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Original article

Changes in epidemiologic features of testicular germ cell cancer: Age at diagnosis and relative frequency of seminoma are constantly and significantly increasing

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Abstract

Objectives: Testicular germ cell tumors (GCTs) have their incidence peak in the third and fourth decades of life. Histologically, GCTs comprise of seminoma and nonseminoma at almost equal proportions with a slight preponderance of nonseminoma in most of the major series. Since decades, there is a shift toward decreasing age at presentation. Recently, there are suggestions of a reversal of the age trend, and also, the histologic subtype ratio appears to shift toward seminoma. We retrospectively looked to our patient populations to verify these recent trends.

Methods: A total of 2,482 patients with histologically proven GCT diagnosed between 1976 and 2010 were retrospectively evaluated regarding the year of diagnosis, histology of primary tumor, and age at presentation. Patients were categorized according to the following time periods of treatment: before 1990, 1990 to 1994, 1995 to 1999, 2000 to 2004, and 2005 to 2010. Mean age and relative proportion of seminoma were compared among patient categories by employing the chi-square test and analysis of variance, respectively.

Results: The mean age significantly increased from 28 to 36 years. The age difference between the 2 histologic subtypes remained constant between 6 and 8 years during the entire observation period. The relative proportion of seminoma continuously increased from 30.9% to 56% ($P < 0.001$).

Conclusion: There is evidence of a significant shift toward older age at diagnosis of GCT. In addition, the proportion of seminoma is constantly increasing at the expense of nonseminoma. The reasons for these developments are obscure. However, 2 old theories regarding the pathogenesis of GCT may receive support from our results: first, the theory of divergent pathogenetic pathways of seminoma and nonseminoma and second, the involvement of postnatal environmental factors in the pathogenesis of GCTs. © 2014 Elsevier Inc. All rights reserved.

Keywords: Testicular germ cell tumor; Epidemiology; Age at diagnosis; Seminoma; Nonseminoma

1. Introduction

Testicular germ cell tumors (GCTs) represent the most frequent malignancy in young men [1]. The incidence of GCTs in Western countries has been increasing since decades, and this trend appears to be ongoing [2,3]. Morphologically, GCTs comprise of 5 morphologic patterns resembling various stages of an embryonic development. Pathogenetically, all forms of adult GCT originate from a common progenitor named testicular intraepithelial neoplasia (also called carcinoma in situ testis; or intratubular germ cell neoplasia unspecified) [4]. According to the pathogenetic theory that is widely accepted but not ultimately proven, these precursor cells probably derive from primordial germ cells secondary to relative excess estrogenic exposure during embryogenesis. Antenatal factors are thus assumed to govern the basic steps of GCT pathogenesis; however, postnatal factors may be involved, too, during later tumorigenesis. With respect to biologic behavior and with regard to clinical management of GCTs, only 2 histologic groups are considered: pure seminoma and

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nonseminoma, respectively [5]. In most of the classical clinicopathologic studies, a slight preponderance of nonseminomas with 55% (vs. 45% seminoma) has been documented [6,5] although opposite ratios have been documented, too [7,8]. Such proportion has also been observed in Central Europe [9,10] in the last century. As a matter of fact, if any change in this proportion of histologic subtypes should occur, this event would be significant with regard to the theory of GCT pathogenesis.

The typical age of clinical presentation of GCT is the third and fourth decades of life, with seminomas occurring roughly 8 to 10 years later than nonseminomas. This rather early presentation is thought to reflect the antenatal foundation of the disease. Since around 1900, a continuous trend to earlier presentation of GCTs is documented in the epidemiologic literature [11,12]. Only very recently [13], this trend appears to abate, but the database is still scarce. Clearly, a shift of predisposition age over time would be of great importance with respect to understanding the pathogenesis of GCT.

To address the issue of trends over time regarding the relative proportion of histologic subtypes and age at first presentation, we looked to these characteristics in a large clinical database of 2 specialized testicular cancer centers in Northern Germany.

2. Material and methods

We retrospectively analyzed the files of all consecutive patients undergoing radical orchiectomy for testicular tumor at 2 urologic institutions (Federal Armed Forces Hospital and Albertinen Hospital, Hamburg) from 1976 through 2010. Only patients with pathologically proven malignant GCT were enrolled. A total number of 2,482 patients were eligible. Relevant data, i.e., histology of primary tumor and age at first presentation, were obtained by retrospective chart analysis. Histologic diagnosis was established by pathologists experienced in the field of GCT pathology.

According to the histologic subtype, patients were grouped into a first group with pure seminomatous GCTs ("seminoma") and a second group with nonseminomatous or mixed histologic subtype ("nonseminoma"). To assess possible trends over time, all patients were categorized according to the year of initial diagnosis into the following 5 cohorts: $\leq$1990, 1990 to 1994, 1995 to 1999, 2000 to 2004, and 2005 to 2010. For each of the 5 time spans, the relative proportion of patients with seminoma and with nonseminoma, respectively, were calculated and tabulated. Also, for each of the 5 time spans, the mean and median age at diagnosis of all patients with GCT, of those with seminoma, and of those with nonseminoma, respectively, were calculated and tabulated.

The chi-square test and the analysis of variance were used to compare proportions and means between groups. All statistical analyses were performed with the Statistical package for Social Sciences (SPSS), version 17. Graphs were created using Sigma Plot 12.0. All statistical tests were two sided with the significance level set at <0.05.

3. Results

The descriptive characteristics of the study population are given in Table 1. Overall, there were 1,179 (47.5%) patients with seminoma and 1,303 patients (52.5%) with nonseminoma.

During the study period, the annual number of patients constantly increased. Specifically, a mean number of 28.3, 58.4, 61.8, 126.8, and 137.2 patients were annually treated during the time intervals before 1990, 1990 to 1994, 1995 to 1999, 2000 to 2004, and 2005 to 2010, respectively. Notably, there was a continuous increase in the number of both histologic subtypes over time with the exception of nonseminomas between 1995 and 2000. The average numbers of seminomas treated annually in the 5 time spans were 8.7, 20.8, 27, 69.6, and 76.8, and the corresponding numbers of nonseminomas were 19.5, 37.6, 34.8, 57.2, and 60.3.

The relative proportion of the histologic subtypes and the corresponding changes over time are presented in Fig. 1. Before 1990, seminoma comprised of only 30.9% of all the malignant GCTs. The relative proportion of seminomas has risen ever since. Conversely, the relative proportion of nonseminomatous GCTs continuously decreased over time from 69.1% (before 1990) to 44% (2005–2010). These changes are statistically significant ($P < 0.001$).

The mean age of the entire population of patients with GCT increased significantly from 28 years ($<$1990) to 36 years (2005–2010). Likewise, age shifts were found in both of the histologic subgroups. Mean age rose from 34 to 39 years in seminomas and from 26 to 31 years in nonseminomas (Table 2). These changes are statistically significant ($P < 0.001$). Notably, the difference between seminoma and nonseminoma regarding age at presentation remained the same (6–8 years) during the entire observation period.

Table 1
Characteristics of 2,482 patients with germ cell tumor of the testis

Variable	*n* (%)
Time of surgery	
Before 1990	424 (17.1%)
1990–1994	292 (11.8%)
1995–1999	309 (12.4%)
2000–2004	634 (25.5%)
2005–2010	823 (33.2%)
Histologic subtype	
Seminomatous	1179 (47.5%)
Nonseminomatous	1303 (52.5%)
Age at diagnosis (y)	
Mean (median)	32.9 (31.5)
Range	13–83

Characteristics of the total population of testicular germ cell tumors investigated.

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