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INCIDENCE AND LONG-TERM EFFECTS OF TREATMENT OF MALIGNANT GERM CELL NEOPLASMS IN UKRAINE

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Aim: **To describe incidence of malignant germ cell neoplasms (GCNs) in Ukraine and assess the medical care to patients with GCNs and its efficacy.** ***Materials and Methods:*** **Records on 6495 males and 1038 females with malignant GCNs diagnosed in 2000–2013 extracted from the database of National Cancer Registry of Ukraine have been analyzed using methods of descriptive epidemiology and survival evaluation.** ***Results:*** **In Ukraine, GCNs covered 79.1% of testicular cancers and 48.9% of ovarian cancers in patients aged 0–19 years, while their proportions in total cancer incidence did not exceed 0.7% in males and 0.1% in females. Most of GCNs in males (75.9%) were diagnosed at the reproductive age (20–49) and in females 72.2% of GCNs were diagnosed at the age of 0–44 years. Female gonadal GCNs were divided by germinomatous and nongerminomatous as 49.3% *vs* 50.7% while in males this proportion was 65.3% *vs* 34.7% Age-specific incidence of genital GCNs in Ukraine reached peak values in males aged 25–39 years and in females aged 10–24 years. Nonseminomatous testicular GCN cases were more common than seminomatous cases in males until the age of 30 years with an incidence of seminomas peaked 10 years later than non-seminomas. Ovarian germinomas were more common than non-germinomas in females aged 15–29. Total GCN incidence rate in 2013 was 1.99 ± 0.09‱ in males and 0.32 ± 0.04‱ in females, being closer to that in the countries of Eastern Europe and Asia. In Ukraine, 5-year survival of patients with testicular GCN of stage I who received surgery combined with chemotherapy or radiotherapy was lower than that reported for Europe and USA, and substantially lower in patients with stages II–IV. Five-year survival of patients with ovarian GCN treated with surgery plus chemotherapy was close to that reported in a study for populations of European countries.** ***Conclusion:*** **The trends and patterns of GCN incidence in Ukraine are similar to those in other European countries, while patterns of treatment and survival in Ukraine are closer to that in countries in transition. Further research and analysis are impossible without due registration of both the diagnosis and the treatment undertaken as well as close follow-up of patients' life status.**

Key Words: **germ cell neoplasms, cancer incidence, survival, cancer registry.**

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Malignant germ cell neoplasms (GCNs) are orphan diseases. According to the definition of WHO, GCNs are heterogeneous and histologically well-defined group of tumors derived from germ cells capable for differentiation toward different degrees of maturity of tissue and organoid structures and localized both inside and outside the gonads [1]. International Classification of Diseases for Oncology, 3rd Edition, includes 23 histological variants of GCN, with 15 of them being malignant [2]:

9060/3	Dysgerminoma
9061/3	Seminoma, NOS
9062/3	Seminoma, anaplastic
9063/3	Spermatocytic seminoma
9064/3	Germinoma
9070/3	Embryonal carcinoma, NOS
9071/3	Yolk sac tumor, NOS
9072/3	Polyembryoma
9080/3	Teratoma, malignant, NOS
9081/3	Teratocarcinoma
9082/3	Malignant teratoma, undifferentiated
9083/3	Malignant teratoma, intermediate
9084/3	Teratoma with malignant transformation
9085/3	Mixed germ cell tumor
9090/3	Struma ovarii, malignant

Little is known about epidemiology of GCNs in Ukraine, as well as the state of health assistance to patients with GCNs, and this was a main reason to conduct present study. Another important fact about GCNs is that patients with GCNs achieve long-term remission after treatment, which includes surgery combined with radiation or cytostatic chemotherapy, and have good prognosis even in case of metastatic dissemination [3].

The National Cancer Registry of Ukraine (NCRU) was established in 1996 in a Department of Cancer Epidemiology of the National Cancer Institute; it includes data of 27 regional population-based cancer registries gaining 100% population coverage since 2000. Its personified database maintained by the NCRU's information technology is a main source of comprehensive information about cancer burden and cancer care in Ukraine. The NCRU is rated as "high-quality cancer registry" by the International Agency for Research on Cancer, with cancer incidence cases diagnosed in 2003–2012 evaluated and included in volumes X and XI of the International Agency for Research on Cancer's "Cancer Incidence in 5 continents" series [4, 5].

The main goal of the study is to describe the burden of GCNs in Ukraine and assess the specialized (anti-cancer) medical care to patients with GCNs with its results.

MATERIALS AND METHODS

As of January 2019, NCRU database contains information about 13,536 cases (11,690 in males and 1846 in females) of malignant GCNs. Records on 7533 cases (6495 males and 1038 females) of malignant GCNs with International Classification of Diseases for Oncology, 3rd Edition codes of morphology 9060/3-9090/3 [2] diagnosed in 2000–2013 were extracted

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Abbreviations used: GCN – germ cell neoplasm, NCRU – National Cancer Registry of Ukraine, OS – observed survival.

from the NCRU database for this study. We also focused on patients with GCNs of male and female genital organs: this cohort included 6926 cases (6118 in males and 808 in females). Here we present data until 2013 because since that time the data on AR of Crimea and parts of Donetsk and Luhansk regions are not available. The stage of cancer diagnosis in NCRU is defined preferentially automatically by its T, N, M components (both clinical and pathologic) in accordance with the rules of TNM classification; ovarian GCNs are not subject to staging by TNM. In this study all treatment records registered in the patient were considered, without dividing them into primary treatment and treatment of relapse of the disease. Age-standardized incidence rates per 100,000 person-years using Segi-Doll world standard population [6] were calculated. Long-term results of cancer treatment were evaluated by examining the observed survival (OS) rates calculated using Kaplan — Meier approach and their 95% confidence intervals. Log-rank test was used to compare survival by gender, morphology, stage and methods of treatment with significance level (p-value) 0.05.

