Characteristics, Incidence Trends and Survival of Nodular Sclerosis in the United States: A Population-based Cohort

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Abstract

With nodular sclerosis (NS) being the most common subtype of Hodgkin Lymphoma in Western countries, we aim to investigate incidence rates and trends and survival rates of NS in the last two decades using the Surveillance, Epidemiology, and End Results (SEER) program. For included patients, we calculated incidence rates, annual percent change (APC) in incidence trends, and performed survival analysis through Kaplan Meier and Cox regression. Our study included 20,216 patients with NS diagnosed between 2000 and 2015, showing that NS incidence decreased over the study period. Unlike previous reports, NS was mostly diagnosed in males. Compared to white patients, black patients had a higher risk of death, which may be due to previously-reported differences in access to care according to patient-related criteria as socioeconomic status and race. This highlights the need of equal access to care, irrespective of patients' demographic criteria, for more effective management of NS.

Introduction

Nodular sclerosis (NS) is the most common subtype of Hodgkin lymphoma (HL) in Western countries, comprising 60–80% of classic Hodgkin lymphoma cases (1). NS possesses distinct features that are both clinically and histologically unique from those of other HL subtypes (1). NS is discriminated from other HL types by a set of histological features, such as broad collagen bands separating the lymphoid tissue into separate nodules (2). The NS subtype was also proven to be more common in well-developed countries with high socioeconomic classes (2, 3).

A previous study, using the National Cancer Institute (NIH) survey data (1969-1980), has shown that Hodgkin's disease (HD) incidence showed considerable declines in incidence rates among whites, particularly above the age of 40 years (4). However, incidence rates among young adults, with the nodular sclerosis (NS) subtype have shown an increasing trend (4), specifically among females (5). The elevated incidence of HD in young adults mostly reflects the increased of NS incidence, as it was the only subtype with increasing incidence (4).

Hodgkin lymphoma rates then remained relatively stable during 1992-2001. For nodular sclerosis specifically, incidence rates remained unchanged for several years, remaining relatively stable until 2007 (6). Following 2007, nodular sclerosis incidence rates declined by almost 5.9% yearly (7).

NS exhibits a significantly younger diagnostic age in females than males (8), which makes it stand out from the previous general incidence/age trend of hematological malignancies, as they were more commonly diagnosed among males and elderly people (6).

NS subtype shows better survival rates overall, in relation to the remaining HD subtypes. These results are in alignment with the results of previous studies of large population-based databases, which also suggest that this might be related to the fact that NS disease preferentially affects the young (9, 10).

Our study aims to investigate the incidence rates and trends and survival rates of NS in the period between 2000 and 2015, stratified by several demographic and tumor criteria. This will provide an updated and more specific in-depth view of NS in the US.

Methods

Data source

We used SEER*stat software version 8.3.8 (11) to access the Surveillance, Epidemiology, and End Results (SEER) cancer registries. SEER is a database comprised of many registries on cancer patients from multiple institutions in the US. It

holds information about demographics, incidence, mortality and survival of cancer patients.

We selected the database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (2000-2015) <Katrina/Rita Population Adjustment> (12) to obtain data of cases of nodular sclerosis diagnosed between 2000 and 2015.

Study population

We selected cases of nodular sclerosis using the "Site and Morphology.Lymphoma subtype recode/WHO 2008" variable set to "1(a)2 Nodular sclerosis". This yielded a total of 20,216 cases that were included in the study. We explored the following variables: age at diagnosis, sex, race, and state using "Race, Sex, Year Dx, Register, County", Ann-Arbor stage using "Stage – AJCC – Lymphoma - Ann Arbor Stage (1983+)", and lymph node site using "Site and Morphology – Primary Site Labelled".

Outcomes

The outcomes studied are the age-adjusted incidence rates and their annual percentage change (APC) between 2000 and 2015 which allows for a more in-depth analysis of the incidence rates over the years. Incidence rates were adjusted for age using the 2000 US standard population and expressed as rates per 100,000 person-years. Moreover, we observed the incidence rates and APC in different subgroups according to the population demographics and tumor site and stage over the study period (2000 – 2015). Survival probabilities and adjusted hazard ratios were used in the survival analysis.

