EUROPEAN JOURNAL OF CANCER 48 (2012) 159–169

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

Burden of testicular, paratesticular and extragonadal germ cell tumours in Europe

A. Trama [a,*], S. Mallone [b], N. Nicolai [c], A. Necchi [c], M. Schaapveld [d,e], J. Gietema [f], A. Znaor [g,h], E. Ardanaz [i,j], F. Berrino [a], The RARECARE working group

[a] Department of Preventive and Predictive Medicine, Fondazione IRCSS, Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy
[b] Department of Cancer Epidemiology, Istituto Superiore di Sanità, Viale Regina Elena 299, Rome, Italy
[c] Department of Medicine, Urology Unit, Fondazione IRCSS, Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy
[d] Department of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
[e] Comprehensive Cancer Center Netherlands, Plesmanlaan 125, PO Box 9236, 1006 AE Amsterdam, The Netherlands
[f] Department of Medical Oncology, University Medical Center Groningen, Hanzeplein 1, 9700 RB Groningen, The Netherlands
[g] Croatian National Cancer Registry, Croatian National Institute of Public Health, Rockefellerova 7, 10000 Zagreb, Croatia
[h] Stampar School of Public Health, University of Zagreb Medical School, Rockefellerova 4, 10000 Zagreb, Croatia
[i] Consortium for Biomedical Research in Epidemiology and Public Health (CIBER Epidemiología y Salud Pública-CIBERESP), Spain
[j] Navarra Cancer Registry, Navarra Public Health Institute, C) Leyre 15, Pamplona 31003, Spain

ARTICLE INFO

Article history:
Available online 3 December 2011

Keywords:
Rare diseases
Testicular cancer
Paratesticular cancer
Germ cell tumour
Sex cord tumour
Cancer registries
Incidence
Prevalence
Survival

ABSTRACT

We provide updated estimates of survival, incidence, complete prevalence, and proportion cured for patients with testicular/paratesticular and extragonadal germ cell cancers in Europe, grouped according to the new list of cancer types developed by RARECARE. We collected data, archived in European cancer registries, with vital status information available to 31st December 2003.

We analysed 26,000 cases of testicular, paratesticular and extragonadal germ cell cancers diagnosed 1995–2002, estimating that about 15,600 new testicular/paratesticular and 630 new extragonadal cancer cases occurred per year in EU27, with annual incidence rates of 31.5/1,000,000 and 1.27/1,000,000, respectively. Slightly more than 436,000 persons were alive at the beginning of 2008 with a diagnosis of testicular/paratesticular cancer, and about 17,000 with a diagnosis of extragonadal germ cell cancer.

Five-year relative survival was 96% for testicular/paratesticular cancer and 71% for extragonadal germ cell cancer; the proportions cured were 95% and 69%, respectively. We found limited variation in survival between European regions except for non-semino matous testicular cancer, for which five-year relative survival ranged from 86% in Eastern Europe to 96% in Northern Europe. Survival for all cancer types considered decreased with increasing age at diagnosis.

Further investigation is required to establish the real reasons for the lower survival in Eastern Europe. Considering the high prevalence of these highly curable cancers, it is important to monitor patients long-term, so as to quantify treatment-related risks and develop treatments having limited impact on quality of life.

* *Corresponding author:* Tel.: +39 02 2390 3535; fax: +39 02 2390 3516.
E-mail address: annalisa.trama@istitutotumori.mi.it (A. Trama).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.08.020

1. Introduction

Although testicular cancers are rare, accounting for only 1% of all cancers in males, in many countries they are the most common malignancy in young men (15–35 years).[1] Approximately 98% of testicular cancers are germ cell cancers; the remaining 2% include sex cord tumours (including Leydig cell and Sertoli cell cancers), rhabdomyosarcoma and lymphoma. Two-to-5% of germ cell cancers are of extragonadal origin.[2]

The age-standardised incidence rate (ASR) for testicular cancers ranges from less than 1/100,000 person-years in Asian and African populations to 12/100,000 person-years in Denmark and Norway, with intermediate rates (3–6/100,000 person-years) in Spain, Italy, France, Poland, Finland and the UK, and somewhat higher rates (9–11) in Switzerland and Slovenia.[3] In Canada and the United States the ASR is around 5/100,000 person-years.[3]

Testicular cancer incidence has increased in many western countries over the last 40 years.[1,4] By contrast, mortality has declined since the mid 1970s, attributable to the development of effective treatments, which are typically multidisciplinary and centred around platinum-based chemotherapy.[5] Thus, in the 1990s EUROCARE estimate pooled 5-year relative survival at over 90% for European testicular cancer patients, with some differences between countries including significantly lower survival in Slovenia and Estonia.[6,7]

The aim of this paper is to provide updated estimates of the burden of testicular, paratesticular and extragonadal germ cell tumours in Europe. Specifically we provide population-based estimates of the survival, incidence, complete prevalence, and proportion of cured patients for these rare cancers grouped according to the new list of cancer types developed by RARECARE.[8] Extragonadal germ cell tumours include a few entities that occur in women: these are also considered in this paper since clinical management is the same for females as for males.

2. Materials and methods

The RARECARE list[8] classifies cancer entities (as defined by the 3rd edition of International Classification of Diseases for Oncology [ICD-O-3][9]) into a two-tier system (Table 1, first column). Tier 1 is the more general category and contains tier 2 subcategories. Tier 1 cancers were considered to involve the same clinical expertise and patient referral structure; tier 2 entities were considered to be similar from the point of view of clinical management and research.

In the present study we investigated cancers belonging to two RARECARE tier 1 categories: 'testicular and paratesticular cancers' and 'extragonadal germ cell tumours' (Table 1). The former comprises six tier-2 entities: paratesticular adenocarcinoma, non-seminomatous testicular cancer, seminomatous testicular cancer, spermatocytic seminoma, teratoma with malignant transformation, and testicular sex cord cancer as well not otherwise specified (NOS) entities which cannot be assigned to a tier 2 category.

Extragonadal germ cell tumours comprise the following tier 2 entities: extragonadal malignant immature teratoma, and extragonadal germ cell tumour; by definition there were no NOS entities among extragonadal germ cell tumours. The corresponding ICD-O-3 morphology and topography codes for these cancers are shown in the last two columns of Table 1.

