Chapter 27
Hodgkin Lymphoma

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INTRODUCTION

Hodgkin Lymphoma (HL) is a cancer of the lymphoid cells with which an estimated 7,800 persons are diagnosed each year in the United States (1). Although it is a relatively rare cancer in the general population, it is one of the most common cancers diagnosed in young persons. A hallmark feature of HL epidemiology is its bimodal age-specific incidence pattern, in which incidence is highest between the ages of 15 and 34 years, declines between ages 35 and 54 years and increases again after age 55 years. Indeed, HL is unique among cancers in that over two-thirds of patients are diagnosed before 50 years of age. HL is also notable among cancers for the availability of curative therapy, which has resulted in relatively favorable outcomes. Despite its relatively low level of occurrence and high curability, it is the propensity of HL to occur in the productive years of life that makes it a significant source of cancer-related morbidity and mortality in the US. In fact, HL ranks third behind childhood cancers and testicular cancer in the average years of life lost to a cancer (2). This chapter examines survival characteristics in a large, population-based cohort of patients diagnosed with HL between 1988 and 2001 and reported to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.

MATERIALS AND METHODS

Patients

Analyses included all patients aged 15 years or over diagnosed with HL between 1988 and 2001 and reported to the SEER program. Patients were followed for vital status until 2002. Table 27.1 details exclusions, resulting in a final series of 11,720 patients. The majority of the eligible patients were young adults, defined as ages 15-44 at diagnosis (n=8,001, 68%), and of white race/ethnicity (n=10,154, 87%). In addition, there were slightly more male (n= 6,428, 55%) than female patients.

Stage classification

HL tumors almost always develop in a lymph node or other lymphoid structure and spread contiguously to nearby nodes (3). In the SEER database, classification of stage of disease at diagnosis for HL follows the Ann Arbor guidelines (4). In brief, the Ann Arbor system provides four stages of tumor spread relative to the diaphragm: I--involvement of a single lymph node region, II-- involvement of two or more lymph node regions on one side of the diaphragm, III--involvement of lymph node regions on both sides of the diaphragm, IV--disseminated

Table 27.1: Hodgkin Lymphoma: Number of Cases and Exclusions by Reason, 12 SEER Areas, 1988-2001

Number selected/remaining	Number excluded	Reason for exclusion/selection
13,302	0	Select 1988-2001 diagnosis (Los Angeles for 1992-2001 only)
12,560	742	Select first primary only
12,498	62	Exclude death certificate only or at autopsy
12,384	114	Exclude unknown race
12,361	23	Exclude alive with no survival time
11,777	584	Exclude children (Ages 0-14)
11,777	0	Exclude in situ cancers for all except breast & bladder cancer
11,720	57	Exclude no or unknown microscopic confirmation
11,720	0	Exclude sarcomas

disease. Each stage can be subclassified as AA" or AB" type according to the absence or presence of B-symptoms, respectively; these include fever, night sweats, generalized pruritus or weight loss of greater than 10 percent of total body mass. In these analyses, stage information was incomplete for 485 patients (4%), while information regarding B-symptoms was incomplete for 3,188 patients with known stage, or 27% of the total. Patients with incomplete stage or B-symptom information were excluded only from analyses addressing those variables.

Histologic classification

HL is distinguished from other lymphomas by the histologic presence of malignant Hodgkin and Reed-Sternberg (HRS) cells. The relative proportion of HRS cells to reactive cells and fibrosis within the tumor define the main histologic subtypes of HL. In this analysis, we defined histologic subtypes according to the WHO classification system (5): nodular sclerosing (NS), mixed cellularity (MC), nodular lymphocyte predominance (nodular LP) and lymphocyte depletion (LD). Beginning with 2001 data, lymphocyte rich (LR) could not be separated out. The subtypes were assigned using ICD-O-2 morphology codes (6): NS (M-9663-9667), MC (M-9652), nodular LP (M-9659) and LD (M-9653-9655). Patients with unknown histologic subtype were described as HL, not otherwise specified (NOS), ICD-O-2 code M-9650, and included in all analyses.

Statistical methods

Survival over time was measured by the relative survival rate, which measures the percentage of cancer patients surviving a given time from diagnosis adjusted for the survival experience of an age-, sex-, race-, and calendar year-matched cohort as determined from US vital statistics life tables. Detailed information regarding the calculation of the relative survival rate is provided in the introduction to this monograph.

