate analysis with overall survival and DSS as end points, and \( P < .05 \) was considered significant. Clinical variables included for univariate analyses were sex, age (≤60 vs >60 years), extent of disease (T category), site of presentation, and complete spontaneous remission of initial skin lesions. Multivariate analysis was performed using significant univariate variables from the Cox proportional hazards regression analysis.

### RESULTS

Clinical characteristics at diagnosis, type of initial treatment, and follow-up data are provided in Table 2. The study group included 97 males (71.9%) and 38 females (28.1%), with a median age at diagnosis of 61 years (age range, 8-89 years). Using the TNM system, 80 patients initially had a solitary skin lesion (T1), 37 had regional skin lesions (T2), and only 18 had generalized skin lesions (T3). Representative examples are shown in Figure 1.

The distribution of the different T categories, the subgroups within these main T categories, and the corresponding 5-year DSS and overall survival rates are given in Table 3. Solitary or regional skin lesions at presentation (T1 and T2 disease) were localized on the head and neck in 42 patients (31.1%), on the trunk in 32 (23.7%), on a single arm in 22 (16.3%), and on a single...
Eighteen patients had generalized skin lesions (T3 disease).

Initial therapy consisted of radiotherapy or excision in most patients (Table 2). Only 8 of 135 patients had been treated with multiagent systemic chemotherapy initially. Twenty-three of 24 patients with spontaneous remission had not received any treatment other than topical corticosteroids in 6 of them because of complete spontaneous remission of the skin lesions. During follow-up, none of these 24 patients, including 4 initially presenting with multifocal skin lesions, showed the waxing and waning of skin lesions typical of lymphomatoid papulosis, thus confirming a diagnosis of C-ALCL.

During follow-up, 53 of 135 patients (39.3%) developed 1 or multiple cutaneous relapses and 20 of 135 (14.8%) developed extracutaneous disease, including 10 patients with involvement of only peripheral lymph nodes draining an area of current or previous skin involvement and 10 with more extensive nodal or visceral disease. The median duration to development of extracutaneous disease was 18 months (range, 2-125 months). Development of extracutaneous disease in these 20 patients was not associated with progression to a higher T category. After median follow-up of 56 months (range,
11-288 months), 95 patients were alive without disease, 9 were alive with disease, 12 patients died of lymphoma, and 19 died of unrelated causes. Ten-year DSS was 89% and 10-year overall survival was 71%.

**PROGNOSTIC VARIABLES**

Univariate analysis showed that sex, age (≤60 vs >60 years), extent of disease (T category), site of presentation, and complete spontaneous remission of initial skin lesions were not significantly related to survival. Multivariate analysis was, therefore, not performed. Regarding extent of disease, 5-year DSS for patients with T1 disease was 93%, with T2 disease was 93%, and with T3 disease was 77%, indicating that patients with T3 disease have a reduced, although statistically nonsignificant, survival rate compared with patients with T1 or T2 disease (P = .19) (Table 3 and Figure 2). Analysis of survival in different subgroups of T categories showed significantly reduced 5-year DSS for patients with T1b vs T1a disease (60% vs 96%, P < .001), but the number of patients (n = 5) with T1b disease does not allow firm conclusions to be drawn. Subgroups of T2 or T3 disease showed no statistically significant differences in survival.

Analysis of site showed a trend toward reduced 5-year DSS in patients with skin lesions on a leg (82% for leg vs 95% for head and neck, 96% for trunk, and 95% for arm; P = .23) (Table 4). Thus, in contrast to previous studies, skin lesions on the head or neck were not associated with a less favorable prognosis.

Further analysis showed that in patients with multifocal skin lesions (category T3), those with involvement of one (n = 4) or both (n = 7) legs had 5-year DSS of 67% compared with 100% in patients without leg involvement (P = .20) (Table 4). Moreover, in the total study group, 5-year DSS of patients with leg involvement (n = 103) and patients without leg involvement were 76% and 96%, respectively (P = .007; after adjustment for T category, P = .03) (Figure 3 and Table 5).

