Clinical presentation features of testicular cancer in public hospitals in the Autonomous Community of Madrid, Spain

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KEYWORDS
Testicular cancer; Epidemiology; Treatment

Abstract
Objective: To study the clinical features of the patients with germ cell tumor of testis in the Autonomous Community of Madrid, emphasizing on the different treatments used.

Material and method: Retrospective analysis of 536 patients with testicular cancer who were obtained from the Community of Madrid cancer registry, during a follow-up period of 15 years (1991–2010). Data analysis has been performed using SPSS 15.0 for Windows. Chi-square test has been used to determine possible relationships among variables. The level of significance was \( p \leq 0.05 \).

Results: An increase in the incidence rate has been detected along study period. Mean age was 33.6 ± 13.6 years. 89.7% of cases were germ cells tumors (46% seminoma and 43.6% non-seminomatous germ cell tumor [NSGCT]) and other histologic subtypes the remaining 10.3% of cases. 74% of patients were diagnosed with stage I disease, 8.2% with stage II and 16.2% with stage III; 54.3% of patients were treated with surgery plus adjuvant chemotherapy and in 5.6% of patients the treatment was surgery plus adjuvant radiotherapy. Surgery alone was used in 27.4% of cases: in 32.7% of stage I tumors, 13.6% of stage II and 9.2% of stage III. Radiotherapy was prescribed in 10% of stage I tumors, in 9% of stage II and in 3.4% of stage III. For the seminomas: the surgery-chemotherapy association was used in 49.8 of cases, surgery alone in 30% and surgery plus radiotherapy in 16.6% of cases. For the NSGCT, surgery plus chemotherapy was used in 70.5% of patients, surgery alone in 23.5% and surgery-radiotherapy association in 0.8% of cases.

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Testicular cancer in the Autonomous Community of Madrid, Spain

Introduction

Testicular cancer accounts for between 1 and 1.5% of all malignancies affecting men, and constitutes the most frequent solid tumors between the age of 20 and 34, with its incidence having increased over the last four decades (between 3 and 6% annually). Treatment for these tumors has evolved considerably, and a multidisciplinary approach model is considered for solid malignancies where surgery, chemotherapy (based on cisplatin) and radiotherapy play a decisive role in improving survival, from 60 to 65% in the 60s to over 95% at present. Testicular germ cell tumors (TGCT) account for between 90 and 95% of the malignancies of the male gonads. The remaining 5% corresponds to non-germ cell testicular tumors, among which we include tumors of the sexual cords and of the gonadal stroma (Leydig cell tumor, Sertoli cell tumor, granulosa tumors [adult and juvenile], and gonadoblastomas, among others) and non-specific stromal tumors (tumors of the collector tubules and of the rete testis and non-specific stromal tumors, benign and malignant). Our aim was to describe the characteristics of the patients and tumors that are diagnosed and treated in public hospitals of the Madrid Health Service, Community of Madrid, Spain.

Materials and methods

The study population results from the hospital records of tumors within the Autonomous Community of Madrid. All patients diagnosed with testicular cancer between 1 January 1995 and 31 December 2010 were included. Testicular cancer was considered in accordance with the International Classification of Diseases for Oncology (ICD-O-3), which encodes it as C62. We studied both the descriptive variables of the subjects, as well as those corresponding to the tumor and the treatment received. Temporal distribution was grouped into five-year periods. Age was classified into 15-year groups, following the criteria of the National Center Data Base (NCD) and age was grouped into patients under the age of 34 and patients aged 34 or older, taking the average age in the series as a cut-off point.

Histology was grouped into two categories: TGCT, the classification of which was based on that described by Mostofi and Price; and “other tumors”, where the...
remaining histological forms are framed. For tumor extension, we used the Surveillance, Epidemiology and End Results (SEER) classification, as modified by the American Joint Committee on Cancer (AJCC). It refers to the following stages at the time of diagnosis: stage I, localized disease with no lymph node or distant organ involvement (pT1–pT4; N0; M0); stage II, regional disease extended to regional lymph nodes, but not to distant lymph nodes or organs (pT1–pT4; N1–N3; M0); and stage III, disseminated disease extended to distant lymph nodes and/or other organs (pT1–pT4; N0–N3; M1). Treatments were grouped into "surgery", "surgery and chemotherapy", "surgery and radiotherapy" and "other treatments". Data analysis was performed using the SPSS package 15.0 for Windows. The analysis of the possible associations was performed using the Chi-square test, always with a level of significance of $p \leq 0.05$.