RESULTS

In 2000–2013, the proportion of new GCN cases among all malignant neoplasms diagnosed in Ukraine did not exceed 0.4%, with the majority of cases diagnosed in male population (86.2%) as compared to females (13.8%) (Table 1). However, GCNs are more characteristic for young patients: in Ukraine they accounted for 3.3% of all cancers registered in males and 3.6% in females of 0–19 years old; the appropriate proportion in males of the reproductive age (20–49 years old) was 3.7% and in females of the reproductive age (20–44) 0.3%.

Age distribution showed that 75.9% of all new GCNs of male population were diagnosed at the reproductive age (20–49), while 7.6% and 10.6% were diagnosed respectively in males of middle (50–59) and elderly age (60+) and 5.9% — in children and adolescents (0–19) (see Table 1). In females, age distribution of GCN cases had different pattern, with 35.2% of cases being diagnosed in childhood and adolescence (0–19) and 37.0% — at the reproductive age of 20–44 years; for middle (45–59) and elderly age (60+) groups respective proportions were 16.1% and 11.8%.

The highest proportion of GCNs was diagnosed in male and female genitals, predominantly in testis (93.8%) and ovary (77.6%) (Table 2). Among primary extragonadal GCNs, 2.6% arose in respiratory and intrathoracic organs (mainly in mediastinum), 2.6% — in mesothelial, connective and other soft tissues, and primary sites of 1.1% tumors were from the group of "eye, brain and other CNS" (mainly in brain).

When stratified by their histology, most of the extragonadal GCNs were nonseminomatous with malignant teratomas prevailed both in males (52.0%) and females (60.0%) (Table 3). Female gonadal GCNs were almost evenly divided by germinomatous and nongerminomatous (mixed included) while in males the proportion of the former was almost double of the proportion of the latter (65.3% *vs* 34.7%). Among gonadal GCNs diagnosed in males, 64.7% were seminomas, 24.3% — embryonal carcinomas, 9.4% — malignant teratomas; 99.5% of these tumors arose in testis. In females, the most frequent GCNs of genitals were dysgerminoma (47.3%) and malignant teratoma (34.7%); respective proportions of mixed germ cell tumors and embryonal carcinomas were 6.3% and 5.8%; other GCNs were rarer; 99.8% of these tumors were ovarian.

Age distributions of germinomatous and nongerminomatous (mixed included) testicular GCNs had different patterns while for ovarian GCNs they were very similar (Fig. 1). As we found, 89.3% of nonseminomatous testicular GCNs were diagnosed in males aged 15–44 years while seminomatous testicular cases were

Table 1. GCN cases by age and gender in Ukraine, 2000–2013

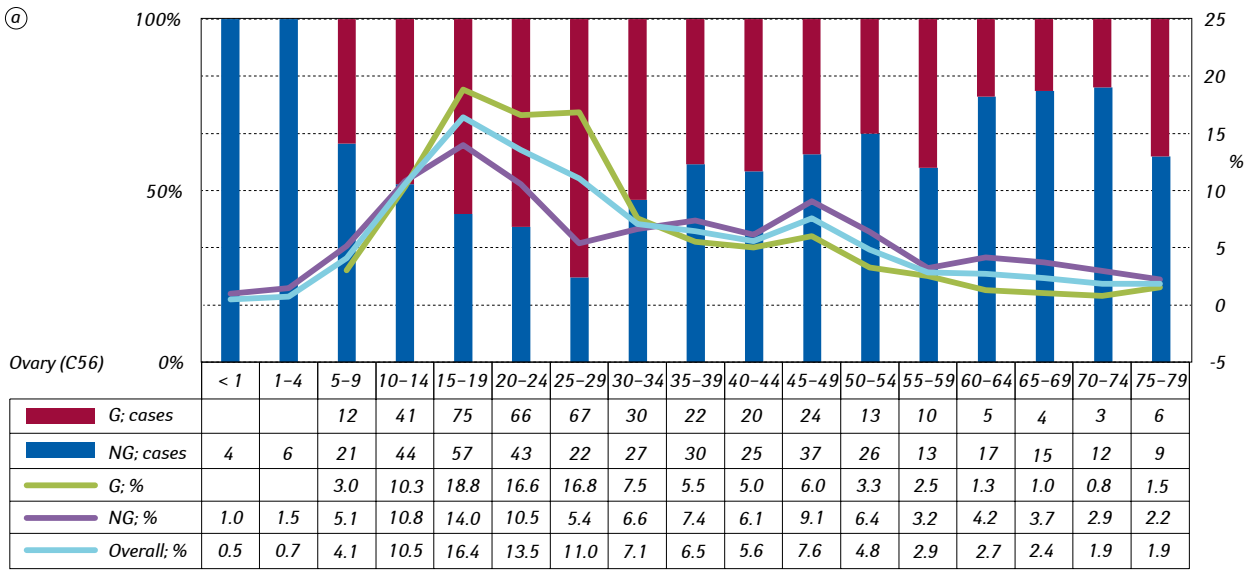
Age,	Males		Females		Persons	
years	n	%	n	%	n	%
< 1	45	0.7	42	4.0	87	1.1
1–4	51	0.8	46	4.3	97	1.3
5–9	13	0.2	46	4.4	59	0.8
10–14	47	0.7	95	9.1	142	1.9
15–19	231	3.5	139	13.3	370	4.9
20–24	718	11.1	114	11.1	832	11.1
25–29	1054	16.2	98	9.3	1152	15.3
30–34	1090	16.7	60	5.8	1150	15.2
35–39	919	14.1	57	5.5	976	12.9
40–44	696	10.7	55	5.3	751	10.0
45–49	459	7.1	72	6.9	531	7.0
50–54	308	4.7	55	5.2	363	4.8
55–59	189	2.9	41	3.9	230	3.0
60–64	205	3.2	35	3.4	240	3.2
65–69	159	2.4	36	3.5	195	2.6
70–74	153	2.3	25	2.4	178	2.3
75–79	114	1.7	26	2.5	140	1.8
80–84	49	0.7	-	0.0	49	0.6
85+	12	0.2	-	0.0	12	0.1
Total	6495	86.2	1038	13.8	7533	100.0

