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Risk of Leukemia Among Survivors of Testicular Cancer: A Population-based Study of 42,722 Patients

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Abstract

Purpose—The aim of this study is to quantify excess absolute risk (EAR) and excess relative risk (ERR) of secondary leukemia among a large population-based group of testicular cancer survivors.

Methods—We identified 42,722 1-year survivors of testicular cancer within 14 population-based cancer registries in Europe and North America (1943–2002). Poisson regression analysis was used to model EAR (per 100,000 person-years [PY]) and ERR of secondary leukemia. Cumulative risks were calculated using a competing risk model.

Results—Secondary leukemia developed in 89 patients (EAR = 10.8 per 100,000 PY, 95% confidence interval [CI] = 7.6–14.6; ERR = 1.6, 95%CI = 1.0–2.2). Statistically significantly elevated risks were observed for acute myeloid leukemia (AML) (EAR = 7.2, 95%CI = 4.7–10.2) and acute lymphoblastic leukemia (EAR = 1.3, 95%CI = 0.4–2.8). In multivariate analyses, AML risk was higher among patients whose initial management included chemotherapy compared to those receiving radiotherapy alone ($p = 0.1$). Excess cumulative leukemia risk was approximately 0.23% by 30 years after testicular cancer diagnosis.

Conclusions—Although ERR of leukemia following testicular cancer is large, EAR and cumulative risk, which are better gauges of the population burden, are small.

Keywords

Testicular Neoplasms; Leukemia; Second Primary Neoplasms; Cohort Studies

Introduction

Testicular cancer is largely curable because of treatment advances, resulting in a 5-year relative survival rate of more than 95% (1). This growing number of survivors is at increased risk of developing leukemia 2, 3, 4, 5, 6, 7 and 8. However, few reports quantify the excess absolute risk (EAR) of secondary leukemia. The EAR is a useful measure for estimating the magnitude of disease burden in a population since it reflects underlying cancer incidence rates. Furthermore, no large, population-based study has estimated EAR and excess relative risk (ERR) according to type of secondary leukemia (i.e., acute myeloid leukemia [AML], acute lymphoblastic leukemia [ALL], and chronic myelogenous leukemia [CML]) following testicular cancer treatment, using multivariate analyses to evaluate the effects of age at diagnosis, attained age, calendar year of testicular cancer diagnosis, time since testicular cancer diagnosis, and initial treatment.

Methods

Men diagnosed with a first primary cancer of the testis between January 1, 1943 and December 31, 2001, and who survived 1 or more years were identified within 14 population-based cancer registries in Ontario (*N* = 6,235; 1964–2000), Denmark (*N* = 7,879; 1943–1998), Finland (*N* = 1,845; 1953–2001), Norway (*N* = 4,934; 1953–1999), Sweden (*N* = 6,157; 1958–2001), and the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (*N* = 15,672; 1973–2002).* Testicular cancer patients were grouped according to the *International Classification of Diseases for Oncology* into seminomas (9060–9063) and nonseminomas (9070–9073, 9080–9085, and 9100–9102). Patients with extragonadal germ cell tumors or testicular lymphomas were excluded. This cohort and characteristics of these registries have been described previously (9), with updated follow-up for SEER added for this investigation. Briefly, all participating cancer registries collect data on patient demographics and vital status at last follow-up. With the exception of Sweden and Ontario, all registries collect information on disease stage and initial type of cancer therapy, given in broad categories. Registries record information on initial therapy only and do not include data on subsequent therapy, including therapy given for a relapse, or details of specific treatment regimens. Detailed information for each individual registry, including the size of the population covered, is provided in *Cancer Incidence in Five Continents*(10). Leukemia cases used in this study overlap with previous investigations 5, 6 and 11.

Leukemia cases diagnosed at least 1 year after testicular cancer were identified through a search of cancer registry incidence files and linked by using unique identifiers within each registry. Follow-up began 1 year after date of testicular cancer diagnosis and ended on date of death, date of diagnosis of a second cancer, or the study end date, whichever occurred first. Study end dates varied by registry as follows: SEER, December 31, 2003; Sweden and Finland, December 31, 2002; Ontario, December 31, 2001; Norway, December 31, 2000; Denmark, December 31, 1999. Since chronic lymphocytic leukemia (CLL) has not been associated with antecedent radiotherapy or chemotherapy, it was not included.

