TESTICULAR CANCER: OUR EXPERIENCE AFTER 10 YEARS

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**Summary.- OBJECTIVES:** Testicular cancer represents about 1% of malignant tumors in men. Of these tumors 95% are germ cell tumors (GCTs), which have a maximum incidence between the second and third decades of life.

Our objective was to carry out a retrospective analysis of testicular tumor cases that had been diagnosed in our Health Area between the years 2000 and 2010.

**METHODS:** We performed a retrospective descriptive study between the years 2000 and 2010 analyzing 43 patients treated for testicular cancer, including in the analysis tumor incidence, the patient’s age, clinical attended, patient’s time until appointment, presence of tumor markers, patient’s time before treatment, use of testicular prostheses, histological type and their typical characteristics, oncological treatment, tumor progression and mortality rate.

**RESULTS:** We found an incidence of 4-5 cases/100,000 population/year in our Health Area. Two-thirds of the cases were detected in Stage I, and 100% of these cases showed complete remission. Among those with higher stage tumors, two out of three patients were cured after chemotherapy. For the remaining one-third, rescue treatments managed to achieve a remission rate of 66%. Mortality was low and was linked to lymphoma or metastatic dissemination.

**CONCLUSION:** The trend towards early diagnosis with detection during the initial cancer stages, together with current chemotherapy protocols, enables a high cure rate for testicular cancer. Mortality in our series was associated with primary or secondary lymphomas.

**Keywords:** Testicular cancer. Orchiectomy. Germ cell tumors.

**Resumen.- OBJETIVO:** El cáncer de testículo representa alrededor del 1% de los tumores malignos en el varón. El 95% corresponde a tumores germinales (TTG) cuya máxima incidencia tiene lugar entre la 2ª y 3ª década de la vida.

Nuestro objetivo es realizar un análisis retrospectivo de los tumores testiculares diagnosticados en nuestra Área de Salud entre los años 2000 y 2010.

**MÉTODOS:** Estudio descriptivo retrospectivo de los pacientes con cáncer testicular entre los años 2000 y 2010, analizándose un total de 43 pacientes, con eva-
INTRODUCTION

Testicular cancer represents about 1% of malignant tumors in men (1) and constitutes an ideal model of curable malignant tumors. It is the most common solid malignant neoplasm for men between the ages of 20 and 34. Of these tumors, 95% are germ cell tumors (GCTs), which are most common between the second and third decades of life. Half of GCTs are seminomas (SGCTs); the other half are nonseminomatous tumors (NSGCTs). Pure germinal tumors represent only 20% of malignant tumors, and mixed neoplasms are more common (80%).

The goal of this study was to evaluate the incidence of testicular cancer at our center and to study multiple variables, such as patient age, clinic attended, time until patient appointment, presence of tumor markers, time until treatment, use of a testicular prosthesis, tumor histological type, oncological treatment, tumor progression and mortality rate.

MATERIALS AND METHODS

We carried out a descriptive retrospective study of patients diagnosed with testicular cancer between January 2000 and December 2010. There were a total of 43 cases in our study.

We found an incidence of 4.5 cases/105/year in our Health Area. The average age of the patients was 35 years. Besides the primary treatment with radical inguinal orchietomy (with previous analysis of testicular tumor markers and scrotal ultrasound), we performed an extensive study to clinically stage the disease progression with abdominopelvic CAT scans coupled with chest x-rays for seminoma patients and chest, abdominal, and pelvic CAT scans for patients with nonseminomatous tumors. In our anatopatological and immunohistochemical analyses, we recorded the size and localization of the tumors in addition to their histological type. Tumor stages were determined according to the classification of the Royal Madsen Hospital (2).

RESULTS

The reasons for which patients sought a urological consultation and the principal signs and symptoms from their physical examinations are described in Table I. The most frequent reason for consultation was scrotal pain, the palpation of a testicular mass and an increase in the size of the scrotum or testicles.

The average time between the patients’ awareness of symptoms and their consultation was 56 days, although these data were available for only 20 cases due to unclear answers of the others patients. The average time between diagnosis and radical orchietomy was 15 days. Over half (53.4%) of the patients chose to use a testicular prosthesis after the operation.

We observed a case in which the patient had had an ascended testicle during childhood, for whichorchidopexy was performed at 4 years of age. He developed seminoma in the same testicle when he was 24 years old. We also observed two cases of metachronic testicular cancer. One patient’s tumors were of the same tumor type (mixed NSGCT), with an interval of 4 years between the detection of one tumor and the detection of the other. The other patient had a mixed NSGCT in the right testicle and a classic seminoma in the left testicle, with a 6-year interval between the appearance of the tumors.
The levels of tumor markers were normal prior to surgery in half of the patients with suspected testicular tumors. In the remainder of patients, $\alpha$-FP and/or $\beta$-HCG were elevated in 94% of the NSGCT cases, and $\beta$-HCG was elevated in 20% of the seminoma cases.

