



## Testicular Cancer: Update Your Diagnosis, Prognosis, and Treatment

### Adrian P Hunis\*

*Emeritus Member of ASCO, Emeritus Member of ESMO, School of Medicine, Universidad de Buenos Aires (UBA), Argentina*

**\*Corresponding Author:** Adrian P Hunis, Emeritus Member of ASCO, Emeritus Member of ESMO, School of Medicine, Universidad de Buenos Aires (UBA), Argentina.

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### Abstract

Germ cell tumors of the testis are relatively rare carcinomas, comprising only 1% of all tumors in men.

However, because it represents a tumor with a high cure rate, affects young individuals in full productive age and is a model of disease curable even in advanced stages, with chemotherapy, it is extremely important to recognize it and increase all efforts in basic and clinical research, to improve not only the already high proportion of cured patients, but also to reduce the toxicity of the treatments.

**Keywords:** Germ Cell Tumors; Testicular Cancer; Chemotherapy

### Introduction

Germ cell tumors of the testis are relatively rare carcinomas, comprising only 1% of all tumors in men.

However, because it represents a tumor with a high cure rate, affects young individuals in full productive age and is a model of disease curable even in advanced stages, with chemotherapy, it is extremely important to recognize it and increase all efforts in basic and clinical research, to improve not only the already high proportion of cured patients, but also to reduce the toxicity of the treatments.

This high curability rate is the result of an interdisciplinary management between surgery, radiotherapy, and chemotherapy, and in relation to the latter of the development and rational management of cytostatic.

### Epidemiology

The highest incidence in the world is in the Scandinavian countries and, on the contrary, they are very rare in the African continent.

In our country (Argentina) they represent 1% of all tumors in man.

The average age-adjusted incidence is 3 to 5 per 100,000.

Its low incidence in African Americans and Africans may indicate an ethnic and/or genetic predisposition.

The affected age group is the young patient population (between 15 and 40 years old), and because of this, the potential for loss of years of productive life has meant that testicular tumors have always been considered important, both medically and economically.

For every case of testicular cancer diagnosed, 20 cases of prostate cancer are diagnosed:

- 1% of tumors in men.
- 11 - 13% of cancer deaths between 15 - 35 years.
- 3 - 5 per 100,000 males/year in developed countries.
- High risk areas (Switzerland, Scandinavia and New Zealand) 11 per 100,000.

- Low risk areas (Cuba, Africa and Asia) 0.3 per 100,000.
- Incidence has doubled in the last 40 years.

### Etiology

Testicular tumors can arise from various types of cells in the seminiferous tubules and interstitial tissue.

However, more than 95% are nevertheless of germinal origin, that is, they originate in the seminiferous tubules.

Germ cell tumors can occasionally originate in other sites (extragonadal tumors), and the possibility of effective treatment for all germ cell tumors highlights the importance of knowing the latter entity, especially when the clinical presentation of the tumor is in the midline (epiphysis, mediastinum, retroperitoneum).

Although environmental factors could influence the etiopathogenesis of these tumors, they are unknown.

A well-established predisposing factor is cryptorchidism, a factor that increases your risk by 20 to 40 times.

But this condition is only involved in 10% of all cases of germ tumors.

Another apparently involved factor would be exposure to diethylstilbestrol (DES) in utero (relative risk 9.8).

Also, those patients with infertility, where the testes are atrophic, those with androgen insensitivity syndrome and intersex conditions, present an increased risk.

Important lines of evidence implicate endocrine factors in the etiology of testicular tumors (increased production of gonadotropins).

The above mentioned refers to acquired factors, but in terms of genetic factors, the association of these tumors, with the expression of the Lewis antigen and the association of the HLABw41 haplotype with seminoma, are factors to be considered in terms of etiology.

- Age
- Race

- **Genetics:** Direct relatives, Klinefelter syndrome, alterations in C12, ploidy.
- Previous testicular pathology:
- Cryptorchidism
- Previous testicular cancer
- Infertility
- Vasectomy, infections, trauma

### Pathogeny

All germ cell tumors appear to originate from a well-characterized precursor called carcinoma in situ (CIS).

CIS has been found very early in life and may be present already during pregnancy.

CIS cells are aneuploid with some potential for invasiveness.

At the genetic level, a specific chromosomal lesion, isochromosome 12p has been well documented in CIS as in all types of germ cell tumors.

