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Age, Race, Gender, Stage and the Incidence of Cutaneous Lymphoma

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Abstract

Background—The incidence of the T and B-cell cutaneous lymphomas (CL) has been well documented, but information pertaining to racial incidence by age, and by burden of disease (stage) have not been extensively documented.

Methods—The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) 2004–2008 public use database was investigated. The relative incidence of CL in different races and age groups was examined. Univariate and multivariate stepwise logistic regression was performed for the likelihood of presenting at a higher stage.

Results—4496 patients were diagnosed with CL between 2004–2008; 1713 patients with mycosis fungoides (MF), 1518 with non-MF cutaneous T-cell lymphoma (NMFCTCL), and 1265 patients with cutaneous B-cell lymphoma (CBCL). For MF, there was a trend for females to be less likely to present with a higher T-stage (T3–T4) than males OR 0.73 on multivariate analysis ($p=0.06$). For race, African Americans (AA) had a significantly increased risk of presenting with higher T-stage (T3–T4) MF, OR 1.72 on multivariate ($p=0.02$), compared to whites. For whites, AA, Asian/Pacific Islanders and Native Americans/other/unknown, the mean age at diagnosis was 59.2, 51.5, 51.3, and 53.8. These groups presented at a significantly different age than whites ($p=0.0001$, 0.0001, and 0.0006).

Conclusions—Non-white racial groups present with MF at an earlier age compared to whites, and AA have increased risk of presenting with higher T-stage compared to whites. These findings have significant implications regarding need for earlier diagnosis and understanding the reasons for racial disparity in age and stage of presentation.

Keywords

CTCL; CBCL; Race; Gender; Age; Stage; Incidence

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Background

The cutaneous lymphomas constitute a variety of clinically distinct disorders of both T and B-cell origin but with differing pathogenesis and varying clinical course.¹ Previous studies have documented incidence rates for the cutaneous T and B-cell lymphomas and much work has been focused on mycosis fungoides (MF) which is the most common cutaneous T-cell lymphoma.^{2,3} Information regarding incidence by age, race, gender and stage for the cutaneous lymphomas, including mycosis fungoides, non-mycosis fungoides cutaneous T-cell lymphomas (CTCL), and the B-cell lymphomas have been reported. Criscione and Weinstock reported CTCL incidence based on data from the Surveillance, Epidemiology and End Results (SEER) program registries spanning 1973–2002.³ The age adjusted incidence of CTCL was 6.4 per 1,000,000 persons and this incidence rate was highest between the ages of 70–79 years of age. The incidence rate of CBCL has been reported as approximately 3 per 1,000,000 persons.^{2,4} The various CTCLs and CBCLs may present with differing natural history and response to therapy.

Data regarding the relationship between race and incidence as well as clinical outcomes have been published, but data pertaining to racial incidence by age and by burden of disease (stage) have not been extensively documented. Retrospective data have demonstrated that African Americans may have an increased incidence of CTCL (specifically MF) compared to whites which may be more pronounced in younger age groups.^{2,3,5,6} Sun et al. reported that females less than 40 years of age presented with MF more often than males and this was consistent with findings reported by Criscione and Weinstock regarding the relationship between earlier age of onset for African Americans compared to other races.^{3,5} Age at presentation was younger in African American females compared to whites and progression was also more frequent in this population. Findings also suggested that African American females may present with disproportionately higher stages of disease than whites. Increased incidence of cutaneous lymphoma for African Americans at a younger age, in addition to higher stage disease at presentation, may have substantial implications for the potential benefits of earlier diagnosis and intensified therapeutic management strategies in this population. The current investigation evaluated the SEER data from 2004–2008 for incidence of cutaneous lymphoma (T and B cell) and the impact of gender, race, age and stage. The current study endeavored to substantiate findings relating to younger age at diagnosis and possible higher stage at presentation for African Americans through the evaluation of data from a large, modern, United States population based registry.

