TESTICULAR CANCER

1. EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY

1.1 EPIDEMIOLOGY AND AETIOLOGY

Testicular cancer represents 1% of male neoplasms and 5% of urological tumours, with 3-10 new cases occurring per 100,000 males/per year in Western societies. Its incidence has been increasing during the last decades especially in industrialised countries. At diagnosis, 1-2% of cases are bilateral and the predominant histology is germ cell tumour (90-95% of cases). Peak incidence is in the third decade of life for non-seminoma, and in the fourth decade for pure seminoma.

Testicular cancers (TC) show excellent cure rates based on, their chemosensitivity especially to cisplatin-based chemotherapy, careful staging at diagnosis, adequate early treatment based on a multidisciplinary approach and strict follow-up and salvage therapies.

Genetic changes have been described in patients with TC. A specific genetic marker, an isochromosome of the short arm of chromosome 12 - i(12p) - has been described in all histological types of germ cell tumours and in germ cell neoplasia *in situ* (GCNIS). Alterations in the p53 locus have been identified in 66% of cases of GCNIS and association between genetic polymorphism in the PTEN tumours suppressor gene and risk of testicular germ cell tumours (TGCT) has been recently described.

Epidemiological risk factors for the development of testicular tumours are components of the testicular dysgenesis syndrome (i.e. cryptorchidism, hypospadias, decreased spermatogenesis evidenced by sub- or infertility) familial history of testicular tumours among first-grade relatives and the presence of a contralateral tumour or GCNIS. A recent systematic review confirmed the association between height and TGCT with an odds ratio (OR) of 1.13 per 5 cm increase in height.

1.2 PATHOLOGICAL CLASSIFICATION

The recommended pathological classification shown below is based on the 2016 update of the World Health Organization (WHO) pathological classification.

1.Germ cell tumours

Derived from germ cell neoplasia *in situ* (GCNIS)