Person-years (PY) and leukemia cases were categorized by histologic type of testicular cancer (seminoma, nonseminoma, other), calendar year of testicular cancer diagnosis (<1975, ⩾1975), initial treatment, registry, and by 5-year intervals of attained age, attained calendar year, time since testicular cancer diagnosis, and age at testicular cancer diagnosis. Calendar year periods were chosen based on general trends in testicular cancer therapy. In the past, standard treatment for testicular cancer after orchidectomy included radiotherapy to the infradiaphragmatic lymph nodes, with larger doses given to nonseminomatous germ cell patients (45–55 Gy) compared to seminoma (25–35 Gy) (9). Chemotherapy for advanced testicular cancer was introduced in the mid-1970s, in the form of platinum-based regimens (12), with etoposide added in the early 1980s (13). Since the 1970s, an increasing number of nonseminomatous germ cell patients have been treated with surgery and chemotherapy, instead of radiotherapy (9). Accumulated PY at risk for each category defined by registry, male sex, and 5-year attained age and calendar year intervals were multiplied by leukemia incidence rates in the corresponding general population to calculate expected cases in each stratum.

In general, O and E are used to denote observed and expected numbers of incident leukemias, respectively. O_i, E_i, and PY_i denote, respectively, observed cases, expected cases, and person-years in a specific cell of the person-year table. Poisson regression methods used in this study have been described elsewhere (9) and were implemented using the AMFIT module of the software package EPICURE (14).

The EAR was defined as the difference in risks between testicular cancer patients and the general population and is expressed as the number of excess cases per 100,000 PY. The ERR was defined as RR-1, where RR denotes the ratio of risk in testicular cancer patients to that in the general population. Simple estimates of the RR are presented as the *O/E* ratio. The statistical expectation of O_i is assumed to be

$$E_i + PY_i \mathrm{EAR}(x_i), \text{ for the EAR model, and}$$

$$E_i\,[1 + \mathrm{ERR}(x_i)], \text{ for the ERR model,}$$

where x is a vector of variables upon which the EAR and ERR depends. Trend tests were obtained by fitting models in which the logarithm of EAR or ERR was expressed as a linear function of the variable of interest. Analyses that included continuous variables were based on mid-points of 5-year intervals. Multivariate analyses were based on models of the form EAR (ax, k, t) or ERR (ax, k, t) = $\theta k \exp[\alpha t + \beta(ax\text{-}35)]$ where k indexes categories of the variable of interest, t = 1 for the 5+ year latency period, 0 otherwise; and ax is age at diagnosis in years. Thus risks are presented for the latency period 1–4 years and 35 years of age at diagnosis. Parameter estimates were computed with maximum likelihood methods. Hypothesis tests and confidence intervals were based on evaluation of the profile likelihood. Two-sided p values were used throughout. Cumulative risks were calculated by using a competing risk analysis similar to that used in a study of solid tumors in the same cohort (9).

Results

The average age at testicular cancer diagnosis for the 42,722 1-year survivors was 35 years (seminoma = 38; nonseminoma = 29). Secondary leukemia (excluding CLL) developed in 89 patients compared to 34.5 expected (*O/E* = 2.6, 95% confidence interval [CI] = 2.1–3.2) (Table 1). Statistically significantly elevated risks were observed for AML (*O* = 53, *O/E* = 3.1, 95% CI = 2.3–3.9) and ALL (*O* = 10, *O/E* = 3.1, 95% CI = 1.5–5.4; EAR = 1.3, 95% CI = 0.4–2.8), with borderline significant excesses for CML (*O* = 16, *O/E* = 1.7, 95% CI = 1.0–2.7; EAR = 1.0, 95% CI, <0–2.8).

Risk of leukemia was highest in the first 5 years after testicular cancer diagnosis (Table 2), with a strong decrease with increasing time since diagnosis observed in both the EAR ($p = 0.051$) and ERR ($p < 0.001$), but remained statistically significantly elevated beyond 15 years. The ERR for developing all leukemia and AML decreased with increasing age at diagnosis and attained age, but there was no evidence of such decrease for the EAR. Both the EAR and ERR for AML were nonsignificantly higher for patients treated after 1975 compared to earlier years; however, risks in the two time periods were comparable among patients receiving radiotherapy only. There were too few patients available for analyses to evaluate the effect of chemotherapy separately for the two treatment eras. Overall the EAR and ERR for AML was higher among patients whose initial management included chemotherapy compared with those who received radiotherapy only.

