

# Classification, epidemiology and therapies for testicular germ cell tumours

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**ABSTRACT** Testicular germ cell tumours (TGCT) account for between 1% and 1.5% of male neoplasms and 5% of urological tumours in general. They are classified broadly into Seminoma, which resemble primordial germ cells (PGCs), and Non-Seminoma, which are either undifferentiated (embryonal carcinoma) or differentiated (exhibiting a degree of embryonic (teratoma) or extra-embryonic (yolk sac choriocarcinoma) patterning). We present the current details of the latest classification, epidemiology and treatment aspects of TGCT in the UK in our review.

**KEY WORDS:** *classification, epidemiology, therapy, testicular germ cell tumor, prognosis*

## Introduction

A Germ cell tumor (GCT) is a neoplasm derived from germ cells. Germ cell tumours are malignant (cancerous) or non-malignant (benign, non-cancerous) tumours that are comprised mostly of germ cells. Germ cells are the cells that develop in the embryo (foetus, or unborn baby) and become the cells that make up the reproductive system in males and females. These germ cells follow a midline path through the body after development and descend into the pelvis as ovarian cells or into the scrotal sac as testicular cells. Most ovarian tumours and testicular tumours are of germ cell origin. The ovaries and testes are called gonads.

The peak incidence of diagnosis and presentation to germ cell tumours in men is between the age of 15-35 years. Only 5% of all germ cell tumours present as extragonadal and the remaining 95% of GCT are purely gonadal in origin and presentation. The key difference between gonadal and extra-gonadal germ cell tumours is the clinical presentation and behaviour.

Testicular Germ Cell tumours (TGCTs) account for between 1% and 1.5% of male neoplasms and 5% of urological tumours in general, with 3-10 new cases occurring per 100,000 males/per year in Western society (La Vecchia *et al.* 2010; Curado *et al.*, 2007; Engholm *et al.*, 2010). Testicular germ cell tumours (TGCTs) are the most frequent solid tumour of Caucasian adolescents and young adult males and are a diverse group of neoplasms that can also present in extragonadal sites. Within Europe, there has been a general increase in the incidence of TGCTs noted initially in the 1970s and 1980s (Huyghe *et al.*, 2003). Over recent years the incidence of TGCTs has risen markedly, making it imperative to understand how and why these tumours arise.

In our paper we describe the - Pathogenesis, Classification, Aetiology, Diagnosis and treatment of Testicular Germ Cell Tumours.

## Pathogenesis

Histologically, TGCTs are broadly divided into Seminoma, which resemble primordial germ cells (PGCs), and Non-Seminoma, which are either undifferentiated (embryonal carcinoma) or differentiated (exhibiting a degree of embryonic (teratoma) or extra-embryonic (yolk sac choriocarcinoma) patterning) (Oosterhuis, *et al.* 2005).

The commonest age range of presentation of TGCTs is between 20-45 years. Patients rarely tend to be younger than 15 years or older than 60 years. Based on the type of TGCTs, Seminomas typically arise later in life, with a mean age at presentation of 35 years of age compared with 25 years of age for non-seminomas. Although these morphologies and differences in age at presentation could suggest underlying differences between seminomas and non-seminomas, several lines of evidence support a common underlying pathogenesis. Approximately 15% of TGCTs are mixed tumours that contain both seminoma and non-seminoma elements (Horwich *et al.*, 2006).

The commonest presentation of TGCTs is a painless unilateral mass in the scrotum when the patient feels the mass itself.

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*Abbreviations used in this paper:* AFP, alpha-fetoprotein; AJCC, American Joint Committee of Cancer; HCG, human chorionic gonadotrophin; IGCCCG, International Germ Cell Cancer Collaborative Group; IGCNU, intratubular germ cell neoplasia; LDH, lactate dehydrogenase; MOE, maternal oestrogen exposure; PGC, primordial germ cell; PLAP, placental alkaline phosphatase; RPLND, retroperitoneal lymph node dissection; TGCT, testicular germ cell tumour; UDT, undescended testis.