Methods

The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) 2004–2008 public use database was investigated, and patients with cutaneous lymphoma were selected. The time span of 2004–2008 was selected given that this time period reflects more formalized AJCC staging (6th edition) for the cutaneous lymphomas. Cases in the SEER database have histology and involved anatomic site recorded by the morphology and topography codes of the International Classification of Disease for Oncology-Third Edition (ICD-O-3). Skin site of disease (c44.0–c44.9) and other sites involved with cutaneous lymphoma, including vulva, penis, scrotum (c51.0–c51.2, c60.0–c60.2, c60.8–c60.9, c63.2) were examined. Histologies analyzed included mycosis fungoides (9700), anaplastic large cell lymphoma (9714), primary cutaneous CD30+ T-cell lymphoproliferative disorder (9718), cutaneous T-cell lymphoma not otherwise specified (9709), B-cell lymphomas (9670–9699), and other T-cell lymphomas (9700–9729). Gender, age, race, skin site and extent of disease, in addition to year of diagnosis and stage, were evaluated. Histologic type was grouped with respect to mycosis fungoides, non-MF cutaneous T-cell lymphomas, and B-cell lymphomas.

Incidence

The relative incidence of cutaneous lymphoma in different races and age groups was examined using the SEER*Stat Program (National Cancer Institute, Bethesda, MD), adjusting for the US Year 2000 Standard Population. Relative incidence trends over time were examined. All variables were examined individually using the Pearson double-sided chi square test for significance. Univariate logistic regression and multivariate stepwise logistic regression was performed for the likelihood of presenting at a higher stage. A logistic regression analysis of the factors associated with a higher T stage (T3–T4 vs. T0–T2) at presentation for patients with mycosis fungoides was performed. As age was not normally distributed, differences in mean age at diagnosis were evaluated using a two sample Wilcoxon rank-sum test. Overall incidence rates are reported per 1 million persons. Race based incidence by stage was not reliably evaluated for the B-cell lymphoma group given concern over accurate staging/reporting for this group within the SEER data set.

Results

Incidence

We identified a total of 4496 patients diagnosed with cutaneous lymphoma between 2004–2008. There were 1713 patients with MF, 1518 with non-MF CTCL, and 1265 patients with cutaneous B-cell lymphoma (Table 1). For mycosis fungoides, non-MF cutaneous T-cell lymphomas, and the cutaneous B-cell lymphomas, the incidence rates were 4.5, 4.0, and 3.3 respectively (per 1 million persons). For MF by race, the incidence was 4.0 for whites, 6.1 for African Americans, 3.0 for Asian/Pacific Islanders, and 0.9 for Native Americans/other/unknown. The incidence rates for the non-white groups were all significantly different than for whites. For non-MF cutaneous T-cell lymphomas, the incidence rates were 4.0 for whites, 4.3 for African Americans, 2.0 for Asian/Pacific Islanders, and 1.9 for Native Americans/other/unknown. For the B-cell lymphomas, the incidence rates were 3.6 for whites, 1.8 for African Americans, 1.9 for Asian/Pacific Islanders and 0.8 for Native Americans/other/unknown and the non-white incidence rates were significantly different compared with the white population as a baseline.

Incidence and Gender

Incidence rates for mycosis fungoides by gender revealed a rate of 5.6 per million persons for males and 3.6 for females. For the non-MF CTCL patients, the rates were 5.2 for males and 3.1 for females. The incidence rates for the B-cell lymphomas were 4.3 for males and 2.5 for females (Table 2).

Incidence of Advanced T Stage by Race for Mycosis Fungoides

With regard to T-stage, incidence was only evaluated for the histology of mycosis fungoides given that the TNM staging system is particular for MF. For non-MF cutaneous lymphomas, incidence per overall stage (i.e higher stage-III–IV versus lower I–II) was evaluated. For patients with MF, non-white populations had significantly different incidence rates for T0–T2 levels of disease compared to whites as a reference group. The incidence of T0–T2 disease for whites was 3.0 per million compared with 4.0 for African Americans ($p=0.0015$), 2.4 for Asian/Pacific Islanders ($p=0.048$), and 0.4 for Native Americans/other/unknown ($p=0.0023$). For those presenting with MF and T3/ T4 disease, the incidence was 0.5 for whites, 0.9 for African Americans, 0.3 for Asian/Pacific Islanders and 0.6 for Native Americans/other/unknown. For those groups, only African Americans had a significant increase compared to whites in incidence by higher T-stage ($p=0.0039$),

