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Original Paper

Improved Survival for Patients with Testicular Cancer in Europe Since 1978

T. Aareleid,[1,2] M. Sant,[3] G. Hédelin[4] and the EUROCARE Working Group*

[1]Department of Epidemiology and Biostatistics, Institute of Experimental and Clinical Medicine, Hiiu 42, 11626 Tallinn; [2]Estonian Cancer Registry, Estonian Cancer Centre, Estonia; [3]Department of Epidemiology, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy; and [4]Cancer Registry of Bas-Rhin, Laboratoire d'Epidémiologie et de Santé Publique, Faculté de Médecine, Strasbourg, France

Within the framework of EUROCARE, a population-based study on survival and care of cancer patients in Europe, we analysed survival of 7426 men with testicular cancer diagnosed between 1985 and 1989 in 17 countries. For comparison between the countries, survival rates were age-standardised to the age structure of the entire study population. Among the participating countries of Northern, Western, Central and Southern Europe and the U.K., the age-standardised 5-year relative survival rate varied from 89% (Finland) to 93% (Spain, Germany). In Eastern Europe, the rate ranged from 48% (Estonia) to 84% (Slovenia). Rates in Poland, Slovakia and Estonia were significantly lower than the summary rate for Europe ($P < 0.05$). Relative survival generally decreased with the age of patients at diagnosis. Based on the weighted analysis of pooled European data, the 5-year relative survival rate was 91% for patients aged 15–44 years; 85% for patients aged 55–64 years; and 59% for patients aged 75 years and over. The time trend in survival by 3-year periods between 1978 and 1989 was studied on the basis of 12 084 cases provided by 12 countries. From 1978–1980 to 1987–1989, the 5-year relative survival rate for Europe increased from 79 to 93% ($P < 0.05$). The inequalities in survival between the more developed European countries were more notable in the 1970s than in the 1980s, suggesting that the treatment for testicular cancer became standardised in the latter period. Poorer survival in Eastern Europe and particularly in Estonia, could be related to later introduction of the effective cytotoxic treatments, but also to longer diagnostic delay and limited availability of modern staging procedures.

Key words: testicular cancer, survival rates, population-based cancer registries, time trends, inter-country comparisons, Europe
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INTRODUCTION

ALTHOUGH TESTICULAR cancer is a rare disease, accounting for less than 1% of all male cancers worldwide, it is among the most frequent malignancies in young men [1, 2]. The incidence of testicular cancer is rising in western populations [3, 4]. During the past 20 years, testicular cancer has become a model for a highly curable malignancy, with 5-year survival of approximately 90% for all patients and 70% survival for patients with disseminated disease [5, 6]. Dramatic improvements in survival rates have resulted, firstly from advances in combination chemotherapy. The introduction of cisplatin, the first heavy metal-based agent in human oncology, has revolutionised the cure rate in this previously highly lethal tumour. Besides progress in chemotherapy, improved survival is also the result of the use of more effective imaging techniques, the introduction of appropriate serum markers which allow for careful follow-up, and the modification of surgical techniques [5, 7].

Based on the results from the EUROCARE I project, the first pan-European study on survival of cancer patients in 11 European countries between 1978 and 1985, the age-

*The EUROCARE Working Group for this study is listed in the Appendix.
Correspondence to T. Aareleid.
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standardised 5-year relative survival rates in testicular cancer were highest in The Netherlands (89%), Denmark (88%) and Italy (87%) [8]. Relatively low rates were revealed for Germany (75%), Finland (78%) and France (80%). Poor survival in Poland and Estonia (crude 5-year relative survival rates 67% and 38%, respectively) was explained by lower quality of medical care compared with the more developed European countries and particularly by inadequate staging and cytotoxic treatment [9]. An increasing trend in survival from 1978–1980 to 1983–1985 has been observed in most participating countries.

The collaboration across Europe in the EUROCARE study has now been extended to 45 cancer registries in 17 countries, having accumulated data currently on approximately 3.5 million cancer cases, diagnosed between 1978 and 1992. In the present paper, we describe survival variation of patients with testicular cancer diagnosed in European countries between 1985 and 1989, and explore time trends in survival since 1978.

