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Ten-year survival and risk of relapse for testicular cancer: A EUROCARE high resolution study

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ABSTRACT

Effective treatments for testicular cancer have been available since the 1970s, yet EUROCARE uncovered marked inter-country survival differences for this disease. To investigate these differences, we reviewed clinical records of 1350 testicular cancer cases diagnosed during 1987–1992 from 13 population-based cancer registries in nine European countries. Patients were followed up for life status and relapse. Ten-year observed survival was estimated by the Kaplan–Meier method. Cox multivariable analyses were performed separately for seminomas and non-seminomas.

Overall, 66% of seminomas and 36% of non-seminomas were limited to the testis. Ten-year survival was 63% (Estonia) to 94% (Switzerland, Slovenia) for seminoma; 47% (Estonia) to 90% (Yorkshire, UK, The Netherlands) for non-seminoma.

Multivariable analysis adjusted for country, age and stage showed that hazard ratios (HRs) of death differed little between western European registries, and were mainly attributable to differing stage at diagnosis. Significantly higher than reference HRs in Estonia and Poland suggest inadequacy or unavailability of treatments.

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1. Introduction

Testicular cancer is not common in Europe, accounting for 1–3% of all male cancers, although it is the commonest cancer in adolescent and young adult males. The world standardised incidence per 100,000 person-years is around 3–4 in France, Italy, Poland, Finland and the United Kingdom (UK). Higher rates (around 7–8) are reported in Denmark and Norway.[1,2] Despite its rarity, the incidence of testicular cancer is increasing,[3–9] while mortality is decreasing in most European countries.[10]

Survival for testicular cancer is better than for all other malignant diseases, reflecting the fact that in most cases it can be cured by adequate treatment.[11] Although effective cisplatin-based chemotherapy regimens have been available since the 1970s,[12] remarkable differences in testicular cancer survival across European populations have been documented, with highest survival in northern Europe/Scandinavia, and lowest survival in former Eastern bloc countries.[13] EUROCARE-3, which analysed cases diagnosed from 1990 to 1994, found that 5-year relative survival was in the range 71% (Estonia) to 95% (Swiss cancer registries).[14]

The findings of clinical studies suggest that survival should approach 100% for patients with early-stage testicular cancer,[15] however, effective treatments have also been developed for advanced disease and 70–80% of these patients can be cured.[16–18] Testicular cancer may therefore serve as a probe for investigating the dissemination and application of effective diagnostic and therapeutic practices throughout the European continent. Significantly lower than average survival in a population would suggest a failure of the health service to provide adequate treatment, although other explanations are possible. For example, the two main morphologic types of testicular cancer, seminoma and non-seminoma, respond differently to systemic therapy and have different prognoses. Non-seminomatous testicular cancers are diagnosed at younger age, more advanced stage and are more responsive to chemotherapy than seminomas;[19–21] hence differing morphological mixes could contribute to between-country differences in survival.

The present study is a high resolution study on the survival of selected populations of European patients diagnosed with testicular cancer in the period 1987–1993. We collected detailed information on diagnostic procedures, stage at diagnosis, morphology, type of treatment and follow-up, by direct examination of the clinical records pertaining to archived cases from cancer registries adhering to the study protocol. Our aims were to explain the differences in prognosis across European populations, to compare diagnostic and treatment procedures in European countries, identify factors influencing survival and study survival after relapse.

2. Patients and methods

Thirteen population-based cancer registries from nine European countries provided 1350 cases of testicular cancer for study. All registries adhered to a common protocol for investigating the diagnostic and therapeutic procedures used for treatment. The cancer registries were grouped by country. Estonia, Slovenia and Slovakia had national cancer registries. Italy was represented by the registries of Varese and Modena; France by the registries of Bas-Rhin, Somme and Isère; the Netherlands by the registries of Eindhoven (south) and Groningen (north); Switzerland by Geneva, the UK by Yorkshire; and Poland by Cracow.