Table 2. GCN cases by primary site and gender in Ukraine, 2000–2013

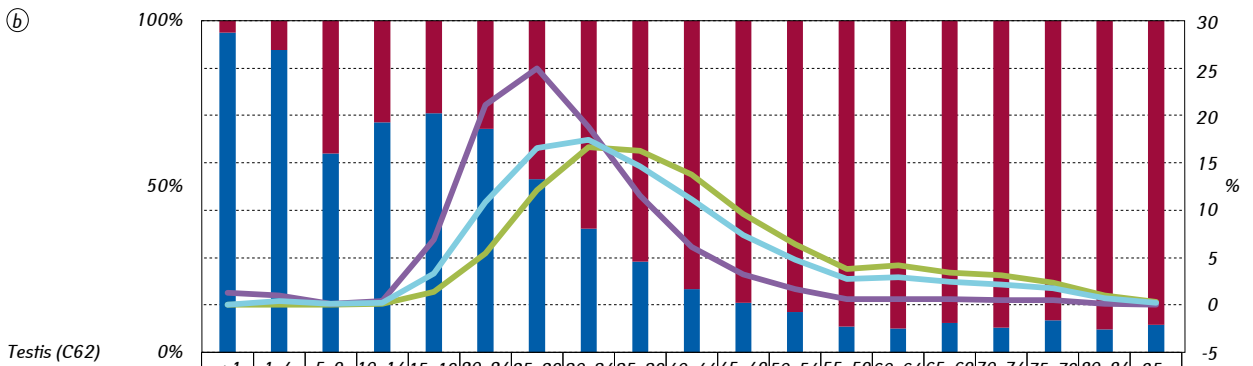
Primary site (ICDO-3 code)	Males		Females		Persons	
	n	%	n	%	n	%
Digestive organs (C15-C26)	31	0.5	33	3.2	64	0.8
Respiratory and intrathoracic organs (C30-C38)	153	2.4	40	3.9	193	2.6
Mediastinum (C38)	135	2.1	29	2.8	164	2.2
Mesothelial, connective and other soft tissues (C45-C49)	90	1.4	106	10.2	196	2.6
Retroperitoneum (C48)	56	0.9	54	5.2	110	1.5
Female genitals (C51-C58)	-	-	808	77.8	808	10.7
Ovary (C56)	-	-	805	77.6	805	10.7
Male genitals (C60-C63)	6118	94.2	-	-	6118	81.2
Testis (C62)	6090	93.8	-	-	6090	80.8
Eye, brain & other CNS (C69-C72)	56	0.9	25	2.4	81	1.1
Brain (C71)	52	0.8	19	1.8	71	0.9
Others	47	0.7	26	2.5	73	1.0
Small pelvic (C76)	13	0.2	15	1.4	28	0.4
All sites	6495	100.0	1038	100.0	7533	100.0

Table 3. GCNs by gender and histology, Ukraine, 2000–2013

Morphological type (ICDO-3 code)	Males				Females			
	Gonadal		Extragonadal		Gonadal		Extragonadal	
	n	%	n	%	n	%	n	%
Germinomatous/Seminomatous (9060/3-9064/3)	3994	65.3	110	29.2	398	49.3	60	26.1
Dysgerminoma (9060/3)	25	0.4	8	2.1	382	47.3	3	1.3
Seminomas (9061/3-9063/3)	3957	64.7	17	4.5	1	0.1	1	0.4
Germinoma (9064/3)	12	0.2	85	22.5	15	1.9	56	24.3
Nongerminomatous/Nonseminomatous (9070/3-9090/3)	2124	34.7	267	70.8	410	50.7	170	73.9
Embryonal carcinoma (9070/3)	1488	24.3	35	9.3	47	5.8	13	5.7
Yolk sac tumor (9071/3)	18	0.3	7	1.9	23	2.8	6	2.6
Polyembryoma (9072/3)	1	0.0	-	-	1	0.1	-	-
Malignant teratomas (9080/3-9084/3)	574	9.4	196	52.0	280	34.7	138	60.0
Mixed germ cell tumor (9085/3)	43	0.7	29	7.7	51	6.3	13	5.7
Struma ovarii, malignant (9090/3)	-	-	-	-	8	1.0	-	-
Total	6118	94.2	377	5.8	808	77.8	230	22.2



	< 1	1–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79
G; cases			12	41	75	66	67	30	22	20	24	13	10	5	4	3	6
NG; cases	4	6	21	44	57	43	22	27	30	25	37	26	13	17	15	12	9
G; %			3.0	10.3	18.8	16.6	16.8	7.5	5.5	5.0	6.0	3.3	2.5	1.3	1.0	0.8	1.5
NG; %	1.0	1.5	5.1	10.8	14.0	10.5	5.4	6.6	7.4	6.1	9.1	6.4	3.2	4.2	3.7	2.9	2.2
Overall; %	0.5	0.7	4.1	10.5	16.4	13.5	11.0	7.1	6.5	5.6	7.6	4.8	2.9	2.7	2.4	1.9	1.9



	< 1	1–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
G; cases	1	2	2	4	55	215	481	665	647	550	380	253	153	168	135	122	95	41	10
NG; cases	28	21	3	9	145	445	527	395	243	130	67	35	13	13	13	10	10	3	1
G; %	0.0	0.1	0.1	0.1	1.4	5.4	12.1	16.7	16.3	13.8	9.6	6.4	3.8	4.2	3.4	3.1	2.4	1.0	0.3
NG; %	1.3	1.0	0.1	0.4	6.9	21.1	25.0	18.7	11.5	6.2	3.2	1.7	0.6	0.6	0.6	0.5	0.5	0.1	0.0
Overall; %	0.5	0.4	0.1	0.2	3.3	10.8	16.6	17.4	14.6	11.2	7.3	4.7	2.7	3.0	2.4	2.2	1.7	0.7	0.2

Fig. 1. Number of cases and age distribution of ovarian (*a*) and testicular (*b*) GCNs in histological groups, Ukraine, 2000–2013. *Note: G — germinomatous (seminomatous); NG — nongerminomatous (nonseminomatous)*

more evenly distributed by age groups 20–79 with peak at age 25–44 that contained 58.9% of these cases.

