Prognosis in cutaneous T-cell lymphoma by skin stage: Long-term survival in 489 patients

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Background: Although a number of studies have documented the long-term survival of patients with cutaneous T-cell lymphoma (CTCL), none have provided data as to the relative survival of all 4 skin stages.
Objective: We document survival of CTCL patients by T stage relative to that of an age-, sex-, and race-matched population.
Methods: The survival of 489 patients with CTCL registered since 1957 was compared with that of a California control population.
Results: For stage T1 (< 10% skin involved) there was no significant difference between the observed and expected survivals. For the other 3 stages the observed survival was significantly inferior to that of the expected survival (P = .002). At 10 years the relative survivals were: T2 (10% or more skin involved) 67.4%, T3 (tumor stage) 39.2%, T4 (generalized erythroderma) 41.0%. T2 plaque stage patients had an inferior relative survival (P = .001), whereas T2 patch stage patients did not. Lymphadenopathy had an unfavorable impact on prognosis. There was a strong trend toward diagnosing CTCL at an earlier stage in more recent years. We estimate that from 15% to 20% of our patients died of CTCL or related complications.
Conclusion: The relative survival of CTCL patients worsens with increasing skin stage, although stages T3 and T4 had closely similar survivals. The great majority of patients with CTCL do not die of their disease.
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Primary "classic" cutaneous T-cell lymphoma (CTCL) (mycosis fungoides (MF)/Sézary syndrome) is an epidermotropic lymphoma whose initial clinical manifestations are in the skin.[1] Other primary CTCLs that are predominantly nonepidermotropic, such as $CD30^+$ or $CD30^-$ large T-cell lymphoma, pleomorphic CTCL, subcutaneous T-cell lymphoma, and CTCLs caused by systemic T-cell lymphomas are not included in this study. Henceforth, in this report CTCL refers only to classic CTCL.

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The relationship between disease stage and survival in cancer patients is well recognized. A number of studies have analyzed the relationship between CTCL stage and survival. Four of these involved at least 100 patients followed up for 5 years or more and were analyzed according to extent and character of skin involvement as well as other parameters.[2-5] However, with the exception of the study of Kim et al,[4] which compared the observed versus the expected survival of patients with limited extent disease, none of the reports have compared survival of CTCL patients with that of a control population. In this study we report the survival of 489 patients with CTCL stratified according to skin stage and compared, according to stage, with an age-, sex-, and race-matched control population. Additional analyses were made of the possible influence of depth and type of skin infiltrate (patch vs plaque), lymph node, and blood status.

METHODS

Patients were registered at the cutaneous lymphoma clinic of the University of California, San Francisco, the

Table I. TNM classification of cutaneous T-cell lymphoma (CTCL)*

T: Skin
T1 Patches, papules, or plaques involving < 10% of skin
T2 Patches, papules, or plaques involving 10% or more of skin
T3 Tumors (one or more)
T4 Generalized erythroderma
N: Lymph nodes
N0 No clinically abnormal peripheral lymph nodes, pathology negative for CTCL (if biopsy obtained)
N1 Clinically abnormal peripheral lymph nodes, pathology negative for CTCL (if biopsy obtained)
N2 No clinically abnormal peripheral lymph nodes, pathology positive for CTCL
N3 Clinically abnormal peripheral lymph nodes, pathology positive for CTCL
B: Blood
B0 No evidence of increased numbers of atypical circulating cells
B1 Evidence of increased numbers of atypical circulating cells
M: Visceral organs
M0 No evidence of visceral involvement
M1 Visceral involvement confirmed by pathology

*Modified from Bunn and Lamberg.[7]

Table II. Demographics of 489 patients with CTCL

	No. (%)	T1	T2	T3	T4
Age (y)					
< 20	11 (2.2)	4	5	1	1
20-29	25 (5.1)	11	11	2	1
30-39	54 (11.0)	28	18	6	2
40-49	62 (12.7)	28	27	3	4
50-59	101 (20.7)	39	39	7	16
60-69	116 (23.7)	39	44	14	19
70-79	96 (19.6)	21	47	11	17
80+	24 (4.9)	4	8	3	9
Total	489 (100)	174	199	47	69
Female	190 (38.9)	70	81	15	24
Male	299 (61.1)	104	118	32	45
Race					
AP	20 (4.1)	5	11	0	4
Black	48 (9.8)	6	33	6	3
White	421 (86.1)	163	155	41	62

AP, Asian Pacific.

Veterans Administration Medical Center, San Francisco, or at the private office of one of us (H. Z.).

