Epidemiological features of testicular cancer in the Slovak Republic – retrospective study

Epidemiologické charakteristiky nádorov testis v Slovenskej republike – retrospektívna štúdia

Ondrusova M.[1,2], Ondrus D.[3,4]

[1] Department of Cancer Epidemiology, Cancer Research Institute, Slovak Academy of Sciences, Bratislava, Slovak Republic
[2] Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic
[3] Department of Oncology, Comenius University Medical School, St. Elisabeth Cancer Institute, Bratislava, Slovak Republic
[4] National Cancer Registry of the Slovak Republic, National Health Information Centre, Bratislava, Slovak Republic

Summary

Backgrounds: Testicular cancer (TC) is quite a rare malignancy, however, its medical importance has risen due to the rapid growth in incidence in the last three decades. Age-adjusted mortality rates have fallen within the space of 20 years. ***Patients and Methods:*** A national retrospective descriptive study evaluated the data of 1,805 patients with 1,832 TC diagnosed in Slovakia from 1993 to 2002. Patients and medical questionnaires, case histories, clinical symptoms and objective parameters in all cases of TC were analyzed. ***Results:*** The average age-adjusted incidence (to the world-standard population) (1993–2002) was 6.2/100,000; mortality 0.5/100,000 of males. When comparing the risk factors between the group of patients with bilateral and unilateral TC, the most frequent risk factor was inguinal hernia (8.6%, p = 0.0026). 3% of patients developed a bilateral TC. Metachronous tumors were found in 70.4% of patients with bilateral TC. The average age at diagnosis of the first tumor in patients with bilateral TC was 27.5 years (p = 0.001); most of them (55%) were diagnosed between the age of 20–29 years. The average age of patients with unilateral TC was 34 years. 8 patients presented with a synchronous bilateral tumor, 47 patients had a second tumor diagnosed 2–302 months after primary orchiectomy. In the case of seminomas, the time interval between the first and second tumor was 85 months, while for nonseminomatous tumors, the same interval was 72 months (a statistically insignificant difference). The median follow-up time of patients with TC was 112.5 months (range of 7–342 months), five-year survival was 96.2%. ***Conclusion:*** Further studies of the epidemiologic characteristics of TC are inevitable in order to define the risk factors of the disease and the possibilities of timely therapeutical intervention.

Key words

testicular cancer – epidemiology – risk factors – survival – population cancer registry

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Martina Ondrušová, Dr., PhD.
Department of Cancer Epidemiology
Cancer Research Institute
Slovak Academy of Sciences
Vlárska 7
831 09 Bratislava
Slovak Republic
e-mail: martinacuninkova@hotmail.com

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Súhrn

Východiská: Nádory testis (NT) sú zriedkavou malignitou, ich medicínska závažnosť však spočíva v prudkom náraste hodnôt incidencie v posledných troch desaťročiach. Mortalita má v posledných 20-tich rokoch klesajúci trend. ***Pacienti a metódy:*** V celonárodnej restrospektívnej deskriptívnej štúdii sa hodnotilo 1 805 pacientov zo Slovenska, u ktorých sa diagnostikovalo 1 832 NT v rokoch 1993–2002. U chorých sa analyzovali údaje v zdravotnej dokumentácii a medicínske dotazníky, klinické príznaky a objektívne parametre pri klinickom vyšetrení. ***Výsledky:*** V rokoch 1993–2002 bola priemerná štandardizovaná incidencia (prepočítaná priamou metódou na svetovú štandardnú populáciu) 6,2/100 000; štandardizovaná mortalita dosiahla 0,5/100 000 mužov. Pri porovnávaní rizikových faktorov medzi skupinou pacientov s bilaterálnymi a unilaterálnymi NT bola najčastejšie sa vyskytujúcim rizikovým faktorom ingvinálna hernia (8,6 %, p = 0,0026). V 3 % prípadov chorých sa zistil bilaterálny NT. Z tohto počtu sa metachrónny výskyt zistil u 70,4 % pacientov. Priemerný vek pacientov v čase diagnózy prvého NT u pacientov s bilaterálnym ochorením bol 27,5 rokov (p = 0,001); väčšina z nich (55 %) mala NT diagnostikovaný vo veku 20–29 rokov. Priemerný vek pacientov s jednostranným NT bol 34 rokov. Osem pacientov malo synchrónny výskyt bilaterálneho nádoru, u 47 pacientov sa druhý NT diagnostikoval v rozpätí 2–302 mesiacov od prvej orchiektómie. V prípade seminómov bol časový interval medzi manifestáciou prvého a druhého NT v priemere 85 mesiacov, u neseminomatóznych nádorov bol tento interval 72 mesiacov (štatisticky nevýznamný rozdiel). Medián sledovania pacientov s NT bol 112,5 mesiacov (rozpätie 7–342 mesiacov), 5-ročné prežívanie bolo 96,2 %. ***Závery:*** Ďalšie štúdium epidemiologických charakteristík NT je nevyhnutné pre definovanie rizikových faktorov ochorenia a možností včasnej liečebnej intervencie.