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In other situations the patient has an incidental mass diagnosed when presenting with other symptoms of a concomitant testicular pathology such as epididymitis. It is interesting to note that 10% of patients presenting with epididymitis present can present with a TGCTs (La Vecchia *et al.*, 2010; Curado *et al.*, 2007). Another common symptom of presentation is testicular pain (La Vecchia *et al.*, 2010) seen in up to 20% of patient with TGCTs. In certain cases up to 27% of patients have local pain which could be attributed to a degree of local invasion (La Vecchia *et al.*, 2010). Up to 1-2% of TGCTs present bilaterally. Paraneoplastic symptoms such as gynaecomastia can be seen in up to 7% of patients at initial presentation. Additional symptoms include lower back pain and loin pain (La Vecchia *et al.*, 2010; Curado *et al.*, 2007).

When a patient presents with a testicular mass it is extremely important to elicit a detailed history which includes duration of symptoms, whether the mass is painful or painless, change in size of mass, sexual history, concomitant lower urinary tract symptoms, previous history of surgery, infertility or mumps and family history of testicular cancer. There is evidence to suggest that delay in presentation is more of a problem than delay in referral and this has prompted some authors to suggest that a public education campaign might be helpful (Thornhill, *et al.*, 1986; Thornhill, *et al.*, 1987).

The radiological investigation of choice for testicular cancer is an ultrasound throughout Europe. The main advantage lies with the fact that an ultrasound is non radiation exposure scan and is relatively inexpensive. The current sensitivity and specificity of an ultrasound of testis is 100% (Kim *et al.*, 2007). In patients with an equivocal diagnosis a Magnetic resonance imaging (MRI) offers a sensitivity of 100% and a specificity of 95-100% (Cassidy *et al.*, 2010), but its high cost does not justify its use for diagnosis.

## Classification

As the 2011 European Association of Urology (EAU) guidelines testicular cancer is classified as per the 2004 World health organization (WHO) guidelines (Eble, *et al.*, 2004). From the perspective of our book chapter we will confine our discussion to Testicular Germ Cell Tumours only.

### Germ cell tumours

- Intratubular germ cell neoplasia, unclassified type (IGCNU)
- Seminoma (including cases with syncytiotrophoblastic cells)
- Spermatocytic seminoma (mention if there is sarcomatous component)
- Embryonal carcinoma
- Yolk sac tumour
- Choriocarcinoma
- Teratoma (mature, immature, with malignant component)
- Tumours with more than one histological type (specify percent-age of individual components)

### Sex cord/gonadal stromal tumours

- Leydig cell tumour
- Malignant Leydig cell tumour
- Sertoli cell tumour
  - lipid-rich variant
  - sclerosing
  - large cell calcifying

- Malignant Sertoli cell tumour
- Granulosa cell tumour
  - adult type
  - juvenile type
- Thecoma/fibroma group of tumours
- Other sex cord/gonadal stromal tumours
  - incompletely differentiated
  - mixed
- Tumours containing germ cell and sex cord/gonadal stromal (gonadoblastoma)

### Miscellaneous non-specific stromal tumours

- Ovarian epithelial tumours
- Tumours of the collecting ducts and rete testis
- Tumours (benign and malignant) of non-specific stroma.

## Aetiology

The commonly association aetiologies and risk factors for the development of Testicular germ cell tumours are:-

### Age

In the paediatric population i.e., patients  $\leq 16$  years the commonest form of Testicular Tumours are Mature teratoma, rhabdomyosarcoma, epidermoid cyst, yolk sac and germ cell tumours. The commonest age group of patients affected with TGCTs is between 20-45 years. Teratomas are common between the ages of 20-35 years while seminomas is more common between the ages of 25-45 years. In men above the age of 60 years the commonest tumour is a lymphoma.