### Results

#### Population characteristics

The study population was comprised of 536 subjects diagnosed with testicular cancer. The temporal distribution found over the study period registered an upward trend, moving up from 6.2% in the first five-year period (33 recruited cases) to 48.3% in the last one (259 recruited cases). This increase was more dramatically observed from the third five-year period onwards (2001–05). The mean age of patients was 33.6 ± 13.6 years; 355 cases (66% of the total) were subjects under the age of 34. The maximum rate was found in the age groups from 20 to 34 years (326 cases; 60.8% of the total), decreasing from 35 years onwards. In the age group corresponding to subjects under 34 years of age, the most frequently diagnosed histology was nonseminomatous germ cell tumor (NSGCT), with a percentage of 58.5%. Seminoma occurred in 35.6% of all the tumors within this group. On the contrary, in the age group of 34 years and over, seminoma was more common, accounting for 62% of cases. 21.1% of the cases within this group corresponded to NSGCT.

#### Tumor characteristics

TGCTs accounted for 89.7% of the total in the series: 247 patients (46%) were seminomas, 234 (43.6%) NSGCTs, and the remaining 55 (10.2%) "other tumors". Histological distribution is shown in Table 1.

The three histological forms were mainly diagnosed at stage I, which accounts for 74.8% (401 patients) of the total of the series. 8.2% (44 patients) were diagnosed at stage II. 16.2% (87 patients) at stage III. Table 2 specifies the different stages by histological group. Five patients (0.9%) were diagnosed with bilateral germ cell tumor.

#### Treatment characteristics

A wide range of treatments has been indicated. Most tumors of the three histological groups reviewed were treated with more than one therapeutic measure, in particular surgery associated with chemotherapy (291 patients, 54.3%) or with radiotherapy (30 patients, 5.6%). 27.4% (147 patients) underwent only surgical treatment. The remaining 12.6% (68 patients) were either not treated or received other kinds of treatment consisting of different associations between surgery, radiotherapy and chemotherapy.

Chemotherapy was the most frequently used treatment in the three stages: 54.9% of stage I tumors, 70% of stage II tumors and 71% of stage III tumors. Surgery alone was used in 32.7% of stage I tumors, 13.6% of those diagnosed at stage II and 9.2% of those at stage III. Radiotherapy was used in 10% of stage I tumors, 9% of stage II cases and 3.4% of those at stage III. Both in the seminoma and the NSGCT groups, chemotherapy was the most frequently indicated treatment in the three stages. Table 3 shows the treatments administered to the patients in the series according to stage and histology.

The association surgery and chemotherapy was the most frequently used treatment in both age groups (62% vs. 53% in subjects under 34 years of age and 34 years or over, respectively); followed by surgery alone, also in both groups (26% vs. 30%, respectively). Surgery was combined with radiotherapy in 6% of the patients under 34 years of age and in 12% of those aged 34 or older.

An association ($p < 0.05$) was demonstrated in this series between the age of presentation and the histological variety, as well as between age and the treatment received. We also demonstrated the well-known association between histology and tumor extension, with advanced stages being more common in NSGCTs, and logically between histology and the therapeutic modality administered. The existing

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>No. of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEMINOMAS</td>
<td>247</td>
<td>46</td>
</tr>
<tr>
<td>Classic</td>
<td>235</td>
<td>43.8</td>
</tr>
<tr>
<td>Anaplastic</td>
<td>9</td>
<td>1.6</td>
</tr>
<tr>
<td>Spermatocytic</td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>NSGCT</td>
<td>234</td>
<td>43.65</td>
</tr>
<tr>
<td>Pure pathological types</td>
<td>113</td>
<td>21.1</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>77</td>
<td>14.4</td>
</tr>
<tr>
<td>Yolk sac tumor</td>
<td>10</td>
<td>1.9</td>
</tr>
<tr>
<td>Teratomas</td>
<td>22</td>
<td>4.1</td>
</tr>
<tr>
<td>Choriocarcinomas</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td>Mixed tumors</td>
<td>103</td>
<td>19.2</td>
</tr>
<tr>
<td>Unspecified NSGCT</td>
<td>18</td>
<td>1.1</td>
</tr>
<tr>
<td>Other tumors</td>
<td>55</td>
<td>10.2</td>
</tr>
</tbody>
</table>

