

Epidemiology and treatment delay in testicular cancer patients: a retrospective study

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Received: 8 February 2007 / Accepted: 22 May 2007
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Abstract

Introduction Testicular cancer (TC) is a quite rare malignancy, although its medical importance is growing due to a rapid growth in incidence. The recent age-adjusted incidence in the Slovak Republic attained 6.9/100,000; mortality was 0.4/100,000. Incidence has increased by 80% in the period 1968–2003. Diagnostic and treatment delay may have an impact on overall survival.

Materials and methods A national descriptive study evaluating the data of patients with TC diagnosed in Slovakia in the period 1993–2002 was designed. Patients were analyzed using medical questionnaires, case histories, clinical symptoms, parameters such as data of treatment onset and treatment approaches, histology of the tumor, the stage of disease, response to treatment, and the follow-up period in all 1,832 cases of TC.

Results The average incidence (1993–2002) was 6.2/100,000; mortality was 0.5/100,000. The median follow-up time of the patients with TC was 112.5 months, overall survival was 91% and 5-year survival was 96.2%. Mortality decrease and survival improvement, despite the incidence increase, are the result of not only an effective treatment, but also early diagnosis of each case. The overall treatment delay (mean time of 150 days) shows that young males are generally poorly informed about the possibility of TC occurrence.

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

Keywords Epidemiology of testicular cancer · Clinical stage · Diagnostic · Survival · Treatment · Treatment-delay

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Introduction

A worldwide increase in testicular cancer (TC) incidence has been noticed over the last two decades. TC is a quite rare malignancy that represents 1–2% of all 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 [4]. The social and epidemiological importance of TC has emerged from the rapid growth of its incidence in the young male population over recent decades, with a peak and plateau at an age between 20 and 40 years. Success achieved in diagnosis and follow-up treatment of TC has placed the Slovak Republic, as far as the relationship between incidence and mortality is concerned, at the same level with some industrialized countries of Northern and Western Europe. However, some treatment delays caused by the patients themselves, general practitioners or specialists may occur.

Aims

Long-term descriptive data on the incidence and mortality of TC are available in the national (population-based) cancer registry of the Slovak Republic. However, because of the relative rarity of the disease, analyses of the quality of diagnostics and therapy are not available. Taking these facts into account, a national retrospective study evaluating the data from patients diagnosed with TC in the Slovak Republic from 1993 to 2002 was designed.

Materials and Methods

The analyzed study group is represented by 1,832 patients with primary TC. They were all diagnosed in the Slovak Republic in 1993–2002. The histopathological diagnosis and tumor classification of most cases (71%) was primarily evaluated or reviewed by a single specialist—urological histopathologist prior to definitive treatment. All patients from the study group were followed-up by the one urologist in the Slovak Centre for Diagnosis and Complex Treatment of Testicular Cancer, the diagnostic and treatment approaches were evaluated, and non-malignant lesions were excluded. Three types of questionnaires focusing on risk factors in personal and family history, diagnostics, therapy, and dispensarization were created and later assigned to all patients, to primary-care physicians of those patients, and to living relatives of dead patients. The questionnaires were tested in a pilot study. The final questionnaires for patients were filled out with the urologist at the

medical examination of the patients. The special postal questionnaires were designed for patients who refused dispensarization and examination. The questionnaire return rate was 72.8%. All patients who did not come to the examination and did not answer the postal questionnaires were contacted by phone or e-mail. Those who arrived at the examination with their previous medical histories were examined again in order to obtain their detailed medical history by means of physical examination, chest X-ray, computed tomography (CT) imaging, and blood tests. The patients' previous diagnosis, histology, and treatment were reviewed by the same urologist. The obtained data were analyzed and revised against that kept in the National cancer registry of the Slovak Republic.