Statistical analysis

Age-adjusted incidence rates were calculated using SEER*stat software (11). Additionally, we used Jointpoint Regression Program version 4.8.0.1 (13) to calculate APC and create jointpoint regression analysis to study the trends in nodular sclerosis incidence rates in the different subgroups over time. Jointpoint uses a sequence of permutation tests created by kim et al (14). First, it compares a simple linear regression model (i.e. with no jointpoints) with a model with one jointpoint and repeats this with models with more jointpoints till it finds the model with the minimum number of jointpoints that shows statistically significant changes.

Survival analysis was conducted using IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp). Survival was defined as the period from diagnosis till death or end of follow up. Sex, age at diagnosis, race and Ann Arbor stage of lymphoma were used as covariates to assess their prognostic value. For ease of reporting, age at diagnosis was stratified into four subgroups – 19 years of age and below, 20-39 years, 40-59 years, and 60 years and above. Survival curves were created using the Kaplan-Meier method to estimate the median survival time and log-rank test was used to assess the statistical significance of the curves for each covariate. Cox proportional hazards model was used to calculate the hazard ratios. All statistical tests were two-sided and P -value < 0.05 was considered statistically significant.

Results

Baseline characteristics

We identified and reviewed 20,216 patients with NS diagnosed during the period 2000 to 2015 (Table 1). Ann Arbor stage II comprised 9,602 (47.5%) of these cases. NS's most prevalent anatomical subsite was the lymph nodes of head, face and neck (in 3,114 patients; 15.4%), followed by intrathoracic lymph nodes (in 1,495 patients; 7.4%) then the axilla and arm lymph nodes (in 529 patients; 2.6%). Table 1 displays NS incidence rates with respect to patients'

demographics, tumor site and Ann Arbor stage at diagnosis from 2000 to 2015. Supplementary table 1 displays annual incidence rates from 2000 to 2015.

Table 1
Nodular Sclerosis Incidence Rates (2000-2015)

	Overall		Lymph Nodes of Head, Face and Neck		Intrathoracic Lymph Nodes		Lymph Nodes of Axilla or Arm	
	Incidence Rate (95% CI)	Count	Incidence Rate (95% CI)	Count	Incidence Rate (95% CI)	Count	Incidence Rate (95% CI)	Count
Overall	1.50 (1.47 - 1.52)	20,217	0.23 (0.22 - 0.24)	3,114	0.11 (0.11 - 0.12)	1,495	0.04 (0.04 - 0.04)	529
Sex								
Male	1.52 (1.49 - 1.55)	10,129	0.23 (0.22 - 0.24)	1,538	0.10 (0.09 - 0.11)	661	0.05 (0.04 - 0.05)	299
Female	1.49 (1.46 - 1.52)	10,088	0.23 (0.22 - 0.24)	1,576	0.12 (0.12 - 0.13)	834	0.03 (0.03 - 0.04)	230
Race								
White	1.64 (1.62 - 1.67)	16,822	0.25 (0.24 - 0.26)	2,597	0.13 (0.12 - 0.13)	1,269	0.04 (0.04 - 0.05)	436
Black	1.24 (1.19 - 1.29)	2,117	0.19 (0.17 - 0.21)	320	0.08 (0.07 - 0.09)	129	0.04 (0.03 - 0.06)	70
American Indian or Alaska Native	0.39 (0.30 - 0.50)	79	0.04 (0.01 - 0.09)	7	0.03 (0.01 - 0.07)	6	0.01 (0.00 - 0.05)	3
Asian or Pacific Islander	0.71 (0.67 - 0.76)	988	0.09 (0.08 - 0.11)	124	0.06 (0.04 - 0.07)	79	0.01 (0.00 - 0.02)	10
Unknown race	-	211	-	66	-	12	-	10
Age at diagnosis								
0-19	0.86 (0.83 - 0.89)	3,113	0.14 (0.13 - 0.16)	511	0.05 (0.04 - 0.06)	180	0.01 (0.00 - 0.01)	22
20-39	2.55 (2.50 - 2.60)	9,850	0.37 (0.35 - 0.39)	1,445	0.21 (0.19 - 0.22)	794	0.05 (0.04 - 0.05)	177
40-59	1.25 (1.22 - 1.29)	4,488	0.20 (0.19 - 0.22)	724	0.11 (0.10 - 0.12)	381	0.04 (0.04 - 0.05)	161
60+	1.25 (1.20 - 1.30)	2,766	0.20 (0.18 - 0.21)	434	0.06 (0.05 - 0.07)	140	0.08 (0.07 - 0.09)	169
Stage								
Stage I	0.20 (0.19 - 0.21)	2,696	0.10 (0.10 - 0.11)	1,378	0.05 (0.04 - 0.05)	620	0.02 (0.02 - 0.02)	248