Germ cell neoplasia *in situ*

Seminoma

Embryonal carcinoma

Yolk sac tumour, post-pubertal type

Trophoblastic tumours

Teratoma, post-pubertal type

Teratoma with somatic-type malignancies

Mixed germ cell tumours

2.Germ cell tumours unrelated to GCNIS

Spermatocytic tumour

Yolk sac tumour, pre-pubertal type

Mixed germ cell tumour, pre-pubertal type

3.Sex cord/stromal tumours

Leydig cell tumour

Malignant Leydig cell tumour

Sertoli cell tumour

Malignant Sertoli cell tumour

Large cell calcifying Sertoli cell tumour

Intratubular large cell hyalinising Sertoli cell neoplasia

Granulosa cell tumour

Adult type

Juvenile type

Thecoma/fibroma group of tumours

Other sex cord/gonadal stromal tumours

Mixed

Unclassified

Tumours containing both germ cell and sex cord/gonadal stromal

Gonadoblastoma

4.Miscellaneous non-specific stromal tumours

Ovarian epithelial tumours

Tumours of the collecting ducts and rete testis

Adenoma

Carcinoma

Tumours of paratesticular structures

Adenomatoid tumour

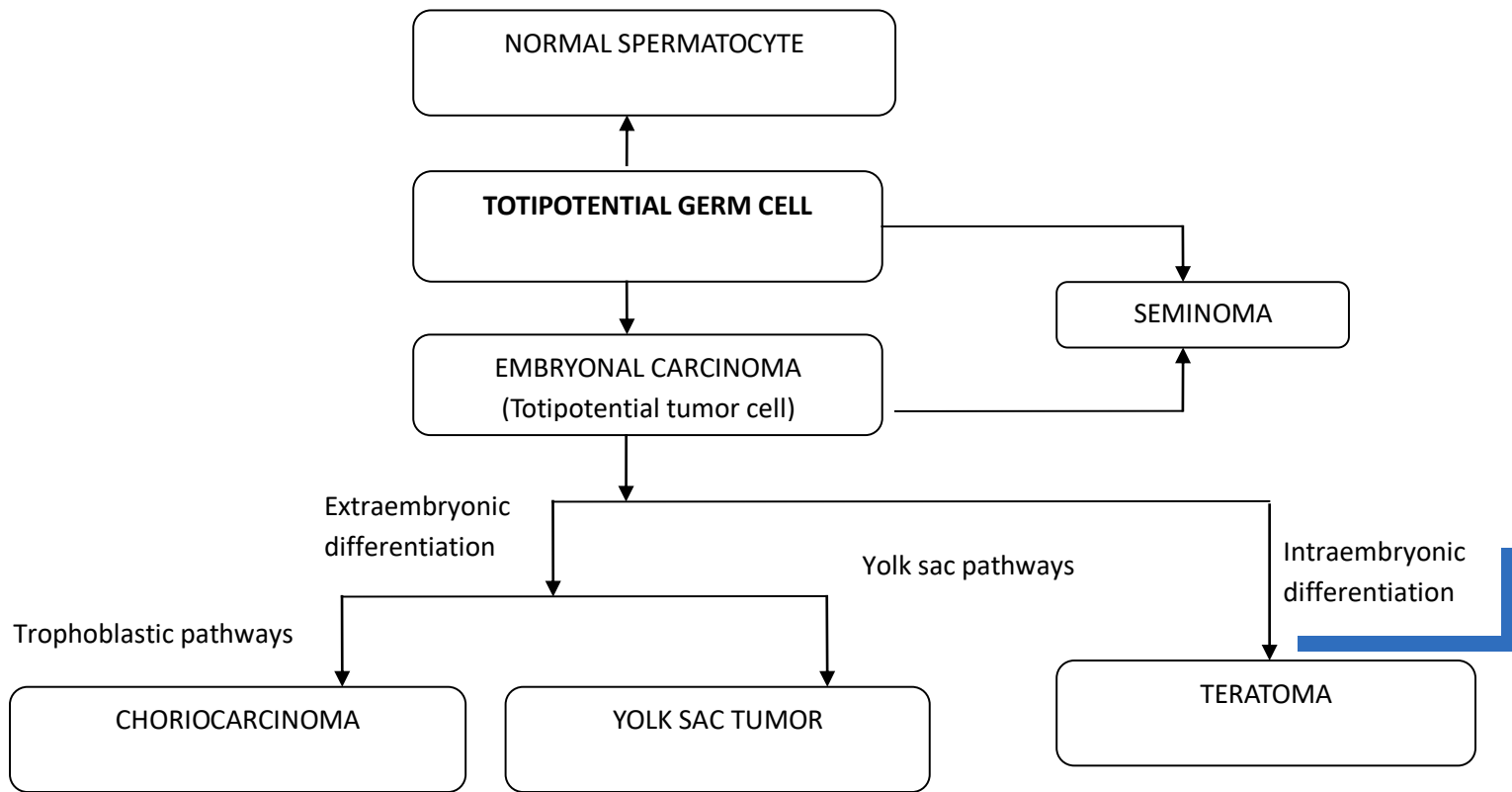Mesothelioma (epithelioid, biphasic)

Epididymal tumours

Cystadenoma of the epididymis

Papillary cystadenoma

Adenocarcinoma of the epididymis

Mesenchymal tumours of the spermatic cord and testicular adnexae.

Figure 1. Tumorigenic model for germ cell tumors of the testis.

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                        ┌─────────────────────────┐
                        │   NORMAL SPERMATOCYTE    │
                        └─────────────────────────┘
                                   ▲
                        ┌─────────────────────────┐
                        │ TOTIPOTENTIAL GERM CELL  │──────────────┐
                        └─────────────────────────┘              ▼
                                   │                    ┌──────────────────┐
                                   ▼                    │    SEMINOMA      │
                        ┌─────────────────────────┐     └──────────────────┘
                        │  EMBRYONAL CARCINOMA     │──────────────▲
                        │  (Totipotential tumor cell)│
                        └─────────────────────────┘
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Extraembryonic differentiation