The isochromosome (12p) is found in 90% of germ cell tumors including all histological subtypes such as anatomical presentations (e.g. extragonadal tumors).

More than a third of all tumors are mixed, that is, they come from different non-seminomatous elements with or without seminoma.

The functional properties of cells, such as the production of fetoprotein alpha tumor markers (AFP) and human chorionic gonadotropin (HCG) beta subunit, are not exclusively linked to the presence of classical choriocarcinoma or the "yolk sac" tumor (endodermal sinus tumor).

These factors indicate that germ cell tumors have a common biology and that there are several intermediate forms.

But, from the clinical point of view, it is important, especially in terms of therapeutics, to maintain the distinction between seminomas and non-seminomas.

The development of germ cell tumors can be characterized as a process where pluripotential precursor cells can gradually develop

in all types of germ cell tumors with seminomatous elements with the least potential for differentiation and therefore generally presenting later in life.

The so-called spermatocyte seminoma is unrelated to the other germ cell tumors.

The lesion is not preceded by CIS, has low metastatic potential, and occurs at a later age.

On the other hand, there is evidence that extragonadal tumors with retroperitoneal clinical presentation are accompanied by CIS in one or both testicles.

This may indicate that some of the extragonadal tumors are not really extragonadal in their pathogenesis.

The appearance of a contralateral testicular germ cell tumor in patients treated for testicular cancer occurs in approximately 5% of cases.

### Pathological anatomy

Germ cell tumors of the testis are traditionally divided into seminomas and non-seminomas.

The WHO classification is used and thus we have the following subdivisions:

- Intratubular germ cell neoplasm, unclassified.
- Malignant pure germ cell tumor (showing only one cell type):
- Seminoma.
- Embryonal carcinoma
- Chorioncarcinoma
- Yolk sac tumor.

Tumor showing only one cell type:

- Seminoma 26.9%.
- Embryonal carcinoma 3.1%.
- Teratoma 2.7%.
- Yolk sac tumor 2.4%.
- Choriocarcinoma 0.03%.

Malignant mixed germ cell tumor (showing more than one histologic pattern):

- Embryonal carcinoma and teratoma with or without seminoma.
- Embryonal carcinoma and yolk sac tumor with or without seminoma.
- Embryonal carcinoma and seminoma.
- Yolk sac tumor and teratoma with or without seminoma
- Choriocarcinoma and any other element.

### Polyembryoma (teratocarcinoma)

In relation to the pathological anatomy, it should be noted that these tumors secrete protein products that we call biological markers.

Thus, we recognize two markers:

- Alpha fetus protein
- Beta subunit of human chorionic gonadotropin.

The half-life of both is different, being 48 hours for beta human chorionic gonadotropin and 7 to 10 days for alpha fetus protein.

Seminomas do not produce biological markers and if they do, it is for 2 different situations, in the first it is a pure seminoma that produces a beta subunit of gonadotropin no greater than 100 Mui/ml.

And, in the other situation, the seminoma may contain non-seminomatous elements (from choriocarcinoma).

As for non-seminomatous tumors, it can be summarized by saying that choriocarcinoma produces the beta subunit of gonadotropin, and the other tumor types secrete the alpha-fetus protein.

Both markers are secreted by the polyembryoma (teratocarcinoma).

Since the germ cell tumor is a pluripotential tumor and its cells divide rapidly, the enzyme LDH is another marker product of these fast-growing tumors, whose activity can be measured in the blood.

### Clinical presentation

The most common form of presentation is the presence of a palpable nodule or mass at the level of a testicle (Photo 1).



Photo 1

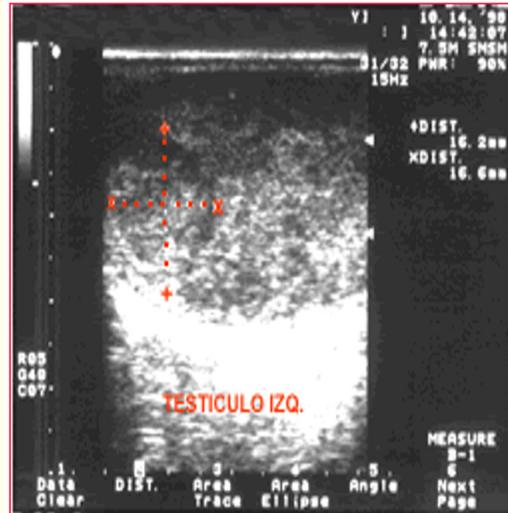


Photo 2: Ultrasound showing a solid mass in the left testicle.