Results

A complete personal and family history from the database of 1,805 patients ($n = 1,832$ testicular tumors) diagnosed in the period 1993–2002 was taken in 92% of the patients, after receiving questionnaires from 72.8% of patients. Ninety seven percent of the patients had their diagnosis of tumor confirmed histologically. The average age-adjusted incidence (to the world-standard population) was 6.2/100,000. The average age-adjusted mortality was 0.5/100,000 (Fig. 1). The highest age-specific incidence was in 30–34-year-old males (19.5/100,000), while most cases were diagnosed in the age group of 15–44 years (75.3%). The median follow-up time of the patients was 112.5 months (range 7–342), overall survival was 91%, and the five-year survival rate was 96.2%.

Three percent of patients from the study group developed a second primary TC. Contralateral testis biopsy was not made at the time of diagnosis. Bilateral tumors were classified as synchronous if they were diagnosed within a month of each other occurrence. Eight patients were presented with synchronous bilateral tumors, 47 patients had a secondary tumor diagnosed 2–302 months after primary orchiectomy (Fig. 2). The mean time interval between the detection of primary and secondary metachronous tumors was five years. In the case of seminomas, the mean time interval between the detection of the first and second tumor was 85 months, while for nonseminomatous TC this interval was

Fig 1 Age-adjusted incidence and mortality of testicular cancer in the Slovak Republic

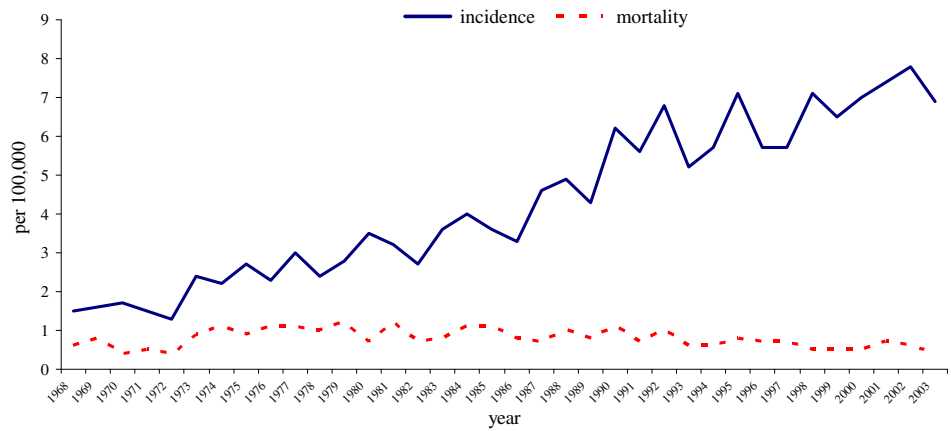
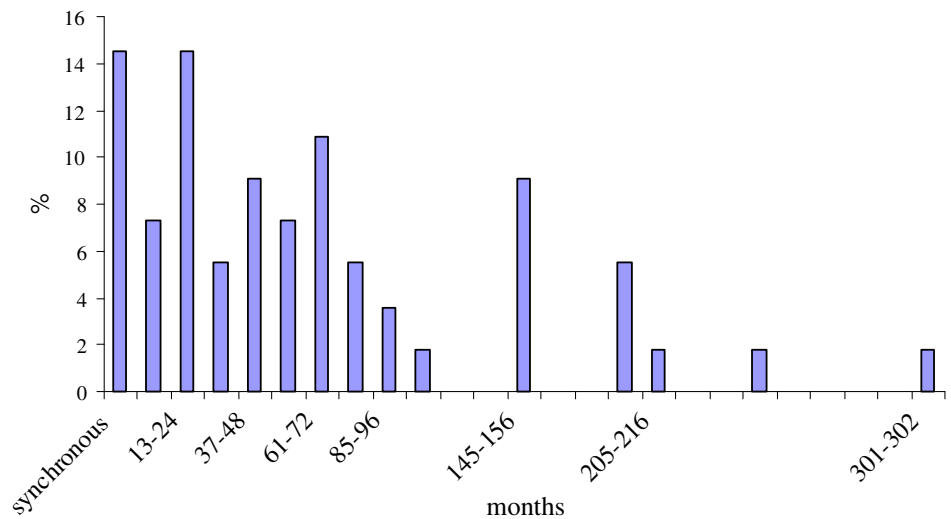


