JOURNAL OF INSURANCE MEDICINE

J Insur Med 2023;50:1–35

MORTALITY

Non-Hodgkin Lymphoma – Nodal and Extranodal: 20-Year Comparative Mortality, Survival & Biologic Behavior Analysis by Age, Sex, Race, Stage, Cell Morphology/Histology, Cohort Entry Time-Period and Disease Duration: *A Systematic Review of 384,651 Total NHL Cases Including 261,144 Nodal and 123,507 Extranodal Cases for Diagnosis Years 1975-2016: (SEER*Stat 8.3.6)*

Anthony F. Milano, MD, MPH, MA, DBIM

During the past 5 decades, there have been reports of increases in the incidence and mortality rates of non-Hodgkin lymphoma (NHL) in the United States and globally. The ability to address the epidemiologic diversity, prognosis and treatment of NHL depends on the use of an accurate and consistent classification system. Historically, uniform treatment for NHL has been hampered by the lack of a systematic taxonomy of non-Hodgkin lymphoma. Before 1982, there were 6 competing classification schemes with contending terminologies for NHL: the Rappaport, Lukes-Collins, Kiel, World Health Organization, British, and Dorfman systems without consensus as to which system is most satisfactory regarding clinical relevance, scientific accuracy and reproducibility and presenting a difficult task for abstractors of incidence information. In 1982, the National Cancer Institute sponsored a workshop[1] that developed a working formulation designed to: 1) provide clinicians with prognostic information for the various types of NHLs, and 2) provide a common language that might be used to compare clinical trials from various treatment centers around the world. Studies imply that prognosis is dependent on tumor stage and histology rather than the primary localization per se.[2] This study utilizes the National Cancer Institute PDQ adaptation of the World Health Organization's (WHO) updated REAL (Revised European American Lymphoma) classification[3] of lymphoproliferative diseases, and the SEER*Stat 8.3.6 database (released Aug 8, 2019) for diagnosis years 1975-2016. In this article, we make use of 40 years of data to examine patterns of incidence, survival and mortality, and selected cell bio-behavioral characteristics of NHL in the United States.

Objective.—To update trends in incidence and prevalence in the United States of non-Hodgkin lymphoma, examine, compare and

Address of Correspondent: PO Box 127, Cummaquid, MA 02637.

Correspondent: Anthony F. Milano, MD.

Key words: Non-Hodgkin lymphoma, disease classification, NHL subtypes, anatomic location, nodal and extranodal subdivision, age and sex stratification, incidence and prevalence trends, short and long-term survival and mortality, SEER Cancer Registry.

Received: March 1, 2020

Accepted: October 1, 2022

contrast short and long-term patterns of survival and mortality, and consider the outcome impacts of anatomic location of NHL nodal and extranodal subdivisions, utilizing selected ICD-O-3 histologic oncotypes stratified by age, sex, race/ethnicity, stage, cell behavioral morphology and histologic typology, cohort entry time-period and disease duration, employing the statistical database of the National Cancer Institute SEER*Stat 8.3.6 program for diagnosis years 1975-2016.[4]

Methods.—A retrospective, population-based cohort study using nationally representative data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program to evaluate 384,651 NHL cases for diagnosis years 1975-2016 comparing multiple variables of age, sex, race, stage, cell behavioral morphology, cohort entry time-period, disease duration and histologic oncotype. Relative survival statistics were analyzed in two cohorts: 1975-1995 and 1996-2016. Survival statistics were derived from SEER*Stat Database: Incidence – SEER 9 Regs Research Data, November 2018 Submission (1975-2016) <Katrina/Rita Population Adjustment> released April 2019, based on the November 2018 submission.

Results.—Incidence rates, relative frequency distributions, survival and mortality by age, sex, stage and cell behavioral morphology, of adult nodal (N) and extranodal (EN) NHL in 2 entrant time-periods as recorded in the SEER Program of the National Cancer Institute for diagnosis years 1975-2016 (SEER Stat 8.3.6) are summarized. Shifts in trends over time are identified, and the findings are correlated with prognosis, including short and long-term observed (actual), expected and relative survival, median observed and relative survival, mortality rates and excess death rates per 1000 people.

Conclusions.—Trends in SEER incidence, prevalence, survival and mortality by age, sex, race, stage, cell behavioral morphology, cohort entry time-period, relative frequency and percent distribution, were examined to provide a current epidemiologic and medical-actuarial risk assessment framework for nodal (N) and extranodal (EN) non-Hodgkin's lymphoma in the 1975-2016 timeframe.

Background and Importance.—Nodal (N) and extranodal (EN) non-Hodgkin lymphomas (NHL), are a remarkably heterogeneous group of immunophenotypic, histo/morphologic and cytogenetic lymphoproliferative malignancies reflecting clinical, biologic and pathologic diversity with differing patterns of epidemiology, biologic behavior and responses to treatment.[5] The 2016 revision of the World Health Organization (WHO) classification of hematopoietic and lymphoid neoplasms,[6] based on morphology and cell lineage, updates the 1995 version of the REAL (Revised European American Lymphoma) system[7] and represents the established guidelines for categorization and diagnosis of malignant lymphomas. Five major neoplastic classifications are recognized: 1) mature B-cell neoplasms, 2) mature T and NK neoplasms, 3) Hodgkin lymphoma, 4) posttransplant lymphoproliferative disorders [PTLD], and 5) histiocytic and dendritic cell neoplasms with approximately 95 subtypes and variants of lymphoid malignancy. Both lymphomas and lymphoid leukemias are included in this classification because both solid and circulating phases are present in many lymphoid neoplasms and distinction between them is artificial. Within the B-cell and T-cell categories, 2 subdivisions are recognized: precursor neoplasms corresponding to the earliest stages

of differentiation, and more mature differentiated neoplasms. The National Cancer Institute PDQ modification of the REAL classification of lymphoproliferative diseases includes a substantive list of: 1) Plasma cell disorders, 2) Hodgkin lymphoma, 3) Indolent lymphoma/leukemia, and 4) Aggressive lymphoma/leukemia; with approximately 55 subclasses. These variant malignancies are encompassed in the National Cancer Institute (NCI) SEER*Stat 8.3.6[8] database (produced Aug 6, 2019) for diagnosis years 1975-2016 and facilitate this study. Continued refinements in classification and terminologies have advanced current understanding of medical risk inherent in non-Hodgkin's lymphomas.

Nodal anatomic localizations were defined as lymph nodes, spleen, thymus and Waldeyer's ring, and *Extranodal anatomic localizations* encompass other organs. Because of selection bias in defining extranodal NHL, the Comprehensive Cancer Centre West (CCCW) population-based NHL registry study, in an original article published in the *Annals of Oncology* in 2003,[9] presented a plausible but liberal definition of primary extranodal NHL. The study included all patients who present with NHL that apparently originated at an extranodal site, even in the presence of disseminated disease, if the extranodal component is clinically dominant. Extranodal marginal zone lymphomas including the gastrointestinal tract, thyroid, lung, breast, orbit, and skin are called mucosa-associated lymphatic tissue (MALT) lymphomas[10,11] Like Hodgkin lymphoma, NHL usually originates in lymphoid tissues and can spread to other organs. NHL, however, is much less predictable than Hodgkin lymphoma and has a far greater predilection to disseminate to extranodal sites.

Epidemiology.—A steady increase in the age-adjusted incidence of NHL has occurred over the last 5 decades, as reported by US and international registries. During the years 1993 to 1995, the age-adjusted incidence increased 3% per year according to data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.[12] Some of this increased incidence can be attributed to the acquired immunodeficiency syndrome (AIDS), but this epidemic does not explain the increase of NHL before 1980. In the elderly population, there has also been a marked increase of NHL, largely the indolent bio-behavioral variants of NHLs.

The morbid importance of NHL is underscored by the estimated new cases diagnosed with NHL in the United States in 2019. Including adults and children, there are 74,200 (41,090 males and 33,110 females). About 19,970 people will die from this cancer (11,510 males and 8460 females).[13] Diffuse large B-cell lymphoma (DLBCL), the most common NHL subtype, has an aggressive behavior and is more common in whites than African Americans in the United States; however, 5-year survival outcomes are worse in African Americans (see Tables 1 & 2). The *BCL2* gene and rearrangement of the *MYC* gene or dual overexpression of the *MYC* gene, or both, confer a particularly poor prognosis.[14] Molecular profiles of gene expression using DNA microarrays may help to stratify patients in the future for therapies directed at specific targets and to better predict survival after standard chemotherapy.[15]

Etiology.—Most cases of aggressive NHL do not have a well-defined cause. For the NHLs that appear to have currently identifiable etiologic drivers, there are 4 groups of drivers: 1) immune suppression (both acquired and primary), 2) infectious agents, 3) toxic exposure, and 4) familial. The greatest factor involved in the worldwide increase in NHL, although lessened with the advent of highly active antiretroviral therapy (HAART), is HIV infection.[16] The risk of NHL is increased by up to 300% in untreated HIV-infected patients, rising in proportion to the duration of the HIV infection. Although the risk of NHL in HIV-infected patients appears to be decreased by HAART, the relative risk of NHL remains much higher than that for those not infected with HIV.[17]

Table 1. SEER Local-Regional-Distant (LRD) Anatomic Extent of Disease System Adapted to the Ann Arbor Lugano Revised Staging Classification for Primary Nodal Lymphomas

STAGE	INVOLVEMENT	EXTRANOD TAL STATUS (E)*
LIMITED		
Stage I (SEER Local)	One node or group of adjacent nodes	Single extranodal region without nodal involvement
Stage II (SEER Regional)	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extra nodal involvement
Stage II bulky	*II as above with bulky disease*	N / A
ADVANCED		
Stage III (SEER Distant)	Lymphatic regions involved on both sides of the diaphragm Nodes above the diaphragm with spleen involvement	Lymphatic regions involved on both sides of the diaphragm
Stage IV (SEER Distant)	Organs involved other than lymphoid tissue or lymph nodes	Organs involved other than those with lymphoid tissue as the primary site

* It is described by adding the letter E (for extranodal) after the stage number, for example 1E

MATERIALS AND METHODS

Population-based frequency[18] and survival[19] data from SEER registries (released April 2019) were analyzed to compare and determine differences in characteristics and patterns of mortality and survival in NHL N and EN subdivisions at diagnosis by age, sex, race, cohort entry time-period, Ann Arbor stage, bio-behavioral grade, disease duration, and frequency and mean age data spanning 1983-2015 and 1975-2016 time-periods. Standard life table methodologies for converting SEER survival data to comparative mortality are described in other publications.[20-23] Excluded were all death certificate only and those alive with no survival time. The percentage of microscopically confirmed malignant behavior cancers for case selections was 100%. Incidence and survival rates were obtained from the most current database of SEER Cancer Statistics Review (CSR)[24] and prevalence counts are based on the average of 2015 and 2016 population estimates from the US Bureau of the Census.

Cell Behavioral Morphology (Grade equivalent) – Grade – biologic behavioral severity of disease at onset – *indolent or aggressive*, is inherent in NHL cell morphology/histology tumor types and are designated by using ICD-O-3 classifications facilitating subsite comparative analysis with Ann Arbor-Lugano Staging. Physician Data Query (PDQ),[25] NCI's comprehensive database modifications of the REAL classification of lymphoproliferative diseases include a complex system of 11 indolent and 12 aggressive lymphoma/leukemia histologic subsites. To simplify for the reader, selected indolent and aggressive ICD-O-3 characterizations, largely based on case frequency, are used in this analysis. B-cell, T-cell and Follicular cell morphology/histology types in the SEER program menu are noted below and are accessed using the appropriate histologic ICD-O-3 Case Selection Variable in the SEER*Stat 8.3.6 program. ICD-O-3 cell morphology/histology codes supplant Berg's[26] 4 grading categories (well differentiated to undifferentiated). The PDQ behaviorally characterized and defined NHL subsite cell morphologies as either indolent or aggressive and treatment protocols remain largely based on classification systems that group diagnosis into indolent (low-grade) and aggressive (high-grade) NHL.

Table 2. 1983-1995 Entrants, Sex, Age & Race; All Stages & Indolent/Aggressive Combined SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6): Index Code 37a: NHL-NODAL

Duration	No. Alive	Exposure	Number of Deaths		Mortality	Mean Ann. Mortality Rate/1,000			Cumul. Surv. Rate		Cum. Surv.
Start-End	at Start	Pt.-Yrs	Observed	Expected	Ratio (%)	Observed	Expected	Excess	Observed	Expected	Ratio (%)
t to t+ch t	***l***	**E**	**d**	**d'**	**100d/d'**	**q**	**q'**	**(q-q')**	**P**	**P'**	**100P/P'**
					Male, Age <65						
0-1	3,368	3,364.0	934	27.92	3,345	0.2776	0.0083	269.3	0.7224	0.9917	72.8
1-2	2,426	2,425.5	347	21.59	1,607	0.1431	0.0089	134.2	0.6190	0.9829	63.0
2-5	2,078	5,749.5	385	55.65	692	0.0670	0.0097	57.3	0.5042	0.9545	52.8
5-10	1,686	7,550.0	365	87.04	419	0.0483	0.0115	36.8	0.3947	0.9005	43.8
10-15	1,313	6,077.5	235	88.53	265	0.0387	0.0146	24.1	0.3239	0.8366	38.7
15-20	1,073	4,936.0	181	90.65	200	0.0367	0.0184	18.3	0.2689	0.7623	35.3
Median survival time (interval = 12 months): Observed = 5.13647 intervals; Relative = 6.0786 intervals.											
					Male, Age 65 up						
0-1	2,842	2,841.5	1,202	177.03	679	0.4230	0.0623	360.7	0.5770	0.9377	61.5
1-2	1,639	1,637.5	397	95.14	417	0.2424	0.0581	184.3	0.4371	0.8832	49.5
2-5	1,239	3,148.5	479	193.01	248	0.1521	0.0613	90.8	0.2680	0.7301	36.7
5-10	759	2,878.0	402	207.82	193	0.1397	0.0722	67.5	0.1261	0.4993	25.3
10-15	357	1,364.0	200	125.37	160	0.1466	0.0919	54.7	0.0553	0.3056	18.1
15-20	155	541.0	99	64.10	154	0.1830	0.1185	64.5	0.0200	0.1608	12.4
Median survival time (interval = 12 months): Observed = 1.55034 intervals; Relative = 1.95769 intervals.											
					Male, All Ages						
0-1	6,210	6,205.5	2,136	204.78	1,043	0.3442	0.0330	311.2	0.6558	0.9670	67.8
1-2	4,065	4,063.0	744	116.61	638	0.1831	0.0287	154.4	0.5357	0.9392	57.0
2-5	3,317	8,898.0	864	248.68	347	0.0971	0.0279	69.2	0.3961	0.8627	45.9
5-10	2,445	10,428.0	767	294.53	260	0.0736	0.0282	45.3	0.2715	0.7475	36.3
10-15	1,670	7,441.5	435	213.93	203	0.0585	0.0287	29.7	0.2007	0.6460	31.1
15-20	1,228	5,477.0	280	154.55	181	0.0511	0.0282	22.9	0.1546	0.5599	27.6
Median survival time (interval = 12 months): Observed = 2.56515 intervals; Relative = 3.54656 intervals.											
					Female, Age <65						
0-1	2,152	2,150.0	437	10.75	4,065	0.2033	0.0050	198.3	0.7967	0.9950	80.1
1-2	1,711	1,710.5	207	8.89	2,327	0.1210	0.0052	115.8	0.7003	0.9898	70.7
2-5	1,503	4,238.0	227	25.23	900	0.0536	0.0060	47.6	0.5944	0.9722	61.1
5-10	1,272	5,816.0	252	43.30	582	0.0433	0.0074	35.9	0.4764	0.9364	50.9
10-15	1,014	4,753.5	143	47.06	304	0.0301	0.0099	20.2	0.4092	0.8908	45.9
15-20	870	4,102.0	113	54.35	208	0.0275	0.0133	14.3	0.3557	0.8331	42.7
Median survival time (interval = 12 months): Observed = 8.79007 intervals; Relative = 10.5963 intervals.											
					Female, Age 65 up						
0-1	3,212	3,212.0	1,349	147.75	913	0.4200	0.0460	374.0	0.5800	0.9540	60.8
1-2	1,863	1,863.0	405	79.36	510	0.2174	0.0426	174.8	0.4539	0.9134	49.7
2-5	1,458	3,835.0	466	178.23	261	0.1215	0.0465	75.0	0.3088	0.7913	39.0
5-10	992	3,860.0	506	226.12	224	0.1311	0.0586	72.5	0.1510	0.5825	25.9
10-15	484	1,847.0	260	143.80	181	0.1408	0.0779	62.9	0.0697	0.3858	18.1
15-20	222	844.5	121	84.57	143	0.1433	0.1001	43.1	0.0312	0.2247	13.9
Median survival time (interval = 12 months): Observed = 1.63457 intervals; Relative = 1.97296 intervals.											
					Female, All Ages						
0-1	5,364	5,362.0	1,786	158.18	1,129	0.3331	0.0295	303.6	0.6669	0.9705	68.7
1-2	3,574	3,573.5	612	88.27	693	0.1713	0.0247	146.6	0.5527	0.9465	58.4
2-5	2,961	8,073.0	693	203.65	340	0.0858	0.0252	60.6	0.4232	0.8766	48.3
5-10	2,264	9,676.0	758	269.51	281	0.0783	0.0279	50.5	0.2813	0.7609	37.0
10-15	1,498	6,600.5	403	191.06	211	0.0611	0.0289	32.1	0.2055	0.6570	31.3
15-20	1,092	4,946.5	234	139.05	168	0.0473	0.0281	19.2	0.1611	0.5696	28.3
Median survival time (interval = 12 months): Observed = 2.96671 intervals; Relative = 4.31578 intervals.											
					White Race; All Ages						
0-5	10,369	32,508.5	6,097	940.97	648	0.1876	0.0289	158.6	0.4114	0.8660	47.5
5-10	4,251	18,143.0	1,374	523.36	263	0.0757	0.0288	46.9	0.2781	0.7480	37.2
Median survival time (interval = 12 months): Observed = 2.77623 intervals; Relative = 4.00818 intervals.											
					Black, Other, Unknown; All ages						
0-5	1,205	3,666.5	738	79.01	934	0.2013	0.0215	179.7	0.3851	0.8984	42.9
5-10	458	1,961.0	151	40.64	372	0.0770	0.0207	56.3	0.2580	0.8092	31.9
Median survival time (interval = 12 months): Observed = 2.4633 intervals; Relative = 2.88937 intervals.											

* All Ann Arbor Stages I-IV plus Unknown Combined; (Ann Arbor Stage 1983-2015)

** Indolent Morpho/Histology-ICD-O-3; 9690, 9699 Aggressive morpho/Histology-ICD-O-3; 9670, 9680, 9702

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

- *Indolent* – "low grade" – grows and spreads slowly; considered to be grade 1-2 and recorded as grade 2. Indolent ICD-O-3 histologies used for the purposes of this article:
    - ICD-O-3; 9690-Follicular lymphoma, NOS; Median Survival Time (MST) >20 years32.
    - ICD-O-3; 9699-Marginal zone B-cell lymphoma, NOS; Median Survival Time – 10 years.
- *Indolent Definition:* despite advanced stages (AJCC-Ann Arbor Stages III and IV), if median survival ranges from 8 to 15 years, the indolent designation, a scientific *a priori* premise, is assigned to a given NHL cell morphology/histology classification.[27,28]
- *Aggressive* – "high-grade" – grows and spreads quickly; considered to be grade 3-4 and recorded as grade 4; Aggressive ICD-O-3 histologies used for the purposes of this article:
    - ICD-O-3; 9670 Small B lymphocytic, NOS; Median Survival Time – 5.9 years
    - ICD-O-3: 9680 Large B-cell, diffuse (includes diffuse mixed-cell, immunoblastic, and T-cell rich large B-cell lymphoma); Median Survival Time – 2.0 years
    - ICD-O-3: 9702 Mature T-cell lymphomas, NOS; Median Survival Time – 0.97 years

Stage–anatomic location – extent of disease at onset is the single most important determinant of prognosis, treatment and survivability. The American Joint Committee on Cancer (AJCC) along with the Union for International Cancer Control (UICC) has adopted the subsequent Lugano classification of the Ann Arbor/Cotswolds modification as the standard for classifying lymphoma tumor extent of anatomic disease.[29] The SEER*Stat program menu selection variable for Stage – ***'Other'*** – includes *Lymphoma – Ann Arbor Stage (1983-2015).* Historically, the SEER local-regional-distant (LRD) anatomic extent of disease system adapts the AJCC Ann Arbor-Lugano Revised Staging Classification for Primary Nodal Lymphomas.[30,31] Ann Arbor principal stages abstracted from Ref. 30 Cheson BD et al JCO 2014 are described in Table 1.

Tonsils, Waldeyer's ring, and spleen are considered nodal tissue. Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and several prognostic factors.

Ann Arbor Stage I and II lymphomas in the SEER system represent *localized* and *regional* disease, respectively. Ann Arbor Stage III disease was originally developed for patients with positive lymphangiograms, but with introduction of laparotomy, it has been enlarged to include patients with splenic lymphoma who should be identified with a subscript (III_s). Ann Arbor Stage IV is restricted to those with lymph-node disease and disseminated involvement of nonlymphoid organs. Ann Arbor-Lugano stage III and IV lymphomas in the SEER program represent *distant* stage disease. Combining Stages I and II is termed ***Limited stage*** and Stages III and IV ***Advanced stage***, and is used in this review to topographically classify NHL anatomic extent of disease at presentation:

Statistical significance—Standard errors are shown for survival rates in the SEER survival tables. Actuarial method: Ederer II method is used for cumulative expected survival. Ederer II method calculates the expected survival rates for patients under observation at each point of follow-up, so the matched individuals are considered to be at risk until the corresponding cancer patient dies or is censored.[32] Confidence interval: Log (-Log ()) Transformation; the level is 95%. Poisson confidence intervals at the 95% level based on the number of observed deaths are used in this study but not displayed here to conserve space on the mortality tables.