In males until the age of 30 years nonseminomatous testicular GCN cases were more common than seminomatous ones while seminomatous cases dominated after the age of 35 years.

In females aged 15–29 ovarian germinomatous GCNs were more commonly diagnosed than nongerminomatous ones; in girls aged 0–4 years only nongerminomatous ovarian GCNs were diagnosed.

Mean age at time of diagnosis of GCN in Ukraine was 37 for males and 31 for females. Mean age at time

of diagnosis of seminoma was 42 years *vs* 29–33 years for other GCNs of male genitals except of 18 years for yolk sac tumor; mean age at time of diagnosis of germinomatous tumor, yolk sac tumor or mixed germ cell tumor in females was 28 years, for embryonal carcinoma it was 34 years, for malignant teratomas — 37 years and 60 years — for malignant struma ovarii.

Analysis of time trends of incidence for all malignant GCNs showed significant growth of rates in both male and female populations with respective 3.5% and 4.2% annual percentage change ($p < 0.05$) (Table 4). Incidence in male population was from 5 to 9 times higher than that of females.

Further research was focused on the most numerous cohort of patients with GCNs of genitals. As our study showed, during 2000–2013 GCNs were the most frequent cancers of testis and amounted to 85.3% (and 7.4% of other testicular cancer cases were of unspecified morphologic type) while the proportion of GCNs among all ovarian malignancies was 1.4%, but in children and adolescents these proportions were different — 79.1% of patients aged 0–19 years diagnosed with cancer of testis had GCNs and the appropriate proportion for ovarian cancer was 48.9%.

Table 4. Incidence of malignant GCNs in Ukraine, 2000–2013

Incidence year	Males		Females	
	ASR(W)	SE	ASR(W)	SE
2000	1.37	0.07	0.21	0.03
2001	1.47	0.08	0.23	0.03
2002	1.59	0.08	0.29	0.04
2003	1.70	0.08	0.26	0.03
2004	1.63	0.08	0.28	0.04
2005	1.70	0.08	0.28	0.04
2006	1.57	0.08	0.28	0.04
2007	1.62	0.08	0.26	0.04
2008	1.83	0.09	0.27	0.04
2009	1.87	0.09	0.28	0.04
2010	1.98	0.09	0.28	0.04
2011	1.86	0.09	0.32	0.05
2012	1.89	0.09	0.22	0.04
2013	1.99	0.09	0.32	0.04

Note: ASR(W) – age standardized incidence rate (world); SE – standard error of ASR.

For more reliable analysis of age specific incidence, the data for the time period 2009–2013 have been summarized. As we found, age specific incidence of males with gonadal GCNs diagnosed in 2009–2013 increased with age up to 25–39 years old to peak values of 4.46–4.91 per 100,000 of population with subsequent decrease, while in females the highest age specific incidence rates were 0.53–0.67 per 100,000 of population aged 10–24 years (Fig. 2). Age specific incidence rates of gonadal GCNs in males exceeded those of females from 5 to 25 times except in young age groups 5–14, where they were 5 times lower.

To assess medical care to patients with GCNs calculation of OS rates depending on age, morphological type, stage of the disease and methods of treatment has been done.

Fig. 3 presents OS rates for patients stratified by age at diagnosis and gender; four groups covering 83% of the total number of cases were selected for analysis.

During the study period, OS rates in girls and adolescents (0–19) were higher than in boys by 10–11%. Survival curves decrease exponentially up to 4 years of observation for boys and up to 2 years for girls, and later become stable with 10-year survival rates 68.5 ± 4.9% and 78.1 ± 4.5%, respectively. The same patterns were found in young adults of 20–29 years old where OS rates during 15 years decreased to 66.2 ± 3.3% in males and 76.7 ± 6.8% in females. In patients of middle age of 30–39 and 40–49 years old survival in males was higher than in females by 5–7% and 10–13%, respectively.

OS of males did not decrease markedly with increasing age at diagnosis, though survival in group of aged 40–49 after 5 years of observation showed distinct decline. Survival rates of females aged 30–49 appeared substantially lower than those of younger patients (0–29) during the whole interval of observation.