### Cryptorchidism

The condition if present on the side of the diagnosis of TGCT or the contralateral side is associated with an increased risk of developing Testicular Cancer in the long term. The risk of TGCT in the Undescended Testis (UDT) is increased by 4 - 13, with up to 7-10% of Testicular Cancers developing in UDT (Schottenfeld *et al.*, 1980). There is a 5-10% risk of developing testicular cancer in the contralateral testis in those with a history of UDT (Henderson, *et al.*, 1979). Premalignant changes within the UDT commence by the age of 3 years. However, an early orchidopexy does not completely eliminate the risk of developing testicular cancer in the long term.

### Intratubular germ cell neoplasia (IGCNU)

Intratubular germ cell neoplasia (IGCNU) is also known as carcinoma *in situ* (CIS) of the testis. The incidence of IGCNU in the overall population is 0.9%. Intratubular germ cell neoplasia is defined as a pre-invasive testicular germ cell lesion and is now believed an important precursor of TGCTs. The only TGCT not associated with IGCNU is a spermatocytic seminoma. When present the probability of progression to TGCTs increases by 50% over a duration of 5 years. At 7 year the cumulative probability of developing a TGCTs increased to 70% (Skakkebaek, *et al.*, 1982).

The incidence of IGCNU is the contralateral testis in patients with TGCTs is 5-9%. The incidence however rises to 34% when the primary TGCTs has been diagnosed before the age of 40 years and the testicular volume is less than 12 ml. In both the above mentioned scenarios, the EAU guidelines recommends a biopsy of the contralateral testis. It is important to note that the presence

of IGCNU in the ipsilateral testis does not have any bearing on the patients overall prognosis. Risk factors for IGCNU include cryptorchidism (UDT), extra-gonadal germ cell tumour, previous or contralateral TGCT (5%), atrophic testicle with a volume of less than 12 ml, early age of diagnosis of TGCTs i.e.,  $\leq 40$  years, 45XO karyotype, Klinefelter's syndrome and infertility. Intratubular germ cell neoplasia shows alterations in the p53 in upto 66% of cases. Once TIN is diagnosed, local radiotherapy (16-20 Gy in fractions of 2 Gy) is the treatment of choice in solitary testis. Because this may produce infertility, the patient must be carefully counselled before treatment commences.

#### **Maternal oestrogen exposure**

Maternal Oestrogen Exposure (MOE) increases during pregnancy and hence increases the risk of cryptorchidism and TGCT in the male offspring. The MOE with diethylstilboestrol increases the risk of TGCTs by a relative risk of 2.8 - 5.3% (Henderson *et al.*, 1979).

#### **Subfertility**

A history of subfertility and poor quality semen analysis increases the risk of testicular cancer by upto 1.6 times and from the Surveillance Epidemiology and End Results database by 20 times.

#### **Family history**

Familial history of testicular tumours among first-grade relatives (father/brothers) has been associated with isochromosome of the short arm of chromosome 12 – i(12p) (Bosi *et al.*, 1997).

#### **Additional factors**

Additional factors such as tallness, previous history of Marijuana exposure, vasectomy, trauma, mumps and Human Immunodeficiency Virus (HIV) infection continue to be evaluated.

#### **Genetic markers**

Current research has identified deregulation in the pluripotent programme of fetal germ cells (identified by specific markers such as M2A, C-KIT and OCT4/NANOG) is probably responsible for the development of Tin and germ cell neoplasia. There is overlap in the development to seminoma and embryonal carcinoma as shown by genomewide expression analysis and detection of alpha-fetoprotein (AFP) mRNA in some atypical seminoma (Looijenga *et al.*, 2007; Reuter *et al.*, 2005). Continued genome wide screening studies and gene expression analysis data suggest testis cancer specific gene mutations on chromosomes 4, 5, 6 and 12 (namely expressing SPRY4, kit-Ligand and Synaptopodin) (Rapley *et al.*, 2009; Kanetsky *et al.*, 2009; Korkola *et al.*, 2009).