NSGCT: non-seminomatous tumor.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Seminomas (%)</th>
<th>NSGCT (%)</th>
<th>Others (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>211 (85.4)</td>
<td>159 (68)</td>
<td>31 (56.3)</td>
<td>401 (74.8)</td>
</tr>
<tr>
<td>II</td>
<td>21 (8.5)</td>
<td>21 (9)</td>
<td>2 (3.6)</td>
<td>44 (8.2)</td>
</tr>
<tr>
<td>III</td>
<td>15 (6.1)</td>
<td>52 (22.2)</td>
<td>20 (36.3)</td>
<td>87 (16.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>2 (0.8)</td>
<td>2 (3.6)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Total</td>
<td>247 (100)</td>
<td>234 (100)</td>
<td>55 (100)</td>
<td>536 (100)</td>
</tr>
</tbody>
</table>

NSGCT: non-seminomatous tumor.
association between tumor extension and the type of treatment administered was also expected and was hereby confirmed (p < 0.05, in all cases). No association was detected between variables such as age, tumor extension, therapeutic delay or multiplicity (p > 0.05).

Discussion

The number of cases increased throughout the study period, as happened in the series provided by the American Cancer Society (ACS), which showed an incidence of 8090 new cases in the USA for the year 2008 and a year later showed 8400; although paradoxically, estimated a slightly lower incidence for the year 2013 (7920 new cases). The SEER found out exactly the same results in a series from 1975 to 2010. Llanes et al. described in 2008 an annual increase since 1991, with a significant peak in the year 2003. This finding was also observed in the series we present, with an increase in the five-year period 2001–05. These results must be consistent, since the above-mentioned series refers to a health area of 300,000 inhabitants from the Autonomous Community of Madrid. Bray et al. considered that in Spain and Slovenia this incidence had increased more dramatically (6% every year) in the last few years with respect to the rest of the countries in the European community.

The mean age is in line with that published by Scheiden et al., who described a mean age of 33.7 years in their review. Cooper et al. reported a lower mean age, 26.6 years. With regard to the age groups we registered, the data also go in line with those of other authors. Similarly, the distribution by histology coincides with the vast majority of the series reviewed, which provide a figure of 50% for seminomas and NSGCTs; however, this proportion does not coincide with what was published by the Spanish Germinal Group (GG) that in 1250 patients detected a 35% of seminomas vs. a 65% of NSGCTs. This may be due, as presupposed by the authors themselves, to the fact that the early stages of seminomatous tumors were directly treated by some radiotherapy services, still unrelated to the GG.

With regard to stage, our patients had localized tumor (77%) in a higher proportion than that published by Fernández-Gómez et al. (59%) or even in the data provided by the SEER (69%). With regard to the proportion of patients with disseminated stage, our statistics (14%) is more similar to that provided by the SEER (12%). In the case of distribution by stages, we were more in line with the experience of Cooper et al.

With regard to the use of surgery as a sole treatment, our series is in line with most of the series reviewed (between 20% and 27%); however, it differs with the data provided in these same studies regarding the associations between surgery and chemotherapy and surgery and radiotherapy. In those series both strategies are used with the same frequency, with percentages ranging from 37–41% and 31–39% respectively; whereas in the case of the series of the Community of Madrid, it is striking the large number of patients (54%) treated with the combined regimen of surgery and chemotherapy versus those treated with the association of surgery and radiotherapy (8%).

As in most of the publications reviewed, in the series we present seminoma was especially diagnosed in older age groups (35–40 years) whereas NSGCTs occurred more frequently among younger subjects (under the age of 34). The most commonly used treatment in both age groups was the combination of surgery and chemotherapy. Age, in overall terms, should not influence treatment choice which is determined by histology and stage.

