Trendovi učestalosti tumora germinativnih ćelija testis (1976-2005)

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Apstrakt

Cilj ove studije je da prospektivno analizira incidenciju tumora germinativnih ćelija testisa (TGĆT) u zavisnosti od kliničkog stadijuma (KS) i histologije, pošto se učestalost ovih malignoma uvećava. Pacijenti sa dijagnozom TGĆT između 1976 i 2005 su podeljeni u 3 vremenska perioda u zavisnosti od datuma dijagnoze TGĆT i određenih karakteristika pri prezentaciji. U cilju svrsishodnosti analize, pacijenti su podeljeni u 1 od 3 slične grupe u pogledu trajanja opservacije (10 godina)(1976-1985, 1986-1995, 1996-2005). Ova 3 perioda su statistički poređena da bi indentifikovali moguće promene u prezentaciji TGĆT. Od 1935 pacijenata, broj dijagnostikovanih u svakom periodu je bio 111(6%), 695(36%) i 1129(58%). Postoji značajan porast procenta pacijenata sa TGĆT tokom perioda od 30 godina, posebno u trećoj u odnosu na drugu i prvu dekadu (P<0.0001). Ukupno, 46% pacijenata je dijagnostikovano sa seminomom i 54% sa neseminomskim tumorom. Veliki procenat od ukupnog broja pacijenata sa TGĆT se prezentirao u KS I (64%). Seminomski i neseminomski tumori su imali veću učestalost u KS I (78% prema 51%). Srednje starosno doba za celu grupu pacijenata je bilo 34 godine. Srednje životno doba sa metastatskim seminomom je bilo 4 godine veće nego u KS I bolesti (42 prema 38 godina), dok je starosno doba u meastatskom i KS I neseminomskih tumora bilo indentično (31 godina). Učestalost seminoma se vremenom značajno povećavala (40% prema 55%), što je praćeno značajnim smanjenjem učestalosti neseminomskih tumora (60% prema 45%) (P<0.001). Procenat pacijenata u KS I se takođe značajno vremenom povećao (45% prema 77%), dok se procenat pacijenata sa metastatskom bolešću smanjivao (55% prema 32%)(P<0.001). Postoji značajan porast procenta pacijenata u KS I seminomskih (27% prema 47%)(P<0.01) i neseminomskih tumora (18% prema 30%)(P<0.01), praćenih sa značajnim smanjenjem metastaskih neminomskih tumora (42% prema 15%)(P<0.001). Međutim, procenat

Trends in the incidence of germ cell testicular tumors (1976-2005)

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Abstract

The aim of the present study is to prospectively investigate the presentation of germ cell testicular tumors (GCCTs) in terms of clinical stage (CS) or histology, as the incidence of this malignancy in increasing. Patients diagnosed with GCTTS between 1976 and 2005 were categorized into 3 period depending on date of diagnosis of GCTTs and presentation characteristics assessed. For purpose of analysis patients were assigned into 1 of 3 similar groups in term of duration (10 years) (1976-1985, 1986-1995, 1996-2005). These 3 periods were compared statistically to identify the possible changes in the presentation of GCTTs. Among 1935 patients, the number diagnosed in each period was 111 (6%), 695 (36%) and 1129 (58%), respectively. There was substantial rise in the percentage of patients with GCTTs during the period of 30 years, particularly in 3rd vs. 2nd and 1st decade (P<0.0001). Overall, 46% of patients were diagnosed with seminoma and 54% with nonseminoma. The greater proportion of the entire cohort of patients presented in CS I (65%). Also, seminoma and nonseminoma occurred more frequently in CS I (78% and 51%, respectively). The median (range) age of the whole cohort of patients was 34 (14-80) years. The median age for developing metastatic seminoma was 4 years more than in CS I disease (38 vs. 42 years, respectively), while the median age for the presentation of CS I and metastatic nonseminoma was identical (31 years). The proportion of seminoma increased significantly in time (40% vs 55%) and this was accompanied by a significant decrease of nonseminoma (60% vs. 45%)(P<0.001). The proportion of patients in CS I disease also increased significantly with time (45% vs. 77%), while the proportion of patients with metastatic disease decreased (55% vs. 23%)(P<0.001). There was a significant rise in proportion of patients with CS I seminoma (27% vs. 47%) (P<0.001) and nonseminoma (18% vs. 30%) (P<0.001), accompanied by a significant decrease in the proportion of patients presenting with metastatic nonseminoma (46% vs. 15%)(P<0.0001). However,