PATIENTS AND METHODS

Survival analysis was carried out on 7426 cases of testicular cancer diagnosed in patients from 15 years of age in 1985–1989 (Table 1). The data were recorded in 38 cancer registries in 17 countries. Out of these, 6 are covered by national registries (Iceland, Finland, Denmark, Slovenia, Slovakia and Estonia); the U.K. is represented by the registries covering Scotland and a large part of England; for the remaining countries, up to 20% of national populations are covered by the participating registries. Approximately 50% of cases came from the U.K., whilst less than 40 cases were provided by Iceland and Austria. Cases discovered at autopsy, patients first diagnosed with another tumour or known only on the basis of a death certificate were not included. The study protocol specified a minimum follow-up of 5 years.

Table 1. *Number of patients with testicular cancer diagnosed in* 1985–1989 *by country and age group (EUROCARE* II*)*

	Age group (years)					
Country	15–44	45–54	55–64	65–74	75+	All
Northern Europe						
Iceland	36	0	0	0	0	36
Finland	227	36	14	5	10	292
Sweden*	140	20	12	2	2	176
Denmark	987	154	61	33	17	1252
U.K.						
Scotland	567	75	30	11	9	692
England	2409	291	136	64	55	2955
Western and Central Europe						
The Netherlands*	70	6	5	5	0	86
Germany*	134	23	11	2	2	172
Austria*	31	4	2	1	0	38
Switzerland*	133	12	8	2	2	157
France*	137	14	7	1	0	159
Southern Europe						
Spain*	81	11	4	7	2	105
Italy*	264	50	29	14	10	367
Eastern Europe						
Slovenia	174	15	6	1	1	197
Slovakia	509	20	13	14	8	564
Poland*	110	5	4	3	2	124
Estonia	36	10	1	4	3	54
Europe	6045	746	343	169	123	7426

* < 20% of the national population covered.

Testicular cancer was diagnosed between 15 and 44 years of age in 6,045 patients (81%). The patients aged 65 years and over accounted only for 4%. The mean age of patients at diagnosis varied from 31 years (Iceland) to 40 years (Estonia). Overall, approximately half of all tumours were seminomas. Other germ cell tumours accounted for 43% and non germ cell tumours for 4% of cases; the histological type was not specified or there was no histological verification of diagnosis for 7% of patients.

The relative survival was computed as the ratio between the observed survival and expected survival, derived from general mortality [10]. For comparison between the countries, survival rates were age-standardised to the age structure of the entire study population. The age groups 15–44, 45–54, 55–64, 65–74 and 75+ were used. Age standardisation was not carried out when there were no cases in an age group for a country. A weighted estimate of summary European survival was computed from the whole set of available data, using the weights based on national incidence statistics [11].

The time trends were analysed for 12 countries that could provide the data for the entire period from 1978 to 1989. The trend analysis was based on 12 084 cases diagnosed in the following 3-year subperiods: 1978–1980; 1981–1983; 1984–1986; and 1987–1989. The relative risk of death in 1987–1989 *versus* 1978–1980 was estimated assuming a proportional hazard model by time intervals. The relative risk was calculated by the formula $ln(S_2(t))/ln(S_1(t))$, where S_1 and S_2 are period-specific relative survival rates.

RESULTS

Inter-country differences in survival

In patients aged 15–44 years at diagnosis, 1-year relative survival rates between 95 and 100%, and 5-year rates between 90 and 95% were observed in most participating countries of Northern, Western, Central and Southern Europe, and the U.K. (Table 2). Five-year rates under 90% were seen for France (87%), Slovenia (88%), Slovakia (82%), Poland (83%) and Estonia (51%).

Age-standardised 1-year rates of 95% or higher and 5-year rates of 89% or higher were revealed for Finland, Sweden, Denmark, the U.K., Germany, Switzerland, Spain and Italy. In Eastern Europe, the 1-year rate ranged from 68% (Estonia) to 93% (Slovenia) and the 5-year rate ranged from 48% (Estonia) to 84% (Slovenia). Based on the pooled European data, the 1-year relative survival rate was 95% and the 5-year rate was 90%. The age standardised 5-year rates for Poland, Slovakia and Estonia were significantly lower than the overall rate for Europe ($P < 0.05$). Furthermore, the rate for Estonia was significantly lower than the rates observed for all the other countries ($P < 0.05$).

Effect of age on survival

Relative survival generally decreased with increasing age of patients. The 5-year relative survival rate, based on the weighted analysis of pooled European data, was 91% for patients aged 15–44 years, 85% for patients aged 55–64 years and 59% for patients aged 75 or over. Thus, even after adjusting for 'competing' causes of death, survival was poorer for older patients.

