Potapov Serhii M., Horhol Nataliia I., Halata Daria I., Pliten Oksana M. Testicular germ cell tumors: tumor grade co-relation with TNS stages and remote metastasis. Journal of Education, Health and Sport. 2019;9(3):577-600. eISNN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.2636815
http://ojs.ukw.edu.pl/index.php/johs/article/view/6833

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 20.02.2019. Revised: 28.02.2019. Accepted: 29.03.2019.

TESTICULAR GERM CELL TUMORS: TUMOR GRADE CO-RELATION WITH TNS STAGES AND REMOTE METASTASIS

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Abstract

The performed 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, is devoted to the investigation of correlation between the degree of tumorous lesion of the testes and categories of pTNM classification in patients with TGCT. According to the obtained data, there are significant differences between the different histological types of the TGCT. It is concluded that the most aggressive TGCT is embryonic cancer and yolk sac tumor, postpubertal-type; the least aggressive of all is seminoma and teratoma, postpubertal-type; the mixed TGCT hold an intermediate position.

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

Testicular tumors are most commonly found among white men, who live in industrially advanced countries, within the period from puberty up to the age of 40, and they equal up to, approximately, 1% out of all the male neoplasms [1-5]. At that, testicular germ cell tumors (TGCT) amount to more than 90% of all the seminal glands' neoplasms [6, 7].

During the past 40 years TGCT sickness rate rose up worldwide, specifically, in North and South America, as well as in northern European countries [1, 8-12].

In 2017, TGCT sickness rate in Ukraine amounted to 2.6 cases per 100.000 population, and in men, aged from 25 to 44, it reached 4.6 cases per 100.000 population [13].

Objectives: to study the TGCT tumorous lesion grade co-relation with TNS stages and remote metastasis.

Material and methods of study. In the furtherance of this goal, morphological examination of surgically removed seminal gland was carried out and analysis of medical case histories of 301patients with different types of TGCT was made. These patients were examined and treated in Kharkiv Regional Clinical Centre of Urology and Nephrology named after Shapoval V.I. The investigation covered period from 1998 to 2017.

Morphological examination included macro- and microscopic description, which specified the volume of the testis and the tumor affecting it, the percentage of the tumorous lesion; it also stated absence or presence of invasion into blood and lymphatic vessels, invasion in epididymis and testicular membranes, spermatic cord and scrotum.

All the observations were classified depending on type of histological structure and in accordance with WHO classification and pathological pTNM classification (Table 1, 2) [14], which is highly important, as the precise diagnosis and staging, which is made in compliance with the advanced science, are fundamental.

Table 1.

Analyzed TGCT (according to pathological pTNM classification, 2016)

pT – Primary tumor		**Number / percentage of cases**
pT_X	Primary tumor cannot be assessed	0 (0.00 %)
pT_0	No evidence of primary tumor (e.g. histological scar in testis)	0 (0.00 %)
pTis	Germ cell neoplasia in situ	0 (0.00 %)
pT_1	Tumor limited to testis and epididymis, without vascular / lymphatic invasion; tumor may invade tunica albuginea but not tunica vaginalis	167 (55.5%)
pT_2	Tumor limited to testis and epididymis with vascular / lymphatic invasion, or tumor extending through tunica albuginea with involvement of tunica vaginalis	94 (31.2%)
pT_3	Tumor invades spermatic cord, with or without vascular / lymphatic invasion	38 (12.6%)
pT_4	Tumor invades scrotum, with or without vascular / lymphatic invasion	2 (0.7 %)
pN – Regional lymph nodes		
pN_X	Regional lymph nodes cannot be assessed	0 (0.00 %)
pN_0	No regional lymph node metastasis	195 (64.8%)
pN_1	Metastasis in ≤ 5 lymph nodes, all ≤ 2 cm in greatest dimension	37 (12.3%)
pN_2	Metastasis in ≤ 5 lymph nodes, > 2 cm but ≤ 5 cm in greatest dimension; or in > 5 lymph nodes, all ≤ 5 cm in greatest dimension; or evidence of extranodal extension of tumor	41 (13.6%)
pN_3	Metastasis in lymph node(s) > 5 cm in greatest dimension	28 (9.3 %)

S – Serum tumor markers		
S_X	Serum marker studies not available or not performed	24 (8.0 %)
S_0	Serum marker study levels within normal limits	162 (53.8%)
S_1	LDH <1,5 × ULN and βhCG (mlU/mL) < 5000 and AFP (ng/ml) < 1000	113 (37.5%)
S_2	LDH = 1,5-10 × ULN or βhCG (mlU/mL) = 5000-50000 or AFP (нг / мл) = 1000-10000	2 (0.7 %)
S_3	LDH > 10 × ULN or βhCG (mlU/mL) > 50000 or AFP (ng/ml) > 10000	0 (0.00 %)

Table 2.

Analyzed TGCT (according to WHO classification of tumors of the testis, 2016)

Germ cell tumors derived from germ cell neoplasia in situ	**Code**	**Number / percentage of cases**
Non-invasive germ cell neoplasia		
Germ cell neoplasia in situ	9064/2	0 (0.00 %)
Specific forms of intratubular germ cell neoplasia		0 (0.00 %)
Tumors of a single histological type (pure forms)		
Seminoma	9061/3	135 (44.9 %)
Seminoma with syncytiotrophoblast cells		15 (5.0 %)
Non-seminomatous germ cell tumors		
Embryonal carcinoma	9070/3	34 (11.3 %)
Yolk sac tumor, postpubertal-type	9071/3	12 (4.0 %)
Trophoblastic tumors		
Choriocarcinoma	9100/3	1 (0.3 %)
Non-choriocarcinomatous trophoblastic tumors		
Placental site trophciblastic tumor	9104/1	0 (0.00 %)
Epithelioid trophoblastic tumor	9105/3	0 (0.00 %)
Cystic trophoblastic tumor		0 (0.00 %)
Teratoma, postpubertal-type	9080/3	9 (3.0 %)
Teratoma with somatic-type malignancy	9084/3	2 (0.7 %)
Non-seminomatous germ cell tumors of more than one histological type		
Mixed germ cell tumors	9085/3	88 (29.2 %)
Germ cell tumors of unknown type		
Regressed germ cell tumors	9080/1	
Germ cell tumors unrelated to germ cell neoplasia in situ		
Spermatocytic tumor	9063/3	3 (1.0 %)
Teratoma, prepubertal-type	9084/0	2 (0.7 %)
Dermoid cyst		1 (0.3 %)
Epidermoid cyst		1 (0.3 %)
Well-differentiated neuroendocrine tumor (monodermal teratoma)	8240/3	0 (0.00 %)
Mixed teratoma and yolk sac tumor, prepubertal-type	9085/3	0 (0.00 %)
Yolk sac tumor, prepubertal-type	9071/3	0 (0.00 %)

