Focus

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Medical insurance
for testicular cancer

SCOR Global Life

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Introduction

In October 1996, a 25 year old cyclist with a promising professional career consulted his physician and was found to have a malignant testicular tumour with lymph node, pulmonary and cerebral metastases. After two surgical procedures, one of which was neurosurgical, and several courses of aggressive chemotherapy, a complete remission was obtained. Since 1999, this outstanding champion has won the Tour de France race seven times!

In the autumn of 2002, an international rugby football player was operated for a testicular tumour. He also underwent aggressive chemotherapy. In October 2003, he played in the Rugby World Cup in Australia.

These two examples illustrate the extraordinary improvement in the prognosis of cancers of the testicle which has taken place in the last twenty years. Our underwriting approach fundamentally respects the advances achieved in this clinical field.

Epidemiology

Despite its low incidence, 0.03‰ per year, testicular cancer is the commonest cancer in men of 15 to 35 years of age. Until 1977, non-seminomatous germinal cell tumours were the highest cause of death in men of 25 to 35 years of age.

From 1985 to 1995, it has become a model for curable neoplasm. Between 1970 and 1975, only **10%** of men with testicular cancer survived whereas, in 1995, the survival rate had risen to **90 to 95%**.

INCIDENCE RATES AND MORTALITY OBSERVED IN THE UNITED STATES (2001-2003)			
	ESTIMATED NEW CASES (2006)	**INCIDENCE RATE**	**MORTALITY RATE**
Genital Organs Cancer	321,490	77.9	10.9
Testis Cancer	8,250	2.7	0.1

Source: SEER tables I-1 et I-4, Cancer Facts & Figures 2006 – American Cancer Society et National Cancer Institute USA.

This spectacular result is due to improved methods of diagnosis, to advances in the measurement and interpretation of tumour markers, to the efficacy of new cytostatic drug associations using platinum salts and, finally, to new surgical techniques which are now well established.

One thousand five hundred new cases of testicular cancer are diagnosed annually in France. The peak frequencies are observed between the ages of 20 and 40 years and around 60 years of age. Although seminoma is rare in patients under 10 years of age and in the over 60s, it is, nevertheless, the commonest histological type.

The global incidence has more than doubled in the last 40 years. There are important geographic variations. The highest incidences are observed in the Scandinavian countries, Germany and New Zealand. The United States of America and temperate western countries have an intermediate incidence; Asia and Africa seem less affected.

AGE-ADJUSTED PERCENT DIAGNOSED WITH CANCER (2001-2003)				
	DIAGNOSED WITH CANCER IN:			
CURRENT AGE	**10 YEARS**	**20 YEARS**	**30 YEARS**	**ENVENTUALLY**
10 years	0.02%	0.12%	0.24%	0.36%
20 years	0.10%	0.22%	0.29%	0.34%
30 years	0.12%	0.19%	0.22%	0.24%
40 years	0.07%	0.11%	0.12%	0.13%
50 years	0.03%	0.05%	0.05%	0.06%
60 years	0.01%	0.02%	0.02%	0.03%

Source: SEER table XXV-7, April 2006, National Cancer Institute USA.

The cause of germinal testicular cancer is unknown. There have been reports of familial cases in brothers.

There is a strong relationship between testicular atrophy and testicular cancer. The atrophied testicle degenerates 20 to 40 times more than a normal testicle. The relationship between cryptorchidism and cancer of the testis has been known since 1851. Ten per cent of cases of testicular cancer occur in cryptorchidism. Kleinfelter's syndrome is also a predisposing factor.

Genetic

The principal characteristic of germinal cells is the passage from 2 x N chromosomes (2 x 23 = 46, 44 + XY in men and 44 + XX in women) to gametes (spermatozoids) only containing N chromosomes (23, 22 + X or 22 + Y). Germinal cell tumours are nearly all hyper diploid, sometimes triploid or even tetraploid. This hyper ploidism implicates the precocity of chromosomal duplication in the process of neoplastic transformation of the germinal cells.