RESULTS

Between 1988 and 2001, the availability of effective therapy for HL is reflected in the favorable relative survival rates for patients diagnosed in SEER areas. Ninety-two percent of all patients survived beyond one year after diagnosis, relative to the general population. However, this rate decreased steadily with time since diagnosis. Relative survival rate was 83% at five years and 78% at ten years (Table 27.2). As detailed below, relative survival for HL varies by age, sex, race/ethnicity, and stage of disease (Table 27.2). Relative survival was not observed to vary substantially by SEER region (data not shown).

Table 27.2: Hodgkin Lymphoma: Number and Distribution of Cases and Relative Survival Rates (%) by Sex, Race, Age (15+), Ann Arbor Stage, and Symptoms, 12 SEER Areas, 1988-2001

Characteristics	Cases	Percent	Relative Survival Rate (%)					
			1-Year	2-Year	3-Year	5-Year	8-Year	10-Year
Total	11,720	100.0	92.0	88.3	86.2	83.0	79.1	78.1
Sex								
Male	6,428	54.8	91.2	87.0	84.5	80.8	76.3	75.5
Female	5,292	45.2	92.9	89.9	88.2	85.6	82.3	81.1
Race								
White	10,154	86.6	92.2	88.6	86.5	83.7	80.2	79.3
Black	1,129	9.6	90.3	85.8	83.9	77.5	70.7	69.4
Age (Years)								
15-44	8,001	68.3	97.3	94.5	92.8	89.9	86.6	85.4
45-64	2,165	18.5	89.1	83.5	79.9	74.8	67.4	64.9
65+	1,554	13.3	67.6	60.2	56.3	50.6	40.4	36.6
Ann Arbor Stage								
I	2,778	23.7	95.9	93.4	91.7	89.0	85.1	84.7
II	4,344	37.1	96.6	93.7	92.1	89.3	85.5	84.4
III	2,220	18.9	90.4	86.4	84.1	80.8	77.5	75.7
IV	1,893	16.2	77.7	71.0	67.4	62.6	57.3	56.0
Unknown	485	4.1	90.0	85.4	82.3	78.4	74.0	74.0
Symptoms								
A	4,015	34.3	96.4	94.5	93.2	91.1	87.7	87.2
B	4,139	35.3	88.0	83.1	80.1	76.2	71.9	69.9
Unknown	3,566	30.4	91.6	87.3	85.1	81.5	77.5	76.8

In general, young-adult female patients with early stage disease were observed to have the most favorable relative survival, while older, male patients with late stage disease had the least favorable survival rates.

Age at diagnosis

Age at diagnosis substantially impacted relative survival. Figure 27.1 shows five and ten-year relative survival rates by detailed age at diagnosis. Both five and ten-year estimates declined with advancing age at diagnosis. Ten-year relative survival rates generally exceeded 80% for persons 15-24, 25-34, and 35-44 years at diagnosis, but were substantially lower in older age groups. For persons diagnosed at age 75 or older, relative survival was poor, 38% at five years and 21% at 10 years.

Based both on observations from Figure 27.2 as well as epidemiologic features, the data were stratified into three age groups for further analysis: young adults (ages 15-44 at diagnosis), middle-aged adults (ages 45-64), and older adults (ages 65+). Figure 27.2 shows relative survival over time for patients diagnosed in these age groupings. In the first two years after diagnosis, relative survival decreased more sharply for older adults (65+) than young or middle-aged adults. At six months after diagnosis, the relative survival rates for older adults was lower than 80%, and at 24 months, had decreased further to nearly 60%. In contrast, relative survival rate exceeded 80% for young-adult patients across the entire ten-year follow-up period. Figure 27.2 also shows that relative survival does not stabilize but rather declines continuously over the ten-year follow-up period irrespective of age at diagnosis.