pacijenata sa metastatskim seminomom ostaje nepromenjen (13% prema 9%). Prikazana studija pokazuje progresivno povećanje učestalosti TGĆT tokom perioda od 30 godina, sa povećanjem proporcije pacijenata sa TGĆT ograničenih samo na testis, na suprot grupe sa metastatskom bolešću. Druga konstatacija je da se povećao broj pacijenata koji se prezentirao sa seminomskim u odnosu na neseminomske tumore. Razlog za ovu konstataciju ostaje nejasan i iziskuje dalja ispitivanja.

Ključne reči: tumori germinativnih ćelija testisa, seminomski, neseminomski, incidencija, prezentacija, epidemiologija.

the proportion of patients with metastatic seminoma remained largery unchanged (13% vs. 9%). The present study shows a progressive increase of GCTTs during the observation period of 30 years, with increase in the proportion of patients with GCTTs confined to the testis, as opposed to metastatic disease. The other finding is that there has been an increase in the proportion of patients presenting with seminoma rather than nonseminoma. The reason for this remain unclear and require further investigation.

Key words: germ cell testicular tumors, seminoma, nonseminoma, incidence, presentation, epidemiology.

Introduction

The incidence of germ cell testicular tumors (GCTTs) has been increasing in the western world since 1940s[1]. However, the reason for this is unclear. An increase in the incidence of GCTTs was detected during the 1970s and 1980s, particularly in northern European countries, and there is a clear trend towards an increased GCTTs incidence in the last 30 years in the majority of the industrialized countries in North America, Europe and Oceania, although surprising differences in incidence rates are seen between countries. Asia and Africa had the lowest incidence[2-4]. Data from The Surveillance Epidemiology and End results Program during the years 1973 to 1998 show a continuing increased risk among Caucasian men in the U.S.A. only for seminoma [5]. Epidemiological risk factors for the development of GCTTs are: a history of cryptorchidism or undescended testis (testicular dysgenesis syndrome), Klinefelter's syndrome, testicular atrophy, infertility, microlithiasis in the testis, familial history of testicular tumors among first- grade relatives (father/brothers), the presence of contralateral tumor or the testicular intraepithelial neoplasia. Maternal smoking during pregnancy, increased maternal age, increased placental weight, decreased parity, prematurity, early age at hernia repair, lower age at puberty, occupational exposure to endocrine disrupting chemicals, viral exposure, history of sexually transmissed disease and HIV infection, have been suggested as a possible cause but never substantiated [6]. Although cryptorchidism is related significantly to total GCTTs in the vast majority of studies have found higher risk for seminoma compared with nonseminoma. In U.K., it appears that there may have been an increase in the incidence of undescended testis between 1960s and 1980s, and this may in part be responsible for the risk in GCTT during this period. However, data from last two decades suggests that the incidence of undescended testis has not changed[7].

Previous publications show that there may be a change in the pattern of presentation of the disease, in terms of histology (seminoma vs. nonseminoma) and clinical stage (CS)[5,8,9]. Overall these reports have been limited in that they assessed both CS and histology, and were often too small to identified changes. In the 1970s an increase in the proportion of nonseminoma at diagnosis was identified, and thought to be a result of improved histological techniques. Recent data from U.S.A. and U.K. suggest that incidence for both histologic types may be increasing, but was only significant for seminoma[5,10]. Increases in incidence were only observed for localized tumors of both histologic types[10,11], but currently there no regional data on this issue.

In the present study we investigated these factors further, and examined how the presentation of GCTTs changed over last 30 years in our region, which has data on over 1900 patients. This includes data for the histology and the CS of disease at presentation.