The analyses in Table 2 indicate that the EAR depended only on latency. Thus a simple description of the data is provided by a model in which the EAR is 17.9 (95% CI = 11.2–26.2) for the period 1–4 years from testicular cancer diagnosis and 7.3 (95% CI = 3.8–11.5) for the period 5 or more years from testicular cancer diagnosis. Based on this model, excess cumulative risk was approximately 0.14% by 15 years after testicular cancer diagnosis and about 0.23% by 30 years after testicular cancer diagnosis.

The unadjusted risk of leukemia was similar in seminoma (EAR = 10.9, 95% CI = 6.5–16.1; ERR = 1.3, 95% CI = 0.8–2.0) and nonseminoma patients (EAR = 10.9, 95% CI = 6.3–16.9; ERR = 2.2, 95% CI = 1.2–3.5) (Table 3). Multivariate analyses according to testicular cancer histology showed that the ERR of leukemia following seminoma decreased strongly with increasing age at testicular cancer diagnosis ($p = 0.005$), whereas the EAR depended only on latency. Among seminoma patients given radiotherapy only, the excess and absolute risk of leukemia decreased nonsignificantly for those patients diagnosed after 1975.

Discussion

To our knowledge, this is the first large, international population-based study to use multivariate modeling to describe and quantify both EAR and ERR of leukemia by subtype following testicular cancer. New findings include the strong decrease in the ERR with increasing age at diagnosis and a decrease in both the EAR and ERR with latency. Additionally, a decreased risk of leukemia was suggested among seminomatous testicular cancer patients receiving radiotherapy only after 1975. This may reflect improvements in radiation therapy, which include decreased radiation dose, more accurate delineation of the

target volumes because of the use of computed tomography, and the abandonment of mediastinal irradiation 12, 15 and 16. We found that risk could be described by an EAR model that depended only on latency, and we were able to use this large cohort study to estimate cumulative risk of excess leukemia, taking account of competing risks.

Previous cohort studies 7 and 11 support our observation that risk of leukemia and AML remain elevated for more than 15 years after testicular cancer diagnosis. Several other cohort investigations specifically document increased leukemia risks associated with chemotherapy for testicular cancer 2, 3, 4, 6, 17 and 18. Results of our study suggest that AML risk is higher among men receiving chemotherapy for testicular cancer as well as those treated after 1975, which marks the introduction of platinum-based chemotherapy, with etoposide being added soon thereafter. A recent pooled analysis (11) attributed a similar finding among nonseminoma survivors to the introduction and increased use of etoposide.

A large analytic case-control study of leukemia following testicular cancer, which collected detailed information on treatment, showed that increasing cumulative dose of cisplatin was associated with an increasing relative risk of leukemia (trend for $p = 0.001$) (6). Furthermore, a significant dose response was demonstrated for radiation dose to active bone marrow delivered during treatment of testicular cancer and subsequent leukemia risk. The radiotherapy techniques largely represented those used in the past (which included chest radiotherapy). A nonsignificant excess of leukemia was observed following modern radiotherapy regimens in which treatment is typically limited to the abdomen and pelvis. Although detailed treatment data were not available in our study, the large number of cases and cohort design allowed us to describe absolute risk and to evaluate modification of risk by several variables that were not possible in previous studies.

Our results should be interpreted within the context of the strengths and limitations of registry-based data. Population-based studies reduce the selection bias associated with hospital or clinical series and allow for evaluation of site-specific risk. The quality of the follow-up data is exceptional for the Nordic countries since they have nationwide registration and comprehensive cancer, mortality, and emigration reporting within their countries. Potential limitations include incomplete treatment data and absence of detailed therapy information, which may serve to attenuate any differences between treatment categories. Furthermore, given the small numbers in substrata analysis and multiple comparisons, some statistically significant associations could be generated by chance alone. However, our risks may represent underestimates because of underreporting of secondary leukemia that has been observed in population-based cancer registries 19, 20 and 21 and because reporting of myelodysplastic syndrome is not uniformly required. In addition, subsequent cancers are not recorded in the SEER database for patients who move from their original SEER geographic area, which is most likely to be important for metropolitan areas, for the longest follow-up observation periods, and for young adults (22). However, observed leukemia risks were similar across all registries.