In the present study, the clinical usefulness of the new TNM classification system for primary cutaneous lymphomas other than MF and SS was tested on a group of 135 patients with C-ALCL. Although primarily meant to document the extent of disease in a consistent manner, we also evaluated the prognostic value of this classification system for this group with C-ALCL. The results of this study show that this new TNM system can be applied well to this group of cutaneous T-cell lymphoma. Five-year DSS in patients with T1 disease was 93%, with T2 disease was 93%, and with T3 disease was 77%, suggesting that patients with generalized skin lesions have a less favorable prognosis than do patients with solitary or localized skin lesions. Previous studies have also suggested a correlation with reduced survival in patients with multifocal skin lesions. In the group of 18 patients with generalized skin lesions (T3 disease), 3 of 11 with involvement of the legs died of lymphoma (all were patients with involvement of both legs) compared with none of the 7 without leg involvement (5-year DSS: 67% vs 100%). Also, in the patients with regional skin lesions (T2 disease), leg involvement was associated with reduced 5-year DSS (76% vs 100%). In the

**Table 4. Different Sites of Skin Involvement in 135 Patients With C-ALCL**

<table>
<thead>
<tr>
<th>Site of Skin Involvement</th>
<th>Patients, No. (%)</th>
<th>Disease Specific</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>42 (31.1)</td>
<td>95</td>
<td>87</td>
</tr>
<tr>
<td>Trunk</td>
<td>32 (23.7)</td>
<td>96</td>
<td>85</td>
</tr>
<tr>
<td>Arm</td>
<td>22 (16.3)</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>Leg</td>
<td>21 (15.6)</td>
<td>82</td>
<td>62</td>
</tr>
<tr>
<td>Generalized skin</td>
<td>18 (13.3)</td>
<td>77</td>
<td>63</td>
</tr>
<tr>
<td>Legs involved</td>
<td>11 (8.1)</td>
<td>87</td>
<td>67</td>
</tr>
<tr>
<td>Legs not involved</td>
<td>7 (5.2)</td>
<td>100</td>
<td>86</td>
</tr>
</tbody>
</table>

 Abbreviation: C-ALCL, cutaneous anaplastic large cell lymphoma.
total group of 135 patients, those with leg involvement had significantly worse survival than did those without leg involvement. These observations are in agreement with those of a previous study, which suggested that patients with extensive limb involvement are at risk for a poor prognosis. The fact that in univariate analysis the site of presentation was not statistically significantly related to survival can be explained by small sample sizes (Table 4). The same holds true when analyzing the association with survival for leg involvement in the 3 T categories separately (Table 5).

Apart from localization on the leg, presentation on the head and neck has also been associated with a less favorable prognosis. In the retrospective cohort analysis of 157 patients with solitary or localized C-ALCL retrieved from the Surveillance, Epidemiology, and End Results (SEER) database, patients with skin lesions on the head and neck showed a significantly increased risk of death. In contrast, in the present study, patients with skin lesions on the head and neck had 5-year DSS of 95%. Only 1 of 42 patients (2.4%) with a solitary skin lesion on the head and neck region died of lymphoma (56 months after diagnosis). These different results are difficult to explain. However, because diagnoses in the SEER database are not verified independently, it cannot be excluded that the SEER cohort contains several patients with folliculotropic MF. Such patients preferentially present at the head and neck region, commonly contain many CD30-positive blast cells, and have a worse prognosis than do patients with C-ALCL.