Material and methods

Information was collected from a prospective data-base, initiated in 1996. Patients diagnosed with histologically confirmed GCTTs between 1976 and 2005 were included: the age, histology and CS were noted. For purposes of analysis, patients were assigned to one of three periods, depending on the date of diagnosis of the GCTTs, selected to create similar groups in terms of duration (10 years), i.e. 1976-1985, 1986-1995 and 1996-2005. These three periods were compared statistically to identify possible changes in the presentation of GCTTs.

Qualitative data were assessed statistically using chi- square tests for trend, and were data were not normally distributed, groups were compared using the Kruskal-Wallis test, with all P values two-tailed and significance indicated at $P<0.05$.

Results

In all, 1935 patients were diagnosed with GCTTs between 1976 and 2005. The number of diagnosed in each period was 111 (6%), 695 (36%) and 1129 (52%), respectively. There was substantial rise in the percentage of patients with GCTTs during the observation period of 30 years, particularly in 3rd vs. 2nd and 1st decade ($P<0.0001$). (Figure 1.)

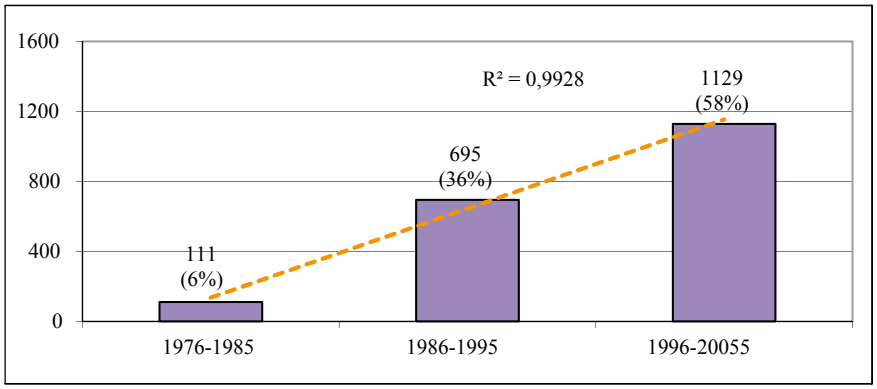

Figure 1. The overall incidence of patients with GCTTs according to decades.

The greater proportion of the entire cohort of patients Presented in CS I disease (64%). Also, seminoma and nonseminoma occurred more frequently in CS I. Of 930 patients with seminoma, 729 (78%) were in CS I and 201 (22%) with metastatic disease, while among 1005 nonseminoma, CS I occurred in 514 (51%) and metastasis in 641 (49%) patients. Overall risk (OR) for the appearance of seminoma in CS I is 3.5-fold higher in comparison to nonseminoma (OR=3.464 +/-1.107, 95% confidence interval = 2.839-4.228). (Table 1.)

Histology, CS	1976-1985		1986-1995		1996-2055		Total	
	No	%	No	%	No	%	No	%
Seminoma CS I	30	27	170	24	529	47	729	38
Seminoma with Metastasis	14	13	90	13	97	9	201	10
Nonseminoma CS I	20	18	157	23	337	30	514	27
Nonseminoma with Metastasis	47	42	278	40	166	15	491	25
Total	111	6	695	36	1129	58	1935	100

Table 1. The proportion of patients stratified according the treatment period, histology and clinical stage.

The median age (range) of the whole cohort of patients was 34 (14-80) years. The median age for developing metastatic seminoma was 4 years more than in CS I disease (38 vs. 42 years, respectively), while the median age for presentation of CS I and metastatic nonseminoma was identical (31 years). (Table 2.)

Histology, CS	1976-1985	1986-1995	1996-2055
	Median (range), Age, Years	Median (range) Age, Years	Median (range) Age, Years
Seminoma CS I	37 (18-68)	39 (19-80)	37 (18-78)
Nonseminoma CS I	31 (15-55)	31 (17-67)	32 (17-74)
Seminoma Metastaticum	41 (24-68)	41 (18-71)	41 (22-67)
Nonseminoma Metastaticum	31 (18-49)	30 (16-65)	31 (15-63)

Table 2. The age of patients diagnosed with GCTTs between 1976-2005.