Yolk sac pathways

Intraembryonic differentiation

Trophoblastic pathways

| CHORIOCARCINOMA | YOLK SAC TUMOR | TERATOMA |

1.2.1 Tumorigenic Hypothesis for Germ Cell Tumor Development

During embryonal development, the totipotential germ cells can travel down normal differentiation pathways and become spermatocytes. However, if these totipotential germ cells travel down abnormal developmental pathways, seminoma or embryonal carcinomas (totipotential tumor cells) develop. If the embryonal cells undergo further differentiation along intraembryonic pathways, teratoma will result. If the embryonal cells undergo further differentiation along extraembryonic pathways, either choriocarcinoma or yolk sac tumors are formed (Figure 1). This model helps to explain why specific histologic patterns of testicular tumors produce certain tumor markers. Note that yolk sac tumors produce alpha-fetoprotein (AFP) just as the yolk sac produces AFP in normal development.

Likewise, choriocarcinoma produces human chorionic gonadotropin (hCG) just as the normal placenta produces hCG.

1.2.2 PATHOLOGY

1.2.2.1 SEMINOMA (35%)

Three histologic subtypes of pure seminoma have been described. Classic seminoma accounts for 85% of all seminomas and is most common in the fourth decade of life. Grossly, coalescing gray nodules are observed. It is noteworthy that syncytiotrophoblastic elements are seen in approximately 10–15% of cases, an incidence that corresponds approximately to the incidence of hCG production in seminomas. Anaplastic seminoma accounts for 5–10% of all seminomas. Diagnosis requires the presence of 3 or more mitoses per high-power field, and the cells demonstrate a higher degree of nuclear pleomorphism than the classic types. Anaplastic seminoma tends to present at a higher stage than the classic variety. When stage is taken into consideration, however, this subtype does not convey a worse prognosis. Spermatocytic seminoma accounts for 5–10% of all seminomas. More than half the patients with spermatocytic seminoma are over the age of 50.

1.2.2.2 EMBRYONAL CELL CARCINOMA (20%)

Two variants of embryonal cell carcinoma are common: the adult type and the infantile type, or yolk sac tumor (also called endodermal sinus tumor). Histologic structure of the adult variant demonstrates marked pleomorphism and indistinct cellular borders. Mitotic figures and giant cells are common. Cells may be arranged in sheets, cords, glands, or papillary structures. Extensive hemorrhage and necrosis may be observed grossly. The infantile variant, or yolk sac tumor, is the most common testicular tumor of infants and children. When seen in adults, it usually occurs in mixed histologic types and possibly is responsible for AFP production in these tumors.

1.2.2.3 TERATOMA (5%)

Teratomas may be seen in both children and adults. They contain more than one germ cell layer in various stages of maturation and differentiation. Grossly, the tumor appears lobulated and contains variable-sized cysts filled with gelatinous or mucinous material. Mature teratoma may have elements resembling benign structures derived from ectoderm, mesoderm, and endoderm, while immature teratoma consists of undifferentiated primitive tissue. In contrast to its ovarian counterpart, the mature teratoma of the testis does not attain the same degree of differentiation as teratoma of the ovary.

1.2.2.4 CHORIOCARCINOMA (<1%)

Pure choriocarcinoma is rare. Lesions tend to be small within the testis and usually demonstrate central hemorrhage on gross inspection. Microscopically, syncytio- and cytotrophoblasts must be visualized. Clinically, choriocarcinomas behave in an aggressive fashion characterized by early hematogenous spread. Paradoxically, small intratesticular lesions can be associated with widespread metastatic disease.

1.2.2.5 MIXED CELL TYPE (40%)

Within the category of mixed cell types, most (up to 25% of all testicular tumors) are teratocarcinomas, which are a combination of teratoma and embryonal cell carcinoma. Up to 6% of all testicular tumors are of the mixed cell type, with seminoma being one of the components. Treatment for these mixtures of seminoma and NSGCT is similar to that of NSGCT alone.