	Overall		Lymph Nodes of Head, Face and Neck		Intrathoracic Lymph Nodes		Lymph Nodes of Axilla or Arm	
Stage II	0.71 (0.70 - 0.73)	9,602	0.08 (0.07 - 0.08)	1,057	0.05 (0.04 - 0.05)	634	0.01 (0.01 - 0.01)	120
Stage III	0.29 (0.28 - 0.30)	3,952	0.02 (0.02 - 0.02)	231	0.01 (0.00 - 0.01)	66	0.00 (0.00 - 0.01)	48
Stage IV	0.23 (0.23 - 0.24)	3,164	0.02 (0.01 - 0.02)	200	0.01 (0.01 - 0.01)	129	0.01 (0.00 - 0.01)	63
N/A	0 (0 - 0)	1	0.00 (0.00 - 0.00)	0	0.00 (0.00 - 0.00)	0	0.00 (0.00 - 0.00)	0
Unknown stage	0.06 (0.06 - 0.06)	802	0.02 (0.02 - 0.02)	248	0.00 (0.00 - 0.00)	46	0.00 (0.00 - 0.01)	50

Incidence rates and trends

NS was most prevalent in males (1.52 [95% CI, 1.49 - 1.55]), whites (1.64 [95% CI, 1.62 - 1.67]) and patients aged 20 - 39 years (2.55 [95% CI, 2.50 - 2.60]) (Table 1).

The overall NS incidence rate significantly decreased by 2.23% (95% CI, -2.93 - -1.53, $P < 0.001$) annually, from 2000 to 2015. NS incidence decreased in both genders and all racial, age and stage at diagnosis subgroups.

Results were subdivided by states. Notably, the incidence rate of NS decreased in all states over the study period with highest drop per year in Washington, by 3.08% (95% CI, -5.62 - -0.47, $P = 0.021$) followed by Georgia 2.71% (95% CI, -4.71 - -0.67, $P = 0.009$) and then, Hawaii -2.54% (95% CI, -6.03 - -1.08, $P = 0.153$).

Table 2 illustrates trends in NS incidence from 2000 to 2015 by gender, race, age and stage at diagnosis. Supplementary table 3 demonstrates trends in NS incidence in different US states.

Table 2
Trends in Nodular Sclerosis Incidence Rates (2000-2015)