Time trend in survival

Weighted 1-year relative survival for Europe increased from 91% in 1978–1980 to 97% in 1987–1989 ($P < 0.05$) and the 5-year rate increased from 79 to 92% ($P < 0.05$), respectively (Table 3). Improvement in survival was observed for all age groups. In patients under 55 years of age at diagnosis, the increase was more pronounced in the 5-year rate than in the 1-year rate, whilst for patients aged 55–74 years, short-term survival increased more markedly.

Among the countries providing a sufficient number of cases for age-standardisation by subperiod, the largest improvement was seen in Finland, where the 5-year survival

Table 2. One- and 5-year relative survival rates (%) of patients with testicular cancer diagnosed in 1985–1989, by country (EUROCARE II)

	Relative survival rates			
	Patients aged 15–44 years		All patients‡	
Country	1-year	5-year	1-year (95% CI)	5-year (95% CI)
Northern Europe				
Iceland†	100	95	–	–
Finland	96	92	95 (92–98)	89 (86–93)
Sweden*	97	94	96 (94–99)	91 (88–95)
Denmark	97	94	96 (95–97)	91 (90–93)
U.K.				
Scotland	97	93	95 (94–97)	92 (89–94)
England	96	91	95 (94–96)	90 (89–91)
Western and Central Europe				
The Netherlands*	99	95	–	–
Germany*	98	93	97 (95–100)	93 (87–99)
Austria*†	94	94	–	–
Switzerland*	98	97	96 (92–99)	–
France*	96	87	–	–
Southern Europe				
Spain*	100	97	95 (91–98)	93 (88–97)
Italy*	98	93	96 (94–98)	91 (88–94)
Eastern Europe				
Slovenia	94	88	93 (90–96)	84 (79–89)
Slovakia	90	82	90 (87–92)	82 (78–86)
Poland*	95	83	90 (85–95)	79 (72–87)
Estonia	67	51	68 (56–82)	48 (35–64)
Europe	97	91	95 (94–96)	90 (88–92)

* < 20% of the national population covered. †Less than 40 cases included in the study. ‡Age-standardised rates with 95% confidence intervals (CI). –, age-standardised rate could not be calculated.

Table 3. One- and 5-year relative survival rates (%) of patients with testicular cancer diagnosed in Europe in 1978–1989, by period of diagnosis and age group (EUROCARE II)*

		Period of diagnosis				
Age (years)	Years since diagnosis	1978–1980	1981–1983	1984–1986	1987–1989	Relative risk of death in 1987–1989 *versus* 1978–1980
15–44	1	92	94	96	96	0.4
	5	80	87	90	93	0.3
45–54	1	96	93	98	97	0.7
	5	91	79	93	96	0.4
55–64	1	78	86	90	97	0.1
	5	69	83	84	91	0.3
65–74	1	69	83	89	91	0.3
	5	60	65	24	73	0.6
75+	1	28	45	39	83	0.1
	5	15	42	26	80	0.1
All	1	91	93	95	97	0.3
	5	79	85	86	92	0.4

*Based on weighted analysis of pooled European data. Only 12 countries provided data for the entire period from 1978–1989 and were included in this analysis.