Each registry was asked to provide at least 100 cases diagnosed over one or more consecutive years within the pre-defined study period (1987–1993). However, some registries (Table 1) provided less than 100 cases due to low incidence or small registration area. The French registries (Bas-Rhin, Isère, Somme) provided all incident cases from 1987 to 1993. Modena (Italy) provided all cases diagnosed in 1990–1992, Varese (Italy) provided all cases diagnosed in 1989–1993, Geneva (Switzerland) provided all cases diagnosed in 1988–1993, Eindhoven (the Netherlands) provided all cases diagnosed in 1990–1993, Groningen (the Netherlands) provided all cases diagnosed in 1990–1992, Cracow, Estonia and Slovenia provided all cases diagnosed in 1990–1993, and Slovakia provided all cases diagnosed in 1992–1993. The UK provided 99 cases sampled from the total incidence in 1990–1993. Detailed clinical information on each case was abstracted from clinical records by trained personnel.

Follow-up for life status employed the procedures normally used by each registry. However, to identify relapses, registries were requested to perform active follow-up for each case. Relapse, distinguished as local or distant, was treated as a single event for the purposes of the analysis. No information on relapse was available from Slovakia.

Mean follow-up was 8.07 years. Nineteen cases (1.5%) were lost to follow-up for life status, range 0–6% (Table 1). Disease stage at diagnosis was defined according to TNM 3rd edition,[22] the edition in use during the study period. Pathological stage was always considered when available. For the analysis, stage information was grouped as follows: disease confined to testis; lymph node metastasis (N+); distant metastasis (M1), with the additional category stage not specified or insufficient information to reconstruct it.

Morphology was coded according to ICD-O, 2nd edition.[23] A requirement of the study protocol was that the microscopic characteristics of the tumour should be described on the study form, to serve as a limited check on coding accuracy. ICD-O codes were grouped into two categories, seminoma and non-seminoma, the latter consisting of embryonal carcinomas and variants. Morphology was not available for 23 cases: these were included in the overall survival analysis, but were excluded from the morphology-specific analyses. Observed survival was represented by the Kaplan–Meier method.[24] Cox multivariable regression analysis was used to assess the influence of putative predictive variables on survival.[25]

3. Results

Table 1 shows the principal overall characteristics of the cases of testicular cancer analysed. Each characteristic (variable) is categorised, and the number of cases and the proportion of the total in each category are given, according to life status. The last column shows the crude 10-year hazard ratio (HR) of death for each categorised variable compared to the reference category. HRs of death were estimated by separate Cox models for each variable. A total of 1152 patients were alive at the end of the study and 179 (13%) had died.

Table 1 – Numbers of cases of testicular cancer per country (registries specified) and distribution of demographic and clinical variables, by life status, with crude hazard ratios (HRs) of death

Variable	Number of cases		Life status (%)			HR[a]
			Alive	Dead	Lost	
Country	233	France (Bas-Rhin, Isère, Somme)	84	15	1	1.23
	105	Italy (Modena, Varese)	86	13	1	Ref
	93	Switzerland (Geneva)	91	9	0	0.67
	308	The Netherlands (Eindhoven, Groningen)	89	11	0	0.97
	99	The UK (Yorkshire)	93	7	0	0.76
	50	Estonia	52	42	6	4.20*
	31	Poland (Cracow)	68	32	0	3.14*
	142	Slovenia	89	11	0	0.90
	291	Slovakia	87	12	1	1.03
Age at diagnosis	455	⩽29	88	12	0	Ref
	752	30–49	89	9	2	0.75
	143	⩾50	58	41	1	3.77*
Surgery	1339	Yes	86	13	1	Ref
	11	No	27	73	0	7.01*
Stage at diagnosis	692	Limited to testis	90	8	2	Ref
	309	N+	87	12	1	1.45*
	179	M+	66	33	1	4.98*
	170	Not specified	82	16	2	1.99*
Morphology	698	Seminoma	86	12	2	Ref
	629	Non-seminoma	86	13	1	1.16
	23	Not specified	44	56	0	7.25*
Vascular or nodal invasion	235	Present	84	14	2	Ref
	312	Not present	91	7	2	0.47*
	803	Not specified	84	15	1	1.02
Main place of treatment	253	Specialised Oncological Hospital	86	13	1	Ref
	1009	Not specialised	86	12	2	0.93
	88	Not specified if specialised or not	74	25	1	1.96*
Adjuvant treatment	440	Chemotherapy only	84	15	1	1.31
	411	Radiotherapy only	89	8	3	0.70
	53	Chemo plus radiotherapy	60	40	0	3.76*
	446	No adjuvant/not specified	87	12	1	Ref
RPLND[b]	275	Yes	88	11	1	0.82*
	933	No	85	13	2	Ref
	142	Not specified	80	20	0	1.68*
Relapse	133	Yes	63	35	2	Ref
	750	No	94	6	0	0.12*
	467	Not specified	77	19	4	0.60*
Total cases	1350		1152	179	19	