The proportion of seminoma increased significantly in time (40%vs55%) (P<0.001) and this was accompanied by a significant decrease in nonseminoma (60%vs45%) (P<0.001) (Figure 2.)

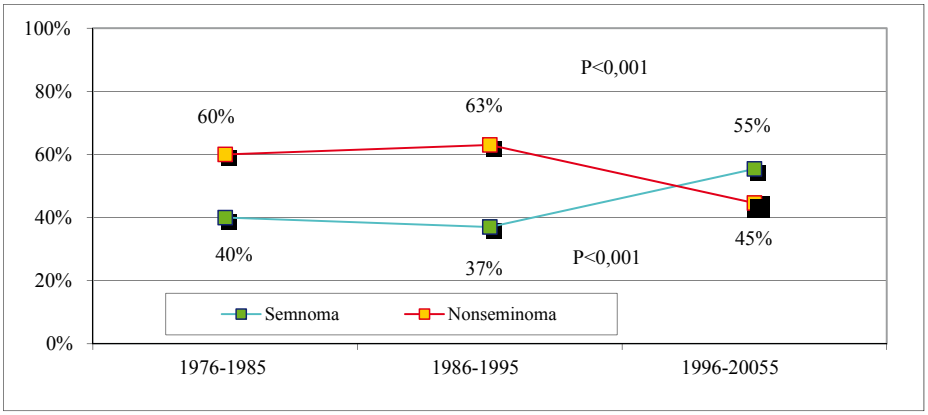

Figure 2. The proportion of patients presented with seminoma and nonseminoma.

The proportion of patients with CS I disease also increased significantly with time (45% vs. 77%)(P<0.001), while the proportion of patients with metastatic disease decreased (55% vs. 23%)(P<0.001). In the most recent period 77% had CS I and 23% had metastatic disease. (Figure 3.)

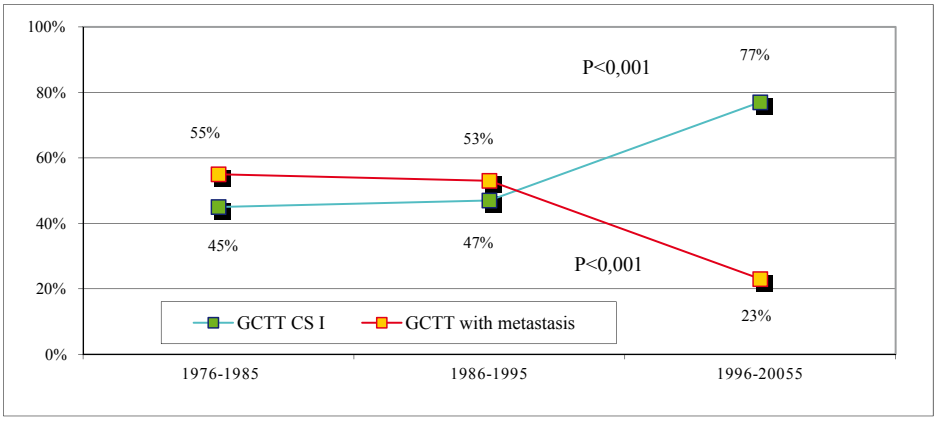

Figure 3. The proportion of patients presented with GCTTs without and with metastasis.

There was significant rise in the proportion of patients with CS I seminoma (27% vs. 47%)(P<0.01) and nonseminoma (18% vs. 30%)(P<0.01), accompanied by a significant decrease in the proportion of patients presenting with metastatic nonseminoma (42% vs. 15%)(P<0.001). However, the proportion of patients with metastatic seminoma remained largerly unchanged (13% vs. 9%). (Figure 4.)