Additional investigations with details on treatment regimens and prolonged follow-up are needed to clarify patterns observed in our study. It should be noted that although the ERR of

leukemia following testicular cancer is large, the EAR and cumulative risk are small. Thus improvements in survival because of treatment advances outweigh the risk of this late effect.

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Table 1

Characteristics of population-based cohort of 43,722 1-year survivors of testicular cancer and risk of leukemia according to subtype*

			All leukemia		AML		ALL		CML	
Characteristic	**No. of patients**	**Person-years of follow-up**	**No.**	***O/E* (95%CI)**	**No.**	***O/E* (95%CI)**	**No.**	***O/E* (95%CI)**	**No.**	***O/E* (95%CI)**
All patients	42,722	501,711	89	2.6 (2.1–3.2)	53	3.1 (2.3–3.9)	10	3.1 (1.5–5.4)	16	1.7 (1.0–2.7)
GCT, seminoma	23,840	287,000	55	2.3 (1.8–3.0)	32	2.6 (1.8–3.7)	6	3.2 (1.3–6.5)	9	1.4 (0.7–2.6)
GCT, nonseminoma	17,664	201,707	32	3.2 (2.2–4.5)	20	4.2 (2.6–6.3)	4	3.1 (1.0–7.2)	6	2.2 (0.9–4.4)
Other/unspecified histology	1,218	13,004	2	2.0 (0.3–6.3)	1	2.1 (0.1–9.2)	0	—	1	4.0 (0.2–17.6)
Age (yr) at testicular cancer diagnosis										
<30	15,653	192,214	27	4.1 (2.8–5.9)	20	6.8 (4.2–10.2)	4	3.4 (1.1–7.9)	1	0.5 (0.0–2.4)
30–39	15,013	179,590	23	2.3 (1.5–3.4)	10	2.0 (1.0–3.5)	3	3.0 (0.8–7.9)	8	2.8 (1.3–5.2)
⩾40	12,056	129,906	39	2.2 (1.6–2.9)	23	2.4 (1.6–3.6)	3	2.7 (0.7–7.1)	7	1.5 (0.7–3.0)
Calendar year of testicular cancer diagnosis										
1943–1974	6,638	139,251	30	2.2 (1.5–3.0)	13	1.9 (1.0–3.1)	4	4.4 (1.4–10.3)	8	2.2 (1.0–4.2)
1975–2002	36,084	362,459	59	2.8 (2.2–3.6)	40	3.8 (2.8–5.1)	6	2.5 (1.0–5.1)	8	1.4 (0.6–2.6)
Initial treatment										
Surgery only	10,007	103,767	10	1.6 (0.8–2.9)	9	2.8 (1.4–5.1)	0	—	1	0.6 (0.0–2.7)
RT, no CT	13,682	184,810	39	2.7 (1.9–3.6)	20	2.5 (1.6–3.8)	5	4.4 (1.6–9.4)	8	2.1 (1.0–3.9)
CT, no RT	5,283	48,333	8	3.9 (1.8–7.3)	7	6.8 (2.9–13.2)	0	—	0	—
RT and CT	842	8,785	2	4.5 (0.7–13.8)	2	8.5 (1.4–26.3)	0	—	0	—
No, of patients entering follow-up interval										
1–4 yr	42,722	146,814	32	4.8 (3.3–6.6)	22	7.1 (4.6–10.6)	5	5.5 (2.0–11.8)	2	1.1 (0.2–3.3)
5–9 yr	32,157	137,261	18	2.5 (1.5–3.8)	12	3.4 (1.8–5.7)	1	1.2 (0.1–5.4)	4	1.9 (0.6–4.5)
10–14 yr	23,053	94,868	13	2.1 (1.1–3.4)	5	1.6 (0.6–3.4)	2	3.4 (0.6–10.5)	5	2.9 (1.0–6.2)
⩾15 yr	15,148	122,767	26	1.8 (1.2–2.6)	14	1.8 (1.0–3.0)	2	2.1 (0.4–6.6)	5	14 (0.5–3.0)

CI = confidence interval; GCT = germ cell tumor; RT = radiotherapy; CT = chemotherapy.