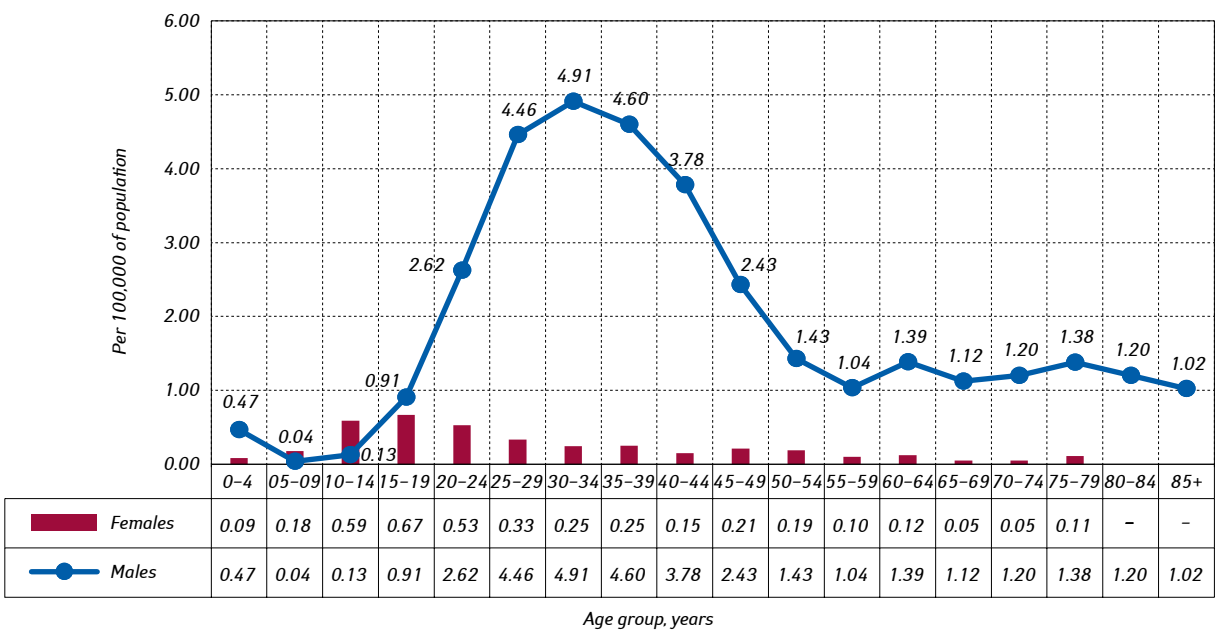


Fig. 2. Age-specific incidence rates of gonadal GCNs in Ukraine, 2009–2013

Fig. 4 presents OS rates for patients with testicular and ovarian GCNs by morphological type. The highest survival rates were observed for seminoma and malignant teratoma of testis and dysgerminoma of ovary; worse prognosis for 5 and 10 years had patients with embryonal carcinoma and mixed germ cell tumors regardless of site, though for testicular GCNs the difference was not evident both after 5 and 10 years of observation (Table 5).

Ten-year OS rates for testicular GCNs were by 6% lower than those for 5 years of observation. Sur-

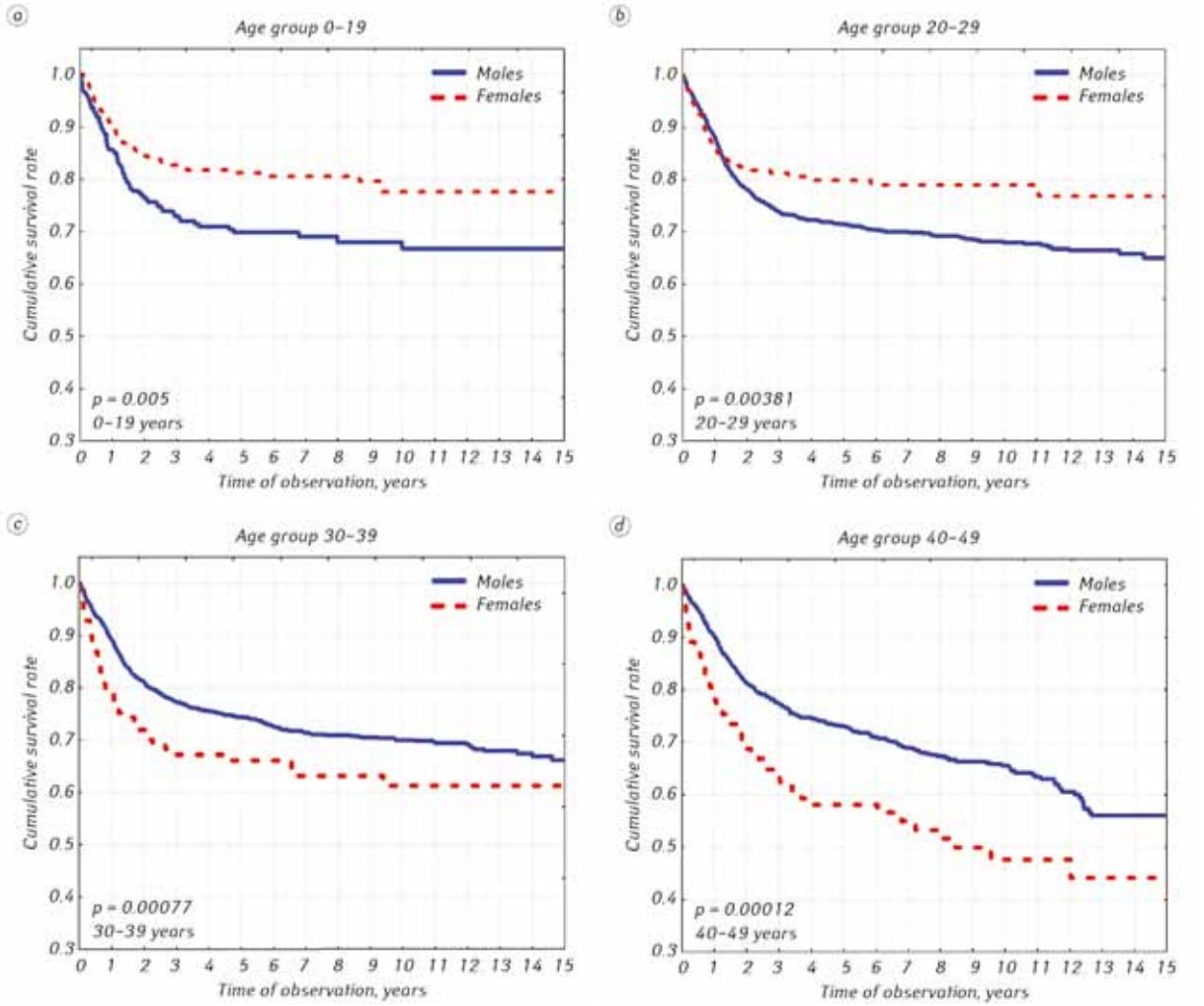


Fig. 3. OS rates in patients with GCNs of genital organs by age at diagnosis and gender, Ukraine, 2000–2013: (*a*) age group 0–19 years; (*b*) age group 20–29 years; (*c*) age group 30–39 years; (*d*) age group 40–49 years