1.2.2.6 CARCINOMA IN SITU (CIS)

In a series of 250 patients with unilateral testicular cancer, Berthelsen et al (1982) demonstrated the presence of CIS in 13 (5.2%) of the contralateral testes. This is approximately twice the overall incidence of bilateral testicular cancer. The presence of contralateral atrophy or ultrasonographic microlithiasis in patients with testicular tumors

warrants contralateral biopsy. If diagnosed, CIS can be treated by external beam radiation therapy.

1.2 PATTERNS OF METASTATIC SPREAD

With the exception of choriocarcinoma, which demonstrates early hematogenous spread, germ cell tumors of the testis typically spread in a stepwise lymphatic fashion. Lymph nodes of the testis extend from T1 to L4 but are concentrated at the level of the renal hilum because of their common embryologic origin with the kidney. The primary landing site for the right testis is the interaortocaval area at the level of the right renal hilum. Stepwise spread, in order, is to the precaval, preaortic, paracaval, right common iliac, and right external iliac lymph nodes. The primary landing site for the left testis is the para-aortic area at the level of the left renal hilum. Stepwise spread, in order, is to the preaortic, left common iliac, and left external iliac lymph nodes. In the absence of disease on the left side, no crossover metastases to the right side have ever been identified. However, right-to-left crossover metastases are common. These observations have resulted in modified surgical dissections to preserve ejaculation in selected patients. Certain factors may alter the primary drainage of a testis neoplasm. Invasion of the epididymis or spermatic cord may allow spread to the distal external iliac and obturator lymph nodes. Scrotal violation or invasion of the tunica albuginea may result in inguinal metastases. Although the retroperitoneum is the most commonly involved site in metastatic disease, visceral metastases may be seen in advanced disease. The sites involved in decreasing frequency include lung, liver, brain, bone, kidney, adrenal, gastrointestinal tract, and spleen. As mentioned previously, choriocarcinoma is the exception to the rule and is characterized by early hematogenous spread, especially to the lung. Choriocarcinoma also has a redilection for unusual sites of metastasis such as the spleen.

STAGING AND CLASSIFICATION SYSTEMS

2.1. DIAGNOSTIC TOOLS

To determine the presence of macroscopic or occult metastatic disease, the half-life kinetics of serum tumour markers as well as the presence of nodal or visceral metastases need to be assessed. Consequently, it is mandatory to assess: the pre- and post-orchiectomy half-life kinetics of serum tumour markers; the status of retroperitoneal and supraclavicular lymph nodes, bone and liver; the presence or absence of mediastinal nodal involvement and lung metastases; the status of brain and bone in cases of suspicious symptoms or high-risk disease, e.g. poor International Germ Cell Cancer Collaborative Group (IGCCCG) risk group, high human chorionic gonadotropin (hCG) and/or multiple pulmonary metastases.The minimum mandatory tests are: serial blood sampling; abdominopelvic and chest computed tomography (CT).

2.2 SERUM TUMOUR MARKERS: POST-ORCHIECTOMY HALF-LIFE KINETICS

The mean serum half-life of AFP and hCG is five to seven days and two to three days, respectively. Tumour markers need to be re-evaluated after orchiectomy to determine half-life kinetics. Marker decline in patients with clinical stage (CS) I disease should be assessed until normalisation has occurred. Markers before the start of chemotherapy are important to classify the patient according to the IGCCCG risk classification. The persistence of elevated serum tumour markers after orchiectomy might indicate the presence of metastatic disease (macro- or microscopically), while the normalisation of marker levels after orchiectomy does not rule out the presence of tumour metastases. During chemotherapy, the markers should decline; persistence has an adverse prognostic value. Slow marker decline in patients with poor prognosis during the first cycle of standard bleomycin, etoposide and cisplatin (BEP) chemotherapy can be used as an indication for early chemotherapy dose intensification.

2.3 RETROPERITONEAL, MEDIASTINAL AND SUPRACLAVICULAR LYMPH NODES AND VISCERA

Retroperitoneal and mediastinal lymph nodes are best assessed by CT. The supraclavicular nodes are best assessed by physical examination followed by CT in cases of suspicion. Abdominopelvic CT offers a sensitivity of 70-80% in determining the state of the retroperitoneal nodes. Its accuracy depends on the size and shape of the nodes; sensitivity and the negative predictive value increase using a 3 mm threshold to define metastatic nodes in the landing zones.