Incidence.—General incidence rates are given for non-Hodgkin lymphoma (NHL) for both nodal and extranodal combined. The SEER Cancer Statistics Review for 1975-2016, Chart 1 below (derived from CSR Tables 19,1-

Table 3. 1996-2015 Entrants, Age, Sex & Race; All Stages & Indol/Aggress Grades Combined SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6): Index Code 37a: NHL-NODAL

Duration	No. Alive	Exposure	Number of Deaths		Mortality	Mean Ann. Mortality Rate/1,000			Cumul. Surv. Rate		Cum. Surv.
Start-End	at Start	Pt.-Yrs	Observed	Expected	Ratio (%)	Observed	Expected	Excess	Observed	Expected	Ratio (%)
t to t+ch t	***l***	**E**	**d**	**d'**	**100d/d'**	**q**	**q'**	**(q-q')**	**P**	**P'**	**100P/P'**
					Male, Age <65						
0-1	8,777	8,745.0	1,413	62.09	2,276	0.1616	0.0071	154.5	0.8384	0.9929	84.4
1-2	7,300	7,116.0	580	52.66	1,101	0.0815	0.0074	74.1	0.7701	0.9856	78.1
2-5	6,352	16,773.5	653	139.27	469	0.0389	0.0083	30.6	0.6847	0.9611	71.2
5-10	4,708	18,119.0	591	186.57	317	0.0326	0.0103	22.3	0.5805	0.9120	63.7
10-15	2,465	8,322.0	245	110.18	222	0.0294	0.0132	16.2	0.5026	0.8521	59.0
15-20	898	2,311.0	62	39.02	159	0.0268	0.0169	9.9	0.4398	0.7809	56.3
	Median survival time (interval = 12 months): Observed = 15.1901 intervals; Relative is greater than 20 intervals.										
					Male, Age 65 up						
0-1	7,773	7,761.5	2,597	417.57	622	0.3346	0.0538	280.8	0.6654	0.9462	70.3
1-2	5,153	5,020.0	700	255.52	274	0.1394	0.0509	88.5	0.5726	0.8980	63.8
2-5	4,187	10,436.0	1,028	578.70	178	0.0985	0.0555	43.1	0.4197	0.7561	55.5
5-10	2,523	8,531.0	914	572.43	160	0.1071	0.0671	40.0	0.2355	0.5299	44.4
10-15	855	2,426.5	304	215.89	141	0.1253	0.0890	36.3	0.1187	0.3267	36.3
15-20	174	346.5	59	39.36	150	0.1703	0.1136	56.7	0.0475	0.1752	27.1
	Median survival time (interval = 12 months): Observed = 3.30688 intervals; Relative = 7.46045 intervals.										
					Male, All Ages						
0-1	16,550	16,506.5	4,010	478.69	838	0.2429	0.0290	213.9	0.7571	0.9710	78.0
1-2	12,453	12,136.0	1,280	308.25	415	0.1055	0.0254	80.1	0.6772	0.9463	71.6
2-5	10,539	27,209.5	1,681	717.98	234	0.0618	0.0264	35.4	0.5601	0.8733	64.1
5-10	7,231	26,650.0	1,505	759.23	198	0.0565	0.0285	28.0	0.4191	0.7552	55.5
10-15	3,320	10,748.5	549	326.04	168	0.0511	0.0303	20.7	0.3245	0.6471	50.2
15-20	1,072	2,657.5	121	78.63	154	0.0455	0.0296	15.9	0.2610	0.5596	46.6
	Median survival time (interval = 12 months): Observed = 6.93841 intervals; Relative = 15.169 intervals.										
					Female, Age <65						
0-1	6,006	5,985.5	704	26.34	2,673	0.1176	0.0044	113.2	0.8824	0.9956	88.6
1-2	5,261	5,123.5	375	23.57	1,591	0.0732	0.0046	68.6	0.8178	0.9910	82.5
2-5	4,611	12,284.0	332	64.02	519	0.0270	0.0052	21.8	0.7541	0.9755	77.3
5-10	3,515	13,955.0	271	95.62	283	0.0194	0.0069	12.6	0.6839	0.9421	72.6
10-15	2,008	6,804.5	170	64.22	265	0.0250	0.0094	15.5	0.6034	0.8974	67.2
15-20	745	1,872.5	56	24.07	233	0.0299	0.0129	17.1	0.5201	0.8381	62.1
	Median survival time (interval = 12 months): Observed is greater than 20 intervals; Relative is > than 20 intervals.										
					Female, Age 65 up						
0-1	7,850	7,831.0	2,588	356.31	726	0.3305	0.0455	285.0	0.6695	0.9545	70.1
1-2	5,224	5,086.0	665	212.59	313	0.1308	0.0418	89.0	0.5819	0.9146	63.6
2-5	4,283	10,826.0	932	504.60	185	0.0861	0.0466	39.5	0.4445	0.7919	56.1
5-10	2,735	9,501.5	945	558.10	169	0.0995	0.0587	40.7	0.2599	0.5807	44.8
10-15	1,011	3,032.5	354	236.94	149	0.1167	0.0781	38.6	0.1337	0.3806	35.1
15-20	224	477.5	75	49.52	151	0.1571	0.1037	53.4	0.0518	0.2051	25.2
	Median survival time (interval = 12 months): Observed = 3.68332 intervals; Relative = 7.70027 intervals.										
					Female, All Ages						
0-1	13,856	13,816.5	3,292	382.72	860	0.2383	0.0277	210.6	0.7617	0.9723	78.3
1-2	10,485	10,209.5	1,040	235.84	441	0.1019	0.0231	78.8	0.6841	0.9498	72.0
2-5	8,894	23,110.0	1,264	568.30	222	0.0547	0.0246	30.1	0.5786	0.8813	65.7
5-10	6,250	23,456.5	1,216	653.23	186	0.0518	0.0278	24.0	0.4430	0.7645	58.0
10-15	3,019	9,837.0	524	300.15	175	0.0533	0.0305	22.8	0.3356	0.6538	51.3
15-20	969	2,350.0	131	73.45	178	0.0557	0.0313	24.5	0.2537	0.5571	45.5
	Median survival time (interval = 12 months): Observed = 7.73 intervals; Relative = 15.9896 intervals.										
					White Race, All Ages						
0-5	25,390	86,947.0	10,377	2,417.19	429	0.1193	0.0278	91.5	0.5738	0.8695	66.0
5-10	11,501	42,880.0	2,398	1,282.49	187	0.0559	0.0299	26.0	0.4301	0.7464	57.6
	Median survival time (interval = 12 months): Observed = 7.39508 intervals; Relative = 16.79 intervals.										
					Black, Other, Unknown						
0-5	5,016	16,041.0	2,190	275.88	794	0.1365	0.0172	119.3	0.5422	0.9181	59.1
5-10	1,980	7,226.5	323	130.09	248	0.0447	0.0180	26.7	0.4321	0.8377	51.6
	Median survival time (interval = 12 months): Observed = 6.72453 intervals; Relative = 11.1051 intervals.										

[*] All Ann Arbor Stages I-IV plus Unknown Combined; (Ann Arbor Stage 1983-2015)

[**] Indolent Morpho/Histology-ICD-O-3; 9690, 9699 Aggressive Morpho/Histology-ICD-O-3; 9670, 9680, 9702

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

3) indicates recent trends in the average annual percent change (AAPC) per 100,000 for non-Hodgkin lymphoma by sex, race, and ethnicity. These consisted of -0.2 per 100,000 for men, -0.6 for women, and -0.6 for both sexes combined. Negative trend rates were also seen in 2007-2016 in the Joinpoint Trend AAPC for all races, both sexes combined, -0.6 per 100,000.

In Chart 2, Age-adjusted incidence rates, examined for broader age groups, 2012-2016, increase with age and vary by race both in the United States and worldwide. Incidence is higher in males (32%) than in females, higher in whites (29%) than in blacks, and higher in the US (25%) than the average elsewhere in the world. There is a clear preponderance in non-Hodgkin lymphoma incidence in both sexes and all races in ages 65 and above and a higher incidence in the United States population at large (25%) compared to the world (WHO 2000-2025) standard million.

Chart 3, adapted from CSR Table 19.5, demonstrates age-adjusted overall progression of incidence rates (1975-2016), decennial progression (1980-2010), and annual progression (2011-2016) per 100,000 by year, race, and sex for all NHL cases in the 1975-2016 SEER database. Incidence rates from 1980 to 2016, all races and both sexes combined, rising from 12.62 per 100,000 to 19.36 per 100,000, an overall increase of 65%, but stabilized since 2000. Incidence among whites from 1980-2016 increased 36% and among blacks 47%. However, in the 2015-2016 interval, incidence rose 15% in black females while falling 5% in whites (both sexes combined) and 2% in black males. NHLs occurring in the elderly (ie, persons older than age 65 years) account for a large share of the increased incidence of lymphoma. Part of the increased incidence of specific categories of NHL may be due to environmental carcinogens (herbicide exposure), congenital & acquired immunodeficiency states, patients with Sjogren's syndrome and other oncogenic viruses.

Prevalence.—Five-year limited duration counts, January 1, 2016, for non-Hodgkin lymphoma: All races, both sexes, 248,946; Males 135,137; Females 133,809 (CSR Table 19.25).

Mortality.—General mortality rates are given in the CSR for Non-Hodgkin's Lymphoma (NHL) for both Nodal and Extranodal combined. In Chart 4, Age-adjusted mortality rates, examined for broader age groups, 2012-2016, increase with age and vary by race both in the United States and worldwide. Mortality is higher in males (40%) than in females, higher in whites (31%) than in blacks, and higher in the United States (46%) than the average elsewhere in the world. There is a clear preponderance in non-Hodgkin lymphoma mortality in both sexes and all races in ages 65 and above and a higher mortality in the US population at large (46%) compared to the world (WHO 2000-2025) standard million.

Chart 5, adapted from CSR Table 19.6, demonstrates age-adjusted overall progression of mortality rates (1975-2016), annual mortality increase (1980-1997), and annual mortality decline (1998-2016) per 100,000 by year, race, and sex for all NHL cases in the 1975-2016 SEER database. Mortality rates from 1980 to 1997, all races and both sexes combined, rose from 6.23 deaths per 100,000 to 8.88 per 100,000, an overall increase of 30%, but then began a steady decline to 5.33 deaths per 100,000 to 2016 consistent with the stabilization of incidence in the same time-period and the release of Rituximab (targeted therapy), a chimeric monoclonal antibody against the protein CD20 primarily found on the surface of immune system B cells, approved for medical use in 1997. When bound to this protein it triggers cancer cell death (apoptosis). Deaths among whites from 1980-1997 increased 30% and among blacks 37%. However, in the 1997-2016 interval, deaths fell in whites and blacks 39% and 40%, respectively.

SEER Nodal & Extranodal Case Statistics. There is a total of 384,651 cases of non-Hodgkin lymphoma in the 1975-2016 SEER frequency database distributed by age, sex, stage and grade. The total number

included 261,144 nodal-NHL (67.9%) and 123,507 (32.1%) extranodal-NHL cases.

Case Characteristics – Chart 6. *FAMA:* Relative frequency and mean age (FAMA) distributions by age, sex and race for Nodal and Extranodal NHL, along with, Ann Arbor stage distributions & cell bio-behavioral grade frequencies (indolent-aggressive) are shown in Chart 6. A total of 261,144 patient-cases of nodal non-Hodgkin's lymphoma (67.9% of all NHL cases) in the 1975-2016 SEER frequency database with a median age of 63 years are included in the study. Frequency and mean age (FAMA) in males are 142,456 (54.6%) and 62 years respectively, and 118,688 (45.4%) with mean age 66 years in females. Also included in this study are a total of 123,507 patient-cases of extranodal NHL in the 1975-2016 SEER frequency database with a median age of 63.5 years. FAMA in males are 66,930 (54.2%) and 62 years respectively, and female FAMA are 56,577 (45.8%) with mean age 65 years. Nodal frequency by race at presentation; 87% of cases were white, black 7%, other 6%, and unknown 6.7%, and mean ages in years were white 64.5, black 56.3, other 62.3 and unknown 57.8, respectively. Extranodal frequency by race at presentation; 82% of cases were white, 8% black, 8% other and 2% unknown, and mean age in years were 64.4, 54.4, 61.9 and 56.4, respectively.

Figure 1 (NHL-Nodal Frequency by Sex), the zenith of cumulative diagnostic frequency by attained age in males occurred at quinquennial age 65-69 (62.2%) and then declined to ages 85+ years. Females reached their zenith at quinquennial ages 75-79 (78.7%) then rapidly declined to ages 85+ years. However, females had a higher percentage of cases with advancing quinquennial ages 65-85+ years than males.

Figure 2 (NHL-Extranodal Frequency by Sex), the zenith of cumulative diagnostic frequency by attained age in males occurred at quinquennial age 65-69 (61.6%) and then declined to ages 85+ years. Females reached their zenith at quinquennial ages 70-74 (66.1%) then slowly declined to ages 85+ years. However, females had a higher percentage of cases with advancing quinquennial ages 65-85+ than males. Although NHL nodal and extranodal total patient-case frequency counts differ by 47%, cumulative percent frequencies by quinquennial attained ages are proportionally similar for each subset.

NHL-NodalStaged Cases: Shown in Chart 6, Ann Arbor staging extended from 1983 to 2015 in the SEER frequency database (Ref. 18), totaled 212,455 staged cases; of these however, only 56,154 (26.4%) were available for survival and mortality analysis from the SEER survival database (Ref. 19) for 1996-2015 entrants (Table 8). NHL-N & EN staged cases for mortality and survival analysis for the 1996-2015 cohort are displayed in Tables 8 and 16, respectively. Limited staging at presentation (Stages I & II combined) for the 1983-2015 cohort displayed in Chart 6 accounted for 76,317 cases (36%) and advanced staging (Stages III & IV combined) accounted for 136,138 cases (64%) of the staged NHL-nodal subdivision. Of the 1983-2015 grand total of all cases staged and unknown stage, 22,422 cases or 9.6% were of unknown stage.

NHL-Extranodal Staged Cases: Also shown in Chart 6, Ann Arbor criteria for staging (1983-2015) in the SEER frequency database (Ref. 18) totaled 91,044 staged cases; of these however, only 25,222 Ann Arbor staged cases (27.7%) were available for survival and mortality analysis from the SEER survival database for 1996-2015 entrants (Table 16). There were more than twice as many total NHL-Nodal than extranodal cases available for survival and mortality analysis from the SEER survival database, see Tables 8 and 16, respectively. Paradoxically, limited staging at presentation (Stages I & II combined) for the 1983-2015 cohort accounted for 63,538 cases (70%) and advanced staging (Stages III & IV combined) accounted for 27,506 cases (30%) of the staged NHL-extranodal subset. Of the 1983-2015 grand total of all cases staged and unknown stage, 8286 cases (8.3%) were of unknown stage.

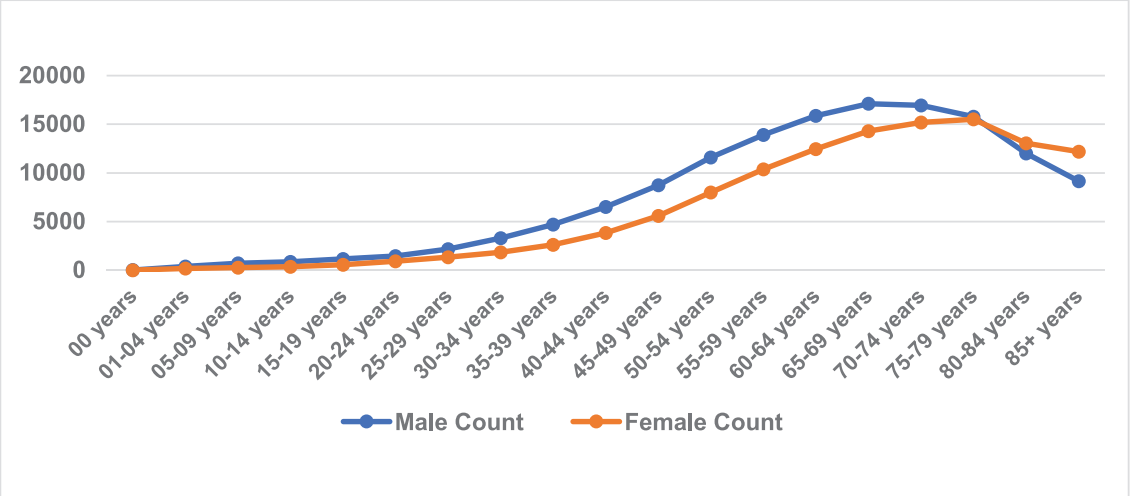

Figure 1. *NHL-Nodal: Diagnostic Frequency at Attained Age 1975-2016.*

Note: When a stage distribution is presented, the percentage given for each stage is the number of cases in a particular stage divided by the total number X 100 of **staged** cases only. However, overall, all stages known and unknown combined, NHL-EN demonstrates modestly improved mortality & survival outcomes, suggesting that NHL extranodal subsites may exert varying but possibly beneficial biologic behavioral influences on extent-of-disease and prognosis at presentation. Further research is needed to understand the biologic and socioeconomic underpinnings that may explain these NHL stage and grading disparities.

Graded Cases: Shown in Chart 6 from the SEER frequency database for the selected ICD-O-3 indolent and aggressive cell histo/morphology counts:

- NHL-Nodal cases were 23,443 (18%) and 104,424 (82%), respectively,
- Paradoxically, NHL-Extranodal indolent-aggressive cases proportionally were 21,902 (31%) and 47,793 (69%), respectively.

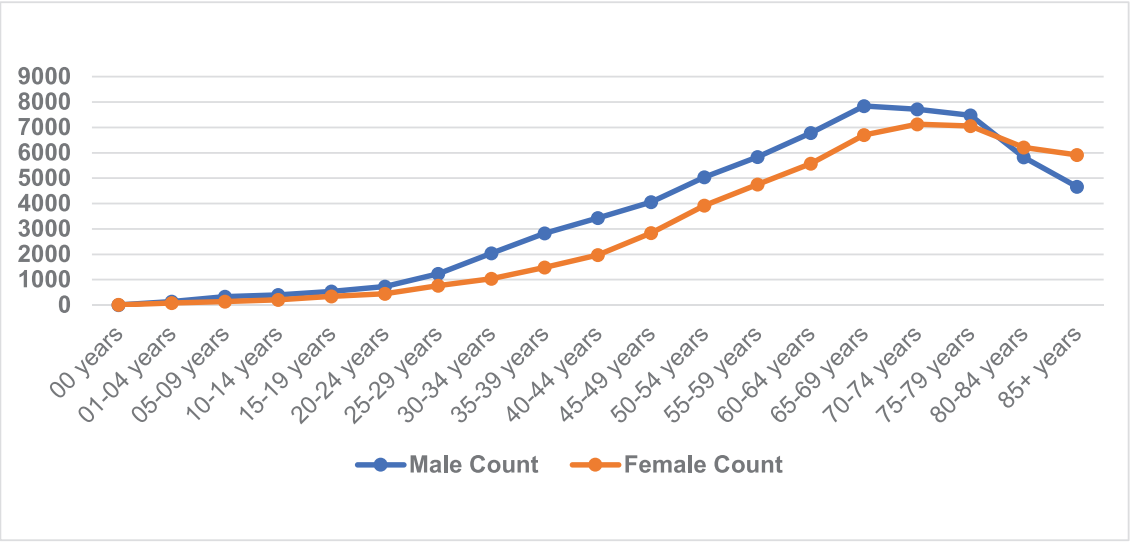

Figure 2. *NHL-Extranodal: Diagnostic Frequency at Attained Age 1975-2016.*

Chart 7 is the SEER Site/Histology Validation List for the selected Nodal and Extranodal NHL bio-behavioral grades employed in this study.

Follow-up (FU). Standard FU procedures were used by the 9 SEER Registries, with only a minimal loss to FU, according to the Cancer Statistics Review.

NODAL NHL: MORTALITY AND SURVIVAL

Results. *Note well*: In the 1975-2016 SEER*Stat 8.3.6 database, Ann Arbor staging data extends only from 1983-2015 and is reflected in this report in all NHL Nodal and Extranodal Tables exhibiting staging data; therefore, Ann Arbor Staged data in the 1975-1995 and 1996-2016 cohort entry-periods actually spans only the 1983-1995 and 1996-2015 time-periods respectively. For ease of NHL-Nodal and Extranodal mortality and survival comparability, Table formats are the same for both nodal and extranodal subdivisions, Tables (2-9) and Tables (10-16), respectively.

Table 2; 20-year FU in the 1983-1995 cohort by age, sex and race, (all stages and indolent & aggressive grades combined) is divided into 6 duration intervals 0-1, 1-2, 2-5, 5-10, 10-15 & 15-20 years. In this cohort, excess death rates (EDRs) in both sexes are extremely high in the 1st duration in all age groups but diminish with duration. EDR also increases with age; in males in the 1st duration, the EDR in age group 65 up is 361 vs female 374 per 1000 per year. In the first year, EDR is in the range of 269 to 361 per 1000 per year in males, and 198 to 374 in females. In 1983-1995, all ages combined, the preponderance of EDR in males over females, is evident. The corresponding MR values in the first year are extremely high: over 4000% in females and 3300% in males in patients under age 65. However, by duration 15-20 years EDR has decreased to about 18 in males at entry-age <65 and to 14 in females but MR values remain relatively high. EDR results are similar in both sexes, but MRs are higher in females, all ages combined because of lower expected deaths. Median survival, all ages combined, is higher in females than males, approximately 3-years vs 2.6-years, respectively. Five-year survival ratios (SR) are about 46% and 48% in males and females respectively, all ages combined. In males, SR diminishes from 53% in age group <65 to 37% in age group >65, and in females, SR diminishes from 61% in age group <65 to 39% in those age >65. Overall data available by race show EDR values higher and 5-year SR and median survival lower in non-white than in white patients.

Table 3 shows patterns of excess mortality in the 1996-2015 cohort for the same age groups in both sexes are consistent but of much lesser magnitude than in Table 1, reflecting earlier diagnosis and more suitable therapy in the latter entry-period. In males, all first-year EDRs are lower than they are in the 1983-1995 cohort. The highest EDR of 281 per 1000 per year is in the 65 up age group. This was based on 2597 (33%) deaths in 7773 entrants, and the EDR of 281 is significantly lower than the EDR of 361 in 1983-95 but significantly higher than the other male EDRs of 155 and 214 (all ages combined) in the 1996-2015 cohort (95% confidence level). EDRs increase with age but diminish with advancing duration in all age groups. EDR values in females (all ages combined) are always lower than the corresponding male age group; EDRs also increase with age but decrease with advancing duration. At duration 5-10 years, EDR values in all age/sex groups in 1996-2015 are consistently lower than their counterparts in 1983-1995. Excess mortality is lower in all white patients than in all non-white patients. Median survival and 5-year SR are lower in non-whites but significantly higher than in the 1983-95 cohort.

Table 4 shows results for the 1983-1995 cohort by Ann Arbor Stage for age groups <65 and 65 up, grade & both sexes combined. Excess mortality (EDR) increases from the local to the regional to the distant stage and is substantially higher in patients aged 65 and up.

