Testis Cancer

Impact of Diagnostic Delay in Testis Cancer: Results of a Large Population-Based Study

Eric Huyghe a,b,*, Audrey Muller a, Roger Mieusset a,b, Louis Bujan a,b, Jean-Marc Bachaud c, Christine Chevreauc, Pierre Plante a,b, Patrick Thonneau a

a Human Fertility Research Group, Paule de Viguier Hospital, Toulouse University III, France
b Urology and Andrology Department, Paule de Viguier Hospital, Toulouse, France
c Claudius Regaud Cancer Center, Toulouse, France

Abstract

Objective: Testis cancer is the most common cancer in young men, and its incidence continues to rise. Even if prognosis is considered as good, a group with bad prognosis still remains. Diagnostic delay (DD), defined as the time elapsing from the onset of tumour symptoms to the day of diagnosis, is a way to evaluate the rapidity of diagnosis. We assessed the relationship between DD, disease stage, and survival rate.

Methods: A series of 542 patients diagnosed with a germ cell tumour between 1983 and 2002 at health facilities in the Midi-Pyrenees region, southwest France, were asked about DD. We analysed DD together with data regarding the disease (histologic type, stage), its treatments, and prognosis (impact on survival).

Results: Mean DD was longer in seminoma (4.9 ± 6.1 mo) than in non-seminomatous germ cell tumour (NSGCT; 2.8 ± 4.0 mo). DD was correlated with disease stage for the whole population (p = 0.014) and for NSGCT (p = 0.0009), but not for seminoma. DD had a significant impact on the 5-yr survival rate in the overall population (p = 0.001) and in the NSGCT group (p = 0.001), but not in the seminoma group. Global trends in mean DD did not change over the 20-yr study period, but we observed a slight decrease during the last decade.

Conclusions: DD is highly correlated with stage and survival in NSGCT. Urologists should promote programmes to enhance awareness and knowledge of testis cancer, so the diagnosis can be made more rapidly.

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1. Introduction

Testis cancer (TC) is the most common cancer in young men and its incidence has been recently rising in nearly all industrialised countries [1]. Before the advent of modern chemotherapy the diagnostic delay (DD), defined as the time elapsing from the onset of tumour symptoms to the day of diagnosis, was correlated with bad prognosis. In 1981, Bosl and colleagues observed that length of DD was highly correlated with cancer stage [2]. Similarly, in patients diagnosed with TC between 1965 and 1977, Ware and colleagues observed that the longer the DD, the more advanced the disease stage in non-seminomatous germ cell tumours (NSGCTs) as well as in seminoma [3].

In more recent studies including patients treated with cisplatin-based chemotherapy, results were much more contradictory. In patients diagnosed with TC between 1970 and 1987 in a urology department, Moul and colleagues observed that in the NSGCT group, DD strongly affected survival in the pre-cisplatin era (1970–1978), but not after 1979 [4]. In a series of patients with NSGCT who had received modern chemotherapies, a DD > 3 mo was associated with lower survival in univariate analysis, but was no longer associated after adjustment for confounding factors (tumour extension, year of diagnosis, and treatment unit) [5]. In 140 consecutive TC cases diagnosed between 1994 and 1995 in a urology department, Toklu and colleagues found no correlation between DD and disease stage [6]. Finally, due to different time series (before and after introduction of modern chemotherapies) and to small patient series, it was difficult to reach a conclusion as to the impact of DD on survival.

In a large regional population-based study over 20 yr, we aimed to (1) describe diagnostic features (DD, symptoms), (2) analyse trends in DD over the study period, and (3) assess the influence of DD on survival.

2. Methods

2.1. Study population

Among 577 patients diagnosed with TC from 1983 to 2002 at health facilities (all private and public urologic and oncologic units) in the Midi-Pyrenees region, southwest France, we selected those who had a germ cell tumour. Seventeen patients with a lymphoma, 17 patients with a Leydig cell tumour, and 1 patient with a Sertoli cell tumour were therefore excluded.

2.2. Data collection

All 542 patients were asked prospectively about diagnosis and first symptoms during the first consultation at the cancer centre. Each patient was asked to provide information about the month and year when he first noticed a symptom related to TC and to describe the type of symptom. If data were missing, a mailed questionnaire was sent to the patient. An informed consent form to be completed by each patient and returned with the questionnaire was also included.