Histological analysis of the tumor type is shown in Table II. Germ cell tumors were the most common, with a similar proportion of SGCTs and NSGCTs.

The average ages were 34.8 years old for patients with SGCT (standard deviation of 11.3 years), 29.6 years old for NSGCT patients (standard deviation of 9.8 years) and 52.1 years old for patients with non-germ cell tumors (standard deviation of 18.1 years). There were significant differences depending on the histological type of the tumor ($p = 0.006$) (Figure 1).

We also studied the lateralization of the affected testicles; 24 cases (55.8%) were in the left testicle and 19 cases (44.1%) in the right testicle. There was no significant difference in the probability of one testicle being more affected than the other ($p = 0.537$).

The average tumor nodule size was 4.11 cm (standard deviation of 3.44 cm), with no significant differences found when comparing different histological types (binomial distribution, $p = 0.558$) (Figure 2) or between different tumor stages ($p=0.250$).
The most common tumor stage for both SGCT and NSGCT was Stage I. The relationship between tumor stage and tumor type is shown in Table IV.

In Tables V and VI, we describe the oncological treatment based on our center’s protocol, which follows European recommendations. Additionally, we present the development of treatment as a function of histological type and tumor stage.

The average time of follow-up was 64 months. The Log-rank test showed a significant difference in survival according to tumor type \((p = 0.003)\), except for the comparison of SGCT and NSGCT with no significant differences in terms of survival \((p=0.148)\). Mortality and the cause of mortality are specified in Table VII, and the analysis of survival according to tumor type is shown in Figure 3.

**DISCUSSION**

Testicular cancer is the most common neoplasia among men between 20 and 34 years of age. In both Spanish (3,4,5) and international studies (6,7), a difference in the age at which different histological tumor types appear has been reported. Seminomas tend to appear between 35 and 40 years of age, whereas nonseminomatous tumors appear earlier, between 25 and 29 years of age. Non-germ cell tumors are more common in older patients. These characteristics coincide with the statistically significant \((p = 0.006)\) findings in our series.

Scrotal pain, regardless of whether it was associated with a palpable mass, was present in 50% of the testicular cancer cases. This pain is usually attributed to intratumoral hemorrhages (8,9,10) and may be responsible for erroneous initial diagnoses of epididymitis.

Because NSGCTs are faster growing than seminomas, they are more frequently associated with an initial painful presentation. By contrast, seminomas have slower growth rates, so a testicular mass and an increase in testicular size are the most common presentation types. In our series, we found that 56% of NSGCT patients presented with pain as a symptom, compared to 37.5% of SGCT patients.

In our series, we did not find significant differences in the lateralization of the affected testicle, with the same likelihood for either testicle to be affected.

Half of the germ-cell tumors inspected were seminomatosus, and among these (in agreement with published literature), the most common type was classic seminoma (75%). On the macroscopic level, the tumors were solid, lobed and yellowish. On the microscopic level, they were composed of a uniform proliferation of cells arranged in nests or sheets that had well-defined and clear cytoplasm along with vesicular nuclei with prominent nucleoli. Four cases were classified as anaplastic seminomas with a high mitotic index. Despite this subgroup having microscopic traits of a more aggressive neoplasia,
the prognosis for this stage seems to be equivalent to that for classic seminoma (11). The characteristic immunohistochemical markers for seminomas are PLAP (Placental Alkaline Phosphatase) and C-KIT (CD 11), which are useful to distinguish classic seminoma, but not spermatocytic seminoma.

The heterogeneous subgroup of mixed germ-cell tumors was the second most common subgroup. On the macroscopic level, they had features that were highly variable depending on their components, with frequent areas of hemorrhage. On the microscopic level, the most frequent type of tumor was the embryonal carcinoma, representing more than 50% of the tumor mass in most of the 15 cases studied. The next most common tumor types were yolk sac tumors, followed by teratomas, seminomas, and choriocarcinomas. In determining prognosis, it is essential to identify the distinct tumor types and the approximate percentage of the cell types in the tumor. This is especially important for embryonal carcinoma, as its presence is a risk factor for the appearance of hidden metastases.

With respect to pure forms of nonseminomatous testicular tumors, we found only one case of embryonal carcinoma and another of immature teratoma. Immunohistochemical studies are very helpful for detecting embryonal carcinoma, especially for developing a differential diagnosis with seminoma using characteristic immunostaining with antibodies against CD30, PLAP, CK7, and CKAE1-AE3.