The patient may notice that the appearance of it has been slowly or quickly, and sometimes the presence of it occurs after a testicular trauma.

There is a minority of patients who present with disseminated disease, for example due to the presence of a supraclavicular adenopathy associated with the testicular mass, and later staging other visceral metastatic deposits can be found.

A posteriori, it is then that the patient generally consults a urologist, who will rule out by palpation and testicular ultrasound, if the present mass is solid (tumor) or liquid (testicular hydrocele) (Photo 2).

Once the tumor is diagnosed as solid, the patient will undergo an orchiectomy through the inguinal route and thus obtain the definitive anatomopathological result.

Diagnostic and staging strategy:

- Anamnesis.
- Physical exam.
- Testicular ultrasound.
- **Tumor markers:** a-f-p, beta-hCG, LDH and F.A. placental.
- Surgical exploration (trans inguinal).
- CT of the chest, abdomen, and pelvis.

### Staging

pT: 1 = Tumor limited to the testis, including the rete testis.

2 = Tumor invading the albuginea or epididymis.

3 = Tumor invading the spermatic cord

4 = Tumor invading the scrotum.

pN N0 = Absence of metastases in regional nodes.

N1 = 2 cm lymph node metastasis. or less in its major dimension.

N2 = Metastasis in 1 lymph node larger than 2 cm. but less than 5 cm. in its greatest dimension, or multiple lymphadenopathies not greater than 5 cm. at its largest diameter.

N3 = Metastasis in a lymph node, greater than 5 cm. at its maximum

Dimension.

Mx: The presence of metastasis cannot be established

M0: Absence of metastasis

M1: presence of metastasis (see Indiana prognostic classification).

Table 1: TNM staging system for testicular cancer.

If we now consider the staging of testicular cancer, it is divided into three stages:

- **Stage I:** Tumor located in the testicle.
- **Stage II:** Tumor spread to sub renal lymphatics: A: microscopic, B: macroscopic and within the latter: B1 with small masses present, and B2: large mass.
- **Stage III:** Tumor spread to suprarenal and supra-diaphragmatic lymphatics or visceral metastases, where A. represents lymphatic metastases and B represents parenchymal metastases.

Before inguinal orchiectomy, the biological markers must be measured in blood.

A radical inguinal orchiectomy is performed a posteriori without violation of the scrotum (this maneuver can produce alterations in lymphatic drainage and in the subsequent evolution of this pathology).

After orchiectomy, sequential dosages of markers are mandatory along with imaging studies.

In patients with seminoma, the staging process consists of a complete clinical examination, a chest X-ray (front and profile), a computed axial tomography of the abdomen and pelvis.

In these patients, alpha fetoprotein is always normal, except for seminoma that presents with massive liver metastases, a process which increases this marker.

Human chorionic beta gonadotropin may be slightly elevated (no greater than 100) in 20% of cases.

For patients with non-seminomatous tumors, the staging procedure consists of the complete physical examination, a CT scan of the chest, abdomen, and pelvis, and in some circumstances a CT scan of the brain.

In these tumors, biological markers such as plasma LDH may be elevated, and therefore must be requested routinely.

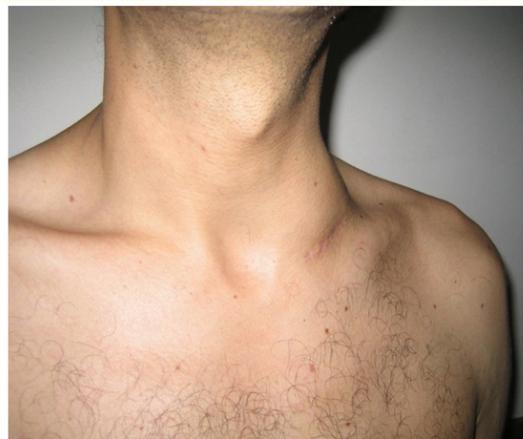
In metastatic disease, patients are classified according to prognosis.

Although several prognostic models have been established, the Indiana University prognostic classification is the most widely used.

It divides metastatic disease into three groups.