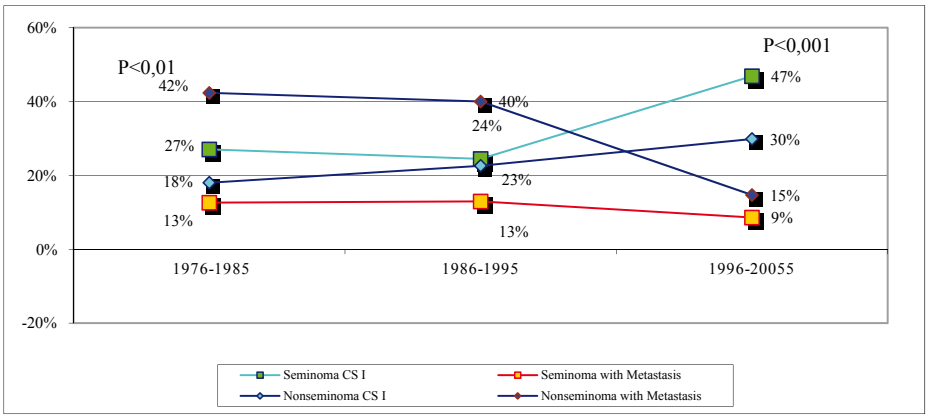

Figure 4. The proportion of patients according to histology and clinical stage of GCTTs

Discussion

There is overall increase of patients with GCTTs, with an increase in the proportion of patients with disease localized to the testis, and increase of seminoma accompanied by decrease of nonseminoma histology between 1976 and 2005. Indeed, during the most recent period (1996-2005) over half of patients with GCTTs presented in CS I seminoma, whereas nonseminoma demonstrated decline in occurrence (77% vs. 23%).

Possible explanation for the increased proportion of patients presenting with CS I disease include improved education and awareness of GCTTs, resulting in earlier diagnosis. This hypothesis was supported by previous observations, which showed that a delay in diagnosis correlate with advanced CS at presentation of disease [12-14].

It is also possible that a greater proportion of patients are presenting with CS I disease because of change in the pathogenesis of the GCTTs. In this series there was an increase in the proportion of patients presenting with seminoma as opposed to nonseminoma, the reason for each is unclear. However, those findings are confirmed in only two studies, which included large number of patients[10,11]. The study from Powles et al.[10] based upon 1546 patients demonstrated significant increase in the proportion of patients presenting in CS I disease and seminoma over period from 1983-2002. There was also a significant reduction in the size of primary tumor (5 to 4 cm). Enewold et al.[11] compared the incidence of GCTTs in U.S military servicemens and general population during the observation time from 1990 to 2003. Nonseminoma incidence was significantly lower in the military than in the general population. Trends in the incidence tended to be similar in both the populations. Increases were observed for both histologic types but were only significant for seminoma. Increases in incidence were only observed for localized GCTTs of both histologic types.

However, it may account for the rise in occurrence of CS I, as seminoma is less aggressive than nonseminoma, take longer to metastasize, and therefore are more frequently confined to the testis at presentation. During the most recent period of time, seminomas comprised 50% to 60% of GCTTs in the majority of registries. The proportion of tumors that were seminomas, however, ranged from 36% in Zaragoza, Spain to 63% in New Zeland. There was no relationship between the proportion of tumors that were seminomas (or nonseminomas) and the overall rate of GCTTs. In all but one registry, rates of seminomas consistently exceeded rates of nonseminoma, although the trends by histology were fairly similar to each population. Only in Bas-Rhin, France did the rates of seminoma and nonseminoma converge around 1985 and begin to decline around 1995. In the U.S white population and in Ontario, Canada, nonseminoma rates seems to plateau around 1990, whereas in seminoma rates continued to the most recent time period [6]. The present study demonstrated increase in seminoma and decrease of nonseminoma over time. In the most recent period 55% patients had seminoma and 45% nonseminoma.