Overall			Jointpoints								
(2000-2015)			1	2			3				
	APC (95% CI)	P value	year	APC (95% CI)	P value	year	APC (95% CI)	P value	year	APC (95% CI)	P value
Overall	-2.23 (-2.93 - -1.53)	<0.001	2000- 2007	-0.01 (-1.23 - 1.22)	0.984	2007- 2015	-4.13 (-5.14 - -3.11)	<0.001			
Sex											
Male	-2.18 (-3.19 - -1.17)	<0.001	2000- 2007	0.28 (-1.54 - 2.01)	0.793	2007- 2015	-4.23 (-5.69 - -2.76)	<0.001			
Female	-2.39 (-3.46 - -1.30)	<0.001	2000- 2008	-0.53 (-2.04 - 1.00)	0.462	2008- 2015	-4.47 (-6.36 - -2.54)	<0.001			
Race											
White	-2.25 (-3.03 - -1.47)	<0.001	2000- 2007	-0.12 (-1.46 - 1.23)	0.845	2007- 2015	-4.08 (-5.22 - -2.93)	<0.001			
Black	-1.63 (-3.84 - 0.63)	0.156	2000- 2006	2.75 (-2.20 - 7.95)	0.252	2006- 2015	-4.45 (-6.99 - -1.84)	<0.001			
American Indian or Alaska Native	-1.84 (-5.36- 1.81)	0.293	2000 - 2015	-1.84 (-5.36 - 1.81)	0.293						
Asian or Pacific Islander	-1.02 (-2.57 - 0.56)	0.188	2000- 2015	-1.02 (-2.57 - -0.56)	0.188						
Unknown race											
Age at diagnosis											
0-19	-1.75 (-3.60 - 0.13)	0.068	2000- 2008	0.98 (-1.71 - 3.62)	0.462	2008- 2015	-4.71 (-7.92 - -1.39)	<0.001			
20-39	-2.27 (-2.96 - -1.58)	<0.001	2000- 2007	-0.53 (-1.71 - 0.67)	0.350	2007- 2015	-3.77 (-4.78 - -2.75)	<0.001			

Overall		Jointpoints									
40-59	-2.20 (-3.07 - -1.32)	<0.001	2000- 2015	-2.20 (-3.07 - -1.32)	<0.001						
60+	-2.22 (-6.12 - 1.85)	0.280	2000- 2009	0.83 (-1.32 - 3.03)	0.402	2009- 2013	-12.84 (-22.76 --1.65)	<0.001	2013- 2015	7.21 (-16.29 - 37.30)	0.535
Stage											
Stage I	-6.26 (-7.10 - -5.41)	<0.001	2000- 2015	-6.26 (-7.10 - -5.41)	<0.001						
Stage II	-1.99 (-3.07 - -0.89)	<0.001	2000- 2006	1.27 (-1.1 - 3.70)	0.267	2006- 2015	-4.10 (-5.38 - -2.80)	<0.001			
Stage III	-0.75 (-2.27 - 0.81)	0.344	2000- 2007	3.58 (0.81 - 6.43)	<0.001	2007- 2015	-4.38 (-6.50 - -2.22)	<0.001			
Stage IV	0.08 (-0.94 - 1.10)	0.871	2000- 2015	0.08 (-0.94 - 1.10)	0.871						
N/A											
Unknown	-5.25 (-6.42 - -4.08)	<0.001	2000- 2015	-5.25 (-6.42 - -4.08)	<0.001						

Table 3
Nodular Sclerosis Incidence rates by site (2000-2015)

Lymph Node Site	Incidence Rate (95% CI)	Number of cases
Lymph nodes of head, face & neck	0.23 (0.22 - 0.24)	3114
Intrathoracic lymph nodes	0.11 (0.11 - 0.12)	1495
Intra-abdominal lymph nodes	0.01 (0.01 - 0.02)	193
Lymph nodes of axilla or arm	0.04 (0.04 - 0.04)	529
Lymph nodes of inguinal region or leg	0.02 (0.02 - 0.03)	306
Pelvic lymph nodes	0.00 (0.00 - 0.00)	38
Lymph nodes of multiple regions	0.92 (0.90 - 0.93)	12396
Lymph node, NOS	0.13 (0.12 - 0.13)	1701

Table 4
Trends in Nodular Sclerosis Incidence rates by site (2000-2015)

Lymph Node Site	Overall			Jointpoint 1		
	2000-2015			2000-2015		
	APC	95%CI	P-value	APC	95%CI	P-value
Lymph nodes of head, face & neck	-5.2	(-6.0 - -4.4)	<0.001	-5.2	(-6.0 - -4.4)	<0.001
Intrathoracic lymph nodes	-3.8	(-5.2 - -2.3)	<0.001	-3.8	(-5.2 - -2.3)	<0.001
Intra-abdominal lymph nodes	-	-	-	-	-	-
Lymph nodes of axilla or arm	-	-	-	-	-	-
Lymph nodes of inguinal region or leg	-	-	-	-	-	-
Pelvic lymph nodes	-	-	-	-	-	-
Lymph nodes of multiple regions	-	-	-	-	-	-
Lymph node, NOS	-	-	-	-	-	-