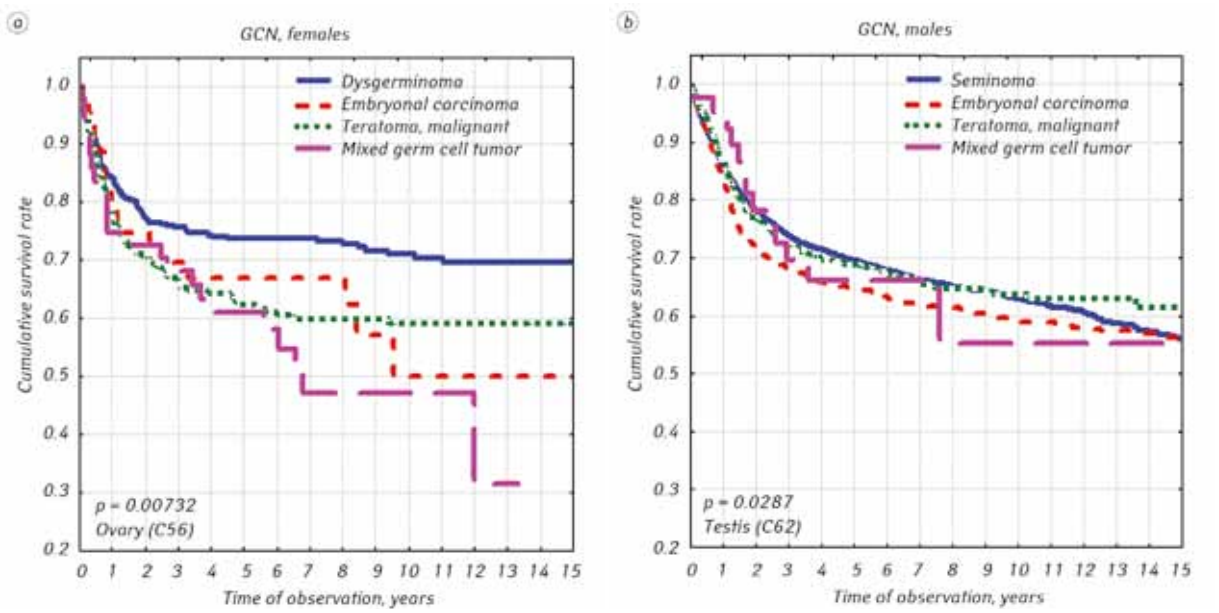


Fig. 4. OS of patients with ovarian (*a*) and testicular (*b*) GCNs by morphology groups, 2000–2013 (%)

vival curve of females with dysgerminoma becomes stable after the 5th year of observation and slightly descends to 70% by the 15th year; survival of females with malignant teratomas decreases after the 7th year of observation below 60%.

The most populated sub-cohort in our study was males with GCNs of testis (6090 cases); in this sub-cohort 96.1% of patients received anti-cancer treatment and stage was not defined in 7.1% of cases. Majority of testicular cases were diagnosed in early stages (67.5% of cases had stages I–II) but in stage IV were diagnosed 16.0% of patients (Table 6). All groups by stage had a homogenous age distribution.

The largest proportion of patients without records on treatment was within a group with unknown stage (Table 7). Among those who received treatment, the proportion of patients who received surgery alone or in combination with radiation decreased substantially with increasing stage; proportion of patients treated with surgery combined with chemotherapy increased from 40.0% for stage I to 51.1% for stage IV.

For patients diagnosed with stage I of testicular GCNs the highest 5-year OS (85.7 ± 3.8%) was after receiving surgery with radiation and a little lower (84.0 ± 2.2%) — after surgery with chemotherapy, while surgery alone or surgery with chemoradiotherapy were not as much effective; this tendency remained after 10 years of observation (Table 8, Fig. 5).

In a group of patients with stage II of testicular GCNs, the best 5-year survival was registered in those who received surgery with chemotherapy (77.4 ± 4.2%) and the lowest 5-year survival was for surgery alone (68.6 ± 5.9%). Radiation was used rarely; its combination with surgery showed a little better effect (5-year OS 77.8 ± 12.5%) than when used combined with surgery plus chemotherapy; the latter combination showed the worst results after the 10th year of observation. Five-year survival rate of patients with stage III who received surgery with chemotherapy was a little higher than for other combinations of therapies; surgery alone was not effective for these patients. For patients with stage IV combinations of surgery with chemotherapy or chemoradiotherapy showed the best long-term effect.

In a sub-cohort of ovarian GCNs (805 cases), vast majority (96.4%) of patients received anti-cancer treatment. Among those who received treatment most of patients received surgery both as a separate therapy (17.0%) and in a combination with other therapies (74.0%). The most common was a combination of surgery with chemotherapy; radiotherapy was mainly combined with surgery plus chemotherapy.

Survival analysis of patients with ovarian GCNs showed the highest 5-year rate in a group of patients received surgery with chemotherapy (77.6 ± 3.7%); results of surgical treatment alone or combined with chemoradiation were much worse (Fig. 6).

Table 5. Five-year observed survival of patients with testicular and ovarian GCNs by morphological type, Ukraine, 2000–2013 (%, 95% CI)

Morphological type	Primary site	
	Ovary (C56)	Testis (C62)
Dysgerminoma (9060/3)	73.6 ± 4.5 n = 382	-
Seminoma (9061/3-9063/3)	-	69.6 ± 1.6 n = 3949
Embryonal carcinoma (9070/3)	66.0 ± 14.5 n = 46	64.8 ± 2.5 n = 1484
Teratoma, malignant (9080/3-9084/3)	62.3 ± 6.1 n = 279	68.9 ± 4.1 n = 566
Mixed germ cell tumor (9085/3)	61.0 ± 14.1 n = 51	66.2 ± 15.7 n = 43

Table 6. Incident cases of testicular GCNs by stage, Ukraine, 2000–2013 (%)

Primary site	Stage				
	I	II	III	IV	Not defined
Testis: all	50.7	16.8	9.4	16.0	7.1
Testis: seminomatous	53.8	17.1	9.2	12.8	7.2
Testis: nonseminomatous	44.9	16.4	9.7	22.1	7.0

DISCUSSION

Epidemiologic data of GCNs in Ukraine has not been reported so far. Information technology of NCRU allows conducting large-scale studies on cancer epidemiology both at the population level and for individual groups of patients with defined nosologic forms of malignancies.

Although GCNs are rather rare, they affect predominantly gonads in population of childhood and reproductive age that aggravates concern about social and demographic consequences of these diseases. In particular, our study showed that in Ukraine 21.9% of malignant GCN cases were diagnosed in girls aged 0–14 years and 50.3% — in females of 15–44 years old, and nearly all of these lesions involved ovary. In male population GCNs were diagnosed mainly in men aged 20–49 years (75.9%) and almost all of them arouse in testis.