Kľúčové slová

nádory testis – epidemiológia – rizikové faktory – prežívanie – onkologický register

Introduction and Aims

In the last two decades there has been noticed a world-wide increase of the testicular cancer (TC) incidence. TC is quite a rare malignancy that presents 1–2% of all the malignancies in the male population with European incidence rates ranging from around 3/100,000 in Spain through to more than 15/100,000 in Denmark and Switzerland [1]. The epidemiological importance has come out from the rapid growth of the incidence in young male population in the last decades, with pick and plateau in the age between 20–40 years. This can cause a long-term disability and/or the invalidity of the fertile male population. It also has a negative influence on their social, economic and psychical life.

Despite the fact that time-trend occurrence of the disease is well-known in various countries with population-based cancer registries, the aetiology is relatively unknown. The success reached in the diagnosis and following treatment of TC has placed the Slovak Republic, as far as the relationship between incidence and mortality is concerned, on the same level with some developed countries of Northern and Western Europe.

In the Slovak Republic there has been long-term descriptive data on the incidence and mortality of TC in the National (population-based) Cancer Registry [2]. However, because of quite rarity of the disease there were not analyses of the potential risk factors, geographical distribution, quality of diagnostics and therapy, and patient's survival. Taking these facts into account, a national retrospective study evaluating the data of patients with TC diagnosed in the Slovak Republic between 1993–2002 was designed as the purpose of this retrospective study.

Patients and Methods

The analysed study group of 1,805 patients is represented by 1,832 primary TC, 55 of them were with bilateral disease (27 patients both TC in the period of 1993–2002). Bilateral tumors were classified as synchronous if they were diagnosed within a month of each other occurrence. Basic identification data about these patients were obtained from the heads of all the departments of urology, oncology and surgery in the Slovak Republic and confirmed through cancer registry. The histology of the removed testicle was primarily evaluated, consulted or revised by pathologist at the Slovak reference centre. All the patients were examined at the Centre for diagnostics and comprehensive treatment of TC, non-malignant lesions were excluded. The questionnaires given to the patients or their family members were focused on the risk factors in personal and familial history, diagnostics, therapy and follow-up had been created and later on assigned to all the patients, to first-contact physicians of the patients and to living relatives of dead patients. The questionnaires for patients were filled out with the urologist at the medical examination of the patients at the mentioned Centre. The special postal questionnaires were designed for the patients who refused the following-up and examination at the Centre. All the patients who did not come up to the examination and did not answer the postal questionnaires were contacted by phone or e-mail. Those ones who arrived at the Centre with their previous medical histories were examined again in order to get their detailed medical history by means of physical examination, chest X-ray, CT imaging and blood tests. The patients' previous diagnosis, histology and treatment were reviewed by the same urologist. When there was a suspected positive familial history in their questionnaires, the blood-related family members were invited to the examination as well. The personal history from the questionnaires was confirmed by the patients' medical histories, which are usually self- delivered. The obtained data was analysed and revised with the one that is kept in the National Cancer Registry of the Slovak Republic. The study was carried out and accomplished as a part of the grant project VEGA 1/9326/2 approved by the ethical board of the Research Grant Agency of the Ministry of Education of the Slovak Republic and Slovak Academy of Sciences.