Magnetic resonance imaging (MRI) produces similar results to CT in the detection of retroperitoneal nodal enlargement. Again, the main objections to its routine use are its high cost and limited availability. Nevertheless, MRI can be helpful when abdominopelvic CT or ultrasound (US) are inconclusive, when CT is contraindicated because of allergy to contrast media containing iodine, or when the physician or the patient are concerned about radiation dose. MRI is an optional test, and there are currently no indications for its systematic use in the staging of TC.

A chest CT is the most sensitive way to evaluate the thorax and mediastinal nodes. This exploration is recommended in all patients with TC as up to 10% of cases can present with small subpleural nodes that are not visible on an X-ray. A CT has high sensitivity, but low specificity.

There is no evidence to support the use of fluorodeoxyglucose-positron emission tomography (PET) (FDG-PET) in the staging of testis cancer. It is recommended in the follow up of patients with seminoma with a residual mass larger than 3 cm and should not be performed before eight weeks after completing the last cycle of chemotherapy in order to decide on watchful waiting or active treatment. Fluorodeoxyglucose-PET is not recommended in the re-staging of patients with NSGCT after chemotherapy.

Other examinations, such as brain or spinal CT, bone scan or liver US, should be performed if there is suspicion of metastases to these organs. A CT or MRI of the brain is advisable in patients with NSGCT, multiple lung metastases and poor prognosis IGCCG risk group (e.g. high beta-hCG values). Table 1 shows the recommended tests at staging.

Table 1: Recommended tests for staging at diagnosis

Test	Recommendation	GR
Serum tumour markers	Alpha-fetoprotein human chorionic gonadotrophin (hCG) Lactate dehydrogenase	A
Abdominopelvic computed tomography (CT)	All patients	A
Chest CT	All patients	A
Testis ultrasound (bilateral)	All patients	A
Bone scan or magnetic resonance imaging (MRI) columna	In case of symptoms	
Brain scan (CT/MRI)	In case of symptoms and patients with metastatic disease with multiple lung metastases and/or high beta-hCG values.	
Further investigations		
Fertility investigations: Total testosterone Luteinising hormone		B

Follicle-stimulating hormone Semen analysis		
Discuss sperm banking with all men prior to starting treatment for testicular cancer.		A

STAGING AND PROGNOSTIC CLASSIFICATIONS

The staging system recommended is the 2017 Tumour, Node, Metastasis (TNM) of the International Union Against Cancer (UICC) (Table 2). This includes: determination of the anatomical extent of disease; assessment of serum tumour markers, including nadir values of hCG, AFP and LDH after orchiectomy (S category); definition of regional nodes; N-category modifications related to node size.

Table 2: TNM classification for testicular cancer (UICC, 2017, 8th edn.)

pT -	**Primary Tumour**	
	pTX	Primary tumour cannot be assessed (see note 1)
	pT0	No evidence of primary tumour (e.g. histological scar in testis)
	pTis	Intratubular germ cell neoplasia (carcinoma *in situ*)
	pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion; tumour may invade tunica albuginea but not tunica vaginalis*
	pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis
	pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
	pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
N -	**Regional Lymph Nodes - Clinical**	
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis

	N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
	N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension.
	N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension dimension
Pn -	**Regional Lymph Nodes - Pathological**	
	pNX	Regional lymph nodes cannot be assessed
	pN0	No regional lymph node metastasis
	pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension
	pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence or extranodal extension of tumour
	pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
M -	**Distant Metastasis**	
	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
		M1a Non-regional lymph node(s) or lung metastasis
		M1b Distant metastasis other than non-regional lymph nodes and lung
S -	**Serum Tumour Markers**	
	SX	Serum marker studies not available or not performed
	S0	Serum marker study levels within normal limits

		LDH (U/l)	hCG (mIU/mL)	AFP (ng/mL)
	S1	< 1.5 x N and	< 5,000 and	< 1,000
	S2	1.5-10 x N or	5,000-50,000 or	1,000-10,000
	S3	> 10 x N or	> 50,000 or	> 10,000

- N indicates the upper limit of normal for the LDH assay.