**Minimal illness:**

- Elevation of alpha fetus protein (AFP) and human chorionic gonadotropin beta subunit (BGCH) only. AFP less than 1000 ng/ml; BGCH less than 5,000 iul/ml; and LDH less than 1.5 times the upper limit of normal.
- Cervical lymphadenopathy (Photo 3) with or without palpable abdominal mass.
- Pulmonary metastases in numbers less than 5 per lung field and less than 2 cm. in its greatest dimension.



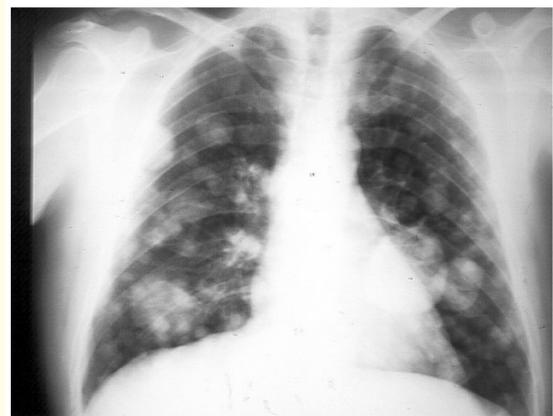
**Photo 3:** 32-year-old patient with left supraclavicular adenopathy. Note the biopsy scar.

**Moderate illness:**

- Palpable abdominal mass as the only anatomical site.
- Pulmonary metastases between 5 and 10 per lung field (Photo 4) and with a maximum diameter of less than 3 cm. or mediastinal mass less than 50% of the intrathoracic diameter or solitary pulmonary metastasis greater than 2 cm. (with or without palpable abdominal mass)



**Photo 4:** Pulmonary metastases between 5 to 10 per lung field.



**Photo 6:** Advanced lung disease (Typical image in "balloon release").

**Advanced disease (high risk):**

- Mediastinal mass greater than 50% of the intrathoracic diameter or more than 10 pulmonary metastases per field or multiple greater than 3 cm. in diameter (with or without palpable abdominal mass) (Photo 6).
- Palpable abdominal mass with any features for lung metastases.
- Liver, bone, or brain metastases (Photo 5).



**Photo 5:** Mts. in CNS.

TNM staging is currently completed with one more item, which is serum tumor markers:

- SX: Marker studies not performed or available.
- S0: The study values of the markers, within the limits of normality.
- S1: LDH less than 1.5 x N AND hCG Less than 5000 ml u/ml AND AFP less than 1000 ng/ml. (Note: N indicates the optimal limit of normal for LDH activity).
- S2: LDH 1.5-10 x N or hCG between 5000-50000 or AFP between 1000 - 10000.
- S3: LDH greater than 10 x N or hCG greater than 50,000 or AFP greater than 10,000.

The group of patients with minimal disease represents 56% of non-seminomatous tumors, with a 90% disease-free survival at 5 years and an overall survival of 92% at 5 years.

Patients with moderate and advanced disease represent 28% and 16% of non-seminomatous tumors, respectively.

The disease-free period is 75% and 41% respectively in these entities, and the overall survival is 80% to 48% respectively.

**Prognostic factors:**

- **Stage:** SV at 5 years in E I and II is > 95%; in E III 75 - 90%.
- **Pathological anatomy:** Embryonal carcinoma "poor prognosis" due to vascular and lymphatic invasion at diagnosis.
- Large primary mediastinal non-seminoma.
- **Tumor markers:** Elevated pretreatment, implies poor prognosis.
- **Metastases:** Lymph nodes and lungs (Good Prognosis), liver, bone, and brain (Bad Prognosis).

**Stage-oriented treatment of testicular seminoma**

Once the T is established, clinical staging is performed in these patients, by determining biological markers, and in low-risk patients with chest X-ray, abdominal and pelvic CT, and in high-risk patients: CT of chest, abdomen and pelvis and eventually magnetic resonance imaging (MRI).

As a result of this staging, testicular seminomas can be classified into:

- **Stage 1:** Disease limited to the testicle.
- **Stage 2:** Infrahilar retroperitoneal lymph node disease: subclassified in 2a: presence of micro metastases; 2b1: small volume disease metastasis: less than 5 cm; and 2b2: metastasis to large masses: greater than 5 cm.
- **Stage 3:** Suprahilar or parenchymal lymph node disease.

Both stages 1 and 2a, which cannot be diagnosed by imaging, will be equated to clinical stage 1 and external radiotherapy is performed at a dose of 3,000 cGy infradiaphragmatic.