Results

From the database of 1,805 patients (n = 1832 TC – because of bilateral dis-

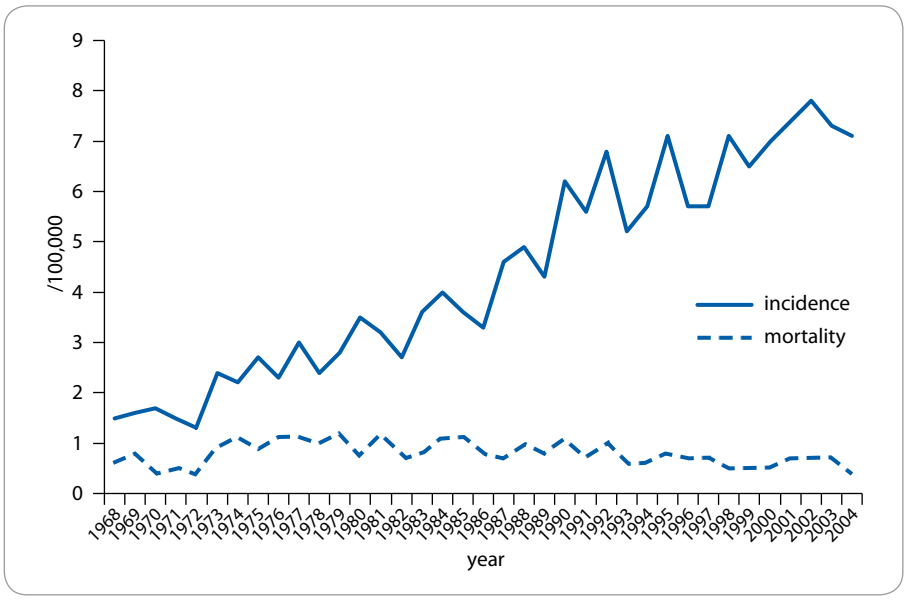

Fig. 1. Age adjusted (to the world standard population) incidence and mortality of testicular cancer in the Slovak Republic, 1968–2004.