*O = Observed number of cases; E = expected number of cases; O/E = observed-to-expected ratio

Table 2

Excess absolute risk and excess relative risk by subtype and variables of interest*

	All leukemia (no CLL)			AML		
	No.	**EAR (95% CI)**	**ERR (95% CI)**	**No.**	**EAR (95% CI)**	**ERR (95%CI)**
Total, unadjusted	89	10.8 (7.6–14.6)	1.6 (1.0–2.2)	53	7.2 (4.7–10.2)	2.1 (1.3–2.9)
Latency†						
1–4yr	32	17.9 (11.2–26.2)	4.6 (2.9–6.8)	22	12.9 (7.6–20.1)	8.0 (4.7–12.4)
5–9 yr	18	8.0 (3.0–14.9)	1.8 (0.6–3.3)	12	6.0 (2.0–11.8)	3.0 (1.1–6.0)
10–14 yr	13	6.8 (1.1–15.3)	1.2 0.2–2.8)	5	2.2 (<0–8.0)	0.8 (<0–3.0)
⩾15 yr	26	8.1 (1.2–17.4)	0.8 (0.1–1.7)	14	5.1 (0.6–12.0)	0.9 (0.2–2.2)
p Trend		0.051	<0.001		0.034	<0.001
Age at TC diagnosis‡						
< 30 yr	27	18.6 (9.8–31.7)	7.7 (41–13.1)	20	16.1 (8.1–38.5)	17.1 (8.8–30.0)
30–39 yr	23	13.3 (5.8–24.7)	3.7 (1.6–7.1)	10	5.6 (1.1–13.7)	4.0 (0.9–9.6)
⩾40 yr	39	23.2 (10.9–40.5)	2.5 (1.0–4.4)	23	17.8 (7.8–33.2)	3.7 (1.4–7.2)
p Trend		0.415	0.006		>0.50	0.002
Attained age‡						
<40yr	27	16.5 (9.5–25.9)	5.7 (3.3–9.1)	17	11.7 (6.1–19.7)	10.2 (5.3–17.3)
40–49 yr	21	19.3 (8.7–36.0)	4.5 (2.0–8.4)	12	13.2 (4.9–27.6)	6.8 (2.6–14.2)
⩾50yr	41	23.9 (9.3–47.8)	1.7 (0.6–3.4)	24	20.0 (7.2–42.9)	2.6 (0.8–5.9)
p Trend		>0.50	<0.001		>0.50	<0.001
Initial treatment§,‖						
Radiotherapy only	39	19.5 (10.0–33.7)	5.3 (2.7–9.2)	20	10.5 (3.9–21.3)	6.3 (2.4–12.8)
Any chemotherapy	10	22.5 (8.0–46.7)	6.1 (2.0–12.8)	9	24.6 (9.5–50.5)	14.6 (5.5–29.9)
p Diff		>0.50	>0.50		0.131	0.142
Calendar year of TC diagnosis						
All treatments§,¶						
<1975	30	19.8 (8.2–39.1)	4.0 (1.5–8.4)	13	7.1 (<0–19.9)	3.3 (<0–10.4)
1975+	59	17.5 (10.7–26.3)	4.7 (2.9–7.1)	40	14.2 (8.2–22.3)	8.7 (5.1–13.6)
p Diff		>0.50	>0.50		0.230	0.103

	All leukemia (no CLL)			AML		
	No.	**EAR (95% CI)**	**ERR (95% CI)**	**No.**	**EAR (95% CI)**	**ERR (95%CI)**
Radiotherapv only[§,//]						
<1975	19	23.5 (7.4–56.3)	5.8 (1.8–14.5)	9	8.7 (<0-30.7)	5.3 (0.5–20.6)
1975+	20	16.2 (5.9–33.7)	4.8 (1.8–9.7)	11	7.9 (1.6–21.4)	5.1 (1.1–13.2)
p Diff		0.491	>0.50		>0.50	>0.50

CLL = chronic lymphocytic leukemia; AML = acute myeloid leukemia; EAR = excess absolute risk; ERR = excess relative risk; TC = testicular cancer; Diff = difference.