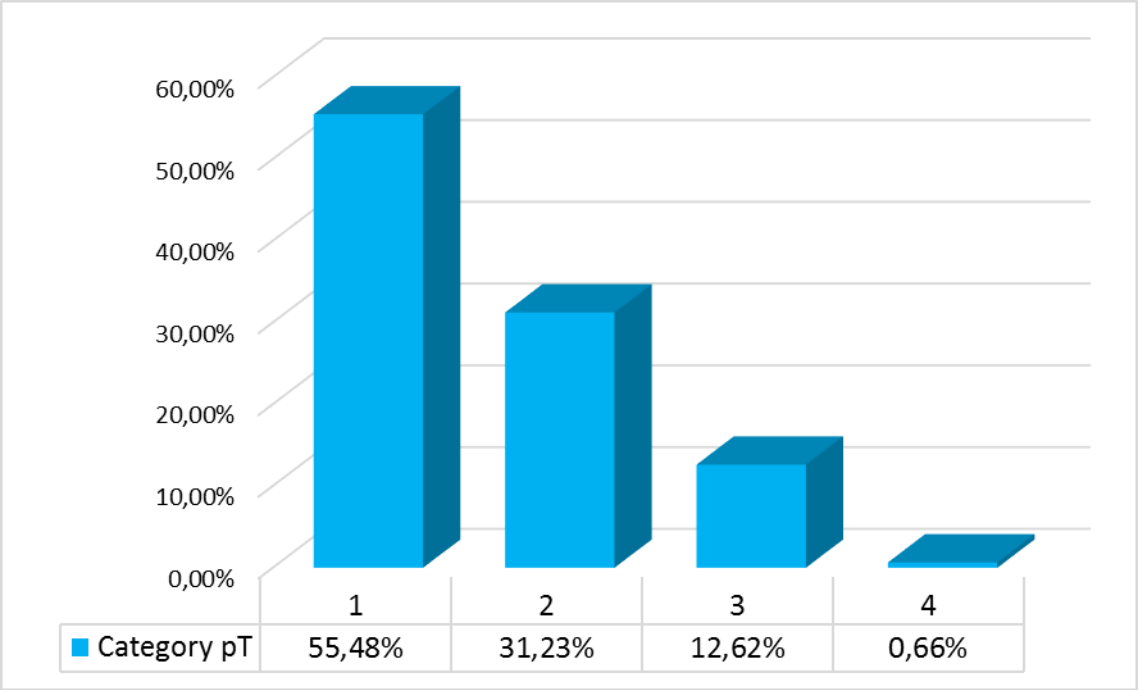
Category pT

The pT stages' grouping of all the analyzed TGCT according to the degree of incidence, presented in Diagram 1, demonstrates progressive decrease in the number of cases at each subsequent stage.

Therefore, it can be stated with complete certainty, that pT_1 stage is the one, which is the most frequently observed in all the analyzed TGCT; and it constitutes more than half of all the cases (55.48 %). The incidence rate of pT_2 stage presented 31.23 %, which is twice as less than the incidence rate of pT_1 stage. As to pT_3 stages of TGCT, they were observed only in 12.62 % of patients, which is more than 4 and 2 times less than in patients with pT_1 and pT_2 stages correspondingly. Concerning pT_4 stage, it was observed in less than 0.66 % of all the cases observed.

Diagram 1.

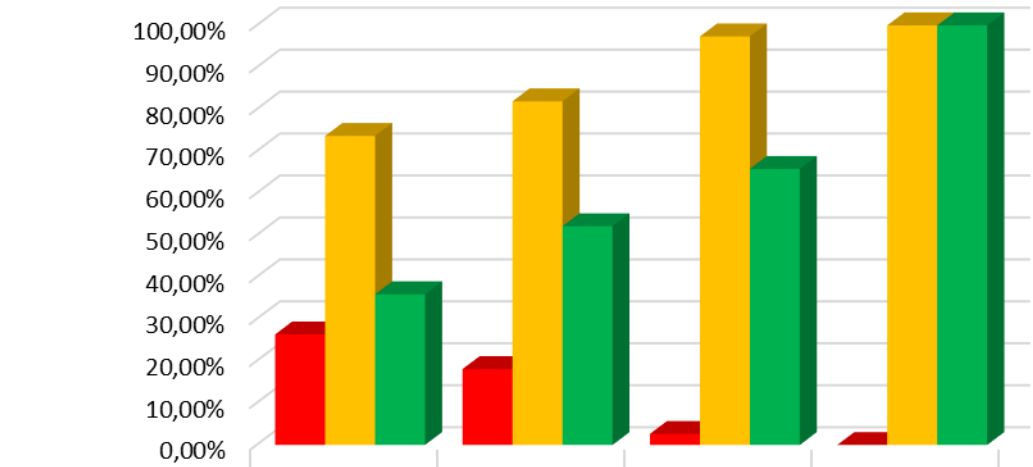
Grouping of analyzed TGCT according to the degree of incidence



At that, with the increase of the number of pT stages, the number of patients with 0-50 % of tumorous lesion progressively decreased from 26.35 % to 0.00 %, as well as the number of patients with 50-100 % and 90-100 % of tumorous lesion, increased from 73.65 % to 100 % and from 35.93 % to 100 %, correspondingly (Diagram 2).

Diagram 2.

Frequency of pT categories depending on the degree of tumorous lesion



	pT1	pT2	pT3	pT4
0-50 % lesion	26,35%	18,09%	2,63%	0%
50-100 % lesion	73,65%	81,91%	97,37%	100%
90-100 % lesion	35,93%	52,13%	65,79%	100%

It also comes under notice that, even being in the low pT_1 tumor stage, the number of patients with 50-100% testicular tumorous lesion, occurred 2.8 times more than that of 0-50 % of tumorous lesion. This confirms that, by the time of operative intervention, as a whole, the considerable tumorous lesion grade was quite typical for the observed TGCT.

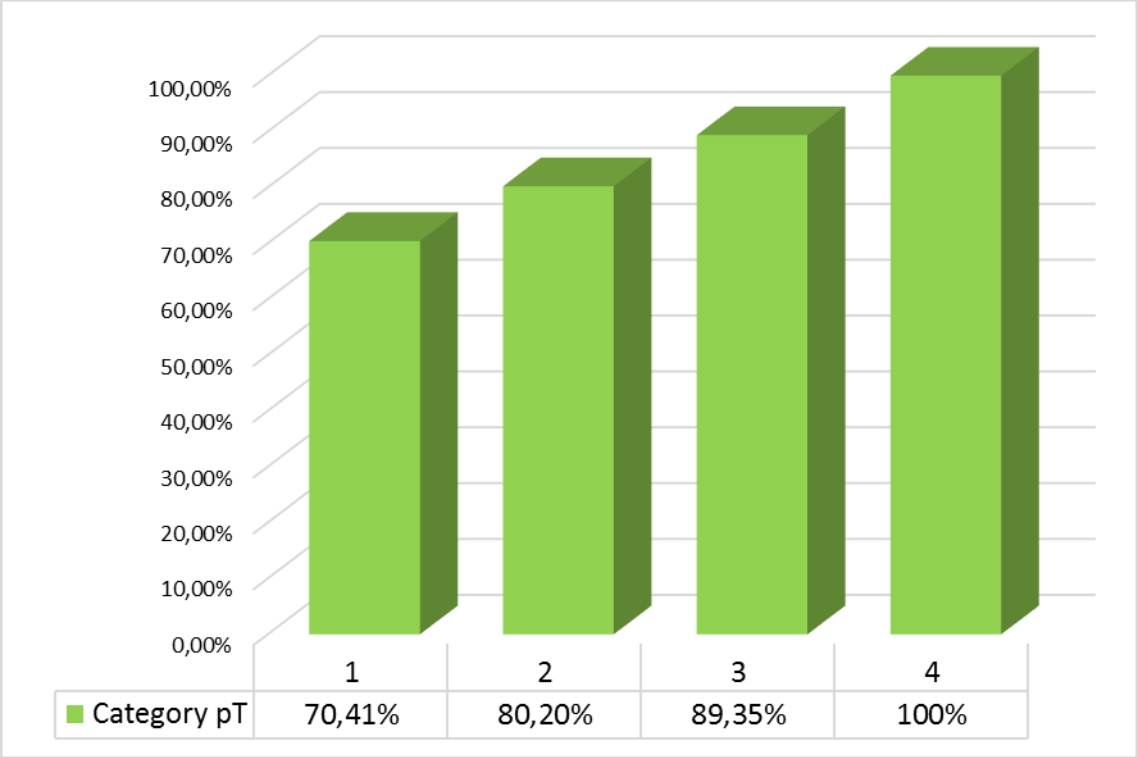
Diagram 3 presents the percentage rate of tumorous lesion of testis in different pT stages. Consequently, the estimated average of TGCT tumorous lesion grade in pT_1 stage amounted to 70.41±3.53 %, which, statistically, did not differ from the general estimated average (76,06 ± 2,46 %); though, a noticeable tendency to its decrease was noted (t=1.31). Tumorous lesion grade of testis in pT_2 stage made 80.20±4.11 %, which, statistically, did not differ from this figure in pT_1 stage, though the tendency to rate increase is rather strong (t=1.81). The percentage rate of tumorous lesion in pT_3 stage amounted to 89.35±5.00 %, it was, statistically, ($p<0.01$), higher than this figure in stage pT_1, and had a tendency to increase (t=1.41), relating to stage pT_2. And, as it has been stated above, pT_4 stage in the analyzed TGCT was observed only in 0.66 % of the all investigated cases, and, at that, all of them presented total tumorous lesion. Therefore, as pT stages grew, the testicular tumorous lesion grade grew as well. And it is well-known that advanced malignancy stages correlate with a bad prognosis [16].

