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Trends in incidence, mortality and survival of testicular cancer patients in Belarus

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Introduction The objective of this study was to assess recent trends in incidence, mortality and relative survival (RS) in testicular cancer (TC) patients in Belarus and to provide international comparisons of our figures.

Material and methods We surveyed the Belarusian Cancer Registry for all male cases diagnosed with International Classification of Diseases for Oncology, third edition (ICD-O-3) topography code C62 between 1990 and 2015. Trends for incidence and mortality rates per 100,000 of the world standard population and annual percentage changes (APCs) were calculated. We also estimated the 1- and 5-year RS rates for the 1990–1998, 1999–2007 and 2008–2015 periods according to the Ederer II method. The RS estimates for the 2008–2015 period were age-standardized and compared with the published EUROCARE-5 data and SEER-18 database analysis.

Results A total of 2,500 and 2,439 cases were included into incidence and survival analyses, respectively. We found a significant increase in the TC age-standardized incidence rate (APC 2.6%) and a decline in the age-standardized mortality (APC-3.0%) over the study period. RS significantly increased in all patients` strata; a relative increase was more pronounced in advanced stages of seminoma and younger age groups. Nevertheless, the most recent figures of age-standardized RS including stage-specific estimates were generally worse than the European and SEER data.

Conclusions We have found a significant increase in TC incidence in Belarus in recent years. Mortality has significantly declined with a corresponding increase in RS which, however, did not reach European or North American figures. Continued effort is required to improve the quality of management of TC patients in our country.

Key Words: testicular neoplasms ‹› testicular germ cell tumor ‹› incidence ‹› mortality ‹› survival analysis ‹› proportional hazards models

INTRODUCTION

Testicular cancer (TC) is an infrequent malignancy accounting for about 1% of all male cancers, however it is the most commonly diagnosed cancer in 15–39-year-old men [1]. Unlike the majority of other solid tumors, TC has become a model for a highly curable neoplasm even in advanced stages. The development of effective platinum-based chemotherapy regimens in the late 1970s significantly improved treatment outcomes in TC patients [2]. In Western countries this led to a dramatic decrease in mortality during the following decade [3] and currently, survival of TC patients exceeds 90%. Yet, that is not the case for a number of Eastern European countries where some progress in survival took place at a much later time and probably has not yet been completed [4].

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Belarus is a relatively blank spot on the cancer map of Europe as our country did not take part in the majority of collaborative epidemiological research assessing comparative survival outcomes [5]. The epidemiology of TC in Belarus is poorly studied and we did not find any publications focused on burden and survival for this disease.
The objective of our study was to assess recent trends in incidence, mortality and relative survival (RS) in TC patients in Belarus and provide international comparisons of our figures.

MATERIAL AND METHODS

Data source and study population

Data were derived from the Belarusian Cancer Registry (BCR) that covers the country's entire population and contains compulsorily notifiable data on all new cancer cases since 1973, including histopathology, extent of disease at diagnosis, date and cause of death.
We surveyed the BCR database for all male cases with International Classification of Diseases for Oncology, third edition (ICD-O-3) topography code C62 and date of diagnosis between January 1990 and December 2015. Morphological verification of the diagnosis was not required. To assess coding errors, we additionally performed a search among males with ICD-O-3 histology codes 9060-9105, excluding extragonadal cases. Bilateral cases were included in the incidence calculations, for the survival analysis only the first tumor per patient was selected. Spermatocytic seminoma was included as there were cases of malignant behavior of this tumor. We excluded cases with non-epithelial histology (mostly lymphoproliferative disorders and sarcomas) and benign tumors. A combination of germ cell and non-epithelial histology was regarded as a teratoma with malignant transformation and included under the non-seminoma category. Patients aged <15 years and cases registered from a death certificate only (DCO) or detected solely at autopsy were excluded from the survival analysis.

Analyzed variables

We analyzed incidence, mortality and survival according to following variables: age at diagnosis, histological variant and extent of the tumor, living in urban or rural areas, administrative region of residence and calendar year of diagnosis.
Age categories were grouped as 0–14, 15–24, 25–34, 35–44, 45–54, and 55 years or more. All the cases were classified as seminoma (ICD-O-3 codes 9060-9064), non-seminoma including mixed germ cell tumors (9065, 9070–9072, 9080–9085, 9100–9102), non-germ cell (8600–8650) and unknown. Histology codes and text pathology reports were assessed for discrepancies. In case of conflicting data, we verified information in other clinical sources if available (the clinical database of N.N. Alexandrov National Cancer Centre) or assigned the case to the 'unknown' category.
The extent of the tumor was classified as confined to the testis (localized), spread to the regional lymph nodes (regional), with metastases to distant organs (distant) or unknown. As the TNM stage did not always match the combination of categories T, N and M we determined the extent of the tumor by the latter if this information was available.
Urban and rural population was defined by registration in either urban or rural settlements according to legislative definitions (an urban settlement is generally a settlement with more than 6,000 residents, or more than 2,000 and the presence of urban infrastructure). Place of residence followed the administrative division of the country into six regions (voblasts) and the city of Minsk. To analyze RS trends, we divided the entire period of cancer diagnosis into three intervals 1990–1998, 1999–2007 and 2008–2015 calendar years.

Statistical analysis

We calculated yearly age-standardized incidence and mortality rates per 100,000 of the world (WHO 2000–2025) standard population [6]. Locally weighted regression (Lowess) curves with a bandwidth of 0.3 were used to smoothen and graphically summarize the direction of the trends. Annual percentage changes (APCs), their 95% confidence intervals (CIs) using weighted least squares method and statistical significance for the difference from zero were calculated for all the analyzed trends.
One- and five-year RS rates with 95% CIs were estimated for the three time intervals 1990–1998, 1999–2007, and 2008–2015 according to the Ederer II method and cohort-based approach. Survival time was calculated from the date of diagnosis to the date of death or last contact. Since the BCR had the most updated follow-up information available for vital status up to December 2018, only patients diagnosed in 2014–2015 did not have a complete 5-year follow-up. Belarusian mortality tables by age, sex and calendar year were derived from the Human Mortality Database [7], checked against published official data and used for RS calculations. For categories with fewer than 10 cases RS rates were not estimated. We used the Z-test to compare trends for RS rates in various strata. To assess significant prognostic factors uni- and multivariate relative excess risk (RER) of death

additive hazard model was fitted based on an expectation-maximization algorithm [8].

RS estimates for the most recent study period (2008–2015) were standardized by age with the direct method using the International Cancer Survival Standard population 3 and age groupings 15–44, 45–54, 55–64, 65–74, and ≥75 years [9]. Because of a lack of patients in the older age groups, in some subgroups age strata were merged into 4 groups. If there were no patients in two or more age strata, we reported only unstandardized estimates. If the last patient in any stratum was censored before 60 months, we presented the last available estimate. For the international comparisons we used the published EUROCARE-5 data [10] and Surveillance, Epidemiology, and End Results (SEER) database query [11]. The same inclusion criteria (ICD-O-3 topography code C62, year of diagnosis 2008–2015), exclusion criteria (<15 years old, benign, non-epithelial tumors), stratification parameters (seminoma and non-seminoma morphology codes, extent of disease) and age-standardized RS methodology were used for the SEER data analysis.