Information regarding the disease, treatments, and follow-up data was obtained through medical files. Histologic type of tumour was recorded according to the World Health Organization (WHO) classification. Stages were defined according to the modified Boden and Gibb classification: stage I, confined to the testis; stage II, with retroperitoneal lymph node metastasis; and stage III, with mediastinal or supraclavicular lymph nodes or generalised visceral metastasis. Lastly, we obtained information regarding the nature and the date of occurrence of the first symptoms and oncologic data for 439 (81%) of patients, who made up our study population.

2.3. DD measurement

Testis cancer DD was defined as the interval of time (calculated in months) from the onset of the first TC symptom to the day of orchiectomy. We were able to obtain the date of orchiectomy for all patients through urologic records.


2.4. Statistical methods

Statistical analysis was performed using STATA® 8.0 software. The χ² test or Fisher exact test was used for comparison of proportions in subgroups. The Student, Mann-Whitney, or Kruskal-Wallis test was used for equality of means between subgroups. An extension of the Wilcoxon test was used for trend across ordered groups. A level of 0.05 was considered as significant. Overall survival and tumour-specific survival were calculated with the Kaplan-Meier method. Differences in survival rates between patient subgroups were evaluated with the log-rank test [7].

3. Results

3.1. Population

In our study population of 439 subjects, seminoma accounted for 196 cases (45%) and NSGCT for the 243 remaining cases (55%). Mean age at diagnosis was 37.0 ± 10.5 yr for seminoma and 27.7 ± 8.4 yr for NSGCT (p < 0.001).

Regarding tumour stage, seminoma stages were significantly lower than those of NSGCTs (p < 0.001; Table 1). All 439 patients had had orchiectomy, 147 patients received lumbaoartic or iliac lymph node irradiation with doses of 2040–3600 cGy, and 174 were treated with cisplatin-based chemotherapy (2–5 cycles Platinol, vinblastine, bleomycin [PVB] in 19 cases; 2–3 cycles adjuvant bleomycin, etoposide,
Platinol [BEP] in 64 cases; 3–4 cycles standard BEP in 74 cases, 2–4 cycles etoposide [EP] in 17 cases). In 99 cases, patients had surgical resection of residual retroperitoneal masses after chemotherapy or radiotherapy (Table 1).

Mean follow-up after treatment was 75.5 mo (range: 1.1–215.1 mo), and 87% (383 of 439) had follow-up >24 mo. Of the overall population, 415 patients were disease-free (95%), 4 were receiving treatment (1%), and 20 had died of their disease (4%).

3.2. Symptoms

Painless swelling was observed in 210 (48%) patients, a change in testicular consistency in 93 (21%), scrotal pain in 97 (22%), and other symptoms (metastasis n = 27, gynecomastia n = 9, infertility n = 3) in 39 patients (9%). Significant differences in type of symptoms were observed according to histologic type: painless testicular swelling was a more frequent symptom of seminoma than of NSGCT (56.6% vs. 42.3%; p = 0.011), whereas scrotal pain was more common in NSGCT than in seminoma (27.3% vs. 16.9%; p = 0.021; Table 2).

3.3. Diagnostic delay

Mean DD was 3.7 ± 5.1 mo (median: 2 mo; range: 1–36 mo) and was significantly longer in seminoma (4.9 ± 6.1 mo) than in NSGCT (2.8 ± 4.0 mo; p < 0.001). Duration of DD was significantly correlated with disease stage in the overall population and in the NSGCT group (p = 0.003 for the overall population, p < 0.001 for NSGT, not significant [NS] for seminoma; Table 3). The shortest DD was

| Table 1 – Distribution of 439 tumours by histologic type, stage, and treatment |
|---------------------------------|-----------------|-----------------|
|                                 | Seminoma (n = 196) | NSGCT (n = 243) |
|                                 | Stage            | Stage           |
|                                 | I  | II | III |    | I  | II | III |
| Surveillance or lymph node dissection (n = 19) | 1  | 0  | 0   | 18 | 0  | 0  | 0   |
| Cisplatin-based chemotherapy (n = 174) | 0  | 9  | 9   | 93 | 49 | 14 |
| Radiotherapy (n = 147) | 124 | 22 | 1   | 0  | 0  | 0  | 0   |
| Chemotherapy or radiotherapy and resection of residual tumour masses (n = 99) | 6  | 18 | 6   | 8  | 23 | 38 |
| Total | 131 | 49 | 16  | 119 | 72 | 52 |