a Crude hazard ratios for death obtained by Cox regression modelling.
b Retroperitoneal lymph-node dissection; Ref: reference category.
* $P < 0.005$.

HRs of death were significantly higher for Estonia and Cracow compared to the Italian registries; for the oldest age group (⩾50 years) compared to the youngest age group (⩽29 years); for the 11 patients who did not receive surgery; and for M+, N+ and stage not specified cases at diagnosis compared to disease limited to the testis. With regard to cancer characteristics, HR of death was significantly higher for unspecified morphology compared to seminoma, and significantly lower for no vascular or lymphatic invasion compared to the presence of such invasion.

Regarding treatment, patients treated in hospitals with no information on whether specialised or not had a higher HR of death than those treated in specialist institutes. Patients who underwent both adjuvant chemotherapy and radiotherapy had significantly higher HRs of death than those with no adjuvant treatment, or with adjuvant treatment not specified. Patients who received retroperitoneal lymph-node dissection (RPLND) had a lower HR of death than those who did not receive RPLND, or did not have this information available. Finally, patients with no relapse had a significantly lower HR of death than those who relapsed.

Tables 2a and 2b show, for seminomas and non-seminomas, respectively, and for each registry, the total number of cases, proportions of young patients (age ⩽29 years), stage

Table 2a – Numbers of cases of seminomatous testicular cancer by cancer registry, with percentages diagnosed at ⩽29 years, and breakdown by stage at diagnosis and adjuvant treatment

Country (Registries)	Number of cases	Age ⩽29 (%)	Stage at diagnosis (%)				Adjuvant treatment (%)		
			Testis	N+	M+	NS[a]	RT[b]	Chemo[c]	RPLND[d]
France (Bas-Rhin, Isère, Somme)	119	11	70	19	5	6	72	18	10
Italy (Modena, Varese)	58	17	83	10	3	4	38	10	5
Switzerland (Geneva)	53	19	79	15	4	2	70	13	6
The Netherlands (Eindhoven, Groningen)	164	19	74	15	3	8	78	15	2
The UK (Yorkshire)	60	13	87	8	0	5	92	8	0
Estonia	31	13	68	16	10	6	45	55	3
Poland (Cracow)	16	6	37	12	19	32	62	37	6
Slovenia	66	20	48	40	9	3	70	24	14
Slovakia	130	17	43	18	5	34	37	12	4
Total	698	16	66	18	5	11	64	17	5

a Not specified.
b Radiotherapy.
c Chemotherapy.
d Retroperitoneal lymph node dissection.

Table 2b – Numbers of cases of non-seminomatous testicular cancer by cancer registry, with percentages diagnosed at ⩽29 years, and breakdown by stage at diagnosis and adjuvant treatment

Country (Registries)	Number of cases	Age ⩽29 (%)	Stage at diagnosis (%)				Adjuvant treatment (%)		
			Testis	N+	M+	NS[a]	RT[b]	Chemo[c]	RPLND[d]
France (Bas-Rhin, Isère, Somme)	114	53	40	22	33	5	1	67	26
Italy (Modena, Varese)	47	45	49	34	13	4	2	43	49
Switzerland (Geneva)	40	62	43	27	25	5	5	55	30
The Netherlands (Eindhoven, Groningen)	139	53	39	27	18	16	2	61	36
The UK (Yorkshire)	39	38	51	18	21	10	5	55	3
Estonia	18	39	17	17	33	33	11	67	44
Poland (Cracow)	15	60	13	33	27	27	0	80	27
Slovenia	74	63	35	45	19	1	3	58	77
Slovakia	143	54	27	28	23	22	3	56	20
Total	629	54	36	29	23	13	3	59	34

a Not specified.
b Radiotherapy.
c Chemotherapy.
d Retroperitoneal lymph node dissection.