Histologic diagnoses were made in accord with published criteria.[6] Categorization as to patch or plaque stage disease was also made on the basis of histologic features.[6] Patients were classified according to the tumor-node-metastasis (TNM) system[7] (Table I). All patients received a minimum work-up of a complete skin examination, palpation for lymph nodes, complete blood cell count, chest x-ray, and blood chemistries for liver and kidney function. Estimation of the extent of skin involvement was usually made by at least 2 observers using the "rule of 9s"[8] and the fact that the palmar surface represents about 1% of the skin surface.[7] Computed tomographic scans were obtained in selected patients with palpable lymphadenopathy, erythroderma, or tumors. Lymph node biopsy specimens were obtained in those with a lymph node at least 2 cm in diameter or with multiple nodes at least 1 cm in diameter. Examination of the blood for evidence of Sézary cells was obtained in all patients with generalized erythroderma, and in selected patients with widespread plaque or tumor stage disease or significant adenopathy. Bone marrow biopsy specimens were obtained in selected patients with advanced disease.

In accord with Lamberg et al,[2] survival was calculated from the date of registration to death or last follow-up. Calculation from time of registration, rather than at time of histologic diagnosis, is necessary to ensure uniformity in criteria for staging. Approximately 85% of the patients were registered within 3 months of histologic diagnosis. Patients still living at the time of last follow-up were considered as censored observations. Deaths from all causes were used in the analysis. Survival probabilities were calculated according to the method of Kaplan and Meier. Differences in survival between different subgroups were evaluated by means of the log-rank test. Multivariate adjustment for potential confounders (eg, age) were made by means of the Cox proportional hazard model.

Expected survival of patients was calculated using the 1990 published life tables for California.[9] (Earlier life tables were not available.) For each year *n* from time of registration, the probability of surviving 1 additional year was calculated for each patient still at risk, and the expected survival at year *n* was obtained by multiplying the expected survival at year *n-1* by the average survival probability of those at risk.

RESULTS

The cohort included 489 patients with CTCL registered since 1957 (Table II). The cut-off date for entry in the study was Dec 31, 1994. The cut-off date for follow-up observation was Dec 31, 1995. Only 10 patients were registered before 1971, the year that one of us (H. Z.) began to see patients with CTCL. The age range at registration was 5^{10} to 93 years (mean, 56.5; median, 59.0

Table III. Observed and expected survival according to T stage

Stage	Year	Sig	Observed survival (%) CI	Expected survival (%)	Relative survival* (%)
T1	5	NS	94.8 (90.9-98.6)	92.2	102.7
	10	NS	83.1 (75.1-91.1)	83.1	100.1
	15	NS	79.5 (70.3-88.6)	74.0	107.4
T2	5	$P < .001$	75.7 (68.8-82.6)	90.4	83.8
	10	$P = .002$	55.2 (46.0-64.3)	81.8	67.4
	15	$P < .001$	47.1 (36.9-57.3)	75.4	62.5
T3	5	$P < .001$	45.0 (30.0-60.0)	87.4	51.5
	10	$P < .001$	28.9 (14.1-43.8)	73.8	39.8
	15	$P < .001$	21.7 (7.6-35.8)	53.6	40.5
T4	5	$P < .001$	50.6 (38.0-63.3)	88.4	57.3
	10	$P < .001$	29.7 (16.2-43.2)	72.4	41.0
	15	n/a	n/a	n/a	n/a

CI, 95% confidence interval; *n/a*, not applicable (there were no 15-year survivors); *NS*, not significant; *Sig*, significance.
*Relative survival is calculated by dividing observed by expected survival.

years). Of the registrants, 2.2% were under age 20, 7.4% were under age 30, and 68.9% were age 50 or older. There were 299 (61.1%) men and 190 (38.9%) women (ratio 1.57). White patients (including Hispanics) numbered 421 (86.1%), blacks 48 (9.8%), and Asian-Pacific 20 (4.1%). Of the Asian-Pacific population, 11 were Chinese, 5 Filipino, 3 East Indian, and 1 undetermined.

A total of 174 patients were classified as stage T1, 199 as T2, 47 as T3, and 69 as T4. Patients tended to be older in the more advanced than the earlier stages. Thus, according to stage, the mean ages were: T1 52.3, T2 56.9, T3 59.4, and T4 64.2. Noteworthy is the higher proportion (37.5%) of stage T4 in patients 80+. There was no significant gender difference as to the proportion in the various stages, or as to the date of registration. Blacks comprised 9.8% of the total cohort, which is slightly larger than the 7.4% of blacks in California[9] ($P = .04$; ratio 1.32). Black patients had a relatively more advanced stage than did whites. Thus, 87.5% of black patients were in either stages T2, T3, or T4 as compared with 61.3% of whites in those stages. The median follow-up for the entire cohort of 489 patients was 4.7 years.