Table 4. 1983-1995 Entrants, Age, Stage; Indolent/Aggressive Grades* & Sex Combined SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6) Index Code 37a: NHL-NODAL

Duration	No. Alive	Exposure	Number of Deaths		Mortality	Mean Ann. Mortality Rate/1,000			Cumul. Surv. Rate		Cum. Surv.
Start-End	at Start	Pt.-Yrs	Observed	Expected	Ratio (%)	Observed	Expected	Excess	Observed	Expected	Ratio (%)
t to t+ch t	***l***	**E**	**d**	**d'**	**100d/d'**	**q**	**q'**	**(q-q')**	**P**	**P'**	**100P/P'**
					Stage I (Local), Age <65						
0-1	1,209	1,208.5	139	7.86	1,770	0.1150	0.0065	108.5	0.8850	0.9935	89.1
1-2	1,069	1,068.5	103	7.37	1,397	0.0964	0.0069	89.5	0.7997	0.9866	81.1
2-5	965	2,776.0	102	21.53	474	0.0367	0.0078	29.0	0.7150	0.9638	74.2
5-10	861	4,009.0	125	38.58	324	0.0312	0.0096	21.6	0.6109	0.9182	66.5
10-15	732	3,463.5	105	43.45	242	0.0303	0.0125	17.8	0.5233	0.8619	60.7
15-20	626	2,948.5	88	47.08	187	0.0298	0.0160	13.9	0.4494	0.7950	56.5
	Median survival time (interval = 12 months): Observed = 16.8437 intervals; Relative is greater than 20 intervals.										
					Stage I (Local), Age 65 up						
0-1	1,223	1,222.5	349	65.89	530	0.2855	0.0539	231.6	0.7145	0.9461	75.5
1-2	873	873.0	139	42.78	325	0.1592	0.0490	110.2	0.6008	0.8997	66.8
2-5	734	1,966.0	223	103.09	216	0.1134	0.0524	61.0	0.4182	0.7651	54.7
5-10	511	2,048.5	229	129.22	177	0.1118	0.0631	48.7	0.2305	0.5500	41.9
10-15	281	1,100.5	133	92.84	143	0.1209	0.0844	36.5	0.1210	0.3518	34.4
15-20	145	542.5	79	59.67	132	0.1456	0.1100	35.6	0.0544	0.1942	28.0
	Median survival time (interval = 12 months): Observed = 3.57286 intervals; Relative = 6.57939 intervals.										
					Stage II (Regional), Age <65						
0-1	873	872.0	171	5.49	3,113	0.1961	0.0063	189.8	0.8039	0.9937	80.9
1-2	700	700.0	86	4.55	1,890	0.1229	0.0065	116.4	0.7051	0.9872	71.4
2-5	614	1,741.0	86	12.51	687	0.0494	0.0072	42.2	0.6063	0.9661	62.8
5-10	526	2,425.5	88	20.99	419	0.0363	0.0087	27.6	0.5046	0.9249	54.6
10-15	437	2,051.0	57	22.77	250	0.0278	0.0111	16.7	0.4385	0.8745	50.1
15-20	376	1,744.5	50	25.04	200	0.0287	0.0144	14.3	0.3796	0.8133	46.7
	Median survival time (interval = 12 months): Observed = 10.3136 intervals; Relative = 15.1189 intervals.										
					Stage II (Regional), Age 65 up						
0-1	897	897.0	342	48.08	711	0.3813	0.0536	327.7	0.6187	0.9464	65.4
1-2	555	554.5	113	26.56	425	0.2038	0.0479	155.9	0.4926	0.9011	54.7
2-5	441	1,166.5	139	61.03	228	0.1192	0.0523	66.8	0.3371	0.7664	44.0
5-10	301	1,158.0	153	71.19	215	0.1321	0.0615	70.7	0.1658	0.5558	29.8
10-15	148	592.0	76	48.70	156	0.1284	0.0823	46.1	0.0806	0.3595	22.4
15-20	72	261.0	42	26.76	157	0.1609	0.1025	58.4	0.0336	0.2072	16.2
	Median survival time (interval = 12 months): Observed = 1.94163 intervals; Relative = 3.03659 intervals.										
					Stage III & IV (Distant), Age <65						
0-1	3,042	3,038.0	1,004	22.48	4,466	0.3305	0.0074	323.1	0.6695	0.9926	67.4
1-2	2,030	2,030.0	324	16.04	2,020	0.1596	0.0079	151.7	0.5626	0.9848	57.1
2-5	1,706	4,640.5	378	40.11	942	0.0815	0.0086	72.8	0.4378	0.9594	45.6
5-10	1,323	5,819.5	347	59.93	579	0.0596	0.0103	49.3	0.3226	0.9107	35.4
10-15	969	4,430.5	187	58.24	321	0.0422	0.0131	29.1	0.2603	0.8522	30.5
15-20	781	3,593.5	136	59.97	227	0.0378	0.0167	21.2	0.2149	0.7831	27.4
	Median survival time (interval = 12 months): Observed = 3.11748 intervals; Relative = 3.46655 intervals.										
					Stage III & IV (Distant), Age 65 up						
0-1	3,431	3,431.0	1,680	182.19	922	0.4897	0.0531	436.6	0.5103	0.9469	53.9
1-2	1,751	1,750.5	474	88.23	537	0.2708	0.0504	220.4	0.3721	0.8992	41.4
2-5	1,276	3,221.0	498	173.72	287	0.1546	0.0539	100.7	0.2269	0.7607	29.8
5-10	778	2,926.5	440	194.62	226	0.1504	0.0665	83.8	0.0984	0.5363	18.4
10-15	337	1,234.0	210	104.78	200	0.1702	0.0849	85.3	0.0371	0.3410	10.9
15-20	127	470.0	73	50.23	145	0.1553	0.1069	48.4	0.0156	0.1915	8.1
	Median survival time (interval = 12 months): Observed = 1.07487 intervals; Relative = 1.31127 intervals.										
					Stage Unknown, All Ages						
0-1	899	898.5	237	31.63	749	0.2638	0.0352	228.6	0.7362	0.9648	76.3
1-2	661	660.0	117	19.60	597	0.1773	0.0297	147.6	0.6057	0.9361	64.7
2-5	542	1,460.0	131	40.02	327	0.0897	0.0274	62.3	0.4589	0.8614	53.3
5-10	409	1,717.0	143	49.44	289	0.0833	0.0288	54.5	0.2979	0.7444	40.0
10-15	264	1,170.5	70	34.07	205	0.0598	0.0291	30.7	0.2186	0.6422	34.0
15-20	193	863.5	46	24.99	184	0.0533	0.0289	24.3	0.1651	0.5545	29.8
	Median survival time (interval = 12 months): Observed = 3.8053 intervals; Relative = 6.00452 intervals.										

* All Ann Arbor Stages I-IV plus Unknown; (Ann Arbor Stage 1983-2015) Limited-Stages I&II combined; Advanced Stages III&IV combined

** Grades: **Indolent Morpho/Histology-ICD-O-3; 9690, 9699 Aggressive Morpho/Histology-ICD-O-3; 9670, 9680, 9702

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

With over 61% of the staged cases of NHL-N classified as distant (Stages III & IV combined), EDR in the patients under 65 ranged from 323 in the first year to 21 per 1000 per year after 15 years. First year excess mortality was even higher in the patients 65 years and older, with an EDR of 437 and an MR of 922%, extremely high for these older patients.

Table 5 shows results for the 1996-2015 cohort by Ann Arbor Stage, EDRs were consistently lower than they were in the corresponding stage/age/duration counterparts in the 1983-1995 cohort. The same trends prevailed by stage, by age, and by duration to 15-20 years. For all ages and stages, 5-year survival ratios (SR), median observed and relative survival were significantly higher, and mortality ratios lower than the earlier cohort.

Table 6 contains results for durations 0-5 and 5-10 years, all male ages combined, by combination of Ann Arbor stage with other factors, such as cell grade/bio-behavioral morphology-indolent vs aggressive for each cohort, and by T cell and B cell morphology in the 1996-2015 cohort. For each combination, data for the 1983-95 and 1996-2015 cohorts are also contrasted. In the local and regional stages, (Ann Arbor Stages I and II, respectively), morphology/histology bio-behavioral severity determinants, *indolent* ICD-O-3 9690, 9699 combined & *aggressive* ICD-O-3 9670, 9680, 9702 combined are seen to be effective prognostic risk predictors: EDR and MR values are higher when tumor cells are bio-behaviorally classified aggressive instead of indolent. In the 1996-2015 cohort, all stages known and unknown combined, at both 5-years and 10-years duration, T-cell cases had a higher EDR but lower MR than the earlier cohort but made up only approximately 5% of the cases. The overall results of Table 5 confirm the results in Tables 1-4, showing a consistent reduction in mortality and improvement in survival, by stage from the earlier to the later cohort. Comparative mortality and survival are also shown in Table 5 for the unstaged cases, and for all cases staged and unknown stages combined. For 6528 NHL cases in 1983-95 cohort, all stages known & unknown and all cell bio-morphology grades combined, the 5-year overall EDR was 166 per 1000 per year; in 1996-2015 16,752 cases were diagnosed, and the EDR was at 98. Although the decrease in EDR is small it is statistically significant at the 95% level because of the very large numbers of deaths involved. In the 1996-2015 cohort the overall EDR for T-cell cases was 206, and for B-cell cases, 116.

Results for duration 5-10 years, 1996-2015, by stage, bio-behavioral grade and cohort. *Stage I (local stage)* indolent grade cases; EDR was 8 per 1000 with 50 deaths (14%) in 352 entrants; aggressive grade, EDR 18 per 1000 with 250 deaths in 1343 entrants (19%); *Stage II (regional stage)* indolent grade, EDR 19 per 1000 in 180 entrants with 32 deaths (18%); aggressive grade, EDR 19 per 1000 in 1,063 entrants with 180 deaths (17%); also, an EDR of 31 and 38 per 1000 respectively for indolent and aggressive cases in stages III and IV combined (advanced stage). Indolent and aggressive cases combined in the unknown stage category (1996-2015) had an EDR of 21 per 1000, and for all known and unknown stages and for all morphology/histology bio-behavioral categories (IATB) combined, an EDR of 28 per 1000. In each of these categories, (T-cell excepted with only 198 cases and 16 deaths), EDR was lower in 1996-2015 than in the 1983-95 cohort.

Table 7 displays comparative mortality and survival for all female cases at duration 0-5 and 5-10 years and is identical in format to Table 5 for males. For females as for males, the same differences in EDR are observed: EDR increases by stage and is higher in aggressive bio-behavioral grade cases in the 1983-1995 time-period than in the 1996-2015 cohort, and in T-cell than in B-cell cases in local and regional stages, as well as T-cells in the 1996-2015 cohort. As was evident in Tables 2-5, excess mortality is consistently lower than in male NHL cases. In the 1983-1995 time-period, overall EDR for all stages known and unknown was 155 per 1000 per year, lower

Table 5. 1996-2015 Entrants, Age, Stage; Indolent/Aggressive Grades* & Sex Combined SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6) Index Code 37a: NHL-NODAL

Duration	No. Alive	Exposure	Number of Deaths		Mortality	Mean Ann. Mortality Rate/1,000			Cumul. Surv. Rate		Cum. Surv.
Start-End	at Start	Pt.-Yrs	Observed	Expected	Ratio (%)	Observed	Expected	Excess	Observed	Expected	Ratio (%)
t to t+ch t	***l***	**E**	**d**	**d'**	**100d/d'**	**q**	**q'**	**(q-q')**	**P**	**P'**	**100P/P'**
					Stage I (Local), Age <65						
0-1	2,915	2,900.0	154	15.66	983	0.0531	0.0054	47.7	0.9469	0.9946	95.2
1-2	2,731	2,673.0	110	15.50	710	0.0412	0.0058	35.4	0.9079	0.9888	91.8
2-5	2,505	6,829.0	144	44.47	324	0.0211	0.0065	14.6	0.8519	0.9696	87.9
5-10	2,009	8,224.5	145	67.67	214	0.0176	0.0082	9.4	0.7784	0.9299	83.7
10-15	1,231	4,428.0	82	48.22	170	0.0185	0.0109	7.6	0.7069	0.8793	80.4
15-20	513	1,357.0	27	19.51	138	0.0199	0.0144	5.5	0.6397	0.8155	78.4
	Median survival time (interval = 12 months): Observed is greater than 20 intervals; Relative is > than 20 intervals.										
					Stage I (Local), Age 65 up						
0-1	2,847	2,841.5	604	146.62	412	0.2126	0.0516	161.0	0.7874	0.9484	83.0
1-2	2,232	2,187.5	218	109.81	199	0.0997	0.0502	49.5	0.7089	0.9008	78.7
2-5	1,925	4,955.5	395	272.75	145	0.0797	0.0550	24.7	0.5520	0.7594	72.7
5-10	1,273	4,587.0	443	313.10	141	0.0966	0.0683	28.3	0.3303	0.5297	62.4
10-15	540	1,676.0	188	150.01	125	0.1122	0.0895	22.7	0.1792	0.3266	54.9
15-20	138	276.5	42	30.88	136	0.1519	0.1117	40.2	0.0791	0.1718	46.0
	Median survival time (interval = 12 months): Observed = 5.9192 intervals; Relative = 16.7734 intervals.										
					Stage II (Regional), Age <65						
0-1	2,557	2,546.5	242	13.75	1,760	0.0950	0.0054	89.6	0.9050	0.9946	91.0
1-2	2,294	2,224.5	164	12.68	1,293	0.0737	0.0057	68.0	0.8383	0.9889	84.8
2-5	1,991	5,286.0	124	34.05	364	0.0235	0.0064	17.0	0.7820	0.9699	80.6
5-10	1,507	5,971.5	105	48.89	215	0.0176	0.0082	9.4	0.7162	0.9303	77.0
10-15	855	2,908.5	72	31.17	231	0.0248	0.0107	14.0	0.6363	0.8804	72.3
15-20	328	830.0	19	11.77	161	0.0229	0.0142	8.7	0.5642	0.8181	69.0
	Median survival time (interval = 12 months): Observed is greater than 20 intervals; Relative is >r than 20 intervals.										
					Stage II (Regional), Age 65 up						
0-1	2,550	2,545.0	782	132.09	592	0.3073	0.0519	255.4	0.6927	0.9481	73.1
1-2	1,758	1,704.0	211	80.09	263	0.1238	0.0470	76.8	0.6069	0.9035	67.2
2-5	1,439	3,654.0	293	188.72	155	0.0802	0.0516	28.5	0.4722	0.7700	61.3
5-10	930	3,168.5	302	201.76	150	0.0953	0.0637	31.6	0.2812	0.5493	51.2
10-15	327	928.0	109	78.06	140	0.1175	0.0841	33.3	0.1357	0.3493	38.8
15-20	56	132.0	16	14.13	113	0.1212	0.1070	14.2	0.0616	0.1845	33.4
	Median survival time (interval = 12 months): Observed = 4.37649 intervals; Relative = 11.6238 intervals.										
					Stage III & IV (Distant), Age <65						
0-1	8,789	8,764.0	1,658	55.21	3,003	0.1892	0.0063	182.9	0.8108	0.9937	81.6
1-2	7,081	6,899.0	652	45.53	1,432	0.0945	0.0066	87.9	0.7342	0.9871	74.4
2-5	6,065	15,880.0	679	117.05	580	0.0428	0.0074	35.4	0.6452	0.9654	66.8
5-10	4,406	16,780.0	576	154.61	373	0.0343	0.0092	25.1	0.5426	0.9210	58.9
10-15	2,234	7,239.5	245	87.01	282	0.0338	0.0120	21.8	0.4597	0.8659	53.1
15-20	738	1,833.5	68	28.93	235	0.0371	0.0158	21.3	0.3850	0.7968	48.3
	Median survival time (interval = 12 months): Observed = 12.2143 intervals; Relative = 17.5156 intervals.										
					Stage III & IV (Distant), Age 65 up						
0-1	9,508	9,490.5	3,540	449.85	787	0.3730	0.0474	325.6	0.6270	0.9526	65.8
1-2	5,933	5,772.0	886	255.70	347	0.1535	0.0443	109.2	0.5308	0.9104	58.3
2-5	4,725	11,677.0	1,183	570.33	207	0.1013	0.0488	52.5	0.3858	0.7827	49.3
5-10	2,808	9,462.0	1,036	563.87	184	0.1095	0.0596	49.9	0.2125	0.5713	37.2
10-15	912	2,588.0	319	203.05	157	0.1233	0.0785	44.8	0.1081	0.3728	29.0
15-20	187	372.0	67	39.59	169	0.1801	0.1064	73.7	0.0450	0.2010	22.4
	Median survival time (interval = 12 months): Observed = 2.54544 intervals; Relative = 4.72639 intervals.										
					Stage Unknown, All Ages						
0-1	1,240	1,235.5	322	48.06	670	0.2606	0.0389	221.7	0.7394	0.9611	76.9
1-2	909	885.5	79	25.59	309	0.0892	0.0289	60.3	0.6734	0.9333	72.2
2-5	783	2,038.0	127	59.52	213	0.0623	0.0292	33.1	0.5563	0.8538	65.2
5-10	548	1,913.0	114	63.59	179	0.0596	0.0332	26.4	0.4140	0.7202	57.5
10-15	240	817.5	58	29.67	195	0.0709	0.0363	34.7	0.2860	0.5989	47.7
15-20	81	206.5	13	6.76	192	0.0630	0.0327	30.2	0.1789	0.5070	35.3
	Median survival time (interval = 12 months): Observed = 6.53624 intervals; Relative = 13.6991 intervals.										

* All Ann Arbor Stages I-IV plus Unknown; (Ann Arbor Stage 1983-2015)

** Indolent Morpho/Histology-ICD-O-3; 9690, 9699 Aggressive Morpho/Histology-ICD-O-3; 9670, 9680, 9702

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

Table 6. Male, Cohort, Stage, Grade-Cell Morph/Hist*, Durations 0-5 & 5-10 Years; All Ages Combined SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6). Index Code IC37a: NHL-NODAL

			No. Alive	Exposure	Number of Deaths		Mortality	Excess	Cumul. Surv. Rate		Cum. Surv.
			at Start	Pt.-Yrs	Observed	Expected	Ratio	Death Rate	Observed	Expected	Ratio (%)
STAGE **Ann Arbor Classification**	**GRADE** **Morphology/ Histology**	**COHORT** **Time/ Period**	***l***	**E**	**d**	**d'**	**MR**	**EDR**	**P**	**P'**	**Cum SR**
					Durational interval 0-5 Years						
Stage I (Local)	Indolent	1983-1995	79	342.0	22	10.58	208	33.4	0.7216	0.8538	84.5
	Indolent	1996-2015	597	2,459.0	125	65.60	191	24.2	0.7717	0.8727	88.4
	Aggressive	1983-1995	1,219	4,536.5	536	124.82	429	90.6	0.5596	0.8710	64.2
	Aggressive	1996-2015	2,410	9,198.0	729	256.20	285	51.4	0.6835	0.8685	78.7
	B-cell	1996-2015	2,042	7,750.0	588	205.24	286	49.4	0.6977	0.8747	79.8
	T-cell	1996-2015	115	392.5	52	8.66	600	110.4	0.5383	0.8966	60.0
Stage II (Regional)	Indolent	1983-1995	26	112.0	11	3.47	317	67.3	0.5769	0.8537	67.6
	Indolent	1996-2015	353	1,319.0	101	35.88	281	49.4	0.6941	0.8719	79.6
	Aggressive	1983-1995	835	2,768.5	446	78.13	571	132.9	0.4647	0.8690	53.5
	Aggressive	1996-2015	2,322	8,078.0	865	216.18	400	80.3	0.6075	0.8744	69.5
	B-cell	1996-2015	2,061	7,117.5	746	180.55	413	79.4	0.6182	0.8810	70.2
	T-cell	1996-2015	109	364.5	48	5.35	897	117.0	0.5450	0.9307	58.6
Stage III & IV (Distant)	Indolent	1983-1995	132	465.5	76	12.50	608	136.4	0.4210	0.8751	48.1
(Advanced)	Indolent	1996-2015	1,695	6,498.0	497	173.30	287	49.8	0.6837	0.8734	78.3
	Aggressive	1983-1995	3,442	9,376.5	2,384	292.62	815	223.0	0.3062	0.8570	35.7
	Aggressive	1996-2015	8,548	26,199.0	4,381	694.67	631	140.7	0.4687	0.8760	53.5
Stage Unknown	Indolent	1983-1995	37	142.0	15	4.34	346	75.1	0.5815	0.8596	67.6
	Indolent	1996-2015	133	534.0	30	15.72	191	26.7	0.7594	0.8615	88.1
	Aggressive	1983-1995	440	1,423.5	254	43.87	579	147.6	0.4219	0.8600	49.1
	Aggressive	1996-2015	492	1,567.0	243	49.13	495	123.7	0.4879	0.8577	56.9
	Indol & Aggress.	1983-1995	477	1,565.5	269	48.21	558	141.0	0.4343	0.8599	50.5
	Indol & Aggress.	1996-2015	625	2,101.0	273	64.77	422	99.1	0.5454	0.8586	63.5
All Stages K&U	I,A,T,B	1983-1995	6,528	20,185.5	3,918	575.81	680	165.6	0.3987	0.8682	45.9
	I,A,T,B	1996-2015	16,752	56,602.5	7,049	1,510.10	467	97.9	0.5608	0.8745	64.1
	B-cell	1983-1995	4,317	12,249.0	2,769	335.81	825	198.6	0.3578	0.8750	40.9
	B-cell	1996-2015	11,060	35,120.5	4,966	899.43	552	115.8	0.5321	0.8804	60.4
	T-cell	1983-1995	481	1,493.5	280	16.21	1,727	176.6	0.4166	0.9502	43.8
	T-cell	1996-2015	880	2,379.5	535	45.46	1,177	205.7	0.3758	0.9109	41.3
					Durational interval 5-10 Years						
Stage I (Local)	Indolent	1983-1995	57	235.0	18	7.61	237	44.2	0.4937	0.7242	68.2
	Indolent	1996-2015	352	1,303.0	50	39.71	126	7.9	0.6355	0.7468	85.1
	Aggressive	1983-1995	680	3,029.5	159	81.38	195	25.6	0.4285	0.7600	56.4
	Aggressive	1996-2015	1,343	5,225.5	250	156.18	160	18.0	0.5359	0.7457	71.9
	B-cell	1996-2015	1,132	4,412.0	187	124.04	151	14.3	0.5618	0.7580	74.1
	T-cell	1996-2015	48	196.5	5	5.36	93	-1.8	0.4730	0.7788	60.7
Stage II (Regional)	Indolent	1983-1995	15	63.0	6	2.05	293	62.7	0.3462	0.7235	47.8
	Indolent	1996-2015	180	660.0	32	19.55	164	18.9	0.5263	0.7480	70.4
	Aggressive	1983-1995	384	1,679.5	109	46.01	237	37.5	0.3325	0.7563	44.0
	Aggressive	1996-2015	1,063	3,939.0	180	104.76	172	19.1	0.4838	0.7638	63.3
	B-cell	1996-2015	932	3,463.5	137	86.12	159	14.7	0.5078	0.7765	65.4
	T-cell	1996-2015	48	181.0	7	2.18	321	26.6	0.4482	0.8768	51.1
Stage III & IV (Distant)	Indolent	1983-1995	55	224.0	23	4.95	465	80.6	0.2450	0.7834	31.3
(Advanced)	Indolent	1996-2015	880	3,103.5	184	89.35	206	30.5	0.5032	0.7542	66.7
	Aggressive	1983-1995	1,049	4,349.5	379	129.84	292	57.3	0.1952	0.7364	26.5
	Aggressive	1996-2015	3,141	11,443.5	758	318.75	238	38.4	0.3321	0.7600	43.7
Stage Unknown	Indolent	1983-1995	20	83.0	9	2.75	327	75.3	0.3198	0.7242	44.2
	Indolent	1996-2015	75	254.0	14	8.84	158	20.3	0.5698	0.7214	79.0
	Aggressive	1983-1995	185	764.5	64	19.98	320	57.6	0.2756	0.7539	36.6
	Aggressive	1996-2015	197	721.5	37	21.63	171	21.3	0.3771	0.7359	51.2
	Indol & Aggress.	1983-1995	205	847.5	73	22.73	321	59.3	0.2793	0.7509	37.2
	Indol & Aggress.	1996-2015	272	975.5	51	30.49	167	21.0	0.4187	0.7320	57.2
All Stages K&U	I,A,T,B	1983-1995	2,587	11,110.0	775	297.31	261	43.0	0.2790	0.7580	36.8
	I,A,T,B	1996-2015	7,346	27,158.0	1,511	760.66	199	27.6	0.4215	0.7582	55.6
	B-cell	1983-1995	1,536	6,857.0	352	170.85	206	26.4	0.2756	0.7712	35.7
	B-cell	1996-2015	4,375	16,237.5	729	422.18	173	18.9	0.4230	0.7712	54.8
	T-cell	1983-1995	198	945.0	16	7.48	214	9.0	0.3829	0.9132	41.9
	T-cell	1996-2015	256	983.0	35	17.91	195	17.4	0.3143	0.8309	37.8