Table 5
Hazard ratios

	Hazard Ratio (95%CI)	P value
Sex		
Female	Reference	
Male	1.29 (1.20 - 1.38)	<0.001
Race		
White	Reference	
Black	1.57 (1.42 - 1.74)	<0.001
Asian or Pacific Islander	1.22 (1.02 - 1.45)	0.026
American Indian / Alaska Native	1.59 (0.98 - 2.56)	0.058
Unknown	0.15 (0.06 - 0.41)	<0.001
Age at diagnosis		
0 -19	Reference	
20 - 39	1.34 (1.15 -1.57)	<0.001
40 - 59	3.01 (2.57 - 3.52)	<0.001
60+	14.59 (12.55 - 16.97)	<0.001
Stage		
Stage I	Reference	
Stage II	0.89 (0.80 - 1.00)	0.04
Stage III	1.33 (1.19 - 1.48)	<0.001
Stage IV	1.74 (1.56 - 1.95)	<0.001
Unknown	1.36 (1.14 - 1.62)	<0.001

Results were subdivided by lymph node site. Of the three commonest sites, the rates of NS dropped most significantly in lymph nodes of axilla or arm, where it decreased by 5.50% (95% CI, -8.03 - -2.90, $p < 0.001$) per year (supplementary tile 4). Rates of NS dropped significantly in the commonest three lymph node sites in all genders, racial groups and stage at diagnosis subgroups over the study period.

Figure 1 shows trends in incidence for the chosen criteria. Supplementary table 4 summarizes trends in incidence of NS of lymph nodes of head, face and neck, intrathoracic lymph nodes, and lymph nodes of axilla or arm by gender, race, age and stage at diagnosis.

Survival analysis

The overall survival estimate of nodular sclerosis is 83.58%. Being female, stage II and below the age of 60 at diagnosis was associated with improved survival ($P < 0.001$) table (5). Females had a better overall survival estimate than males;

86.24% and 80.93% respectively figure(6). Males had 29% higher risk of death (HR = 1.29, 95% CI, 1.20 – 1.38, $P < 0.001$).

As for race, Asian or Pacific Islander patients (86.54%) as well as white patients (83.72%) had better overall survival probability than black (79.87%) and American Indian / Alaska Native patients (78.21%) figure (7). Compared to white patients, black patients had significantly the lowest overall survival (HR = 1.57, 95% CI, 1.42 – 1.74, $P < 0.001$). Also, despite Asian or Pacific Islander patients having a higher survival probability than white patients, the adjusted hazard ratio shows that they had a significantly higher risk of death (HR = 1.22, 95% CI, 1.02 - 1.45, $P = 0.026$).

Overall survival decreases significantly with the age at diagnosis. Patients who are 60 years of age or above at diagnosis have a statistically significant higher hazard ratio compared to younger age groups (HR = 14.59, 95% CI, 12.55 – 16.97, $P < 0.001$). Median survival time was not reached for any of the subgroups of each variable except for the age group above 60 which was 61 months. figure (8)

The percentage of stage II patients who survived till the end of follow up (2015) was 89.23% compared to 80.93% of stage I patients and 75.76% of stage IV patients figure (9). As in the Kaplan-Meier curve, the cox proportional hazards model showed that stage II patients had better survival compared to stage I patients (HR=0.89, 95% CI, 0.80 – 1.00, $P = 0.04$).

Discussion

NS is the most prevalent subtype of HL accounting for about 70% of classic HL cases (15), compared to relatively lower incidence in Asian countries (1). In this study, we aimed to investigate recent trends in NS incidence and survival in the US, from 2000 to 2015, using the SEER database.

In the US, NS rates were reported to be stable until 2007 (6, 16–18), then decreased by an average of 6% per year (7). Our study showed that NS incidence in the US decreased over the study period, unlike the rise in rates observed in other countries such as Australia through 2006 (17) and Japan through 2008 (18).