In Table III we present data as to the observed and expected survival at 5, 10, and 15 years according to stage, adjusted for age, sex, and race, and state the corresponding relative survival (observed as a proportion of the expected). Plots of the observed and expected survival for each stage are shown in Fig 1.

The relative survival of T1 patients was comparable to the general population; in fact, their prognosis was somewhat better at 5 and 15 years. This may reflect a higher socioeconomic status of our patients as compared with the general population. The relative survival of the other 3 stages was significantly ($P < .001$) inferior to that of the general population. For T2 the relative survival at 10 years was 67.4%. The relative survivals at 10 years for T3 and T4 were lower and were not greatly different from each other—T3: 39.2% and T4: 41.0%.

Because we used 1990 life tables the expected survivals may be slightly higher than would have been obtained using earlier life tables. Two percent of the patients were registered before 1970, 19.2% before 1980, and 61.1% before 1990.

Data were analyzed as to the possible influence of patch versus plaque stage on survival (Table IV). An analysis of the data for stage T1 is not relevant because the survival of those patients is comparable with that of the general population. The relative survival of patch stage T2 patients is little different from that of the general population. However, the relative survival for plaque stage T2 patients was significantly lower than that for an age-, sex-, and race-matched population ($P = .002$).

Data were also analyzed as to the possible influence of nodal status on survival. This included all degrees of nodal abnormality (N1 to N3). After adjusting for stage and demographics, nodal abnormality had a marginally significant effect on survival ($P = .03$). The estimated hazard ratio (relative risk of dying) was 1.48 in patients with nodal