Incidence of Advanced Stage by Race for Non-MF CTCL and CBCL patients

With regard to non-MF cutaneous T-cell lymphomas, the incidence rate for stage I–II was 2.8 per million for whites, 2.3 for African Americans, 1.0 for Asian/Pacific Islanders and 0.9 for Native Americans/other/unknown. The incidence rates for Native Americans/other/unknown and Asian/Pacific Islanders were significantly different than the white reference group but not for African Americans. With regard to incidence for stage III–IV disease for non-MF cutaneous T-cell lymphomas, whites had an incidence of 0.6 per million, blacks 1.2, Asian/Pacific Islanders 0.7, and Native Americans/other/unknown 0.4. Within this group, only the incidence rate for African Americans was significantly different ($p=0.0006$) compared to the white reference group.

Disease Severity at Diagnosis-Multivariate Analysis

With regard to gender, there was a trend for females to be less likely to present with a higher T-stage (T3–T4) than males with an odds ratio of 0.74 on univariate, and 0.73 on multivariate analysis ($p=0.06$), adjusted for registry, age, race and marital status. With respect to race, African Americans had a significantly increased risk of presenting with higher T-stage (T3–T4) disease than other groups with an odds ratio of 1.34 on univariate and 1.72 on multivariate ($p=0.02$) compared with the white reference group. The odds ratios for Asian/Pacific Islanders and Native Americans/other/unknown were 0.64 and 0.60 and not significantly different than the white reference group. Those with unknown marital status had a decreased risk of presenting with higher stage disease. For the non-MF cutaneous T-cell lymphoma group, females had a lower risk of presenting with higher stage (overall stage III–IV vs. stage I–II) disease than males with an odds ratio of 0.83 univariate and 0.73 in multivariate ($p=0.04$) analysis. Regarding race and likelihood of presentation of higher stage (III–IV) for the non-MF cutaneous T-cell patients, African Americans and Asian/Pacific Islanders had increased odds ratios at 2.48 and 2.21 respectively on multivariate analysis ($p=0.01$) (Table 3, 4).

Age at Diagnosis

For patients with MF, the mean age at diagnosis was higher for males vs. females (58.6 years for males vs. 55.4 for females ($p=0.0005$)). For whites, African Americans, Asian/Pacific Islanders and Native Americans/other/unknown, the mean age at diagnosis was 59.2, 51.5, 51.3, and 53.8. African Americans, Asian/Pacific Islanders, and Native Americans/other/unknown patients presented at a significantly different age than the white group. For African Americans, Asian/Pacific Islanders, Native American/other/unknown, the p values in reference to differences in age at diagnosis compared to whites are 0.0001, 0.0001, and 0.0006. The differences between Asian/Pacific Islanders and African Americans, and native American/other/unknown and African Americans, were not significantly different.

For patients with non-MF T-cell lymphoma, the mean age at diagnosis was 60.2 for males and 60 for females ($p=.82$). The mean age at diagnosis was 61.2 for whites, 54.5 for African Americans, 57.1 for Asian/Pacific Islanders, and 56.2 for Native American/other/unknown. The difference between whites and African Americans was significant ($p=0.0001$) as was the difference between whites and Native Americans/other/unknown ($p=0.01$). There were no significant differences between Asian/Pacific Islanders and African Americans, Asians and whites, and African Americans compared to Native Americans/other/unknown.

For those with cutaneous B-cell lymphoma, the mean age at diagnosis for males was 61.3 and for females was 65.6 ($p=0.0001$). The mean age at diagnosis for whites, African Americans, Asian/Pacific Islanders and Native Americans/other/unknown were 63.7, 56.7, 60.4, and 61.5. The difference between whites and African Americans was significant ($p=0.0006$). Differences between Asian/Pacific Islanders and African Americans, Asians

and whites, whites and Native Americans/other/unknown, and African Americans compared to native American/other/unknown are not significantly different (Table 5).