Newer developments continued to be made with regards to further molecular profiling of TGCTs. The current molecular developments include characterization of newer markers such as MAGEC2 expression. This newer allows a reliable distinction of seminoma from embryonal carcinomas. Therefore, MAGEC2 represents an additional tool for the differential diagnosis of testicular germ cell tumours (Bode *et al.*, 2011).

### **Diagnosis**

#### **Tumour markers**

For the successful management of TGCTs it is crucial to un-

derstand the molecular details, half lives and clinical applications of testicular tumour markers. In clinical practice with Europe and the UK, the three common tumour markers used include Alpha-fetoprotein (AFP),  $\beta$ - human chorionic gonadotrophin ( $\beta$ -HCG) and lactate dehydrogenase (LDH). All testicular tumour markers contribute to the patients diagnosis and more importantly to the final prognosis. When a patient is diagnosed with a TGCTs, tumour markers will be elevated in 51% of cases (Wanderas *et al.*, 1992).

Alpha-fetoprotein (AFP) is expressed by trophoblastic elements within 50-70% of non-seminomatous germ cell tumour (NSGCT) and yolk sac tumours. In patients with an elevated AFP with Seminoma alone, this raises the suspicion of the presence of Non-seminomatous elements. The half life of AFP is 5-7 days and the normal serum levels  $<10$  ng/ml.  $\beta$ - human chorionic gonadotrophin ( $\beta$ -HCG) is produced by syntiotrophoblast elements. In patients with choriocarcinomas,  $\beta$ -HCG is elevated in 100% of cases. From the perspective of other TGCTs,  $\beta$ -HCG is elevated in 40% of cases of NSGCT and 10% of Seminomas. The half-life of  $\beta$ -HCG is 24-36 hours and normal serum levels  $<5$  mIU/ml. About 90% of non-seminomatous tumours present with a rise in one or two of the markers.

Lactate dehydrogenase (LDH) is a less specific marker and is an ubiquitous enzyme elevated in serum from various causes, therefore is less specific. It is elevated in 10-20% of seminomas but may be elevated in 80% of patients with advanced testicular cancer (Peyret *et al.*, 1993). Other markers studied include placental alkaline phosphatase (PLAP), which may be of value in monitoring patients with pure seminoma. Placental alkaline phosphatase (PLAP) is a foetal enzyme and may be falsely elevated in smokers. Cytogenetic and molecular markers are available in specific centres, but at present only contribute to research studies. Measurement of serum AFP, hCG and LDH is mandatory, while that of PLAP is optional.

Testicular tumour markers are normally measured when a patient presents with a TGCT clinically. In Europe the Testicular tumour markers are measure 1-2 weeks following radical orchidectomy. The testicular tumour markers play an important role in assessing response to treatment and follow up. The presence of normal testicular tumour markers prior to orchidectomy does not normally exclude the presence of micrometastatic disease. However, the persistence of testicular tumour markers following post radical inguinal orchidectomy may occur in patients with hepatic dysfunction, hypogonadotropism and most importantly in metastatic disease.

It is also important to note that other malignancies may cause an elevation of testicular tumour markers. Liver, pancreatic, gastric and lung malignancies may cause an elevated AFP level. Pancreatic, liver, gastric, lung, breast, kidney and bladder cancer may cause an elevated  $\beta$ -HCG level.

Markers before start of chemotherapy are important to classify the patient according to the International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification.

#### **Radiological imaging**

The radiological investigation of choice for testicular cancer is an ultrasound throughout Europe. The main advantage lies with the fact that an ultrasound is non radiation exposure scan and is relatively inexpensive. The current sensitivity and specificity of an ultrasound of testis is 100% (Kim *et al.*, 2007). In patients with an equivocal diagnosis a Magnetic resonance imaging (MRI) offers

a sensitivity of 100% and a specificity of 95-100% (Cassidy *et al.*, 2010), but its high cost does not justify its use for diagnosis.