In accordance with WHO pathological pTNS classification, pT_1 stage includes tumors which damage only testis and epididymis, not including blood and lymphatic vessels'

invasion, at that, the tumor may invade tunica albuginea but not the vaginal tunic (Table 2). That is, the tumors which relate to this stage are less aggressive. In seminoma and teratoma, postpubertal-type the amount of pT_1 stage tumors was the most numerous and made 67.33 % and 88.89 % correspondingly; with embryonal carcinoma pT_1 stage was less registered – 20.59 %. Intermediate data values of the incidence rate in low pT_1 stage relate to mixed TGCT and yolk sac tumor, postpubertal-type – 48.86 % and 41.67 % correspondingly (table 3).

Diagram 3.

Percentage rate of tumorous lesion of testis in different pT categories



The study of the testicular lesion rate in each group of the analyzed TGCT showed that in pT_1 stage the 0-50% lesion was observed least often and, as a result, 50-100 % damage was the most frequent with yolk sac tumor, postpubertal-type and seminoma (20.00 % and 80.00 %; and 20.79 % and 79.21 % of cases correspondingly). 0-50 % tumorous lesion was registered more often with embryonal carcinoma and teratoma, postpubertal-type (42.86 % and 37.50 %). As to 90-100% lesion, it was found more often with yolk sac tumor, postpubertal-type and seminoma (60.00 % and 44.55 % of the patients correspondingly) and more rare with mixed TGCT and embryonal carcinoma (18.60 % and 28.57 % correspondingly). Therefore, the type of tumor, with almost the biggest testicular tumorous lesion grade (seminoma), showed high indices, relating to low pT_1 tumor stage; and, vice

versa, the type of tumor, which was less often presented in pT_1 stage (embryonal carcinoma), is characterized with a low level of testicular lesion (Table 3).

Table 3.

Distribution of TGCT depending on pT categories and tumorous lesion level

TGCT	pT category	Tumorous lesion level									
		0-90 %		90-100 %		0-50 %		50-100 %		Всього	
		Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value
Seminoma	T_1	56	55.45	45	44.55	21	20.79	80	79.21	101	67.33
	T_2	12	37.50	20	62.50	3	9.38	29	90.63	32	21.33
	T_3	6	37.50	10	62.50	0	0.00	16	100.0	16	10.67
	T_4	0	0.00	1	100.0	0	0.00	1	100.0	1	0.67
Embryonal carcinoma	T_1	5	71.43	2	28.57	3	42.86	4	57.14	7	20.59
	T_2	10	71.43	4	28.57	8	57.14	6	42.86	14	41.18
	T_3	5	38.46	8	61.54	1	7.69	12	92.31	13	38.24
	T_4	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Yolk sac tumor, postpubertal-type	T_1	2	40.00	3	60.00	1	20.00	4	80.00	5	41.67
	T_2	2	40.00	3	60.00	2	40.00	3	60.00	5	41.67
	T_3	1	50.00	1	50.00	0	0.00	2	100.0	2	16.67
	T_4	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Teratoma, postpubertal-type	T_1	6	75.00	2	25.00	3	37.50	5	62.50	8	88.89
	T_2	1	100.0	0	0.00	0	0.00	1	100.0	1	11.11
	T_3	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	T_4	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Spermatocytic tumor	T_1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	T_2	2	66.67	1	33.33	0	0.00	3	100.0	3	100.0
	T_3	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	T_4	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Teratoma with somatic-type malignancy	T_1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	T_2	1	100.0	0	0.00	0	0.00	1	100.0	1	50.00
	T_3	0	0.00	1	100.0	0	0.00	1	100.0	1	50.00
	T_4	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Teratoma, prepubertal-type	T_1	2	100.0	0	0.00	2	100.0	0	0.00	2	100.0
	T_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	T_3	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	T_4	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Choriocarcino-ma	T_1	1	100.0	0	0.00	0	0.00	1	100.0	1	100.0
	T_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	T_3	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	T_4	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mixed TGCT	T_1	35	81.40	8	18.60	14	32.56	29	67.44	43	48.86
	T_2	17	44.74	21	55.26	4	10.53	34	89.47	38	43.18
	T_3	1	16.67	5	83.33	0	0.00	6	100.0	6	6.82
	T_4	0	0.00	1	100.0	0	0.00	1	100.0	1	1.14

Stage pT_2 differs from low tumor grade by the fact of presence of blood and/or lymphatic vessels' invasion or vaginal tunic lesion (Table 2). Thus, the tumors of this category are more aggressive and invasive. The highest percentage rate of pT_2 stage tumors was registered with mixed TGCT, yolk sac tumor, postpubertal-type and embryonal carcinoma – 43.18 %, 41.67 % and 41.18 % correspondingly; the least percentage rate – with teratoma, postpubertal-type and seminoma – 11.11 % and 21.33 %. In pT_2 stage, 50-100 % of tumorous lesion of the testis was more often registered with seminoma and mixed TGCT – 90.63 % and 89.47 %; 90-100 % – with seminoma, yolk sac tumor, postpubertal-type and mixed TGCT (62.50 %, 60.00 % and 55.26 % correspondingly). Minimum rate of 50-100 % and 90-100 % tumorous lesion was observed with embryonal carcinoma – 42.86 % and 28.57 % correspondingly (Table 3).

In group pT_2, as well as in group pT_1, some tumors with the highest testicular lesion rate (seminoma) were registered here much more seldom than the tumors with less grade of tumorous lesion (embryonal carcinoma). Therefore, nevertheless the estimated average of tumorous lesion in stage pT_2 was higher than this figure in stage pT_1, its high rate is not typical for the seminoma in stage pT_2.

Stage pT_3 is more invasive than the previous ones, as the tumor spreads to spermatic cord in this stage (Table 2). Thus, the majority of patients were diagnosed embryonal carcinoma – 38.24 %, the second highest percentage rate was registered with yolk sac tumor, postpubertal-type – 16.67 %. The least percentage rate was observed with mixed TGCT and seminoma – 6.82 and 10.67 % correspondingly. It should be noted that stage pT_3 in TGCT the 0-50 % of tumorous lesion was not registered in any of the cases observed, except for the embryonal carcinoma cases, which was identified in 7,69 % of patient. The less frequent 90-100 % tumorous lesion within this stage were registered with yolk sac tumor, postpubertal-type and embryonal carcinoma – 50.00 and 61.54 % correspondingly and the most frequent – with mixed TGCT, which amounted to 83.33 % (Table 3). The given data testify that major tumorous lesion grade is highly typical for this stage.