Sex

Figure 27.2 also shows that sex differentially impacts relative survival rate among young, middle-aged, and older adults. In young adults, females exhibit more favorable survival across the entire ten-year follow-up period, while male-female relative survival differences are smaller for middle-aged HL patients. These patterns are also evident in the five-year relative survival rates for males and females by age group. In young adults, five-year relative survival rate was 87% for males and 93% for females. In middle-aged adults, five-year rates were 74% for males and 77% for females, and females continued to exhibit better survival than males between five and ten years after diagnosis (Figure 27.2). There was little evidence of an influence by sex on relative survival among older adult patients aged 65 across the follow-up period, particularly at 48 months (males, 53%; females, 53%).

Race

The small numbers of non-white patients diagnosed with HL (total n=1,566) hinders detailed comparison of relative survival rates between racial/ethnic groups, particularly within older age groups. Regardless, relative survival rates was generally lower for persons of black race than for persons of white or "other" race/ethnicity. Among young adults aged 15-44 years at diagnosis, five-year relative survival rate for black males was 76%, substantially lower than the 88% rate observed in white males These racial/ethnic differences appeared to be independent of sex (Figure 27.3).

Figure 27.1: Hodgkin Lymphoma: 5- and 10-Year Relative Survival Rates (%) by Age at Diagnosis (15+), 12 SEER Areas, 1988-2001

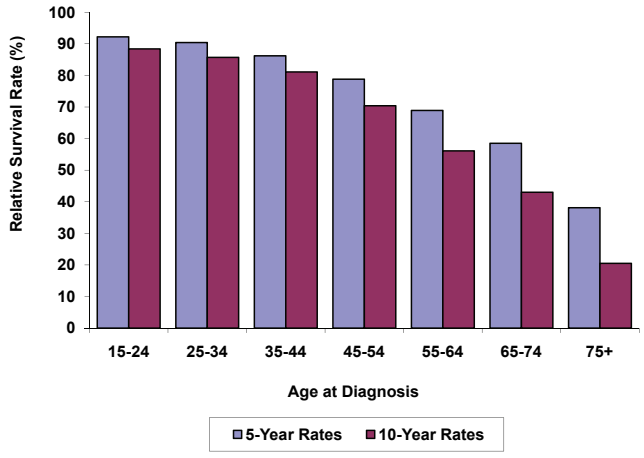


Figure 27.2: Hodgkin Lymphoma: Relative Survival Rates (%) by Age Group (15+) and Sex, 12 SEER Areas, 1988-2001

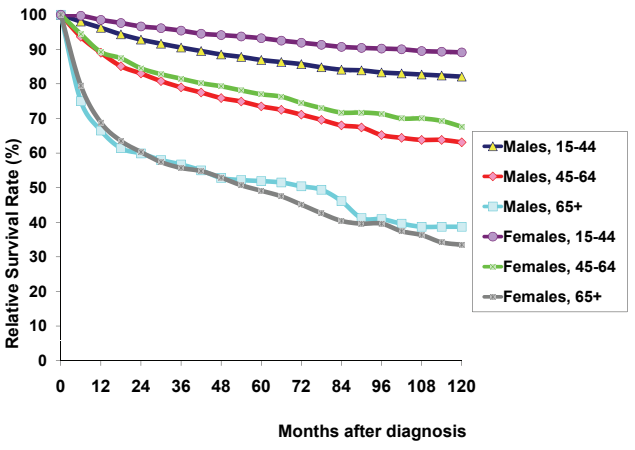


Table 27.3: Hodgkin Lymphoma: Number of Cases and 5-Year (Yr) Relative Survival Rates (RSR) (%) by Sex, Age (15+) and Ann Arbor Stage, 12 SEER Areas, 1988-2001 (Patients with Complete Stage Information: 8,047 Cases)

Sex/Age (Years)	Stage									
	Stages I-IV		IA		IB		IIA		IIB	
	Cases	5-Yr RSR (%)	Cases	5-Yr RSR (%)	Cases	5-Yr RSR (%)	Cases	5-Yr RSR (%)	Cases	5-Yr RSR (%)
Total	8,047	83.7	1,125	93.5	424	81.2	1,957	92.9	1,458	85.7
15-44	5,618	90.3	705	96.8	274	88.0	1,564	95.8	1,151	89.4
45-64	1,463	74.1	271	90.7	86	72.0	272	87.3	187	77.2
65+	966	51.5	149	79.1	64	56.9	121	58.5	120	52.2
Male	4,464	81.9	685	94.1	252	77.0	856	93.4	781	84.1
15-44	3,030	87.7	424	96.9	163	84.6	663	94.4	589	88.3
45-64	927	73.6	186	89.2	51	66.0	142	90.4	124	76.0
65+	507	53.0	75	84.1	38	52.2	51	73.5	68	49.9
Female	3,583	86.0	440	92.6	172	86.6	1,101	92.4	677	87.4
15-44	2,588	93.3	281	96.5	111	92.7	901	96.7	562	90.6
45-64	536	75.0	85	94.0	35	80.3	130	83.6	63	79.1
65+	459	49.2	74	71.7	26	61.0	70	43.2	52	52.9