## Management

### Staging

Once a patient is diagnosed with a TGCTs the patient is staged with a thorough history and clinical examination. In the patients history it is important to ask the following questions with regards to the testicular lump. The crucial points in the history include the duration of symptoms, whether the lump is painful or painless, change in size of the lump, previous surgical history of UDT, sexual history, history of lower urinary tract symptoms and family history. Clinical examination includes assessment of supraclavicular lymph node, chest examination and abdominal examination for inguinal lymph nodes. At this stage a full set of Testicular tumour markers is performed which includes serum AFP,  $\beta$ -hCG and LDH is mandatory, while that of PLAP is optional. In cases of disseminated disease and life-threatening metastases, it is current practice to start with up-front chemotherapy, and orchidectomy may be delayed until clinical stabilisation has occurred.

In patients with a suspected testicular mass a radical inguinal orchidectomy is performed. The main principal of this procedure lies with exteriorisation of the testicle within its tunics. Prior to mobilization of the testis and cord, the cord is isolated and clamped to allow control of the draining lymphatics in order to minimize spillage and metastatic spread. If the diagnosis is not clear, a testicular biopsy (an enucleation of the intraparenchymal tumour) is taken for frozen section histological examination.

When the testicle is sent for pathological analysis, the EAU 2011 guidelines recommend a mandatory assessment of the specimen for the following features as these features further help prognosticate the patients outcome. The features include:

1. Macroscopic features: side, testis size, maximum tumour size, and macroscopic features of epididymis, spermatic cord, and tunica vaginalis.
2. Sampling: a 1 cm<sup>2</sup> section for every centimetre of maximum tumour diameter, including normal macroscopic parenchyma (if present), albuginea and epididymis, with selection of suspected areas. At least one proximal and one distal section of spermatic cord plus any suspected area.
3. Microscopic features and diagnosis: histological type (specify individual components and estimate amount as percentage) according to WHO 2004 (Eble *et al.*, 2004):
  - A. Presence or absence of peri-tumoural venous and/or lymphatic invasion;
  - B. Presence or absence of albuginea, tunica vaginalis, rete testis, epididymis or spermatic cord invasion;
  - C. Presence or absence of intratubular germ cell neoplasia (TIN) in non-tumour parenchyma intratubular germ cell neoplasia.
  - D. pT category according to Tumour Node Metastasis (TNM) 2009.
  - E. Immunohistochemical studies: in seminoma and mixed germ cell tumour, AFP and hCG.

Following radical inguinal orchidectomy, the main aim of clinical staging is to determine whether the patient has metastatic or occult disease at the time of presentation. The investigations of choice to determine the above and accurately stage the TGCTs at presentation include the post-orchidectomy half-life kinetics of serum tumour

markers; the status of retroperitoneal and supraclavicular lymph nodes, and the liver; the presence or absence of mediastinal nodal involvement and lung metastases; the status of brain and bone, if any suspicious symptoms are present. At this point all patients must have a serial testicular tumour markers measured and a thorough assessment of the retroperitoneum staging CT of the Chest, Abdomen and Pelvis. Retroperitoneal and mediastinal lymph nodes are best assessed by means of a CT scan. The supraclavicular nodes are best assessed by physical examination.

Hence, in Europe and the UK all patients with newly diagnosed TGCTs have the following investigations performed:

- A. Serum testicular tumour markers (AFP,  $\beta$ -hCG and LDH)
- B. CT - Chest, Abdomen and Pelvis
- C. Ultrasound Testis (Bilateral)

A bone scan is organized in patients with suspected advanced metastatic disease. A Brain CT is organized in patients in case of symptoms and patients with metastatic disease with multiple lung metastases and high beta-hCG levels. In some centres a detailed hormonal profile (Serum Testosterone, FSH, LH) and semen analysis is performed.