distribution at diagnosis, proportions treated by chemotherapy and radiotherapy, and proportions that received RPLND. Overall, 16% of patients with seminoma and 54% with non-seminoma were ⩽29 years, with little variation across countries. In all registries, seminomas were diagnosed at an earlier stage than non-seminomas, with 66% of seminomas and 36% of non-seminomas limited to the testis. For both morphologies, Estonia, Poland and Slovakia had the lowest percentages of cancers limited to the testis. Estonia also had the highest proportion of non-seminoma cases with metastasis at diagnosis. Poland had the highest percentage of seminomas with metastases at diagnosis. The UK had the highest percentage of cancers limited to the testis, for both morphologies. Considering all registries, the percentages of cases with non-specified stage were similar for seminoma and non-seminoma (11% and 13%, respectively). Poland and Slovakia had the highest proportions of cases with no stage information. Estonia had the highest proportion of cases with no stage information for non-seminoma (33%), whereas for seminoma this proportion was comparable to the other countries (5%). Among the western European registries, those of France had high proportions of M+ cases at diagnosis for non-seminoma, similar to Estonia (33%). For seminoma, the proportion of M+ cases was also high in the French registries, but on par with the other regions.

For seminoma, 64% of patients received adjuvant radiotherapy, 17% received chemotherapy and 6% received RPLND. The corresponding figures for non-seminoma were 3%, 59% and 34%. The UK, the Netherlands and France, in that order, had the highest proportions of seminoma treated with radiotherapy: in these registry areas 71% or more of such patients received adjuvant radiotherapy. Italy, Slovakia and Estonia

had the lowest proportions of seminoma (45% or less) treated by radiotherapy. In Estonia, low percentages received radiotherapy and high percentages received chemotherapy for adjuvant treatment of seminoma. The UK had the highest proportion of seminoma patients receiving radiotherapy and the lowest proportion of patients receiving chemotherapy.

For non-seminoma, Poland (80%), France (67%) and Estonia (67%) had the highest proportions of patients receiving chemotherapy. Slovenia had the highest proportion of non-seminoma patients (77%) receiving RPLND.

Tables 3a and 3b show for seminoma and non-seminoma, respectively, the observed 10-year survival with 95% confidence intervals (CI) by country, age, stage and morphology. The fourth and fifth columns of these tables show the results of the Cox multivariable survival analysis including all variables shown in the tables. The last two columns in each table show the proportions of relapsed and lost to follow-up patients.

Overall, 10-year observed survival was slightly higher for seminoma (87%) than for non-seminoma (85%). Survival for non-seminoma was lower than for seminoma in all registries except those of the Netherlands, the UK and Poland, where survival figures for the two morphologies were closely similar.

Ten-year observed survival for seminoma ranged from 63% (Estonia) to 94% (Switzerland and Slovenia). Ten-year survival for non-seminoma ranged from 47% (Estonia) to 90% (UK and the Netherlands).

Slovakia provided only 5-year follow-up: five year observed survival was 93% (95% CI 89–98) for seminoma and 89% (95% CI 84–95) for non-seminoma.

In both morphologies, survival decreased with advancing age at diagnosis. Seminoma patients in the age category 30–49 years had the highest 10-year survival (93%); those aged $\geqslant$50 years had the worst survival in both morphologies (60% seminoma; 65% non-seminoma).

For both morphologies, survival decreased with advancing stage at diagnosis; non-seminoma was associated with slightly better survival than seminoma in each stage category except M+.

Considering the multivariable analyses carried out for seminoma, the model adjusted by country, age and stage at diagnosis showed that most of the geographic differences in HRs for death were not statistically significant (Table 3a). Only Estonia and Poland had significantly higher HRs for death than Italy (reference country). Switzerland and Slovenia had somewhat lower, and the UK somewhat higher HRs for death than reference, but these differences were not significant. The prognostic significance of age and stage was confirmed by the multivariable analyses: seminoma patients aged $\geqslant$50 years had a significantly greater HR for death than those aged $\leqslant$29; the risk of death increased significantly with advancing stage compared to disease limited to the testis, while cases with stage information not available had a HR for death almost twice as high as reference (not significant).