Fig 2 Time interval to the occurrence of the second primary testicular tumor



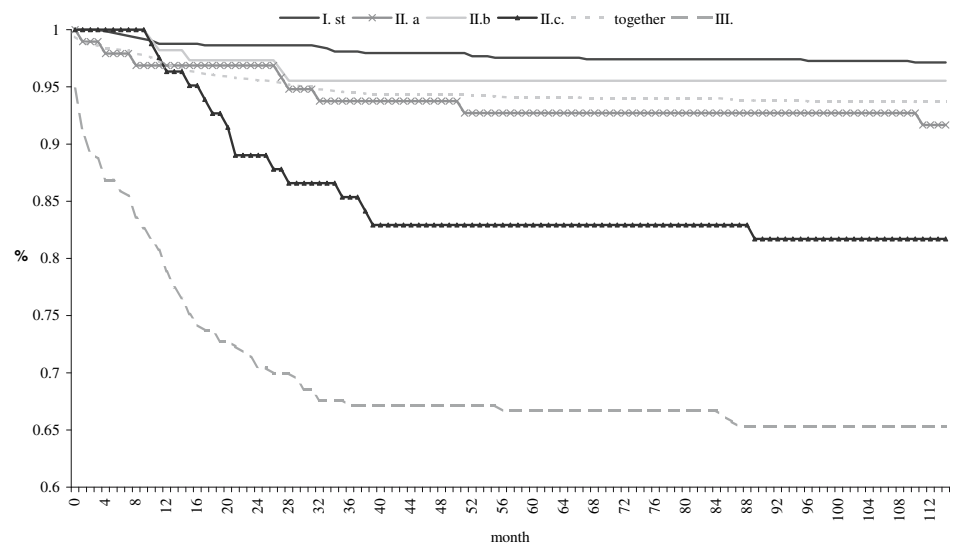
72 months. However, no statistically significant difference between these intervals was observed.

Diagnostic delay and treatment delay were analyzed in 1,807 patients, as in cases of bilateral metachronous tumors there were no analyzed dates of the symptoms of the second tumors and in the group of simultaneous bilateral tumors these dates were identified in only two patients. The date of diagnosis was the date of orchiectomy or the beginning of the primary neo-adjuvant chemotherapy. Patient's delay (from onset of the initial symptoms to visiting a doctor's office) was analyzed in only 143 patients (7.9%), with a median of 35 days (range 0–3,267 days, mean 140.5 days). The general practitioner's delay (from visiting a GP's office to visiting a specialist's office) was analyzed in 106 patients (5.9%), with a mean time of 5.7 days (range 0–90 days, median 1 day). Specialist's delay (from the visit to a specialist's office to the date of correct diagnosis of testicular cancer) was analyzed in 343

patients (19%), with a of median five days (range 0–2,980 days, mean 20.1 days). The most frequent misdiagnosis made by GPs and/or specialists and analyzed in 148 patients was orchiepididymitis (31%), the median of treating the supposed inflammation was 30 days (range 7–2,160 days, mean time of 189 days). Other nonstandard diagnoses and/or treatment were: scrotal orchiectomy (10.1%), puncture of the testis (10%), analgesic symptomatic treatment (8.1%), and enucleation of a tumor in unilateral disease (6.1%). About 2.7% of the patients were treated symptomatically despite the higher specific tumor markers. About 6.1% of the patients had inguinal lymph-node dissection with findings of TC metastasis, which meant previous surgery by the scrotal approach (e.g., after diagnostic puncture of the testis, puncture of the hydrocele, orchidopexy, etc.).