In all patients undergoing a radical inguinal orchidectomy it is important to counsel patients on the options of sperm banking and insertion of a testicular prosthesis. The 2011 EAU guidelines recommend cryopreservation of sperm prior to orchidectomy. This should be specifically offered in all patients with a history of Subfertility and atrophic contralateral testis. In patients keen to pursue the insertion of a testicular prosthesis at the time of an inguinal orchidectomy, the risk of a possible delay to chemotherapy secondary to prosthesis related infection (0.6-2%) (Marshall *et al.*, 1986) must be highlighted.

### Staging and prognostic classifications

The staging system recommended in these guidelines is the 2009 TNM of the International Union Against Cancer (UICC) (Sobin, *et al.* 2009) include the following parameters:

- A. Determination of the anatomical extent of disease
- B. Assessment of serum tumour markers, including nadir values of hCG, AFP and LDH after orchidectomy (S category)
- C. Clear definition of regional nodes
- D. N-category modifications related to node size

#### pT Primary tumour

- pTX Primary tumour cannot be assessed
- pT0 No evidence of primary tumour (e.g. histological scar in testis)
- pTis Intratubular germ cell neoplasia (testicular intraepithelial neoplasia)
- 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

#### Regional lymph nodes clinical

- NX Regional lymph nodes cannot be assessed

TABLE 1

**TNM CLASSIFICATION FOR TESTICULAR CANCER AS PER SERUM TESTICULAR TUMOUR MARKER LEVEL**

	<b>LDH (U/l)</b>	<b>hCG (mIU/ml)</b>	<b>AFP (ng/ml)</b>
S1	<1.5 X N and	< 5000 and	< 1000
S2	1.5 - 10 X N or	5000 - 50,000 or	1,000-10,000
S3	> 10 X N or	> 50,000 or	> 10,000

- 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

*pN 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 of 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
- M1b Other sites

*S Serum tumour markers*

- Sx Serum marker studies not available or not performed

S0 Serum marker study levels within normal limits

On the attaining the TNMS information using the 2009 TNM of the International Union Against Cancer (UICC), patients are then staged using the American Joint Committee of Cancer (AJCC) staging classification (Testis - AJCC) summarized in Table 2.

The AJCC staging system helps prognosticate all patients with testicular tumours. Patients with stage 1A disease are defined as those with tumours limited to the testis and the epididymis with no evidence of vascular or lymphatic invasion by tumour cells on microscopy. There is no sign of metastasis on clinical imaging and post-orchidectomy serum tumour marker levels within normal limits. Stage 1B have a more locally advanced tumour with no evidence of metastatic disease. Patients with Stage 1S disease have persistently elevated testicular marker levels post orchidectomy. In 1997, the IGCCCG defined a prognostic factor-based staging system for metastatic testis tumour based on identification of some clinical 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 prechemotherapy marker levels in serum as prognostic factors to categorise patients into 'good', 'intermediate' or 'poor' prognosis (Table 3) (International Germ Cell Cancer Collaborative Group).

A good way to translate the staging details as per the AJCC stage includes the following:

- Stage I: Cancer is found only in the testicle. Removing the testicle alone should cure the patient, though many will choose some form of additional treatment just to be sure.
- Stage II: Cancer has spread to the lymph nodes in the abdomen. Removing the testicle alone will not cure the patient, and more treatment is necessary.
- Stage III: Cancer has spread to areas above the diaphragm such as the lungs, neck or brain. There may be also be cancer in parts of the body such as the bones or liver. In this situation, chemotherapy is absolutely required. Surgery may also be needed.
- Stage IV: To the best of my knowledge, there is no such thing as Stage IV testicular cancer. However, it is possible that Stage IV may still be used in some places in Europe. Suffice to say that Stage IV is probably very similar to Stage III.
- Recurrent: Recurrent disease means that the cancer has come back after it has been treated. It may recur in the same place or in another part of the body.