RARECARE collected data on patients diagnosed with the above-defined cancers from 1978 to 2002, the data were archived in 89 European population-based cancer registries (CRs), all of which had vital status information available up to at least 31st December 2003. In the present paper we considered data from 76 CRs, since we excluded childhood CRs, and those that did not classify according to ICD-O-3. The CRs were grouped by country and the countries were grouped into regions: Northern Europe (Iceland, Norway, Sweden), United Kingdom and Ireland (England, Scotland, Wales, Northern Ireland, Republic of Ireland), Central Europe (Belgium, Austria, France, Germany, The Netherlands, Switzerland), Eastern Europe (Poland, Slovakia), and Southern Europe (Italy, Malta, Portugal, Slovenia, Spain).

The incidence analyses were carried out on cases from only 64 CRs, as it was necessary to exclude specialised CRs and other non-specialised CRs with information available only for some anatomical sites. Incidence rates were estimated as the number of new cases occurring in 1995–2002 divided by the total person-years in the general population (male and female) in each CR area over the same period. When estimating age-standardised incidence rates, the weightings of the European standard population were applied.[10]

The observed prevalence per 100,000 at the index date 1st January 2003 was estimated by the counting method[11] using data from cases incident 1988–2002. Only 22 CRs had continuous cancer registration over this 15-year period, and thus only the cases from these CRs were used to estimate the observed prevalence. To estimate the complete prevalence, the completeness index method[12] was used, and involved adding the estimated surviving cases diagnosed prior to 1988 to those counted (observed) in 1988–2002.

The expected numbers of new cases per year in Europe (EU27) and of prevalent cases in EU27 were estimated multiplying the crude incidence and prevalence estimates (obtained as described above) to the 2008 European population (497,455,033) provided by EUROSTAT.[13] In providing testicular, paratesticular and extragonadal germ cell tumours burden estimates, we assumed that the population covered by our CRs was representative of the population of the EU27 as a whole. Further details on methods and representativeness of RARECARE data are reported in the papers of Gatta et al.[14]

Five-year relative survival was estimated for cases diagnosed 2000–2002 using the period method of Brenner[15] since follow-up was only available to 2003. In this method, survival for the unavailable years is estimated from the survival experience of patient cohorts diagnosed in preceding periods. Specifically, survival in the first year after diagnosis was estimated directly from the survival data of the 2000–2002 patients, since they were followed to 31 December 2003. Conditional survival in the second year after diagnosis (conditional on being alive at the beginning of the second year of follow-up) was estimated from data on patients diagnosed in 1999–2001. Conditional survival in the third, fourth, and fifth years after diagnosis was estimated from the follow-up data of

Table 1 – Data quality indicators for testicular, paratesticular and extragonadal germ cell cancers diagnosed 1995–2002 and archived in 76 RARECARE cancer registries.

Tier	Entity	Cases (*N*)	Data quality indicator					ICD-O-3 codes	
			DCO only (%)	Autopsy only (%)	Microscopic verification (%)	1995–1998 cases censored before five years (%)	Morphology code NOS (%)[a]	Topography	Morphology (all malignant)
1	TESTICULAR AND PARATESTICULAR CANCERS	25,769	0.2	0.1	96.4	2.9	2.6	C62, C63.0, C63.1, C63.8	8000, 8001, 8010, 8011, 8120, 8123, 8140–8141, 8147, 8190, 8210–8211, 8221, 8231, 8255, 8260, 8261–8263, 8290, 8310, 8320, 8323, 8333, 8380–8384, 8401, 8430, 8440–8441, 8470, 8480–8490, 8504, 8510, 8512, 8514, 8525, 8542, 8550–8551, 8560, 8562–8576, 8590, 8630–8640, 8650, 8670, 9060–9102
2	Paratesticular adenocarcinoma with variants	12	0.0	0.0	100.0	8.3	NA	C63.0, C63.1	8120, 8123, 8140–8141, 8147, 8190, 8200, 8210–8211, 8221, 8230, 8231, 8255, 8260, 8261–8263, 8290, 8310, 8320, 8323, 8333, 8380–8384, 8401, 8430, 8440–8441, 8470, 8480–8490, 8504, 8510, 8512, 8514, 8525, 8542, 8550–8551, 8560, 8562–8576
2	Non-seminomatous testicular cancer	10,029	0.0	0.1	98.2	2.4	NA	C62	9080–9083, 9085, 9100–9102, 9065, 9070–9072
2	Seminomatous testicular cancer	13,906	0.0	0.1	98.4	3.2	NA	C62	9060–9062
2	Spermatocytic seminoma	223	0.4	0.4	96.9	7.6	NA	C62	9063
2	Teratoma with malignant transformation	11	0.0	0.0	100.0	9.1	NA	C62	9084
2	Testicular sex cord cancer	177	0.0	0.0	98.3	4.0	NA	C62	8630–8640, 8650, 8590–8592
1	EXTRAGONADAL GERM CELL TUMOURS	1141	0.1	0.5	95.9	1.8	NA	All cancers sites except C56 and C62	9060–9072, 9080–9085, 9101, and 9100 if not in placenta (C589)
2	Extragonadal malignant immature teratoma	366	0.3	0.8	97.0	1.1	NA	All sites except C56 and C62	9080–9085, 9101
2	Extragonadal germ cell tumour	775	0.0	0.4	95.4	2.2	NA	All sites except C56 and C62	9060–9072 and 9100 if not in placenta

ICD-O-3 = International Classification of Diseases for Oncology, 3rd revision.
DCO = cases identified on death certificate only; Morphology codes NOS (Not otherwise specified) are M8000-8001.
NA = Not applicable.

Table 2 – Observed cases with crude incidence (rate per million/year) and standard errors (SE) in Europe. Rates and SE by sex and age, with estimated incident cases in Europe (EU27). Cases diagnosed 1995–2002 in 64 European CRs.