NSGCT = non-seminomatous germ cell tumour.

| Table 2 – Distribution of symptoms according to histologic type |
|---------------------------------|-----------------|-----------------|
|                                 | NSGCT n (%) | Seminoma n (%) | Overall population n (%) |
| Painless testis swelling | 103 (43) | 107 (55) | 210 (48) |
| Change in testicular consistency | 56 (23) | 37 (19) | 93 (21) |
| Pain | 65 (27) | 32 (16) | 97 (22) |
| Metastasis | 14 (6) | 13 (6) | 27 (6) |
| Other* | 5 (2) | 7 (3) | 12 (3) |

NSGCT = non-seminomatous germ cell tumour.

* Gynecomastia, 9 cases (5 NSGCT, 4 seminoma), infertility, 3 cases (3 seminoma).

| Table 3 – Diagnostic delay according to histologic type and stage |
|---------------------------------|-----------------|-----------------|
|                                 | Seminoma (n = 196) | NSGCT (n = 243) | Overall population (n = 439) |
|                                 | DD, mo mean ± SD | DD, mo mean ± SD | DD, mo mean ± SD |
| Stage | n (%) | DD, mo mean ± SD | n (%) | DD, mo mean ± SD | n (%) | DD, mo mean ± SD |
| I | 131 (66.8) | 4.5 ± 5.6 | 119 (49.0) | 2.1 ± 2.8 | 250 (56.9) | 3.4 ± 4.6 |
| II | 49 (25.0) | 5.2 ± 6.6 | 72 (29.6) | 2.3 ± 2.1 | 121 (27.6) | 3.5 ± 4.7 |
| III | 16 (8.2) | 6.8 ± 8.6 | 52 (21.4) | 4.9 ± 6.7 | 68 (15.5) | 5.4 ± 7.2 |
| p | NS | <0.001 | NS | 0.003 |

NSGCT = non-seminomatous germ cell tumour; DD = diagnostic delay; SD = standard deviation; NS = not significant.
observed in patients who consulted for male infertility (mean DD, 1 ± 1 mo) and in patients whose first symptom was a metastasis-related symptom (mean DD, 2.2 ± 2.1 mo).

Analysis of duration of DD subdivided into three classes: within the first 3 mo, between 4 and 6 mo, and after 6 mo, showed that in the overall population, 316 (72%) patients were diagnosed within 3 mo, 63 (14%) between 4 and 6 mo, and the remaining 60 (14%) waited >6 mo (Table 4). According to histologic type, 63% of seminomas versus 79% of NSGCTs were diagnosed within 3 mo, 16% of seminomas versus 13% of NSGCTs between 4 and 6 mo, and 21% of seminomas versus 7% of NSGCTs waited >6 mo before diagnosis.

The trends in DD did not change significantly over the 20-yr study period: 3.0 mo for 1983–1986, 4.0 mo for 1987–1990, 4.6 mo for 1991–1994, 3.5 mo for 1995–1998, and 3.1 mo for 1999–2002 in both seminomas and NSGCTs. Nevertheless, we observed a slight decrease (NS) in duration of DD during the last decade, from 4.6 mo in 1991–1994 to 3.5 mo in 1995–1999 and 3.1 mo in 1999–2002, with the same trends in seminoma and NSGCT (Fig. 1).

Tumour-specific survival rates at 5 yr were 97.3% for seminoma and 94.0% for NSGCT. As shown in Fig. 2, duration of DD had a significant impact on survival in the overall population (p = 0.001). This effect was essentially due to the NSGCT group (p = 0.001) and was nonsignificant for the seminoma group.