TABLE 2

**AMERICAN JOINT COMMITTEE OF CANCER (AJCC) STAGING CLASSIFICATION OF TESTICULAR TUMOURS**

<b>Stage 0</b>	<b>Stage I</b>	<b>Stage II</b>	<b>Stage III</b>
pTis, N0, M0, S0	pT1-4, N0, M0, SX	Any pT/Tx, N1-3, M0, SX	Any pT/Tx, Any N, M1, SX
	<b>Stage IA</b>	<b>Stage IIA</b>	<b>Stage IIIA</b>
	pT1, N0, M0, S0	Any pT/Tx, N1, M0, S0	Any pT/Tx, Any N, M1a, S0
	<b>Stage IB</b>	Any pT/Tx, N1, M0, S1	Any pT/Tx, Any N, M1a, S1
	pT2, N0, M0, S0	<b>Stage IIB</b>	<b>Stage IIIB</b>
	pT3, N0, M0, S0	Any pT/Tx, N2, M0, S0	Any pT/Tx, N1-3, M0, S2
	pT4, N0, M0, S0	Any pT/Tx, N2, M0, S1	Any pT/Tx, Any N, M1a, S2
	<b>Stage IS</b>	<b>Stage IIC</b>	<b>Stage IIIC</b>
	Any pT/Tx, N0, M0, S1-3	Any pT/Tx, N3, M0, S0	Any pT/Tx, N1-3, M0, S3
		Any pT/Tx, N3, M0, S1	Any pT/Tx, Any N, M1a, S3
			Any pT/Tx, Any N, M1b, Any S

## Treatment

Within Europe and the UK the management of TGCTs differs mainly for the indications of Retroperitoneal Lymph Node Dissection (RPLND) in both Stage I and Stage II disease. We classify the management of TGCTs as followed in Europe and the UK based on whether the tumour is a Seminoma or Non-Seminoma.

### Management of seminoma

Of all Seminomas diagnosed, 75% are confined to the testicle itself at the time of clinical presentation and a complete cure is thus achieved with a thorough radical inguinal orchidectomy. In upto 10-15% of patients metastasis is present at the time of diagnosis with a further 5-10% of patients having more advanced disease.

In patients with Non-metastatic Stage I seminoma (T1N0M0S0-1) the risk of subsequent para-aortic lymph node relapse is 20%. Adjuvant therapy with either chemotherapy or radiotherapy reduces the risk of recurrence to <1%.

### Management of stage II seminoma

The options in a patient with Stage 1 Seminoma include surveillance, adjuvant chemotherapy or adjuvant radiotherapy. The option of surveillance is indicated as 75% of Seminoma are cured following a radical inguinal orchidectomy. In a large study of 1500 patients (Chung *et al.*, 2002) indicated the overall rate of retroperitoneal disease relapse to be 16.8%. It is important to characterize patients with high risk Stage I Seminoma based on initial pathology. The 2 most important factors associated with poor prognosis includes the presence of rete-testis invasion and tumours size of  $\geq 4$  cm. The overall cancer-specific survival rate reported with surveillance performed by experienced centres is 97-100% for seminoma stage I (Warde *et al.*, 1998; Aparicio *et al.*, 2003; Tandstad *et al.*, 2011). The main drawback of surveillance is the need for more intensive

follow-up, especially with repeated imaging examinations of the retroperitoneal lymph nodes, for at least 5 years after orchidectomy.

Patients with Stage I Seminoma can also be given adjuvant chemotherapy with one cycle of Carboplatin. The dose of Carboplatin is calculated as the area under the curve (AUC) as per the Calvert formula (Calvert *et al.*, 1989). This formula uses the Total Dose (mg) = (target AUC) x (GFR + 25). In a joint trial by the Medical Research Council (MRC) and the European Organisation for Research and Treatment of Cancer (EORTC) (MRC TE 19 trial), which compared one cycle of carboplatin (area under curve [AUC] 7) with adjuvant radiotherapy, did not show a significant difference with regard to recurrence rate, time to recurrence and survival after a median follow-up of 4 years (Oliver *et al.*, 2005).

