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CLINICAL AND PATHOLOGIC CHARACTERISTICS OF TESTICULAR GERM CELL TUMORS

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Abstract

The performed analyses of incidence rate of testicular germ cell tumors and clinical and pathologic analysis, based on the examination of pathologists' reports and medical case histories of the patients of Kharkiv regional clinical center of urology and nephrology named after Shapovalov V.I., for the period covering years 1998-2017, revealed: unfavorable increasing tendency in testicular GCT incidences, the most typical age of patients with mentioned pathology, and average duration of the disease by the time the patient visited the doctor; determined the possible risk factors of testicular GCT development, as well as the morphological traits in accordance with WHO updated classification.

Key words*:* testicular germ cell tumors, clinical and pathologic characteristics, pTNM classification.

Testicular tumors, though being equal up to 1 % out of all the male neoplasms all over the world, are the most popular with Caucasians within the period from puberty up to the age of 40 in industrially advanced countries [1]. At that, testicular germ cell tumors (GCT) amount to more than 90 % of all the testicular tumors [2, 3].

During the past 40 years testicular GCT sick rate rose up worldwide; and in North and South America, as well as in northern European countries, testicular GCT sick rate rebound by over twice as much. In countries with traditionally low sick rate (Finland, Spain, Slovenia, Chile and Australia), the sick rate tempo is quickly growing up and approaching the criteria of the countries with a high sick rate [1, 4, 5].

According to the National Cancer Institute of Ukraine, the testicular tumors' ratio in males, at the age of 18 to 29, makes 29,7 % [6]. However, scholarly literature lacks the thorough analysis of testicular tumors' morbidity in Ukrainians.

Objectives: to study GCT incidence rate and to carry out clinical and pathological analysis based on the examination of pathologists' reports and medical case histories of the patients of Kharkiv Regional Clinical Centre of Urology and Nephrology named after Shapovalov V.I., for the period covering 1998-2017.

Within this period, 301 patients, with different cases of testicular GCT, were examined and treated in the Centre. All the observations were classified due to the minute structure and in accordance with WHO classification [7]. For illustration purposes, as to the morbidity rate dynamics, all the testicular GCT cases were distributed in two decades. As Table 1 shows, the second decade demonstrates growth of number of cases with testicular GCT up to 18,12 % (138 out of 163 cases) mostly due to seminoma, mixed germ cell tumors and embryonal carcinoma – 17,39 %, 31,58 % and 83,33 % correspondingly. The occurrence rate index of yolk sac's tumors, on the contrary, decreased by 66,67 % in the second decade. The occurrence rate of other testicular GCT had no considerable influence as to the general index, due to a small absolute cell count.

The average age of patients with testicular GCT is 33,91±0,57, which is coincident with data in scholarly literature [1, 8]. All the patients are distributed into 8 age categories (Table 2).

As is evident from the tables, testicular GCT occur most frequently with the following age categories: "at the age of 20-30" (32,89 %), "at the age of 30-40" (36,54 %) and "at the age of 40-50" (20,61 %), which makes 90, 04 % out of all the cases. The age categories "until 20 years of age" (4,32 %) and "at the age of 50-60" (3,32 %) were less affected. As to the category "at the age of 60" and more, the total percentage makes only 2,32 %.