In Ukraine, GCNs were the most common (80.6–88.1%) testicular cancers regardless of age and accounted for about half of ovarian cancers in patients aged 0–19 years. Some sources [7–9] cited the proportion of 2–5% for ovarian malignant GCNs in total

Table 7. Patients with testicular GCNs by stage and treatment, Ukraine, 2000–2013 (%)

Type of treatment	Stage					
	I	II	III	IV	Not defined	All
Surgery	27.5	27.6	16.4	13.2	25.6	24.1
Surgery + chemotherapy	40.0	42.8	44.4	51.1	38.3	42.6
Surgery + radiation therapy	12.2	5.8	4.9	2.9	4.6	8.4
Surgery + chemoradiation therapy	13.7	16.2	19.6	14.3	5.8	14.2
Surgery + other therapy	**93.4**	**92.4**	**85.3**	**81.5**	**74.4**	**89.2**
Chemotherapy	3.0	4.0	6.6	8.5	7.6	4.7
Radiation therapy	0.6	0.1	1.4	0.4	1.2	0.6
Chemoradiation therapy	1.0	1.1	2.4	2.6	2.5	1.5
Conservative therapy	**4.6**	**5.2**	**10.5**	**11.5**	**11.3**	**6.8**
No treatment	1.9	2.4	4.2	7.0	14.3	3.9

Table 8. Five-year observed survival of patients with testicular GCNs by stage and treatment methods, Ukraine, 2000–2013 (%, 95% CI)

Type of treatment	Stage			
	I	II	III	IV
Surgery	75.7 ± 3.3 n = 851	68.6 ± 5.9 n = 283	29.5 ± 10.0 n = 94	18.3 ± 7.0 n = 129
Surgery + chemotherapy	84.0 ± 2.2 n = 1237	77.4 ± 4.2 n = 440	64.8 ± 5.7 n = 254	46.6 ± 4.7 n = 498
Surgery + radiotherapy	85.7 ± 3.8 n = 376	77.8 ± 12.5 n = 60	67.5 ± 18.8 n = 28	22.5 ± 16.3 n = 28
Surgery + chemoradiation therapy	73.3 ± 4.4 n = 424	71.7 ± 7.1 n = 166	59.9 ± 9.8 n = 112	42.4 ± 9.0 n = 139

ovarian cancers registered globally, while in Ukraine the same proportion accounted for 1.3–1.5%. As to testicular GCNs, various sources [10–11] cited their typical proportion of 95–98% in all testicular cancers, which may imply incomplete registration of such tumors in Ukraine, given that 6–10% of testicular cancers registered were of unspecified morphology.

In general, incidence level of GCNs in Ukrainian male population is lower than in industrialized countries [10], while in female population it is a little higher than EUROCARE reported [12]. Our study showed that during 2000–2013 GCN incidence in Ukraine significantly increased by 45.3% in males and 52.4% in females. In comparison, during the same period overall cancer incidence in Ukraine has increased by 4.5% in males and by 14.8% in females, incidence of ovarian cancer increased by 13.4% and for cancer of testis — by 35.5%. Though GCN incidence in Ukrainian male population was 3 times lower than testicular GCN incidence [12] and 2–6 times lower than testicular cancer incidence [13, 14] in male populations of European countries, its annual percent increment of 3.5% ($p < 0.05$) was one of the highest. Among other reasons, such a high increase may be explained