Discussion

The cutaneous lymphomas have been somewhat difficult to study given the rarity of the disorders compared to most other malignancies. Through publication of several relatively large single institution studies, multicenter consortium projects, and through population-based registry analysis, various details regarding the diseases have been elucidated. The incidence rates in our study reveal findings that are consistent with previous publications.^{2,3,4,5,7} The finding that African Americans present with MF at an earlier age than whites has been reported based on single institution experience⁵, and was demonstrated in an analysis of the SEER data spanning a period from 1973–2002.³ This has also now been confirmed through the use of the current SEER dataset which is from a more recent time period (2004–2008). In the current study we report that African Americans were found to be diagnosed with non-MF cutaneous T-cell lymphoma and cutaneous B-cell lymphoma at an earlier age than whites. In the SEER study evaluating the period from 1973–2002, all cutaneous T-cell lymphomas were included but not cutaneous B-cell lymphomas.³ Our data reveal a greater risk of presenting at a higher T-stage for African Americans with MF, and for African Americans with non-MF CTCL compared to white patients. This is a novel and concerning finding. Data from the SEER study spanning 1973–2002 revealed that for patients with CTCL, and during the time period 1992–2002, incidence was correlated with high physician density, high density of medical specialists, high median family income, high percentage of adults with a bachelor's degree or higher, and high median value of housing.³ These variables were examined for the white population only. Given the potential for relatively poor clinical outcomes relating to higher disease stage, presentation with higher stage disease in African Americans compared with whites is obviously of concern. Further investigation may lead to correlation with factors such as population density, physician density, income, or other factors. It is also possible that correlations may not exist with following examination of such variables, but rather there may be a fundamental biological difference in pathogenesis among various racial groups. Regardless of potential correlations, it is important for clinicians to be aware of these differences and have increased awareness of these findings so that CTCL and CBCL can be identified as early as possible and appropriate therapeutic interventions rapidly initiated.

Incidence rates have been increasing over the years and it is challenging to discern whether these increases are related to a 'real' increase in incidence versus enhanced vigilance on behalf of clinicians leading to more accurate diagnosis and/or more accurate diagnosis with the assistance of enhanced diagnostic methods. Regardless of the reason for an apparent increase, younger age at presentation and higher stage disease at presentation in the African American population of patients with cutaneous lymphoma should serve as an alert to clinicians to consider the diagnostic possibility of cutaneous T/B-cell lymphoma sooner. Further study is clearly warranted to evaluate the clinical outcomes associated with these concerning findings given the higher stage at presentation and younger age for African Americans with MF, non-MF CTCL. Those concerns are also very relevant for Asian Pacific Islanders with respect to higher stage disease at presentation for non-MF subtype. Younger age (MF) at presentation appears to be a factor for all non-white groups.

One of the great challenges in evaluating next research steps for such patients is that there are relatively few prospective clinical trials given the rare nature of the cutaneous lymphomas. Complicating matters further is the fact that there are a variety of treatment modalities that are considered in the management of a patient with mycosis fungoides. Additionally, although there is some consensus regarding the efficacy of various treatment

modalities, different institutions have biases with respect to sequencing and combining of such therapies. Total skin electron beam radiotherapy (TSEBT), for example, is extremely effective in providing cutaneous palliation with overall response rates of 95–100% and complete response rates in the range of 50%, even for patients with T3 disease and much higher complete response rates for those with T1–T2 disease.^{8,9,10} However, the administration of TSEBT is extremely complicated and labor intensive. Access to centers in North America that have the clinical expertise to provide this treatment on a regular and high quality basis is somewhat limited. This is one of the substantial challenges in mounting even moderately large prospective clinical trials to address therapeutic outcomes or comparative effectiveness between the various therapeutic options.

Limitations of the current study may have some impact on interpretation of the results. There are a variety of factors that are not reliably reported in the SEER public use data.¹¹ The use of systemic therapy is not documented, and details regarding the multitude of medical therapies available for patients with cutaneous lymphoma are not provided within the framework of the SEER registry. Although the use of radiotherapy is reported, details and intent of radiotherapy are not available and hence evaluation of this therapeutic modality is challenging and limited. Lack of therapeutic data reporting should not have an impact though on incidence and stage at presentation. Evaluation of the registry is of course retrospective, and the accuracy of data is based on the ability of clinicians and institutions to report case details properly. It is also assumed that cancer registrars are abstracting data from medical records accurately. Another potential limitation is the lack of information regarding HTLV-1 status. Given the potential for misclassification between MF and lymphoma involving the skin related to HTLV-1, without HTLV-1 information, it is impossible to prove that all cases were indeed actually MF. It is possible that a relatively small group of HTLV-1 infected patients could impact the findings but an analysis regarding country of origin was performed and revealed that only 5 African American patients had a country of origin that was the Caribbean or Africa. None of those 5 patients fell into the high stage disease category. The SEER registry represents over 26% of the US population and is considered by many to be a useful tool with respect to fundamental epidemiologic evaluation relating to incidence data such as that presented in this report.