The clinical stages at the time of diagnosis were recorded in only 68.8% of all patients. Clinical stage I was most frequent (40.1%), followed by clinical stage

Fig 3 Survival of testicular cancer patients according to clinical stage



IV (11.6%). The probability of five-year survival according to the clinical stage at the time of diagnose is shown at Fig. 3. However, in the clinical stage IS (elevated tumor markers only, 0.9% of patients) and in the clinical stage III (0.3% of the patients) nobody died.

Discussion

The epidemiological and clinical significance of TC is due to the rapid growth of its incidence, mainly over the last few decades; in some countries this reflects epidemic proportions [1, 5, 10, 27]. A 3–4 times higher increase of incidence has been recorded in several European countries with high-quality cancer registries [13, 18], and the greatest increases have been recorded in countries with previously higher rates than others [29]. In 1993–1997 there were about 49,000 TC diagnosed annually, which represented 0.9% of all tumors in males [9].

The highest incidence rate of TC was recorded between 1993 and 1997 in Western Europe (8.1/100,000) and Northern Europe (5.9/100,000). In Australia and New Zealand the incidence rate was 6.2/100,000, in Northern America and Southern America with medium temperatures it was about 4/100,000. The lowest incidence was recorded in Africa (0.1–0.6/100,000), Asia (0.8–1.5/100,000), some countries of Eastern and Southern Europe, tropical America, and Polynesia (2.2–2.4/100,000) [9, 14, 24, 25].

Over the last three decades the National cancer registry of the Slovak Republic has noticed a quadrupling of the standardized incidence of TC, from 1.5/100,000 in 1968 to 7.3/100,000 in 2002 and 6.9/100,000 in 2003 [23]. According to the results of this study there is strong evidence that this increasing incidence will continue over the next years. The results of many analytical studies [2, 16, 17, 20, 28, 30] prove this increase of TC incidence in many countries of the world. The Slovak Republic has intermediate rates of standardized TC incidence.

One of the epidemiological characteristics of TC is stabilization or decrease of mortality, mainly in the developed countries of the world. TC mortality rates have fallen by about 70% in the United States and Western Europe since the 1970s. In Central and Eastern Europe, however, these rates have decreased since the late 1980s [15] as a result of the later availability of modern treatment modalities in these (mainly former communist) countries. In several Eastern Europe countries, where death rates are currently highest (Bulgaria, Czech Republic, Hungary, Poland, with rates of more than 1/100,000), the rate of decrease was 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-favorable trends [4]. In males aged 45 and younger, mortality rates fell by about a third in the late 1980s compared with rates registered in the 1970s, 500 deaths per year in Europe are now prevented [15]. Decrease of the age-adjusted testicular cancer mor-

tality has been confirmed in this study as well, from 0.6/100,000 in the year 1968 (when the incidence was 1.5/100,000) to 0.3/100,000 in 2002 (when the incidence grew to 7.3/100,000).

Mortality decrease and survival improvement despite the incidence increase are the result of not only effective treatment, but also early diagnosis of each case. There is evidence that patients with a longer time between the occurrence of the initial symptoms of the disease and the delivery of correct diagnosis have a higher risk of metastasis, and a worse prognosis [3]. Early diagnosis of TC is determined by the biologic features of the tumor, patients' knowledge about the disease, and the availability of GPs and specialists to analyze initial symptoms to determine a correct diagnosis and begin adequate treatment [12]. Since the biologic features of tumors are hardly unbiased, other causes of treatment delay were analyzed in our study. The overall treatment delay (mean time of 150 days) shows that young males are generally poorly informed about the possibility of TC occurrence. They do not pay attention to the initial symptoms of the disease and most think that the enlargement of the testicle is a sign of their masculinity. When comparing the time interval between the onset of initial symptoms and the GP's visit with the study of Hornak et al. [12], we found an extension of this interval from 4.1 months in 1968–1976, to 2.8 months in 1977–1985, to the current value of 4.7 months in 1993–2002.

However, in our study we recorded a reduction of treatment delay caused by GPs from 0.3 months in 1968–1985 [12] to 0.2 months in the present study (1993–2002) without being able to evaluate its statistical significance because of the lack of data in the older study. This means that general practitioners correctly redirected the patients to specialists, who started the treatment. However, it is still important to emphasize that every painless palpable mass in the scrotum is potentially malignant until proved otherwise [8, 21].