Entity	EU overall			Sex						Age						Estimated cases in EU27 per year
				Male		Female		0–14		15–24		25–64		65+		
	Observed cases 1995–2002	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	
TESTICULAR AND PARATESTICULAR CANCERS	25,357	31.52	0.20	64.53	0.41			1.09	0.09	36.30	0.59	48.03	0.33	6.49	0.23	15,679
Paratesticular adenocarcinoma with variants	12	0.01	0.00	0.03	0.01			NE	NE	NE	NE	0.02	0.01	0.04	0.02	7
Non-seminomatous testicular cancer	9754	12.12	0.12	24.82	0.25			0.86	0.08	26.98	0.51	15.70	0.19	0.67	0.07	6031
Seminomatous testicular cancer	13,777	17.12	0.15	35.06	0.30			0.08	0.02	7.08	0.26	29.44	0.26	3.19	0.16	8518
Spermatocytic seminoma	221	0.27	0.02	0.56	0.04			NE	NE	0.07	0.03	0.35	0.03	0.50	0.06	137
Teratoma with malignant transformation	11	0.01	0.00	0.03	0.01			NE	NE	0.01	0.01	0.02	0.01	0.01	0.01	7
Testicular sex cord cancer	177	0.22	0.02	0.45	0.03			0.04	0.02	0.16	0.04	0.29	0.03	0.24	0.04	109
EXTRAGONADAL GERM CELL TUMOURS	1019	1.27	0.04	1.87	0.07	0.69	0.04	1.73	0.11	2.24	0.15	1.13	0.05	0.42	0.06	630
Extragonadal malignant immature teratoma	335	0.42	0.02	0.58	0.04	0.26	0.03	0.73	0.07	0.63	0.08	0.34	0.03	0.15	0.03	207
Extragonadal germ cell tumour	684	0.85	0.03	1.29	0.06	0.43	0.03	0.99	0.08	1.60	0.12	0.79	0.04	0.27	0.05	423

NE = Not estimated (observed cases = 0).

Table 3 – Age-standardised incidence rates (per 1,000,000) for testicular, paratesticular and extragonadal germ cell cancers in 1995–2002, with standard errors (SE) by European region.

Entity	Region											
	Northern Europe (*N* = 3845 testis and paratestis; *N* = 176 extragonadal)		Central Europe (*N* = 6406 testis and paratestis; *N* = 279 extragonadal)		Eastern Europe (*N* = 1924 testis and paratestis; *N* = 35 extragonadal)		Southern Europe (*N* = 3481 testis and paratestis; *N* = 226 extragonadal)		UK and Ireland (*N* = 9701 testis and paratestis; *N* = 303 extragonadal)		EU overall	
	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE	Rate	SE
TESTICULAR AND PARATESTICULAR CANCERS	35.75	0.58	35.75	0.58	25.60	0.59	22.62	0.39	33.00	0.34	30.64	0.19
Paratesticular adenocarcinoma with variants	NE	NE	NE	NE	0.01	0.01	0.00	0.00	0.01	0.01	0.01	0.00
Non-seminomatous testicular cancer	15.47	0.38	15.47	0.38	10.90	0.38	8.97	0.25	12.71	0.21	12.01	0.12
Seminomatous testicular cancer	19.51	0.42	19.51	0.42	11.84	0.40	11.71	0.28	18.07	0.25	16.52	0.14
Spermatocytic seminoma	0.09	0.03	0.09	0.03	0.24	0.06	0.28	0.04	0.23	0.03	0.25	0.02
Teratoma with malignant transformation	0.03	0.02	0.03	0.02	NE	NE	NE	NE	0.02	0.01	0.01	0.00
Testicular sex cord cancer	0.12	0.03	0.12	0.03	0.23	0.06	0.14	0.03	0.21	0.03	0.21	0.02
EXTRAGONADAL GERM CELL TUMOURS	1.73	0.13	1.73	0.13	0.56	0.10	1.68	0.12	1.10	0.06	1.34	0.04
Extragonadal malignant immature teratoma	0.58	0.08	0.58	0.08	0.20	0.06	0.53	0.07	0.42	0.04	0.45	0.03
Extragonadal germ cell tumour	1.15	0.11	1.15	0.11	0.35	0.08	1.15	0.09	0.68	0.05	0.89	0.03

NE = Not estimated (observed cases = 0).

[a]Northern Europe (Iceland, Norway, Sweden), Central Europe (Austria, Belgium, France, Germany, The Netherlands, Switzerland), Eastern Europe (Poland, Slovakia), Southern Europe (Italy, Malta, Slovenia, Portugal, Spain).

patients diagnosed, respectively, in 1998–2000, 1997–1999, and 1996–1998. Five-year survival estimates for 2000–2002 were obtained as the product of these conditional survival estimates.

The proportion of patients considered cured of their cancer was estimated by parametric cure models, which assume cured cases have the same mortality as the general population, while the complementary fraction (fatal cases) have an excess death rate attributed to the cancer in question.[16]

Table 1 shows the main data quality indicators for the 26,910 testicular, paratesticular and extragonadal germ cell tumours, diagnosed in 1995–2002, considered in the present study. Overall, 0.2% of these cases were diagnosed by death certificate only (DCO) and 0.1% were diagnosed at autopsy. A high proportion of cases (96% overall) was verified microscopically. The proportion of cases diagnosed in 1995–1998 and censored before 5 years of follow-up was 3% overall, ranging from 2.4% for non-seminomatous testicular cancer to 8.3% for paratesticular adenocarcinoma (with variants). About 3% of testicular and paratesticular cancers had unspecified morphology (ICD-O-3 code 8000 or 8001).

3. Results

3.1. Incidence

The total crude incidence of testicular and paratesticular cancers was 31.5/1,000,000 person-years, 55% of which were seminomatous and 38% were non-seminomatous. The crude incidence of these cancers in the male population was 65/1,000,000. A total of 15,679 of these cancers were estimated to be diagnosed each year in EU27. Seminomatous testicular cancer was the most common entity with a total crude incidence of 17/1,000,000, followed by non-seminomatous testicular cancer (12/1,000,000) (Table 2). For seminomatous cancers, incidence peaked in the 35–39 age group (50/1,000,000; data not shown). For non-seminomatous cancers, incidence was highest in the 15–24 age class (Table 2), even though incidence peaked at a later age (39/1,000,000 in the 25–29 age group; not evident in Table 2). Among boys (0–14 years), non-seminomatous cancers were the predominant histologic type, 51% of which were yolk sac tumours. Among the elderly (65 years and over) 80% of testicular and paratesticular cancers were seminomatous.

The total crude incidence of extragonadal germ cell tumour was 1.27/1,000,000 person-years. Incidence was highest in the 15–24 year age class (2.2/1,000,000), followed by ⩽14 years (1.7/1,000,000). Sites were predominantly mediastinum (24%), followed by pineal gland (13%), retroperitoneum (12%), brain (11%), female genital tract (8%) endocrine system (3%) and soft tissue (3%), with primary site unknown in 14%. The remaining 12% of cases occurred at disparate sites including head and neck, digestive tract, lung, prostate, urinary tract and other not specified sites (C76.0–76.8). Incidence was greater in men than in women.