Therefore, the occurrence regularities, received due to the investigation in TGCT, namely, a massive reduction of number of patients with respect to advance in pT stage, is characteristic only of seminoma and teratoma, postpubertal-type. As to embryonal carcinoma, the number of patients with stage pT_2 and pT_3 was, on the contrary, 2 and 1,9 times bigger than the number of patients with stage pT_1. The percentage of patients with yolk sac tumor, postpubertal-type and mixed TGCT, in stages pT_1 and pT_2, was almost the same and was rather high (from 40 to 50 %); the decrease in the number of patients was observed only in

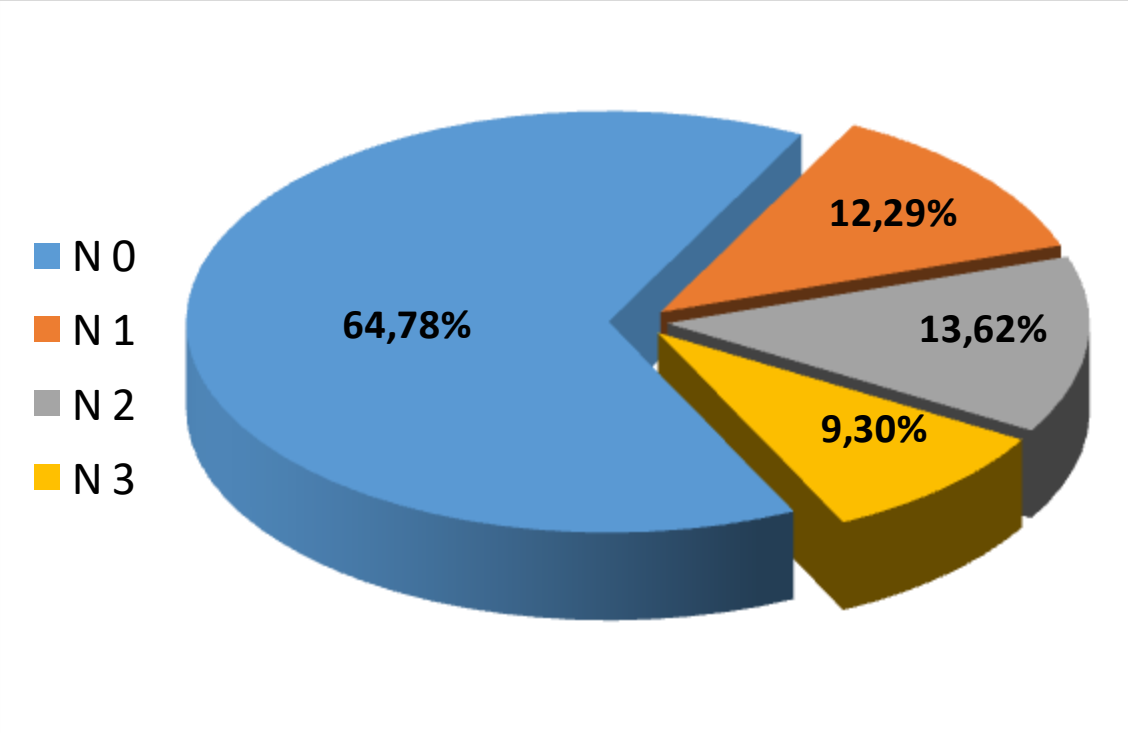
stage pT_3; at that, it was less characteristic of yolk sac tumor, postpubertal-type, than of mixed TGCT. The significant discrepancy between the total data rate and the data rate of a number of certain histological types of tumors occurs due to the following: out of all the cases of TGCT in stage pT_1, which can be considered as 100 %, seminoma produced 60.48 %, mixed TGCT made 25.75 %, whereas, other tumors' rate in this stage was no more than 5%.

Category pN

When analyzing the ordering of pN stage as to the incidence rate in investigated TGCT, it should be noted that stage pN_0 significantly prevails (64.78 %) over stage pN_1 (12.29 %), pN_2 (13.62 %) and pN_3 (9,30 %). Besides, although the amount of occurrences of stage pN_3 was less numerous than the one, registrated in stages pN_1 and pN_2, as a whole, the amount of occurrences of stage pN_0 was 1,8 times more numerous than the one in stages pN_1, pN_2 and pN_3, taken together (diagram 4). Therefore, active lymphogenic metastasis in observed TGCT was not that severe and was registered in 35.22 % overall.

Diagram 4.

Frequency of pN categories



Analyses of the correlation of stages pT and pN demonstrated that lymphogenic metastases were not observed in patients with stage pT_1. Though, stages pT_2 and pT_3 presented quite a different result – number of patients with lymphogenic metastases amounted to 84.04 % and 65.79 % correspondingly. A special attention should be given to the fact that,

during the investigation, lymphogenic metastasis occurred more frequently at the early stage of pT_2, than it did at the same stage of pT_3; and the number of patients, who did not have lymphogenic metastasis in stage pT_3, was twice as big as the number of patients in stage pT_2. This can be explained by the fact that the percentage rate of patients in stage pT_2, who did not have vascular invasion, made 8.51%, and that of patients in stage pT_3 – 23.68 %, which lays emphasis on the highly important role of vascular invasion as to the development of lymphogenic metastasis. Concerning stage pT_4, metastatic affection of lymph nodes was registered in both observations (Table 4).

Table 4.

Distribution of pN categories depending on pT categories

	pT_1 (n=167)		**pT_2 (n=94)**		**pT_3 (n=38)**		**pT_4 (n=2)**	
	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value
pN_0	167	100.0	15	15.96	13	34.21	0	0.00
pN_1	0	0.00	29	30.85	8	21.05	0	0.00
pN_2	0	0.00	32	34.04	7	18.42	2	100.0
pN_3	0	0.00	18	19.15	10	26.32	0	0.00

The average percentage of the testicular lesion in pN_0 stage was statistically ($p<0,05$) less than that of stage pN_2, and had a strong tendency to its decrease in stages pN_1 and pN_3 ($t=1,84$ and $t=1,85$ correspondingly). At that, stages pN_1, pN_2 and pN_3, which are associated with lymphogenic metastasis, did not differ statistically (Table 5).

Table 5.

Average percentage of the tumorous lesion in various pN categories

pN_0	**pN_1**	**pN_2**	**pN_3**
71.47 ± 3.23 %	84.05 ± 6.02 %	84.36 ± 5.67 %	85.23 ± 6.71 %

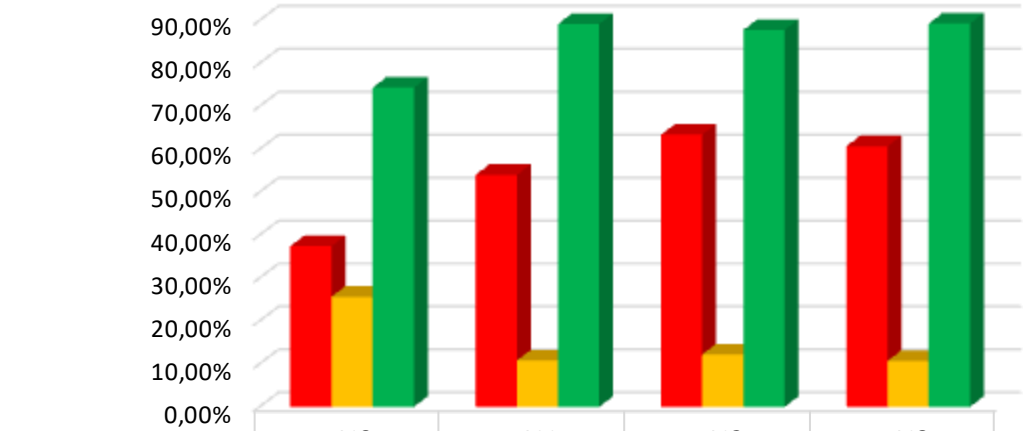
After a more detailed investigation of the grade of TGCT, it was determined that the amount of patients in stage pN_0, with 0-50% of tumorous lesion, was the most numerous, and that of with 50-100 % of tumorous lesion – therefore, less numerous (with 90-100 % of tumorous lesion, likewise) among all the pN stages. Besides, the stated data of stages pN_1, pN_2 and pN_3 were just insignificantly different (diagram 5).