In the three histological groups defined, most tumors were diagnosed at localized stages. With regard to seminoma, the percentage of diagnosed cases decreases progressively as tumor stage increases; however, in the case of NSGCTs, the number of patients diagnosed at disseminated stages is twice the number of those diagnosed at a regional stage, data consistent with the series from the Spanish Germinal Group (GG), where the presence of metastasis at the beginning in patients with seminoma is less common (14% in our series, 21% in the GG series) than in the case of NSGCTs (31% in our series, 48% in the GG series).

The treatment most frequently used was surgery combined with chemotherapy. In some of the works consulted, surgery combined with radiotherapy was mainly used. This association is basically used in seminoma stages I and II, the association of surgery and chemotherapy being reserved for disseminated stages. In the series by Lakomý et al., when it came to treating seminomas, a clear preference for the adjuvancy with radiotherapy was observed, whereas in nonseminomatous tumors prevailed the use of adjuvant treatment with chemotherapy. This did not happen in our series, which showed a preference for

<table>
<thead>
<tr>
<th>Stages</th>
<th>S.</th>
<th>S. + CT.</th>
<th>S. + RT.</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>69 (33%)</td>
<td>100 (47.4%)</td>
<td>37 (17.5%)</td>
<td>5 (2.3%)</td>
<td>211 (100%)</td>
</tr>
<tr>
<td>II</td>
<td>2 (9.5%)</td>
<td>14 (67%)</td>
<td>4 (19%)</td>
<td>1 (4.7%)</td>
<td>21 (100%)</td>
</tr>
<tr>
<td>III</td>
<td>4 (26.6%)</td>
<td>9 (60%)</td>
<td>0 (0%)</td>
<td>2 (13.3%)</td>
<td>15 (100%)</td>
</tr>
<tr>
<td>NSGCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>48 (30.2%)</td>
<td>108 (67.9%)</td>
<td>0 (0%)</td>
<td>3 (1.9%)</td>
<td>159 (100%)</td>
</tr>
<tr>
<td>II</td>
<td>3 (14.4%)</td>
<td>16 (76.2%)</td>
<td>0 (0%)</td>
<td>2 (9.5%)</td>
<td>21 (100%)</td>
</tr>
<tr>
<td>III</td>
<td>3 (5.8%)</td>
<td>40 (76.9%)</td>
<td>2 (3.8%)</td>
<td>2 (13.5%)</td>
<td>52 (100%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td></td>
<td></td>
<td>2 (100%)</td>
</tr>
</tbody>
</table>

S: surgery; CT: chemotherapy; RT: radiotherapy.
adjuvant chemotherapy for both histological groups. In the series by Aparicio et al.\textsuperscript{18} comprised of 314 seminomas in stage I, surgery alone was used in 31.8% of cases, whereas in our experience it was performed in 33% of cases. In this same series, surgery was combined with chemotherapy (carboplatin) in 68% of cases, a slightly higher figure than that of our experience which stands at 47.4%. We coincided less with Osswald et al.\textsuperscript{19} since they treated seminomas in stage I with surgery and radiotherapy in over 80% of cases, which only occurred in 17.5% of cases in our series.

In conclusion, both in the case of seminomas and NSGCTs, adjuvant chemotherapy is more frequently used as stage progresses. The study by Germá et al.\textsuperscript{16} also highlighted, as in the case of our experience, this trend of change in the therapeutic approach to be taken in seminomas that has been followed over the past few years: radiotherapy, due to its medium- and long-term toxicity, is being replaced by adjuvant chemotherapy, which is indicated depending on stage and on the prognostic factors according to the classification provided by the International Germ Cell Cancer Consensus Group (iGCCCG). We acknowledge the main limitation of this study, which lies on the fact that the data reflected were extracted from a record without having been possible to analyze the different risk factors of these malignancies and neither was it possible to analyze in depth the different subtypes of the indicated treatments, nor their toxicity or the final results achieved.

Conflict of interest

The authors declare that they have no conflict of interest.

References