Table 3 shows age-standardised incidence rates by European region. Non-seminomatous cancers had highest incidence (15.5/1,000,000) in Northern Europe and lowest (8.9/1,000,000) in Southern Europe. The incidence of seminomatous cancer was highest in Northern and Central Europe (19.5/1,000,000) followed closely UK and Ireland (18/1,000,000) and more distantly by Eastern and Southern Europe (12/1,000,000). Incidence rates for the other cancers varied relatively little between regions.

3.2. Survival

One-year relative survival was 97.9% for testicular and paratesticular cancers, and 83.3% for extragonadal germ cell tumours. Five-year relative survival was 96% for testicular

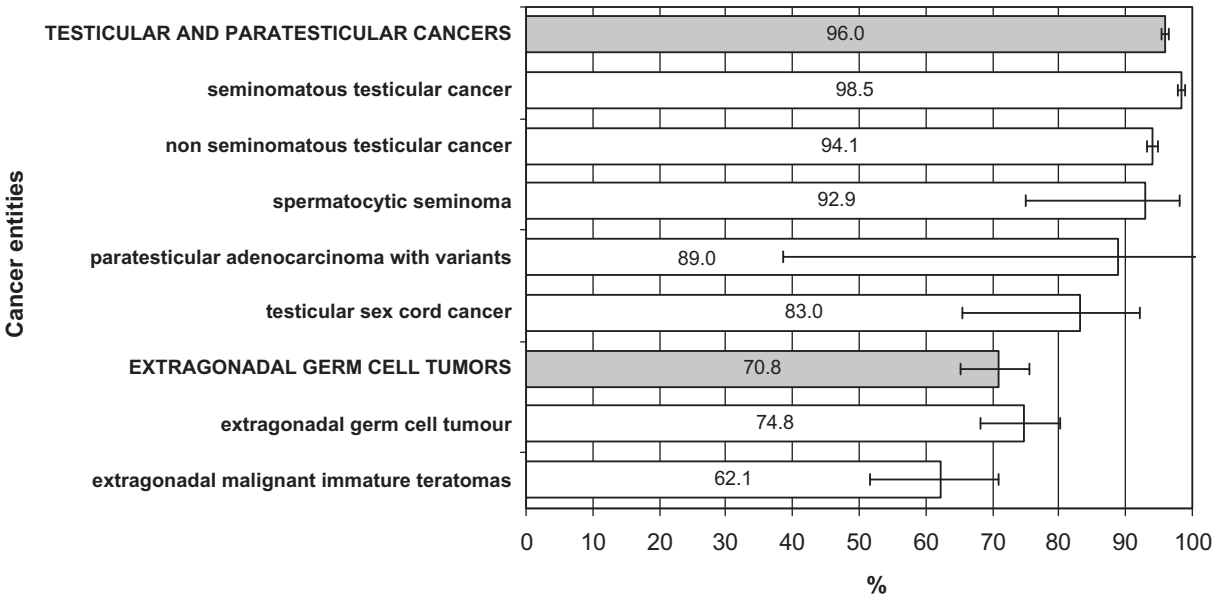

Fig. 1 – Five-year relative survival (%) for testicular, paratesticular and extragonadal germ cell tumors in Europe in 2000–2002. Error bars are 95% confidence intervals.

Table 4 – Five-year relative survival (number of cases and%) for testicular, paratesticular and extragonadal germ cell cancers with standard errors (SE) by age and European region for 2000–2002.

		Five-year relative survival									
		TESTICULAR AND PARATESTICULAR CANCERS			Non-seminomatous testicular cancer			Seminomatous testicular cancer			EXTRAGONADAL GERM CELL TUMOURS		
		Cases (N)	Survival (%)	SE	Cases (N)	Survival (%)	SE	Cases (N)	Survival (%)	SE	Cases (N)	Survival (%)	SE
Age	0–14	64	95.0	3.6	50	96.2	3.9	7	100.2	0.0	89	79.2	4.6
	15–24	1201	96.7	0.6	894	97.2	0.6	254	98.1	1.0	81	86.3	4.2
	25–64	6871	96.2	0.3	2248	93.0	0.6	4258	98.6	0.3	152	62.5	4.1
	65+	270	80.4	4.3	31	74.3	13.1	143	91.5	5.3	22	24.4	13.6
Region	Northern Europe	1544	97.3	0.5	642	96.3	0.8	872	99.0	0.6	76	77.5	5.4
	Central Europe	2325	96.1	0.5	809	94.1	1.0	1326	97.8	0.6	105	63.0	5.3
	Eastern Europe	765	91.5	1.2	350	86.2	2.0	341	99.1	1.1	18	77.8	13.0
	Southern Europe	1186	95.5	0.8	448	95.0	1.1	624	98.6	0.8	64	65.8	6.4
	UK and Ireland	2662	96.5	0.5	988	94.8	0.8	1564	98.6	0.5	98	74.0	5.0
	EU Overall	8360	96.0	0.3	3183	94.1	0.5	4636	98.5	0.3	343	70.8	2.7

and paratesticular cancers and 71% for extragonadal germ cell tumours (Fig. 1). Among testicular and paratesticular cancers, seminomatous forms had highest survival (98.5%; 95% Confidence Intervals (CI) 97.8–98.9) followed by non-seminomatous forms (94.1%; 95% CI 93.1–95.0) and spermatocytic seminomas (93%; 95% CI 75–98.1). Five-year relative survival was also good for sex cord tumours (83%; 95% CI 65.4–92.2) and paratesticular adenocarcinomas (89%; 95% CI 0–99), although the estimate for the latter was based on five cases only (Fig. 1). Survival was consistently lower for patients of 65 years or over than for younger patients (Table 4).

As regards survival by European region, 5-year relative survival for testicular and paratesticular cancers was 97% in Northern Europe, 96% in Central Europe and UK and Ireland, 95% in Southern Europe and 91% in Eastern Europe. Survival differences between the regions were small for seminomatous cancer, but more marked for non-seminomatous cancer, ranging from 86% in Eastern Europe to 96% in Northern Europe (Table 4).

For extragonadal germ cell tumours, 5-year relative survival was higher for females (80%) than males (67%), lower for patients aged 65 or over, and ranged from 63% in Central Europe to 77% in Eastern and Northern Europe (Table 4). The Eastern Europe estimates were based on 18 cases only.

Considering the most frequent sites, the extragonadal germ cell tumours of mediastinum had the worst 5 year relative survival (53%). Survival was better for extragonadal tumours of retroperitoneum (73%), brain (84%) and pineal gland (90%).