Stage pN_0 was more frequently registered in the investigated TGCT of patients with teratoma, postpubertal-type and seminoma – 88.89 % and 76.67 % of cases correspondingly; it was less frequent in patients with yolk sac tumor, postpubertal-type and embryonal carcinoma (41.67 % and 47.06 % of cases correspondingly). Intermediate data value of the

incidence rate of tumorous progression, which is characterized with the absence of lymphogenic metastasis, demonstrated the group of mixed TGCT and amounted to 54.55 % of cases (Table 6).

Diagram 5.

Frequency of pN categories depending on tumorous lesion level



	pN0	pN1	pN2	pN3
90-100 % lesion	37,44%	54,05%	63,41%	60,71%
0-50 % lesion	25,64%	10,81%	12,20%	10,71%
50-100 % lesion	74,36%	89,19%	87,80%	89,29%

The analysis of testicular lesion grade in every group of the observed TGCT states that seminoma and yolk sac tumor, postpubertal-type were most frequently registered in stage pN_0 with 50-100 % and 90-100% of tumorous lesion (81.74 % and 46.09 %; 80.00 % and 60.00 % of patients correspondingly). At that, 0-50 % of tumorous lesion was more often detected with embryonal carcinoma and teratoma, postpubertal-type (43.75 % and 37.50 % of cases). Thus, the analysis of stage pN_0 showed the same regularity as that of pT_1 stage, that was presented earlier, namely, the tumor, characterized by a considerable testicular damage (seminoma), is highly rated as to relation to less advanced malignancy stage, and it is characterized by the absence of lymphogenic metastasis (pN_0); and, alternatively, certain tumors, which were less demonstrated in category pN_0 (embryonal carcinoma), are characterized by less damaged testis (Table 6).

Stage pN_1 was most frequently observed with embryonal carcinoma and yolk sac tumor, postpubertal-type – 17.65 % and 16.67 % of patients correspondingly; it was less frequent with seminoma, teratoma, postpubertal-type and mixed TGCT – 10.67 %, 11.11 % and 11.36 % of cases correspondingly. The most considerable testicular lesion (90-100 %) in stage pN_1

was registered with seminoma (68.75 % of cases), it was also an important sign with yolk sac tumor, postpubertal-type and mixed TGCT – 50.00 % of patients each; and embryonal carcinoma gave the least percent – 33.33 % of patients (Table 6).

Table 6.

Distribution of TGCT depending on pN categories and tumorous lesion level

TGCT	pN category	Tumorous lesion level									
		0-90 %		90-100 %		0-50 %		50-100 %		Всього	
		Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value
Seminoma	N_0	62	53.91	53	46.09	21	18.26	94	81.74	115	76.67
	N_1	5	31.25	11	68.75	2	12.50	14	87.50	16	10.67
	N_2	3	33.33	6	66.67	0	0.00	9	100.0	9	6.00
	N_3	4	40.00	6	60.00	1	10.00	9	90.00	10	6.67
Embryonal carcinoma	N_0	11	68.75	5	31.25	7	43.75	9	56.25	16	47.06
	N_1	4	66.67	2	33.33	2	33.33	4	66.67	6	17.65
	N_2	4	57.14	3	42.86	2	28.57	5	71.43	7	20.59
	N_3	1	20.00	4	80.00	1	20.00	4	80.00	5	14.71
Yolk sac tumor, postpubertal-type	N_0	2	40.00	3	60.00	1	20.00	4	80.00	5	41.67
	N_1	1	50.00	1	50.00	0	0.00	2	0.00	2	16.67
	N_2	2	66.67	1	33.33	2	66.67	1	33.33	3	25.00
	N_3	0	0.00	2	100.0	0	0.00	2	100.0	2	16.67
Teratoma, postpubertal-type	N_0	6	75.00	2	25.00	3	37.50	5	62.50	8	88.89
	N_1	1	100.0	0	0.00	0	0.00	1	100.0	1	11.11
	N_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	N_3	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Spermatocytic tumor	N_0	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	N_1	1	50.00	1	50.00	0	0.00	2	100.0	2	66.67
	N_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	N_3	1	100.0	0	0.00	0	0.00	1	100.0	1	33.33
Teratoma with somatic-type malignancy	N_0	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	N_1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	N_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	N_3	1	50.00	1	50.00	0	0.00	2	100.0	2	100.0
Teratoma, prepubertal-type	N_0	2	100.0	0	0.00	2	100.0	0	0.00	2	100.0
	N_1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	N_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	N_3	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Choriocarcino-ma	N_0	1	100.0	0	0.00	0	0.00	1	100.0	1	100.0
	N_1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	N_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	N_3	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mixed TGCT	N_0	38	79.17	10	20.83	16	33.33	32	66.67	48	54.55
	N_1	5	50.00	5	50.00	0	0.00	10	100.0	10	11.36
	N_2	6	27.27	16	72.73	1	4.55	21	95.45	22	25.00
	N_3	4	50.00	4	50.00	1	12.50	7	87.50	8	9.09

Thus, seminoma in this stage, which demonstrated the highest level of tumorous lesion, was detected most seldom. The same tendency was observed with mixed TGCT as well. As for embryonal carcinoma, which presented the highest rate in stage pN_1, it was characterized by relatively low level of tumorous lesion.

Stage pN_2 occurred most often with yolk sac tumor, postpubertal-type and mixed TGCT –25.00 % of cases each; at that, in the group of embryonal carcinoma this stage was detected frequently enough – 20.59 % of cases, whereas stage pN_2 occurred only in 6 % of patients with seminoma; teratoma, postpubertal-type did not present this stage at all. Besides, 90-100 % of testicular tumorous lesion occurred in this stage most frequently with mixed testicular TGCT and seminoma – in 72.73 % and 66.67 % of patients correspondingly, and less frequently – with yolk sac tumor, postpubertal-type (33.33 % of patients). The same proportion of the observed TGCT was registered during the analysis of 50-100 % of the tumorous lesion (Table 6).

Therefore, patients with seminoma in stage pN_2, though having almost the highest testicular tumorous lesion rate, like in group pN_1, present the lowest percentage rate of the cases. Patients with yolk sac tumor, postpubertal-type were observed more frequently with the lowest stage of tumorous lesion in this group. With mixed TGCT, with respect to pN stages progressing, the advancement of testicular tumorous lesion stages was observed.

Embryonal carcinoma and yolk sac tumor, postpubertal-type presented the stage pN_3 most often – 14.71 % and 16.67 % of patients correspondingly; the least in number of cases in this stage were seminoma and mixed TGCT – 6.67 % and 9.09 % of patients correspondingly. At the same time, teratoma, postpubertal-type did not present stage pN_3, like in the previous group. At that, 90-100 % of tumorous lesion in stage pN_3 was most often presented by embryonal carcinoma and yolk sac tumor, postpubertal-type – 80.00 % and 100.0 % of patients correspondingly; and 50-100 % of tumorous lesion was frequently registered in all the observed TGCT and it ranged from 80.00 to 100.0 % of cases (Table 6).

So, in stage pN_3, embryonal carcinoma and yolk sac tumor, postpubertal-type are the TGCT, which were registered most frequently and had the highest grade of tumorous lesion.

Besides, during the analysis of the given classification category, it was detected that, though the overall percentage of patients in stage pN_0 was much higher than total percentage rate of stages pN_1, pN_2 and pN_3, this concerned only seminoma and teratoma, postpubertal-type. As well as, with embryonal carcinoma and yolk sac tumor, postpubertal-type things were different – the percentage of patients with lymphogenic metastasis prevailed the analogous index without lymphogenic metastasis.

Taking into consideration the stated above, it may safely be said that, on the whole, the level of tumorous lesion was higher in the observed TGCT, which had lymphogenic metastasis, than in the observed TGCT without lymphogenic metastasis. At that, yolk sac tumor, postpubertal-type, embryonal carcinoma and mixed TGCT, to a lesser extent though, are the most aggressive as to lymphogenic metastasis, even with the low level of tumorous lesion. As well as the tumors, which metastasize by lymphogenic way, though having a considerable level of tumorous lesion, include seminoma and teratoma, postpubertal-type.