Table 1. *Characteristics of the study population**

	Total n (%)	Study period			P†
		1990–1998 n (%)	1999–2007 n (%)	2008–2015 n (%)	
Number of patients	2475 (100)	657 (100)	894 (100)	924 (100)	
Seminoma					
Localized	852 (34.4)	174 (26.5)	319 (35.7)	359 (38.9)	0.84
Regional	220 (8.9)	38 (5.8)	87 (9.7)	95 (10.3)	
Distant	125 (5.1)	23 (3.5)	46 (5.1)	56 (6.1)	
Unknown stage#	148 (6.0)	112 (17.0)	26 (2.9)	10 (1.1)	
Seminoma total	1345 (54.3)	347 (52.8)	478 (53.5)	520 (56.3)	
Nonseminoma					
Localized	376 (15.2)	80 (12.2)	142 (15.9)	154 (16.7)	0.25
Regional	246 (9.9)	43 (6.5)	104 (11.6)	99 (10.7)	
Distant	225 (9.1)	32 (4.9)	94 (10.5)	99 (10.7)	
Unknown stage#	70 (2.8)	56 (8.5)	13 (1.5)	1 (0.1)	
Nonseminoma total	917 (37.1)	211 (32.1)	353 (39.5)	353 (38.2)	
Non germ-cell					
Localized	17 (0.7)	3 (0.5)	5 (0.6)	9 (1.0)	1.00‡
Regional	2 (0.1)	0	1 (0.1)	1 (0.1)	
Distant	4 (0.2)	0	2 (0.2)	2 (0.2)	
Unknown#	5 (0.2)	0	1 (0.1)	4 (0.4)	
Non germ-cell total	28 (1.1)	3 (0.5)	9 (1.0)	16 (1.7)	
Unknown histology					
Localized	58 (2.3)	23 (3.5)	17 (1.9)	18 (1.9)	0.15‡
Regional	16 (0.6)	6 (0.9)	4 (0.4)	6 (0.6)	
Distant	38 (1.5)	15 (2.3)	18 (2)	5 (0.5)	
Unknown#	73 (2.9)	52 (7.9)	15 (1.7)	6 (0.6)	
Unknown histology total	185 (7.5)	96 (14.6)	54 (6.0)	35 (3.8)	
Age at diagnosis					
0–14 years	26 (1.1)	10 (1.5)	10 (1.1)	6 (0.6)	<0.0001
15–24 years	363 (14.7)	115 (17.5)	142 (15.9)	106 (11.5)	
25–34 years	888 (35.9)	234 (35.6)	312 (34.9)	342 (37.0)	
35–44 years	607 (24.5)	118 (18.0)	238 (26.6)	251 (27.2)	
45–54 years	256 (10.3)	43 (6.5)	81 (9.1)	132 (14.3)	
≥55 years	335 (13.5)	137 (20.9)	111 (12.4)	87 (9.4)	
Region					
Brest voblast	330 (13.3)	92 (14.0)	135 (15.1)	103 (11.1)	0.044
Vitebsk voblast	358 (14.5)	103 (15.7)	109 (12.2)	146 (15.8)	
Homyel voblast	322 (13.0)	90 (13.7)	107 (12.0)	125 (13.5)	
Hrodna voblast	299 (12.1)	79 (12.0)	106 (11.9)	114 (12.3)	
Minsk voblast	366 (14.8)	97 (14.8)	134 (15.0)	135 (14.6)	
Mahilyow voblast	243 (9.8)	62 (9.4)	106 (11.9)	75 (8.1)	
Minsk city	557 (22.5)	134 (20.4)	197 (22.0)	226 (24.5)	
Place of residence					
Urban	1933 (78.1)	484 (73.7)	722 (80.8)	727 (78.7)	0.003
Rural	542 (21.9)	173 (26.3)	172 (19.2)	197 (21.3)	

* – bilateral cases are not shown; † – Pearson's chi-square test unless otherwise indicated; ‡ – Fisher's exact test; # – treated as missing for p-value calculation

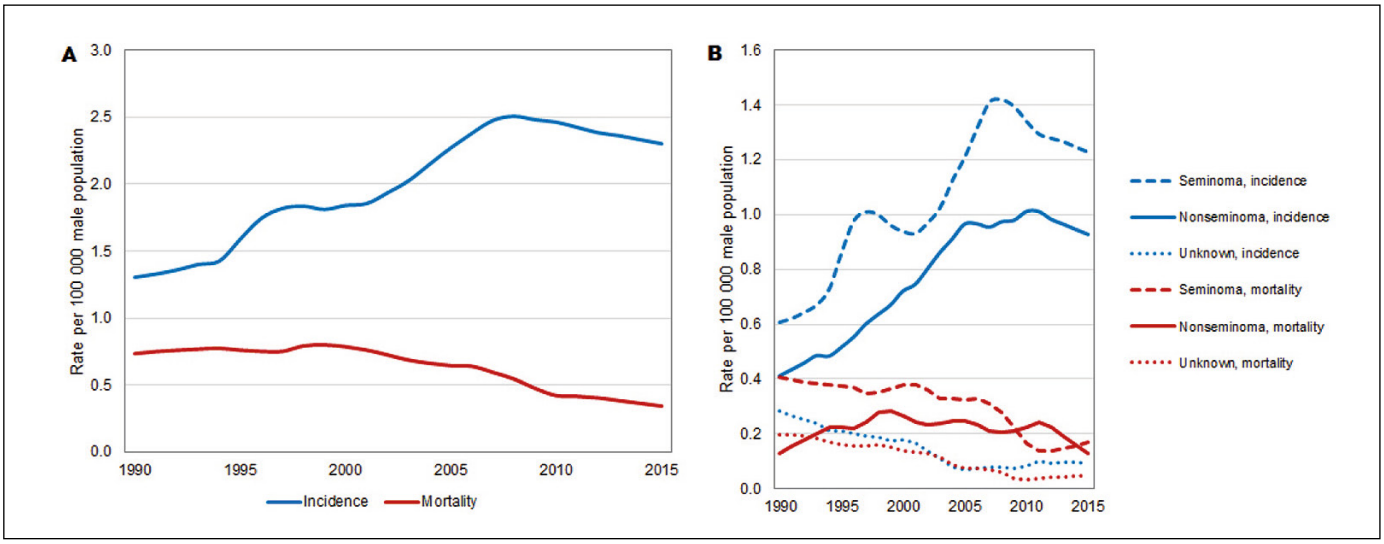

Figure 1. *Smoothed trends for age-standardized incidence and mortality rates for testicular cancer in Belarus, 1990-2015:* **(A)** *in total cohort,* **(B)** *by histologic variant.*

All the statistical analyses were performed with SEER*Stat software (seer.cancer.gov/seerstat) version 8.3.5 and R statistics (r-project.org) version 3.5.3 using the relsurv package.