This study of the SEER population-based registry inclusive of 2004–2008 has allowed evaluation of patients who were reported to SEER utilizing the updated AJCC, T-staging system for patients with MF-cutaneous T-cell lymphoma. Based on this information, previously described general incidence rates of cutaneous lymphoma by age, gender, and race were confirmed. Our finding of a greater risk of higher T-stage at presentation for African Americans with MF and for higher overall stage for Asian/Pacific Islanders for non-MF CTCL is novel. This finding in conjunction with confirmation of earlier age at diagnosis for African Americans with mycosis fungoides, non-MF cutaneous T-cell lymphoma and CBCL, should serve as a basis for further study into potential biological differences in the pathogenesis of disease by racial group and for evaluation of potential contributing factors such as access to healthcare, and other socio-economic factors. The subsequent impact of the findings is substantial as they suggest at minimum, a need for the development of enhanced vigilance on behalf of clinicians.

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Clinical Practice Points

- Cutaneous T and B cell lymphomas are rare clinical entities.
- The general epidemiologic characteristics for cutaneous T and B cells have been well documented but data regarding age at presentation and stage have not been studied extensively for specific racial groups.
- Mycosis fungoides is the most common of the T cell cutaneous lymphomas.
- The prognosis for patients with mycosis fungoides is variable, depending on the extent of disease at presentation.
- African Americans (AA) had a significantly increased risk of presenting with higher T-stage (T3–T4) compared to whites. For whites, African Americans, Asian/Pacific Islanders and Native Americans/other/unknown, the mean age at diagnosis was 59.2, 51.5, 51.3, and 53.8. These differences were significant.
- These findings have significant implications regarding need for earlier diagnosis and understanding the reasons for racial disparity in age and stage of presentation.

Table 1

Patient Characteristics

	MF N=1713	Non-MF CTCL N=1518	CBCL N=1265
Male	975	891	734
Female	738	627	531
Race			
White	1240	1218	1096
African American	228	152	64
Asian/Pacific Islander	108	67	65
Native American/other/unknown	137	81	40
Marital status			
Not married	488	433	363
Married	806	776	720
Unknown	419	309	182
Age			
Mean	57	60	63
Median	58	62	64
Stage *			
Low stage	1240	1012	
High stage	211	258	
Unstaged	262	248	

MF-mycosis fungoides; CTCL-cutaneous T-cell lymphoma; CBCL-cutaneous B-cell lymphoma

* For MF, low stage = T0–T2, and high stage = T3–T4. For non-MF CTCL, low stage = overall stage 0–II, high stage = overall stage III–IV. CBCL patients were not broken out into high and low staging.

Table 2

Incidence Rates by low stage-high stage and gender

	All stages Rate*	Standard Error	Rate Ratio	Rate Ratio P value	Low stage Rate***	Standard Error	Rate Ratio	Rate Ratio P value	High stage Rate***	Standard Error	Rate Ratio	Rate Ratio P value
All MF Patients	4.5	0.1	1**		3.2	0.1	1**		0.5	0	1**	
Male	5.6#	0.2	1.2449	<0.001	3.9#	0.2	1.2079	0.0001	0.8#	0.1	1.4078	0.0031
Female	3.6#	0.1	0.8141	<0.001	2.7#	0.1	0.8395	0.0007	0.4#	0	0.6799	0.0038
All non-MF CTCL Patients	4	0.1	1**		2.7	0.1	1**		0.7	0	1**	
Male	5.2#	0.2	1.2973	<0.001	3.4#	0.1	1.289	<0.001	0.9#	0.1	1.3744	0.0024
Female	3.1#	0.1	0.7675	<0.001	2.1#	0.1	0.7747	<0.001	0.5#	0	0.691	0.0021
All CBCL Patients	3.3	0.1	1**									
Male	4.3#	0.2	1.2913	<0.001								
Female	2.5#	0.1	0.7599	<0.001								

MF-mycosis fungoides; CTCL-cutaneous T-cell lymphoma; CBCL-cutaneous B-cell lymphoma

* Rates are per 1,000,000 and age-adjusted to the 2000 US Std. Population standard

** Reference value

*** For MF, low stage = T0-T2, and high stage = T3-T4. For non-MF CTCL, low stage = overall stage 0-II, high stage = overall stage III-IV. CBCL patients were not broken out into high and low staging.