* Grade = cell morph/hist Indolent ICD-O-3; 9690, 9699. Aggressive ICD-O-3; 9670, 9680, 9702 I,A,T,B: Indolent, Aggressive, T-Cell, B-Cell B-cell: ICD-O-3; 9680, 9728. T-cell: ICD-O-3; 9702, 9727 I,A,T,B: 9670, 9680, 9690, 9699, 9702, 9727-9728

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

Table 7. Female, Cohort, Stage, Grade-Cell Morph/Hist*, Durations 0-5 & 5-10 Years; All Ages Combined SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6). Index Code IC37a: NHL-NODAL

			No. Alive	Exposure	Number of Deaths		Mortality	Excess	Cumul. Surv. Rate		Cum. Surv.
			at Start	Pt.-Yrs	Observed	Expected	Ratio	Death Rate	Observed	Expected	Ratio (%)
STAGE **Ann Arbor Classification**	**GRADE** **Morphology/ Histology**	**COHORT** **Time/ Period**	***l***	**E**	**d**	**d'**	**MR**	**EDR**	**P**	**P'**	**Cum SR**
					Durational interval 0-5 Years						
Stage I (Local)	Indolent	1983-1995	80	344.0	25	8.99	278	46.5	0.6876	0.8768	78.4
	Indolent	1996-2015	668	2,803.5	110	67.30	163	15.2	0.8193	0.8850	92.6
	Aggressive	1983-1995	1,054	3,892.0	472	104.14	453	94.5	0.5519	0.8746	63.1
	Aggressive	1996-2015	2,087	7,926.0	661	215.43	307	56.2	0.6702	0.8718	76.9
	B-cell	1996-2015	1,798	6,726.5	567	177.50	319	57.9	0.6705	0.8758	76.6
	T-cell	1996-2015	74	263.5	33	5.72	577	103.5	0.5408	0.8952	60.4
Stage II (Regional)	Indolent	1983-1995	28	111.0	12	1.30	922	96.4	0.5714	0.9435	60.6
	Indolent	1996-2015	388	1,522.5	88	35.50	248	34.5	0.7593	0.8888	85.4
	Aggressive	1983-1995	881	2,939.5	468	75.25	622	133.6	0.4683	0.8804	53.2
	Aggressive	1996-2015	2,044	7,040.5	762	173.46	439	83.6	0.6121	0.8841	69.2
	B-cell	1996-2015	1,836	6,243.5	685	148.73	461	85.9	0.6106	0.8880	68.8
	T-cell	1996-2015	70	226.0	34	5.03	676	128.2	0.5058	0.8943	56.6
Stage III & IV (Distant)	Indolent	1983-1995	122	483.0	54	11.85	456	87.3	0.5574	0.8813	63.2
(Advanced)	Indolent	1996-2015	1,688	6,480.0	474	157.88	300	48.8	0.6930	0.8834	78.4
	Aggressive	1983-1995	2,777	7,786.0	1,844	205.62	897	210.4	0.3355	0.8776	38.2
	Aggressive	1996-2015	6,366	19,305.5	3,246	468.74	692	143.9	0.4723	0.8863	53.3
Stage Unknown	Indolent	1983-1995	38	153.0	16	3.10	515	84.3	0.5789	0.9042	64.0
	Indolent	1996-2015	184	728.0	40	23.28	172	23.0	0.7654	0.8495	90.1
	Aggressive	1983-1995	384	1,300.0	200	39.97	500	123.1	0.4777	0.8580	55.7
	Aggressive	1996-2015	431	1,330.0	215	45.03	477	127.8	0.4838	0.8505	56.9
	Indol & Aggress.	1983-1995	422	1,453.0	216	43.07	501	119.0	0.4869	0.8629	56.4
	Indol & Aggress.	1996-2015	615	2,058.0	255	68.31	373	90.7	0.5675	0.8492	66.8
All Stages K&U	I,A,T,B	1983-1995	5,494	17,430.5	3,163	453.72	697	155.4	0.4238	0.8786	48.2
	I,A,T,B	1996-2015	13,970	47,567.0	5,635	1,189.20	474	93.5	0.5792	0.8821	65.7
	B-cell	1983-1995	3,764	10,975.5	2,331	272.11	857	187.6	0.3803	0.8862	42.9
	B-cell	1996-2015	9,116	28,777.5	4,120	704.89	584	118.7	0.5306	0.8859	59.9
	T-cell	1983-1995	247	768.5	143	9.66	1,480	173.5	0.4191	0.9424	44.5
	T-cell	1996-2015	546	1,486.0	324	27.43	1,181	199.6	0.3946	0.9148	43.1
					Durational interval 5-10 Years						
Stage I (Local)	Indolent	1983-1995	55	240.0	22	7.66	287	59.7	0.4126	0.7437	55.5
	Indolent	1996-2015	429	1,626.0	67	45.54	147	13.2	0.6584	0.7666	85.9
	Aggressive	1983-1995	580	2,553.0	155	71.20	218	32.8	0.4038	0.7590	53.2
	Aggressive	1996-2015	1,158	4,657.0	221	138.16	160	17.8	0.5247	0.7495	70.0
	B-cell	1996-2015	970	3,882.0	164	109.22	150	14.1	0.5392	0.7591	71.0
	T-cell	1996-2015	34	137.0	6	3.62	166	17.4	0.4364	0.7825	55.8
Stage II (Regional)	Indolent	1983-1995	16	68.0	6	0.71	844	77.8	0.3571	0.8952	39.9
	Indolent	1996-2015	223	840.5	39	22.62	172	19.5	0.5883	0.7750	75.9
	Aggressive	1983-1995	412	1,773.0	120	43.37	277	43.2	0.3319	0.7779	42.7
	Aggressive	1996-2015	971	3,700.5	156	103.86	150	14.1	0.4927	0.7661	64.3
	B-cell	1996-2015	844	3,236.0	115	87.75	131	8.4	0.5095	0.7736	65.9
	T-cell	1996-2015	32	98.5	9	2.32	387	67.8	0.3042	0.7941	38.3
Stage III & IV (Distant)	Indolent	1983-1995	68	271.5	36	7.71	467	104.2	0.2591	0.7636	33.9
(Advanced)	Indolent	1996-2015	868	2,996.0	172	81.95	210	30.1	0.5200	0.7679	67.7
	Aggressive	1983-1995	929	3,901.0	349	111.99	312	60.8	0.2093	0.7584	27.6
	Aggressive	1996-2015	2,325	8,699.0	498	228.10	218	31.0	0.3514	0.7754	45.3
Stage Unknown	Indolent	1983-1995	22	99.0	6	1.56	385	44.9	0.4210	0.8355	50.4
	Indolent	1996-2015	110	356.5	24	14.30	168	27.2	0.5727	0.6902	83.0
	Aggressive	1983-1995	182	770.5	64	25.15	254	50.4	0.3089	0.7266	42.5
	Aggressive	1996-2015	166	581.0	39	18.85	207	34.7	0.3409	0.7205	47.3
	Indol & Aggress.	1983-1995	204	869.5	70	26.72	262	49.8	0.3191	0.7381	43.2
	Indol & Aggress.	1996-2015	276	937.5	63	33.15	190	31.8	0.4090	0.7080	57.8
All Stages K&U	I,A,T,B	1983-1995	2,322	9,952.0	763	270.78	282	49.5	0.2842	0.7652	37.1
	I,A,T,B	1996-2015	6,321	23,756.0	1,218	654.73	186	23.7	0.4449	0.7663	58.1
	B-cell	1983-1995	1,426	6,247.0	380	155.51	244	35.9	0.2787	0.7811	35.7
	B-cell	1996-2015	3,617	13,669.0	604	360.07	168	17.8	0.4228	0.7746	54.6
	T-cell	1983-1995	103	477.0	20	5.03	397	31.4	0.3378	0.8939	37.8
	T-cell	1996-2015	176	637.5	36	10.77	334	39.6	0.2981	0.8410	35.4

* Grade = cell morph/hist Indolent ICD-O-3; 9690, 9699. Aggressive ICD-O-3; 9670, 9680, 9702 I,A,T,B: Indolent, Aggressive, T-Cell, B-Cell B-cell: ICD-O-3; 9680, 9728. T-cell: ICD-O-3; 9702, 9727 I,A,T,B: 9670, 9680, 9690, 9699, 9702, 9727-9728

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

than the EDR of 166 in males. In females in 1996-2015 the EDR (94 per 1000) had also fallen to a level lower than the EDR of 98 in males. With very large numbers of deaths, all of these differences are significant at more than the 95% confidence level. In the 1996-2015 cohort the overall EDR (all stages known and unknown) for T-cell cases was 200, and 119 for B-cell cases. EDR in females at 5-10 years in 1996-2015, all stages known and unknown and cell bio-morphology grades IATB combined was 24, in B-cell cases 18, and in T-cell cases 40 (higher than the male counterpart T-cell EDR of 17 per 1000).

Table 8 shows NHL-Nodal 20-year mortality and survival results by Ann Arbor Stage distribution, 1996-2015, all ages, grades, and both sexes combined. In the SEER survival database, there were a total of 56,154 staged patient-cases of Nodal-NHL with 19,818 (35.3%) limited stage, and 36,336 (64.7%) advanced stage cases. Excess mortality increased in magnitude with stage progression, and observed, relative and median survival diminished with advancing stages I to IV.

Limited Stage: In 19,818 (35.%) limited stage patient-cases (Ann Arbor Stages I & II combined), there were 2806 deaths (15%) in the 1st duration, MR 528%, and EDR ranged from 115 to 13 per 1000 per year after 15 years duration with 5-year observed & relative survival 69% & 79% respectively; median observed and relative survival ranged from 12 to >20 years.

Advanced Stage: In 36,336 patient-cases (Ann Arbor Stages III & IV combined), there were 9001 deaths (25%) in the 1st interval, MR 948%, and EDR ranged from 222 to18 per 1000 per year after 15 years with 5-year observed and relative survival 55% and 62%, respectively; median observed and relative survival ranged from 6 to 11 years. Overall excess mortality for Nodal NHL, all stages known & unknown, is very high because regional and distant stages (advanced stage) predominate, and many cases of unknown stage (2,832) have high mortality persisting beyond 15 years of FU duration. In general, mortality was approximately twice the magnitude in advanced stage relative to limited stage NHL-Nodal disease.

Unknown Stage: Mortality is intermediate when the stage is unknown (not reported).

Table 9*:* Utilizing 14 selected cell subtypes, both indolent and aggressive grades, Table 9 shows a side-by-side comparative mortality and survival analysis for both NHL-N & EN subdivisions by bio-behavioral ICD-O-3 histology code at 0-5 and 5-10-years duration, all ages and both sexes combined. This kind of typing was generally not done in the earlier cohort, so results are only for the 1996-2016 cohort. It will be seen that most of the cell subtypes are small in number especially in the extranodal subdivision.

NHL-N Indolent grades in Table 9 totaled 17,786 patient-cases including rare cell types consisting of 251 patient-cases (1.4%). The lowest subtype groups were ICD-O-3 9679 (Mediastinal large B-cell lymphoma) with 63 cases (0.4%) and ICD-O-3 9729 (Precursor T-cell lymphoblastic lymphoma, NOS) with 188 cases (1.1%). Comprehensive annualized EDRs, MRs, and SRs as well as median observed and relative survival data are shown for each of the cell categories. In indolent cases, EDR per 1000 per year at 0-5 years ranged from a minimum of 17 per 1000 per year in mediastinal large B-cell lymphomas to a maximum of 96 in precursor T-cell lymphoblastic lymphoma, NOS cases. Median observed and relative survival ranged from approximately 11 to >20 years in marginal zone B-cell lymphoma, NOS cases to approximately 16 to >20 years in grades 1 & 2 follicular lymphoma cases.

NHL-N Aggressive grades totaled 31,598 patient cases. The overall number of selected indolent & aggressive cell types for the NHL-Nodal subdivision totaled 49,384 patient cases, more than twice the number of equivalent selected cell type cases present in the NHL-Extranodal subdivision.

Table 8. NHL-NODAL, 1996-2015, Ann Arbor Stages I-IV & Unknown;Sex & All Ages Combined SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6). Index Code IC37a: NHL-NODAL

Duration	No. Alive	Exposure	Number of Deaths		Mortality	Mean Ann. Mortality Rate/1,000			Cumul. Surv. Rate		Cum. Surv.
Start-End	at Start	Pt.-Yrs	Observed	Expected	Ratio (%)	Observed	Expected	Excess	Observed	Expected	Ratio (%)
t to t+ch t	***l***	**E**	**d**	**d'**	**100d/d'**	**q**	**q'**	**(q-q')**	**P**	**P'**	**100P/P'**
					Stage I (Local stage)						
0-1	11,056	11,016.0	1,256	296.33	424	0.1140	0.0269	87.1	0.8860	0.9731	91.0
1-2	9,720	9,496.0	584	236.45	247	0.0615	0.0249	36.6	0.8315	0.9489	87.6
2-5	8,688	23,058.0	1,018	599.82	170	0.0441	0.0260	18.1	0.7262	0.8766	82.8
5-10	6,426	25,107.5	1,103	715.62	154	0.0439	0.0285	15.4	0.5800	0.7580	76.5
10-15	3,536	12,540.0	541	393.27	138	0.0431	0.0314	11.8	0.4645	0.6459	71.9
15-20	1,467	3,791.5	179	124.65	144	0.0472	0.0329	14.3	0.3666	0.5480	66.9
	Median survival time (interval = 12 months): Observed = 13.4184 intervals; Relative is greater than 20 intervals.										
					Stage II (Regional stage)						
0-1	8,762	8,735.0	1,550	234.97	660	0.1774	0.0269	150.5	0.8226	0.9731	84.5
1-2	7,158	6,949.0	594	158.44	375	0.0855	0.0228	62.7	0.7523	0.9509	79.1
2-5	6,146	15,913.0	744	377.28	197	0.0468	0.0237	23.0	0.6522	0.8847	73.7
5-10	4,312	16,303.5	692	425.34	163	0.0424	0.0261	16.4	0.5246	0.7746	67.7
10-15	2,157	7,120.0	333	199.60	167	0.0468	0.0280	18.7	0.4115	0.6719	61.2
15-20	760	2,003.0	78	55.30	141	0.0389	0.0276	11.3	0.3325	0.5826	57.1
	Median survival time (interval = 12 months): Observed = 10.9519 intervals; Relative is greater than 20 intervals.										
					Stages I&II, (Limited stage)						
0-1	19,818	19,751.0	2,806	531.30	528	0.1421	0.0269	115.2	0.8579	0.9731	88.2
1-2	16,878	16,445.0	1,178	394.68	298	0.0716	0.0240	47.6	0.7965	0.9497	83.9
2-5	14,834	38,971.0	1,762	977.26	180	0.0452	0.0251	20.1	0.6934	0.8799	78.8
5-10	10,738	41,411.0	1,795	1,141.08	157	0.0433	0.0276	15.8	0.5554	0.7646	72.6
10-15	5,693	19,660.0	874	592.16	148	0.0445	0.0301	14.3	0.4415	0.6558	67.3
15-20	2,227	5,794.5	257	179.84	143	0.0444	0.0310	13.3	0.3513	0.5607	62.7
	Median survival time (interval = 12 months): Observed = 12.3612 intervals; Relative is greater than 20 intervals.										
					Stage III (Distant stage III)						
0-1	12,076	12,041.5	2,379	309.47	769	0.1976	0.0257	171.9	0.8024	0.9743	82.4
1-2	9,628	9,291.0	916	209.98	436	0.0986	0.0226	76.0	0.7233	0.9523	76.0
2-5	8,038	20,192.5	1,246	470.28	265	0.0617	0.0233	38.4	0.5993	0.8872	67.5
5-10	5,231	18,668.0	1,014	465.20	218	0.0543	0.0249	29.4	0.4551	0.7815	58.2
10-15	2,301	7,292.5	351	192.82	182	0.0481	0.0264	21.7	0.3583	0.6828	52.5
15-20	739	1,972.0	79	52.54	150	0.0401	0.0266	13.4	0.2940	0.5949	49.4
	Median survival time (interval = 12 months): Observed = 8.20881 intervals; Relative = 17.9147 intervals.										
					Stage IV (Distant IV)						
0-1	24,260	24,207.5	6,622	641.50	1,032	0.2736	0.0265	247.1	0.7264	0.9735	74.6
1-2	17,533	17,063.0	1,905	395.86	481	0.1116	0.0232	88.4	0.6453	0.9509	67.9
2-5	14,688	37,473.0	2,580	916.00	282	0.0688	0.0244	44.4	0.5219	0.8827	59.1
5-10	9,742	35,414.5	2,180	931.41	234	0.0616	0.0263	35.3	0.3801	0.7720	49.2
10-15	4,343	14,284.0	756	401.89	188	0.0529	0.0281	24.8	0.2908	0.6690	43.5
15-20	1,489	3,759.0	185	110.10	168	0.0492	0.0293	19.9	0.2292	0.5768	39.7
	Median survival time (interval = 12 months): Observed = 5.68183 intervals; Relative = 9.57869 intervals.										
					Stages III&IV, (Advanced stage)						
0-1	36,336	36,249.0	9,001	949.72	948	0.2483	0.0262	222.1	0.7517	0.9738	77.2
1-2	27,161	26,354.0	2,821	606.14	465	0.1070	0.0230	84.0	0.6713	0.9514	70.6
2-5	22,726	57,665.5	3,826	1,384.81	276	0.0663	0.0240	42.3	0.5474	0.8844	61.9
5-10	14,973	54,082.5	3,194	1,395.78	229	0.0591	0.0258	33.2	0.4045	0.7754	52.2
10-15	6,644	21,576.5	1,107	594.27	186	0.0513	0.0275	23.8	0.3125	0.6739	46.4
15-20	2,228	5,731.0	264	162.77	162	0.0461	0.0284	17.7	0.2497	0.5830	42.8
	Median survival time (interval = 12 months): Observed = 6.44805 intervals; Relative = 11.4901 intervals.										
					Stage Unknown						
0-1	2,832	2,821.0	664	108.61	611	0.2354	0.0385	196.9	0.7646	0.9615	79.5
1-2	2,146	2,087.5	181	63.46	285	0.0867	0.0304	56.3	0.6983	0.9323	74.9
2-5	1,848	4,755.0	333	143.30	232	0.0700	0.0301	39.9	0.5629	0.8505	66.2
5-10	1,257	4,477.5	258	144.77	178	0.0576	0.0323	25.3	0.4226	0.7208	58.6
10-15	592	2,099.0	133	67.59	197	0.0634	0.0322	31.2	0.3059	0.6131	49.9
15-20	245	653.0	34	19.69	173	0.0521	0.0302	21.9	0.2346	0.5264	44.6
	Median survival time (interval = 12 months): Observed = 6.72652 intervals; Relative = 14.9508 intervals.										
					All Stages Known & Unknown						
0-1	58,986	58,821.0	12,471	1,594.05	782	0.2120	0.0271	184.9	0.7880	0.9729	81.0
1-2	46,185	44,886.5	4,180	1,063.81	393	0.0931	0.0237	69.4	0.7146	0.9498	75.2
2-5	39,408	101,391.5	5,921	2,505.97	236	0.0584	0.0247	33.7	0.5974	0.8810	67.8
5-10	26,968	99,971.0	5,247	2,680.43	196	0.0525	0.0268	25.7	0.4568	0.7685	59.4
10-15	12,929	43,335.5	2,114	1,255.23	168	0.0488	0.0290	19.8	0.3563	0.6631	53.7
15-20	4,700	12,178.5	555	362.21	153	0.0456	0.0297	15.8	0.2835	0.5702	49.7
	Median survival time (interval = 12 months): Observed = 8.27757 intervals; Relative = 19.4658 intervals.										