We estimated that 95% of European patients with testicular and paratesticular cancers were cured; the corresponding figure for extragonadal cancers was 69% (data not shown in tables).

3.3. *Prevalence*

Table 5 shows the observed prevalence of cases diagnosed within 2, 5 and 15 years of the index date, and also the estimated complete prevalence for EU27. Over 436,000 persons were estimated alive at the beginning of 2008 with a diagnosis of testicular/paratesticular cancer in EU27. Eight percent and 19%, respectively, were diagnosed within 2 and 5 years of the index date; the 11% difference represents cases diagnosed 3–4 years prior to the index data, who were presumably still in clinical follow-up. The remaining 81% represents those who had survived at least 5 years after diagnosis and included 229,000 (52% of total) who had survived more than 15 years after diagnosis.

The most prevalent testicular cancers were seminomatous forms (228,916 cases), followed by non-seminomatous forms (166,812 cases).

Over 17,000 persons were estimated alive at the beginning of 2008 in EU27 with a diagnosis of extragonadal germ cell tumour. The distribution of the prevalence by time since diagnosis was similar to that for testicular/paratesticular cancers: 8% of cases were diagnosed within the preceding 2 years, 17% within the preceding 5 years, and 9370 (64%) had survived more than 15 years after diagnosis.

Table 5 – Observed prevalence per 100,000 (Prev) with standard errors (SE) by time (2, 5, and 15 years) from diagnosis, with estimated complete prevalence per 100,000 and estimated total prevalent cases in EU27 of testicular, paratesticular and extragonadal germ cell cancers.

Entity	Observed prevalence						Estimated prevalence		
	Two years after diagnosis		Five years after diagnosis		15 years after diagnosis		Complete		EU27
	Prev.	SE	Prev.	SE	Prev.	SE	Prev.	SE	No. of cases
TESTICULAR AND PARATESTICULAR CANCERS	7.0	0.1	16.9	0.2	41.8	0.3	87.7	0.7	436,638
Paratesticular adenocarcinoma with variants	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	60
Non-seminomatous testicular cancer	2.7	0.1	6.4	0.1	15.7	0.2	33.5	0.5	166,788
Seminomatous testicular cancer	3.9	0.1	9.7	0.1	22.4	0.2	46.0	0.6	228,900
Spermatocytic seminoma	0.1	<0.1	0.1	<0.1	0.4	<0.1	0.8	0.1	3731
Teratoma with malignant transformation	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	199
Testicular sex cord cancer	0.1	<0.1	0.1	<0.1	0.2	<0.1	0.4	<0.1	2207
EXTRAGONADAL GERM CELL TUMORS	0.2	<0.1	0.5	<0.1	1.1	<0.1	3.4	0.2	17,027
Extragonadal malignant immature teratoma	0.1	<0.1	0.1	<0.1	0.3	<0.1	0.9	0.1	4549
Extragonadal germ cell tumour	0.2	<0.1	0.4	<0.1	0.8	<0.1	2.5	0.2	12,478

4. Discussion

4.1. *Data quality*

The data were derived from the largest available database on rare cancers collected from high quality European CRs. The major indicators of data quality – DCO and autopsy cases, not microscopically verified cases, and lost-to-follow-up cases, were all acceptably low (Table 1) indicating a high quality dataset. Nevertheless 2.6% of testicular/paratesticular cancers were not characterised morphologically (NOS) and this percentage appears fairly high. To investigate this we sent a random sample of 188 NOS testicular cases (that had been microscopically verified) back to the CRs, asking them to check the pathological reports and confirm or correct the NOS morphology code. NOS morphology was confirmed in 84% of cases. Among the corrected cases, most turned out to be germ cell cancer. If this finding were typical of all NOS cases then only a small proportion would require reassignment, providing reassurance that the quality of the data is high at the CR level (and that incidence rate estimates for the various subtype are reliable), although there is room for improvement at the level of the pathology units.

4.2. *Epidemiological indicators*

Our findings confirm that testicular/paratesticular cancers are rare with an incidence of 31/1,000,000/year in the population (65/1,000,000/year among men) and an estimated 15,679 new cases per year in EU27. Nevertheless we should not forget that testicular cancer incidence varies considerably in different geographical areas. It is highest (>10/100,000) in Nordic countries[3] and intermediate (9–10/100,000) in Slovenia, Slovakia and Switzerland[3] thus testicular cancer may not be so rare in countries of north and western Europe. Testicular cancers are the most common cancers in young men and their incidence is increasing[1,5] especially with regard to stage 1 patients.[17–20] This finding is relevant because early diagnosis increases the opportunity to apply less aggressive treatment with less morbidity to most patients resulting in better final outcomes and improved survival rates.[19]

Our complete prevalence estimates point to testicular/paratesticular cancers being among the most curable solid cancers. Of the 436,000 persons alive at the beginning of 2008 with a diagnosis of one of these cancers, 229,000 (52%) had survived more than 15 years. Prevalence is pushed up by the young age of patients and the increasing incidence trend, but high survival (discussed below) appears as the most important contributor to the prevalence of these survivors. Studies show that mortality for testicular cancer has declined in many countries since the mid 1970s.[5,21] The main factors contributing to this are considered to be interdisciplinary management involving careful staging; adequate early treatment (chemotherapy, radiotherapy and surgery) attentive follow-up and use of salvage treatments (particularly high-dose chemotherapy with peripheral haematopoietic

stem cell support).[22,23] We found that at 96%, 5-year relative survival for testicular and paratesticular cancers was better than for most other cancers.[7,24] We estimated that 95% of these patient were cured of their disease.

Survival for testicular and paratesticular cancers decreased with increasing age at diagnosis. Apart from age-related biological differences, late diagnosis, more advanced stage at presentation, difficult access to specialist treatment centres, and incomplete application of treatment protocols are likely to contribute to worse outcomes in the elderly.[24–26] However information on these supposed factors was not systematically available from CRs and could not be analysed in this study.

