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Staging and classification of testicular tumours: pitfalls from macroscopy to diagnosis

D M Berney

**ABSTRACT**
The accurate assessment of testicular tumours is vital for appropriate treatment to be instituted. The assessment begins at specimen receipt, as careful macroscopic examination is vital for staging, and this, in part, determines whether adjuvant treatment is given. More challenging specimens may include partial orchidectomies, biopsies and resection of lymph node or visceral metastases. Accurate histological typing is also a potential source of error as two classifications are in use, and this may lead to misunderstanding between clinician and pathologist. A specialist and multidisciplinary approach is advocated. Microscopic staging includes assessment of vascular invasion which may be complicated by artifactual spread at the dissecting bench, local invasion, assessment of the cord and occasionally lymph node deposits. From careful macroscopic examination, to accurate histological typing and reporting of adverse pathological parameters, the pathologist plays a major role in the successful treatment of a group of rare, but largely treatable, tumours.

Testicular pathology provides a challenging landscape of polymorphous neoplasms of almost unrivalled diversity. Testicular pathology also matters. Making a correct and accurate diagnosis has a profound impact on the treatment that will be given. From initial assessment of the surgical specimen through to diagnosis and interpretation, the pathologist’s opinion may have a profound impact on staging of the tumour and hence on the patient’s treatment.

The difficulties in the diagnosis of testicular tumours are multiple and reflect their complexity. Firstly, they are rare and despite an increase in incidence in the past 50 years, individual experience is often limited. A genitourinary pathologist in a general hospital will see hundreds of bladder or prostate cancers in a year, but may see only a handful of testicular neoplasms. In the UK, there is a move to centralise the examination of testicular lesions into specialist centres, so that a critical mass of knowledge can be reached by a fewer number of uropathologists. However, as most suspected testicular tumours are removed urgently, they are not seen initially at specialist centres. However, all pathologists with an interest in uropathology ought to have an awareness of the potential pitfalls in the diagnosis of testicular lesions. Accurate assessment macroscopically is as important as diagnosis down the microscope.

This review will examine the techniques necessary for the accurate staging and typing of testicular tumours, concentrating on the germ cell tumours, which are the main challenge in this field. It will also consider the importance of accurate classification, and the dangers that may be encountered through misunderstandings between pathologists and clinicians.

**MACROSCOPIC TESTICULAR ASSESSMENT**
The vast majority of men with a testicular mass undergo a radical orchidectomy. Partial orchidectomies are also rarely performed for bilateral tumours, to preserve natural hormonal production and allow the opportunity for natural reproduction. They are also occasionally performed for small radiographically equivocal lesions, when the diagnosis is unlikely to be malignant. Other testicular pathological specimens include subcapsular orchidectomies for hormonal castration in prostate cancer and simple orchidectomies for benign diseases such as torsion, or undescended testes where only a short section of cord is removed.

Frozen section for testicular lesions is difficult and rarely necessary in straightforward cases. The vast majority of cases can be diagnosed by ultrasound examination and assessment of tumour markers prior to orchidectomy. Occasionally, a difficult lesion may be encountered; usually when there are normal tumour markers, and equivocal radiology. If the lesion is small, the options may include “active surveillance” orchidectomy, or a partial orchidectomy with frozen section for the margins and diagnosis. Frozen sectioning may be utilised in some centres for this type of case, but caution should be exercised in identification of specific entities by frozen section alone. It may be difficult to distinguish teratomas from epidermoid or dermoid cysts unless multiple blocks are taken, which is impractical by frozen section. Also, seminomas and sex cord/stromal tumours may be difficult to differentiate. Granulomatous inflammatory lesions can also be difficult to differentiate from seminomas, where the florid inflammatory reaction can mask the malignant seminoma component.

Fixation is important for testicular tumours, but before the tumour is bivalved for better fixation, it is important to observe a number of features. Specimens should be measured, including the spermatic cord length. The problem of artifactual carry over of tumour onto the cord after the tumour has been bivalved has led to the recommendation of taking the distal cord block before incising the testis. The main culprit of this annoying phenomenon is seminoma, which often liquefies and spreads like porridge over all surfaces. This most frequently occurs after inadequate fixation, but is sometimes inevitable in cases with
extensive necrosis. Ideally, the tumour should be bivalved as early as possible, to ensure fixative permeation throughout the whole tumour.

Most authors recommend assessment of the cord margin before tumour incision. This is to avoid “contamination” of the distal cord block by carry-over from the main tumour. However, I believe it is usually perfectly possible to work out what is artifactual tumour spread, and what is genuine invasion. Artifactual spread to other tumour blocks is unavoidable as part of routine assessment, and it seems illogical to “protect” the distal cord block, while pathologists cope perfectly well with pathological interpretation of other, often more important, blocks of testicular parenchyma.

Invasion of the tunica vaginalis is best assessed at cut up and can be impossible to assess on referred material, if a good macroscopic assessment is not available. The tunica vaginalis should be palpated and proven to be separate from the tunica albuginea; this is the best evidence that a testicular tumour has not invaded the tunica vaginalis. When blocked, the vaginalis often floats off in processing, and cannot be easily assessed.

After bivalving the tumour through the epididymis and rete, and leaving for 24 hours fixation, the tumour location and size can be described in relation to the other testicular structures, as well as the appearances in the normal testicular parenchyma. Invasion outside the testis should be noted; inking of the specimen is generally unnecessary, unless the specimen is a subcapsular orchidectomy, or if the specimen is widely invading the peri-testicular tissues.