* All Ann Arbor Stages I-IV plus Unknown; (Ann Arbor Stage 1983-2015)

** Indolent Morpho/Histology-ICD-O-3; 9690, 9699 Aggressive Morpho/Histology-ICD-O-3; 9670, 9680, 9702

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

Table 9. 1996-2016 Entrants: NHL-N & EN Comparative Mortality & Survival by Bio-behavioral Grade & Duration; All Ages and Stages Combined SEER Cancer Data (SEER*Stat 8.3.6). Index Code 37: Non-Hodgkin's Lymphoma - Nodal and Extranodal

NHL-Nodal									BioBehavioral Grade	NHL-Extranodal								
No. Alive	Exposure	Number of Deaths		Mortality	Excess	Cumul. Surv. Rate		Cum. Surv.		No. Alive	Exposure	Number of Deaths		Mortality	Excess	Cumul. Surv. Rate		Cum. Surv.
at Start	Pt.-Yrs	Observed	Expected	Ratio (%)	Death Rate	Observed	Expected	Ratio (%)	ICD-O-3 Histo/Morph.	at Start	Pt.-Yrs	Observed	Expected	Ratio (%)	Death Rate	Observed	Expected	Ratio (%)
									Duration from Dx									
l	*E*	d	d'	100d/d'	EDR/M	P	P'	100P/P'	t to t+ch t	*l*	*E*	d	d'	100d/d'	EDR/M	P	P'	100P/P'
									Indolent Grade									
		Follicular lymphoma, NOS							ICD-O-3 9690			**Follicular lymphoma, NOS**						
3,679	13,845.0	908	327.16	278	42.0	0.7241	0.8871	81.6	0-5 years	1,034	3,955.0	178	104.17	171	18.7	0.8007	0.8743	91.6
1,945	7,046.0	327	185.92	176	20.0	0.5710	0.7750	73.7	5-10	570	2,035.5	88	59.30	148	14.1	0.6427	0.7531	85.3
		Median observed & relative survival time-yrs				*13.0 to >20*						*Median observed & relative survival time-yrs*				*15.7 to >20*		
		Follicular lymphoma, grade 2							ICD-O-3 9691			**Follicular lymphoma, grade 2**						
4,820	17,999.0	873	380.78	229	27.3	0.7828	0.8978	87.2	0-5 years	622	2,378.5	98	66.98	146	13.0	0.8067	0.8653	93.2
2,495	9,352.0	393	238.72	165	16.5	0.6320	0.7878	80.2	5-10	327	1,239.0	52	46.65	111	4.3	0.6450	0.7125	90.5
		Median observed & relative survival time-yrs				*15.4 to >20*						*Median observed & relative survival time-yrs*				*16.3 to >20*		
		Follicular lymphoma, grade 1							ICD-O-3 9695			**Follicular lymphoma, grade 1**						
4,179	17,457.0	824	347.51	237	27.3	0.7878	0.9040	87.1	0-5 years	627	2,812.5	84	78.11	108	2.1	0.8563	0.8681	98.6
2,735	10,790.0	465	246.11	189	20.3	0.6318	0.8048	78.5	5-10	464	1,837.5	78	61.03	128	9.2	0.6839	0.7316	93.5
		Median observed & relative survival time-yrs				*15.5 to >20*						*Median observed & relative survival time-yrs*				*16.3->20*		
		Follicular lymphoma, grade 3							ICD-O-3 9698			**Follicular lymphoma, grade 3**						
2,504	9,343.0	583	205.02	284	40.5	0.7377	0.8947	82.4	0-5 years	350	1,376.0	60	32.62	184	19.9	0.8087	0.8864	91.2
1,335	5,154.0	206	129.99	158	14.7	0.6031	0.7866	76.7	5-10	212	832.5	32	21.90	146	12.1	0.6663	0.7760	85.9
		Median observed & relative survival time-yrs				*13.8 to >20*						*Median observed & relative survival time-yrs*				*17.3 to >20*		
		Marginal zone B-cell, NOS							ICD-O-3 9699			**Marginal zone B-cell, NOS (MALT Lymphomas)**						
2,353	8,672.0	577	252.24	229	37.4	0.7166	0.8621	83.1	0-5 years	5,234	20,310.5	772	549.14	141	11.0	0.8254	0.8712	94.7
1,172	4,093.5	255	135.95	188	29.1	0.5182	0.7272	71.3	5-10	2,951	10,852.5	462	344.04	134	10.9	0.6632	0.7405	89.6
		Median observed & relative survival time-yrs				*10.6 to >20*						*Median observed & relative survival time-yrs*				*15.6 to >20*		
		Mediastinal large B-cell lymphoma							ICD-O-3 9679			**Mediastinal large B-cell lymphoma**						
63	255.5	5	0.66	758	17.0	0.9172	0.9873	92.9	0-5 years	241	715.0	30	2.60	1,152	38.3	0.8293	0.9818	84.5
39	146.0	0	0.51	0	-3.5	0.9172	0.9703	94.5	5-10	73	260.0	3	0.94	318	7.9	0.7668	0.9643	79.5
		The width of the confidence interval is >25% larger than if the normal approximation was applied.										*The width of the confidence interval is >25% larger than if the normal approximation was applied.*						
		Precursor T-cell lymphoblastic lymphoma, NOS							ICD-O-3 9729			**Precursor T-cell lymphoblastic lymphoma, NOS**						
188	706.5	70	2.04	3,433	96.2	0.6234	0.9867	63.2	0-5 years	9	35.0	3	0.11	2,765	82.6	0.6667	0.9867	67.6
115	491.0	3	1.26	238	3.5	0.6056	0.9738	62.2	5-10	6	24.0	1	0.01	7,092	41.1	0.5555	0.9840	56.5
		The width of the confidence interval is >25% larger than if the normal approximation was applied.										*The width of the confidence interval is >25% larger than if the normal approximation was applied.*						
									Aggressive Grade									
		Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia)							ICD-O-3 9671			**Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia)**						
861	3,248.5	295	108.93	271	57.3	0.6350	0.8430	75.3	0-5 years	564	1,824.5	120	66.62	180	29.3	0.7180	0.8283	86.7
459	1,688.5	134	59.21	226	44.3	0.4232	0.7043	60.1	5-10	195	631.5	42	22.67	185	30.6	0.5055	0.6900	73.3
		Median observed & relative survival time-yrs				*7.7 to 14.5*						*Median observed & relative survival time-yrs*				*10.8 to >20*		
		ML, Small B lymphocytic, NOS							ICD-O-3 9670			**ML, Small B lymphocytic, NOS**						
3,414	14,062.0	1,274	447.20	285	58.8	0.6260	0.8508	73.6	0-5 years	402	1,678.0	131	60.87	215	41.8	0.6737	0.8316	81.0
2,126	8,247.5	743	283.23	262	55.7	0.3908	0.7134	54.8	5-10	269	1,101.5	75	39.58	189	32.2	0.4752	0.6920	68.7
		Median observed & relative survival time-yrs				*7.3 to 11.7*						*Median observed & relative survival time-yrs*				*9.3 to >20*		
		Diffuse large B-cell, NOS (DLBCL)							ICD-O-3 9680			**Diffuse large B-cell, NOS (DLBCL)**						
21,272	64,406.0	9,281	1,623.50	572	118.9	0.5307	0.8825	60.1	0-5 years	11,478	35,290.5	4,950	1,046.23	473	110.6	0.5366	0.8619	62.3
7,965	29,794.0	1,332	782.20	170	18.5	0.4220	0.7721	54.7	5-10	4,427	16,287.5	866	510.02	170	21.9	0.4085	0.7345	55.6
		Median observed & relative survival time-yrs				*6.3 to 14.7*						*Median observed & relative survival time-yrs*				*6.3 to 15.5*		
		Burkitt lymphoma							ICD-O-3 9687			**Burkitt lymphoma**						
1,286	3,877.5	536	27.51	1,949	131.1	0.5686	0.9674	58.8	0-5 years	549	1,775.0	191	15.01	1,273	99.2	0.6331	0.9595	66.0
539	2,023.0	42	14.82	283	13.4	0.5160	0.9321	55.4	5-10	254	962.0	19	7.79	244	11.6	0.5662	0.9213	61.5
		Median observed & relative survival time-yrs				*11.7 to >29*						*The width of the confidence interval is >25% larger than if the normal approximation was applied.*						
		Mantle cell lymphoma							ICD-O-3 9673			**Mantle cell lymphoma**						
2,958	9,127.5	1,345	260.44	516	118.8	0.4812	0.8662	55.6	0-5 years	619	2,048.5	220	69.27	318	73.6	0.5797	0.8419	68.9
948	3,050.0	302	90.03	335	69.5	0.2911	0.7452	39.1	5-10	230	747.5	65	28.31	230	49.1	0.3678	0.6910	53.2
		Median observed & relative survival time-yrs				*4.6 to 6.3*						*Median observed & relative survival time-yrs*				*6.5 to 11.9*		
		Peripheral T-cell lymphoma, NOS							ICD-O-3 9702			**Peripheral T-cell lymphoma, NOS**						
1,221	2,894.5	777	69.47	1,118	244.4	0.3235	0.8865	36.5	0-5 years	592	1,710.5	271	35.88	755	137.5	0.5059	0.9027	56.0
273	925.5	64	26.02	246	41.0	0.2270	0.7676	29.6	5-10	200	683.5	32	13.08	245	27.7	0.3932	0.8196	48.0
		Median observed & relative survival time-yrs				*1.4 to 1.5*						*Median observed & relative survival time-yrs*				*5.4 to 9.0*		
		Angioimmunoblastic T-cell lymphoma							ICD-O-3 9705			**Angioimmunoblastic T-cell lymphoma**						
586	1,488.5	340	35.50	958	204.6	0.3623	0.8917	40.6	0-5 years	11	22.5	9	0.29	3,113	387.1	0.1818	0.9650	18.8
143	489.0	34	11.23	303	46.6	0.2520	0.7909	31.9	5-10									
		Median observed & relative survival time-yrs				*2.1 to 2.5*						*Median observed & relative survival time-yrs*				*1.3 to 1.32*		

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

The largest cell type group was diffuse large B-cell, NOS (DLBCL) with 21,272 patient cases (67% of NHL-Nodal aggressive grade cases) and the least was angioimmunoblastic T-cell lymphoma with 586 patient-cases. EDR results correlate well with the indolent "low-grade" and aggressive "high grade" designations used in this prognostic/histological classification; the aggressive category has an EDR minimum of 57 per 1000 (lymphoplasmacytic lymphoma) to 205 and higher (angioimmunoblastic and peripheral T-cell lymphomas) to indolent of 17 per 1000 to 96 per 1000 per year in the 0-5 years durational interval.

NHL-EN Indolent grades in Table 9 totaled 8117 patient cases including rare cell types amounted to only 250 patient-cases (mediastinal large B-cell lymphoma – 241 cases, and precursor T-cell lymphoblastic lymphoma, NOS – 9 patient-cases). In indolent cases, EDR per 1000 per year at 0-5 years ranged from a minimum of 2 per 1000 per year in follicular lymphoma, grade 1 to a maximum of 83 in precursor T-cell lymphoblastic lymphoma, NOS cases. Median observed and relative survival ranged from approximately 16 to >20 years. The largest cell type category of patient-cases, marginal zone B-cell lymphoma, NOS (MALT lymphomas) with 5234 patient cases in the 0-5-year interval (64% of indolent grade cases) displayed an EDR of 11 per 1000 per year and relative survival (SR) of 95% compared to its nodal counterpart with 2353 patient-cases (13% of indolent nodal cases), EDR of 37 per 1000 per year, and SR of 83%.

NHL-EN Aggressive grades in Table 9 totaled 14,215 patient-cases. The overall number of selected indolent and aggressive cell types for the NHL-Extranodal subdivision totaled 22,332 patient cases, just 45% of the total number of NHL-N cases. The most frequent cell type was DLBCL with 11,478 patient-cases (81% of NHL-EN aggressive grade cases): EDR 111 per 1000 per year, observed and relative survival (SR) 54% and 62% respectively, like DLBCL in the nodal subdivision.

EXTRANODAL NHL: MORTALITY AND SURVIVAL

Results. In Table 10; 20-year FU in the 1983-1995 cohort by age, sex and race, (all stages and indolent-aggressive grades combined) is divided into six duration intervals 0-1, 1-2, 2-5, 5-10, 10-15 & 15-20 years. In this cohort, excess death rates (EDRs) in both sexes are extremely high in the 1st duration in all age groups but diminish with duration. EDR also increases with age, but in males in the 1st duration of age group 65 up, the EDR is 324 vs 332 per 1000 in females, following the same pattern as in the nodal subdivision (Table 2). Below age group 65, first year EDR in males is 348 per 1000 and 179 in females with corresponding MR values of 4566% in males and 3606% in female patients. However, by duration 15-20 years EDR has decreased to about 24 in males at entry-age <65 and to 17 in females. For all ages combined, the preponderance of EDR in males over females, is evident with 1st year male EDR of 337 per 1000 and 276 in females with MR values of 1185% and 967% respectively. EDR results are similar in both sexes, but MRs are higher in females, at ages below and above 65-years because of lower expected deaths. Median observed and relative survival, all ages combined, is higher in females than males, 4.9 to 8.4-years vs approximately 2.8 to 4.6 years, respectively. Five-year survival ratios are about 49% and 58% in males and females, respectively, all ages combined. In males, SR diminishes from 50% in cases age <65 to 48% in those age >65, and in females, SR diminishes from 69% in cases age <65 to 50% in those age >65. Overall data available by race show EDR values higher and 5-year SR & median survival lower in non-white than in white patients.

Table 11 shows that patterns of excess mortality in the 1996-2015 cohort for the same age groups in both sexes are consistent but of much lesser magnitude than in Table 2 reflecting earlier diagnosis and more suitable therapy in the latter entry-period. In males all first-year EDRs are lower than they are in 1983-1995. The highest EDR of 249 per 1000

Table 10. 1983-1995 Entrants, Age, Sex & Race; All Stages & Indol/Aggress Grades Combined SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6): Index Code 37b: NHL-EXTRANODAL

Duration	No. Alive	Exposure	Number of Deaths		Mortality	Mean Ann. Mortality Rate/1,000			Cumul. Surv. Rate		Cum. Surv.
Start-End	at Start	Pt.-Yrs	Observed	Expected	Ratio (%)	Observed	Expected	Excess	Observed	Expected	Ratio (%)
t to t+ch t	***l***	**E**	**d**	**d'**	**100d/d'**	**q**	**q'**	**(q-q')**	**P**	**P'**	**100P/P'**
					Male, Age <65						
0-1	1,552	1,550.0	552	12.09	4,566	0.3561	0.0078	348.3	0.6439	0.9922	64.9
1-2	996	995.5	118	8.86	1,332	0.1185	0.0089	109.6	0.5676	0.9834	57.7
2-5	877	2,464.5	143	25.08	570	0.0580	0.0102	47.8	0.4749	0.9536	49.8
5-10	731	3,393.0	114	43.73	261	0.0336	0.0129	20.7	0.4007	0.8935	44.8
10-15	615	2,875.0	95	48.48	196	0.0330	0.0169	16.2	0.3385	0.8204	41.3
15-20	516	2,349.0	105	49.46	212	0.0447	0.0211	23.6	0.2694	0.7373	36.5
	Median survival time (interval = 12 months): Observed = 4.0998 intervals; Relative = 4.91348 intervals.										
					Male, Age 65 up						
0-1	1,260	1,258.5	483	75.26	642	0.3838	0.0598	324.0	0.6162	0.9402	65.5
1-2	774	773.5	148	44.48	333	0.1913	0.0575	133.8	0.4983	0.8861	56.2
2-5	625	1,674.0	182	103.11	177	0.1087	0.0616	47.1	0.3529	0.7317	48.2
5-10	441	1,774.0	195	133.45	146	0.1099	0.0752	34.7	0.1969	0.4925	40.0
10-15	246	942.5	126	91.82	137	0.1337	0.0974	36.3	0.0960	0.2935	32.7
15-20	119	440.0	63	49.47	127	0.1432	0.1124	30.8	0.0448	0.1604	27.9
	Median survival time (interval = 12 months): Observed = 1.98563 intervals; Relative = 4.15342 intervals.										
					Male, All Ages						
0-1	2,812	2,808.5	1,035	87.34	1,185	0.3685	0.0311	337.4	0.6315	0.9689	65.2
1-2	1,770	1,769.0	266	53.25	500	0.1504	0.0301	120.3	0.5365	0.9397	57.1
2-5	1,502	4,138.5	325	128.23	253	0.0785	0.0310	47.5	0.4203	0.8549	49.2
5-10	1,172	5,167.0	309	177.19	174	0.0598	0.0343	25.5	0.3093	0.7177	43.1
10-15	861	3,817.5	221	140.24	158	0.0579	0.0367	21.2	0.2296	0.5953	38.6
15-20	635	2,789.0	168	99.00	170	0.0602	0.0355	24.7	0.1687	0.4969	33.9
	Median survival time (interval = 12 months): Observed = 2.78598 intervals; Relative = 4.62443 intervals.										
					Female, Age <65						
0-1	833	832.0	153	4.24	3,606	0.1839	0.0051	178.8	0.8161	0.9949	82.0
1-2	678	677.0	49	3.66	1,340	0.0724	0.0054	67.0	0.7570	0.9895	76.5
2-5	627	1,800.0	73	11.49	635	0.0406	0.0064	34.2	0.6687	0.9706	68.9
5-10	550	2,568.0	78	21.37	365	0.0304	0.0083	22.1	0.5738	0.9307	61.6
10-15	470	2,192.0	64	25.60	250	0.0292	0.0117	17.5	0.4954	0.8775	56.5
15-20	402	1,877.0	63	30.63	206	0.0336	0.0163	17.2	0.4172	0.8078	51.6
	Median survival time (interval = 12 months): Observed = 14.6603 intervals; Relative is greater than 20 intervals.										
					Female, Age 65 up						
0-1	1,425	1,424.5	541	67.52	801	0.3798	0.0474	332.4	0.6202	0.9526	65.1
1-2	883	882.0	120	37.93	316	0.1361	0.0430	93.1	0.5358	0.9116	58.8
2-5	761	2,064.5	201	101.66	198	0.0974	0.0492	48.1	0.3941	0.7830	50.3
5-10	559	2,236.5	249	134.20	186	0.1113	0.0600	51.3	0.2177	0.5721	38.1
10-15	305	1,188.0	145	95.48	152	0.1221	0.0804	41.7	0.1133	0.3744	30.3
15-20	156	574.5	90	59.80	150	0.1567	0.1041	52.6	0.0463	0.2140	21.6
	Median survival time (interval = 12 months): Observed = 2.70637 intervals; Relative = 5.14449 intervals.										
					Female, All Ages						
0-1	2,258	2,256.5	694	71.76	967	0.3076	0.0318	275.8	0.6924	0.9682	71.5
1-2	1,561	1,559.0	169	41.63	406	0.1084	0.0267	81.7	0.6173	0.9423	65.5
2-5	1,388	3,864.5	274	113.16	242	0.0709	0.0293	41.6	0.4954	0.8618	57.5
5-10	1,109	4,804.5	327	155.66	210	0.0681	0.0324	35.7	0.3489	0.7306	47.8
10-15	775	3,380.0	209	121.14	173	0.0618	0.0358	26.0	0.2543	0.6087	41.8
15-20	558	2,451.5	153	90.58	169	0.0624	0.0369	25.5	0.1837	0.5042	36.4
	Median survival time (interval = 12 months): Observed = 4.86442 intervals; Relative = 8.38628 intervals.										
					White Race; All Ages						
0-5	4,382	14,258.0	2,378	448.19	531	0.1668	0.0314	135.3	0.4563	0.8530	53.5
5-10	1,988	8,635.5	581	300.40	193	0.0673	0.0348	32.5	0.3227	0.7142	45.2
	Median survival time (interval = 12 months): Observed = 3.77672 intervals; Relative = 6.77168 intervals.										
					Black, Other, Unknown; All ages						
0-5	688	2,138.0	385	47.22	815	0.1801	0.0221	158.0	0.4371	0.8941	48.9
5-10	293	1,336.0	55	32.51	169	0.0412	0.0243	16.8	0.3548	0.7904	44.9
	Median survival time (interval = 12 months): Observed = 2.94871 intervals; Relative = 4.51681 intervals.										

* All Ann Arbor Stages I-IV plus Unknown Combined; (Ann Arbor Stage 1983-2015)

** Indolent Morpho/Histology-ICD-O-3; 9690, 9699 Aggressive morpho/Histology-ICD-O-3; 9670, 9680, 9702

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

Table 11. 1996-2015 Entrants, Age, Sex & Race; All Stages & Indol/Aggress Grades Combined SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6): Index Code 37b: NHL-EXTRANODAL

Duration	No. Alive	Exposure	Number of Deaths		Mortality	Mean Ann. Mortality Rate/1,000			Cumul. Surv. Rate		Cum. Surv.
Start-End	at Start	Pt.-Yrs	Observed	Expected	Ratio (%)	Observed	Expected	Excess	Observed	Expected	Ratio (%)
t to t+ch t	***l***	**E**	**d**	**d'**	**100d/d'**	**q**	**q'**	**(q-q')**	**P**	**P'**	**100P/P'**
					Male, Age <65						
0-1	4,493	4,469.5	721	29.95	2,408	0.1613	0.0067	154.6	0.8387	0.9933	84.4
1-2	3,725	3,611.0	192	26.00	738	0.0532	0.0072	46.0	0.7941	0.9861	80.5
2-5	3,305	8,686.0	243	69.51	350	0.0280	0.0080	20.0	0.7305	0.9626	75.9
5-10	2,466	9,399.5	220	94.54	233	0.0234	0.0101	13.3	0.6487	0.9145	70.9
10-15	1,309	4,597.5	115	59.54	193	0.0250	0.0129	12.1	0.5702	0.8559	66.6
15-20	531	1,372.5	35	24.08	145	0.0255	0.0175	8.0	0.5056	0.7789	64.9
	Median survival time (interval = 12 months): Observed is greater than 20 intervals; Relative is > than 20 intervals.										
					Male, Age 65 up						
0-1	4,274	4,265.0	1,303	239.27	545	0.3055	0.0561	249.4	0.6945	0.9439	73.6
1-2	2,953	2,854.0	320	153.83	208	0.1121	0.0539	58.2	0.6166	0.8930	69.1
2-5	2,435	6,054.0	514	352.09	146	0.0849	0.0582	26.7	0.4729	0.7454	63.4
5-10	1,495	4,956.0	503	348.51	144	0.1015	0.0703	31.2	0.2708	0.5132	52.8
10-15	502	1,514.0	171	140.80	121	0.1129	0.0930	19.9	0.1427	0.3087	46.2
15-20	113	226.5	40	25.77	155	0.1766	0.1138	62.8	0.0583	0.1637	35.6
	Median survival time (interval = 12 months): Observed = 4.35576 intervals; Relative = 12.6589 intervals.										
					Male, All Ages						
0-1	8,767	8,734.5	2,024	269.02	752	0.2317	0.0308	200.9	0.7683	0.9692	79.3
1-2	6,678	6,465.0	512	179.73	285	0.0792	0.0278	51.4	0.7075	0.9423	75.1
2-5	5,740	14,740.0	757	421.68	180	0.0514	0.0286	22.7	0.6050	0.8635	70.1
5-10	3,961	14,355.5	723	442.98	163	0.0504	0.0309	19.5	0.4659	0.7377	63.2
10-15	1,811	6,111.5	286	200.53	143	0.0468	0.0328	14.0	0.3649	0.6240	58.5
15-20	644	1,599.0	75	50.10	150	0.0469	0.0313	15.6	0.2949	0.5342	55.2
	Median survival time (interval = 12 months): Observed = 8.72741 intervals; Relative is greater than 20 intervals.										
					Female, Age <65						
0-1	3,304	3,286.5	306	14.13	2,165	0.0931	0.0043	88.8	0.9069	0.9957	91.1
1-2	2,963	2,878.0	103	13.24	778	0.0358	0.0046	31.2	0.8744	0.9911	88.2
2-5	2,690	7,128.0	123	37.39	329	0.0173	0.0052	12.0	0.8304	0.9755	85.1
5-10	2,045	7,910.0	149	53.59	278	0.0188	0.0068	12.1	0.7541	0.9424	80.0
10-15	1,124	3,924.0	81	36.94	219	0.0206	0.0094	11.2	0.6817	0.8978	75.9
15-20	437	1,112.0	27	15.84	170	0.0243	0.0142	10.0	0.6120	0.8305	73.7
	Median survival time (interval = 12 months): Observed is greater than 20 intervals; Relative is > than 20 intervals.										
					Female, Age 65 up						
0-1	4,734	4,718.0	1,331	221.27	602	0.2821	0.0469	235.2	0.7179	0.9531	75.3
1-2	3,371	3,276.5	304	149.41	203	0.0928	0.0456	47.2	0.6513	0.9096	71.6
2-5	2,878	7,255.5	574	363.10	158	0.0791	0.0500	29.1	0.5089	0.7792	65.3
5-10	1,819	6,383.0	570	398.54	143	0.0893	0.0624	26.9	0.3188	0.5603	56.9
10-15	735	2,171.5	249	172.78	144	0.1147	0.0796	35.1	0.1709	0.3680	46.4
15-20	169	359.0	51	35.67	143	0.1421	0.0994	42.7	0.0736	0.2049	35.9
	Median survival time (interval = 12 months): Observed = 5.19985 intervals; Relative = 13.1158 intervals.										
					Female, All Ages						
0-1	8,038	8,004.5	1,637	235.33	696	0.2045	0.0294	175.1	0.7955	0.9706	82.0
1-2	6,334	6,154.5	407	162.48	250	0.0661	0.0264	39.7	0.7429	0.9450	78.6
2-5	5,568	14,383.5	697	399.95	174	0.0485	0.0278	20.7	0.6406	0.8682	73.8
5-10	3,864	14,293.0	719	450.48	160	0.0503	0.0315	18.8	0.4953	0.7385	67.1
10-15	1,859	6,095.5	330	209.64	157	0.0541	0.0344	19.7	0.3768	0.6212	60.6
15-20	606	1,471.0	78	51.34	152	0.0530	0.0349	18.1	0.2902	0.5171	56.1
	Median survival time (interval = 12 months): Observed = 9.77646 intervals; Relative is greater than 20 intervals.										
					White Race, All Ages						
0-5	13,640	47,779.0	4,927	1,469.38	335	0.1031	0.0308	72.4	0.6202	0.8560	72.5
5-10	6,419	23,546.5	1,223	787.78	155	0.0519	0.0335	18.5	0.4744	0.7212	65.8
	Median survival time (interval = 12 months): Observed = 8.97973 intervals; Relative is greater than 20 intervals.										
					Black, Other, Unknown						
0-5	3,165	10,703.0	1,107	199.39	555	0.1034	0.0186	84.8	0.6304	0.9105	69.2
5-10	1,406	5,102.0	219	105.78	207	0.0429	0.0207	22.2	0.5061	0.8190	61.8
	Median survival time (interval = 12 months): Observed = 10.3101 intervals; Relative is greater than 20 intervals.										

