Classification, Epidemiology and Therapies for Testicular Germ Cell Tumours

Suleyman N *, Moghul M †, Gowrie-Mohan S ‡, Lane T ¤ and Vasdev N ¶

Abstract
Testicular Germ Tumours (TGCTs) have come to be well defined and managed, thanks to a number of international consortia and collaborations. The incidence of TGCTs continues to rise, with a growing number of risk factors which are discussed in this article. Genetic studies have also revealed specific markers that confer risk for TGCTs. We discuss the widely accepted treatment regimens as well as areas that novel therapies may target in the future.

Keywords
Testicular germ cell tumours; Testicular cancer; Genetic marker; Sperm abnormalities

Introduction
Testicular Germ Cell Tumours (TGCTs) have come to be well defined and managed, thanks to a number of international consortia and collaborations.

Classification
The 2015 European Association of Urology (EAU) guidelines [1] classify testicular germ cell tumours according to the 2004 World Health Organization (WHO) guidelines [2]. Sex cord/gonadal stromal tumours and miscellaneous non-specific stromal tumours will not be discussed in this article.

Testicular germ cell tumours are derived from primordial germ cells [3].

Germ cell tumours

- Intratubular germ cell neoplasia, unclassified type (Germ Cell Neoplasia In Situ (GCNIS))
- 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 percentage of individual components)

The revised World Health Organisation term for precursor lesions of invasive germ cell tumours is germ cell neoplasia in situ of the testis (GCNIS) [4]. TGCTs are now separated into those derived from GCNIS and those unrelated to GCNIS [4]. Spermatocytic seminoma has been designated as a spermatocytic tumour and placed within the group of non-GCNIS-related tumours in the updated classification [4].

Epidemiology
The incidence of testicular cancer has been increasing in the last decades, especially in industrialized countries [5-7]. Testicular cancer now represents 1% of male malignancies and 5% of urological tumours [8,9]. In 90-95% of cases, the histology is germ cell tumour [8], with bilateral disease in 1-2%. Non-seminomas have a peak incidence in the third decade, and seminomas peak in the fourth decade [1].

A specific genetic marker has been described in all histological types of TGCTs; an isochromosome of the short arm of chromosome 12 – i(12p) [10]. In addition, a deregulation in the pluripotent program of foetal germ cells is likely responsible for the development of TGCTs [1]. There is overlap in the development of seminoma and embryonal carcinoma, demonstrated by genome-wide expression analysis and the detection of alpha-fetoprotein mRNA in some atypical seminomas [11,12].

Risk factors for testicular tumours are components of the testicular dysgenesis syndrome [1]. These include cryptorchidism, hypospadia and sub- or infertility indicating decreased spermatogenesis [12]. The risk of testicular cancer in the undescended testicle increases by 4-13 times [12], with up to 10% of all testicular tumours arising from an undescended testicle [13,14].

Additional risk factors include history of testicular tumour in a first-degree relative, which increases risk by up to eight times [15], and the presence of contralateral tumour or testicular intraepithelial neoplasia (TIN). Extremes of height seem to influence risk, with tall men at a higher risk of TGCTs and short stature protecting against it [16]. Exposure to diethylstilboestrol (oestrogen) in utero confers a relative risk of up to 5.3% for testicular cancer [17]. Additional risk factors such as Marijuana exposure, vasectomy, trauma, mumps and Human Immunodeficiency Virus (HIV) continue to be evaluated [18].

Therapies

Radical orchidectomy
A radical inguinal orchidectomy must be performed urgently, generally within one week. An exception to this is the presence of widespread testicular metastases on chest X-ray. This is an oncological emergency and immediate chemotherapy may be indicated before radical orchidectomy [1]. Consideration must be given as to whether

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the contralateral side must be biopsied. Men aged under 40 with a contralateral testis volume of less than 12 ml are at 34% risk of intra-
tubular germ-cell neoplasia (ITGCN) on biopsy [19]. Risk factors
for ITGCN also include a normal volume undescended testis and
subfertility, therefore biopsy should also be considered [19].

Adjuvant therapies for TGCT

The requirement for further therapy after radical orchiectomy
depends on the clinical and pathological staging of the malignancy. The American Joint Committee on Cancer (AJCC) staging classification is
used primarily in the UK, as summarized in Table 1 [1].