Among the group of sex cord tumors, we detected two Leydig cell tumors that presented as small, clearly outlined nodules, one measuring 0.7, the other 0.4 cm. The characteristic immunohistochemical

<table>
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<th>ESTAGE</th>
<th>Action</th>
<th>Histología</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>I</td>
<td>Observation (34.4%)</td>
<td>SGCT (6 cases) NSGCT (4 cases)</td>
<td>Complete remission (100%)</td>
</tr>
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<td></td>
<td>Radiotherapy (7%)</td>
<td>SGCT (2 cases)</td>
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<td>Chemotherapy (58.6%)</td>
<td>SGCT (8 cases) NSGCT (9 cases)</td>
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</tr>
<tr>
<td>II y III</td>
<td>Chemotherapy (100%)</td>
<td>SGCT (9 cases) NSGCT (6 cases)</td>
<td>Complete remission (66.7%) Progression (3 cases)</td>
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<tr>
<th>Case</th>
<th>Therapeutic action</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>SGCT III b (anaplastic seminoma)</td>
<td>RT+ rescue CT</td>
<td>Remission</td>
</tr>
<tr>
<td>Mixed IIc NSGCT (embryonal carcinoma + seminoma)</td>
<td>Rescue CT + lymphadenectomy + new CT</td>
<td>Remission</td>
</tr>
<tr>
<td>Mixed NSGCT IIIb (embryonal carcinoma + immature teratoma + endodermal sinus tumor)</td>
<td></td>
<td>Died due to multiple unresectable lung metastases</td>
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profile was positive for inhibin, Melan-A, calretinin, cytokeratin, and S-100.

In other tumor groups, we observed two testicular lymphomas that both showed histological and immunohistochemical characteristics of diffuse large B cell lymphoma, the type of lymphoma that most frequently affects the testicle. On the macroscopic level, they presented the characteristic appearance of lymphomas, including a poorly defined solid mass that was whitish-gray. Histologically, we observed atypical lymphoid cells infiltrating and replacing the normal testicular architecture. It is important to note that for one of the two cases described, was a testicular metastasis of a primary cerebral lymphoma.

In conclusion, in our series, we observed three non-germ cell tumors: an undifferentiated sarcoma and the two Leydig tumor above-mentioned.

We did not find significant correlations between tumor size and histological type.

In our study, Stage I was the most common classification, for both SGCTs (80%) and NSGCTs (72%). It is important to note the high percentage of early diagnosis found on this last group respect to other broad population studies describing 55% of NSGCT with Stage I when diagnosed. There is more coincidence respect to the SGCT (75-80%)4,6,12-15.

There are no controlled, randomized studies comparing the results of monitoring and subsequent rescue treatment (if it was necessary) with post-orchietectomy adjuvant treatment using chemotherapy or radiotherapy. However, studies conducted at centers with experience in these procedures show that the overall survival rate for Stage I seminoma, with proper monitoring, is 97–100%16,17. Monitoring should be performed for at least 10 years.

We know that about 15–20% of patients with Stage I seminoma experience disease recurrence due to hidden micrometastases that are undetectable by imaging techniques. However, because seminomas are highly sensitive to chemotherapy and radiotherapy, the

<table>
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<th>Diagnosis</th>
<th>Cause</th>
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<tr>
<td>Diffuse centroblastic B cell lymphoma</td>
<td>Septic shock</td>
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<td></td>
<td>Post-CT neutropenia</td>
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<tr>
<td>Testicular metastasis of cerebral lymphoma</td>
<td>Metastatic explosion</td>
</tr>
<tr>
<td>NSGCT mixed IIIB (60% embryonal carcinoma +20% immature teratoma + 20% yolk sac)</td>
<td>Unresectable multiple pulmonary metastasis</td>
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prognoses for this tumor at Stage I are excellent, with a cure rate that is close to 100%. Traditionally, Stage I testicular cancer has been generally treated with orchietomy and adjuvant radiotherapy with 25–30 Gy to the retroperitoneum and the ipsilateral pelvic lymphatic chain. Now, with the availability of highly effective rescue chemotherapy and data indicating overtreatment of 80–85% of these patients, this radiation-based therapeutic paradigm has been questioned.

To compare the administration of radiotherapy (whether para-aortic or angle beam) with adjuvant chemotherapy by means of a single dose of carboplatin, a clinical trial was conducted. In 1477 patients in 14 countries, there was no significant difference in the relapse rate, the time until relapse, or patient survival after an average monitoring period of 4 years [22]. Thus, adjuvant therapy with carboplatin is an alternative to radiotherapy or monitoring in Stage I seminoma [16,17,22].