In stage 2b1, radiotherapy is also performed with the addition of a 600 cGy boost.

In both stages 2b2 and 3, chemotherapy is performed.

Although historically there are several regimens of the same, the most used at present are: either 4 cycles of etoposide - cisplatin (5 days each cycle, every 28 days), or 3 cycles of BEP scheme (bleomycin, etoposide and cisplatin, 5 days each cycle and every 28 days as well).

Once the response to chemotherapy has been evaluated, we can find ourselves faced with a complete response; residual masses

less than 3 cm., residual masses greater than 3 cm. and less than 5 cm., or: residual masses greater than 5 cm.

In the case of a complete response or residual masses smaller than 3 cm, the patient remains under clinical control.

Yes, the residual masses are greater than 3 cm and less than 5 cm., an observation period of 3 months is established.

If after that, there is a reduction in the mass, the patient goes to clinical control.

If the tumor mass remains unchanged or undergoes growth as in the case of residual masses greater than 5 cm, surgical rescue of these residual masses should be performed.

Thus, the result of the rescue we can have fibrosis or necrosis, in which case the patient goes to control; persistence of the tumor with the presence of non-seminomatous tumor elements, in which case the behavior that we will see later for non-seminomatous tumors will be applied; or finally, the observation of the preservation of the same tumor type, that is, seminoma.

If the seminoma is unresectable or if the patient has already received radiotherapy for it, chemotherapy will be indicated with the schemes mentioned above.

If the seminoma is resectable and radiotherapy has not been previously performed, it will be indicated.

**Stage-oriented treatment of non-seminomatous testicular tumors**

Also here, with the T established, clinical staging is performed, by determining biological markers, in low-risk patients a chest X-ray, abdominal and pelvic CT, and in high-risk patients, chest CT, abdomen and pelvis and eventually an MRI.

The therapeutic behavior will be different depending on whether the markers are negative or positive.

With the presence of positive markers, chemotherapy is always indicated.

With negative markers, behavior depends on the outcome of retroperitoneal or parenchymal node disease.

In the absence of images of parenchymal retroperitoneal lymph node disease in the studies performed, the patient will undergo a selective lymphadenectomy for the correct staging of the tumor.

This lymphadenectomy is selective, because it tries to save the innervation of the region, avoiding later problems in the patient's ejaculation.

It is also for this reason that the patient's sperm can be preserved, given the imminence of a still selective retroperitoneal emptying.

But it should be emphasized that in our environment, the most used therapeutic attitude in this situation is the strict control of the patient with images and markers.

Of course, this must be done in institutions that have the appropriate means to do so.

In stage 1 (disease limited to the testicle), if N is negative and pathological stage 1 is confirmed, the patient goes to control.

If N is positive, it is classified as stage 2a and 2b1.

Stage 2 (infrahilar retroperitoneal lymph node disease): According to the anatomical-pathological findings, it will be subclassified into: Pathological stage 2a (micro metastases) in which the lymphadenectomy will be limited or, Stage 2b1 (metastasis to a small mass less than 5 cm), in which the lymphadenectomy will be unilateral or bilateral.

In the case of the presence by CT of retroperitoneal or parenchymal lymph node disease, chemotherapy will be indicated: And this corresponds to clinical Stage 2b1 (metastasis to a small mass, less than 5 cm); stage 2b2 (metastasis to a large mass, greater than 5 cm) and stage 3 (suprahilar or visceral lymph node disease).

After chemotherapy is performed, the determination of markers is performed:

- If the markers are positive, it is recycled into chemotherapy.
- If there is chemoresistance, and if only alpha-fetus protein is elevated and the residual mass is unique, rescue surgery can be performed.
- If the biological markers are negative: If there is no residual mass and if there was no teratoma in the primary tumor, the patient goes to control.

If there is a residual mass or if there is a teratoma in the primary, surgical rescue will be performed.

Once the latter has been carried out, there may be the presence of fibrosis, necrosis or teratoma in which case the patient remains in control.

In the presence of tumor persistence, the patient was admitted to another salvage chemotherapy scheme.

The germ cell tumor of the testis has become a model of curable neoplasia.

The success of chemotherapy in schemes with cisplatin in advanced disease, laid the foundations for treatment in earlier stages.

Approximately 25% of patients who undergo retroperitoneal dissection for clinical stage I will have evidence of microscopic lymph node metastases.