RESULTS

A total of 2,559 cases with ICD-O-3 C62 code were selected from the BCR; 60 cases were excluded because of non-epithelial morphology and one – because of extragonadal primary. The additional search among 340 male cases with other topography codes and morphology suggestive of TC identified only two cases with erroneous coding that were also included. Thus 2,500 cases were included into the incidence calculations and 2,439 patients into the survival analysis with the exclusion of 6 autopsy only, 4 DCO diagnoses, 25 second bilateral and 26 pediatric cases. TC patients' characteristics are shown in Table 1. Only 58 of the 2,500 included cases (2.3%) were not confirmed by histology or cytology and 44 (1.8%) patients in the survival analysis were censored within 1 year of diagnosis.

Table 2. *Average annual percent changes for testis cancer age-standardized incidence and mortality*

	Incidence		Mortality	
	APC (95% CIs)	p	APC (95% CIs)	p
Total cohort	2.62 (1.91, 3.32)	<0.0001	-3.01 (-4.21,-1.80)	<0.0001
Histology*				
Seminoma	2.97 (1.91, 4.05)	<0.0001	-3.50 (-5.12,-1.86)	0.0002
Nonseminoma	3.57 (2.55, 4.59)	<0.0001	-0.24 (-1.89, 1.43)	0.77
Unknown	-5.03 (-6.98,-3.04)	<0.0001	-11.4 (-20.4,-1.41)	0.028
Tumor extension				
Localized	4.22 (2.93, 5.52)	<0.0001	-1.76 (-4.55, 1.11)	0.22
Regional	4.58 (2.68, 6.52)	<0.0001	3.27 (-5.27, 12.59)	0.45
Distant	4.21 (1.96, 6.50)	0.0007	2.50 (-2.75, 8.02)	0.34
Unknown	-12.5 (-14.6,-10.3)	<0.0001	-12.0 (-15.4,-8.36)	<0.0001
Age at diagnosis*				
15–24 years	0.39 (-0.84, 1.64)	0.52	-21.6 (-34.4,-6.29)	0.0077
25–34 years	2.85 (1.51, 4.21)	0.0002	-3.96 (-6.15,-1.73)	0.0014
35–44 years	5.95 (4.18, 7.74)	<0.0001	-0.06 (-7.08, 7.49)	0.99
45–54 years	5.28 (3.65, 6.94)	<0.0001	-2.34 (-10.14, 6.14)	0.56
55+ years	-1.83 (-3.27,-0.37)	0.016	-3.51 (-5.32,-1.67)	0.0007

APC – annual percent change, CI – confidence interval, * – estimates for 'non germ-cell' histology and '0–14 years' age group were not calculated due to low number of cases/deaths

Table 3. *Trends for 1- and 5-year relative survival rates in testis cancer patients in Belarus*