~ Statistic not displayed due to less than 25 cases.

Table 27.3 (continued): Hodgkin Lymphoma: Number of Cases and 5-Year (Yr) Relative Survival Rates (RSR) (%) by Sex, Age (15+) and Ann Arbor Stage, 12 SEER Areas, 1988-2001 (Patients with Complete Stage Information: 8,047 Cases)

Sex/Age (Years)	Stage									
	Stages I-IV		IIIA		IIIB		IVA		IVB	
	Cases	5-Yr RSR (%)	Cases	5-Yr RSR (%)	Cases	5-Yr RSR (%)	Cases	5-Yr RSR (%)	Cases	5-Yr RSR (%)
Total	8,047	83.7	622	88.0	1,109	77.3	259	75.7	1,093	60.1
15-44	5,618	90.3	436	95.6	736	87.1	158	88.2	594	71.0
45-64	1,463	74.1	121	73.8	201	63.6	53	60.6	272	52.5
65+	966	51.5	65	53.5	172	39.7	48	42.5	227	33.5
Male	4,464	81.9	332	87.8	690	76.8	142	72.6	726	58.2
15-44	3,030	87.7	230	94.7	461	84.9	83	85.3	417	66.8
45-64	927	73.6	69	77.1	139	66.2	32	60.4	184	50.5
65+	507	53.0	33	51.0	90	40.6	27	35.7	125	32.2
Female	3,583	86.0	290	88.1	419	77.7	117	79.1	367	63.8
15-44	2,588	93.3	206	96.6	275	90.7	75	91.3	177	80.9
45-64	536	75.0	52	69.6	62	58.3	21	~	88	56.5
65+	459	49.2	32	53.6	82	38.2	21	~	102	34.2

~ Statistic not displayed due to less than 25 cases.

Stage and B-symptoms

Certain clinical presentations of HL had substantially worse five-year survival than others. Patients diagnosed with disseminated disease, stage IV (n=1,893) had markedly worse outcome than those with earlier stage disease, stage I (n= 2,778), stage II (n=4,344), and stage III (n=2,220), as captured by five-year relative survival rates (63% vs. 89%, 89%, and 81%, respectively) (Table 27.2). However, the presence of B-symptoms was a potent modifier of stage-specific survival, particularly for stage IV. Among the 8,047 patients with known stage and B-symptom status, comprising 69% of the HL patients in this analysis, patients with B-symptoms showed poorer survival across the ten-year follow-up period when compared to patients with similarly staged disease but without B-symptoms (Figure 27.4). In fact, patients with stage IIIA disease showed better survival than patients with stages IB and IIB disease. Survival curves for patients with stage IIIB disease were similar to those for patients with IVA, and survival time was substantially worse for patients with stage IVB than any of the other stages. Relative survival rate for patients with stage IVB was 76% at one year, 60% at five years, and 53% at ten years.

Figure 27.3: Hodgkin Lymphoma: 5-Year Relative Survival Rate (%) for Ages 15-44 by Race and Sex, 12 SEER Areas, 1988-2001