Also, approximately 10 to 15% of patients who undergo lymph node dissection will relapse at a distance.

Thus, randomized studies have shown that two cycles of chemotherapy with cisplatin, vinblastine, and bleomycin, or with etoposide and cisplatin, a cure will be obtained in approximately 98% of treated patients.

Postoperative adjuvant chemotherapy is therefore recommended in patients with pathological stage II.

On the other hand, we know that in clinical stage I, there are negative prognostic factors for a greater propensity to metastasize: Invasion of the albuginea, invasion of the epididymis, the spermatic cord, and mainly vascular invasion.

In the advanced disease model, combination chemotherapy made testicular cancer the first advanced curable solid tumor model.

In the early 1970s, researchers at the Memorial Sloan-Kettering Cancer Center began to evaluate the combination of drugs such as vinblastine, D-actinomycin, and bleomycin (BAV-I scheme).

Prior to this, patients in a metastatic situation received monotherapy preferably with actinomycin-D.

Using the VAB I scheme, an objective response rate of 36% was obtained with a complete response rate of 14%.

The addition of cyclophosphamide and cisplatin to the BAV 1 scheme generated the BAV VI scheme, which increased the response rate to 78%.

Concomitant, the group from Indiana University began using the combination of cisplatin, vinblastine, and bleomycin in these patients, demonstrating a 70% complete response rate and a 60% survival rate at 10 years.

Given that cisplatin was already perfectly manageable with hyperhydration before and after its infusion, the PVB scheme only had the toxicity of vinblastine due to its high doses (0.4 mg/kg).

Subsequent clinical studies evaluated the dose of vinblastine and led to the randomized study of PVB compared with BEP (cisplatin, etoposide, and bleomycin).

This trial demonstrated significantly lower toxicity in the BEP arm, with equal or better response and survival rates than PVB (83% for BEP versus 71% for PVB in terms of complete response rate).

Then later studies and to decrease the toxicity even more, compared the BEP regimen, versus the EP (without bleomycin).

The first study conducted in patients with minimal disease from the Indiana classification was conducted by the ECOG (Eastern Cooperative Oncology Group).

It was discontinued as response rates were lower in the EP arm.

Finally, later studies showed that 3 cycles of BEP scheme are equally effective as 4 cycles of EP.

Regarding second-line or salvage therapy after a first line with cisplatin, this agent is used again together with vinblastine (doses of 0.11 mg / kg days 1 and 2) ifosfamide and cisplatin. This scheme is repeated every 3 weeks for 4 cycles of chemotherapy.

Thus, 50% of patients reach the complete response.

Bone marrow transplantation was initially used as 3<sup>rd</sup> line therapy, and today peripheral precursor cells with colony-stimulating

factors and transplant-dose chemotherapy are used as initial salvage therapy.

The persistence of pathological images in the re-staging of the post-chemotherapy patient and generally with negative biological markers, leads to the concept of salvage surgery.

It should be as aggressive as possible, in terms of total resection of large masses and or metastases to leave the patient without post-surgical disease.

One aspect to consider important in patients cured with chemotherapy is its late toxicities, so it is here where the equation benefit (less toxic scheme) versus risk (no cure) is the axis of the therapy in question.

The response rates in patients with seminomatous tumors of the testis to combination chemotherapy and based on cisplatin, is as effective as in non-seminomatous tumors mentioned above in their chemotherapy history.

### **Chemotherapy**

Chemotherapy is the use of drugs to kill cancer cells, usually by preventing cancer cells from growing, dividing, and making more cells. Chemotherapy is given by a clinical oncologist, a doctor who specializes in treating cancer with drugs.

Chemotherapy for testicular cancer is given directly into a vein, so it enters the bloodstream and reaches cancer cells throughout the body. There are also types of chemotherapy that can be taken by mouth, but they are not generally used for testicular cancer.

A chemotherapy regimen or program usually consists of a specific number of treatment cycles that are given within a specified time frame. A cycle of chemotherapy for testicular cancer usually lasts 3 weeks. Testicular cancer can be treated with 1 to 4 cycles of chemotherapy, depending on the stage of the cancer. During treatment, a patient may receive one drug at a time, or a combination of different drugs given at the same time.