Turning now to the multivariable analyses for non-seminoma (Table 3b), we note first that the rank of HR for death by country was similar to that of seminoma. The UK was an exception in that the HR of death for non-seminoma was 0.40, while for seminoma it was 1.17 (HRs not significantly different from reference – Italy – for either morphology). The only HR significantly different from reference was that for Estonia. Patients aged $\geqslant$50 years had a significantly greater HR for death than those aged $\leqslant$29. The HR of death

Table 3a – Ten-year observed survival for seminomatous testicular cancer with hazard ratio (HR) for death 10 years after diagnosis, and proportions of relapsing and lost cases

Country (Registries)	10-year observed survival (%)	95% CI[a]	HR[b]	95% CI[a]	% Relapses	% Lost to follow-up for	
						Life status	Relapse
Italy (Modena, Varese)	90	82–98	Ref		10	0	2
France (Bas-Rhin, Isère, Somme)	85	78–92	0.98	0.40–2.41	21	1	31
Switzerland (Geneva)	94	87–100	0.52	0.15–1.83	9	0	4
The Netherlands (Eindhoven, Groningen)	84	77–92	0.94	0.39–2.29	5	0	12
The UK (Yorkshire)	89	79–100	1.16	0.33–4.09	0	0	18
Estonia	63	46–81	3.39	1.25–9.15	16	6	23
Poland (Cracow)	68	43–92	4.20	1.23–14.30	6	0	19
Slovenia	94	88–100	0.61	0.19–2.01	4	0	17
Age at diagnosis (years)							
$\leqslant$29	91	85–97	Ref				
30–49	93	90–95	0.76	0.35–1.64			
$\geqslant$50	60	50–71	5.40	2.54–11.48			
Stage							
Limited to testis	90	87–93	Ref				
N+	83	75–91	1.31	0.73–2.35			
M+	73	57–88	3.22	1.45–7.15			
Not specified	86	78–94	1.72	0.85–3.48			
Overall	87	84–90			8		

a 95% confidence intervals.
b Hazard ratio for death adjusted by country, age and stage (Cox model); Ref: reference category.

Table 3b – Ten-year observed survival for non-seminomatous testicular cancer with hazard ratio for death 10 years after diagnosis, and proportions of relapsing and lost cases

Country (Registries)	10-year observed survival (%)	95% CI[a]	HR[b]	95% CI[a]	% Relapses	% Lost to follow-up for	
						Life status	Relapse
Italy (Modena, Varese)	85	75–95	Ref		4	2	8
France (Bas-Rhin, Isère, Somme)	83	76–90	0.99	0.39–2.49	34	0	28
Switzerland (Geneva)	88	77–100	0.59	0.16–2.08	30	0	22
The Netherlands (Eindhoven, Groningen)	90	84–96	0.61	0.23–1.64	15	0	15
The UK (Yorkshire)	90	78–100	0.40	0.10–1.64	0.0	0	3
Estonia	47	23–72	3.90	1.37–11.10	17	6	34
Poland (Cracow)	67	42–91	2.77	0.83–9.27	7	0	33
Slovenia	86	77–95	1.04	0.36–2.97	11	0	19
Age at diagnosis (years)							
⩽29	87	83–91	Ref				
30–49	85	81–90	1.04	0.65–1.67			
⩾50	65	44–85	5.81	2.43–13.85			
Stage							
Limited to testis	94	90–97	Ref				
N+	89	83–94	1.68	0.77–3.67			
M+	65	57–73	9.12	4.60–18.09			
Not specified	92	87–98	1.39	0.49–3.94			
Overall	85	79–86			12		

a 95% confidence intervals.
b Hazard ratio for death adjusted by country, age and stage (Cox model); Ref: reference category.

increased with advancing stage at diagnosis, and was significantly above reference (disease limited to testis) for M+ cancers.