	RS, % (96% CIs), total cohort		RS, % (96% CIs), 1990–1998		RS, % (96% CIs), 1999–2007		RS, % (96% CIs), 2008–2015		p-value*	
	1-year	5-year	1-year	5-year	1-year	5-year	1-year	5-year	1-year	5-year
Total cohort	86.5 (85.0–87.9)	74.5 (72.5–76.4)	77.1 (73.6–80.3)	58.8 (54.5–62.8)	86.9 (84.3–89.0)	73.9 (70.5–77.0)	92.9 (90.9–94.5)	86.7 (83.7–89.1)	<0.0001	<0.0001
Seminoma										
Localized	96.8 (95.0–97.9)	91.3 (88.4–93.5)	90.2 (84.3–94.0)	81.4 (73.3–87.2)	98.3 (95.0–99.5)	91.9 (86.8–95.1)	98.3 (95.2–99.4)	95.3 (90.3–97.8)	0.0006	<0.0001
Regional	88.7 (83.4–92.4)	72.9 (65.6–78.8)	82.3 (65.2–91.5)	61.7 (43.2–75.8)	87.5 (77.8–93.2)	66.6 (54.4–76.2)	92.2 (84.0–96.3)	82.8 (71.4–89.9)	0.13	0.015
Distant	66.1 (56.8–73.9)	46.1 (36.6–55.1)	33.6 (15.2–53.2)	19.6 (06.1–38.6)	62.0 (46.0–74.5)	31.7 (18.2–46.1)	82.6 (69.2–90.6)	68.7 (53.6–79.7)	<0.0001	<0.0001
Unknown stage	75.2 (66.9–81.7)	55.2 (45.7–63.8)	73.4 (63.7–80.9)	54.8 (43.7–64.5)	86.2 (63.9–95.2)	58.5 (35.3–75.8)	NC	NC	NC	NC
Total	90.2 (88.4–91.8)	80.6 (77.9–83.0)	80.4 (75.5–84.3)	67.0 (61.1–72.3)	92.4 (89.3–94.6)	80.5 (75.9–84.3)	95.0 (92.3–96.7)	89.9 (85.9–92.8)	<0.0001	<0.0001
Nonseminoma										
Localized	95.5 (92.5–97.3)	85.7 (81.0–89.3)	93.9 (84.7–97.6)	70.8 (58.0–80.4)	94.1 (88.1–97.1)	82.7 (74.4–88.5)	97.7 (92.7–99.3)	96.3 (88.5–98.8)	0.17	<0.0001
Regional	93.3 (89.1–95.9)	82.4 (76.5–87.0)	93.3 (79.8–97.9)	68.3 (51.8–80.1)	90.6 (82.7–95.0)	82.4 (72.6–89.0)	96.0 (89.1–98.6)	88.8 (80.0–93.9)	0.51	<0.0001
Distant	73.4 (67.0–78.8)	50.5 (43.4–57.1)	69.7 (49.6–83.0)	34.9 (18.4–52.0)	69.1 (58.6–77.5)	46.2 (35.5–56.1)	78.7 (69.0–85.7)	59.7 (48.6–69.1)	0.34	<0.0001
Unknown stage	66.7 (53.9–76.7)	42.9 (30.4–54.9)	66.0 (51.6–77.0)	37.8 (24.4–51.1)	67.1 (33.7–86.4)	59.8 (27.2–81.6)	NC	NC	NC	NC
Total	87.2 (84.7–89.3)	72.9 (69.6–75.9)	82.7 (76.6–87.3)	56.2 (48.7–63.1)	85.3 (81.0–88.7)	72.0 (66.6–76.6)	91.8 (88.3–94.4)	83.9 (79.1–87.8)	0.002	<0.0001
Non germ-cell										
Total	93.8 (71.3–98.8)	80.8 (52.7–93.2)	NC	NC	NC	NC	94.6 (58.4–99.4)	84.8 (48.7–96.3)	NC	NC
Other										
Total	53.1 (45.2–60.5)	34.1 (26.3–42.2)	52.8 (41.9–62.6)	31.4 (21.1–42.2)	45.7 (31.5–58.8)	26.4 (14.8–39.4)	67.9 (46.4–82.3)	56.9 (32.2–75.5)	0.27	0.008
Tumor stage										
Localized	95.7 (94.3–96.8)	88.8 (86.4–90.8)	90.3 (85.8–93.5)	76.0 (69.5–81.2)	96.4 (93.8–97.9)	88.5 (84.5–91.5)	98.0 (95.8–99.1)	95.5 (91.9–97.5)	<0.0001	<0.0001
Regional	90.7 (87.5–93.1)	76.6 (72.1–80.5)	87.9 (78.6–93.4)	63.2 (51.6–72.7)	89.0 (83.4–92.8)	73.9 (66.4–80.0)	93.4 (88.7–96.2)	85.4 (78.5–90.2)	0.15	0.0002
Distant	66.1 (61.0–70.7)	44.7 (39.4–49.8)	48.2 (35.7–59.6)	26.2 (16.0–37.6)	61.5 (53.3–68.6)	36.6 (28.9–44.4)	78.4 (70.9–84.1)	60.7 (52.1–68.3)	<0.0001	<0.0001
Unknown	65.8 (59.7–71.1)	46.1 (39.6–52.4)	65.0 (58.0–71.1)	44.3 (36.8–51.6)	69.6 (54.7–80.4)	49.4 (34.2–62.9)	63.2 (35.0–81.8)	57.6 (29.9–77.7)	0.69	<0.0001
Age at diagnosis										
15–24	86.4 (82.4–89.6)	70.3 (65.1–74.9)	77.3 (68.3–84.0)	54.0 (44.1–62.9)	87.4 (80.7–92.0)	70.2 (61.7–77.2)	95.2 (88.8–98.0)	89.0 (80.3–94.0)	0.0003	<0.0001
25–34	90.0 (87.8–91.9)	79.3 (76.3–82.0)	83.5 (78.0–87.8)	62.3 (55.5–68.4)	88.1 (83.8–91.3)	79.5 (74.3–83.8)	96.4 (93.6–98.0)	90.9 (86.7–93.8)	<0.0001	<0.0001
35–44	92.2 (89.7–94.2)	82.3 (78.5–85.4)	86.9 (79.0–91.9)	70.5 (60.6–78.4)	93.5 (89.2–96.1)	82.2 (76.0–87.0)	93.6 (89.4–96.1)	87.7 (82.2–91.6)	0.040	0.0001
45–54	88.9 (84.0–92.4)	77.9 (71.0–83.3)	75.6 (59.2–86.1)	65.3 (47.0–78.6)	90.2 (80.3–95.3)	72.7 (59.5–82.3)	92.5 (85.7–96.1)	84.9 (75.0–91.2)	0.005	0.006
55+	64.7 (58.8–70.0)	47.7 (40.5–54.5)	57.8 (48.4–66.1)	43.0 (32.1–53.5)	65.6 (55.0–74.3)	41.9 (30.1–53.2)	74.8 (62.6–83.5)	60.2 (44.7–72.7)	0.022	0.015
Region										
Brest voblast	82.3 (77.5–86.1)	67.6 (61.8–72.7)	68.9 (57.9–77.6)	45.6 (34.4–56.2)	86.1 (78.6–91.1)	70.9 (61.8–78.2)	88.9 (80.7–93.8)	81.2 (71.3–87.9)	0.0008	<0.0001
Vitebsk voblast	84.3 (79.9–87.9)	69.4 (63.7–74.4)	73.2 (63.1–81.0)	57.1 (45.8–66.8)	86.6 (78.0–92.0)	66.6 (55.9–75.2)	90.5 (83.9–94.5)	80.2 (71.4–86.5)	0.0007	0.0001
Homyel voblast	88.6 (84.2–91.8)	79.9 (74.0–84.7)	84.6 (74.7–90.9)	71.6 (59.3–80.8)	88.5 (80.3–93.4)	77.7 (67.2–85.1)	91.4 (84.2–95.4)	86.6 (76.6–92.5)	0.19	0.021
Hrodna voblast	83.6 (78.6–87.5)	65.1 (58.7–70.7)	74.8 (63.0–83.3)	51.2 (38.5–62.5)	85.7 (77.0–91.2)	63.1 (52.4–72.1)	87.5 (79.3–92.6)	76.3 (66.0–83.8)	0.023	0.0005
Minsk voblast	85.3 (81.0–88.7)	74.6 (69.1–79.2)	71.0 (60.3–79.3)	49.8 (38.4–60.1)	87.4 (80.1–92.1)	76.3 (67.6–82.9)	93.8 (87.4–97.0)	90.2 (81.7–94.9)	<0.0001	<0.0001
Mahilyow voblast	87.4 (82.1–91.2)	73.1 (66.0–78.9)	77.6 (64.4–86.5)	55.7 (41.1–68.1)	88.5 (79.8–93.6)	75.2 (64.3–83.2)	93.9 (83.8–97.7)	83.7 (70.2–91.4)	0.007	0.0004
Minsk city	91.3 (88.4–93.5)	83.8 (79.9–87.0)	86.1 (78.7–91.2)	70.4 (61.0–77.9)	85.9 (79.9–90.3)	78.7 (71.5–84.3)	98.7 (95.7–99.6)	96.1 (90.7–98.4)	<0.0001	<0.0001

Table 3. *Continued*

	RS, % (96% CIs), total cohort		RS, % (96% CIs), 1990–1998		RS, % (96% CIs), 1999–2007		RS, % (96% CIs), 2008–2015		p-value*	
	1-year	5-year	1-year	5-year	1-year	5-year	1-year	5-year	1-year	5-year
Place of residence										
Urban	89.5 (87.9–90.9)	79.0 (76.8–81.0)	81.3 (77.3–84.6)	64.9 (60.0–69.5)	89.7 (87.1–91.8)	77.7 (74.0–80.9)	94.8 (92.7–96.4)	89.8 (86.7–92.2)	<0.0001	<0.0001
Rural	75.9 (71.9–79.4)	58.6 (53.8–63.1)	65.5 (57.6–72.3)	41.3 (33.1–49.3)	75.0 (67.5–81.0)	58.0 (49.5–65.6)	85.7 (79.6–90.1)	74.2 (66.3–80.6)	<0.0001	<0.0001

RS – relative survival; CI – confidence interval; NC – not calculated due to <10 cases per category; *comparison of values in 1990–1998 period versus 2008–2015

Incidence and mortality

A significant increase in the TC age-standardized incidence rate from 1.2 (95% CI 0.9, 1.6) to 2.3 (95% CI 1.9, 2.8) per 100,000 male population was noted over the study period with APC of 2.6% (95% CI 1.9%, 2.8%) (Figure 1A). This increase was comparable for seminoma and non-seminoma histology and all tumor stages as shown in Table 2, Figure 1B and Figure 2. The rise in incidence was limited to the age group 25-54 years and was negative in older men (Figure 3). A total of 807 deaths from TC were registered between 1990 and 2015. The age-standardized mortality significantly declined with APC -3.0% (95% CI -4.2%, -1.8%), mainly because of improvement in seminoma patients (Figure 1B). There was no clear mortality decline in 35–54 age group (Figures 4–5).