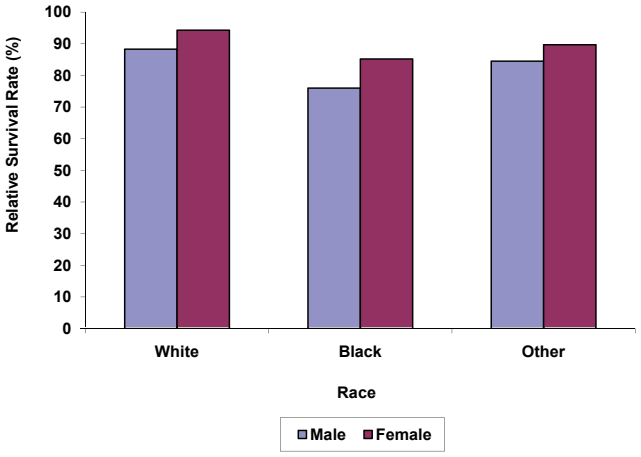


Figure 27.4: Hodgkin Lymphoma: Relative Survival Rates (%) by Stage and B-Symptoms, Ages 15+, 12 SEER Areas, 1988-2001 (Patients with Complete Stage & B Symptom Information: 8,047)

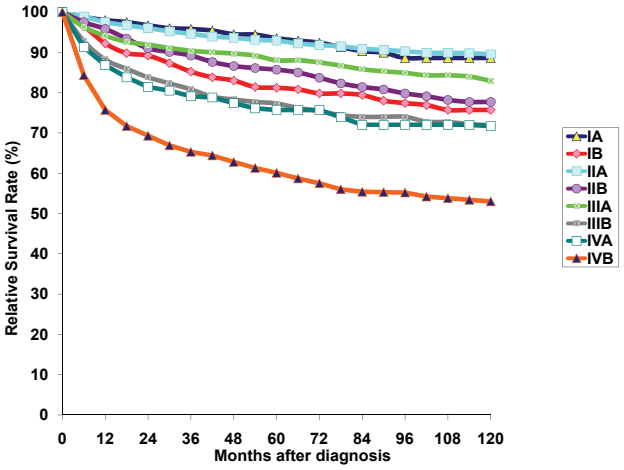


Table 27.4: Hodgkin Lymphoma: Number and Distribution of Cases and 1-, 2-, 3-, 5-, 8-, & 10-Year Relative Survival Rates (%) by Age (15+) and Histology, 12 SEER Areas, 1988-2001

Age (Years) /Histology (ICD-O Code)	Cases	Percent	Relative Survival Rate (%)					
			1-Year	2-Year	3-Year	5-Year	8-Year	10-Year
All Ages	11,720	100.0	92.0	88.3	86.2	83.0	79.1	78.1
Unknown HD, NOS (9650-9651,9661-9662)	1,666	14.2	84.9	80.4	77.8	74.0	69.5	68.3
HD MC (9652)	2,097	17.9	87.0	82.0	79.5	74.7	69.5	68.1
HD LD (9653-9655)	209	1.8	57.1	52.2	51.0	48.6	46.1	44.0
HD NS (9663-9667)	7,435	63.4	95.6	92.4	90.4	87.6	84.1	83.2
Nodular LP (9659)	313	2.7	98.1	96.9	95.0	91.2	88.4	85.7
Ages 15-44	8,001	100.0	97.3	94.5	92.8	89.9	86.6	85.4
Unknown HD, NOS (9650-9651,9661-9662)	908	11.3	92.3	88.6	86.4	83.5	79.5	78.5
HD MC (9652)	986	12.3	95.2	92.6	90.9	86.4	81.9	80.7
HD LD (9653-9655)	71	0.9	80.5	74.8	71.9	67.1	65.3	65.3
HD NS (9663-9667)	5,833	72.9	98.5	95.9	94.2	91.7	88.6	87.4
Nodular LP (9659)	203	2.5	97.7	96.8	95.9	92.5	90.9	89.8

Figure 27.5: Hodgkin Lymphoma: Relative Survival Rates (%) by Age Group (15+) and Stage, 12 SEER Areas, 1988-2001 (Patients with Complete Stage & B Symptom Information: 8,047)