The cancerous cells of germinal tumours contain at least one X and Y chromosome. This observation proves that cancerous transformation takes place before the anaphase of meiosis.

The iso-chromosome of the short arm of chromosome 12, i(12p), is a specific genetic marker for germinal cell tumours. It has been identified in all histological types and in the in situ tumours. The cells of germinal cell tumours which do not express i(12p) have an amplified expression of genes 12p which has been shown on genetic markers such as aberrant bands of repetitive 12p segments. Consequently, the excess 12p genetic material is constant in germinal cell tumours and it represents one of the earliest genetic events in the cancerous transformation of this cell line. It also demonstrates the monoclonal origin of these tumours.

In addition to this excess genetic material (hyper ploidism, excess 12p), there have also been demonstrated numerous and important losses of genes. The 12q chromosome has two very frequent sites of acquired loss which are not chance findings. The homozygotic deletion of the 12q 22.2 band suggests the presence of a tumour suppressing gene at this site which may be specific to germinal cell tumours.

The iso-chromosome i(12p) has been identified in acute leukaemia associated with mediastinal germinal cell tumours.

Clinical Signs

Survival in testicular cancer is closely related to the extension of the tumour at the time of diagnosis. The symptoms are banal and usually relate to a sensation of partially or globally increased size of the testis observed by the patient or his partner.

The other symptoms are:
▸ Testicular or scrotal pain (10%),
▸ Presentation due to metastatic disease (10%),
▸ Vaginal hydrocoele,
▸ Rarely, sterility.

EVERY TESTICULAR LUMP SHOULD BE CONSIDERED TO BE A CANCER UNTIL PROVED OTHERWISE.

Histology

The anatomy explains the histological variety of testicular tumours

The seminiferous tubules contain two types of cell:

> The SERTOLI cells which line the basal membrane of the seminiferous tubules and surround the germinal cells throughout their maturation to spermatazoids.
> The stroma which joins all the seminiferous tubules contains LEYDIG cells which produce the androgens essential for spermatogenesis amongst other things.

Classification of Testicular Cancer

Testicular cancer is classified as germinal cell or non germinal cell tumours.

Germinal Cell Tumours

Germinal cell tumours account for 95% of all testicular cancer. The carcinoma in situ (intra-tubular germinal cell carcinoma) is the precursor of invasive germinal cell cancer. An in situ component is found in practically all germinal cell tumours. It takes an in situ tumour, on average, 5 years to become invasive. These tumours are then divided into two groups: seminomatous and non-seminomatous tumours.

Seminomas

Seminomas account for about half of all germinal cell tumours.

Typical seminoma or semino-gonioma, represents 85% of all seminomas and occurs usually between the ages of 40 or 50 years.

Anaplastic seminoma is the form responsible for 30% of deaths from seminoma. Anaplastic seminoma is more aggressive. Its diagnosis is based on a high mitotic activity. These tumours may be constituted by giant syncytio-trophoblastic cells which secrete β-HCG. Their prognosis is the same as non-seminomatous tumours. The extension of these tumours is often underestimated.

Spermatocytic seminomas account for 10% of all seminomas. They are usually observed in patients over 50 years of age. This histological variety is not associated with in situ carcinoma and, therefore, its relation to other germinal cell tumours is uncertain. Its metastatic potential is very low and the prognosis is excellent. Surgery alone is the treatment of choice.

Non-seminomatous tumours

Teratoma and teratocarcinoma. Both forms secrete alpha 1 foetoprotein.

Embryonal cancer often takes the form of an epithelioma. Its pleiomorphism, giant cells and high numbers of mitoses indicate the very malignant character of this form of tumour.

Choriocarcinoma is a histological variety with two cell types:

> Syncytio-trophoblastic and cytotrophoblastic components. The syncytial component is particularly aggressive.
> The vitelline sack or endodermal sinus tumours.

Histological analysis of germinal cell tumours often reveals mixed lesions with two or even three distinct components.