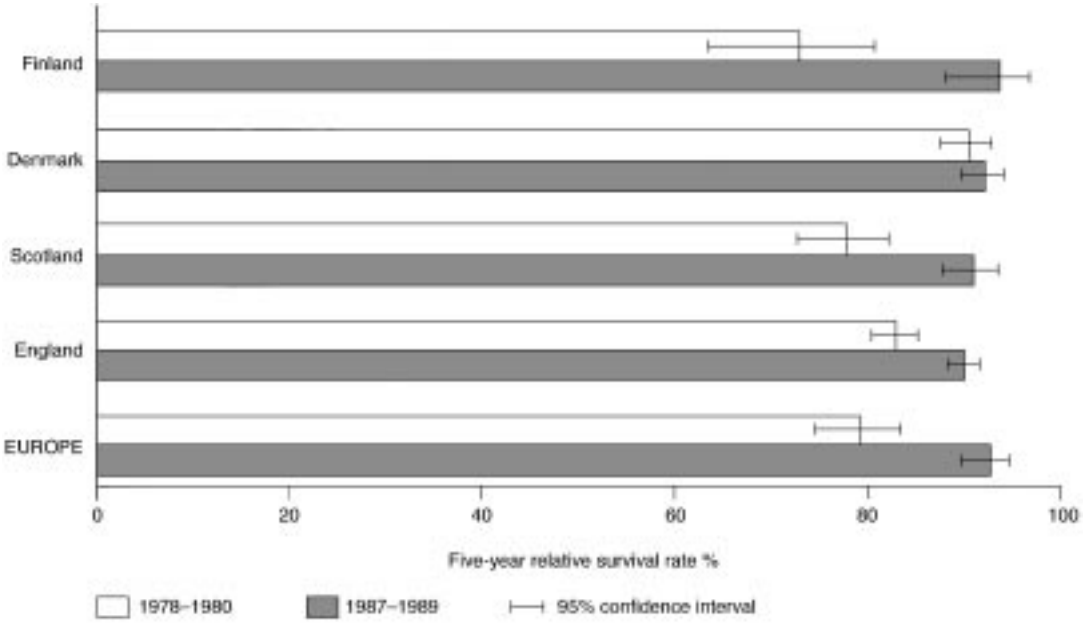

Figure 1. Change in age-standardised 5-year relative survival for patients with testicular cancer in selected European countries from 1978–1980 to 1987–1989 (EUROCARE II).

rate increased from 73% in 1978–1980 to 94% in 1987–1989 ($P < 0.05$) (Figure 1). A marked increase was also observed in the U.K. For Denmark, the rate was over 90% in all sub-periods.

DISCUSSION

The frequency of testicular cancer varied 4-fold in the European Union in 1990: the age-standardised rate (world population) per 100 000 ranged from 2.3 in Finland to 9.0 in Denmark [1]. Among the countries of Eastern Europe, included in the EUROCARE II study, the age-standardised incidence rate varied from 1.6 (Estonia) to 4.6 (Slovakia) in 1988–1992 [2]. Despite the increasing incidence, mortality from testicular cancer has fallen substantially in most European countries since the 1970s, but there is variation in the starting point and intensity of the decline, which began, for example, after 1970 in The Netherlands and Italy and after 1975 in the U.K. and most Nordic countries [3] and even more recently in Eastern Europe [12].

The increasing trend in survival in testicular cancer, revealed by the EUROCARE II study in 12 European countries between 1978 and 1989, is similar to that observed for the other populations: e.g. in the U.S.A. [13], Australia [14] and Norway [15] (Table 4). Cisplatin-based cytotoxic treatment was introduced mainly during the 1970s, but there could have been differences between the countries in following new treatment protocols. The results of the present study show that the differences in survival rates between the developed European countries were more pronounced in the late 1970s than in the late 1980s, when the treatment for testicular cancer became uniform. However, inter-country variation in survival of patients with testicular cancer was observed even during the pre-cisplatin era. For example, the 5-year relative survival rate for patients diagnosed in Finland in 1967–1973 was 57% [16] *versus* 67% in Denmark in 1968–1973 [17]. In Denmark, the major improvement in survival due to early introduction of effective treatment for testicular cancer occurred by the late 1970s.

Table 4. *Temporal changes in population-based* 5*-year relative survival rates of testicular cancer patients in selected countries and territories of the world*

Country/territory	Period of diagnosis	5-year relative survival rate %
U.S.A. (SEER)*	1974–1976	79
	1977–1979	87
	1980–1982	92
	1983–1985	91
	1986–1993	95
South-Australia†	1977–1980	84
	1981–1984	93
	1985–1990	94
Norway‡	1972–1976	67
	1977–1981	82
	1982–1986	93
	1987–1991	95
Europe§	1978–1980	79
	1981–1983	85
	1984–1986	86
	1987–1989	92

*Follow-up of patients through 1994 [13]. †Rates for the age group 0–39 years [14]. ‡ [15]. §Rates based on the present study.

According to the results from EUROCARE II, survival rates of patients diagnosed with testicular cancer in Europe between 1985 and 1989 could be divided into three classes:

(1) High rates (age-standardised 5-year relative survival rate 89–93%);
(2) Intermediate rates (79–84%); and
(3) Low rate(s) (under 50%).

The high rates were revealed for the participating countries of Northern, Western, Central and Southern Europe, and the U.K. The 'intermediate survival' group included the post-socialist countries of Eastern Europe (Slovenia, Slovakia,

Poland) and the 'low survival' group was represented by Estonia, which was a part of the USSR from 1940 to 1991.