Considering survival by morphology (RARECARE tier 2 groups), survival was highest for seminomatous (98%) followed by non-seminomatous (94%) forms. These small survival differences may be due to differing biology: seminomatous cancers are more often localised, spread (metastasize) via the lymphatic system, are radiosensitive and occur in somewhat older patients. By contrast, non-seminomatous cancers are prone to haematogenous as well as lymphatic spread, are less radiosensitive, and occur in younger patients.[27,28]

We also found good 5-year relative survival for spermatocytic seminoma (93%). This entity is clinically and pathologically distinct from classic seminomatous cancer, in particular for its almost complete inability to metastasize: very few convincing metastatic cases are described in the literature.[29] This has the important clinical implication that surgery may be the only treatment necessary for spermatocytic seminoma[30], while multimodal treatments are the rule for classic seminomatous cancer.[31]

Five-year survival was also good (83%) for sex cord cancer. Treatment is primarily surgery; adjuvant therapy had not been shown to be beneficial.[32] Most sex cord cancers have a benign clinical course following surgery, but about 20% are metastatic at diagnosis and 10–12% behave aggressively, often with fatal outcome.[33]

On rare occasions teratomas (and even other germ cell tumours) undergo somatic malignant transformation. The most common transformations are to sarcoma, primitive neuroectodermal tumour, and adenocarcinoma.[34] Treatment is cisplatin-based chemotherapy followed by radical surgery when possible; cisplatin is also the mainstay of salvage treatment.[34]

We had too few cases of teratoma with malignant transformation to estimate survival. However, studies published over the last 30 years, all of limited size, suggest that transformation has a negative impact on prognosis compared to the non-transformed counterpart.[34]

Extragonadal germ cell tumours are more aggressive than testicular germ cell cancers. Mediastinal non-seminomatous cancer (most common subtype in our database) has the worst survival of the extragonadal forms[35,36] in relation to generally large tumour bulk at diagnosis, resistance to chemotherapy, difficulty of removing all residual disease after chemotherapy, and a predisposition to develop haematologic neoplasia and other non-germ cell malignancies.[37–39] In our series the mediastinic lesions were less frequent in Eastern (11%) than in the other European regions (around 25%). This suggests that other prognostic factors than site of the neoplasm contributed survival variation across Europe.

Regarding testicular cancers, we found limited variation in survival between European regions. However, 5-year relative survival in Eastern Europe, particularly for non-seminomatous cancer, was lower than for the other regions. Differences in morphological case mix could, in theory, contribute to this survival difference; however among non-seminomatous cancers the proportion of low-prognosis entities (mainly trophoblastic tumours) was low everywhere and is unlikely to have affected the regional comparison. The nearly 10 percentage point survival difference between Eastern Europe and the rest of Europe for non-seminomatous forms is, therefore, of major concern since testicular cancer is one of the most curable of all solid malignancies. Differences in survival could be due to different stage at diagnosis, inadequate treatment and follow-up or to limited access to drugs. Information on stage and diagnostic procedures are essential to control for stage migration and determine whether survival differences are explained by the different stage at diagnosis. Stage related information was not systematically available from CRs and could not be analysed in this study. Anyway, a previous experience reported, after adjustment by stage (and age) at diagnosis, that for Estonia and Poland, lower survival was not due entirely to advanced stage at diagnosis, but also to inadequate treatment.[40] In addition, centralisation of treatment for testicular cancers improves outcomes[31,41–43] and while in much of Northern and Western Europe, multidisciplinary specialist care is well developed[44,45] in some Eastern European countries, cancer treatment is commonly provided by 'general' oncologists and surgeons not specialised in the treatment of particular cancer sites.[31,44] An exception is Slovakia where in 1982, was established a specialist treatment centre for non-seminomatous testicular cancer in the Department of Urology, Bratislava School of Medicine. In Slovakia the gap between incidence and mortality is increasing—an indication of the increasingly efficacious therapy that is given to patients with testicular cancer in Slovakia.[31] Nevertheless further investigation is required to establish the real reasons for the lower survival from these cancers in Eastern Europe, particularly since Eastern European countries are poorly represented in the present study and the overall number of cases from this region is lower than for the other European regions.

To conclude, our study delineated the burden of testicular/paratesticular cancers in Europe. We have provided complete prevalence data which are very useful for health care planning and resource allocation. We have shown differences in burden by European region, but we had insufficient information to interpret such differences. Interpretation would be possible if, in future RARECARE studies, CRs will collect more information on stage at diagnosis, diagnostic procedures and treatment. Further research using data collected through population based registers must be strongly encouraged also to be able to assess future trends in testicular cancer incidence rates and to help to identify risk factors.

Finally we should not forget that although testicular cancer is now highly curable, life threatening conditions such as second malignancy and cardiovascular disease, occur more frequently in testicular cancer patients than the general population.[45] Long-term monitoring of the generally young

testicular cancer survivors is necessary to quantify the treatment-related risks[46]; and in view of the high prevalence of these malignancies (due to curability and occurrence in young patients), the aim should be to develop treatments having limited impact on quality of life.

Funding

This research was supported by the European Commission through the Executive Agency for Health and Consumers (Grant No. 2006113), and the Programma Italia-USA Malattie Rare (Grant No. 526D/42).

Conflict of interest statement

None declared.

Acknowledgements

We thank Don Ward for help with the English and Samba Sowe for editorial support.