* All Ann Arbor Stages I-IV plus Unknown Combined; (Ann Arbor Stage 1983-2015)

** Indolent Morpho/Histology-ICD-O-3; 9690, 9699 Aggressive Morpho/Histology-ICD-O-3; 9670, 9680, 9702

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

per year is in the 65 up age group. This was based on 1,303 deaths (30%) in 4,274 entrants, and the EDR of 249 is significantly lower than the EDR of 324 in 1983-95 but significantly higher than the other male EDRs of 155 and 201 (all ages combined) in the 1996-2015 cohort (95% confidence level). EDRs increase with age but diminish with advancing duration in all age groups. Females EDR values (all ages combined) are always lower than the corresponding male age group, and EDRs increase with age but decrease with advancing duration. At duration 5-10 years EDR values in all age/sex groups in 1996-2015 are consistently lower than in their counterparts in 1983-1995. Excess mortality is lower in all white patients than in all non-white patients. Median observed survival is higher in non-whites (10.3 years) than whites (9 years) and 5-year SR are lower in non-whites but significantly higher than in the 1983-95 cohort.

Table 12 shows results for the 1983-1995 cohort by Ann Arbor Stage for age groups <65 and 65 up, indolent and aggressive grade & both sexes combined. Excess mortality (EDR) increases from the local to the regional and distant stages and is substantially higher in patients age 65 and up in the regional and distant stages. With 23% of the staged cases of NHL-EN classified as distant (stages III & IV combined), EDR in the patients under 65 ranged from 406 per 1000 per year in the first year to 34 per 1000 per year after 15 years. First year excess mortality was even higher in the patients 65 years and older, with an EDR of 485 and an MR of 1036%, extremely high for these older patients, higher than their NHL-N counterparts.

Table 13 shows results for the 1996-2015 cohort by Ann Arbor Stage, EDRs were consistently lower than they were in the corresponding stage/age/duration counterparts in the 1983-1995 cohort (but higher than the NHL-N Counterpart-Table 4). The same trends prevailed by stage, by age, and by duration to 15-20 years. For all ages and stages, 5-year survival ratios (SR), median observed and relative survival were significantly higher, and mortality ratios lower than the earlier cohort.

Table 14 contains results for durations 0-5 and 5-10 years, all male ages combined, by combination of Ann Arbor Stage with other factors, including cell grade/bio-behavioral morphology-indolent vs aggressive each cohort, and by T cell and B cell morphology in the 1996-2015 cohort. For each combination, data for the 1983-95 and 1996-2015 cohorts are also contrasted. In the local and regional stages, (Ann Arbor Stages I and II respectively), morphology/histology bio-behavioral severity determinants, *indolent* (ICD-O-3 9690, 9699 combined) and *aggressive* ICD-O-3 9670, 9680, 9702 combined) are seen to be effective prognostic risk predictors: EDR and MR values are higher when tumor cells are bio-behaviorally classified aggressive instead of indolent. In the 1996-2015 cohort (all stages combined) and unlike their NHL-N counterpart, T-cell cases had a lower EDR & lower MR than the earlier cohort, but made up only approximately 4% of the cases. The overall results of Table 14 confirm the results in Tables 10-13, showing a consistent reduction in mortality and improvement in survival, by stage from the earlier to the later cohort. Comparative mortality and survival are also shown in Table 13 for the unstaged cases, and for all cases staged and unknown stages combined. For 2848 NHL cases in 1983-95 cohort (all stages known & unknown and all cell bio-morphology grades (IATB) combined, the 5-year overall EDR was 156 per 1000 per year; in 1996-2015, 8830 cases were diagnosed, and the EDR was at 81. Although the decrease in EDR is small, it is statistically significant at the 95% level because of the very large numbers of deaths involved. In the 1996-2015 cohort, the overall EDR for T-cell cases was 139, and for B-cell cases it was 112.

Results for duration 5-10 years are given by stage, bio-behavioral grade and cohort. EDR in 1996-2015 was 14 per 1000 per year in stage I (local stage) indolent cases and 17 in aggressive grade cases, 16 in 152 entrants in stage II (regional stage) indolent cases with 23 deaths,

Table 12. 1983-1995 Entrants, Age, Stage*; Indolent/Aggressive Grades & Sex Combined SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6) Index Code 37b: NHL-EXTRANODAL

Duration	No. Alive	Exposure	Number of Deaths		Mortality	Mean Ann. Mortality Rate/1,000			Cumul. Surv. Rate		Cum. Surv.
Start-End	at Start	Pt.-Yrs	Observed	Expected	Ratio (%)	Observed	Expected	Excess	Observed	Expected	Ratio (%)
t to t+ch t	***l***	**E**	**d**	**d'**	**100d/d'**	**q**	**q'**	**(q-q')**	**P**	**P'**	**100P/P'**
					Stage I (Local), Age <65						
0-1	1,251	1,250.5	321	8.38	3,831	0.2567	0.0067	250.0	0.7433	0.9933	74.8
1-2	929	929.0	65	7.06	921	0.0700	0.0076	62.4	0.6913	0.9858	70.1
2-5	864	2,449.0	130	21.02	619	0.0531	0.0086	44.5	0.5872	0.9605	61.1
5-10	732	3,410.5	107	37.30	287	0.0314	0.0109	20.4	0.5012	0.9089	55.1
10-15	622	2,909.0	91	42.27	215	0.0313	0.0145	16.8	0.4275	0.8446	50.6
15-20	525	2,442.0	88	46.44	190	0.0360	0.0190	17.0	0.3555	0.7669	46.4
	Median survival time (interval = 12 months): Observed = 10.1007 intervals; Relative = 16.0259 intervals.										
					Stage I (Local), Age 65 up						
0-1	1,344	1,343.0	409	71.58	571	0.3045	0.0533	251.2	0.6955	0.9467	73.5
1-2	933	932.0	139	46.88	297	0.1491	0.0503	98.8	0.5918	0.8991	65.8
2-5	792	2,137.5	224	118.71	189	0.1048	0.0555	49.3	0.4240	0.7570	56.0
5-10	565	2,272.5	234	151.04	155	0.1030	0.0665	36.5	0.2477	0.5344	46.4
10-15	328	1,287.0	148	114.69	129	0.1150	0.0891	25.9	0.1353	0.3332	40.6
15-20	176	655.0	101	71.89	140	0.1542	0.1098	44.4	0.0563	0.1846	30.5
	Median survival time (interval = 12 months): Observed = 3.57485 intervals; Relative = 7.35887 intervals.										
					Stage II (Regional), Age <65						
0-1	409	408.5	97	3.02	3,209	0.2375	0.0074	230.1	0.7625	0.9926	76.8
1-2	311	311.0	37	2.39	1,545	0.1190	0.0077	111.3	0.6718	0.9850	68.2
2-5	274	779.5	31	6.61	469	0.0398	0.0085	31.3	0.5954	0.9601	62.0
5-10	238	1,128.0	31	12.44	249	0.0275	0.0110	16.5	0.5179	0.9081	57.0
10-15	207	978.5	26	14.63	178	0.0266	0.0150	11.6	0.4525	0.8420	53.7
15-20	180	841.5	29	16.80	173	0.0345	0.0200	14.5	0.3794	0.7610	49.9
	Median survival time (interval = 12 months): Observed = 11.1889 intervals; Relative = 19.8403 intervals.										
					Stage II (Regional), Age 65 up						
0-1	505	504.5	182	26.74	681	0.3608	0.0530	307.8	0.6392	0.9470	67.5
1-2	322	321.5	51	16.01	319	0.1586	0.0498	108.8	0.5378	0.8998	59.8
2-5	270	733.0	66	40.80	162	0.0900	0.0557	34.4	0.4064	0.7573	53.7
5-10	204	805.0	102	54.01	189	0.1267	0.0671	59.6	0.2032	0.5325	38.2
10-15	102	391.0	59	32.51	182	0.1509	0.0831	67.8	0.0857	0.3436	24.9
15-20	43	158.5	24	15.64	153	0.1514	0.0987	52.7	0.0374	0.2023	18.5
	Median survival time (interval = 12 months): Observed = 2.67846 intervals; Relative = 6.40736 intervals.										
					Stage III & IV (Distant), Age <65						
0-1	595	594.0	245	4.10	5,978	0.4125	0.0069	405.6	0.5875	0.9931	59.2
1-2	348	347.5	50	2.43	2,055	0.1439	0.0070	136.9	0.5030	0.9861	51.0
2-5	297	838.0	46	6.91	666	0.0549	0.0082	46.6	0.4250	0.9619	44.2
5-10	251	1,134.5	47	11.89	395	0.0414	0.0105	30.9	0.3452	0.9123	37.8
10-15	203	943.5	31	13.07	237	0.0329	0.0139	19.0	0.2923	0.8506	34.4
15-20	171	759.0	39	13.18	296	0.0514	0.0174	34.0	0.2251	0.7789	28.9
	Median survival time (interval = 12 months): Observed = 2.09334 intervals; Relative = 2.34801 intervals.										
					Stage III & IV (Distant), Age 65 up						
0-1	653	652.5	350	33.80	1,036	0.5364	0.0518	484.6	0.4636	0.9482	48.9
1-2	302	302.0	62	14.56	426	0.2053	0.0482	157.1	0.3684	0.9025	40.8
2-5	240	633.0	80	33.09	242	0.1264	0.0523	74.1	0.2456	0.7676	32.0
5-10	160	651.0	69	42.65	162	0.1060	0.0655	40.5	0.1393	0.5443	25.6
10-15	89	329.5	47	28.81	163	0.1426	0.0874	55.2	0.0651	0.3435	19.0
15-20	41	146.0	19	15.50	123	0.1301	0.1062	24.0	0.0342	0.1950	17.5
	Median survival time (interval = 12 months): Observed = 0.932143 intervals; Relative = 0.978374 intervals.										
					Stage Unknown, All Ages						
0-1	313	312.0	125	11.33	1,104	0.4006	0.0363	364.3	0.5994	0.9637	62.2
1-2	186	185.0	31	5.59	555	0.1676	0.0302	137.4	0.4989	0.9346	53.4
2-5	153	433.0	22	14.08	156	0.0508	0.0325	18.3	0.4272	0.8462	50.5
5-10	131	570.0	46	23.46	196	0.0807	0.0412	39.5	0.2772	0.6853	40.4
10-15	85	359.0	28	15.32	183	0.0780	0.0427	35.3	0.1858	0.5521	33.7
15-20	57	238.5	21	9.93	212	0.0881	0.0416	46.4	0.1167	0.4458	26.2
	Median survival time (interval = 12 months): Observed = 1.9893 intervals; Relative = 5.39054 intervals.										

* All Ann Arbor Stages I-IV plus Unknown; (1983-2015) Limited-Stages I&II combined; Advanced Stages III&IV combined

** Grades: **Indolent Morpho/Histology-ICD-O-3; 9690, 9699 Aggressive Morpho/Histology-ICD-O-3; 9670, 9680, 9702

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

Table 13. 1996-2015 Entrants, Age, Stage; Indolent/Aggressive* & Sex Combined SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6). Index Code IC37b: NHL-EXTRANODAL

Duration	No. Alive	Exposure	Number of Deaths		Mortality	Mean Ann. Mortality Rate/1,000			Cumul. Surv. Rate		Cum. Surv.
Start-End	at Start	Pt.-Yrs	Observed	Expected	Ratio (%)	Observed	Expected	Excess	Observed	Expected	Ratio (%)
t to t+ch t	***l***	**E**	**d**	**d'**	**100d/d'**	**q**	**q'**	**(q-q')**	**P**	**P'**	**100P/P'**
					Stage I (Local stage), Age <65						
0-1	4,246	4,223.0	419	23.65	1,772	0.0992	0.0056	93.6	0.9008	0.9944	90.6
1-2	3,781	3,671.5	124	21.66	572	0.0338	0.0059	27.9	0.8704	0.9885	88.0
2-5	3,438	9,152.5	181	61.10	296	0.0198	0.0067	13.1	0.8203	0.9688	84.7
5-10	2,644	10,275.5	205	88.23	232	0.0200	0.0086	11.4	0.7410	0.9273	79.9
10-15	1,462	5,185.0	103	59.40	173	0.0199	0.0115	8.4	0.6701	0.8744	76.6
15-20	607	1,557.0	34	25.71	132	0.0218	0.0165	5.3	0.6024	0.7993	75.4
	Median survival time (interval = 12 months): Observed is > than 20 intervals; Relative is > than 20 intervals.										
					Stage I (Local), Age 65 up						
0-1	4,678	4,664.5	1,062	242.55	438	0.2277	0.0520	175.7	0.7723	0.9480	81.5
1-2	3,589	3,482.0	305	178.63	171	0.0876	0.0513	36.3	0.7046	0.8994	78.3
2-5	3,070	7,747.5	609	431.05	141	0.0786	0.0556	23.0	0.5521	0.7568	73.0
5-10	1,972	6,858.5	634	463.67	137	0.0924	0.0676	24.8	0.3358	0.5294	63.4
10-15	763	2,291.5	259	196.99	131	0.1130	0.0860	27.1	0.1805	0.3333	54.2
15-20	181	385.0	58	42.20	137	0.1506	0.1096	41.0	0.0688	0.1762	39.1
	Median survival time (interval = 12 months): Observed = 6.1582 intervals; Relative = 17.0656 intervals.										
					Stage II (Regional), Age <65						
0-1	1,368	1,360.5	139	7.48	1,858	0.1022	0.0055	96.7	0.8978	0.9945	90.3
1-2	1,214	1,173.0	66	6.80	970	0.0563	0.0058	50.5	0.8473	0.9887	85.7
2-5	1,066	2,847.0	57	18.72	304	0.0200	0.0066	13.4	0.7981	0.9693	82.3
5-10	821	3,130.5	67	25.40	264	0.0214	0.0081	13.3	0.7164	0.9301	77.0
10-15	437	1,475.0	34	15.79	215	0.0231	0.0107	12.3	0.6363	0.8806	72.3
15-20	157	381.0	12	5.40	222	0.0315	0.0142	17.3	0.5600	0.8155	68.7
	Median survival time (interval = 12 months): Observed is > than 20 intervals; Relative is > than 20 intervals.										
					Stage II (Regional), Age 65 up						
0-1	1,489	1,484.5	454	75.12	604	0.3058	0.0506	255.2	0.6942	0.9494	73.1
1-2	1,026	994.0	101	46.12	219	0.1016	0.0464	55.2	0.6237	0.9053	68.9
2-5	861	2,179.5	173	109.85	157	0.0794	0.0504	29.0	0.4857	0.7747	62.7
5-10	545	1,923.0	169	118.70	142	0.0879	0.0617	26.2	0.3027	0.5589	54.2
10-15	210	605.0	72	50.57	142	0.1190	0.0836	35.4	0.1531	0.3561	43.0
15-20	42	81.5	14	7.68	182	0.1718	0.0943	77.5	0.0742	0.2099	35.4
	Median survival time (interval = 12 months): Observed = 4.68512 intervals; Relative = 12.5418 intervals.										
					Stage III & IV (Distant), Age <65						
0-1	1,901	1,896.0	432	11.57	3,735	0.2278	0.0061	221.7	0.7722	0.9939	77.7
1-2	1,459	1,418.5	100	9.08	1,102	0.0705	0.0064	64.1	0.7178	0.9875	72.7
2-5	1,278	3,268.5	111	23.43	474	0.0340	0.0072	26.8	0.6489	0.9664	67.1
5-10	896	3,340.5	84	29.72	283	0.0251	0.0089	16.2	0.5725	0.9236	62.0
10-15	455	1,544.0	54	17.79	304	0.0350	0.0115	23.5	0.4808	0.8702	55.2
15-20	161	423.5	13	7.11	183	0.0307	0.0168	13.9	0.4165	0.7959	52.3
	Median survival time (interval = 12 months): Observed = 13.6945 intervals; Relative is greater than 20 intervals.										
					Stage III & IV (Distant), Age 65 up						
0-1	2,411	2,408.5	978	117.53	832	0.4061	0.0488	357.3	0.5939	0.9512	62.4
1-2	1,428	1,384.0	195	64.22	304	0.1409	0.0464	94.5	0.5102	0.9071	56.2
2-5	1,145	2,788.0	249	141.00	177	0.0893	0.0506	38.7	0.3861	0.7754	49.8
5-10	658	2,111.0	225	135.26	166	0.1066	0.0641	42.5	0.2195	0.5520	39.8
10-15	211	610.0	71	50.27	141	0.1164	0.0824	34.0	0.1157	0.3563	32.5
15-20	40	67.0	10	5.85	171	0.1493	0.0874	61.9	0.0652	0.2219	29.4
	Median survival time (interval = 12 months): Observed = 2.21762 intervals; Relative = 4.86877 intervals.										
					Stage Unknown, All Ages						
0-1	712	702.0	177	26.75	662	0.2521	0.0381	214.0	0.7479	0.9619	77.8
1-2	515	496.5	28	15.39	182	0.0564	0.0310	25.4	0.7057	0.9321	75.7
2-5	450	1,140.5	74	37.32	198	0.0649	0.0327	32.2	0.5750	0.8435	68.2
5-10	289	1,009.5	58	34.67	167	0.0575	0.0343	23.1	0.4307	0.7073	60.9
10-15	132	496.5	23	19.34	119	0.0463	0.0389	7.4	0.3380	0.5808	58.2
15-20	62	175.0	12	7.38	163	0.0686	0.0421	26.4	0.2531	0.4672	54.2
	Median survival time (interval = 12 months): Observed = 6.99008 intervals; Relative is greater than 20 intervals.										