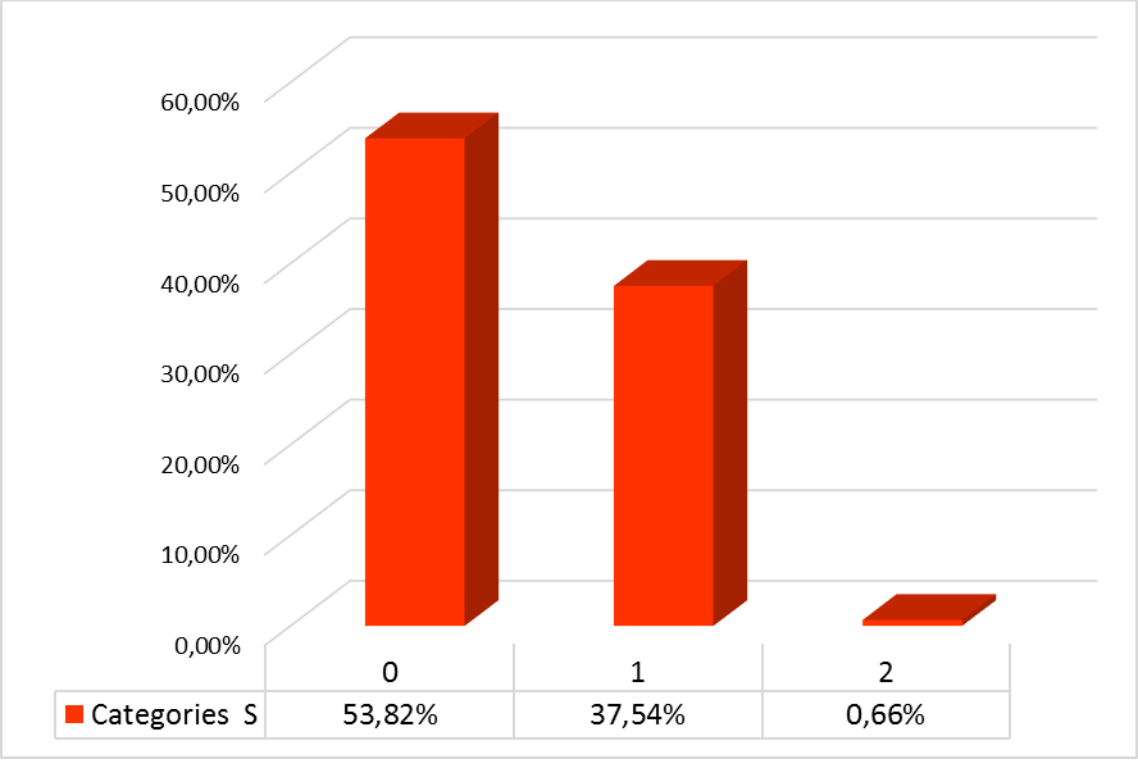
Category S

The investigations of seromarkers – alpha-fetoprotein (AFP), β-human chorionic gonadotropin (βhCG), lactate dehydrogenase (LDH) are highly important for diagnosing and staging of TGCT [10, 17].

The stage of the investigated TGCT, in which the seromarkers' indices fall within normal limits (S_0), occurred most frequently and amounted to 53.82 % of cases. Second frequent stage was S_1 stage, which was registered in 37.54 % of patients. As to stage S_2 , it presented only 0.66 % of the observed patients (Diagram 6).

Diagram 6.

Frequency of S categories



When analyzing the correlation of stages pT and pN with category S, it was revealed that with the advance from stage pT_1 to stage pT_3, (pT_4 presented only two cases), the

percentage of patients, with the seromarkers' indices falling within normal limits, progressively decreased, as well as the number of patients with stage S_1 increased; the same was registered with the progression from pN_0 to pN_4. At that, only two S_2 stage cases were registered, which referred to the stages pT_1N_0 and pT_3N_3 (Table 7).

Table 7.

Distribution of S categories depending on pT and pN categories

	pT categories							
	pT_1 (n=167)		**pT_2 (n=94)**		**pT_3 (n=38)**		**pT_4 (n=2)**	
	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value
S_0	110	65.87	38	40.43	13	34.21	1	50.00
S_1	40	23.95	51	54.26	21	55.26	1	50.00
S_2	1	0.60	0	0.00	1	2.63	0	0.00
	pN categories							
	pN_0 (n=195)		**pN_1 (n=37)**		**pN_2 (n=41)**		**pN_3 (n=28)**	
	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value
S_0	120	61.54	20	54.05	15	36.59	7	25.00
S_1	56	28.72	16	43.23	25	60.98	16	57.14
S_2	1	0.51	0	0.00	0	0.00	1	3.57

The average percentage of the testicular tumorous lesion in S_0 and S_1 stages was not, statistically, much different from each other, and it amounted to 75.36±3.39 % and 76.80±3.97 % correspondingly. As it was stated before, concerning stage S_2, it was presented with only two cases: 100 % of testicular lesion in stage pT_3N_3 and 35 % of testicular lesion in stage pT_1N_0. In general, the indices of the TGCT tumorous lesion in S_0 and S_1 stages were not statistically much different from each other (Diagram 7).

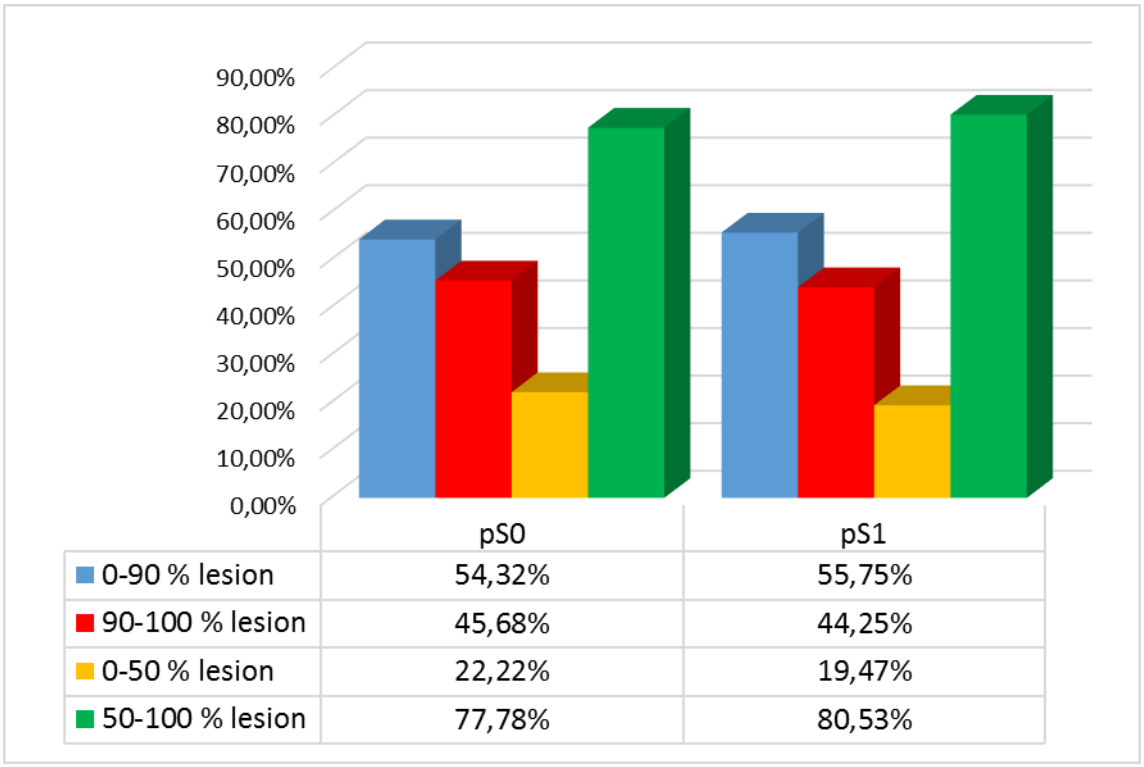
Stage S_0 was most frequently observed on in patients with seminoma and teratoma, postpubertal-type – 81.33 % and 77.78 % of cases correspondingly; less frequently it occurred in patients with yolk sac tumor, postpubertal-type (8.33 % of cases). The intermediate data frequency indices of stage S_0 were stated with embryonal carcinoma and mixed TGCT – 26.47 % and 20.45 % of patients correspondingly. Besides, the analysis of the level of the testicular tumorous lesion in every group of the investigated TGCT showed, that in stage S_0

the 90-100 % of testicular lesion was most often registered with seminoma – 52.46 % of patients, and it occurred less frequently with mixed TGCT – 22.22 % of patients (Table 8).