The present study correlate with the previous analysis of published testicular cancer incidence data which suggest that incidence continued to increase in many populations world wide. The increase, however, was most notable among some European-descended populations. Eastern Asian population, in contrast, continued to have low rates that remained stable or declined. The increase in testicular cancer rates over 30-year argue that environmental risk factor are likely to be involved, although the great discrepancy in rates among persons of different racial and ethnic groups suggests that genetic susceptibility may be also an important determinant[6]. Weir et al.[15] reported that the incidence of GCTTs had risen in Ontario, Canada, by almost 60% between 1964 and 1996. When analyzing by histologic type,Weir et al. found that the rates of both seminoma and nonseminoma had increased during the interval, although the rate of seminoma increased by 72%, whereas the rate of nonseminoma rose by only 54%. These increases are very similar to the increases among the white population in U.S., where the overall increase was 52%, the increase in seminoma was 79%, and increase in nonseminoma was about 32%[5]. We reported similar results, with overall increase by 58%, although the rate in seminoma increased by 67% and in nonseminoma by 50%.

Little is known about the development of seminoma and nonseminoma as separate entities. There has been long controversy about seminoma being the separate branch from embryonal cell carcinoma, with seminoma developing from sperm cell percursors and embryonal cell carcinoma from embryonic nests. The discovery of the carcinoma in situ (CIS) CS of testicular tumor led to an elaboration of these concepts, with the view that the 1st stage of malignant transformation takes place in uterus. Cytogenetic and clinical data indicate a progression of seminoma into seminoma [16]. However, more recent immunohistochemical data showed that a proportion of GCTTs develop embryonal characteristics (CD 30 – positive) directly from CIS, with no intermediate seminoma stage, contradicting previous findings[17,18].

Several other causal factors should also be considered further. Higher pregnancy estrogens in mother, such as increased maternal age, increased placental weight, decreased parity, low birth order, early hernia repair have a stronger association with seminoma compared with nonseminoma. Nonseminoma was associated more closely with variables indicative of intrauterine growth retardation,i.e., low birth weight and decreased maternal age, testicular trauma, early puberty, history of sexually transmissed diseases and HIV infection. The effect of socioeconomic status on GCTTs are not conclusive, although men belonging to higher socioeconomic groups are often reported to be higher risk of GCTTs relative to less-privileged groups. As with other variable, the risk estimates tend not, however, to be consistent by subtypes[19,20]. One of the most intriguing aspects of GCTTs epidemiology in the U.S.A. has been the disparity in incidence rate between white men and black men. Although the rates in black men remained strikingly lower compared with rates in white, it was found that, in the final interval, black men had experienced a noticeable increase in the incidence of seminoma and, to a much lesser extent in increase in nonseminoma[5].

Previously mentioned studies have found an increase in the presentation of early-stage disease. Most of these studies have been small and the results not statistically significant, but togheter they suggest that the changes may be confined to certain periods such as early 1980s[8,9]. These studies also concluded that increasing in CS I disease may be a result of the earlier diagnosis of GCTTs because of greater awareness by the general public. These tumors are also becoming smaller at presentation, which may be results of greater awareness of the disease in general population and self-examination[10]. This may vary among countries, and may explain why the change occur at different time.

There are three possible confounding factors which may be taken in account for the present. There may have been a change in demografics of the population in sense of vaste number of refugees coming in Serbia from ex Yugoslavian republics or a change in the refferal patterns to the hospitals in the area over the years. Therefore. Over the time our insitution has become the centre of excellence for the diagnosis, treatment and follow-up of patients with GCTTs. Suggested culprit for the development of GCTTs, is associated with contamination of the environment with depleted uranium (DU) for ammunitions used during the war conflict in Bosnia and Serbia. This constation supports the hypothesis that the war related exposure to the DU could lead to GCTTs after prolonged latency.

Conclusions

The present study shows an increase in proportion of patients with GCTTs between 1976 and 2005, with increase of patients with GCTTs confined to the testis, as opposed to metastatic disease. This is good news for patients with GCTTs, as not only that it reduces the need for chemotherapy and cytoreductive surgery, but it is also associated with better long-term survival. The other finding is that there has been an increase in the proportion of patients presented with seminoma rather than nonseminoma. The reason for this remains unclear and requires further investigations.