The following drugs are used for testicular cancer, usually in the combinations listed below. However, the drugs used for testicular cancer change, and drugs other than those listed below may be used:

- Bleomycin (available as a generic drug).
- Carboplatin (available as a generic drug).
- Cisplatin (available as a generic drug).
- Etoposide (available as a generic drug).
- Gemcitabine (Gemzar).
- Ifosfamide (Ifex).
- Oxaliplatin (Eloxatin).
- Paclitaxel (available as a generic drug).
- Vinblastine (available as a generic drug).

The following chemotherapy regimens can be used for testicular cancer:

- BEP: Bleomycin, etoposide, and cisplatin.
- Carboplatin (for pure stage I seminoma only).
- EP: Etoposide and cisplatin.
- TIP: Paclitaxel, ifosfamide, and cisplatin.
- VeIP: Vinblastine, ifosfamide, and cisplatin.
- VIP: Etoposide, ifosfamide, and cisplatin.
- High-dose carboplatin and etoposide.
- Gemcitabine, paclitaxel, and oxaliplatin.

Combination chemotherapy studies based on cisplatin allow to conclude that:

- Short-term intensive induction therapy with the most active agents, in optimal dose, is more important than maintenance chemotherapy.
- Moderate dose elevation increases toxicity, without improving therapeutic efficacy.
- Salvage curative therapy is possible for refractory germ cell tumors.
- Preclinical prognostic models of synergism, such as vinblastine + bleomycin or cisplatin + etoposide have clinical relevance.

Combination chemotherapy regimens:

- BEP: bleomycin + etoposide + cisplatin.
- PE: etoposide + cisplatin (4 courses in patients with a favorable prognosis).

- Other regimens appear to produce similar survival outcomes but have been less extensively studied or are used less frequently.
- PVB: cisplatin + vinblastine + bleomycin.
- POMB/ACE: platinum + vincristine + methotrexate + bleomycin + dactinomycin + cyclophosphamide + etoposide.
- VIP: etoposide + ifosfamide + cisplatin.

The germ cell tumor has become a model for the development of new drugs.

Thus, cisplatin was approved by the FDA (Food and Drug Administration) for testicular and ovarian cancer, and etoposide and ifosfamide for refractory germ cell tumors.

### Follow-up of patients with testicular tumors

The follow-up of tumors in patients with testicular cancer is debated as to how it should be done, in terms of studies and frequency.

The latter varies depending on whether the tumor is seminoma or non-seminoma and should be greater the more advanced the stage.

For example, at the level of the T, negative prognostic factors are the existence of embryonic elements, vascular or lymphatic invasion, invasion of the albuginea or epididymis and the absence of elements of the yolk sac, and thus in these cases, follow-up should be extreme.

In the case of seminoma treated with radiotherapy, in the first year it is followed with a clinical examination, markers, and Rx. chest and CT every 6 months.

Then from the second year to the tenth year, it is followed with the elements previously mentioned and annually.

In the case of a clinical stage 1 non-seminomatous tumor, it is followed during the first year with symptoms, markers, and images every 2 months; with the same items every 3 months in the second year; every 6 months with the same elements from the 3rd to the 5th year; and annually from 6 to 10 years.

In the case of a pathological stage 1, it is followed during the first year every 2 months with symptoms, markers, and chest X-ray,

with CT every 6 months; then during the 2<sup>nd</sup> year, with symptoms, chest X-ray and markers every 3 months and CT every 6 months; during the 3<sup>rd</sup> to 5<sup>th</sup> years: with all the elements together every 6 months; and from the 6<sup>th</sup> to the 10<sup>th</sup> year, annually with all the elements.

Finally, in the case of stages 2 and 3: During the first year every 2 months with symptoms, chest X-ray and markers and CT every 3 months; during the 2<sup>nd</sup> year with symptoms, chest X-ray and markers every 3 months and CT every 6 months; after the 3<sup>rd</sup> to the 5<sup>th</sup> year, with clinical chest X-ray and markers every 6 months and annual CT; and finally, from the 6<sup>th</sup> to the 10<sup>th</sup> year with all these elements on an annual basis.

### Management of recurrence of testicular tumors

The decision for further treatment depends on several factors such as tumor type, previous treatment, site of disease relapse, as well as individual considerations for each patient.

Salvage chemotherapy regimens consisting of ifosfamide, cisplatin, and/or etoposide or vinblastine can induce complete responses in approximately 25% of patients with disease that has persisted or relapsed after other cisplatin-based regimens.

The patients with the most favorable prognosis are those who have had a complete response to the initial chemotherapy performed and those without extensive disease.