Table 1

Grouping of GCT according to the minute structure, years and decades

Tumor type / Year	Seminoma	Seminoma with cyncytiotrophoblast cells	Embryonal carcinoma	Yolk-sac tumor, after-pubertal type	Spermatocytal tumor	Teratoma after-pubertal type (mature teratoma)	Teratoma after-pubertal type (immature teratoma)	Teratoma with somatic type of malignancy	Teratoma, pre-pubertal type (Epidermoid cyst, Dermoid cyst)	Choriocarcinoma	Mixed germ cell tumors	Total in years and decades
1998	10	0	0	1	0	0	1	0	1	0	8	**21**
1999	5	0	0	0	0	0	0	0	0	0	5	**10**
2000	3	0	4	0	0	0	0	0	0	0	4	**11**
2001	7	1	1	0	0	0	0	0	0	0	3	**12**
2002	12	0	3	0	0	1	0	0	0	0	1	**17**
2003	6	1	0	2	0	0	1	0	0	0	2	**12**
2004	9	0	0	2	1	0	0	0	0	0	2	**14**
2005	5	0	2	4	0	0	0	0	0	1	4	**16**
2006	3	1	0	0	0	1	0	0	1	0	5	**11**
2007	6	0	2	0	0	0	1	1	0	0	4	**14**
First decade	**66**	**3**	**12**	**9**	**1**	**2**	**3**	**1**	**2**	**1**	**38**	**138**
2008	2	1	4	0	0	1	0	0	0	0	8	**16**
2009	4	1	2	0	0	1	1	0	0	0	6	**15**
2010	8	2	2	0	0	0	0	0	0	0	4	**16**
2011	6	1	3	0	0	1	0	0	0	0	6	**17**
2012	12	1	2	1	1	0	0	0	0	0	4	**21**
2013	15	2	0	2	0	0	0	0	0	0	4	**23**
2014	5	1	0	0	0	0	0	0	0	0	4	**10**
2015	1	2	3	0	1	0	0	1	0	0	9	**17**
2016	10	1	2	0	0	0	0	0	0	0	0	**13**
2017	6	0	4	0	0	0	0	0	0	0	5	**15**
Second decade	**69**	**12**	**22**	**3**	**2**	**3**	**1**	**1**	**0**	**0**	**50**	**163**
TOTAL	**135**	**15**	**34**	**12**	**3**	**5**	**4**	**2**	**2**	**1**	**88**	**301**

Table 2

Age grouping of patients with testicular GCT

Age category	Until 20 years of age	At the age of 20-30	At the age of 30-40	At the age of 40-50	At the age of 50-60	At the age of 60-70	At the age of 70-80	At the age of 80-90	Total
Number of cases, abs.	13	99	110	62	10	5	1	1	301
%	4,32	32,89	36,54	20,61	3,32	1,66	0,33	0,33	100

The analysis of patients' complaints (Table 3) shows, that the most frequently registered ones were: enlargement of testicles and their tenderness; less frequent (every sixth patient), but no less vivid, were: induration in testicles and temperature rise. The patients commonly complained of fatigue. Complaints of weight loss, malaise, hyperemia of the scrotum skin, burning in testicles, tumor-like mass, dysuria, pain in the ileum and inguinal area, as well as lumbar pain and pain in right hypochondrium, decrease of testicles in size and dyspnea were occasional. It should be noted that, with the majority of patients, a collection of several complaints in various combinations was registered.

Table 3

Variants and occurrence rate of testicular GCT patients' complaints

Complaints	Number of cases, abs.	%
Enlargement of testicles	264	87,71
Testicles' tenderness	181	60,13
Induration in testicles	53	17,61
Temperature rise	50	16,61
Fatigue	21	6,98
Weight loss	10	3,32
Tumor-like mass	10	3,32
Dysuria	6	1,99
Hyperemia of the scrotum skin	5	1,66
Malaise	3	1,00
Lumbar pain	2	0,66
Iliac pain	2	0,66
Inguinal pain	1	0,33
Pain in right hypochondrium	1	0,33
Testicles' burning	1	0,33
Decrease of testicles in size	1	0,33
Dyspnea	1	0,33

The right testicle was harmed by a testicular GCT in 169 cases (56,15 %), the left one – in 132 cases (43,85 %); i.e., the right testicle was afflicted with a testicular GCT by 28,03 % more often than the left one.

The first-listed diagnosis, made by medical establishments that referred the patients for further examination and treatment, was testicular tumor in 253 cases (84,06 %), inflammatory conditions (acute orchitis or exacerbation of chronic orchitis, acute orchiepididymitis or exacerbation of acute orchiepididymitis) – in 37 cases (12,30 %) and hydrocele – in 5 cases (1,66 %). Testicular atrophy, varicocele, tumor of epididymis, spermatic cord cyst, testicular cyst and acute pyelonephritis were diagnosed once each (0,33 %). As one can see, 15,94 % of cases prove that the first-listed diagnosis, when being further referred to a hospital, was different from the final diagnosis. The most common false diagnosis was an inflammatory process.

According to patients, the duration of the disease, by the time the patient visited the doctor, ranged from 0,03 to 48 months, which made 4,73±0,33 months in average (Table 4).