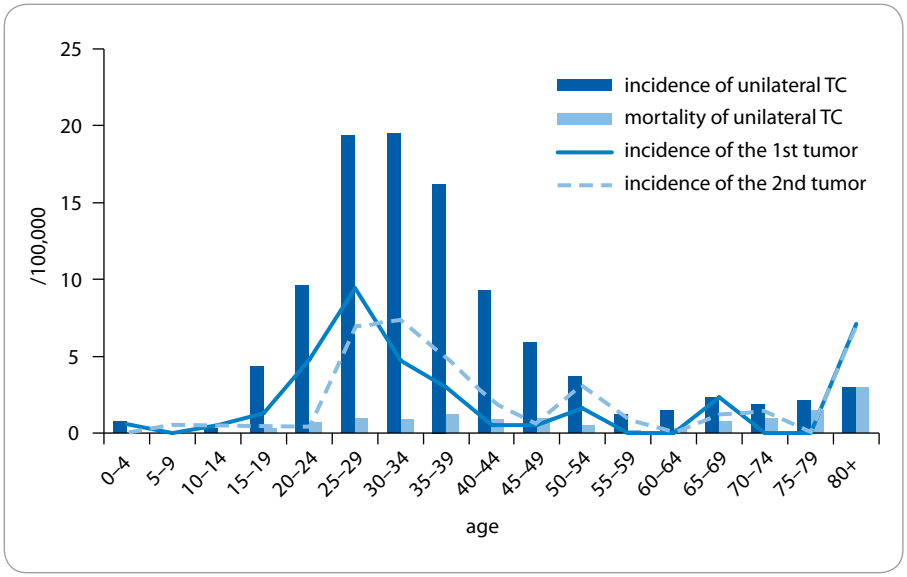

Fig. 2. Age-specific incidence and mortality of unilateral testicular cancer, compared to the age-specific incidence of the first and the second primary cancer in bilateral disease.

ease in this period) diagnosed between 1993–2002 a complete personal and family history was found out in 1,660 patients (92%), after having back the questionnaires from 1,314 patients (72.8%). 1,751 patients (97%) had their diagnosis of tumor confirmed histologically. The average age-adjusted incidence (to the world-standard population) was 6.2/100,000, while the age-adjusted mortality reached 0.5/100,000 (Fig. 1) supplemented by the contemporary data from the National Cancer Registry of the Slovak Republic. The highest age-specific incidence was in 30–34 years old males (19.5/100,000), when the most of cases were diagnosed in the age group of 15–44 years (75.3%) (Fig. 2). The median follow-up time of the patients was 112.5 months (range 7–342), overall survival was 91% and the expectation of a 5-year survival was 96.2%.

From the study group, 3% of the patients developed a TC in the solitary testicle. Contralateral testicular biopsy was not made at the time of diagnosis. The age-specific incidence of bilateral TC shows a significant shift to lower age groups when diagnosed with the first tumor (mean age 27.5 years, p = 0.001), as well as the second primary tumor (mean age 32 years, p = 0.05) (Fig. 2). Metachronous tumors were found in 70.4% of the patients with bilateral disease. The mean age at diagnosis of the first tumor was 27.5 years; most of them (55%) were diagnosed between the ages of 20–29. The mean age of the metachronous second tumor occurrence was 32 years. Thus, the patients who had developed TC before the age of 30 and the histology of that tumor was a seminoma were at a higher risk of developing a contralateral tumor. Eight patients presented with synchronous bilateral tumors, 47 patients had the second metachronous tumor diagnosed 2–302 months (mean 5 years) after primary orchiectomy. In the case of seminomas, the mean time interval between the detection of the first and second tumor was 85 months, while for nonseminomatous tumors this interval was 72 months. However, no statistically significant difference between these intervals was remarked.

Germ cell TC represented 95.8%; tumors consisted of only one histological type represented 58.2%. The most frequent pure histological type was seminoma (38.4%) and mixed tumors with seminoma (12%).

Analysed risk factors are divided into two groups: objective, found in patients' medical history and the ones that were obtained from the patients' questionnaires and interviews (without previous medical record). The most frequent objective risk factor was inguinal hernia (8.6%), cryptorchidism (6.4%), congenital genetic diseases (e. g. Down syndroma – 3.4%), bilateral TC (3%) and familial occurrence of the TC (2.8%). From the group of non-confirmed risk factors obtained from medical histories the most frequent were: testicular trauma in 8.4%, history of orchitis (4.6%) and epididymitis (2.8%). The statistical significance of the risk factors occurrence

was compared between the groups of unilateral and bilateral TC. The risk factor must have influenced the testis with a tumor, which means that in the case of bilateral tumors it must have been diagnosed on both testes. The analysis proved a statistically significant influence of family occurrence ($p < 0.001$), inguinal hernia ($p = 0.002$) and cryptorchidism ($p = 0.05$), however testicular trauma and other factors mentioned above were not statistically significant.

When comparing the risk factors and histological types of tumors, no relation between histological type with a higher metastatic potential and occurrence of the risk factor was found. On the contrary, there was found a weak statistic significance ($p = 0.02$) in lower diagnosing of embryonal carcinoma (histological type with worse prognosis) when cryptorchidism occurs in history. When the occurrence of seminomas and nonseminomas in the groups of patients with and without risk impact was analysed, there was a statistically significant ($p = 0.001$) higher occurrence of seminomas among patients with inguinal hernia.