High-dose chemotherapy with autologous bone marrow transplantation has also been used in the case of refractory disease.

Thus, complete, and durable remissions are obtained in 10 to 20% of patients with disease resistant to standard cisplatin-based regimens and who are treated with high doses of carboplatin and etoposide with autologous bone marrow transplantation.

The durable complete remission rate could exceed 50% if high-dose chemotherapy is used as salvage chemotherapy during the initial relapse of primary testicular cancer.

In general, patients with tumors that progress to baseline or salvage therapies and those with extragonadal refractory mediastinal tumors do not appear to benefit as much from high-dose chemotherapy followed by transplantation, as do those who relapse after an initial response.

In some highly selected patients with disease refractory to chemotherapy and confined to a single site, surgical resection can provide long-term disease-free survival.

The choice of salvage surgery versus bone marrow transplantation for refractory disease is based on resectability, the number of metastatic disease sites, and the degree to which the tumor is resistant to cisplatin.

In selected patients, oral etoposide for 21 to 28 days may benefit patients who achieve a complete response after salvage therapy.

A special case of late relapse may be that of patients who relapse after more than 2 years after achieving a complete remission; this population represents less than 5% of patients who are in complete remission after 2 years.

In this subgroup of patients, the results with chemotherapy are marginal and surgical treatment is usually superior, if it is technically feasible.

This may be because teratoma may be amenable to surgery during relapse and has a better prognosis after late relapse than carcinoma.

Mature teratoma is a relatively resistant histologic subtype, so chemotherapy may not be appropriate.

Clinical trials are appropriate and should always be considered, including phase 1 and 2 studies for those patients who do not achieve a complete remission with induction therapy or who do not achieve a complete response after etoposide and cisplatin in their initial relapse or for those patients who have a second relapse.

### Long-term effects of treatment

Since most testicular cancer patients who receive chemotherapy are curable, it is important to understand the long-term effects of chemotherapy.

At the fertility level, it is noteworthy that several patients present oligospermia or abnormalities in the sperm before therapy.

Virtually everyone becomes oligospermic during chemotherapy.

However, several recover sperm productions and retain the ability to procreate.

Children do not appear to be at special risk for birth defects.

As soon as regarding secondary leukemias, there have been several reports of elevated risks of contracting secondary acute leukemia, primarily non-lymphocytic.

In some cases, these were associated with the prolonged use of alkylating drugs or with the use of radiotherapy.

Etoposide-containing regimens are also associated with an increased risk of secondary acute leukemias, usually in myeloid lines, and with a peculiar 11q23 chromosomal aberration.

Etoposide-related leukemias typically present earlier after treatment than alkylating drug-related leukemias and often demonstrate balanced chromosomal abnormalities of the long arm of chromosome 11.

At the level of renal function, there are small decreases in creatinine clearance (about a 15% decrease on average) during treatment with cisplatin, but these alterations appear to remain stable in the long term, without significant deterioration.

At the level of hearing, bilateral hearing deficits occur during cisplatin chemotherapy, usually at sound frequencies of 4 to 8 kilohertz, outside of the conversational tone scale.

Therefore, hearing aids with standard doses of cisplatin are rarely required.

Although bleomycin-derived pulmonary toxicity can occur, it is rarely fatal with total cumulative doses below 400 international units of bleomycin.

Although declines in lung function are common, they are rarely symptomatic and are reversible after completion of chemotherapy.

At the metabolic level, there is a report, but not confirmed by other studies, in which patients treated with cisplatin may present a posteriori elevation in total serum cholesterol.

Nor have long-term effects been demonstrated at the level of coronary artery disease.

Radiation therapy, which is used in seminomas, has been linked to the development of secondary tumors, especially solid tumors in the irradiated region, and usually after a period of a decade or more. These tumors include cancer of the stomach, prostate, bladder, colon, rectum, and possibly pancreas.

Radiation therapy and chemotherapy for testicular cancer is associated with an approximate 2.5 increase in cardiovascular morbidity.

In retrospective series with many patients, the actuarial risks of cardiovascular events were 7.2% for radiotherapy, and 3.4% for chemotherapy, especially in schemes with cisplatin.

## Conclusion

This high curability rate is the result of an interdisciplinary management between surgery, radiotherapy, and chemotherapy, and in relation to the latter of the development and rational management of cytostatic.

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