The RARECARE Working Group consists of:
Austria: N. Zielonk (Austrian National Cancer Registry); **Belgium:** E. Van Eycken (Belgian Cancer Registry); D. Schrijvers (Antwerp Hospital Network); H. Sundseth (European Cancer Patient Coalition); S. Marreaud (European Organisation for Research and Treatment of Cancer); R. Audisio (European Society of Surgical Oncology); **France:** G. Hedelin (Bas-Rhin Cancer Registry); A.M. Bouvier (Côte d'Or Dogestive Cancer Registry); A.S. Woronoff (Doubs Cancer Registry); A. Buemi (Haut-Rhin Cancer Registry); B. Tretarre (Hérault Cancer Registry); M. Colonna (Isère Cancer Registry); S. Bara (Manche Cancer Registry); O. Ganry (Somme Cancer Registry); P. Grosclaude (Tarn Cancer Registry); E. Benhamou (Institute Gustave Roussy); I.R. Coquard (Centre Léon Bérard); S. Baconnier (Connective tissue cancer network – CONTICANET); **Germany:** B. Holleczek (Saarland Cancer Registry); J. Geissler (CML Advocates Network); R. Hehlmann (European LeukemiaNet); M. Wartenberg (Global GIST Network); **Iceland:** L. Tryggvadottir (Icelandic Cancer Registry); **Ireland:** S. Deady (National Cancer Registry of Ireland); **Italy:** F. Bellù (Alto Adige Cancer Registry); S. Ferretti (Ferrara Cancer Registry); D. Serraino (Friuli Venezia Giulia Cancer Registry); M. Vercelli (Liguria Cancer Registry c/o IST/UNIGE, Genoa); S. Vitarelli (Macerata Province Cancer Registry); M. Federico (Modena Cancer Registry); M. Fusco (Napoli Cancer Registry); M. Michiara (Parma Cancer Registry); A. Giacomin (Piedmont Cancer Registry, Province of Biella); R. Tumino (Cancer Registry and Histopathology Unit, 'M.P. Arezzo' Civic Hospital, Ragusa); L. Mangone (Department of Research Azienda Ospedaliera Arcispedale Santa Maria Nuova – IRCCS, Reggio Emilia); F. Falcini (Romagna Cancer Registry); G. Senatore (Salerno Cancer Registry), M. Budroni (Sassari Cancer Registry); S. Piffer (Trento Cancer Registry); E. Crocetti (Tuscan Cancer Registry); F. La Rosa (Umbria Cancer Registry); P. Contiero (Varese Cancer Registry); P. Zambon (Veneto Cancer Registry); P.G. Casali, G. Gatta, A. Gronchi, L. Licitra, M. Ruzza, S. Sowe (Fondazione IRCCS Istituto Nazionale dei Tumori); R. Capocaccia, R. De Angelis, A. Tavilla (Centro Nazionale di Epidemiologia, Istituto Superiore di Sanità); A.P. Dei Tos, J. Fleming (Local Health Unit No. 9, Region of Veneto); **Malta:** K. England (Malta National Cancer Registry); **Norway:** G. Ursin (Cancer Registry of Norway); **Poland:** J. Rachtan (Cracow Cancer Registry); S. Gozdz, (Kielce Cancer Registry); M. Zwierko (Warsaw Cancer Registry); M. Bielska-Lasota (National Institute of Public Health – National Institute of Hygiene, Warsaw); J. Slowinski (Department of Neurosurgery in Sosnowiec, Medical University of Silesia); **Portugal:** A. Miranda (Southern Portugal Cancer Registry); **Slovakia:** Ch. Safaei Diba (National Cancer Registry of Slovakia); **Slovenia:** M. Primic-Zakelj (Cancer Registry of Slovenia); **Spain:** A. Mateos (Albacete Cancer Registry); I. Izarzugaza (Basque Country Cancer Registry); A. Torrella-Ramos (Castillon Cancer Registry); R. Marcos-Gragera (Epidemiology Unit and Girona Cancer Registry, Oncology Coordination Plan, Department of Health and Catalan Institute of Oncology); M.D. Chirlaque (Department of Epidemiology, Murcia Regional Health Authority, Murcia, CIBER Epidemiología y Salud Pública (CIBERESP)); E. Ardanaz (Navarra Cancer Registry); J. Galceran (Tarragona Cancer Registry); J.A. Virizuela-Echaburu (Hospital Universitario Virgen Macarena, Sevilla); C. Martinez-Garcia, M.J. Sanchez Perez, J.M. Melchor (Escuela Andaluza de Salud Pública), A. Cervantes (University of Valencia); **Sweden:** J. Adolfsson (Stockholm-Gotland Cancer Registry); M. Lambe (Uppsala Regional Cancer Registry); T.R. Möller (Lund University Hospital); U. Ringborg (Karolinska Institute); **Switzerland:** G. Jundt (Basel Cancer Registry); M. Usel, (Geneva Cancer Registry); S.M. Ess (St. Gallen Cancer Registry); A. Spitale (Ticino Cancer Registry); I. Konzelmann (Valais Cancer Registry); J.M. Lutz (National Institute for Cancer Epidemiology and Registration); **The Netherlands:** J.W.W. Coebergh (Eindhoven Cancer Registry); R. Otter, S. Siesling, O. Visser, J.M. van der Zwan (Comprehensive Cancer Centre the Netherlands), H. Schouten (University of Maastricht); **UK-England:** D.C. Greenberg (Eastern Cancer Registration and Information Centre); J. Wilkinson (Northern and Yorkshire Cancer Registry); M. Roche (Oxford Cancer Intelligence Unit); J. Verne (South West Public Health Observatory); D. Meechan (Trent Cancer Registry); G. Lawrence (West-Midlands Cancer Intelligence Unit); M.P. Coleman (London School of Hygiene and Tropical Medicine); J. Mackay (University College of London); **UK-Northern Ireland:** A. Gavin (Northern Ireland Cancer Registry); **UK-Scotland:** R.J. Black (Scottish Cancer Registry); I. Kunkler (University of Edinburgh); **UK-Wales:** C. White (Welsh Cancer Intelligence & Surveillance Unit).

REFERENCES

1. Chia VM, Quraishi AM, Devesa SS, et al. International trends in the incidence of testicular cancer, 1973–2002. *Cancer Epidemiol Biomarkers Prev* 2010;**19**(5):1151–9.
2. Schmoll HJ. Extragonadal germ cell tumors. *Ann Oncol* 2002;**13**:265–72.
3. Ferlay J, Shin HR, Bray F, et al. Globocan 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Lyon, France: International Agency for Research on Cancer; 2010. Available from: <http://globocan.iarc.fr>.
4. McGlynn KA, Cook MB. Etiologic factors in testicular germ-cell tumors. *Future Oncol* 2009;**5**(9):1389–402.