Relative survival and international comparisons

One- and five-year RS rates are shown in Table 3 and Figures 6–11. There was a significant increase in RS over the three analyzed periods in all patients` strata, a relative increase was more pronounced in advanced stages of seminoma and younger age groups. In the multivariate analysis the earlier study period, age at diagnosis ≥55 years, higher extent of disease, residence in western regions of the country or in rural areas were associated with statistically significant RER of death (Table 4). It should be noted that there were no statistically significant differences in RER between seminoma and non-seminoma patients.

One- and five-year age-standardized RS rates with corresponding figures derived from Trama et al. [10] and the SEER database presented in Tables 5 and 6. As shown in Figure 12A our results were significantly worse than the European average and close to Eastern European rates. A more detailed comparison of stage-specific 1- and 5-year age-standardized RS rates with the SEER data demonstrated a significantly worse prognosis in almost all the strata, except for localized non-seminoma patients (Figure 12B).

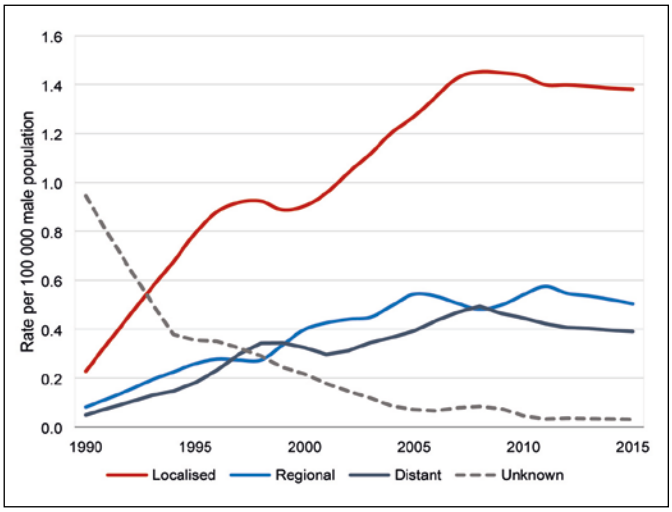

Figure 2. *Smoothed trends for stage-specific age-standartized incidence rates for testicular cancer in Belarus, 1990–2015.*

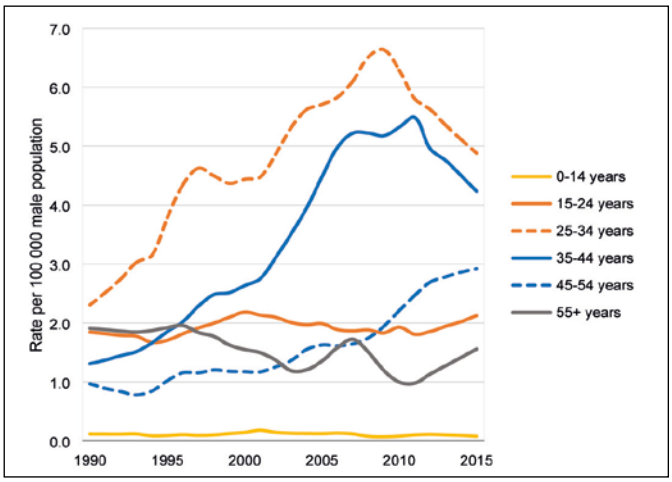

Figure 3. *Smoothed trends for age-specific age-standartized incidence rates for testicular cancer in Belarus, 1990–2015.*

DISCUSSION

Although TC is a highly aggressive and deadly malignancy if left untreated, modern multidisci-

Table 4. *Results of uni- and multivariate analysis of relative excess risk of death*

Variable	Univariate RER (95% CIs)	p	Multivariate RER (95% CIs)	p
Study period:				
1990–1998	Reference	–	Reference	–
1999–2007	0.54 (0.45–0.65)	<0.0001	0.69 (0.56–0.85)	0.0005
2008–2015	0.24 (0.19–0.30)	<0.0001	0.33 (0.26–0.43)	<0.0001
Age at diagnosis:				
15–24 years	Reference	–	Reference	–
25–34 years	0.68 (0.53–0.86)	0.002	0.86 (0.67–1.11)	0.25
35–44 years	0.56 (0.43–0.75)	<0.0001	0.91 (0.68–1.22)	0.53
45–54 years	0.72 (0.51–1.02)	0.061	1.08 (0.75–1.56)	0.69
≥55 years	2.49 (1.94–3.19)	<0.0001	2.34 (1.75–3.12)	<0.0001
Histologic variant:				
Seminoma	Reference	–	Reference	–
Non-seminoma	1.52 (1.25–1.83)	<0.0001	1.16 (0.95–1.43)	0.15
Non germ-cell	0.84 (0.26–2.70)	0.77	1.16 (0.46–2.88)	0.76
Unknown	5.57 (4.4–7.05)	<0.0001	2.20 (1.72–2.82)	<0.0001
Extent of disease:				
Localized	Reference	–	Reference	–
Regional	2.33 (1.76–3.09)	<0.0001	2.25 (1.72–2.95)	<0.0001
Distant	7.71 (6.08–9.79)	<0.0001	6.90 (5.44–8.75)	<0.0001
Unknown stage	7.43 (5.76–9.58)	<0.0001	2.90 (2.22–3.79)	<0.0001
Place of residence:				
Urban	Reference	–	Reference	–
Rural	2.38 (2.00–2.84)	<0.0001	1.46 (1.21–1.77)	<0.0001
Region:				
Brest voblast	Reference	–	Reference	–
Vitebsk voblast	0.91 (0.68–1.21)	0.51	0.83 (0.62–1.12)	0.22
Homyel voblast	0.60 (0.43–0.84)	0.003	0.61 (0.44–0.84)	0.003
Hrodna voblast	1.02 (0.76–1.37)	0.87	1.06 (0.79–1.41)	0.70
Minsk voblast	0.78 (0.58–1.04)	0.093	0.74 (0.55–0.99)	0.043
Mahilyow voblast	0.77 (0.55–1.07)	0.12	0.69 (0.49–0.96)	0.029
Minsk city	0.45 (0.33–0.60)	<0.0001	0.68 (0.50–0.92)	0.013

RER – relative excess risk; CI – confidence interval

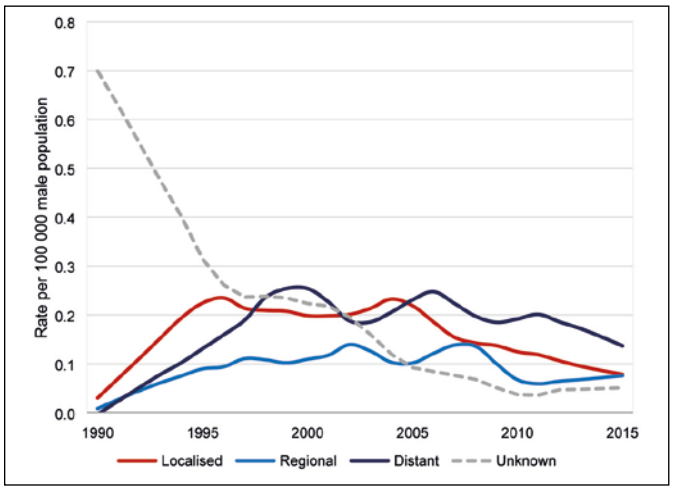

Figure 4. *Smoothed trends for stage-specific age-standartized mortality rates for testicular cancer in Belarus, 1990–2015.*