Table 4

Grouping of patients with testicular GCT according to the duration of the disease

Duration of the disease, months	**Prior to 1**	**1-2**	**2-3**	**3-6**	**6-9**	**9-12**	**12 і >**	**Total**
Number of cases, abs.	57	46	35	64	47	13	39	301
%	18,94	15,28	11,63	21,26	15,61	4,32	12,96	100

History with cryptorchidism is the risk factor for testicular GCT, that has been established by now [9-11]. Besides, scrotum injury is widely believed to aid in the development of testicular tumor, which causes hypertrophy and atrophy of testicles [12, 13], varicocele, anatomical defects of the kidneys [14], inguinal hernia [9, 10].

Our research includes the factors that can be related to the development of testicular GCT; these are the following: varicocele – in 36 cases (11,96 %), hydrocele and cryptorchidism – 27 cases of each (8,97 %), scrotum injury – 9 cases (2,99 %), malformations of the genitourinary apparatus – 8 cases (2,66 %), inguinoscrotal hernia, phimosis and «spina bifida» – 1 case of each (0,33 %). A combination of these risk factors was registered in few patients.

When being admitted to a hospital, diagnosis was made according to the study of the

medical history, physical and visual examination of the testicle and retroperitoneal space (ultrasonic diagnosis, CT or MRT) with the mandatory testing of the level of serum tumor markers (alpha fetoprotein, beta-HCG and LDH).

Analysis of the examination data showed that there are some differences in patients' complaints, which are subjective (Table 3) and objective data (Table 5), and which were obtained during physical examination. Hence, the majority of patients could not evaluate on their own (did not complain of it) the fact of presence of induration in testicles and scrotum skin hyperemia.

Table 5

Variants and occurrence rate of objective characteristics of the testicles with testicular GCT

Objective data	Number of cases, abs.	%
Enlargement of the testicle	291	96,68
Induration in the testicle	254	84,39
Tenderness of the testicle	178	59,14
Testicle roughness	55	18,27
Scrotum skin hyperemia	22	7,31
Presence of tumor-like (nodular) mass in the testicle	9	2,99
Presence of mollities in the testicle	6	1,99

The 267 patients (88,70 %) underwent ultrasonography; according to the latter, 221 patients (82,77 %) were diagnosed testicular tumor, and 35 patients (13,12 %) – testicular tumor in combination with tumor of lymph nodes. The ultrasonography of nine patients (3, 37 %) resulted in hydrocele, extra testicle, orchiepididymitis and posttraumatic hematoma. One case of each were revealed by ultrasonography, namely: tumor lymphadenopathy and metastatic liver lesions (0,37 %).

CT scanning of 251 patients (83,39 %) was performed. Testicular tumor was diagnosed in 98 patients (39,04 %), testicular tumor in combination with tumor of lymph nodes – in 75 patients (29,88 %). The prescribed screening of retroperitoneal space alone revealed tumor lymphadenopathy in16 patients (6,37 %), and 52 patients (20,72 %) had no pathological changes. Distant metastases were registered in nine patients (3,59 %), metastases in the lungs – in five patients, metastases in the liver – in five patients, and metastases in the

bone – in three patients. The four patients (1,59 %) were misdiagnosed (hydrocele, testicular atrophy, testicular hypoplasia and orchiepididymitis).

If needed, X-ray examination of chest organs was prescribed for the patients – 160 (53,16 %) cases. Hence, metastatic lung injury was detected in 27 cases (16,88 %). Consequently, in 10,30 % out of 301 patients, distant metastases were revealed during complex examination.

According to the results of ultrasonography and CT, the accuracy of the diagnosis and study of the testicular GCT was high enough.

Analysis of belonging of patients with testicular GCT to certain blood groups and Rh factor showed, that the number of patients with blood group II (A) was bigger by 7,18 %, and the number of patients with blood groups I (0) and III (B) was lower than the average Ukrainian indices by 2,45 % and 4,71 % (Table 6).

Table 6

Variants and occurrence rate of blood groups and Rh factor in patients with testicular GCT

		I (0)		II (A)		III (B)		IV (AB)	
		Rh+	Rh-	Rh+	Rh-	Rh+	Rh-	Rh+	Rh-
Research data	Number of cases, abs.	84	20	125	17	33	4	15	3
	%	27,91	6,64	41,53	5,65	10,96	1,33	4,98	1,00
		34,55		47,18		12,29		5,98	
Ukraine	%	37		40		17		6	

Literature sources mention the high stature, being a causative factor of testicular GCT development, while the overweight is not among these factors [15].