It is essential to understand that the prognosis of testicular cancer is determined by the most aggressive component and treatment is adapted accordingly. The analysis of tumour markers before and after surgery may help identify small cellular contingents which were not observed at microscopic examination of the resected tumour.

Non Germinal Cell Tumours

These tumours are very rare, less than 5% of all testicular cancer.
Examples are Leydig cell tumours, Sertoli cell tumours and other tumours of the testicular stroma : gonadoblastoma, adenocarcinoma of the rete testis, sarcoma of the testis, mesothelioma and carcinoid tumour.
In addition, testicular lymphoma and metastases from other primary tumours have been reported.

Immunohistochemical Markers

Germinal cell tumours do not express the usual markers of somatic tumours such as keratin or vimentin. Nevertheless, seminomas and non-seminomatous tumours express placental alkaline phosphatase. The immunohistochemical search for this substance may help type some tumours of uncertain origin.

Work up of testicular tumours

The imaging methods are: postero-anterior and lateral chest X-Ray, cerebral, thoracic and abdominal CT scan. Lymphography is no longer used since the introduction of radiological scanning techniques.

The PET scan (Positron Emission Tomography) is very valuable. The high sensitivity of this investigation allows detection of very small tumour extensions.

The lymph nodes of interest are situated in the retroperitoneal space opposite the renal pedicle, in the inter aorto-caval space, and in the lateral aortic region. Embryologically, the testicles originate from the renal area and their vascular and lymphatic pedicles also arise there before following the migration of the testes to the scrotal sacks during development. The iliac lymph nodes are only invaded retrogradely.

The main biological markers are the β fraction of the human chorionic gonadotropin (β-HCG), the alpha 1 foetoprotein (AFP) and lactic dehydrogenase (LDH), the increase in which indicates a large tumour mass.

The AFP is not secreted by pure seminomas and any increase in this marker would put in doubt such a histological classification of a testicular tumour. AFP has a half-life of 5 to 7 days. It usually indicates the presence of a teratocarcinoma, an endodermal sinus tumour or an embryonal carcinoma.

With the exception of germinal cell tumours, AFP increases when there is liver damage (infection, alcohol or drug toxicity), in primary hepatocellular carcinoma and, rarely, in certain tumours of the gastrointestinal tract.

A raised β-HCG is often synonymous with a choriocarcinomatous component. Its half-life is 8 to 36 hours. Analysis of the slope of decrease of the β-HCG after surgery provides a prognostic index and helps decide the necessity for adjuvant treatment. It may be raised in certain metastatic forms of seminoma (15 to 20% of cases). The β fraction of HCG is common to a number of pituitary hormones and, therefore, the measurement of total HCG is of limited use for assessing the prognosis of testicular cancer.

The third marker, LDH, is useful because it is independent of other markers in patients with advanced tumours. The LDH is a non-specific indicator of tumour mass.

These three markers should be measured before and after primary orchidectomy and then regularly during the follow-up of these patients. When raised before surgery, the slope of decrease is very important in deciding treatment.

To establish prognostic factors for localised testicular tumours, the oncological teams of four large hospitals (Princess Margaret Hospital, the Danish Testicular Cancer Study Group, the Royal Marsden Hospital and the Royal London Hospital) united their efforts and pooled their results of follow-up of 638 patients with seminomas which had not extended beyond the testis (Stage I). The following parameters were studied:

> Size of tumour,
> Involvement of the Rete Testis,
> Histological subtype,
> Age of the patient at diagnosis,
> Presence of tumour emboli.

Over an average follow-up period of 7 years, the investigators observed 121 recurrences. In univariable analysis, the predictive factors of recurrence were: **tumour size** (≤ 4 cm 87% no recurrence versus 76% no recurrence when > 4 cm, p = 0.003); **invasion of the rete testis** with no recurrence in 86% in its absence and 76% of no recurrences when present (p = 0.003); **vascular embolism** (86% no recurrence in its absence versus 77% when present, p = 0.038). In multivariate analysis, the size of the tumour and involvement of the rete testis emerged as important significant risk factors of recurrence.