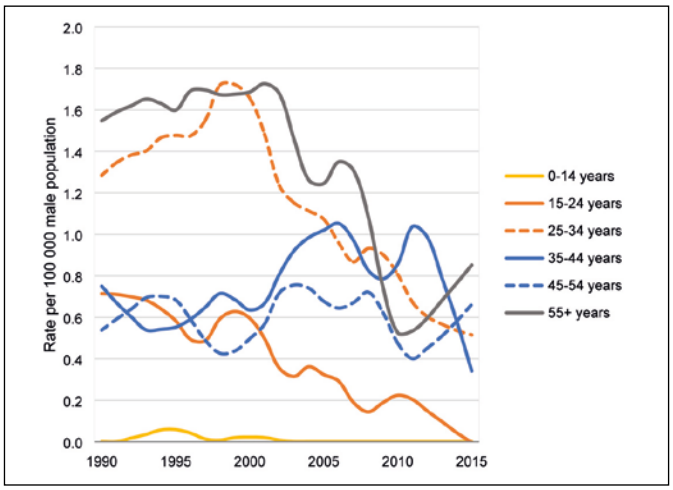

Figure 5. *Smoothed trends for age-specific age-standartized mortality rates for testicular cancer in Belarus, 1990–2015.*

plinary management leads to a remarkable cure rate, which, coupled with patients' young age, provides a huge benefit in saved life years. Consequently, monitoring and comparing survival across different countries may demonstrate certain gaps in the organization of medical care and enable these shortcomings to be addressed in the future.

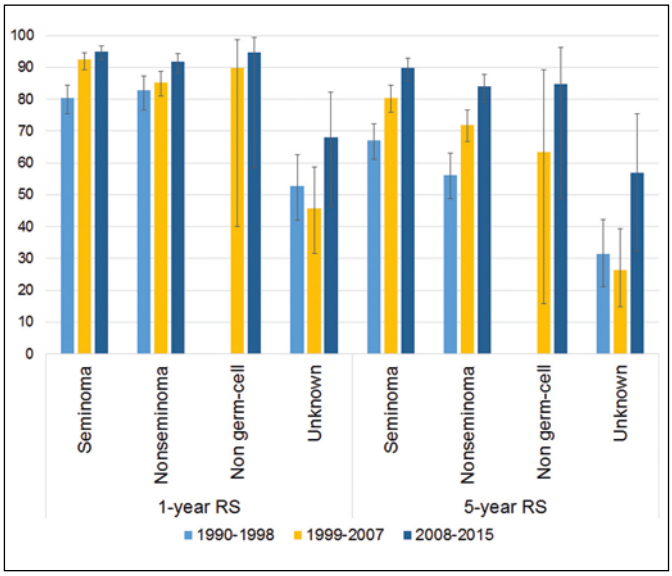

Figure 6. *Trends for relative survival (RS) estimates (%) with 95% confidence intervals according to histologic variant of testicular cancer in Belarus, 1990–2015.*

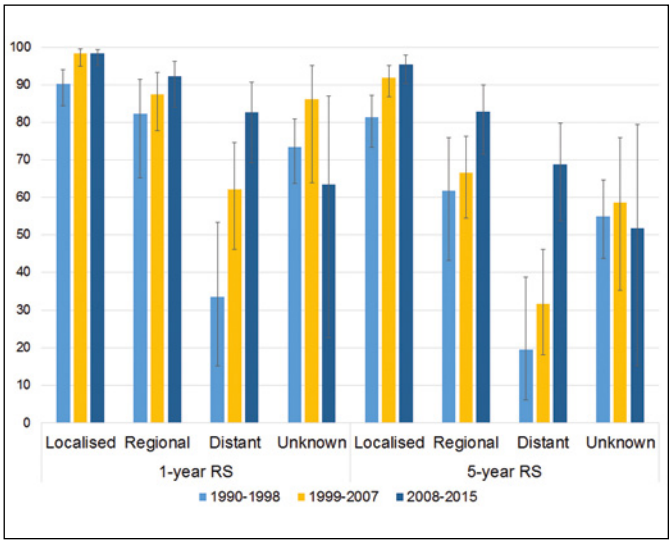

Figure 7. *Trends for relative survival (RS) estimates (%) with 95% confidence intervals according to extent of disease in seminoma testicular cancer patients in Belarus, 1990–2015.*

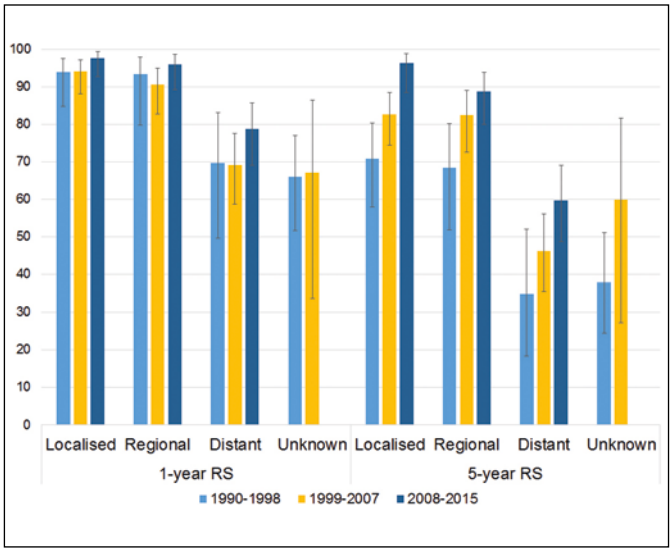

Figure 8. *Trends for relative survival (RS) estimates (%) with 95% confidence intervals according to extent of disease in non-seminoma testicular cancer patients in Belarus, 1990–2015.*

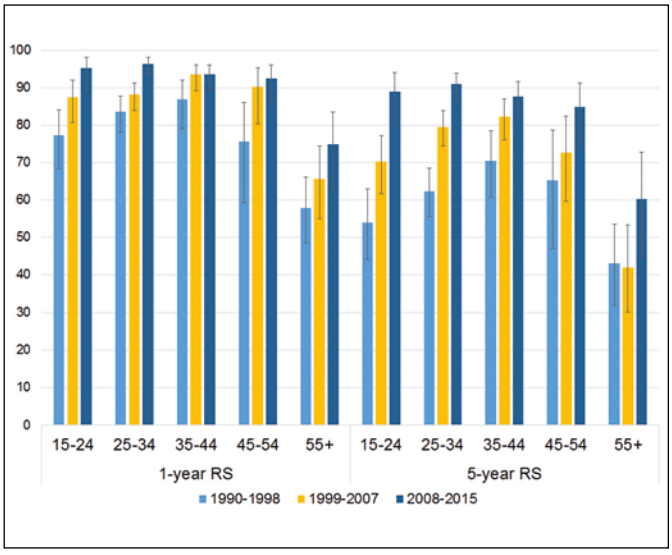

Figure 9. *Age-specific for relative survival estimates (%) with 95% confidence intervals in testicular cancer patients in Belarus, 1990–2015.*

In our study, we identified several important points: a significant increase in TC incidence in Belarus, a decrease in mortality accompanied by RS rise which, however, did not reach European or North American figures. In addition, we found some important regional differences in survival, which were seen irrespective of other significant prognostic factors.