The inter-country variation cannot be regarded as incompleteness of case ascertainment, or differences in tumours' biological behaviour. Given the peak in the young age, the underdiagnosing and/or under-registration of testicular cancer is less likely than for other cancers, which mainly occur in the elderly. Also, in the present study, the proportions of the histological subtypes were relatively similar across Europe (data not shown). Thus, the differences in population-based survival rates could primarily reflect the differences in the access to and the quality of care [9, 18].

Low survival rates in Poland and Estonia were observed in EUROCARE I [8]. It could be that effective cytotoxic regimens were introduced later in Eastern Europe [12, 19], and particularly in Estonia, than in other European countries. A relatively high mean age of patients at diagnosis, as in Estonia, may reflect longer diagnostic delay. It has been shown that a delay of more than 3 months is correlated with a significantly decreased 5-year survival rate [20]. Limited availability of modern diagnostic methods, inadequate staging and less careful follow-up of patients could have influenced survival. The high-resolution study on testicular cancer, carried out in the framework of EUROCARE II, will probably shed some light on causes of the inter-country variation in survival rates. According to the study protocol, detailed data on morphology, stage, diagnostic procedures and treatment were collected from 12 registries, including those from Eastern Europe.

In the context of cancer control, achievements in the management of testicular cancer can be considered as an example of a major breakthrough in cancer treatment [21]. However, not only the availability of the efficient treatment protocols, but also access to the medical care system, offering high-quality treatment to all individuals who need it, is crucial for cancer patients' survival.

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APPENDIX

The EUROCARE Working Group for this study is: Austria: W. Oberaigner (Cancer Registry of Tirol). Denmark: H. Storm (Danish Cancer Society). Estonia: T. Aareleid (Estonian Cancer Registry). Finland: T. Hakulinen (Finnish Cancer Registry). France: J. Mace-Lesec'h (Calvados General Cancer Registry), P. Arveux (Doubs Cancer Registry), J. Estève (International Agency for Research on Cancer), N. Raverdy (Somme Cancer Registry). Germany: H. Ziegler (Saarland Cancer Registry). Iceland: L. Tryggvadottir, H. Tulinius (Icelandic Cancer Registry). Italy: F. Berrino (Project Leader), P. Crosignani, G. Gatta, A. Micheli, M. Sant (Lombardy Cancer Registry), E. Conti (Latina Cancer Registry), M. Vercelli (Liguria Cancer Registry-NCI, Genova), M. Federico, L. Mangone (Modena Cancer Registry), V. De Lisi (Parma Cancer Registry), R. Zanetti (Piedmont Cancer Registry), L. Gafà, R. Tumino (Ragusa Cancer Registry), F. Falcini (Romagna Cancer Registry), A. Barchielli (Tuscan Cancer Registry), R. Capocaccia, G. De Angelis, F. Valente, A. Verdecchia (National Institute of Health, Rome). Poland: J. Pawlega, J. Rachtan (Cracow Cancer Registry), M. Bielska-Lasota, Z. Wronkowski (Warsaw Cancer Registry). Slovakia: A. Obsitnikova, I. Plesko (National Cancer Registry of Slovakia). Slovenia: V. Pompe-Kirn (Cancer Registry of Slovenia). Spain: I. Izarzugaza (Basque Country Cancer Registry), I. Garau (Mallorca Cancer Registry), E. Ardanaz, C. Moreno (Navarra Cancer Registry), J. Galceran (Tarragona Cancer Registry). Sweden: T. Möller (Southern Swedish Regional Tumour Registry). Switzerland: J. Torhorst (Basel Cancer Registry), C. Bouchardy, L. Raymond (Geneva Cancer Registry). The Netherlands: J.W.W. Coebergh (Eindhoven Cancer Registry). Scotland: A. Gould, R.J. Black (Scottish Cancer Registry). England: T.W. Davies, D. Stockton (East Anglian Cancer Registry), M.P. Coleman (London School of Hygiene and Tropical Medicine), E.M.I. Williams, J. Littler (Merseyside and Cheshire Cancer Registry), D. Forman (Northern and Yorkshire Cancer Registry and Information Service), M.J. Quinn (Office for National Statistics), M. Roche (Oxford Cancer Intelligence Unit), J. Smith (South and West Cancer Intelligence Unit), J. Bell (Thames Cancer Registry), G. Lawrence (West Midlands Cancer Intelligence Unit).