Patients with Stage I seminoma with a tumour size > 4 cm or invasion of the rete testis should have postoperative adjuvant chemotherapy or radiotherapy and a closer follow-up.

> Ward p, Specht L, Horwich A et al. "Prognostic factors for relapse in Stage I seminoma managed by surveillance: a pooled analysis" J Clin Oncol. 2002 Nov. 15; 20 (22): 4448-52.

Classification of Stages

There are two main classifications of testicular cancer:

The North American (Walter Reed) Classification in three Stages:

Stage I:
Disease localised to the testicle, the epididymis and spermatic cord.

Stage II:
With retroperitoneal lymph node invasion which is subdivided into:
▸ Stage IIA: lymph nodes < 2 cm diameter
▸ Stage IIB: lymph nodes 2 to 5 cm diameter
▸ Stage IIC: lymph nodes > 5 cm diameter

Stage III:
Includes all supra-diaphragmatic lymph node invasion and visceral Metastases.

The Union Internationale Contre le Cancer (UICC) and American Joint Committee on Cancer (AJCC) have recently revised the "TNM" classification. The tumour is studied after orchiectomy of primary intention. It is therefore always pathological (pT or T_x).

pT: only applies to germinal tumours

pT_x: primary tumour cannot be classified (for example without orchidectomy).
pT_0: absence of primary tumour.
pT_{is}: in situ tumour.
pT_1: tumour localised to the testis, the epididymis, with eventual invasion of the tunica albuginea but not the tunica vaginalis. No signs of vascular or lymphatic spread.
pT_2: tumour localised to the testis, epididymis but with signs of vascular or lymphatic spread; or, tumour invasion beyond the albuginea to the tunica vaginalis.
pT_3: tumour invasion of the spermatic cord (with or without vascular or lymphatic spread).
pT_4: tumour invasion of the scrotal sack (with or without vascular or lymphatic spread).

N : only concerns regional lymph nodes

N_x: lymph nodes cannot be classified.
N_0: no regional lymph node metastasis.
N_1: less than 5 lymph nodes involved, each measuring < 2 cm diameter.
N_2: one node measuring 2 to 5 cm diameter or several nodes each measuring < 5 cm; or, extra-lymph node extension.
N_3: one or more nodes measuring > 5 cm diameter.

M: indicates the presence of metastasis

M_x: distant metastasis cannot be classified.
M_0: no distant metastasis.
M_1: distant metastasis.
M_{1a}: non regional lymph node metastasis or pulmonary metastasis.
M_{1b}: other localisations.

In addition, a complementary parameter to the TNM classification was introduced by the World Health Organisation and the UICC which has therefore become the TNMS classification:

S: classification by serum markers

S_x: markers not measured.
S_0: markers normal.
S_1: LDH <1.5 x N and β-HCG < 5 000 IU/ml and AFP < 1 000 ng/ml.
S_2: LDH 1.5 to 10 x N or β-HCG 5 000 to 50 000 IU/ml or AFP 1 000 to 10 000 ng/ml.
S_3: LDH > 10 x N or β-HCG > 50 000 IU/ml or AFP > 10 000 ng/ml.

Stage I are patients with tumours which are apparently localised to the testis and may be subdivided according to the presence or absence of vascular or lymphatic infiltration in the spermatic cord. Another subclass is devoted to patients with raised tumour markers but no clinical or radiological signs of visceral or lymph node involvement.

Stage II are patients with retroperitoneal lymph node invasion but no visceral metastases, with or without raised tumour markers.

Stage III are patients with visceral metastases or high levels of tumour markers.