From the questionnaires, mother's age was analysed at the time of delivery in 91% of the cases. Median of the mother's age was 31 years (range 17–45 years, mean 25.9 years, modus 23 years).

Discussion

Epidemiological and clinical significance of TC has come out from a rapid growth of their incidence mainly in the last decades, in some countries to epidemic proportions [3,4,5,6]. The important socio-economic factor of this disease is its high increase of the incidence mainly in adolescent and adult males.

In several European countries with cancer registries of a high quality there was recorded 3–4 times fold increase of the disease [7,8], and the highest increase was recorded in countries with previously higher rates than others [9]. In 2002 there was estimated 48.613 new testicular cancer diagnosis in the world, which represented 0,9% of all the tumors in males and the age-adjusted incidence (to the world standard ratio) 1,5/100.000 [10].

The highest incidence rate of TC was estimated in countries of Western Europe (7,9/100,000) and Northern Europe (5.4/100,000), in the USA it was mainly in the North. The lowest incidence was recorded in Africa (0.4–0.8/100.000), Asia (0.5–1.4/100,000), some countries of Eastern and Southern Europe, tropical America and Polynesia (1,7/100,000) [11,12,13,14,15].

During more than three last decades the National Cancer Registry of the Slovak Republic noticed a 4-times fold increase of the TC standardized incidence, from 1.5/100,000 in 1968 to 7.1/100,000 in 2004 [14]. According to the results of this study there is strong evidence that the increase of the incidence will continue in the next years. Rising of the TC incidence in many countries of the world, documents the results of many analytical studies [15,16,17,18,19,20]. The Slovak Republic is a country with middle rates of the standardized TC incidence.

One of the epidemiological characteristics of TC is stabilisation or decrease of their mortality, mainly in the well-developed countries of the world. TC mortality rates have fallen by about 70% in the United States and Western Europe since 1970s. In Central and Eastern Europe, however, such rates have decreased since the late 1980s as a result of later availability of these (mainly former communistic) countries to modern treatment modalities [21]. In several Eastern Europe countries, where death rates are currently highest (Bulgaria, Czech Republic, Hungary, Poland – more than 1/100,000), the rate of decrease was relatively low, slower and later declines imply that the high cost of appropriate treatments together with inadequate patient management systems are responsible for the high mortality rates and less favourable trends [1]. In males aged 45 and younger, mortality rates fell by about a third in the late 1980s by comparison with rates registered in the 1970s, 500 deaths per year in Europe are prevented now [21]. Decrease of the age-adjusted TC mortality has been confirmed in this study as well, from 0.6/100,000 in the year 1968 (when the incidence was 1.5) to 0.3/100,000 in 2002 (when the incidence grew to 7.3).

The age-specific TC incidence has bimodal shape, with the peak and plateau in 20–44-year-old males caused mainly by the occurrence of germ cell tumors (most of them seminomas) and the second peak in their 60-ties, caused mainly by lymphomas and non-germ cell tumors. There can also be a first smaller peak in the youngest age groups, caused mainly by the occurrence of yolk sac tumors and teratomas in childhood. The age-specific incidence curve reflects the histological composition of tumors in the specific ages [22]. Patients' mean age is about 10 years lower when occurrence of nonseminomatous tumors, comparing to seminomas. In our study there was a peak for nonseminomatous tumors in 25–29-year-old males, while in seminomas the age ranged from 35 to 39. The highest overall incidence rate was recorded in 30–34-year-old males, which was also confirmed by the results of other studies [23,24]. Nevertheless, there is some information on lowering of the age groups mainly in bilateral occurrence of the disease [25], which was found out also in our study. The average age of patients when the first tumor occurred was 27.5 years, compared to 34 years at unilateral disease ($p = 0.001$) and 32 years when the second primary tumor in bilateral disease ($p = 0.05$) occurred. It is important to mention that some scientists recorded the fact that a birth-cohort effect is more important determinant factor of the risk than the age of diagnosis [26,27].