- LDH=lactate dehydrogenase; hCG=human chorionic gonadotrophin; AFP=alpha-fetoprotein.

- *AJCC subdivides T1 by T1a and T1b depending on size no greater than 3 cm or greater than 3 cm in greatest dimension.

- 1 Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

- According to the 2009 TNM classification, stage I testicular cancer includes the following substages:

Stage grouping				
Stage 0	pTis	N0	M0	S0
Stage I	pT1-T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2 - pT4	N0	M0	S0
Stage IS	Any patient/TX	N0	M0	S1-3
Stage II	Any patient/TX	N1-N3	M0	SX
Stage IIA	Any patient/TX	N1	M0	S0
	Any patient/TX	N1	M0	S1

Stage IIB	Any patient/TX	N2	M0	S0
	Any patient/TX	N2	M0	S1
Stage II	Any patient/TX	N3	M0	S0
	Any patient/TX	N3	M0	S1
Stage III	Any patient/TX	Any N	M1a	SX
Stage IIIA	Any patient/TX	Any N	M1a	S0
	Any patient/TX	Any N	M1a	S1
Stage IIIB	Any patient/TX	N1-N3	M0	S2
	Any patient/TX	Any N	M1a	S2
Stage IIIC	Any patient/TX	N1-N3	M0	S3
	Any patient/TX	Any N	M1a	S3
	Any patient/TX	Any N	M1b	Any S

Stage IA patients have primary tumours limited to the testis and epididymis, with no evidence of microscopic vascular or lymphatic invasion by tumour cells on microscopy, no sign of metastases on clinical examination or imaging, and post-orchiectomy serum tumour marker levels within normal limits. Marker decline in patients with CS I disease should be assessed until normalisation.

Stage IB patients have a more locally invasive primary tumour, but no sign of metastatic disease.

Stage IS patients have persistently elevated (and usually increasing) serum tumour marker levels after orchiectomy, indicating subclinical metastatic disease (or possibly a second germ cell tumour in the remaining testis).

In large population-based patient series, 75-80% of seminoma patients, and about 55% of patients with NSGCT cancer have stage I disease at diagnosis. True stage IS (persistently

elevated or increasing serum marker levels after orchiectomy) is found in about 5% of non-seminoma patients.

In 1997, the IGCCCG defined a prognostic factor-based staging system for metastatic testis tumours based on identification of clinically independent adverse factors. This staging system has been incorporated into the TNM Classification and uses histology, location of the primary tumour, location of metastases and pre-chemotherapy marker levels in serum as prognostic factors to categorise patients into 'good', 'intermediate' or 'poor' prognosis (Table 3).

Table 3: Prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group)*

Good-prognosis group	
Non-seminoma (56% of cases) 5-year PFS 89% 5-year survival 92%	*All of the following criteria:* • Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP < 1,000 ng/mL • hCG < 5,000 IU/L (1,000 ng/mL) • LDH < 1.5 x ULN
Seminoma (90% of cases) 5-year PFS 82% 5-year survival 86%	*All of the following criteria:* • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate prognosis group	
Non-seminoma (28% of cases)	*Any of the following criteria:*

5-year PFS 75% 5-year survival 80%	• Testis/retro-peritoneal primary • No non-pulmonary visceral metastases • AFP 1,000 - 10,000 ng/mL or • hCG 5,000 - 50,000 IU/L or • LDH 1.5 - 10 x ULN
Seminoma (10% of cases) 5-year PFS 67% 5-year survival 72%	*All of the following criteria:* • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor prognosis group	
Non-seminoma (16% of cases) 5-year PFS 41% 5-year survival 48%	*Any of the following criteria:* • Mediastinal primary • Non-pulmonary visceral metastases • AFP > 10,000 ng/mL or • hCG > 50,000 IU/L (10,000 ng/mL) or • LDH > 10 x ULN
Seminoma	No patients classified as poor prognosis

*Pre-chemotherapy serum tumour markers should be assessed immediately prior to the administration of chemotherapy (same day). PFS=progression-free survival; AFP=alpha-fetoprotein; hCG=human chorionic gonadotrophin; LDH=lactate dehydrogenase.