An alternative to surveillance or chemotherapy in patients is the additional option of radiotherapy. Seminomas are known to be radiosensitive and hence a Adjuvant radiotherapy to a para-aortic (PA) field or to a hockeystick field (para-aortic and ipsilateral iliac nodes), with moderate doses (total 20-24 Gy), will reduce the relapse rate to 1-3% (Fossa *et al.* 1999). The potential side effects of radiotherapy include the risk of post radiotherapy recurrence. Based on the results of a large randomised MRC trial (Fossa *et al.*, 1999) recommended radiotherapy to a PA field as standard treatment for patients with testicular seminoma stage I, T1-T3 and with undisturbed lymphatic drainage. The recommended dose of radiation is 20 Gy.

Within Europe and the UK, a RPLND is not recommended in patients with Stage 1 Seminoma. prospective, non-randomised study comparing radiotherapy and RPLND in stage I seminoma, there was a trend towards a higher incidence of retroperitoneal relapses (9.5%) after RPLND as primary treatment (Warszawski *et al.*, 1997).

In summary, it is important to stratify patients with Stage 1 Seminoma into high risk based on the presence of rete testis invasion and

TABLE 3

### PROGNOSTIC-BASED STAGING SYSTEM FOR METASTATIC GERM CELL CANCER

Prognostic Group	Progression free survival (PFS) and overall survival (OS)	Clinical Criteria
Good prognostic group (Non Seminoma)	<i>Non-seminoma (56% of cases)</i> 5-year PFS 89% 5-year survival 92%	<i>All of the following criteria:</i> • Testis/retroperitoneal 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
Good prognostic group (Seminoma)	<i>Seminoma (90% of cases)</i> 5-year PFS 82% 5-year survival 86%	<i>All of the following criteria:</i> • Testis/retroperitoneal 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
Intermediate prognosis group (Non Seminoma)	<i>Non-seminoma (28% of cases)</i> 5 years PFS 75% 5-year survival 80%	• Testis/retroperitoneal 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
Intermediate prognosis group (Seminoma)	<i>Seminoma (10% of cases)</i> 5-year PFS 67% 5-year survival 72%	<i>Any of the following criteria:</i> • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor prognosis group (Non Seminoma)	<i>Non-seminoma (16% of cases)</i> 5-year PFS 41% 5-year survival 48%	<i>Any of the following criteria:</i> • 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
Poor prognosis group (Seminoma)	No patients classified as poor prognosis	N/A

tumour volume of  $\geq 4$  cm. In these patients the option of adjuvant chemotherapy and radiotherapy is justifiable. In patients without rete testis invasion or in whom the testicular tumour volume is  $\leq 4$  cm the option of surveillance alone is recommended.

According to the most recommendations of the European Germ Cell Cancer Consensus Group Conference (EGCCCG) low-risk patients should be primarily offered active surveillance, whereas systemic chemotherapy with two cycles of PEB represents the treatment of choice for high-risk patients. Currently, a prospective, randomized phase III trial is ongoing comparing the oncological efficacy and the treatment-associated side effects of two cycles of PEB versus one cycle of PEB in clinical stage I high-risk NSGCT. Reflecting the published new data, both therapeutic approaches might be challenged

### Role of RPLND

In Europe and the UK, RPLND is offered to patients with high risk clinical stage I NSGCT. In patients with post chemotherapy retroperitoneal lymph nodes a RPLND is offered to removed persistent retroperitoneal lymph nodes that may contain mature teratoma in approximately 30–40% and vital cancer in about 10–20% of the patients.

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