The age-specific mortality rate is decreasing with the age of the patients and since it is an official mortality, it can be influenced by other causes of deaths in the older age-groups, mainly cardiovascular diseases.

So far, the aetiology of TC has been poorly characterized, despite a considerable research effort [28]. In our study the most frequent risk factor was the inguinal hernia, however, it does not take into consideration simultaneous occurrence of cryptorchidism, which can sometimes be a counfounding factor when evaluating the risk [29]. In some prospective studies, which only evaluated the influence of inguinal hernia without simultaneous cryptorchidism, no relation with TC was found [30]. High occurrence of inguinal hernia and its significant influence to the risk of TC described in some case-control studies [31] and also our study (when com-

paring the groups of patients with unilateral and bilateral TC with the risk factors ($p = 0.0026$) is probably affected by this selective bias. Moreover, we found out a significant occurrence of pure seminomas ($p = 0.0006$) and other germ cell tumours with a seminoma component ($p = 0.0125$) when inguinal hernia occurred. This is in a contradiction with the theory of Matoska et al [32] on higher occurrence of poor prognosis histological types when any risk factor was performing. However, it does agree with the results of Prener et al [33] for the risk of inguinal hernia and the occurrence of seminomas. According to the Evidence Based Medicine (EBM) at the level I in occurrence of TC there is only cryptorchidism, with odds ratio 3.5–17.1 [31,34]. Newborn with cryptorchidism have 2.5–9 times higher risk of TC developing [35], however, only 5–10% of all the TC patients had cryptorchidism before [36,37]. According to the analysis, orchidopexy is needed to be done between the 6th month and the 2nd year of male life [18]. A surgical correction of cryptorchidism does not decrease the risk of TC occurrence significantly, but the spontaneous testicular descensus does [26]. The analysis of the influence of trauma testis can be affected by a recall bias. In our study group of 148 patients with trauma testis, only 11.5% visited their urologist regarding this problem. When comparing the occurrence of trauma in the group of patients with unilateral and bilateral TC, no statistical significance was confirmed. On the other hand, testis with clinically asymptomatic tumor can be more fragile and more inclined to a volume of traumatic consequences, which may be the cause of clinical manifestation of a tumor [38]. Recall bias is less evident in a positive association between some sporting activi ties (e. g. horseback riding, cycling etc.) and the occurrence of TC [3,38,39], in the instances when scrotum and testes can be injured for a long time or in touch with leather and some chemicals [37]. If trauma has influence on the risk of TC, it is mainly in seminomas and older patients with longer exposition and possibility of more extensive tumor development [39]. However, we did not confirm significantly this fact ($p = 0.5489$) in our study.

According to level II.A of EBM, the second more important risk factor is bilateral occurrence of TC. Bilateral occurrence is about 2–5% of all the cases [40,41], cumulative incidence in 15-year-old males is 1.2–3.4% and in 25-year-old males it is 5.2%. We recorded 3% of bilateral TC, the risk of occurrence of contralateral tumor was 16 times higher, compared to Dieckmann et Pichlmeier [31] who described 25 times higher risk. The second primary tumor develops mainly within 5–10 years after the first tumor [41,42]. Whereas the present study says that most of the tumors (21.5%) developed within two years after the first cancer (range, 2–302 months). With lower age of the patient when manifesting the first tumour, there is higher risk of the occurrence of second primary tumor. There is controversial evidence that chemotherapy could prevent or more likely delay the appearance of invasive or clinically manifested tumors [41]. The most frequent histological type of metachronous bilateral tumor is seminoma [40] and in our study it was presented in 54% and 51% respectively (the first and second primaries), histological types where not the same on both testes in 59% of cases. We recorded simultaneous tumors in 0.43% of all the study cases, which correlates with findings of Ondrus et al [43] – 0.5%; however, the histological findings were different in 71%. The same histology occurs in metachronous tumors in about 33%, a little bit more in simultaneous tumors [40]. In conclusion, since the patients with unilateral TC have a higher risk of bilateral occurrence, Oliver [44] advises a contralateral biopsy at the time of first tumor diagnosis. When finding carcinoma in situ diagnosis, it is necessary to follow up the patient.