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Literature

1. Zheng T, Holfild TR, Ma Z, Ward BA, Flannery J, Boyle P. Continuing increase in the incidence of germ-cell testis cancer in young adults: experience from Connecticut, USA, l935-92. Int J Cancer 1996;65:723-9.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009; 59:225-49.
3. Huyghe E, Matsuda T, Thonneau P. Increasing incidence of testicular cancer worlwide: a review. J Urol 2003; 170: 5-11.
4. Rosen A, Jayram G, Drazer M, Eggener SE. Global trends in testicular cancer incidence and mortality. Eur Urol 2011;60:374-9.
5. Mc Glynn KA, Deresa SS, Sigurtson et al. Trens in the incidence of testicular germ cell tumours in the United States. Cancer 2001;93:63-70.
6. Chia VM, Quarishi SM, Deresa SS, Purdue MP, Cook MB, Mc Glynn KA. International treens in the incidence of testicular cancer, 1973-2002. Cancer Epidemiologic Biomarkers Prev 2010;19:1151-9.
7. Coupland CA, Chilvers CE, Davey G, Pikl MC, Oliver RT; Forman DT. Risk facors for testicular tumors by histological tumour type. United kingdom Testicular Cancer Study Group. Br J Cancer 1999,80:1859-63.
8. Sonneveld DJ, Hoekstra HJ, Van Der Graft WT, Shuiter WJ, Chraffordt Koops H, Sleifer DT. The changing distribution of stage in nonseminomatous germ cell tmors, from 1977 to 1996. BJU Int 1998;84:68-74.
9. Heindal K, Fossa SD, Johansen A. Increasing incidence and changing stage distribution of testicular carcinoma in Norway 1970-87. Br J Cancer 1990:62:277-8.
10. Powles TB, Bhardwa J, Shamosh J, Mandalia S, Oliver T. The changing presentation of germ cell testicular tumours of the testis between 1983 and 2002. BJU Int 2005;95:1197-1200.
11. Enewold L, Zhon J, deresa SS, Erickson RL, Zhu K, Mc Glynn KA. Trends in testicular germ cell tumors among U.S. military servicemen, 1990-2003. Mil Med 2011; 176:1184-7.
12. Bosl GJ, Vogelzang NJ, Goldman A, et al. Impact of delay in diagnosis on clinical stage testicular cancer. Lancet 1981;2:970-3.
13. Chilvers CE, Saunders M, Biss JM, Nicholls J, Horwich A. Influnce of delay in diagnosis on progression in testicular teratoma. Br J Cancer 1989;59:126.8.
14. Moul JW, Paulson DF, Dodge RK, Walther PJ. Delay in diagnosis and survival in testicular cancer: impact of effective therapy and changes during 18 years. J Urol 1990;143: 520-3.
15. Weir HK, Marret LD, Moravan V. Trends in the incidence of testicular germ cell cancer in Ontario by histologic subgroup, 1964-1996. Can Med Assoc J 1999:160:201-5.
16. Oliver RT, Leahey M, Ong J. Combined seminoma/non-seminoma should be considered as intermediate grade germ cell cancer (GCC). Eur J Cancer 1995;314:1392-4.

17. Berney DM, Lee A, Randle SJ, Jordan S, Shamash J, Olivert RT. Tzhe frequency of intratubular embryonal carcinoma: implications for the pathogenesis of germ cell tumors. Histopatology 2004;45:155-61.
18. Bray F, Richiardi L, Ekborn A, et al. Do testicular seminoma and nonseminoma have the same etiology? Evidence from an age-period-cohort analysis of incidence trends in eight european countries. Cancer Epidemiologic Biomarkers Rev 2006;15:652-8.
19. Pearce N, Sheppard RA, Howard JK, Fraser J, Lilley BM. Time trends and occupational differences in cancer of the testis in New Zeland. Cancer 1987; 59:1677-82.
20. Pukkala E, Weiderpass E. Socio-economic differences in incidence rates of cancer of the male genital organs in Finland, 1975-95. Int J Cancer 2002;102:643-8.

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