In conclusion, these results show that the new TNM system can be applied well to patients with C-ALCL and may provide prognostic information, in particular when combined with site of presentation. Patients with T2 or T3 disease with skin lesions on the leg were found to have a worse prognosis compared with patients without leg involvement. However, we do not believe that there is enough reason to adapt the current guidelines for the initial treatment of C-ALCL in these patients. These guidelines indicate that patients with solitary or localized skin lesions can best be treated with excision or radiotherapy, whereas in patients with multifocal skin lesions, low-dose oral methotrexate or, in the case of few scattered skin lesions, radiotherapy is preferred. However, patients with regional or generalized skin lesions that involve the leg should be controlled very closely and may require systemic chemotherapy in an earlier phase of disease progression.

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Author Contributions: Dr Benner had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Benner and Willemze. Acquisition of data: Benner and Willemze. Analysis and interpretation of data: Benner and Willemze. Drafting of the manuscript: Benner and Willemze. Critical revision of the manuscript for important intellectual content: Willemze. Statistical analysis: Benner. Study supervision: Willemze.

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Table 5. Five-Year DSS in 135 Patients With and Without Leg Involvement in the Different T Categories

<table>
<thead>
<tr>
<th>T Category</th>
<th>Patients, No. (%)</th>
<th>Legs Not Involved (n=103)</th>
<th>Legs Involved (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D+, No. (%)</td>
<td>5-y DSS, %</td>
<td>D+, No. (%)</td>
</tr>
<tr>
<td>T1</td>
<td>80 (59.3)</td>
<td>4/70 (6)</td>
<td>1/10 (10)</td>
</tr>
<tr>
<td>T2</td>
<td>37 (27.4)</td>
<td>2/26 (8)</td>
<td>2/11 (18)</td>
</tr>
<tr>
<td>T3</td>
<td>18 (13.3)</td>
<td>0/7</td>
<td>3/11 (27)</td>
</tr>
<tr>
<td>Total</td>
<td>135 (100)</td>
<td>6/103 (6)</td>
<td>6/32 (19)</td>
</tr>
</tbody>
</table>

Abbreviations: DSS, disease-specific survival; D+, patients who died of lymphoma/patients in each T category.

A Adjusted for T category.

REFERENCES


Notable Notes

SunSmart Sprint 5K Run/Walk for Melanoma Awareness: A Student Initiative

The 5K Run/Walk for Melanoma Awareness was initiated in 2008 by 2 medical students to raise funds and awareness for skin cancer (Figure). This early-morning run, which takes place in association with free skin screenings, is an educational event for adults and children of all ages. The funds that are raised support patient care and research efforts by the Department of Dermatology and Cutaneous Surgery at the University of Miami Miller School of Medicine, Miami, Florida. The Student-led community event is the first of its kind not only at the University of Miami but also in the Miami-Dade community. It represents a novel, fund-raising, public health initiative. Every participant and community member who requests a skin screening receives one from a dermatologist that day and is referred for future care as necessary. Monetary and product donations are provided by major corporations and numerous local sponsors, and the donations also support educational booths and sunblock face painting.

This family-friendly event increases community awareness about this devastating disease, and it raises funds for research and prevention. Many physicians, residents, medical students, and community volunteers commit their time, participation, and dedication to this project each year. With the help of these volunteers, as well as the Miami Dermatological Society, the South Florida community, and our sponsors, we, as a team, are able to educate the public and to prevent future cases of skin cancers.

The inaugural run was a great success: 400 runners registered, 150 people were screened for skin lesions, and $14 000 was raised for melanoma research and care. Numerous suspicious lesions were detected, many of which would have been unnoticed had it not been for the free skin screenings. In fact, one runner expressed his gratitude in a letter to the dermatology department in which he stated that a squamous cell carcinoma had been found at the skin screening and most likely would otherwise have gone without treatment. Now in its third year, the SunSmart Sprint has become popular not only with running enthusiasts but also with the entire South Florida community as an annual event that is essential to continuing health maintenance.

Besides increasing awareness about melanoma, this targeted prevention effort has gained attention for the cancer community as a whole. It is our hope that this type of endeavor may expand to other universities and communities to promote promising research efforts that will enhance the quality and availability of dermatologic health care to all.

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