Our protocol, in accordance with the above-mentioned, offers monitoring, chemotherapy or radiotherapy treatment for patients with Stage I seminoma following appropriate patient information. In our studies, we found that 50% of patients chose chemotherapy, 12.5% chose radiotherapy, and 37.5% chose active monitoring. Using these three modalities, we achieved complete remission for 100% of patients. In accordance with the above-mentioned, we still need to perform studies to identify the profile of patients who would benefit from oncologic treatment of seminoma at Stage I.

With respect to Stage I NSGCTs, monitoring, retroperitoneal lymphadenectomy (RPL), and chemotherapy with two cycles of bleomycin-etoposide-cisplatin (BEP x 2) are the established options for treatment. With these treatments, the rates of long-term survival are more than 97% [23]. About 25–30% of patients with NSGCT in Clinical Stage I (CS1) have subclinical metastases; therefore, these patients would suffer relapses if treated only with orchietomy. However, any adjuvant treatment is overtreatment for 65–75% of patients with NSGCT in CS1. Thus, initial monitoring with deferred chemotherapy after recurrence is an accepted treatment option.

More than 90% of relapses are seen in the first two years after orchietomy, but later relapses are observed (> 5 years) in 1% of patients [24]. The primary risk factors for hidden metastases are the presence of lymphovascular invasion and a predominant component of the tumor being embryonal carcinoma-derived. Taking all this into account, another accepted therapeutic possibility is a treatment whereby the patient is administered adjuvant chemotherapy with two cycles of BEP (in patients with lymphovascular invasion) or simply monitored (in patients without invasion) [25]. RPL would also be indicated for patients with these risk factors, but, as chemotherapy is better tolerated, RPL has been gradually abandoned in favor of the latter [26]. In our study, 69% of patients with Stage I NSGCT were treated with chemotherapy, and 31% were simply monitored after they had been divided into risk groups according to the presence or absence of lymphovascular invasion. In both groups, there was a complete remission in 100% of the patients.

For seminoma in CSII, there are two therapeutic possibilities: radiotherapy or chemotherapy with either four cycles of EP (etoposide and cisplatin) or three of BEP. Both options achieve a similar degree of disease control [27,28]. Carboplatin alone is not an alternative to conventional chemotherapy with BEP [29]. In Stage II NSGCT, we recommend that the initial treatment be chemotherapy using three cycles of BEP. However, this treatment can be used as an alternative (if tumor markers are not elevated) to primary lymphadenectomy or monitoring. Stages III and IV are considered to have poor prognoses. Treatment in these cases is chemotherapy with three or four cycles of BEP depending on the risk group to which patients belong according to the classification of the International Germ-Cell Cancer Collaborative Group (IGCCCG) [18].

All patients with germ cell tumors in Stages II and III in our study (9 cases) were treated with chemotherapy, which resulted in complete remission in 66% of the cases. The three patients who progressed presented with SGCT in Stage IIIb, for which we administered radiotherapy and chemotherapy to achieve remission. Another patient who presented with Stage IIc NSGCT required rescue chemotherapy, retroperitoneal lymphadenectomy (because of a residual mass), and then more chemotherapy before remission was achieved. Finally, a patient with Stage IIIb NSGCT that progressed despite chemotherapy treatment presented with multiple unresectable pulmonary metastases.

There was a statistically significant relationship (p = 0.003) between tumor type and prognosis. We found that in our group of patients, 100% of those who had had an SGCT and 86% of those who had had a NSGCT survived to 100 months of monitoring after orchietomy, whereas only 33% of patients with non-germ cell tumors survived until 60 months post-orchiectomy. In this last group, the two patients who died had testicular lymphoma. One patient had diffuse centroblastic B lymphoma;
the other had a metastatic lymphoma that originated in the brain. Primary testicular lymphoma is the most common malignant testicular tumor in men over 60 years of age, representing between 25 and 50% of testicular tumors for this age group. The evolution of these tumors is aggressive, with a 5-year survival rate between 10 and 40% and a recurrence rate of 50% in the first two years in the extraganglionic areas (30,31,32).

CONCLUSION

The age for NSGCT presentation is earlier when compared to other tumor groups, as shown in other Spanish studies. The most frequent tumor stage at the time of diagnosis is Stage I, independent of the histological type, with complete remission in 100% of patients. Our high percentage of detention in the initial stages according to the trend toward early diagnosis, as is associated with current chemotherapy protocols, allows for high cure rates for testicular cancer. However, the similarity of results for complementary treatments and active surveillance for the EC I germ cell tumors implies a need to improve the classification of patients into risk groups to discern which patients would benefit from active treatment to avoid overtreatment. Mortality in our series was low and was associated primarily with lymphomous involvement.

REFERENCES AND RECOMMENDED READINGS

(*of special interest, **of outstanding interest)