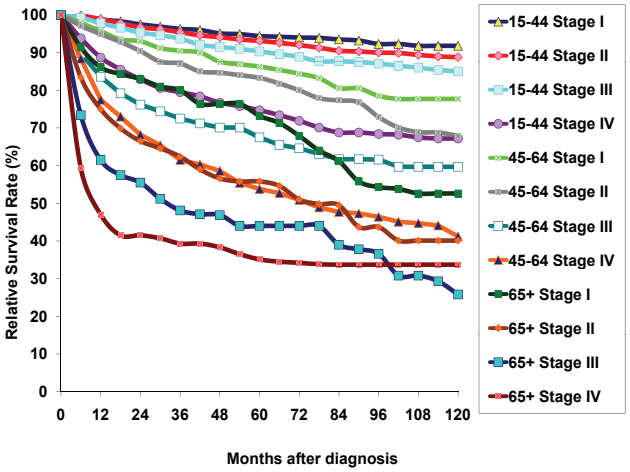
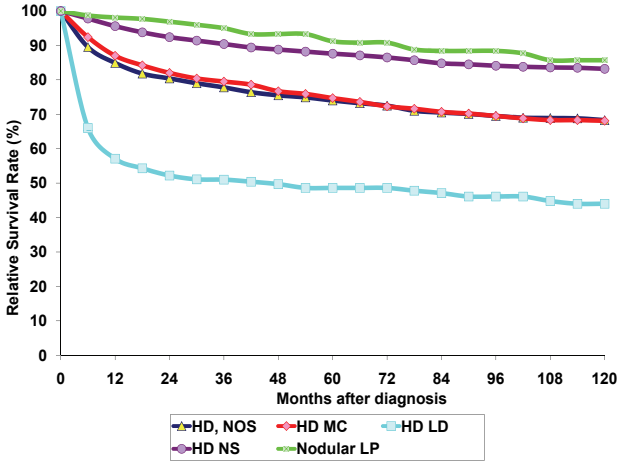


Figure 27.6: Hodgkin Lymphoma: Relative Survival Rates (%) by Histologic Subtype, Ages 15+, 12 SEER Areas, 1988-2001



However, like most features of HL, stage-specific survival is influenced strongly by age at diagnosis. Relative survival curves for young, middle-aged, and older adult HL patients by stage are shown in Figure 27.5. These curves show that stage at diagnosis modifies relative survival differently in young adults as compared to middle-aged and older adults. For young adults, there was little difference in relative survival rate over time for stages I, II, or III disease, but substantially poorer survival for persons with stage IV disease. For middle-aged and older adults, survival patterns were well-differentiated by stage and tended to show steeper declines in the first two years after diagnosis. Figure 27.5 also shows that relative survival did not level off but rather continually declined over time for nearly all age and stage groups, with the possible exception of stage IV disease in older adults. When B-symptoms are considered in addition to age and stage, it is additionally evident that age generally influences relative survival independently of these factors. Matched for stage and B-symptom status, relative survival rate decreased with increasing age at diagnosis. The survival deficit experienced by older adult patients became more profound with increasing disease spread. In patients with stage IA, five-year relative survival rate was 18 percentage points lower in older adults (79%) than in young adults (97%), but was 31-37 percentage points lower for patients with stages IB (57% vs. 88%), IIA (59% vs. 96%), and IIB (52% vs. 89%), and 37-47% lower for stages IIIA (54% vs. 96%), IIIB (40% vs. 87%), IVA (43% vs. 88%) and IVB (34% vs. 71%) (Table 27.3). Table 27.3 also shows five-year relative survival rates by stage and B-symptom status by age and sex. These data show that five-year relative survival rate were generally lower for males than females matched for stage/B-symptom status and age, although male-female differences were more pronounced for some age/stage combinations than for others. For example, relative survival rates for young adult males with stage IA or IIA disease were nearly equivalent to those for young adult females, but the rate for young adult males with stage IVB disease was 14 percentage points lower than that for young adult females. Overall, the range of five-year relative survival rates was wide; with the most favorable survival rates (97%) observed in young adult females and males with stage IA disease, and the poorest rates observed in older adult males with stage IVB (32%).

Histology

Histologic subtype additionally influences relative survival rates, although the relative rarity of some subtypes and the strong association of subtype with other prognostic factors (e.g., age, sex, race) make this influence difficult to examine. As shown in Table 27.4, NS comprised 73% of all young-adult cases and 63% of all ages, while the second most common subtype, MC, was observed in only 12% of young-adult patients, and 18% overall. The other specific subtypes, nodular LP, and LD, together comprised less than 5% of all cases. Across all ages, five-year relative survival was higher for NS (88%) and nodular LP (91%) subtypes and was intermediate for the MC subtype (75%) and non-specified types (74%). These patterns were additionally evident when limiting the series to young adults only (Table 27.3). The LD histologic subtype represented less than 2% of all cases but exhibited a substantially poorer five-year relative survival rate than other subtypes both in young adults (67%) and across all ages (49%). Figure 27.6 shows relative survival rates for

histologic subtypes across the ten-year follow-up period. The starkly different survival profile of the LD subtype is evident throughout the ten years.