* All Ann Arbor Stages I-IV plus Unknown; (1983-2015) Limited-Stages I&II combined; Advanced Stages III&IV combined

** Grades: **Indolent Morpho/Histology-ICD-O-3; 9690, 9699 Aggressive Morpho/Histology-ICD-O-3; 9670, 9680, 9702

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

Table 14. Male, Cohort, Stage, Grade-Cell Morph/Hist*, Durations 0-5, 5-10 Years, All Ages Combined SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6). Index Code IC37b: NHL-EXTRANODAL

			No. Alive	Exposure	Number of Deaths		Mortality	Excess	Cumul. Surv. Rate		Cum. Surv.
			at Start	Pt.-Yrs	Observed	Expected	Ratio	Death Rate	Observed	Expected	Ratio (%)
STAGE **Ann Arbor Classification**	**GRADE** **Morphology/ Histology**	**COHORT** **Time/ Period**	***l***	**E**	**d**	**d'**	**MR**	**EDR**	**P**	**P'**	**Cum SR**
					Durational interval 0-5 Years						
Stage I (Local)	Indolent	1983-1995	47	204.0	13	6.51	200	31.8	0.7234	0.8505	85.1
	Indolent	1996-2015	1,510	6,250.5	198	177.15	112	3.3	0.8507	0.8652	98.3
	Aggressive	1983-1995	1,405	4,664.0	757	139.89	541	132.3	0.4602	0.8581	53.6
	Aggressive	1996-2015	3,075	10,465.5	1,249	316.28	395	89.1	0.5751	0.8586	67.0
	B-cell	1996-2015	2,841	9,597.0	1,173	291.97	402	91.8	0.5675	0.8578	66.2
	T-cell	1996-2015	190	660.5	68	15.12	450	80.1	0.6289	0.8913	70.6
Stage II (Regional)	Indolent	1983-1995	14	53.0	5	1.72	290	61.8	0.6429	0.8465	75.9
	Indolent	1996-2015	272	1,055.0	68	26.07	261	39.7	0.7301	0.8824	82.7
	Aggressive	1983-1995	475	1,545.5	249	51.97	479	127.5	0.4746	0.8436	56.3
	Aggressive	1996-2015	1,207	4,040.5	450	107.29	419	84.8	0.6120	0.8762	69.8
	B-cell	1996-2015	1,165	3,914.5	428	103.27	414	83.0	0.6176	0.8767	70.5
	T-cell	1996-2015	25	75.5	11	0.96	1,142	132.9	0.5281	0.9437	56.0
Stage III & IV (Distant)	Indolent	1983-1995	14	47.0	11	2.98	369	170.5	0.2143	0.6949	30.8
(Advanced)	Indolent	1996-2015	452	1,720.0	119	52.11	228	38.9	0.7112	0.8576	82.9
	Aggressive	1983-1995	698	1,750.5	493	50.04	985	253.0	0.2913	0.8680	33.6
	Aggressive	1996-2015	1,888	5,250.0	1,053	150.23	701	172.0	0.4248	0.8675	49.0
Stage Unknown	Indolent	1983-1995	8	34.0	3	0.93	322	60.8	0.6250	0.8675	72.0
	Indolent	1996-2015	150	567.0	39	19.80	197	33.9	0.7066	0.8371	84.4
	Aggressive	1983-1995	151	418.0	95	14.58	652	192.4	0.3658	0.8355	43.8
	Aggressive	1996-2015	213	591.0	117	21.81	537	161.1	0.4153	0.8344	49.8
	Indol & Aggress.	1983-1995	159	452.0	98	15.50	632	182.5	0.3789	0.8380	45.2
	Indol & Aggress.	1996-2015	363	1,158.0	156	41.61	375	98.8	0.5360	0.8351	64.2
All Stages K&U	I,A,T,B	1983-1995	2,848	8,835.0	1,648	270.02	610	156.0	0.4199	0.8562	49.0
	I,A,T,B	1996-2015	8,830	30,151.5	3,322	873.14	380	81.2	0.6044	0.8641	70.0
	B-cell	1983-1995	2,374	7,076.0	1,425	214.11	666	171.1	0.3979	0.8577	46.4
	B-cell	1996-2015	5,889	18,720.5	2,644	548.49	482	111.9	0.5323	0.8635	61.6
	T-cell	1983-1995	105	341.0	60	5.43	1,105	160.0	0.4286	0.9238	46.4
	T-cell	1996-2015	376	1,134.0	181	23.12	783	139.2	0.5022	0.9050	55.5
					Durational interval 5-10 Years						
Stage I (Local)	Indolent	1983-1995	14	69.0	1	1.82	55	-11.8	0.6500	0.7837	82.9
	Indolent	1996-2015	923	3,309.5	155	109.11	142	13.9	0.6660	0.7310	91.1
	Aggressive	1983-1995	642	2,820.5	165	94.86	174	24.9	0.3417	0.7229	47.3
	Aggressive	1996-2015	1,397	5,271.5	256	166.05	154	17.1	0.4466	0.7308	61.1
	B-cell	1996-2015	1,266	4,785.0	231	152.09	152	16.5	0.4413	0.7290	60.5
	T-cell	1996-2015	95	339.5	14	7.32	191	19.7	0.5073	0.8018	63.3
Stage II (Regional)	Indolent	1983-1995	9	39.0	5	1.46	342	90.7	0.2857	0.7009	40.8
	Indolent	1996-2015	152	546.0	23	14.52	158	15.5	0.5859	0.7704	76.1
	Aggressive	1983-1995	223	999.0	58	35.07	165	23.0	0.3511	0.7055	49.8
	Aggressive	1996-2015	550	2,004.5	101	54.73	185	23.1	0.4736	0.7627	62.1
	B-cell	1996-2015	536	1,948.5	97	53.48	181	22.3	0.4788	0.7625	62.8
	T-cell	1996-2015	7	29.0	2	0.22	929	61.5	0.3772	0.9095	41.5
Stage III & IV (Distant)	Indolent	1983-1995	3	12.0	1	1.32	76	-26.5	0.1429	0.3883	36.8
(Advanced)	Indolent	1996-2015	221	737.5	38	24.65	154	18.1	0.5472	0.7217	75.8
	Aggressive	1983-1995	202	874.5	57	27.33	209	33.9	0.2088	0.7398	28.2
	Aggressive	1996-2015	577	2,002.0	120	56.74	211	31.6	0.3124	0.7523	41.5
Stage Unknown	Indolent	1983-1995	5	21.0	2	0.95	211	50.2	0.3750	0.6875	54.5
	Indolent	1996-2015	75	264.5	11	9.88	111	4.2	0.5552	0.6916	80.3
	Aggressive	1983-1995	54	234.0	18	10.36	174	32.6	0.2439	0.6657	36.6
	Aggressive	1996-2015	66	220.0	19	7.24	263	53.5	0.2652	0.7062	37.6
	Indol & Aggress.	1983-1995	59	255.0	20	11.31	177	34.1	0.2505	0.6674	37.5
	Indol & Aggress.	1996-2015	141	484.5	30	17.10	175	26.6	0.3835	0.6976	55.0
All Stages K&U	I,A,T,B	1983-1995	1,186	5,231.0	311	177.52	175	25.5	0.3096	0.7201	43.0
	I,A,T,B	1996-2015	3,991	14,487.5	725	443.71	163	19.4	0.4662	0.7391	63.1
	B-cell	1983-1995	935	4,102.5	251	137.11	183	27.8	0.2910	0.7234	40.2
	B-cell	1996-2015	2,372	8,706.5	450	262.52	171	21.5	0.4074	0.7405	55.0
	T-cell	1983-1995	45	202.0	8	2.71	296	26.2	0.3524	0.8632	40.8
	T-cell	1996-2015	141	488.0	21	8.89	236	24.8	0.4009	0.8274	48.5

* Grade = cell morph/hist Indolent ICD-O-3; 9690, 9699. Aggressive ICD-O-3; 9670, 9680, 9702 I,A,T,B: Indolent, Aggressive, T-Cell, B-Cell B-cell: ICD-O-3; 9680, 9728. T-cell: ICD-O-3; 9702, 9727 I,A,T,B: 9670, 9680, 9690, 9699, 9702, 9727-9728

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

and interestingly, (EDR) 23 in 550 aggressive stage II cases with 101 deaths; also, an EDR of 18 and 32 per 1000 respectively for indolent and aggressive cases in stages III and IV combined (distant stage). Indolent and aggressive cases combined in the unknown stage category had an EDR of 27 per 1000, and for all known and unknown stages and for all morphology/histology bio-behavioral categories (IATB) combined, an EDR of 19 per 1000. In each of these categories EDR was lower in 1996-2015 than in the 1983-95 cohort.

Table 15 displays comparative mortality and survival for all female cases at duration 0-5 and 5-10 years and is identical in format to Table 14 for males. For females as for males the same differences in EDR are observed: EDR increases by stage and is higher in aggressive bio-behavioral grade cases in the 1983-1995 time-period than in the 1996-2015 cohort. In 1996-2015 stage I, EDR in T-cell cases is 68 per 1000, lower than the 88 per 1000 in B-cell cases. In the regional stage (II), T-cell EDR in the 1996-2015 cohort is 179 per 1000, however, with only 28 entrants and 15 deaths. As was evident in Tables 10-13, excess mortality is consistently lower than in male NHL cases. In the 1983-1995 time-period, overall (all stages known & unknown), EDR was 118 per 1000 per year, lower than the EDR of 156 in males. In females in 1996-2015, the EDR (68) had fallen to a level also lower than the EDR of 81 in males. With very large numbers of deaths, all of these differences are significant at more than the 95% confidence level. In the 1996-2015 cohort, the overall EDR (all stages known and unknown) for T-cell cases was 126 and 107 for B-cell cases. EDR in females at 5-10 years in 1996-2015, all stages known and unknown and cell bio-morphology grades IATB combined was 19, in B-cell cases 22, and in T-cell cases 21.3.

Table 16 shows NHL-Extranodal 20-year mortality and survival results by Ann Arbor stage distribution, 1996-2015, all ages, grades, and both sexes combined. In the SEER survival database, there were 25,222 staged patient-cases of Extranodal-NHL with 17,664 (70%) limited stage and 7588 (30%) advanced stage cases. Although the proportion of NHL EN cases classified as local is much higher (13,480) than in Nodal NHL (11,056), even these cases have a very high first-year EDR – 130 per 1000 per year vs 87 per 1000 per year – with some excess mortality persisting beyond 15 years. Excess mortality increased in magnitude with stage progression, and observed, relative and median survival diminished with advancing stages I to IV. However, overall mortality for the extranodal NHL subdivision, all stages known and unknown combined, is less than nodal NHL because local and regional stages (limited stage) predominate. Limited & advanced stage patient-case frequency juxtapositions between NHL-N & EN subdivisions have been previously addressed.

Comments & Conclusions. Non-Hodgkin lymphomas (NHLs), with approximately 95-100 variant subtype diseases and considerable clinical, histologic and biologic heterogeneity are a group of lymphoproliferative cancers, of which 80% to 90% of cases arise from B-cells and the remaining from T-cells. Nodal and extranodal NHLs present a complex challenge in table design for many reasons: (1) the nature of this tissue; (2) its wide distribution in lymph nodes and other bodily sites; (3) bio-behavioral importance of cell types; (4) decades of changes including use of cytogenetic markers and immunophenotyping in tumor classification; (5) molecular profiling of gene expression in each NHL variant disease; (6) terminology modifications; (7) recent steps to merge the lymphomas with acute and chronic lymphatic leukemia. In spite of this, we utilized the National Cancer Institute PDQ practical adaptation of the World Health Organization's (WHO) updated REAL (Revised European American Lymphoma) classification (Ref 3) of lymphoproliferative diseases, and the SEER*Stat 8.3.6 database (released 8/8/2019) for diagnosis years 1975-2016, making use of 40 years of data to examine patterns of incidence, survival and mortality, and selected cell bio-behavioral char-

Table 15. Female, Cohort, Stage, Grade-Cell Morph/Hist*, Durations 0-5, 5-10 Years, All Ages Combined SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6). Index Code IC37b: NHL-EXTRANODAL

			No. Alive	Exposure	Number of Deaths		Mortality	Excess	Cumul. Surv. Rate		Cum. Surv.
			at Start	Pt.-Yrs	Observed	Expected	Ratio	Death Rate	Observed	Expected	Ratio (%)
STAGE **Ann Arbor Classification**	**GRADE** **Morphology/ Histology**	**COHORT** **Time/ Period**	***I***	**E**	**d**	**d'**	**MR**	**EDR**	**P**	**P'**	**Cum SR**
					Durational interval 0-5 Years						
Stage I (Local)	Indolent	1983-1995	45	216.0	8	6.99	114	4.7	0.8222	0.8482	96.9
	Indolent	1996-2015	1,754	7,379.5	227	187.02	121	5.4	0.8568	0.8789	97.5
	Aggressive	1983-1995	1,098	3,957.0	510	120.34	424	98.5	0.5348	0.8576	62.4
	Aggressive	1996-2015	2,585	8,845.5	1,026	277.43	370	84.6	0.5854	0.8534	68.6
	B-cell	1996-2015	2,416	8,191.5	979	257.40	380	88.1	0.5772	0.8532	67.7
	T-cell	1996-2015	116	407.0	35	7.51	466	67.5	0.6752	0.9128	74.0
Stage II (Regional)	Indolent	1983-1995	15	67.0	4	1.24	322	41.1	0.7334	0.9108	80.5
	Indolent	1996-2015	338	1,384.0	57	32.33	176	17.8	0.8080	0.8873	91.1
	Aggressive	1983-1995	410	1,392.5	206	40.59	507	118.8	0.4958	0.8623	57.5
	Aggressive	1996-2015	1,040	3,559.0	415	98.40	422	89.0	0.5819	0.8709	66.8
	B-cell	1996-2015	989	3,376.0	394	93.04	423	89.1	0.5828	0.8715	66.9
	T-cell	1996-2015	28	76.5	15	1.29	1,165	179.2	0.3840	0.9240	41.6
Stage III & IV (Distant)	Indolent	1983-1995	18	75.0	8	2.06	389	79.2	0.5556	0.8739	63.6
(Advanced)	Indolent	1996-2015	484	1,904.0	109	48.15	226	32.0	0.7528	0.8789	85.6
	Aggressive	1983-1995	518	1,494.5	321	39.76	807	188.2	0.3798	0.8762	43.3
	Aggressive	1996-2015	1,488	4,289.5	784	116.35	674	155.6	0.4554	0.8736	52.1
Stage Unknown	Indolent	1983-1995	8	38.0	1	0.98	102	0.4	0.8750	0.8779	99.7
	Indolent	1996-2015	164	636.5	30	20.84	144	14.4	0.7837	0.8456	92.7
	Aggressive	1983-1995	146	440.0	79	14.49	545	146.6	0.4550	0.8514	53.4
	Aggressive	1996-2015	185	544.5	93	17.03	546	139.5	0.4680	0.8616	54.3
	Indol & Aggress.	1983-1995	154	478.0	80	15.48	517	135.0	0.4770	0.8533	55.9
	Indol & Aggress.	1996-2015	349	1,181.0	123	37.89	325	72.1	0.6158	0.8517	72.3
All Stages K&U	I,A,T,B	1983-1995	2,282	7,771.0	1,146	227.90	503	118.1	0.4967	0.8626	57.6
	I,A,T,B	1996-2015	8,084	28,717.0	2,756	798.12	345	68.2	0.6407	0.8689	73.7
	B-cell	1983-1995	1,851	6,007.5	996	177.70	561	136.2	0.4607	0.8622	53.4
	B-cell	1996-2015	4,920	15,885.0	2,171	469.10	463	107.1	0.5404	0.8623	62.7
	T-cell	1983-1995	57	202.0	27	2.45	1,101	121.5	0.5264	0.9414	55.9
	T-cell	1996-2015	254	790.5	113	13.42	842	126.0	0.5271	0.9219	57.2
					Durational interval 5-10 Years						
Stage I (Local)	Indolent	1983-1995	37	167.0	9	5.38	167	21.7	0.6222	0.7199	86.4
	Indolent	1996-2015	1,128	4,213.0	167	127.44	131	9.4	0.6994	0.7527	92.9
	Aggressive	1983-1995	584	2,528.5	164	82.29	199	32.3	0.3840	0.7264	52.9
	Aggressive	1996-2015	1,168	4,340.0	261	147.64	177	26.1	0.4292	0.7170	59.9
	B-cell	1996-2015	1,074	3,970.5	241	135.66	178	26.5	0.4220	0.7162	58.9
	T-cell	1996-2015	53	209.0	6	3.24	185	13.2	0.5735	0.8433	68.0
Stage II (Regional)	Indolent	1983-1995	11	52.0	2	1.51	133	9.5	0.6001	0.7855	76.4
	Indolent	1996-2015	195	709.0	34	21.50	158	17.6	0.6213	0.7591	81.8
	Aggressive	1983-1995	199	843.0	68	28.44	239	46.9	0.3264	0.7262	44.9
	Aggressive	1996-2015	469	1,794.0	78	52.98	147	13.9	0.4656	0.7482	62.2
	B-cell	1996-2015	443	1,681.0	72	48.62	148	13.9	0.4686	0.7512	62.4
	T-cell	1996-2015	8	26.5	1	0.67	150	12.6	0.3249	0.8024	40.5
Stage III & IV (Distant)	Indolent	1983-1995	10	48.0	2	1.28	157	15.1	0.4444	0.7630	58.3
(Advanced)	Indolent	1996-2015	265	938.0	52	28.52	182	25.0	0.5706	0.7515	75.9
	Aggressive	1983-1995	196	851.0	56	24.61	228	36.9	0.2711	0.7562	35.8
	Aggressive	1996-2015	491	1,774.0	99	55.06	180	24.8	0.3439	0.7451	46.2
Stage Unknown	Indolent	1983-1995	7	31.0	2	0.96	208	33.5	0.6249	0.7494	83.4
	Indolent	1996-2015	85	304.0	16	11.44	140	15.0	0.6180	0.6970	88.7
	Aggressive	1983-1995	65	284.0	24	11.20	214	45.1	0.2870	0.6960	41.2
	Aggressive	1996-2015	63	221.0	12	6.12	196	26.6	0.3571	0.7463	47.9
	Indol & Aggress.	1983-1995	72	315.0	26	12.15	214	44.0	0.3048	0.7005	43.5
	Indol & Aggress.	1996-2015	148	525.0	28	17.55	160	19.9	0.4788	0.7168	66.8
All Stages K&U	I,A,T,B	1983-1995	1,124	4,879.5	327	157.20	208	34.8	0.3518	0.7320	48.1
	I,A,T,B	1996-2015	3,890	14,405.0	720	451.31	160	18.7	0.4962	0.7399	67.1
	B-cell	1983-1995	844	3,661.0	253	116.50	217	37.3	0.3223	0.7332	44.0
	B-cell	1996-2015	2,007	7,421.0	402	237.81	169	22.1	0.4100	0.7317	56.0
	T-cell	1983-1995	30	138.0	4	2.27	176	12.6	0.4562	0.8662	52.7
	T-cell	1996-2015	90	326.0	12	5.04	238	21.3	0.4270	0.8508	50.2

* Grade = cell morph/hist Indolent ICD-O-3; 9690, 9699. Aggressive ICD-O-3; 9670, 9680, 9702 I,A,T,B: Indolent, Aggressive, T-Cell, B-Cell B-cell: ICD-O-3; 9680, 9728. T-cell: ICD-O-3; 9702, 9727 I,A,T,B: 9670, 9680, 9690, 9699, 9702, 9727-9728

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

Table 16. NHL-EXTRANODAL, 1996-2015, All Ages Combined; Ann Arbor Stages I-IV & Unknown SEER Cancer Data 1975-2016 (SEER*Stat 8.3.6) Index Code 37b: NHL-EXTRANODAL 10/30/2004

Duration	No. Alive	Exposure	Number of Deaths		Mortality	Mean Ann. Mortality Rate/1,000			Cumul. Surv. Rate		Cum. Surv.
Start-End	at Start	Pt.-Yrs	Observed	Expected	Ratio (%)	Observed	Expected	Excess	Observed	Expected	Ratio (%)
t to t+ch t	***l***	**E**	**d**	**d'**	**100d/d'**	**q**	**q'**	**(q-q')**	**P**	**P'**	**100P/P'**
					Stage I (Local)						
0-1	13,480	13,423.5	2,119	378.54	560	0.1579	0.0282	129.7	0.8421	0.9718	86.7
1-2	11,248	10,918.0	643	289.33	222	0.0589	0.0265	32.4	0.7925	0.9460	83.8
2-5	9,945	25,896.0	1,177	716.71	164	0.0455	0.0277	17.8	0.6900	0.8695	79.4
5-10	7,086	26,789.0	1,209	815.27	148	0.0451	0.0304	14.7	0.5469	0.7443	73.5
10-15	3,599	12,496.0	564	410.38	137	0.0451	0.0328	12.3	0.4337	0.6296	68.9
15-20	1,401	3,575.0	154	124.06	124	0.0431	0.0347	8.4	0.3459	0.5255	65.8
	Median survival time (interval = 12 months): Observed = 12.0138 intervals; Relative is greater than 20 intervals.										
					Stage II (Regional)						
0-1	4,184	4,167.5	821	113.36	724	0.1970	0.0272	169.8	0.8030	0.9728	82.5
1-2	3,330	3,225.5	249	73.86	337	0.0772	0.0229	54.3	0.7410	0.9505	78.0
2-5	2,872	7,472.5	333	180.67	184	0.0446	0.0242	20.4	0.6466	0.8831	73.2
5-10	2,030	7,571.5	330	204.14	162	0.0436	0.0270	16.6	0.5161	0.7693	67.1
10-15	981	3,213.0	150	100.81	149	0.0467	0.0314	15.3	0.4033	0.6552	61.5
15-20	319	739.5	47	21.62	217	0.0636	0.0292	34.3	0.3154	0.5656	55.8
	Median survival time (interval = 12 months): Observed = 10.8487 intervals; Relative is greater than 20 intervals.										
					Stages I&II, (Limited stage)						
0-1	17,664	17,591.0	2,940	492.55	597	0.1671	0.0280	139.1	0.8329	0.9720	85.7
1-2	14,578	14,143.5	892	363.49	245	0.0631	0.0257	37.4	0.7803	0.9470	82.4
2-5	12,817	33,368.5	1,510	897.92	168	0.0453	0.0269	18.3	0.6797	0.8725	77.9
5-10	9,116	34,360.5	1,539	1,019.49	151	0.0448	0.0297	15.1	0.5397	0.7497	72.0
10-15	4,580	15,709.0	714	510.86	140	0.0455	0.0325	12.9	0.4268	0.6351	67.2
15-20	1,720	4,314.5	201	145.67	138	0.0466	0.0338	12.8	0.3388	0.5330	63.6
	Median survival time (interval = 12 months): Observed = 11.7655 intervals; Relative is greater than 20 intervals.										
					Stage III (Distant stage III)						
0-1	1,013	1,010.0	235	26.97	871	0.2327	0.0267	206.0	0.7673	0.9733	78.8
1-2	772	744.5	75	18.09	415	0.1007	0.0243	76.4	0.6900	0.9496	72.7
2-5	642	1,625.5	99	43.49	228	0.0609	0.0268	34.1	0.5730	0.8750	65.5
5-10	422	1,543.0	89	49.76	179	0.0577	0.0323	25.4	0.4206	0.7414	56.7
10-15	183	545.5	28	18.17	154	0.0513	0.0333	18.0	0.3217	0.6289	51.2
15-20	42	110.0	3	2.65	113	0.0273	0.0241	3.2	0.2840	0.5525	51.4
	Median survival time (interval = 12 months): Observed = 7.6717 intervals; Relative = 15.7311 intervals.										
					Stage IV (Distant IV)						
0-1	6,545	6,526.5	1,942	194.49	999	0.2976	0.0298	267.8	0.7024	0.9702	72.4
1-2	4,566	4,398.0	437	120.95	361	0.0994	0.0275	71.9	0.6326	0.9435	67.0
2-5	3,793	9,233.0	575	262.21	219	0.0623	0.0284	33.9	0.5231	0.8654	60.4
5-10	2,288	7,877.0	447	229.28	195	0.0567	0.0291	27.6	0.3926	0.7464	52.6
10-15	963	3,180.0	178	91.83	194	0.0560	0.0289	27.1	0.2955	0.6453	45.8
15-20	333	827.0	40	22.97	174	0.0484	0.0278	20.6	0.2400	0.5588	42.9
	Median survival time (interval = 12 months): Observed = 5.6807 intervals; Relative = 11.641 intervals.										
					Stages III&IV, (Advanced stage)						
0-1	7,558	7,536.5	2,177	221.57	983	0.2889	0.0294	259.5	0.7111	0.9706	73.3
1-2	5,338	5,142.5	512	138.85	369	0.0996	0.0270	72.6	0.6403	0.9444	67.8
2-5	4,435	10,858.5	674	305.90	220	0.0621	0.0282	33.9	0.5298	0.8667	61.1
5-10	2,710	9,420.0	536	279.20	192	0.0569	0.0296	27.3	0.3962	0.7453	53.2
10-15	1,146	3,725.5	206	109.95	187	0.0553	0.0295	25.8	0.2990	0.6426	46.5
15-20	375	937.0	43	25.62	168	0.0459	0.0273	18.5	0.2453	0.5574	44.0
	Median survival time (interval = 12 months): Observed = 5.91214 intervals; Relative = 12.0004 intervals.										
					Stage Unknown						
0-1	1,367	1,351.0	307	48.37	635	0.2272	0.0358	191.4	0.7728	0.9642	80.1
1-2	1,028	988.0	62	29.84	208	0.0628	0.0302	32.6	0.7243	0.9351	77.5
2-5	886	2,252.5	118	70.66	167	0.0524	0.0314	21.0	0.6149	0.8497	72.4
5-10	589	1,980.5	101	63.43	159	0.0510	0.0320	19.0	0.4720	0.7219	65.4
10-15	253	916.0	39	30.96	126	0.0426	0.0338	8.8	0.3775	0.6078	62.1
15-20	110	322.0	22	13.32	165	0.0683	0.0414	27.0	0.2724	0.4909	55.5
	Median survival time (interval = 12 months): Observed = 9.02263 intervals; Relative is greater than 20 intervals.										
					All Stages Known & Unknown						
0-1	26,589	26,478.5	5,424	762.58	711	0.2048	0.0288	176.0	0.7952	0.9712	81.9
1-2	20,944	20,274.0	1,466	531.18	276	0.0723	0.0262	46.1	0.7377	0.9458	78.0
2-5	18,138	46,479.5	2,302	1,274.26	181	0.0495	0.0274	22.1	0.6342	0.8699	72.9
5-10	12,415	45,761.0	2,176	1,360.65	160	0.0476	0.0297	17.8	0.4966	0.7474	66.4
10-15	5,979	20,350.5	959	651.76	147	0.0471	0.0320	15.1	0.3895	0.6350	61.3
15-20	2,205	5,573.5	266	184.56	144	0.0477	0.0331	14.6	0.3094	0.5347	57.9
	Median survival time (interval = 12 months): Observed = 9.85838 intervals; Relative is greater than 20 intervals.										