When comparing the treatment delay caused by specialists, we noted a lengthening of this interval from 0.3 months in 1968–1977 [12] to 0.7 months in the present study (1993–2002). This time delay is mainly caused by inadequate treatment due to many specialists applying treatment for diseases other than

testicular cancer (e.g., antibiotics therapy for epididymitis or orchitis).

The statistics from the Slovak Republic show a retrograde tendency despite the fact that preventive, urological, and oncological centers regularly publish information on testicular self-examination. A meta-analysis by Gascoigne and Whitear [11] showed insufficient knowledge of young males about TC occurrence, its symptoms, risk factors, and ways of self-examination in the secular community in the years 1986–1994. It is possible to reduce the delay between the initial symptoms and a GP's visit with self-examination, which can lead to earlier diagnosis and better prognosis for the disease. However, self-examination is not a suitable screening method [6, 11, 19]. According to Boyle [7] and Ondrus et al. [22] patient visits to a well-arranged medical centers is a very important factor for mortality decrease.

The survival of oncologic patients is an important indicator of diagnostic and treatment quality. TC survival strictly depends on the clinical stage [26] at the time of diagnosis. Our study shows the expectation of a 10-year survival in clinical stage I of patients on the level of 97.1%, compared to 95% recorded among patients diagnosed from 1980 to 1990 [21]. The same improvement in survival was recorded in all other clinical stages (stage IIA: 92.7% vs. 83.8%, stage IIB: 95.5% vs. 92.8%, stage IIC: 81.7% vs. 76.9%, nobody died in stage III compared to 80% patient survival in 1982–1996, stage IV: 65.2% vs. 59.9%) in our study [22]. The study of Ondrus et al. [22] used in this comparison analyzes patients from one specialized center in Slovakia. Despite this, the survival rates based on the whole country were better than from this specialized center. This is due to the fact that mainly patients with worse prognosis are transferred to specialized centers, so the results of Ondrus et al. [22] may be affected by selective bias.

Conclusion

A secular trend of increasing incidence of TC has been recorded over almost all of the world. It has increased fivefold in the Slovak Republic since 1968, which is one of the highest increases of all malignant diseases, including lung cancer in males and breast cancer in females.

Results from this national retrospective study on epidemiological features of TC show a persistent lack of the knowledge about the symptoms of TC in the general population, in spite of extended health education (particularly in schools). However, the surprising result was the detection of an increased treatment delay caused by specialists (urologists, oncologists), who are responsible for most treatment approaches in this diagnosis. Therefore the only methods to decrease mortality and improve the survival of patients with TC may be early detection and risk-adapted treatment in specialized and adequately equipped centers experienced in TC management according to the appropriate guidelines and evidence-based medicine.