The increase in TC incidence is documented in numerous studies yet without clear understanding of its cause [12, 13]. In Europe incidence has been rising since 1945 [13] and although in some countries (e.g. Denmark, Switzerland) this rise has slowed down, in others (e.g. Croatia, Slovenia, Norway) it is still significant [1, 14]. The projections have been made about a 24% increase in new cases between 2005 and 2025 [15]. It is also shown to be a global trend for an increase in TC incidence [16], although there are highly variable rates of this disease which correspond closely with the Human De-

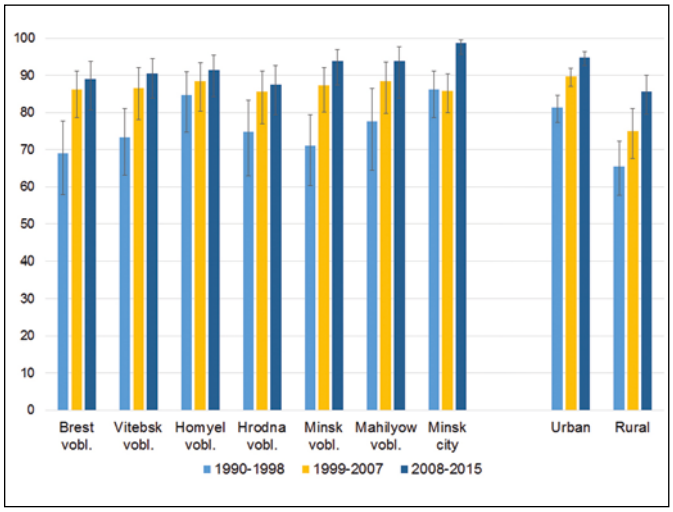

Figure 10. *Trends for 1-year relative survival estimates (%) with 95% confidence intervals according to region and place of residence in testicular cancer patients in Belarus, 1990–2015.*

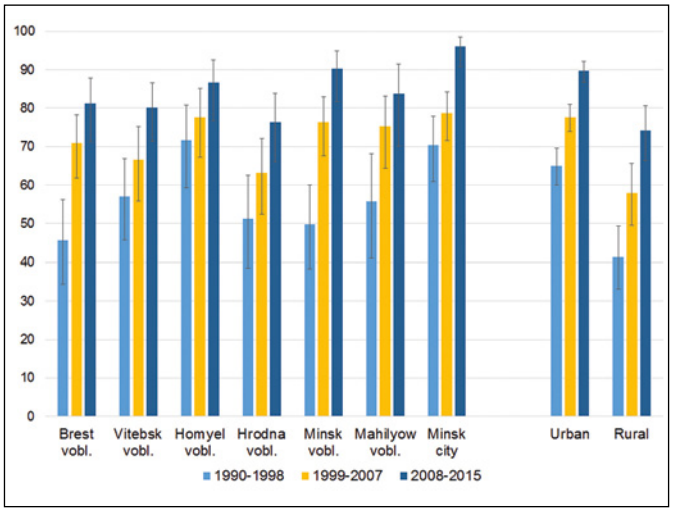

Figure 11. *Trends for 5-year relative survival estimates (%) with 95% confidence intervals according to region and place of residence in testicular cancer patients in Belarus, 1990–2015.*

Table 5. *Comparison of age-standardized relative survival with European population (EUROCARE-5)*

	Seminoma, 5–year ASRS, % (95% CIs)	Nonseminoma, 5–year ASRS, % (95% CIs)	Total C62, ASRS, % (95% CI)	
			1–year	5–year
Belarus, 2008–2015	83.4 (78.0–87.6)	72.8 (63.3–80.3)	88.1 (84.2–91.1)	79.2 (73.8–83.7)
Europe, 1999–2007†	93.9 (92.6–95.3)	88.3 (84.3–92.5)	93.2 (92.3–94.0)	88.6 (87.4–89.8)
Northern Europe, 1999–2007†	97.7 (95.4–100)	90.2 (84.4–96.5)	95.1 (93.8–96.5)	92.8 (90.5–95.1)
Ireland and UK, 1999–2007†	96.6 (95.2–98.1)	90.2 (86.3–94.2)	94.4 (93.5–95.2)	91.8 (90.3–93.3)
Central Europe, 1999–2007†	95.0 (93.5–96.5)	88.7 (85.1–92.5)	95.1 (94.2–96.0)	91.8 (90.2–93.5)
Southern Europe, 1999–2007†	93.8 (91.6–96.1)	90.0 (86.7–93.5)	93.5 (92.3–94.8)	89.1 (87.1–91.1)
Eastern Europe, 1999–2007†	87.5 (85.3–89.7)	82.4 (76.7–88.4)	87.4 (86.0–88.9)	80.1 (77.9–82.4)

ASRS – age-standardized relative survival; CI – confidence interval, † – estimates derived from [12]

Table 6. *Comparison of age-standardized relative survival with SEER data*

	Belarus, 2008–2015			SEER, 2008–2015		
	N (%)	1–year ASRS, % (95% CIs)	5–year ASRS, % (95% CIs)	N (%)	1–year ASRS, % (95% CIs)	5–year ASRS, % (95% CIs)
Seminoma*						
Localized	359 (69)	96.3 (90.3–98.6)	91.5 (85.1–95.2)	7 841 (77)	99.7 (98.9–99.9)	99.3 (98.6-99.6)
Regional	94 (18)	88.4 (81.4–92.9)	78.7 (70.2–85.0)	1 665 (16)	96.0 (92.3–98.0)	94.6 (90.7-96.9)
Distant	56 (11)	76.6 (67.7–83.2)	57.2 (46.2–66.7)#	606 (6)	84.9 (79.3–89.0)†	78.7 (72.8-83.5)†#
Total	517 (100)	90.6 (86.0–93.7)	83.4 (78.0–87.6)	10 210 (100)	98.3 (97.6–98.8)	97.4 (96.6-98.0)
Nonseminoma*						
Localized	150 (43)	98.1 (94.2–99.4)†	95.8 (89.0–98.4)†	4 678 (58)	98.4 (92.0–99.7)	94.6 (82.7-98.4)
Regional	98 (28)	96.0 (89.1–98.6)‡	88.8 (80.0–93.9)‡	1 738 (22)	94.0 (80.8–98.2)†	96.1 (94.7-97.1)‡
Distant	97 (28)	67.1 (61.6–72.0)	53.3 (43.4–62.3)§	1 560 (19)	72.4 (65.3–78.4)	61.2 (55.5-66.5)†§
Total	346 (100)	81.6 (74.9–86.7)	72.8 (63.3–80.3)	8 042 (100)	90.9 (86.8–93.7)	85.9 (80.6-89.8)
Testicular cancer, total*						
Localized	536 (59)	96.0 (90.5–98.3)	91.2 (81.7–95.9)	12 701 (68)	99.2 (98.3–99.7)	98.6 (97.7-99.2)
Regional	199 (22)	85.3 (75.3–91.4)	73.9 (64.5–81.3)	3 434 (18)	95.4 (91.7–97.5)	93.3 (89.6-95.7)
Distant	160 (18)	69.0 (60.3–76.2)	49.2 (42.4–55.7)#	2 243 (12)	75.0 (70.9–78.6)	65.9 (61.9-69.7)#
Total	911 (100)	88.1 (84.2–91.1)	79.2 (73.8–83.7)	18 633 (100)	95.4 (94.4–96.3)	93.0 (90.9-94.6)