Our research analysis of anthropometric characteristics presented average height of patients, which made 1,79±0,003 m, the latter exceeding the average Ukrainian index – 1, 75 m (according to the Statistical Reporting Service in Ukraine). The majority of patients' height was more than 1,75 m (221 / 73,42 %). Body weight index of Kettle calculation showed that in the age category "up to 25" (52 patients / 17,28 %) the body weight index made 23,11±0,48, in the age category "26 and more" (249 patients / 82,72 %) it amounted to 25,91±0,23. The received indices of anthropometric characteristics are presented in Table 7.

According to the data given in the table, overweight of various severity was registered in 140 patients (46,51 %), which made less than half of all the cases. As well as, the weight loss was detected in 14 cases (4,65 %); at that, the weight loss was highly pronounced in 5 cases (1,66 %).

The removed tumorous testicles after orchifuniculectomy underwent organometric investigations, with the estimation of the tumor volume and the volume of the affected testicle. Thus, the average volume of the removed testicle made $(197,95\pm9,78)\times10^{-6}$ m^3, as well as, the average volume of the tumor – $(170,95\pm9,93)\times10^{-6}$ $м^3$. Besides, the degree of the testicle damage was estimated with the mean percent which amounted to 76,06±2,46 %.

Grouping of patients according to different severity rate of the testicles' damage is given in Table 8. As is seen, a considerable damage of testicles has been presented: severity rate index of 239 patients (79,41 %) made 50 % and more, and severity rate index of 185 patients (61,46 %) – 80-100 % of the affected area.

Table 7

Anthropometric indices in patients with testicular GCT

Hieght, m	**Number, abs.**	**%**
1,5-1,6	1	0,33
1,6-1,7	14	4,65
1,7-1,8	136	45,18
1,8-1,9	133	44,19
1,9-2,0	17	5,65

Body weight index of Kettle	**Number, abs.**	**%**
insufficient, dangerous to health	5	1,66
Slightly lowered, safe for health	9	2,99
Normal	147	48,84
Overweight	81	26,91
Obesity 1 degree	40	13,29
Obesity 2 degree	16	5,32
Obesity 3 degree	2	0,66
Obesity 4 degree	1	0,33

Table 8.

Grouping of patients according to the testicular GCT severity rate

Testicular lesion degree, %	Up to 10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100	Total
Number of cases, abs.	6	18	8	15	15	10	18	26	49	136	301
% of cases	1,99	5,98	2,66	4,98	4,98	3,32	5,98	8,65	16,28	45,18	100

The morphological study of a part of testicular GCT revealed secondary changes: hemorrhage, necrosis and inflammation. Each of the mentioned above was registered in different combinations with the same frequency – 174 cases of each (57,81 %).

The microscopy of tumor tissue was carried out to reveal its severity and proliferation and for its better study; therefore, the microscopy was performed to reveal presence or absence of vascular invasion, malignant invasion in the tunica albuginea, epididymis, spermatic cord and scrotum (table 9).

As is evident, the vascular invasion occurred most frequently, and it was registered in more than one third of cases; as well as malignant invasion in the tunic of testis (every fifth case).

All the testicular GCT are distributed into two groups agreeable to WHO classification: GCT derived tumors «in situ» and tumors non-derived from GCT «in situ». In our research the 296 cases of testicular GCT (98,34 %) referred to the first group; neoplasia of germ cells in situ (GCNIS) was discovered in 237 patients out 296 (80,07 %), and it was not registered in 59 patients (19,93 %), mostly due to total tumor lesion of the testicle.

Table 9

Occurrence rate of testicular GCT severity and neoplastic proliferation

Microscopic evidence	Number of cases, abs.	% of cases
Vascular invasion	118	39,20
Malignant invasion in epididymis	63	20,93
Malignant invasion in spermatic cord	39	12,96
Malignant invasion in the tunica albuginea	25	8,31
Malignant invasion in vaginal tunic	25	8,31
Malignant invasion in scrotum	2	0,66

Morphological diagnostics was carried out, visual examination of the testicle and retroperitoneum was done, assessment of the serum tumor markers level was performed to study all the cases of testicular GCT according to pTNM classification (Table 10).