Stage S_1 occurred most frequently with yolk sac tumor, postpubertal-type (83.33 % of patients), though embryonal carcinoma and mixed TGCT occurred rather frequently at the same stage, too (64.71 % and 70.45 % of cases correspondingly). In stage S_1 90-100 % of testicular lesion occurred most frequently with yolk sac tumor, postpubertal-type (70.00 % of patients); the least percentage rate – with seminoma (20.00 % of cases) (Table 8).

Diagram 7.

Frequency of S categories depending on tumorous lesion level



	pS0	pS1
0-90 % lesion	54,32%	55,75%
90-100 % lesion	45,68%	44,25%
0-50 % lesion	22,22%	19,47%
50-100 % lesion	77,78%	80,53%

It should be emphasized that the decrease in the amount of patients in stage S_1, in relation to stage S_0, occurs only with seminoma and teratoma, postpubertal-type. As well as the amount of patients with embryonal carcinoma, yolk sac tumor, postpubertal-type and mixed TGCT in stage S_1, is, on the contrary, higher than the one in stage S_0 (Table 8).

Thus, we may come to the conclusion that, in general, irrespective the difference in the level of TGCT tumorous lesion in stages S_0 and S_1, the increased level of LDH, βhCG and AFP indicates a more unfavorable course of the disease, and it is approved by the increase in the amount of the patients with high level of the hormones mentioned above, when progressing in stages pT and pN. This fact is largely congruent with some of the publications [18-21]. At the same time, some literature presents the investigations, which prove that high

level of some seromarkers may be pseudopositive. For instance, it may respond to the production of βhCG by the pituitary gland in case of hypogonadism, which may develop with TGCT [22].

Besides, due to the mentioned above, it may be concluded that considerable tumorous lesion does not indicate the hormonal activity of the tumor and its relation to stages S_1 or S_2. But, on the contrary, the correlation between the high level of some seromarkers and embryonal carcinoma, yolk sac tumor, postpubertal-type and mixed TGCT is evident – the higher is the percentage of testicular tumorous lesion, the higher is the level of suspicion that the tumor may be hormonally active.

Table 8.

Distribution of TGCT depending on S categories and tumorous lesion level

TGCT	S category	Tumorous lesion level									
		0-90 %		90-100 %		0-50 %		50-100 %		Всього	
		Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value
Seminoma	S_0	58	47.54	64	52.46	20	16.39	102	83.61	122	81.33
	S_1	12	80.00	3	20.00	3	20.00	12	80.00	15	10.00
	S_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Embryonal carcinoma	S_0	6	66.67	3	33.33	5	55.56	4	44.44	9	26.47
	S_1	13	59.09	9	40.91	7	31.82	15	68.18	22	64.71
	S_2	0	0.00	1	100.0	0	0.00	1	100.0	1	2.94
Yolk sac tumor, postpubertal-type	S_0	1	100.0	0	0.00	1	100.0	0	0.00	1	8.33
	S_1	3	30.00	7	70.00	1	10.00	9	90.00	10	83.33
	S_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Teratoma, postpubertal-type	S_0	5	71.43	2	28.57	3	42.86	4	57.14	7	77.78
	S_1	1	100.0	0	0.00	0	0.00	1	100.0	1	11.11
	S_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Spermatocytic tumor	S_0	2	66.67	1	33.33	0	0.00	3	100.0	3	100.0
	S_1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	S_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Teratoma with somatic-type malignancy	S_0	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	S_1	1	50.00	1	50.00	0	0.00	2	100.0	2	100.0
	S_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Teratoma, prepubertal-type	S_0	2	100.0	0	0.00	2	100.0	0	0.00	2	100.0
	S_1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	S_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Choriocarcinoma	S_0	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	S_1	1	100.0	0	0.00	0	0.00	1	100.0	1	100.0
	S_2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mixed TGCT	S_0	14	77.78	4	22.22	5	27.78	13	72.22	18	20.45
	S_1	32	51.61	30	48.39	11	17.74	51	82.26	62	70.45
	S_2	1	100.0	0	0.00	1	100.0	0	0.00	1	1.14

Category «Distant metastasis»

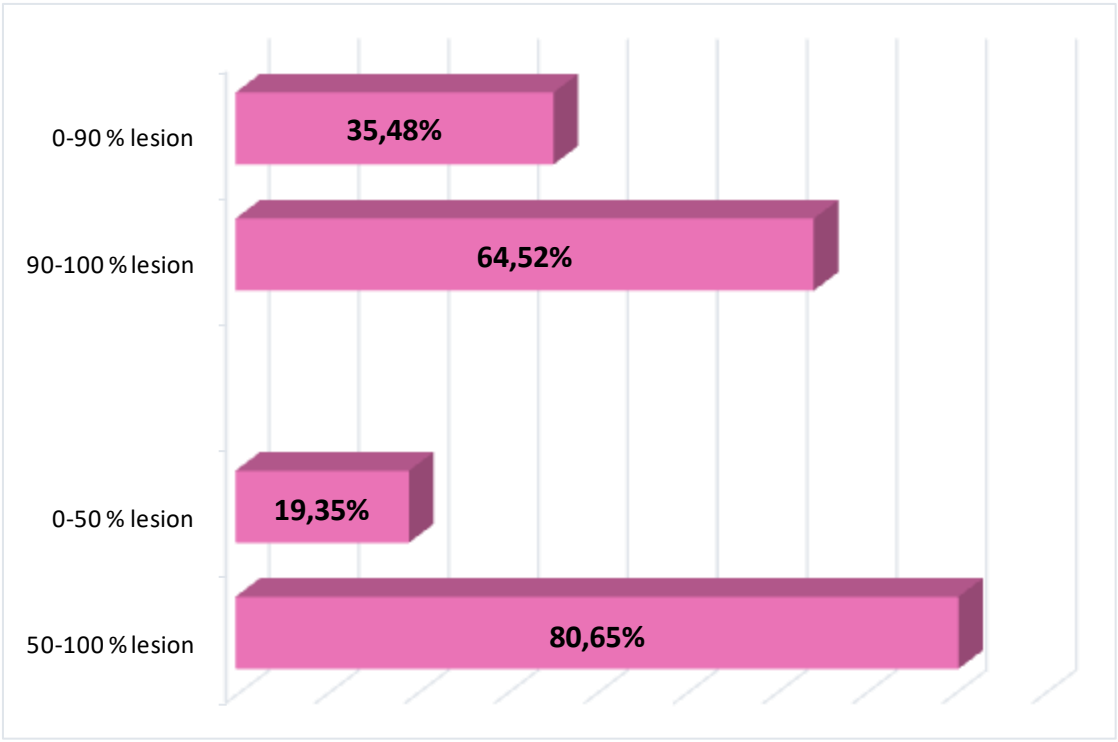
Distant metastasis were detected only in 10.30 % of all the observed TGCT cases. Among them, in 87.10 % of cases metastasis were located in lungs, 16.13 % and 6.45 % of cases – in liver and bones correspondingly. At that, 9.98 % of cases presented multiple localization, in 6.45 % of cases the lungs and liver were both damaged, in 3.23 % of cases – bones and the lungs.