3.DIAGNOSTIC EVALUATION

3.1. CLINICAL EXAMINATION

Testicular cancer usually presents as a painless, unilateral testicular scrotal mass, as a casual US finding or is revealed by a scrotal trauma. Scrotal pain may be the first symptom in 20% of cases and it is present in up to 27% of patients with TC. Gynaecomastia appears in 7% of cases (more common in non-seminomatous tumours). Back and flank pain due to metastasis is present in about 11% of cases.

Diagnosis is delayed in around 10% of cases of testicular tumour that mimic orchioepididymitis, physical examination reveals the features of the mass and must always be carried out together with a general examination to find possible (supraclavicular) distant metastases, a palpable abdominal mass or gynaecomastia. Ultrasound must be performed in any doubtful case. A correct diagnosis must be established in all patients with an intrascrotal mass.

3.2. IMAGING OF THE TESTIS

Currently, US is used to confirm the presence of a testicular mass and explore the contralateral testis. Ultrasound sensitivity is almost 100%, and US has an important role in determining whether a mass is intra- or extra-testicular. Ultrasound is an inexpensive test and should be performed even in the presence of clinically evident testicular tumour.

Ultrasound of the testis should be performed in young men with retroperitoneal or visceral masses and/or elevated serum hCG or AFP and/or consulting for fertility problems and without a palpable testicular mass.

Magnetic resonance imaging of the scrotum offers higher sensitivity and specificity than US in the diagnosis of TC, but its high cost does not justify its routine use for diagnosis.

3.3 SERUM TUMOUR MARKERS AT DIAGNOSIS

Serum tumour markers are prognostic factors and contribute to diagnosis and staging. The following markers should be determined before, and 5-7 days after, orchiectomy: alpha-

fetoprotein (produced by yolk sac cells) (AFP); human chorionic gonadotrophin (expression of trophoblasts) (hCG); lactate dehydrogenase (LDH). Tumour markers are of value for diagnosis (before orchiectomy) as well as for prognosis (after orchiectomy). They are increased in approximately every second patient with TC. Alpha-fetoprotein and hCG are increased in 50-70% and in 40-60% of patients with NSGCT, respectively. About 90% of NSGCT present with a rise in one or both of the markers. Up to 30% of seminomas can present or develop an elevated hCG level during the course of the disease. Lactase dehydrogenase is a less specific marker, its concentration being proportional to tumour volume. Its level may be elevated in 80% of patients with advanced TC. Of note, negative marker levels do not exclude the diagnosis of a germ cell tumour. Placental alkaline phosphatase (PLAP), is an optional marker in monitoring patients with pure seminoma, but not recommended in smokers. Cytogenetic and molecular markers are available in specific centres, but at present only contribute to research. There is preliminary evidence that some micro-RNAs (miRNA 371-373) may be of diagnostic value in the future.

Table 4. Incidence of Elevated Tumor Markers by Histologic Type in Testis Cancer.

	hCG (%)	AFP (%)
Seminoma	30	0
Teratoma	25	38
Teratocarcinoma	57	64
Embryonal	60	70
Choriocarcinoma	100	0

3.4 INGUINAL EXPLORATION AND ORCHIECTOMY

Every patient with a suspected testicular mass must undergo inguinal exploration with exteriorisation of the testis within its tunics. Orchiectomy with division of the spermatic cord at the internal inguinal ring must be performed if a malignant tumour is found. If the diagnosis is not clear, a testicular biopsy (and enucleation of the intraparenchymal tumour) is taken for frozen (fresh tissue) section histological examination. Even though only limited data are available, it has been shown that during orchiectomy, a testicular prosthesis can be inserted without increased infectious complications or rejection rates. In cases of life-threatening disseminated disease, lifesaving chemotherapy should be given up-front, especially when the clinical picture is very likely TC and/or tumour markers are increased. Orchiectomy may be delayed until clinical stabilisation occurs or in combination with resection of residual lesions.