* All Ann Arbor Stages I-IV plus Unknown; (Ann Arbor Stage 1983-2015)

** Indolent Morpho/Histology-ICD-O-3; 9690, 9699 Aggressive Morpho/Histology-ICD-O-3; 9670, 9680, 9702

Expected Survival Table: U.S. 1970-2012 by individual year (White, Black, Other (AI/API), Ages 0-99, All races for Other Unspecified

Chart 1. Non-Hodgkin Lymphoma AAPC 2012-2016 *Trends in SEER Incidence. By Sex & Race; 2012-2016 CSR 1975-2016; Tables 19.1-3*

Race	Male	Female	Male & Female
White	– 0.7	– 0.6	– 0.6
Black	– 0.2	– 0.6	0.2
Hispanic	0.0	0.4	0.2
All Races	– 0.2	– 0.6	– 0.6

acteristics of NHL in the United States. The Ann Arbor staging classification (1983-2015), adopted by the AJCC and UICC as a standard for classifying extent of anatomic disease, allowed us to examine 32 years of NHL data by stage. The selection principles of this report refer to the impact of age, sex, race, stage, grade (biologic behavior), cohort entry time-period and disease duration determining short and long-term nodal and extran-

Chart 2. SEER Age-Adjusted Incidence Rates 2012-2016* SEER Age-Adjusted Incidence Rates, 2012-2016: CSR 1975-2016; Table 19.7

	All Races			Whites			Blacks		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
All ages	19.6	23.9	16.2	20.6	25.0	17.0	14.7	17.7	12.4
Under 65	9.4	11.1	7.8	9.6	11.3	8.0	9.1	10.9	7.6
65 & over	90.4	112.6	74.3	96.6	119.9	79.4	53.2	64.6	46.1
WHO All ages	14.7	17.7	12.2	15.4	18.4	12.7	11.7	14.0	9.8

* Age-Adjusted Incidence Rates per 100,00 to the 2000 U.S. Std Population by Age, Race, Sex
** Rates are per 100,000 and are age-adjusted to the world (WHO 2000-2025) standard million.

Chart 3. SEER Annual Age-Adjusted Incidence Rates by Year, Race and Sex: CSR 1975-2016; Table 19.5

		All Races			Whites			Blacks	
Year of Dx.	Total	Males	Females	Total	Males	Females	Total	Males	Females
1975-2016	18.46	22.67	15.13	19.25	23.57	15.81	14.14	17.69	11.35
1975-1979	11.60	13.44	10.18	12.09	13.93	10.68	6.96	8.74	5.52
1980	12.62	15.01	10.81	12.98	15.28	11.22	8.70	10.74	7.20
1990	18.51	22.97	14.81	19.34	23.96	15.49	13.92	17.63	11.02
2000	19.81	24.34	16.13	20.99	25.71	17.12	13.93	18.23	10.74
2010	21.41	26.62	17.15	22.37	27.42	18.20	17.67	23.23	13.23
2011	19.82	24.33	16.26	20.76	25.44	17.02	14.55	17.49	12.37
2012	20.31	24.89	16.59	21.25	25.91	17.39	16.58	18.97	14.44
2013	19.73	24.14	16.13	20.76	25.29	16.99	15.58	18.07	13.68
2014	20.20	24.97	16.29	21.38	26.12	17.49	15.12	19.98	11.28
2015	20.03	24.78	16.15	21.18	26.00	17.18	15.10	19.47	11.74
2016	19.36	23.44	16.00	20.18	24.28	16.76	16.25	19.09	13.82

Rates are / 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).
* NHL Age-adjusted SEER Incidence Rates by Year, Race, and Sex; CSR 1975-2016; Table 19.5

odal non-Hodgkin's lymphoma mortality and survival.

NHL Staging Criteria: Although the SEER historic staging program remains a very important factor for displaying disease severity, it adapted its L-R-D anatomic extent of disease system to the AJCC Ann Arbor-Lugano principal stages I – IV contained in the Revised Staging Classification for Primary Nodal Lymphomas (Ref. 30, 31) as follows:

Localized (Stage I): confined to one lymphatic region above or below the diaphragm.

Regional (Stage II): more than one lymphatic region involved above or below the diaphragm.

Distant (Stage III): lymphatic regions involved on both sides of the diaphragm.

Distant (Stage IV): organs involved other than lymphoid tissue or lymph nodes. Our text and tables have shown that 68% of all nodal NHL cases were advanced staging (Stages III & IV combined) or unknown stage (5%), an overall high degree of anatomic extent of malignancy. Paradoxically, extranodal NHL cases show a juxtaposition in staging with 30% in the advanced stage and 70% in the limited stage (Stages I & II combined).

Relative Frequency & Mean Age: Relative frequency and mean age (FAMA) distributions by age, sex and race for Nodal and

Chart 4. SEER Age-Adjusted Mortality Rates 2012-2016* SEER Age-Adjusted Mortality Rates, 2012-2016: CSR 1975-2016; Table 19.7

	All Races			Whites			Blacks		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
All ages	5.6	7.3	4.4	5.9	7.6	4.5	4.1	5.2	3.3
Under 65	1.3	1.7	1.0	1.3	1.7	0.9	1.6	2.1	1.2
65 & over	35.2	45.3	27.9	37.2	47.7	29.5	21.0	26.5	17.6
WHO**All ages	3.0	3.9	2.3	3.1	4.0	2.3	2.5	3.2	2.0

* Age-Adjusted Mortality Rates per 100,00 to the 2000 U.S. Std Population by Age, Race, Sex (19 age groups - Census P25-1130).

** Rates are per 100,000 and are age-adjusted to the world (WHO 2000-2025) standard million.

Chart 5. SEER Annual Age-Adjusted Death Rates by Year, Race & Sex CSR 1975-2016: Table 19.6 All Races Whites Blacks

Year of Death	Total	Males	Females	Total	Males	Females	Total	Males	Females
1975-2016	7.01	8.80	5.70	7.32	9.15	5.96	4.78	6.13	3.80
1975-1979	5.80	7.08	4.84	6.02	7.33	5.03	3.75	4,83	2.92
1980	6.23	7.47	5.29	6.47	7.74	5.52	3.99	5.15	3.12
1990	7.87	9.97	6.34	8.16	10.32	6.58	5.39	7.13	4.17
1997	8.88	11.03	7.25	9.21	11.35	7.57	6.34	8.45	4.87
2000	8.17	10.20	6.70	8.54	10.63	7.01	5.20	6.61	4.17
2010	6.14	7.83	4.85	6.37	8.11	5.04	4.57	5.84	3.64
3011	6.03	7.85	4.64	6.29	8.17	4.83	4.36	5.74	3.40
2012	5.91	7.62	4.61	6.17	7.95	4.80	4.26	5.38	3.48
2013	5.72	7.38	4.44	5.95	7.67	4.62	4.11	5.27	3.33
2014	5.65	7.26	4.43	5.89	7.55	4.60	4.18	5.28	3.42
2015	5.47	7.13	4.18	5.69	7.41	4,34	4.04	5.19	3.21
2016	5.37	6.91	4.17	5.62	7.21	4.36	3.83	4.81	3.11

Rates are / 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).

Chart 6. Non-Hodgkin Lymphoma, Nodal and Extranodal Case Characteristics 1975-2016

Nodal FAMA* **Age**	**Male** No.	**Percent** %	**Female** No.	**Percent** %	**M&F** No.	**Percent** %
<35	10,111	7.1	5,522	4.7	15,633	6.0
35-44	11,224	7.9	6,482	5.5	17,706	6.8
45-54	20,345	14.3	13,594	11.5	33,939	13.0
55-64	29,765	20.9	22,842	19.2	52,607	20.1
65-74	34,952	24.5	29,511	24.9	63,563	24.3
75 up	36,959	25.9	40,737	34.3	77,696	29.8
All ages	142,456	54.6%	118,688	45.4%	261,144	(67.9)
Sex-Mean x-yrs.	62,0		65.9		63.8	
Race	**White**	**%**	**Black**	**%**	**Other**	**Unknown**
Number	226,034	86.6	18,441	7.1	14,802; 6%	1,867; 0.7%
Mean x-yrs.	64.5		56.3		62.3	57.8
Extranodal FAMA	**Male**	**%**	**Female**	**%**	**M&F**	**Percent**
All ages	66,930	54.2	56,577	45.8	123,507	(32.1)
Sex-Mean x-yrs.	61.7		65.4		63.5	
Race	**White**	**%**	**Black**	**%**	**Other**	**Unknown**
Number	101,764	82.4	9,939	8.1	9,880; 8%	1,924; 2%
Mean x-years	64.4		55.4		61.9	56.4
NHL-N: Stage	**I**	**11**	**111**	**IV**	**Unknown**	**Total Staged**
M&F	42,066	34,251	44,847	91,291	22,422	212,455
%	19.8%	16.1%	21.1%	43.0%	9.6%	81.4%
NHL-EN: Stage	**I**	**11**	**111**	**IV**	**Unknown**	**Total Staged**
M&F	48,894	14,644	3,539	23,967	8,286	91,044
%	53.7%	16.4%	3.9%	26.3%	8.3%	91.7%
NHL-Cell Morph	**Indolent**	**%**	**Aggress.**	**%**	**Total**	
M&F	45,345	23.0	152,217	77.0	197,562	
NHL-N, Cell Morph	**Indolent**	**%**	**Aggress.**	**%**	**Total**	
M&F	23,443	18.3	104,424	81.7	127,867	
NHL-EN, Cell Mor.	**Indolent**	%	**Aggress.**	%	**Total**	
M&F	21,902	31.4	47,793	68.6	69,695	

* FAMA-Frequency and Mean Age (-) indicate N and EN percent of total number of NHL cases
* SEER*Stat 8.3.6 Selection Statement {Stage – Other. Lymphoma – Ann Arbor Stage (1983-2015)}
** Cell Bio-behavior: ICD-O-3: *INDOLENT*-9690, 9693; *AGGRESSIVE*-ICD-O-3; 9670, 9680, 9702

Extranodal NHL, and Ann Arbor stage distributions & cell bio-behavioral grade frequencies (indolent-aggressive) are shown in Chart 6. A total of 261,144 patient-cases of nodal non-Hodgkin's lymphoma (67.9% of all NHL cases) in the 1975-2016 SEER frequency database with a mean age of 63 years are included in the study. Frequency and mean age (FAMA) in males are 142,456 (54.6%) and 62 years respectively, and 118,688 (45.4%) with mean age 66 years in females. Also included in this study are a total of 123,507 patient-cases of extranodal NHL in the 1975-2016 SEER frequency database with a mean age of 63.5 years. FAMA in males are 66,930 (54.2%) and 62 years respectively, and female FAMA are 56,577 (45.8%) with mean age 65 years.

NHL Epidemiologic Signatures (ES): Trends in population-based data on cancer burden (ES) provide insight into true cancer occurrence, over diagnosis, and treatment advances.[33] Mortality and incidence patterns were examined from 1975 through 2016 for non-Hodgkin's lymphoma in the United States. Incidence rates in the USA

Chart 7. ICD-O-3 Seer Site/Histology Validation List

Selected Cell Bio-behavioral Grade	ICD-O-3	Cell Morphologic Terminology
Indolent	9690	Follicular Lymphoma, NOS
	9699	Marginal zone B-cell lymphoma, NOS
Aggressive	9670	ML, small B-cell lymphocytic, NOS
	9680	ML, large B-cell diffuse, NOS
	9702	Mature T-cell Lymphoma, NOS
B-cell	9680	ML, large B-cell diffuse, NOS
	9728	Precursor B-cell lymphoblastic lymphoma
T-cell	9702	Mature T-cell lymphoma, NOS
	9727	Precursor cell lymphoblastic lymphoma, NOS.

ML-Malignant Lymphoma NOS-Not Otherwise Specified.
Selected Cell Bio-behavior Grades: ICD-O-3: *Indolent*-9690, 9699; *Aggressive*-ICD-O-3; 9670, 9680, 9702 taken from December 5, 2012 SEER publication.

vary according to age, ethnicity, gender and time-period (see Charts 1 & 2). Mortality and incidence data presented here, aside from the tabular nodal and extranodal mortality displays, came from SEER Cancer Statistics Review (CSR), 1975-2016 (Ref. 24).

Much improved NHL mortality and survival indices in the 1996-2016 cohort entry time-period coincides with the 1997 release of Rituximab, a chimeric monoclonal antibody against the protein CD20 and causing cancer cell apoptosis. The NHL epidemiologic signature of stable incidence since the 1990s and declining mortality rates since 1997 corresponds with the efficacy of Rituximab targeted therapy and its addition to the anthracycline-based chemotherapeutic regimen of CHOP – cyclophosphamide, doxorubicin, vincristine and prednisone.

Mortality & Survival: Mortality is consistently higher and survival less in:

(1) NHL-Nodal vs NHL-Extranodal disease
(2) Cell type: T-cell vs B-cell
(3) Sex: males vs females
(4) Race: blacks vs whites
(5) Age: older (age >65) vs younger (age <65)
(6) Disease duration:
    0-5 years, consistently highest EDRs and MRs,
    5-20 years, consistently diminishing EDRs and MRs
(7) Stage: Advanced stage vs limited stage disease
(8) Bio-behavioral Grade: Aggressive morphology vs indolent morphology
(9) Cohort entry time-period: 1983-1995 vs 1996-2016

Further Directions: Since 1975 improved patient-outcomes shown in the 1996-2015 cohort entry time-period are attributable to advances in understanding of NHL classification and epidemiologic signatures, oncogene and tumor suppressor gene genetics, and application of immunologic and molecular techniques for refined diagnosis and targeted treatment. Patient treatment is determined by the specific type of lymphoma, with the addition of grade within the tumor type, if applicable, and clinical prognostic factors such as the International Prognostic Index (IPI).[34] Recent national and international collaborations have resulted in promising randomized controlled trials that revealed significant benefits of targeted biologic therapies such as antigen receptor T-cells[35,36] and adoptive T-cell therapies (ACT)[37] with administration of specific antitumor immune cells. These include the use of both tumor infiltrating lymphocytes (TILs) extracted from fresh tumor samples and peripheral blood lymphocytes that can be selected and used either in their natural state or modified genetically to overcome limita-

tions of conventional therapies. Targeted therapeutics and sustained remissions with improved progression-free survival are encouraging and lessen the disease burden of non-Hodgkin's lymphoma.

Profound appreciation to my esteemed colleague Dr. Richard B. Singer, M.D. (deceased) for his friendship, invaluable collaboration and scholarly expertise, encouragement, and assistance in the initial (unpublished) iterations of long-term comparative mortality and survival in patients with nodal & extranodal non-Hodgkin's lymphoma in 2003.

REFERENCES

1. Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Summary and description of a working formulation for clinical usage. *Cancer.* 1982;49:2112-2135.
2. Economoboulos I, Ashrou N, Stathakis N, et al. Primary extranodal non-Hodgkin's lymphoma in adults: clinicopathological and survival characteristics. *Leuk Lymphoma.* 1996;21:131-136. [PUBMED Abstract]
3. Pileri SA, Milani M, Fraternali-Orcioni G, et al. From the R.E.A.L. Classification to the upcoming WHO scheme: a step toward universal categorization of lymphoma entities? *Ann Oncol*. 1998;9:607-612. [PUBMED Abstract]
4. Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat) version 8.3.6., *Built* 2019.
5. Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin lymphoma. *Lancet.* 2012;380:848-857.
6. Swerdlow SH, Campo E, Pileri SA, et al. THE UPDATED WHO CLASSIFICATION OF HEMATOLOGICAL MALIGNANCIES: The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375-2390.
7. Pileri SA, Milani M, Fraternali-Orcioni G, et al. From the R.E.A.L. Classification to the upcoming WHO scheme: a step toward universal categorization of lymphoma entities? *Ann Oncol.* 1998;9:607-612. [PUBMED Abstract]
8. Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat): Latest Release: Version 8.3.6 - 2019.
9. Krol1 ADG, le Cessie S, Snijder JC, et al. Primary extranodal non-Hodgkin's lymphoma (NHL): the impact of alternative definitions tested in the Comprehensive Cancer Centre West population-based NHL registry. *Annals of Oncology.* 2003;14:131-139.
10. Bertoni F, Zucca E: State-of-the-art therapeutics: marginal-zone lymphoma. *J Clin Oncol.* 2005;23:6415-6420. [PUBMED Abstract]
11. Zucca E, Bertoni F: The spectrum of MALT lymphoma at different sites: biological and therapeutic relevance. *Blood.* 2016;127:2082-2092. [PUBMED Abstract]
12. Groves FD, Linet MS, Travis LB, Devesa SS. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. *J Natl Cancer Inst*. 2000;92:1240-1251.
13. *American Cancer Society: Cancer Facts and Figures* 2019. Atlanta, Ga: American Cancer Society, 2019.
14. Scott DW, King RL, Staiger AM, et al. High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with diffuse large B-cell lymphoma morphology. *Blood* 2018;131:2060-2064. [PUBMED Abstract]
15. Schmitz R, Wright GW, Huang DW, et al. Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. *N Engl J Med.* 2018;378:1396-1407. [PUBMED Abstract]
16. Cote TR, Biggar RJ, Rosenberg PS, et al. Non-Hodgkin's lymphoma among people with AIDS: incidence, presentation and public health burden. AIDS/Cancer Study Group. *Int J Cancer*. 1997;73:645-650.
17. Singer RB, Milano AF. Comparative Mortality in HIV-Infected Patients in Denmark, 1995–2005. *J Insur Med.* 2008;40:116-119.
18. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2018 Sub (1975-2016 varying) - Linked To County Attributes - Total U.S., 1969-2017 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2019, based on the November 2018 submission.
19. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2018 Sub (1975-2016) <Katrina/Rita Population Adjustment>- Linked To County Attributes - Total U.S., 1969-2017 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2019, based on the November 2018 submission.

20. Singer RB, Kita MW, Avery JR, eds. *Medical Risks - 1991 Compend of Mortality and Morbidity.* Westport, Conn: Praeger Publishers; 1994.
21. Brackenridge RDC, Croxson RS, Mackenzie R, eds. *Medical Selection of Life Risks.* 5th ed. New York, NY: Palgrave Macmillan; 2006:chaps 3-5.
22. Pokorski RJ. Mortality Methodology and Analysis Seminar Text. Sponsored by the Association of Life Insurance Medical Directors of America. *J Insur Med.* 1988;20:1-26.
23. Milano AF, Singer RB. The Cancer Mortality Risk Project – Cancer Mortality Risks by Anatomic Site: Part I – Introductory Overview; Carcinoma of the Colon: 20-Year Mortality Follow-up Derived from 1973-2013 (NCI) SEER*Stat Survival Database. *J Insur Med.* 2017;47: 65-94.
24. Howlader N, Noone AM, Krapcho M, et al. (eds). *SEER Cancer Statistics Review,* 1975-2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019.
25. Physician Data Query (*PDQ*). https://www.cancer.gov/publications/pdq
26. Berg JW. Morphologic classification of human cancer. In: Schottenfeld D, Fraumeni JF, eds. *Cancer Epidemiology and Prevention.* Philadelphia: Saunders; 1982.
27. Swenson WT, Wooldridge JE, Lynch CF, et al. Improved survival of follicular lymphoma patients in the United States. *J Clin Oncol.* 2005;23:5019-5026. [PUBMED Abstract]
28. Liu Q, Fayad L, Cabanillas F, et al. Improvement of overall and failure-free survival in stage IV follicular lymphoma: 25 years of treatment experience at The University of Texas M.D. Anderson Cancer Center. *J Clin Oncol.* 2006;24:1582-1589. [PUBMED Abstract]
29. Hodgkin and non-Hodgkin lymphoma. In: Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017:937-958.
30. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32:3059-3068.
31. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol.* 2014;32:3048-3058.
32. Cho H, Howlader N, Mariotto AB, Cronin KA**.** Estimating relative survival for cancer patients from the SEER Program using expected rates based on Ederer I versus Ederer II method**.** *Surveillance Research Program, National Cancer Institute;* 2011. *Technical Report*. 2011;1:1-17. Available from: https://surveillance.cancer.gov/reports/.
33. Welch HG, Kramer BS, Black WC. Epidemiologic Signatures in Cancer. *N Engl J Med.* 2019;381: 1378-1386.
34. Harris NL, Jaffe ES, Diebold J, et al. Lymphoma classification—from controversy to consensus: the R.E.A.L. and WHO Classification of lymphoid neoplasms [review]. *Ann Oncol.* 2000;11(Suppl 1): 3-10.
35. Maud SL, Frey N, Shaw PA, et al. Chimeric Antigen Receptor T Cells for Sustained Remission in Leukemia. *N Engl J Med.* 2014;371:1507-1517.
36. Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol*. 2015;33:540-549.
37. Baruch EN, Berg AL, Besser MJ, et al. Adoptive T-Cell Therapy: An Overview of Obstacles and Opportunities. *Cancer.* 2017;123:2154-2162. (2017 American Cancer Society)