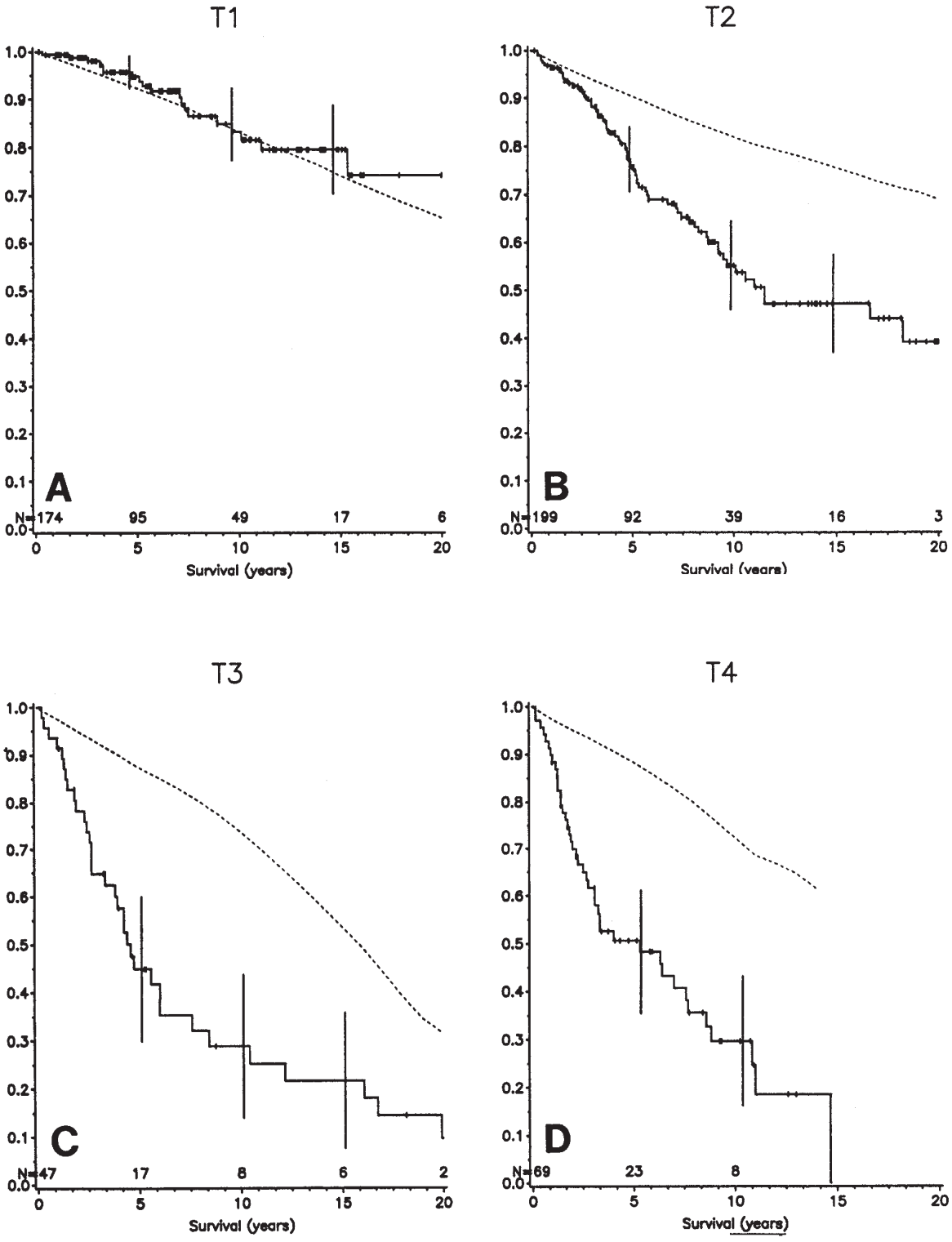

Fig 1. Kaplan-Meier estimates of survival. Dashed lines track expected survival for a group of individuals with age, sex, and race characteristics similar to those of our study population. Vertical lines are 95% confidence intervals for observed survival. Numbers above time axis are number of patients at risk. Tics indicate patients who are still alive. **A,** T1. There is no significant difference between observed and expected survival. **B,** T2. $P = .002$ that observed survival differs from expected. **C,** T3. $P < .001$ that observed survival differs from expected. **D,** T4. $P < .001$ that observed survival differs from expected.

Table IV. Stage T2 observed and expected survival of patch and plaque stage*

	Year	Sig	Observed survival (%) CI	Expected survival (%)	Relative survival (%)
PA	5	NS	82.9 (73.4-92.5)	90.6	91.5
	10	NS	71.9 (57.1-86.7)	81.4	88.3
	15	NS	71.9 (57.1-86.7)	75.2	95.6
PL	5	$P = .001$	72.7 (62.6-82.7)	89.3	81.3
	10	$P < .001$	48.9 (36.9-61.0)	80.5	60.8
	15	$P < .001$	38.1 (25.4-50.7)	73.5	51.8

PA, Patch stage; *PL*, plaque stage.
*See footnotes for Table III.

Table V. CTCL stage relative to time of registration

Stage	1957-1979 No. of patients (%)	1990-1994 No. of patients (%)
All	94 (100)	190 (100)
T1	22 (23.4)	79 (41.6)
T2	45 (47.9)	72 (37.9)
T3	16 (17.0)	13 (6.8)
T4	11 (11.7)	26 (13.7)

abnormality relative to patients without nodal abnormality (N0). However, when data were analyzed separately by stage, there was a trend for nodal status to be more important in the earlier stages; the hazard ratio was estimated at 3.0 in T1, 1.9 in T2, 1.3 in T3, and 0.93 in T4. However, this trend was not statistically significant ($P = .18$), and our data do not provide sufficient statistical power to detect such a trend. We estimate that more than 1700 subjects would be required to provide 80% power to detect a trend of this magnitude.

The blood was examined for evidence of Sézary cells in 62 patients, and was positive in 50 patients and negative in 12. These numbers were too small to permit a statement as to possible effect of blood involvement on survival. Similarly, the number of patients with bone marrow or other visceral biopsies was too small to permit analysis of visceral involvement as an independent factor.

A definite trend for diagnosing CTCL at an earlier stage in more recent years is evident (Table V). Particularly striking, when comparing the period of 1957 to 1979 with the period of 1990 to 1994, is the marked increase in the percentage of patients in T1 from 23.4% to 41.6%, and the decrease in T3 patients from 17.0% to 6.8%.

Equally striking were the differences between those periods as to patients with patch versus plaque stage. Thus, in the period of 1957 to 1979, of 67 patients (combined T1 and T2) 9 (13.4%) were patch stage, 47 (70.1%) were plaque stage, and 11 (16.4%) were not classified as either. In 1990 to 1994, of 151 T1 and T2 patients 122 (80.8%) were patch stage, 24 (15.9%) were plaque stage, and 5 (3.3%) were not categorized as either.

We made an analysis for improvement in prognosis for time trend. The only significant difference was in patch stage T2 where later registrants seem to be doing better. There was a nonsignificant trend for improved prognosis for plaque stage in more recent years.

Although in our estimate of survival all causes of death are included, we also estimate the probable cause of death based on available information (Table VI).

The highest proportion of deaths for which the cause was not known was in stage T1 (73.7%). This is understandable because patients who do well are more likely to be lost to follow-up as compared with those with advanced disease. We estimated the number of deaths caused by CTCL according to the method of Weinstock and Reynes.[11] According to that method the number of deaths attributable to CTCL can be calculated by subtracting the number of expected deaths from the observed deaths. The excess represents the deaths attributal to the disease. The expected deaths were determined from the life table for California.[9]

For stage T1 19 deaths were observed, whereas for the age-, sex-, and race-matched control population 24 deaths were expected. Thus, conversely, there were 5 fewer deaths than expected, but the

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