References

- Aareleid T, Sant M, Hédelin G, the EUROCORE Working Group (1998) Improved survival for patients with testicular cancer in Europe since 1978. *Eur J Cancer* 34:2236–2240
- Adami HO, Bergström R, Möhner M et al (1994) Testicular cancer in nine northern European countries. *Int J Cancer* 59:33–38
- Bosl GJ, Sheinfeld J, Bajorin DF et al (1997) Cancer of the testis. In: DeVita VT, Hellman S, Rosenberg SA (eds) *Cancer: principles and practice of oncology*, 5th edn. Lippincott-Raven Publ., Philadelphia, pp 1397–1425
- Bray F, Richiardi L, Ekbom A et al (2006) Trends in testicular cancer incidence and mortality in 22 European countries: continuing increases in incidence and declines in mortality. *Int J Cancer* 118:3099–3111
- Buetow SA (1995) Epidemiology of testicular cancer. *Epidemiol Rev* 17:433–449
- Buetow SA (1996) Testicular cancer: to screen or not to screen. *J Med Screen* 3:3–6
- Boyle P (2004) Testicular cancer: the challenge for cancer control. *Lancet Oncol* 5:56–61
- Dieckmann K-P, Krain J, Gottschalk W et al (1994) Atypical symptoms in patients with germinal testicular tumors. *Urologe A* 33:325–330
- Ferlay J, Bray F, Pisani P et al (2001) *Globocan 2000. Cancer incidence, mortality and prevalence worldwide*. IARC Cancer Base No 5, Lyon, IARC
- Garner MJ, Turner MC, Ghadirian P et al (2005) Epidemiology of testicular cancer: an overview. *Int J Cancer* 116:331–339
- Gascoigne P, Whitear B (1999) Making sense of testicular cancer symptoms: a qualitative study of the way in which men sought help from the health-care services. *Eur J Oncol Nurs* 3:62–69
- Hornak M, Ondrus D, Bardos A Jr (1987) Testicular tumors, the causes of therapeutic delay (in Slovak). *Prakt Lék (Praha)* 67:555–556
- Huyghe E, Matsuda T, Thonneau P (2003) Increasing incidence of testicular cancer worldwide: a review. *J Urol* 170:5–11
- Levi F, Lucchini F, Boyle P et al (1998) Cancer incidence and mortality in Europe, 1988–1992. *J Epidemiol Biostat* 3:295–373
- Levi F, La Vecchia C, Boyle P et al (2001) Western and eastern European trends in testicular cancer mortality. *Lancet* 357:1853–1854
- Levi F, Te V-C, Randimbison L et al (2003) Trends in testicular cancer incidence in Vaud, Switzerland. *Eur J Cancer Prev* 12:347–349
- Liu S, Wen SW, Mao Y et al (1999) Birth cohort effects underlying the increasing testicular cancer incidence in Canada. *Can J Public Health* 90:176–180
- Moger TA, Aalen OO, Heimdal K et al (2004) Analysis of testicular cancer data a frailty model with familial dependence. *Statist Med* 23:617–632
- Morris J (1996) Should testicular self-examination be recommended? *J Med Screen* 3:2
- Nakata S, Ohtake N, Kubota Y et al (1998) Incidence of urogenital cancers in Gunma Prefecture, Japan: a 10 year summary. *Int J Urol* 5:364–369
- Ondrus D, Hornak M (1994) Orchiectomy alone for clinical stage I nonseminomatous germ cell tumors of the testis (NSGCTT): a minimum follow-up period of 5 years. *Tumori* 80:362–364
- Ondrus D et al (2004) Testicular tumors, diagnostics and treatment (in Slovak). *Osveta, Martin*
- Ondrusova M, Plesko I, Safaei-Diba Ch et al (2006) Cancer incidence in the Slovak Republic 2003. *National Cancer Registry, NHIC, Bratislava*
- Parkin DM, Whellan SL, Ferlay J et al (eds) (1997) *Cancer incidence in five continents, vol. 7*. IARC Scientific Publ., IARC, Lyon
- Parkin DM, Whellan SL, Ferlay J et al (eds) (2002) *Cancer incidence in five continents, vol. 8*. IARC Scientific Publ., IARC, Lyon
- Peckham MJ, McElwain TJ, Barrett A et al (1979) Combined management of malignant teratoma of the testis. *Lancet* 2:267–270
- Plesko I, Obsitnikova A, Cuninkova M et al (2004) Increasing occurrence of urological cancers in Slovakia. *Neoplasma* 51:248–254
- Power DA, Brown RSD, Brock CS et al (2001) Trends in testicular carcinoma in England and Wales, 1971–1999. *BJU Int* 87:361–365
- Purdue MP, Devesa SS, Sigurdson AJ et al (2005) International patterns and trends in testis cancer incidence. *Int J Cancer* 111:822–827
- Weir HK, Marrett LD, Moravan V (1999) Trends in the incidence of testicular germ cell cancer in Ontario by histologic subgroup, 1964–1996. *CMAJ* 160:201–210