[*] EAR = excess cases per 100,000 person-years, *p* Values represent likelihood ratio test. As indicated below, estimates adjusted for latency are shown for period 1—4 years since testicular cancer diagnosis and estimates adjusted for age at testicular diagnosis are presented for age 35 years.

[†] Adjusted for age at testicular cancer diagnosis only.

[‡] Adjusted for latency only.

[§] Adjusted for latency and age at diagnosis ot testicular cancer.

[//] Includes only those registries that collect data on initial treatment (i.e., SEER Program, Denmark, Finland, Norway).

[¶] Reflects all registries, including those registries that do not collect initial treatment data.

Table 3

Excess absolute risk and excess relative risk for all leukemias (except CLL) by testicular cancer histology*

	Seminoma			Nonseminoma		
	No.	**EAR (95% CI)**	**ERR (95% CI)**	**No.**	**EAR (95% CI)**	**ERR (95% CI)**
Total, unadjusted	55	10.9 (6.5–16.1)	1.3 (0.8–2.0)	32	10.9 (6.3–16.9)	2.2 (1.2–3.5)
Latency†						
1–4 yr	22	21.1 (11.5–34.2)	6.2 (3.4–9.9)	10	15.1 (5.9–29.2)	3.9 (1.5–7.6)
5–14 yr	12	1.7 (<0–7.3)	0.4 (<0–1.6)	17	15.0 (6.5–26.7)	3.2 (1.5–5.5)
⩾15 yr	21	13.8 (3.5–27.4)	1.2 (0.2–2.4)	5	2.0 (<0–15.1)	0.3 (<0–1.7)
p Trend		0.389	0.004		0.057	0.003
Age at TC diagnosis‡						
<30 yr	9	21.9 (6.7–50.3)	9.4 (3.1–21.2)	18	16.1 (5.9–33.8)	6.5 (2.4–13.5)
30–39 yr	15	17.7 (6.5–36.6)	5.3 (1.9–11.2)	7	9.3 (0.8–27.0)	2.4 (<0–7.6)
⩾40 yr	31	27.2 (10.7–50.2)	2.8 (0.8–5.3)	7	14.4 (<0–51.7)	2.1 (<0–6.7)
p Trend		>0.50	0.005		0.407	0.435
Attained age‡						
<40 yr	10	16.5 (6.6–32.1)	5.8 (2.3–11.3)	17	14.1 (5.5–27.7)	5.1 (1.9–10.1)
40–49 yr	12	23.0 (8.6–47.1)	5.4 (2.0–11.0)	8	12.6 (2.6–38.3)	3.2 (0.7–9.4)
⩾50 yr	33	37.1 (13.8–74.0)	2.5 (0.7–5.2)	7	2.4 (<0–30.9)	0.7 (<0–3.5)
p Trend		>0.50	0.007		>0.50	0.049
Calendar year of TC diagnosis						
All treatments§,‖						
<1975	22	29.7 (9.7–65.5)	7.1 (2.2–16.6)	8	12.6 (1.3–41.1)	2.5 (0.1–8.7)
⩾1975	33	20.0 (10.2–34.1)	6.0 (3.2–10.1)	24	15.5 (6.1–30.5)	4.1 (1.5–8.1)
p Diff		0.464	>0.50		>0.50	0.448
Radiotherapy only§,¶						
<1975	16	40.4 (13.2–96.0)	10.0 (3.1–25.1)			
⩾1975	17	18.5 (6.6–38.6)	5.7 (2.1–11.5)			
p Diff		0.180	0.325			

CLL = chronic lymphocytic leukemia; EAR = excess absolute risk; ERR = excess relative risk; TC = testicular cancer; Diff = difference.

[*] EAR = excess cases per 100,000 person-years. *p* Values represent likelihood ratio test. As indicated below, estimates adjusted for latency are shown for period 1–4 years since testicular cancer diagnosis and estimates adjusted for age at testicular diagnosis are presented for age 35 years.

[†] Adjusted for age at testicular cancer diagnosis.

[‡] Adjusted for latency only.

[§] Adjusted for latency and age at diagnosis of testicular cancer.

[//] Reflects all registries, including those registries that do not collect initial treatment data.

[¶] Includes only those registries that collect data on initial treatment (i.e., SEER Program, Denmark, Finland, Norway).