Stage I TGCTs

• Seminomas

Options for seminoma are surveillance, one cycle of adjuvant
carboplatin chemotherapy or adjuvant irradiation of the paraaortic
lymphatics [1]. Of the patients who opt for surveillance, up to 20% will
relapse, with relapse rates of 4% in those having either chemotherapy
or radiotherapy [20]. Treatment options after local relapse are either
radiotherapy or Bleomycin, Etoposide and Cisplatin (BEP) chemotherapy
[1]. The only option following systemic relapse is BEP chemotherapy [1].

• Non-seminomatous TGCTs

Risk of non-seminomatous TGCT is stratified according to
whether vascular invasion or not. Treatment options include
surveillance, adjuvant chemotherapy with two cycles of BEP
chemotherapy or nerve sparing retroperitoneal lymph node dissection
(RPLND) [1]. The patient should be counselled bearing in mind that
vascular invasion is the most important prognostic factor for distant
relapse [1]. Independent of vascular invasion, all non-seminomatous
TGCTs are associated with a 30% relapse rate with surveillance alone, after
radical orchiectomy alone [20].

Metastatic TGCTs: The treatment of metastatic disease is
based on the International Germ Cell Cancer Collaborative Group
(IGCCCG) prognostic classification [21].

• IIA/B Seminoma

The usual therapeutic option is chemotherapy, either three
cycles of BEP or four cycles of Etoposide and Cisplatin (EP) only.
Radiotherapy is occasionally an option [22].

• IIA/B Non-seminomatous TGCTs

Patients who are classified in the good prognosis group [20] can
be offered three cycles of BEP chemotherapy, extending treatment
to four cycles in the intermediate and poor prognosis groups [20].
Subsequently, if there is residual mass, RPLND is performed, with
salvage chemotherapy if the histology is positive [22].

• Stages IIC and III

Patients with a good prognosis [21] are offered three cycles of
BEP, which is extended to four cycles in the intermediate prognosis
group [21,22]. The recommendation [21] is that poor prognosis
patients are enrolled in trials and receive either four cycles of BEP or
Cisplatin, Etoposide and Ifosfamide (PEI/VIP) chemotherapy [22].

Novel Therapeutic Targets

It has been postulated that TGCTs begin as intratubular germ cell
neoplasia unclassified (IGCNU), which is a product of suppressed
apoptosis, increased proliferation and accumulation of mutation
in gonocytes [23]. Invasive TGCTs show gain of chromosome 12p and
single gene mutations are uncommon [23]. Different histologic
subtypes have different gene expression profiles, likely due to
epigenetic regulation [23]. Resistance to chemotherapy has been
linked to karyotype aberrations, single-gene mutations and epigenetic
regulation of gene expression [23].

The discovery of novel biomarkers will aid further discrimination
between histological subgroups of TGCTs and are potential targets for
novel treatments for this malignancy [24]. Genome-wide association
studies have also implicated gene loci that predispense to development
of TGCTs [3]. The functions of the proteins encoded by these genes go
some way to explain the development and dissemination of TGCTs and
thus have clinical relevance for management of these tumours [3].

References

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Table 1: AJCC stage groupings as compared to TNM classification (T= primary
tumour, N= lymph nodes, M = distant metastasis, S = serum tumour markers).

<table>
<thead>
<tr>
<th>Stage</th>
<th>AJCC Classification</th>
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<tbody>
<tr>
<td>IIA</td>
<td>Any pT/Tx, N1, M1a, S0</td>
</tr>
<tr>
<td>IIB</td>
<td>Any pT/Tx, N1, M1a, S1</td>
</tr>
<tr>
<td>IIC</td>
<td>Any pT/Tx, N1, M1a, S2</td>
</tr>
<tr>
<td>IIIA</td>
<td>Any pT/Tx, N1-3, M0, S0</td>
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<tr>
<td>IIIB</td>
<td>Any pT/Tx, N1-3, M0, S1</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any pT/Tx, N1-3, M0, S2</td>
</tr>
<tr>
<td>IVA</td>
<td>Any pT/Tx, N1-3, M1a, S0</td>
</tr>
<tr>
<td>IVB</td>
<td>Any pT/Tx, N1-3, M1a, S1</td>
</tr>
<tr>
<td>V</td>
<td>Any pT/Tx, N1-3, M1a, S2</td>
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</table>

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