ASRS – age-standardized relative survival; CI – confidence interval; * – unknown stages are not shown; †for age standardization age strata were merged into four (15–44, 45–54, 55–64 and 65+ years); ‡ – non-standardized estimates, § – 36-month estimate, # – 46-month estimate

velopment Index [17]. Despite the near doubling in our age-standardized incidence rates during the study period, the trajectory of smoothed trend lines rises the possibility of stabilization and even incidence decrease from the late 2010s, which needs further monitoring.

Our second observation is a significant mortality decline with an increase in RS. It is worth noting that in the majority of Western countries the most significant mortality drop took place in 1980s–1990s and currently, mortality has stabilized and it is not changing considerably or decreasing in small subgroups of patients [18]. However, in Eastern Europe this decrease started at a much later time point has had a protracted course and might not have finished yet. This is thought to reflect a delayed adoption of good management practices of this disease and results in the east-west mortality gradient in Europe [4].

This is generally in line with our study's third observation of inferior age-standardized RS rates compared to all European regions, except for Eastern Europe. High global variability in TC prognosis is a well-known fact. For example, Greiman et al. [17] showed high discrepancy in the mortality-to-incidence ratio between developed and developing countries and the strongest inverse relationship between the Human Development Index and mortality-to-incidence ratio for others genitourinary cancers. This variability in prognosis is mainly attributed to quality of disease management as there were no accepted early detection programs and the effect of hyperdiagnosis on net mortality seems to be negligible. However, survival in TC is influenced by a number of social factors, such as race [19, 20, 21], socioeconomic [20, 21, 22], marital [21, 23] and insurance status [24]. It is also shown that even among highly developed countries there are important survival differences attributed to universal health coverage utilization [25]. Our detailed comparison with the SEER data showed a different pattern in survival gaps between seminoma and non-seminoma variants: the greatest differences are seen in seminoma and they seem to progress with the increase in the disease extent. In non-seminoma patients the differences are much smaller and limited to regional and distant stages.

Our next finding is prominent regional and urban-rural disparities within the country. Previous studies demonstrated that survival is worse [26] in rural cancer patients, which can be explained by the complex interplay among environmental hazards, health literacy, delayed diagnoses, socioeconomic deprivation and remote access to healthcare. These factors may also be responsible for a higher RER of death in western parts of our country (Hrodna and Brest voblasts). Our results are also consistent with previous observations of a significant decrease in survival in older patients (>55 years old). Fosså et al. found TC-specific mortality doubled among U.S. patients diagnosed with seminoma or non-seminoma after the age of 40 [21]. Although reduced intensity of treatment and increased toxicity may be responsible for poor results in older patients, some biological resistance mechanisms in metastatic tumors may be implicated [27].

Contrary to common belief about better prognosis in seminoma compared to non-seminoma patients, we did not find significant differences in RER in the multivariate analysis between these histological subtypes. However, unknown histology accounts for

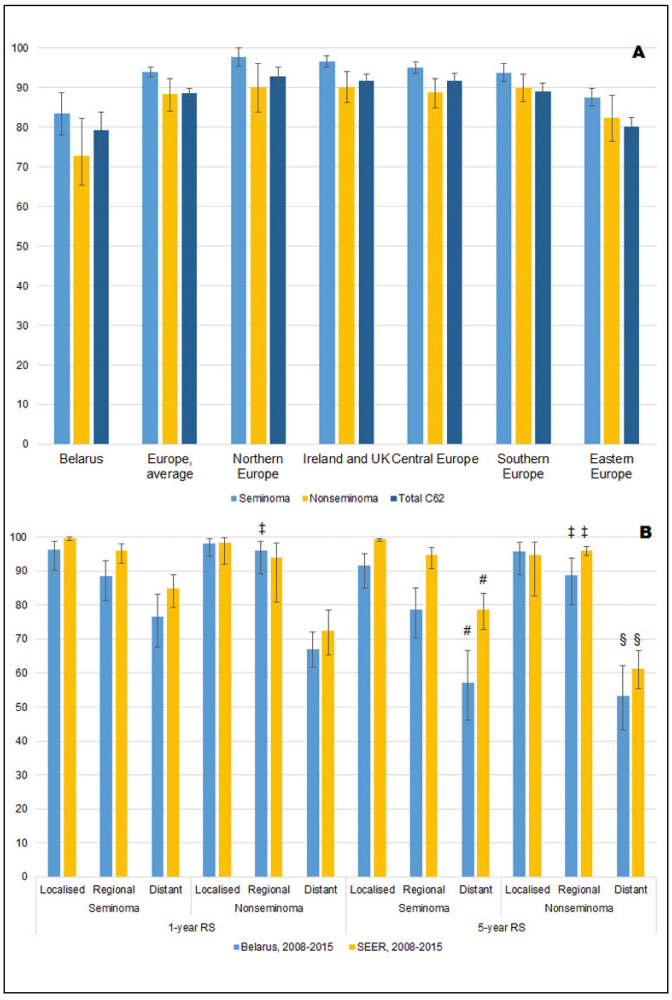

Figure 12. *Comparison of 5-year age-standardized relative survival rates (%) with 95% confidence intervals for Belarus (2008–2015):* **(A)** *with other European regions (1999–2007) from the EUROCARE-5 study [12],* **(B)** *with the SEER-18 database (2008–2015).*

‡ – non-standardized estimates, § – 36-month estimate, # – 46-month estimate

a considerable proportion of patients in our study especially in the earlier years of diagnosis. In addition, as we could not track tumor marker status, some patients with pure seminoma histology and high alpha-fetoprotein or very high beta-chorionic gonadotropin serum levels in our cohort should be in fact regarded as non-seminoma patients.

The primary strengths of our study include its country-wide nature and good cancer registry quality indicators: a high proportion of microscopically confirmed cases, low DCO and autopsy diagnosis, low rates of drop-out from the follow-up. Limitations are less reliable and sometimes conflicting information on the histologic variant or extent of disease and the absence of data on some important clinical variables (e.g. tumor marker status) and therapy.

CONCLUSIONS

We have found a significant increase in TC incidence in Belarus in recent years. Mortality has significantly declined with a corresponding increase in RS which, however, did not reach European or North American figures. Continued effort is required to improve the quality of management of TC patients in our country.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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