According to the III.A level of EBM there is a strong influence of familial occurrence of TC, which was supported by some case-control studies [31, 45]. The ratio of patients whose father or brother had TC produces 2.8% in present study, against 1.67% in the study of Hemminki et Li [45] and overall range 1–2.8% [31,46]. An overall family risk for sons of TC fathers is 3.78 and 8.58 for brothers. There was not found out a significant difference between the occurrence of seminomas and teratomas among family occurrence in fathers and sons, but significant difference between brothers and pure versus mixed tumors [45]. In our study we did not confirm a significant difference between the occurrence of seminomas and nonseminomatous tumors ($p = 0.1136$), however, according to Hemminki et Li [45] the risk increase with pure teratomas to 12 and seminomas to 10 in both brothers. In the case-control study of Coupland et al [47] a higher risk of TC was recorded in sons of very young mothers, premature born males and males with lower birth weight. However, this is in a contradiction with some other studies that describe a rise of the risk with increasing mother's age at the time of childbirth. Weir et al [18] described odds ratio 0.5 for mothers who were 20 year old and younger at the time of conception, compared to 20–24-year-old women. Swerdlow et al [48] discovered an influence of mother's age on a risk of TC only in first born sons, in whom seminomas develop predominantly, with odds ratio 22.5 for mothers older than 40. On the contrary, in the study of Dieckmann et al [49] the odds ratio for 30 years old mothers was only 0.67. In our study the average mothers' age at the time of childbirth was 25.9 years. Dusek et al [50] suggest that maternal age over 20 years significantly reduced the risk of TC, however the influence of mothers' age on the risk of the occurrence of TC is still not clear. It is probably higher with the lowest as well as highest age groups. Descriptive studies recorded an influence of testicular viral infections, mainly mumps orchitis [29]. When comparing the groups of patients with bilateral and unilateral disease occurrence in our study, we did not find significant difference in orchitis and epididymitis occurrence ($p = 0.6986$, 0.7444 respectively), as these two diseases can be misinterpreted. Also orchitis was not significantly connected to any histological type of tumors, not even the seminomas compared to nonseminomatous tumours. It was not possible to evaluate HIV infection, because in the Slovak Republic there are only about 150 patients diagnosed with HIV + and none of them has TC. We also did not evaluate the influence of EBV and CMV infections, which can be connected to TC [29].

Genetic diseases were recorded in our study in 3.4% patients, most of them (41.9%) were congenital heart diseases, oligofrenias not otherwise specified (21%), urogenital anomalies (12.9%) and Down syndroma (4.8%). According to Krizan [51] some of the chromosomal aberations of autosomas (e. g. Down syndroma) can be associated with immunity failure and higher risk to all tumors, testicular included. In our study we confirmed more frequent occurrence of tumors with histologically worse prognosis, mainly embryonal carcinoma ($p = 0.05$) and immature teratoma ($p = 0.05$) in a group of patients with genetic diseases.

Conclusion

The secular trend of TC increase was recorded almost all over the world. It has increased in the Slovak Republic 4–5 times since 1968, which is one of the highest increase in all the malignant diseases (lung cancer in males and breast cancer in females included).

The only methods how to decrease mortality of patients with TC, can be early detection and risk-adapted treatment in specialised centres according to the histology and clinical stage using standardized guidelines and long-term follow-up of patients with this malignancy.

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