### Table 4 – Diagnostic delay subdivided into three classes according to testis cancer stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>1–3 mo n (%)</th>
<th>4–6 mo n (%)</th>
<th>&gt;6 mo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>189 (60)</td>
<td>31 (50)</td>
<td>30 (50)</td>
</tr>
<tr>
<td>II</td>
<td>90 (28)</td>
<td>16 (25)</td>
<td>15 (25)</td>
</tr>
<tr>
<td>III</td>
<td>37 (12)</td>
<td>16 (25)</td>
<td>15 (25)</td>
</tr>
<tr>
<td>Total</td>
<td>316 (100)</td>
<td>63 (100)</td>
<td>60 (100)</td>
</tr>
</tbody>
</table>

### Fig. 1 – Changes in diagnostic delay (by interval) during the study period.

### Fig. 2 – Kaplan-Meier estimates of survival according to diagnostic delay, by histologic type.

### 4. Discussion

This large-scale study confirms that DD still has a significant impact on survival in TC patients receiving modern treatments, including cisplatin-based chemotherapy. This finding is supported by
other reports. In a series of 352 patients diagnosed with TC from 1981 to 1992, Hernes and colleagues highlighted a relationship between DD of >3 mo and the 5-yr survival rate \( p = 0.02 \) [8]. Impact of length of DD on stage and survival was also observed in 154 patients treated for NSGCT in the M.D. Anderson Cancer Center (Houston, TX) between 1983 and 1986. The authors recorded a single death among the 65 patients (1.5%) whose DD was <1 mo, whereas the death rate was 12.5% when DD was >1 mo, rising to 17% for those who underwent orchiectomy >3 mo after the onset of symptoms [9].

In our series, we observed that DD was correlated with survival and also with stage, but in the NSGCT group only. It is well established that NSGCT and seminoma differ from each other in metastatic potential as well as in response to treatment. Seminoma is highly radiosensitive and chemoresistant and often remains localised to the testis, even if DD is long. On the other hand, NSGCT is more often diagnosed when it is already metastatic. The US National Cancer Data Base (NCDB) Report on Patterns of Care for Testicular Carcinoma for the period 1985–1996 estimated that the ratio of early disease to advanced disease was 9:1 in seminoma and 3:2 in NSGCT [10]. Up to now, almost half the patients with NSGCT with a high level of tumour markers or visceral metastasis (other than the lung) remain resistant to all associations of cytotoxic agents [11]. Therefore, the NSGCT group with bad prognosis should particularly benefit from earlier diagnosis.

Regarding the change over time of DD duration in the region of France that we studied, we observed a slight decrease (NS) in duration during the last decade: 4.6 mo in 1991–1994, 3.5 mo in 1995–1999, and 3.1 mo in 1999–2002, with the same trends in both seminoma and NSGCT. Similarly, other European data also indicate a recent trend to shorter DD [12]. In Germany, Dieckmann and colleagues observed that DD had continuously decreased from 1969 to 1986 and that the number of men diagnosed within 2 wk after the onset of symptoms had almost doubled since 1969 [13]. In Norway, Hernes and colleagues found that median DD decreased from 18 to 14 wk between 1981 and 1992 [8]. In the United States, NCDB data revealed that the proportion of cases reported with early-stage disease increased slightly over the period 1985–1996. This increase was due to NSGCT cases, their early stage rising from 62% in 1985–1986 to 65% in 1995–1996. On the contrary, no significant change regarding diagnosis occurred in the seminoma group [10].

4.1. Urologic and public health implications

Given that DD with TC is linked to morbidity and mortality, a key question is certainly now how to reduce the time elapsing between symptom onset and treatment. Accordingly, two types of public health recommendations should be encouraged: testicular self-examination (TSE) and information campaigns on TC symptoms.

TSE is recommended as a regular monthly practice by the American Medical Association and the American Urological Association, but only in men at high risk of developing TC by the American Cancer Society. On the contrary, the National Cancer Institute and the United States Preventive Services Task Force conclude that TC screening by TSE would not result in an appreciable decrease in mortality and leads to numerous unnecessary diagnostic procedures. In fact, and although TSE is inexpensive and relatively easy to teach, it is little practised in the United States and Europe.

In a cross-sectional study conducted among American pediatric residents, only 29% reported performing TSE on themselves at least once a month, and one third reported teaching TSE to their male patients aged 12–21 [14]. A survey conducted in New Orleans and Rochester on 415 healthy adult men showed that only 9% knew the method for TSE, and among them, fewer than 1 in 5 actually performed TSE [15].