The prognosis of patients with visceral metastases depends on the following criteria:

Good prognosis
▸ **Seminomas:** no extra-pulmonary metastases
▸ **Non Seminomatous tumours:** S_0 or S_1 and no extra-pulmonary metastases

Intermediate prognosis
▸ **Seminomas:** extra-pulmonary metastases
▸ **Non Seminomatous tumours:** S_2 and no extra-pulmonary visceral metastases

Bad prognosis
▸ **No seminomas** in this group
▸ **Non Seminomatous tumours:** S_3 and extra-pulmonary metastases

This is the only tumour classification to take into account biological parameters.

Treatment

Treatment and diagnosis are intimately associated at the outset because ALL testicular tumours should be operated surgically by an approach from the spermatic cord.

Treatment of localised or regional seminomas: Stages I, IIA and IIB

Orchiectomy is followed by radiotherapy of 25 to 35 Gy (depending on Stage I or II) of the aortic retroperitoneal and homo-lateral pelvic lymph nodes.

4% of Stage I and 10% of Stage II tumours relapse. 90% of these relapses will respond to chemotherapy. Globally, 99% of patients with localised seminomas will be cured.

Follow-up alone has been proposed as an alternative to systematic radiotherapy for patients with seminomas apparently localised to the testicle. 15 to 20% relapses were observed with this protocol, half of them in the first year but some only after 5 years' follow-up. Some teams suggest radiotherapy if the relapse is in the lymph nodes and chemotherapy if there are visceral metastases. Others propose chemotherapy from the outset. In the United States, simple surveillance is not recommended.

Treatment of Seminomas: Stages IIC and III

Chemotherapy is indicated. In principle, this consists of 4 cycles of the "EP" protocol which comprises Etoposide 100 mg/m^2 from Days 1 to 5 with Cisplatin 20 mg/m^2 from Days 1 to 5. This results in 80 to 95% of cures. The poor prognostic factor is the presence of extra-pulmonary metastases. Second and third line chemotherapy, Velp, VAB-6 or others, is associated with radiotherapy and, possibly, tumour reduction surgery. Hopefully, this results in cure rates of about 50%.

Treatment of Non Seminomatous Tumours: Stage I

Over 95% of patients will be cured but 20% of patients with Stage I tumours and no extension to the albuginea, spermatic cord or scrotum have undetected involvement of the regional lymph nodes or a distant metastasis at the time of the initial work up.

Two attitudes may be proposed to manage these Stage I tumours: simple surveillance, which is based on the high potential for cure of chemotherapy or of systematic retroperitoneal lymph node dissection.

One condition for this approach is the absolute compliance of the patient with the very strict surveillance regime as 20% will relapse, usually by invasion of the retroperitoneal lymph nodes which will require chemotherapy with etoposide and platinum salts.

The alternative is retroperitoneal lymph node dissection sparing the sympathetic nerve plexus. Twenty per cent of patients undergoing this surgery have anatomical disease. Unfortunately, this approach may be complicated by problems of sterility or of ejaculation which are difficult to accept in young men. Preference is therefore given to the non interventionist approach with eventual chemotherapy.

When lymph node dissection shows no disease, simple surveillance is recommended. On the other hand, when there is lymph node involvement, the patient must be managed as Stage II disease. This lymph node extension is strongly suspected when histological examination of the orchiectomy specimen shows vascular or lymphatic infiltration, involvement of the spermatic cord or of the peri-testicular walls. Some workers advise two cycles of chemotherapy followed by several years close follow-up for the high risk Stage I tumours. Relapse is rare. Nevertheless, some feel that the long term complications of chemotherapy have not yet been fully assessed and prefer lumbar aortic lymph node surgery with sparing of the sympathetic nervous plexus.

The cure rates are comparable with all these approaches and range from 90 to 100%. The patient often takes the final decision as to choice of treatment after being fully informed by the treating physician of the consequences of each approach.

Treatment of Non Seminomatous Tumours: Stages II and III

The first course of chemotherapy is the reference. Some authors, especially the Americans, advise retroperitoneal node clearance in patients with regional lymph node involvement with node size < 3 cm on CT scan. The relapse rate is, however, about 35% when the size of each infiltrated node is under 2 cm at histological examination. Irrespective of the stage when chemotherapy has been decided upon, it is essential to obtain normalisation of the tumour markers. A follow up radiological examination should be undertaken to assess the residual tumour mass. Surgical ablation is nearly always performed in these cases. If there is any residual "active" tumour, a second course of chemotherapy is usually prescribed.