We next tested the inclusion of each of the clinical variables listed in Table 1 (vascular/nodal invasion, place of main treatment, adjuvant treatment, RPLND and surgery) in the separate multivariable analyses for seminoma and non-seminoma, adjusted by region, age, stage and treatment (categorised as in Table 1). These models showed that the group of 13 non-seminoma patients who received chemotherapy and radiotherapy had a significantly higher HR of death than those who received no adjuvant treatment (HR 2.2, 95% CI 1.3–3.2). The 38 seminoma patients who received chemotherapy and radiotherapy had a non-significantly higher HR of death than those not so treated (HR 1.08, 95% CI 0.94–1.04). The other variables listed in Table 1 maintained their prognostic values in the multivariable model (adjusted for country, age and stage), in that their HRs of death were similar to the crude HRs of death reported in Table 1. Inclusion of each of the other clinical variables in the model only slightly altered the HRs of the other variables and they are not reported.

Overall, 8% of seminomas and 12% of non-seminomas relapsed (column 6, Tables 3a and 3b).

For both morphologies, the lowest percentages of relapse were in the UK (0%) and the highest in France (21% seminoma, 34% non-seminoma).

The probability of survival after relapse was calculated for the 134 cases for which the date of relapse was available. The overall 5- and 10-year observed survival after relapse were 62% (95% CI 53–71) and 58% (95% CI 48–68), respectively (not shown in the table).

4. Discussion

This study has confirmed the survival variation for testicular cancer across Europe previously reported in a EUROCARE study[13] that analysed Europe-wide 5-year survival but did not have access to information on stage at diagnosis or treatment.

The present study is one of the largest population-based studies ever carried out on testicular cancer in which the influence on survival of stage at diagnosis, treatment and morphology was analysed. Other large population studies examining care procedures on a population basis have been carried out in the UK[6] and in the United States of America (USA) on the SEER database.[26] However, adjustment for stage at diagnosis was performed only in the latter.

We analysed survival and patterns of treatment by the two main morphological types of testicular cancer. We relied on the morphology codes provided by the registries. It is possible that coding criteria were not well standardised among the participating registries, each of which followed its usual coding practice. It has been shown that the diagnostic accuracy and the consistency of diagnostic coding can vary across centres and over time.[27] However, our study protocol required, in addition to the assigned ICD-O code, a brief morphological description of cancer, such as that found on the pathology report of the clinical record. The ICD-O codes reported in the forms were checked against these descriptions by one of the authors.

Consistent with previously published data,[19] we found that stage at diagnosis was generally less advanced and survival slightly better for seminoma than for non-seminoma. However, a new and important finding of the present study

is that differences in stage at diagnosis between registries, for both morphologies were marked (Tables 2a and 2b). After adjustment by stage (and age) at diagnosis, only Estonia and Poland (seminoma) and Estonia (non-seminoma) had significantly higher HRs of death than reference. These findings suggest that for these eastern European populations, lower survival was not due entirely to advanced stage at diagnosis, but also to inadequate treatment. Some geographic differences in HR of death also persisted between the western European regions, although they were not statistically significant.

The survival ranking of the western European registries differed for the two morphologies. For seminoma, highest survival (and lowest HR of death) were found in Switzerland and Slovenia; while highest survival for non-seminoma (and lowest HR of death) characterised the UK and Dutch registries. Thus, for the UK, non-seminoma survival was amongst the highest, and seminoma survival was on par with that of the other study regions. This finding is in line with the good overall survival for testicular cancer in the UK found by the previous EUROCARE studies and contrasts with the poor survival for many solid tumours in the UK, in comparison with other European populations over the same time period.[13,14]

With regard to the French registries, we found that for both morphologies, survival was slightly lower (HR of death higher) among these populations than in the other western European populations. However, in the multivariable Cox analyses, HRs of death in France became practically 1 for both morphologies. This suggests that patients were diagnosed at more advanced stage in France than in the other regions, and that patients with advanced disease were treated appropriately. It is possible that the higher proportion of advanced stage cancers in France is due to more thorough work-up for metastases. However, our data do not support this hypothesis: the overall frequencies of chest, pelvic and abdominal imaging were 95%, 47% and 82%; whereas the corresponding frequencies for the French registries were 94%, 48% and 92%. Inclusion of adjustment for diagnostic examinations in the model did not change HRs by country (data not shown).