Table 10

Grouping and occurrence rate of GCT according to pTNM classification

TNS stage	Number of cases, abs.	% of cases	TNS stage	Number of cases, abs.	% of cases
$T_1N_0S_0$	109	36,21	$T_2N_3S_1$	11	3,66
$T_1N_0S_1$	40	13,29	$T_2N_3S_X$	2	0,66
$T_1N_0S_2$	1	0,33	$T_3N_0S_0$	4	1,33
$T_1N_0S_X$	16	5,33	$T_3N_0S_1$	7	2,33
$T_1N_1S_0$	2	0,66	$T_3N_0S_X$	1	0,33
$T_1N_1S_1$	1	0,33	$T_3N_1S_0$	4	1,33
$T_2N_0S_0$	6	1,99	$T_3N_1S_1$	4	1,33
$T_2N_0S_1$	9	2,99	$T_3N_2S_0$	2	0,66
$T_2N_0S_X$	1	0,33	$T_3N_2S_1$	5	1,66
$T_2N_1S_0$	14	4,65	$T_3N_3S_0$	3	1,00
$T_2N_1S_1$	11	3,66	$T_3N_3S_1$	5	1,66
$T_2N_1S_X$	1	0,33	$T_3N_3S_2$	1	0,33
$T_2N_2S_0$	12	3,99	$T_3N_3S_X$	2	0,66
$T_2N_2S_1$	19	6,32	$T_4N_2S_0$	1	0,33
$T_2N_2S_X$	1	0,33	$T_4N_2S_1$	1	0,33
$T_2N_3S_0$	5	1,66			

When analyzing categories of TNM it is discovered that, 169 cases (56,15 %) are attributable to T1, 92 cases (30,57 %) – to T2, 38 cases (12,62 %) – to T3 and 2 cases (0,66 %) – to T4; 194 cases (64,46 %) are attributable to N_0, 37 cases (12,29 %) – to N_1, 41cases (13,62 %) – to N_2 and 29 cases (9,63 %) – to N_3; 24 cases (7,97 %) are attributable to the category S_x, 162 (53,82 %) – to S_0, 113 cases (37,55 %) – to S_1, 2 cases (0,66 %) – to S_2. Category T_1 is observed in a larger number of cases – 169 (56,15 %), and tumors with categories T_2 i T_3 made 130 cases (43,19 %). The total number of N_1, N_2 and N_3 categories amounted to 107 cases (35,54 %), and 194 cases (64,46 %) are attributable to N_0. 162 cases (59,82 %) are attributable to the category S_0, 113 cases (37,55 %) – to S_1.

Conclusions:

1. The period under the analysis (years1998-2017) is characterized by an increasing tendency for the occurrence rate of GCT, mainly due to seminoma, mixed germ cell tumors and embryonal carcinoma.

2. The average age of the patients with testicular GCT was 33,91±0,57; the age categories of male "from 20 to 50 years of age" (90,04 % of all the cases) were affected by testicular GCT most often; the duration of the disease by the time the patient visited the doctor, ranged from 0,03 to 48 months, which made 4,73±0,33 months in average; the right testicle was affected by testicular GCT more often than the left testicle by 28,03 %.

3. The most common registered factors, that can be associated with the development of testicular GCT are: varicocele – 11,96 %, hydrocele and cryptorchidism – 8,97 % each, in combination with the mentioned risk factors registered in a part of the observed cases.

4. In the majority of cases a considerable tumor lesion of testicles was registered: the damage level made 50 % and more in 79,41 % of patients, and 61,46 % of patients had 80-100 % of the testicles' damage.

5. The testicular GCT under observation were derived from germ cell neoplasms «in situ» in 98,34 % of cases; GCNIS was detected in 80,07 % of them, and it was not detected in 19,93 % of cases due to the total tumor lesion of the testicle.

6. In testicular GCT investigations, according to pTNM classification category T_1 was registered in its majority – 169 cases (56,15 %), tumors with categories T_2 and T_3 were detected in 130 cases (43,19 %), which is indicative of the dominance of low tumor stage in this type neoplastic proliferation.

7. The percentage rate of patients with no lesion of the lymph nodes (category N_0) was larger by 81,31 %, if compared with the corresponding percentage rate of patients with registered lesion of the lymph nodes (categories N_1, N_2 i N_3); patients with distant metastases made 10,30 % of cases.

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