Three courses of the BEP (Bleomycin, Etoposide, Cisplatin) protocol is the treatment of first intention or four courses without bleomycin (EP protocol) in patients with good prognostic factors. Those with poor prognostic factors are given four courses of BEP from the outset.

All tumours with good prognoses have a cure rate of 80 to 90% versus only 50% for patients with poor prognostic factors.

Subjects who do not achieve complete remission and those who relapse will be given a salvage therapy. The reference is the VeIP (Velbe, Ifosfamide, Cisplatin) protocol. Some may benefit from intensive chemotherapy with haematological support but this approach is still in the experimental stage. Twenty five to thirty percent of patients needing second line treatment will have long standing remissions.

Side effects of Treatment

Short term

Nausea, vomiting, hypomagnesaemia, renal and peripheral nerve toxicities are possible with chemotherapy with platinum salts. Bleomycin sometimes induces pulmonary fibrosis. The replacement of vinblastine by etoposide in most protocols has considerably reduced the incidence of neuro-muscular toxicity. Severe medullary hypoplasia is rare with most of the first line chemotherapy protocols used for testicular cancer. On the other hand, the salvage therapies are very aggressive to the haemopoietic bone marrow, making the use of haemopoietic growth factors almost unavoidable.

Retroperitoneal lymph node clearance may be complicated by disorders of ejaculation, especially retrograde ejaculation which may cause sterility. This is a serious problem in young men. The choice of treatment must take this factor into account. Radiotherapy to the lumbar aortic and homo-lateral iliac regions at 25 to 35 Gy is rarely a source of complications.

Medium and Long term

The major complications are gonadal toxicity and the risk of a second cancer or leukaemia.

Spermatogenesis is nearly always affected by chemotherapy. The quality of its recovery depends on the number of courses of treatment and, above all, the quality of the sperm before treatment. Therefore, patients are systematically offered the services of the sperm bank, if possible before orchidectomy and always before any other aggressive treatment. Recovery of spermatogenesis is observed in 75% of patients without any previous abnormality but only in 45% of the remaining patients.

The risk of a second non germinal tumour or of leukaemia have been analysed in retrospective studies. The relative risk is increased by a factor of 1.5 to 2. It is a very small risk compared with the benefit of the cure rates obtained by modern chemotherapy.

Two to five per cent of patients followed up for testicular cancer will present a tumour in the remaining testis. These second tumours usually have an excellent prognosis because they are detected at an early stage. Clinical and echographic surveillance is essential. Limited surgery may be envisaged.

Follow-Up Schedule

This is determined by the risk of relapse which is high in the first two years of non seminomatous tumours. The pure seminomas, on the other hand, may relapse 5 to 7 years after diagnosis.

Follow-up includes clinical examination and measurement of tumour markers every three months. A CT scan is usually performed twice a year. The periodicity of follow-up can then be progressively increased. Annual follow-up is then advised.

Underwriting

As the rating is directly related to the initial extension of the tumour, the underwriting criteria are very strict.

In addition to the medical questionnaire and attending physician's report, it is necessary to obtain copies of the surgical report of the initial orchiectomy, the results of the tumour markers **before and after surgery** and the histology report of the operated specimen, i.e. **the definitive histological report.**

Other information may be required such as the results of the initial work up, reports of complementary operations (lymph node clearance or ablation of residual masses) with their histological results, the details of the treatments prescribed with dosages and durations, specialist follow-up investigations such as the results of CT scans and surveillance of tumour markers.

Conclusion

Very few medical conditions have seen such radical change in prognosis in the space of a single human generation.

Our approach as insurers should take these advances into account without losing sight of the risks related to treatment which is essential but aggressive.