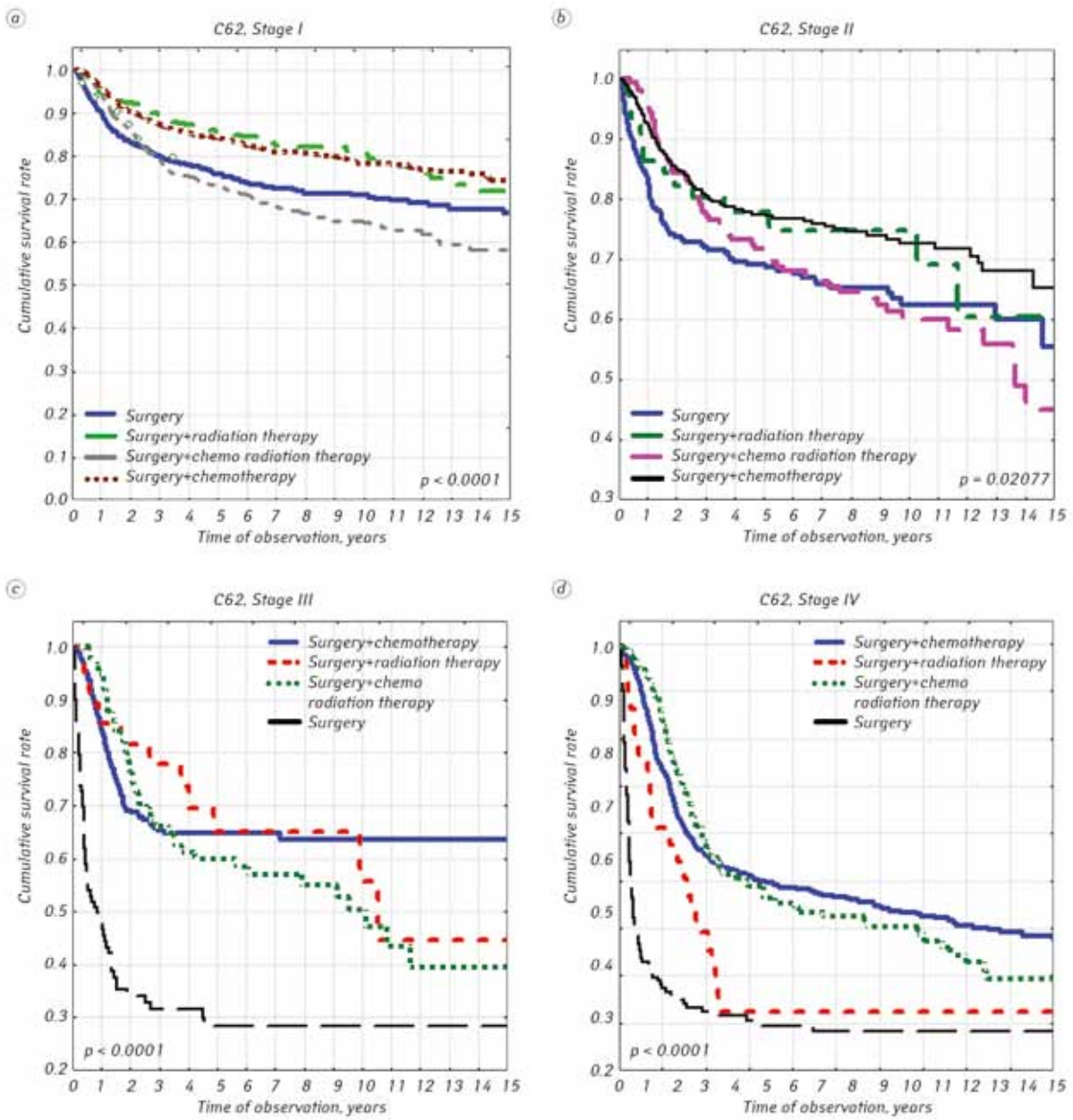


Fig. 5. OS rates of patients with GCNs of testis by stage and treatment, Ukraine, 2000–2013 ($p < 0.05$): (*a*) stage II; (*b*) stage II; (*c*) stage III; (*d*) stage IV

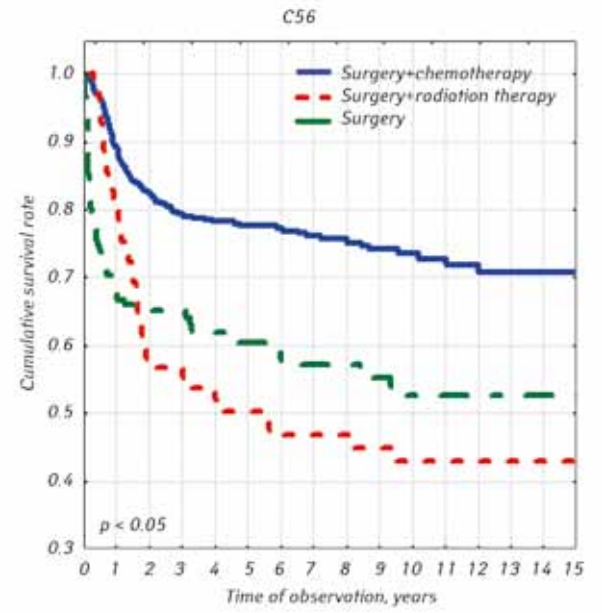


Fig. 6. OS rates of patients with ovarian GCNs by treatment methods, 2000–2013 ($p < 0.05$)

Table 9. Five-year observed survival of patients with ovarian GCNs by treatment methods, Ukraine, 2000–2013 (%, 95% CI)

Type of treatment	Proportion of patients,%	5-year OS rate,%
Surgery	17.0	60.4 ± 8.2 n = 132
Surgery + chemotherapy	64.2	77.6 ± 3.7 n = 499
Surgery + radiotherapy	0.6	-
Surgery + chemoradiation therapy	9.1	50.0 ± 12.2 n = 71
Chemotherapy	7.3	-
Radiation therapy	0.5	-
Chemoradiation therapy	1.2	-

by the improved diagnostics and registration of such cases in Ukraine.

Age specific incidence of genital GCNs in Ukraine reaches peak values in males aged 25–39 years and in females aged 10–24 years. The age ranges of peaks coincide with those in the EUROCARE study [12]. However, these values in Ukraine are lower than in the European populations covered by this study for males (4.46–4.91 *vs* 7–8 per 100,000 of population) and higher for females (5.3–6.7 *vs* 2–3.4 per 1,000,000 of population).

Analysis of GCNs by histology showed that non-seminomatous testicular malignant tumors were more common in Ukraine than seminomas in males until the age of 30 years, which is quite similar to results of EUROCARE study [12]. Ovarian germinomatous GCNs were more commonly diagnosed in females aged 15–29 and non-germinomas prevailed in other age groups, and this result differs from EUROCARE study where non-germinomas were more common in almost every age group. In Ukraine, nongerminomatous GCNs in testis were mainly represented by embryonal carcinoma in contrast to predominant mixed germ cell tumors in EUROCARE study, while in ovary they were mainly malignant teratomas, which is consistent with the data of this study.

OS rates over 5–15 years of observation of young patients (0–29 years at diagnosis) with genital GCNs were higher in females than in males by nearly 10%; on the contrary, males in age groups 30–49 survived better than females. OS of males was similar in age groups 0–19, 20–29 and 30–39; survival of age group 40–49 showed distinct falling after 5 years of observation. Survival rates of females in age groups 30–49 were substantially lower than those of younger patients (0–29) during the whole 15-year interval of observation.

Observed 5-year survival of patients with testicular GCNs in Ukraine, even at early stages of the disease, was substantially lower than relative survival rate in other European countries (94.4 ± 0.4%) [12] and USA [10, 13, 15] where 95–100% survival for patients with stage I and 70–85% for patients with stages II–IV has been reported; however for more deprived populations they reported survival about 6% lower [10]. Given that GCNs are diagnosed primarily in young people, relative survival rates in Ukraine may be slightly higher than those observed, which does not improve, however, the overall survival situation under the treatment patterns used. Relative 5-year survival of patients with ovarian GCNs from EUROCARE study [12] (83.9 ± 2.8%) was closer to the Ukrainian observed rates for patients treated with surgery plus chemotherapy.

As a conclusion, incidence patterns for GCNs in Ukraine principally followed trends and patterns of other countries, while patterns of treatment and survival are closer to countries in transition. Summing up, we can say that more detailed studies are required to establish the reasons for the lower survival of such a highly curable disease. Attention has to be paid to early detection, proper diagnostics and appropriate treatment of specific subtypes of GCNs within targeted cancer control activities. Especially important components for further research and analysis are due registration of both the diagnosis and the treatment undertaken as well as close follow-up of patients' life status.

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