5. Bray F, Richiardi L, Ekboom A, et al. Trends in testicular cancer incidence and mortality in 22 European countries: continuing increases in incidence and declines in mortality. *Int J Cancer* 2006;**118**:3099–111.
6. Sant M, Aareleid T, Berrino F, et al. EUROCARE-3: survival of cancer patients diagnosed 1990–1994. Results and commentary. *Ann Oncol* 2003;**14**(5):61–118.
7. Sant M, Allemani C, Santaquilani M, et al. EUROCARE-4. Survival of cancer patients diagnosed in 1995–1999. Results and commentary. *Eur J Cancer* 2009;**45**:931–91.
8. RARECARE: www.rarecare.eu [accessed 5/11/2010].
9. Percy C, Fritz A, Jack A, et al. *International Classification of Diseases for the Oncology (ICD-O), 3rd ed*. World Health Organisation; 2000.
10. Doll R, Cook P. Summarizing indices for comparison of cancer incidence data. *Int J Cancer* 1967;**2**:269–79.
11. Capocaccia R, Colonna M, Corazziari I, et al. Measuring cancer prevalence in Europe: the EUROPREVAL Project. *Ann Oncol* 2002;**13**:831–9.
12. Capocaccia R, De Angelis R. Estimating the completeness of prevalence based on cancer registry data. *Stat Med* 1997;**16**:425–40.
13. EUROSTAT <http://epp.eurostat.ec.europa.eu/tgm/refreshTableAction.do;jsessionid=9ea7974b30e8913a6291f74c4afca4aa83e45e410058.e34SbxiOchiKc40LbNmLahiKb3uQe0?tab=table&plugin=1&pcode=tps00001&language=en> [accessed 02/04/2009].
14. Gatta G, van der Zwan JM, Casali PG, et al. Rare cancers are not so rare: The rare cancer burden in Europe. *Eur J Cancer* 2011;**47**(17):2493–511.
15. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer* 1996;**78**:2004–10.
16. De Angelis R, Capocaccia R, Hakulinen T, Soderman B, Verdecchia A. Mixture models for cancer survival analysis: application to population-based data with covariates. *Stat Med* 1999;**18**:441–54.
17. Schultzj HP, Arends J, Barleb J, et al. Testicular carcinoma in Denmark 1976–1980. Stage and selected clinical parameters at presentation. *Acta Radiol Oncol* 1984;**23**(4):249–53.
18. Heimdall K, Foss'al SD, Johansen A. Increasing incidence and changing stage distribution of testicular carcinoma in Norway 1970–1987. *Br J Cancer* 1990;**62**:277–8.
19. Sonneveld AJA, Hoekstra HJ, Van der Graaf WTA, et al. The changing distribution of stage in nonseminomatous testicular germ cell tumours, from 1977 to 1996. *BJU Int* 1999;**84**:68–74.
20. Gudbjartsson T, Magnusson K, Bergthorsson J, et al. A population-based analysis of increased incidence and improved survival of testicular cancer patients in Iceland. *Scand J Urol Nephrol* 2003;**37**:292–8.
21. Levi F, La vecchia C, Boyle P, et al. Western and eastern European trends in testicular cancer mortality. *Lancet* 2001;**357**:1853–4.
22. Einhorn LH. Testicular cancer as a model for a curable neoplasm: The Richard and Hinda Rosenthal Foundation Award Lecture. *Cancer Res* 1981;**41**:3275–80.
23. Dearnaley DP, Huddart RA, Horwich A. Managing testicular cancer. *BMJ* 2001;**322**:1583–8.
24. Gatta G, Ciccolallo L, Kunkler I, et al. Survival from rare cancer in adults: a population-based study. *Lancet Oncol* 2006;**7**:132–40.
25. Berney DM, Warren AY, Verma M, et al. Malignant germ cell tumours in the elderly: a histopathological review of 50 cases in men aged 60 years or over. *Modern Pathol* 2008;**21**:54–9.
26. Fossa SD, Cvancarova M, Chen L, et al. Adverse prognostic factors for testicular cancer-specific survival: a population-based study of 27,948 patients. *J Clin Oncol* 2011;**29**:963–70.
27. Gori S, Porrozzi S, Roila F, et al. Germ cell tumours of the testis. *Crit Rev Oncol Hematol* 2005;**53**:141–64.
28. Van Dijk MR, Steyerberg EW, Habbema JD. Survival of non-seminomatous germ cell cancer patients according to the IGCC classification: an update based on meta-analysis. *Eur J Cancer* 2006;**42**:820–6.
29. Lombardi M, Valli M, Brisigotti M, et al. Review article: spermatocytic seminoma: review of the literature and description of a new case of the anaplastic variant. *Int J Surg Pathol* 2011;**19**(1):5–10.
30. Aggarwal N, Parwani AV. Spermatocytic seminoma. *Arch Pathol Lab Med* 2009;**133**:1985–8.
31. Boyle P. Testicular cancer: the challenge for cancer control. *Lancet Oncol* 2003;**5**:56–61.
32. Conkey DS, Howard GCW, Grogor KM, et al. Testicular sex cord-stromal tumours. The Edinburgh experience 1988–2002, and a review of the literature. *Clin Oncol* 2005;**17**:322–7.
33. Acar C, Gurocak D, Sozen S. Current treatment of testicular sex cord-stromal tumors. Critical review. *Urology* 2009;**73**(6):1165–71.
34. Necchi A, Colecchia M, Nicolai N, et al. Towards the definition of the optimal management and prognostic factors of teratoma with malignant transformation: a single-institution case series and new proposal. *BJU Int* 2010 [Epub ahead of print].
35. International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. *J Clin Oncol* 1997;**15**(2):594–603.
36. International Prognostic Factors Study Group. Prognostic factors in patients with metastatic germ cell tumors who experienced treatment failure with cisplatin-based first-line chemotherapy. *J Clin Oncol* 2010;**28**:4906–11.
37. Hartmann JT, Nichols CR, Droz JP, et al. Hematologic disorders associated with primary mediastinal nonseminomatous germ cell tumors. *J Natl Cancer Inst* 2000;**92**:54–61.
38. Bokemeyer, Nichols CR, Droz J-P, et al. Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. *J Clin Oncol* 2002;**20**(7):1864–73.
39. Ikdahl T, Josefsen D, Jakobsen E, et al. Concurrent mediastinal germ-cell tumour and haematological malignancy: case report and short review of literature. *Acta Oncol* 2008;**47**(3):466–9.
40. Sant M, Aareleid T, Artioli ME, et al. Ten-year survival and risk of relapse for testicular cancer. A EUROCARE high resolution study. *Eur J Cancer* 2007;**43**:585–92.
41. Aass N, Klepp O, Cavallin-Stahl E, et al. Prognostic factors in unselected patients with nonseminomatous metastatic testicular cancer: a multicenter experience. *J Clin Oncol* 1991;**9**:818–26.
42. Harding MJ, Paul J, Gillis CR, Kaye SB. Management of malignant teratoma: does referral to a specialist unit matter? *Lancet* 1993;**341**(8851):999–1002.
43. Plesko I, Ondrus D, Boyle P. Testicular-cancer incidence and mortality in Slovakia, 1968–90. *Lancet* 1996;**347**:900–1.
44. Micheli A, Coebergh JW, Mugno E, et al. European health systems and cancer care. *Ann Oncol* 2003;**14**(5):41–60.
45. van den Belt-Dusebout AW, de Wit R, Gietema JA, et al. Treatment-specific risks of second malignancies and cardiovascular disease in five-year survivors of testicular cancer. *J Clin Oncol* 2007;**25**:4370–8.
46. Travis LB, Beard C, Allan JM, et al. Testicular cancer survivorship: research strategies and recommendations. *J Natl Cancer Inst* 2010;**102**:1114–30.