NS is perceived to be mostly diagnosed in young adults (6, 19–21). In fact, in the 1960s, it was believed that nodular sclerosis is one of the histological types of HL presenting in young adults (8, 22). Our analysis showed that the patients aged 20-39 years were the most commonly affected by NS. Moreover, our study showed that NS was diagnosed more in males, which is inconsistent with the literature where some studies reported NS to be more commonly diagnosed in females than males (5), and other studies reporting no sex differences in NS incidence (1, 6).

Furthermore, most of the NS cases were diagnosed at stage 2, consistent with an analysis using the National Cancer Data Base (NCDB) reporting that stage 2 accounted for the majority of NS cases. This might reflect a need for improvement of the diagnosis of nodular sclerosis, earlier in stage 1, before progressing to stage 2 (9).

NS has been shown to have a striking tendency to involve the mediastinal, supraclavicular, and lower cervical lymph nodes (23). Our study shows that through the study period, most patients presented with NS in lymph nodes of head, face and neck, intrathoracic lymph nodes, and lymph nodes of axilla or arm. Although NS has better prognosis than other classical HL subtypes, it can commonly present in mediastinal lymph nodes (1). Massive involvement of mediastinal lymph nodes carries adverse risks. Hence, screening of the population for NS subtype is crucial for earlier diagnosis, and thus more effective management, especially in the risky young adult population.

NS has the best survival compared to other classical HL subtypes (8, 24). Our study showed that females diagnosed with NS have better survival than males, consistent with a previous study reporting better 5-year survival in females vs.

males, ~85% vs. ~75%, respectively (8).

Our analysis showed that Asians had the best prognosis, and whites had better prognosis than blacks. Compared to white patients, black patients had 57% higher hazard of death. NS treatment has been witnessing improvements recently (23), through advancement of chemotherapy and radiotherapy in patients with early- and late-stage disease (25–27), contributing to greater possibilities of long-term survival (28, 29). However, it is worth mentioning that treatment selection has been shown to be impacted by socioeconomic factors (9), which may contribute to discrepancies in survival among different subgroups of the population, mostly due to nonadherence to guideline-based therapeutic pathways, rather than being due to biological differences in the different subgroups. Hence, it is crucial to maintain same level of care across the population, irrespective of demographic factors such as gender, race, age, or socioeconomic status. Currently, there are undergoing efforts to advance treatment, minimize its toxicity, and more importantly, lessen the socioeconomic disparities in treatment delivery, and thereby, disease outcomes (9).

Our study is limited by the retrospective nature of our analysis. In addition, being a SEER-based studies, it is limited by the availability of data in the registries. For example, some comparisons and analyses may not be feasible due to the incompleteness or unavailability of certain variables. Moreover, data on the treatment course and the factors that might contribute to a certain approach may also be missing, among the SEER-related limitations described in separate reports (30, 31).

Conclusion

Our analysis showed that NS incidence decreased over the study period. Unlike previous reports, NS was mostly diagnosed in males. Compared to white patients, black patients had a higher hazard of death, which may be due to previously-reported differences in access to care and adherence to therapeutic clinical guidelines, according to patient-related criteria as socioeconomic status and race. This highlights the need of equal access to care and adherence to evidence-based therapeutic pathways, irrespective of patients' demographic criteria, for more effective management of NS.

Declarations

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Ethical Approval: This article does not contain any studies with human participants performed by any of the authors.

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Figures

Figure 1

Nodular Sclerosis Incidence Trends by Sex

Figure 2

Nodular Sclerosis Incidence Trends by Race

Figure 3

Nodular Sclerosis Incidence Rates by Age

Figure 4

Nodular Sclerosis Incidence Rates by Stage

Figure 5

Nodular Sclerosis Incidence Rates by Site

Figure 6

Kaplan Meier Survival Curve for Sex

Figure 7

Kaplan Meier Survival Curve for Race

Figure 8

Kaplan Meier Survival Curve for Age

Figure 9

Kaplan Meier Survival Curve for Stage

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