The average percentage of the testicular tumorous lesion in cases with distant metastasis amounted to 83.55±6.66 % and it was not statistically different from the one in cases without distant metastasis (75.19±2.63 %), though, it had a tendency to increase in the moderate range (t=1.17).

It should also be emphasized that when TGCT damaged the 90-100 % of the testis, the frequency rate of the distant metastasis was 1.8 times higher than that of the 0-90 % of testicular lesion. If to compare the frequency rate of the distant metastasis development between 0-50 % and 50-100 % of testicular lesion cases, the result is even more evidently shows that distant metastasis developed 4.2 times more often in patients with a considerable tumorous lesion (Diagram 8).

Diagram 8.

Frequency of distant metastasis depending on tumorous lesion level



When analyzing the correlation of categories pT, pN and S with distant metastasis it was revealed that with the advance from stage pT_1 to stage pT_3 (pT_4 presented only two

cases), their percentage rate increased; at that, the distant metastasis were not registered in pT_1 stage patients. Patients in stages pN_2 and pN_3 with distant metastasis cases presented the percentage, much higher than the one in stages pN_0 and pN_1, which demonstrated a very low percentage rate. Besides, the indices of pN_0 stage were a bit higher than the ones in pN_1 stage, which can be explained by a higher percentage rate of more aggressive embryonal carcinoma and yolk sac tumor, postpubertal-type in stage pN_0. As to category S, only 1.23 % of patients presented distant metastasis in stage S_0, whereas every fifth patient in stage S_1 presented distant metastasis. Patients with TGCT in stage S_2 presented only two cases, one of them – with distant metastasis (Table 9).

Table 9.

Distribution of patients with distant metastasis depending on pT, pN and S categories

		pT categories							
		pT_1 (n=167)		**pT_2 (n=94)**		**pT_3 (n=38)**		**pT_4 (n=2)**	
		Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value
Distant metastasis	+	0	0.00	16	17.02	14	36.84	1	50,00
	–	167	100.0	78	82.98	24	63.16	1	50,00
		pN categories							
		pN_0 (n=195)		**pN_1 (n=37)**		**pN_2 (n=41)**		**pN_3 (n=28)**	
		Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value
Distant metastasis	+	7	3.59	1	2.70	12	29.27	11	39,29
	–	188	96.41	36	97.30	29	70.73	17	60,71
		S categories							
		S_0 (n=162)		**S_1 (n=113)**		**S_2 (n=2)**			
		Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value		
Distant metastasis	+	2	1.23	24	21.24	1	50.00		
	–	158	97.53	88	77.88	1	50.00		

In general, as it was mentioned above, distant metastasis affected every tenth TGCT patient, though embryonal carcinoma presented distant metastasis more often, if to be compared with other tumors (38.24 % of cases). Second frequent, as to the distant metastasis frequency rate, were mixed TGCT (14.77 % of patients). This is proved by the fact that, in the majority of cases (76.92 %), one of the component of TGCT was presented by embryonal carcinoma. At that, none of the patients with yolk sac tumor, postpubertal-type and teratoma, postpubertal-type presented distant metastasis, and seminoma presented only 2.67 % of cases. It should also be noted that the 90-100 % of tumorous lesion was registered much more often in patients with distant metastasis than in cases without the latter (Table 10).

Table 10.

Distribution of TGCT with distant metastasis depending on tumorous lesion level

TGCT	Distant metastasis	Tumorous lesion level									
		0-90 %		90-100 %		0-50 %		50-100 %		Всього	
		Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value	Absolute value	Percentage value
All TGCT	+	11	35.48	20	64.52	6	19.35	25	80.65	31	10.30
	–	154	57.04	116	42.96	56	20.74	214	79.26	270	89.71
Seminoma	+	1	25.00	3	75.00	0	0.00	4	100.0	4	2.67
	–	73	50.00	73	50.00	24	16.44	122	83.56	146	97.33
Embryonal carcinoma	+	6	46.15	7	53.85	3	23.08	10	76.92	13	38.24
	–	14	66.67	7	33.33	9	42.86	12	57.14	21	61.76
Yolk sac tumor, postpubertal-type	+	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	–	5	41.67	7	58.33	3	25.00	9	75.00	12	100.0
Teratoma, postpubertal-type	+	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	–	7	77.78	2	22.22	3	33.33	6	66.67	9	100.0
Spermatocytic tumor	+	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	–	2	66.67	1	33.33	0	0.00	3	100.0	3	100.0
Teratoma with somatic-type malignancy	+	0	0.00	1	100.0	0	0.00	1	100.0	1	50.00
	–	1	100.0	0	0.00	0	0.00	1	100.0	1	50.00
Teratoma, prepubertal-type	+	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	–	2	100.0	0	0.00	2	100.0	0	0.00	2	100.0
Choriocarcinoma	+	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	–	1	100.0	0	0.00	0	0.00	1	100.0	1	100.0
Mixed TGCT	+	4	30.77	9	69.23	3	23.08	10	76.92	13	14.77
	–	49	65.33	26	34.67	15	20.00	60	80.00	75	85.23

Therefore, the development of distant metastasis in TGCT occurs due to a considerable tumorous lesion level (especially in 90-100 % of tumorous lesion), which is a significant risk

factor of distant metastasis development, as well as the lymphogenic metastasis in advanced pN stages, and increased level of diagnostically significant hormones, though to a lesser degree.

We may also state that, taking into consideration distant metastasis, and on the whole, embryonal carcinoma is the most aggressive TGCT, when it is either single-component or is presented as an element of a multicomponent tumor, which is coherent with literature data [23].

Summary

1. On the time of presentation and examination of patients with seminoma and teratoma, postpubertal-type the number of patients in low tumor stage pT_1 typically prevail the one in stages pT_2–pT_4. And the number of patients with embryonal carcinoma, yolk sac tumor, postpubertal-type and mixed TGCT in more advanced stages of category pT prevailed the one in stage pT_1.

2. In TGCT, the pT stages increase was generally present with the increase of testicular tumorous lesion level, except for seminoma and embryonal carcinoma: seminoma was characterized by a high testicular tumorous lesion level, when presenting high index rate in initial pT_1 stage identification; as well as embryonal carcinoma, on the contrary, was less presented in category pT_1, though, at the same time, it was characterized by a low tumorous lesion of the testis.

3. Lymphogenic metastasis in TGCT, generally, did not occur frequently; at that, the testicular tumorous lesion level in patients with lymphogenic metastasis was higher than in the patients without lymphogenic metastasis. yolk sac tumor, postpubertal-type, embryonal carcinoma and mixed TGCT, though to a lesser extent, are the neoplasms, which metastasize by lymphogenic way even in case of low tumorous lesion level. As for seminoma and teratoma, postpubertal-type, they, on the contrary, metastasize by lymphogenic way less frequently, despite high testicular tumorous lesion level.

4. Increase in LDH, βhCG and AFP indicates a more unfavorable course of TGCT. Besides, considerable tumorous lesion in patients with seminoma it is not associated with hormonal activity of the tumor, and it is vice versa with embryonal carcinoma, yolk sac tumor, postpubertal-type and mixed TGCT.

5. Considerable tumorous lesion is connected with the development of distant metastasis in TGCT and is a significant risk factor of their development together with lymphogenic metastasis at the advanced stages of pN and increase in LDH, βhCG and AFP. The patients with embryonal carcinoma are most frequently affected by distant metastasis.

6. As to the pTNS categories, the most aggressive TGCT are: embryonal carcinoma and, in a lesser extent, yolk sac tumor, postpubertal-type. Less aggressive are: seminoma and teratoma, postpubertal-type; as for mixed TGCT, they are in intermediate position.

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