Unlike the other eastern European countries, Slovenia had the highest survival for seminoma (together with Switzerland), and survival for non-seminoma was on par with that of the western European registries. Paradoxically, Slovenia was characterised by higher proportions of patients with advanced stage at diagnosis, for both seminoma and non-seminoma, than most other registries. However, most testicular cancer patients are treated at two cancer institutes in Ljubljana (personal communication) where in all probability, surgical techniques are optimised, postoperative complications reduced to the minimum, and standardised adjuvant systemic therapy regimens applied.

Residual differences in HRs for death between registries, after adjustment for age and stage could be due to differences in treatment. Unfortunately, information on what chemotherapy agents were used was not available for most registries, and it was not possible to analyse the effects of treatment on survival in more detail. Published data[28] indicate that the decline in mortality for testicular cancer is less marked in eastern than western European countries, suggesting insufficient availability of adequate care in those countries.

Variations in survival for testicular cancer with level of affluence have been reported in the UK.[6,29] In the USA, it has been shown that racial and ethnic minorities have lower survival for testicular cancer than non-Hispanic whites.[26] Information on the socio-economic status of patients was not available in the present study.

The relapse rate was 10% overall (8% for seminoma and 12% for non-seminoma), with remarkable between-country differences – from 0% in the UK to 22% in France. These relapse percentages are lower than those reported in the literature: 15–20% of seminoma patients receiving simple orchidectomy relapse, 5% of seminoma patients receiving adjuvant radiotherapy relapse;[15,16] about 30% of patients with non-seminoma relapse.[15,30] The Swiss and French registries had the highest frequencies of relapse for both morphologies, which were, however, most consistent with the literature. Our study protocol defined relapse as local recurrence or distant metastases. This definition might not be consistent with that used in clinical studies. For example, elevated serum markers (α-fetoprotein and βHCG) in an asymptomatic patient may be interpreted as relapse by some clinicians. Furthermore, the active follow-up required by the study protocol may have been hindered by legal and confidentiality restraints, and may have resulted in systematic underestimation of relapse rates.

In addition to the main variables included in the multivariable analyses, we also investigated the other clinical variables listed in Table 1, which were found to have prognostic significances consistent with the literature. These variables were not included in the final models since they did not contribute to explaining differences in HRs.

Only 11 patients, evenly distributed across registries, were not operated on; they had a sevenfold greater risk of death than those who underwent surgery and most had advanced cancer at diagnosis (2 were N+, 7 were M+ and 2 had no information on stage). Surgery can thus be considered a proxy of stage, and this would explain why inclusion of surgery in the models did not explain more variability than stage itself.

The HR of death for patients without vascular or lymphatic invasion was significantly lower than for those with such invasion. However, information on the presence of invasion was available only for 40% patients, and this would explain why its inclusion in the model did not contribute to explaining differences in HR of death between countries.

Patients who received adjuvant therapy had better survival (lower HR of death) than those who did not. However, intensively treated patients (chemotherapy and radiotherapy) had a higher HR of death than reference. Of the 53 intensively treated patients, 38 had advanced stage (N+ or M+), 13 had embryonal carcinoma, 38 had seminoma, 2 had no information on morphology and 1 did not undergo surgery. Adjustment for stage at diagnosis was insufficient to explain their poorer survival, suggesting the presence of unfavourable prognostic factors not discernible from the clinical records. For example, information on vascular/lymphatic invasion was available in only a minority of cases and no information on comorbidities was available.

To conclude, this high resolution study has confirmed the presence of disparities in testicular cancer survival across Europe. Lowest survival was found for Estonia and Poland

and was not explained entirely by more advanced stage at diagnosis, suggesting inadequate treatment and a failure of these countries' health systems to implement effective treatment protocols. Stage at diagnosis varied markedly across the remaining (western European) populations. In the French registries stage at diagnosis was more advanced than in other western European registries, nevertheless our data indicate good quality treatment in these areas, since no excess risk of death remained in the multivariable analysis after adjusting for stage. The Swiss and English registries (Geneva and Yorkshire) had the highest survival and the most favourable stage distribution.

Conflict of interest statement

None declared.

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