The rate ratio indicates that the rate is significantly different between male-female.

Table 3
 Logistic regression (univariate and multivariate) for odds of being high T-stage (T3–T4) for MF

	Univariate	P	95% CI Lower limit	95% CI Upper limit	Multivariate**	P	95% CI Lower limit	95% CI Upper limit
Sex	OR				OR			
Male	1*				1*			
Female	0.74	0.05	0.55	1.00	0.73	0.06	0.54	1.01
Race								
White	1*				1*			
African American	1.34	0.15	0.90	2.01	1.72	0.02	1.08	2.74
Asian/Pacific Islander	0.67	0.24	0.34	1.31	0.64	0.22	0.31	1.32
Native American/other/unknown	0.54	0.10	0.26	1.13	0.60	0.22	0.26	1.36
Marital status								
Not married	1*				1*			
Married	0.90	0.54	0.66	1.25	0.93	0.66	0.66	1.31
Unknown	0.39	<0.001	0.24	0.64	0.44	0.003	0.26	0.76
Age (continuous Variable)	1.010	0.02	1.002	1.019	1.012	0.01	1.003	1.021

MF-Mycosis fungoides;

* Reference value

** Model is adjusted for SEER registry. Variables with p < 0.1 included for entry for multivariate model.

Table 4
 Logistic regression (univariate and multivariate) for odds of being high overall stage for non-MF CTCL

	Univariate		P	95% CI Lower limit		95% CI Upper limit	Multivariate		P	95% CI Lower limit		95% CI Upper limit
	OR			OR								
Sex												
Male	1*						1*					
Female	0.83	0.20	0.63		1.10		0.73	0.04		0.54		0.99
Race												
White	1*						1*					
African American	2.55	<0.01	1.71		3.81		2.48	<0.01		1.58		3.90
Asian/Pacific Islander	2.96	<0.01	1.72		5.12		2.21	<0.01		1.20		4.05
Native American/other/unknown	0.73	0.48	0.31		1.76		0.88	0.78		0.35		2.18
Marital status												
Not married	1*						1*					
Married	0.62	<0.01	0.46		0.83		0.67	0.01		0.49		0.91
Unknown	0.31	<0.01	0.19		0.50		0.37	<0.001		0.22		0.62
Age (continuous Variable)	1.114	0.310	0.996		1.012							

* Reference value

** Model is adjusted for SEER registry. Variables with p < 0.1 included for entry for multivariate model.

Table 5

Comparison of age at diagnosis

	MF	Non-MF CTCL	CBCL
	Mean ages (P Value*)	Mean ages (P value*)	Mean ages (P Value*)
African American vs. White	51.5 vs. 59.2 (<0.0001)	54.5 vs. 61.2 (<0.0001)	56.7 vs. 63.7 (0.0006)
Asian/Pacific Islander vs. African American	51.3 vs. 51.5 (0.81)	57.1 vs. 54.5 (0.28)	60.4 vs. 56.7 (0.21)
Asian/Pacific Islander vs. White	51.3 vs. 59.2 (<0.0001)	57.1 vs. 61.2 (0.11)	60.4 vs. 63.7 (0.18)
Native American/other/unknown vs. white	53.8 vs. 59.2 (0.0006)	56.2 vs. 61.2 (0.01)	61.5 vs. 63.7 (0.55)
Native American/other/unknown vs. African American	53.8 vs. 51.5 (0.22)	56.2 vs. 54.5 (0.6)	61.5 vs. 56.7 (0.09)

MF-mycosis fungoides; CTCL-cutaneous T-cell lymphoma; CBCL-cutaneous B-cell lymphoma

* Wilcoxon Rank Sum comparison