DISCUSSION

Compared to other cancers, the one-year relative survival rate for HL was generally favorable at 92%. This relatively good survival rate reflects the availability of curative therapies for HL, including radiation or combination chemotherapeutic regimens, the introduction of which in the 1960's resulted in immediate reductions in HL mortality rates (2). Additionally, the 5-year relative survival rate after diagnosis has improved markedly from 40% in the early 1960's to 84 % in 1999 (2).

However, unlike some other cancers, relative survival rates after HL declined steadily with time since diagnosis, to 83% at five years and 78% at ten years. The fact that relative survival does not level off for most groups likely reflects ongoing risks of disease recurrence and long-term complications of treatment. Because most HL patients are young adults at the time of diagnosis, exposure to radiation and chemotherapy intended to cure HL at young ages has been shown to substantially increase risks of second or later malignancies (7) particularly breast cancer in young women (8). Other second malignancies observed in cohorts treated for HL include acute leukemias and non-Hodgkin's lymphomas (9). Within the first 15 years after diagnosis, HL is the major cause of death among HL patients, but soon after this time, cumulative mortality from second malignancies exceeds cumulative mortality from HL (10). Long-term risks of treatment-associated heart disease (11) and reproductive sterility are additionally important quality-of-life issues for HL survivors.

We observed substantial variation in relative survival rates by age at diagnosis. Most epidemiologic and clinical features of HL differ between young and older-adults (12), and relative survival is no different. The relative ten-year survival rate was nearly 90% for ages 15-24, but only 21% for persons diagnosed at age 75 or older. Age differences in survival patterns have been examined in detail by other authors and have also been interpreted as further evidence of the "two-disease" theory holding that young-adult and older-adult HL are etiologically distinct diseases (13).

As is the case with most cancers, stage or degree of disease spread at time of diagnosis profoundly impacts survival after HL, as patients with stage IVB disseminated disease had significantly shorter 5-year survival rate (60%) than those with less advanced disease, regardless of age (76-94%). The impact of stage on survival, however, was modified by age, reflecting the clinically more aggressive nature of the disease in older adults.

In these data, B-symptom status clearly altered survival, and like age, it modified the impact of stage on survival. Patients with no B-symptoms but diagnosed with stage III disease had higher survival rates than those diagnosed with early stage (I and II) disease with B-symptoms. B-symptom status has been long associated with poor prognosis in lymphoma patients and may be caused by tumor-related dysregulation of certain cytokines.

HL survival also varied by histology. Histologic subtypes were strongly associated with age, with younger patients more likely to have NS, the subtype associated with the most favorable survival rate. However, within histologic categories, younger patients consistently had higher survival rates than older patients. Patients with the LD subtype had considerably worse survival than patients with other subtypes, as described previously (14).

In this relatively large, population-based series of patients, we were able to examine the influences of demographic characteristics like race and sex. The poorer survival rates observed for blacks than whites have been reported previously and appear to be independent of stage and other prognostic factors (15). We also observed intriguing differences by sex in survival after HL. Males exhibited poorer relative survival rates than females in young adults across nearly all stages of disease, but not in persons over 45 years of age. In young adults, male sex has been shown to be associated with HL survival independently of other factors in previous analyses using SEER data (13).

In summary, survival following HL is relatively favorable, and the 83% five-year relative survival rate observed in this population-based cohort is comparable to those reported in clinical settings. However, relative survival rate was observed to vary substantially with sex, stage at diagnosis, B-symptom status, histology, and, especially, age at diagnosis. Indeed, the generally good average survival rates for HL largely represent the outcome of patients diagnosed at ages 45 and younger, who comprise the majority of patients in the US. However, the relatively young average age of the HL patient amplifies the effect of this cancer on the overall cancer burden; it ranks third in the average years of life lost to a cancer. Although substantial progress has been made against HL, the current challenges facing HL clinicians and researchers include reducing treatment-related side effects to improve the quality-of-life for long-term HL survivors and improving outcomes for older patients.

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