In Europe, TSE was evaluated by questionnaire in 16,486 students recruited in 19 European countries: 87% reported never having practised TSE and only 3% reported monthly practice [16]. Similarly, in a survey conducted in Ireland, only 8% of 500 men aged 20–65 had learned how to perform TSE [17].

Information campaigns on testis cancer symptoms is another strategic option. In 1997, a public campaign for TC awareness called “Everyman” featuring rock stars was promoted in Great Britain by the Institute of Cancer Research. The aim of “Everyman” was to break the taboos surrounding men and cancer and to gain media coverage that encouraged men to feel more comfortable about facing up to TC. The results 1 yr later were assessed in 250 men attending two London general practices (response rate 81%). Regarding knowledge of TC, 91% claimed to be aware of the disease and 49% had a good knowledge of it [18].

In terms of impact on DD, this campaign for TC awareness also resulted in faster diagnosis. A prospective cohort study performed in 331 men diagnosed with TC in Yorkshire, United Kingdom, between 1998 and 2002, focused on DD and information on the men’s preexisting knowledge of testis
cancer [19]. Interestingly, a similar study had been performed in the same region in 1985, that is, before the public campaign for TC awareness, enabling comparisons [20]. This study revealed that between 1985 and 2004, median time between first symptoms and first medical advice decreased from 5 to 2 mo. Following the information campaign, 91% of men had heard about TC prior to diagnosis, mainly through television and radio programmes, newspapers and magazines, and to a lesser extent from health leaflets. This study was the first to find some evidence for an impact of a health education programme on increasing men’s awareness of TC [19].

The results of the Hungarian early detection programme for TC also plead for the promotion of educational programmes in the population at risk and the training of staff engaged in health care of the young [21]. These authors also found a reduction of DD in recent years.

This latter point is of primary importance, as noted by Bosl and colleagues in an earlier retrospective study. The authors observed that TC was not suspected by physicians in 43.8% of cases, mainly due to misdiagnosis (trauma, hydrocele, benign tumour, infection) or absence of physical examination. A correlation between the duration of DD and accuracy of diagnosis was found [2]. We can carry over these results to current practice because TC is a rare disease and many doctors are not familiar with the symptoms of this malignancy. The contribution of physicians to DD should be considered and should be a target of information campaigns.

4.2 Limitations

DD is difficult to measure accurately. Whereas the date of orchiectomy can be reliably known through surgical records, it is more difficult to date the onset of symptoms. Date of occurrence of first symptoms was obtained by directly questioning the patient, and we cannot rule out miscalculation or memory bias. Furthermore, it is possible that some men, whether intentionally or unconsciously, exaggerated the extent of the delay, especially in the case of advanced stages. This being so, by calculating the DD in months rather in weeks or days, we limit the bias of memory.

For patients who had a metastasis-related symptom, even if DD is short, prognosis is bad. This rare situation, which occurs in 6% of cases, could decrease the prognostic value of DD. However, despite this limitation, we have a significant correlation between DD and survival in the overall population.

Outcome of the disease (disease control, survival) is clearly associated with quality of treatment and depends on treatment failures. Such bias is difficult to assess in a retrospective study. Moreover, various modifications in standard treatment occurred during the study period. Some authors have also reported changes in testis cancer presentation over recent decades [22]. Because of these various limitations, we must interpret our results with caution.

5. Conclusions

Our results in a large-scale population-based study over two decades confirm that TC DD is correlated with stage and survival. This evidence of an impact of DD deserves close attention, especially in the context of the recent increase in TC incidence that we have observed in industrialised countries. The challenge now facing the urologic community is how to reduce DD. Of the two suggested approaches, TSE and campaigns for TC awareness, the latter seems to be more effective. However, before deciding on one option rather than another, further studies are certainly required to understand the attitudes and behaviour of men faced with TC and also to provide general practitioners with better information on the management of its early symptoms.

Conflicts of interest

The authors have nothing to disclose.

Acknowledgements

We thank our urologist colleagues, Michel Soulié and Mehdi Khedis, for their help, Leslie Schover from the M.D. Anderson Cancer Center, Houston, TX for her help in methodology, and Nina Crowte for English translation.

References