3.5 ORGAN-SPARING SURGERY

Although organ-sparing surgery is not indicated in the presence of non-tumoural contralateral testis, it can be attempted in special cases with all the necessary precautions. In synchronous bilateral testicular tumours, metachronous contralateral tumours, or in a tumour in a solitary testis with normal pre-operative testosterone levels, organ preserving surgery can be performed when tumour volume is less than approximately 30% of the testicular volume and surgical rules are respected. In those cases, the rate of associated GCNIS is high (at least up to 82%).

3.6 DIAGNOSIS AND TREATMENT OF GERM CELL NEOPLASIA *IN*

***SITU* (GCNIS)**

Contralateral biopsy has been advocated to rule out the presence of GCNIS. Although routine policy in some countries, the low incidence of GCNIS and contralateral metachronous testicular tumours (up to 9% and approximately 2.5%, respectively), the morbidity of GCNIS

treatment, and the fact that most of metachronous tumours are at a low stage at presentation make it controversial to recommend a systematic contralateral biopsy in all patients.

It is still difficult to reach a consensus on whether the existence of contralateral GCNIS must be identified in all cases. However, biopsy of the contralateral testis should be offered to patients at high risk for contralateral GCNIS, i.e. testicular volume < 12 mL, a history of cryptorchidism or poor spermatogenesis (Johnson Score 1-3). A contralateral biopsy is not necessary in patients older than 40 years without risk factors. A double biopsy increases sensitivity. Patients should be informed that a testicular tumour may arise in spite of a negative biopsy.

Once GCNIS is diagnosed, local radiotherapy (16-20 Gy in fractions of 2 Gy) is the treatment of choice in the case of a solitary testis. Testicular radiotherapy in a solitary testis will result in infertility and increased long-term risk of Leydig cell insufficiency. Fertile patients who wish to father children may delay radiation therapy and be followed by regular testicular US. Chemotherapy is significantly less effective and the cure rates are dose-dependent.

If GCNIS is diagnosed and the contralateral testis is healthy, the options for management are orchiectomy or close observation (with a 5-year risk of developing TC of 50%).

4.SCREENING

There are no high level evidence studies proving the advantages of screening programmes, but it has been demonstrated that stage and prognosis are directly related to early diagnosis. In the presence of clinical risk factors, and especially in patients with a family history of testis cancer, family members and the patient should be informed about the importance of physical self-examination.

Table 5. Guidelines for the diagnosis and staging of testicular cancer

Recommendations	GR

Perform testicular ultrasound in all patients with suspicion of testicular cancer.	A
Offer biopsy of the contralateral testis and discuss its consequences with patients at high risk for contralateral germ cell neoplasia *in situ*.	A
Perform orchiectomy and pathological examination of the testis to confirm the diagnosis and to define the local extension (pT category). In a life-threatening situation due to extensive metastasis, start chemotherapy before orchiectomy.	A
Perform serum determination of tumour markers (alpha-fetoprotein, human chorionic gonadotrophin, and lactate dehydrogenase), both before and five-seven days after orchiectomy for staging and prognostic reasons.	A
Assess the state of the retroperitoneal, mediastinal and supraclavicular nodes and viscera in testicular cancer.	A
Advise patients with a familiar history of testis cancer, as well as their family members, to perform regular testicular self-examination.	A

Table 6.1: Risk factors for occult metastatic disease in stage I testicular cancer

	For seminoma	For non-seminoma
Pathological (for stage I)		
Histopathological type	• Tumour size (> 4 cm) • Invasion of the rete testis	• Vascular/lymphatic in or peri-tumoural invasion • Proliferation rate > 70% • Percentage of embryonal carcinoma > 50%

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