Comprehensive sampling is mandatory as the identification of tiny areas of non-seminoma can affect patient management. A minimum of one block per centimetre of tumour is often quoted, though more may be taken to represent the different areas and the invasion of surrounding structures, especially in small tumours of 2 cm or less. It has been advocated that a large seminoma requires at least 10 blocks to rule out small non-seminomatous foci. Other blocks which are necessary include the cord margin, though in fact this is extremely rarely involved by tumour deposits (and virtually never if this has not been noted macroscopically). Therefore, blocks from lower down the cord, where invasion is more likely, should be taken. It should be noted that there is a difference between vascular invasion of the cord (which equates in prognostic terms with vascular invasion elsewhere in the specimen) and solid invasive tumour within the cord tissue. True involvement of the cord margin is rare and usually obvious macroscopically. Uninvolved testicular tissue should be sampled. Vascular invasion is often present at the tumour periphery, so this should always be extensively sampled.

Partial orchidectomies have to be sampled in a different manner. Here it is essential to ink the incised testicular parenchyma and assess this for presence of in-situ or invasive disease. Multiple biopsies are also usually taken. Multiple transverse blocks are sampled when the distance of the tumour to the inked margin can be easily assessed.

**HANDLING OF BIOPSY SPECIMENS**

Testicular biopsies are very rarely taken to make a diagnosis of neoplasia. Most are taken for assessment of fertility, though rarely intratubular germ cell neoplasia, unclassified (IGCNU) may be seen incidentally. To preserve good morphology, many centres use Bouin’s fixative as opposed to formalin for these specimens. However, immunochemistry on Bouin’s fixed specimens is often very variable, and interpretation of any immunochemistry should be treated with caution: notably the use PLAP to confirm IGCNU on a biopsy specimen may well give a false negative result.

Some centres offer contralateral biopsies in patients with germ cell tumours (GCTs). This is to prevent the later development of a tumour, by administering low-dose irradiation to prevent the development of a GCT. Bilateral orchidectomy is obviously associated with complete androgen ablation. However, the value of biopsy is controversial, as IGCNU is only seen in 5% of contralateral testes of patients with GCT and up to 25% of men given low dose radiation therapy develop androgen insufficiency in any case.

**METASTATIC GERM CELL TUMOURS**

Lymph node dissection is an integral part of treatment for metastatic germ cell tumours. Some centres, especially in the USA, perform primary retroperitoneal dissections. However, many other centres pursue a more conservative policy of dissection, only after surgery and primary chemotherapy. Thorous sampling of the nodes is essential with a minimum of one block per cm of lymph node, particularly in the post-chemotherapy specimens, where the findings are frequently complex and require extensive study. Close macroscopic examination for unusual areas should be sampled, especially as the retroperitoneal masses may be much larger than the testicular lesion and show discordant morphology. Correlation with clinical factors is even more important in these cases.

**MICROSCOPIC ASSESSMENT**

**Tumour type**

It is sobering that lives have been lost through misinterpretation of pathological words in testicular cancer. Words like “teratoma”, “trophoblast” and “MTI” are often used with a great potential for misunderstanding between the members of the multidisciplinary team. The situation is complicated by the existence of two classification systems.

The classification of germ cell tumours has had a somewhat convoluted history. The British Testicular Tumour Panel (BTTP) classification is derived from work by Pugh. The BTTP collection consisted of referral cases diagnosed between 1950 and 1980, for which each of the panel of experts gave their opinion. The collection is supplemented by a wealth of detail such as macroscopic pictures and clinical follow-up. This archive is now kept at St Bartholomew’s Hospital by The Orchid Appeal. All cases of germ cell tumour in the BTTP were recently tissue micro-arrayed and re-examined with immunochemistry performed. Only one of nearly 400 cases, which was a sex cord/stromal tumour, proved to be an erroneous diagnosis. The incredible accuracy of the BTTP panel members is a testament to the fact that careful H&E examination remains the best way to make a diagnosis of testicular tumours. The BTTP classification is still in widespread use in the UK and Ireland.

The WHO classification has been recently revised and is derived from work by Friedman et al. Table 1 compares the modified 2004 WHO classification with that of the BTTP. Pathologists have very strong opinions on which classification is used. My personal strong preference is for the WHO classification which has proven to be more prognostically robust. As seen from table 1, the BTTP “lumps” some of the non-seminomatosus components together into single entities; it should now be standard practice to list all the different tumour elements present, and their varying proportions. I encourage all UK
Table 1  Comparison of the World Health Organization (WHO) and British Testicular Tumour Panel (BTTP) classifications

<table>
<thead>
<tr>
<th>2004 WHO classification</th>
<th>BTTP classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumours of one histological type</td>
<td></td>
</tr>
<tr>
<td>Seminoma</td>
<td>Seminoma</td>
</tr>
<tr>
<td>With syncytiotrophoblastic giant cells</td>
<td></td>
</tr>
<tr>
<td>Spermatocytic seminoma</td>
<td>Spermatocytic seminoma</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>Malignant teratoma, undifferentiated</td>
</tr>
<tr>
<td>Yolk sac tumour</td>
<td>Yolk sac tumour (pure neoplasms only)</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Malignant teratoma, trophoblastic</td>
</tr>
<tr>
<td>Other trophoblastic tumours</td>
<td></td>
</tr>
<tr>
<td>Monophasic choriocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Placental site trophoblastic tumour</td>
<td></td>
</tr>
<tr>
<td>Teratoma</td>
<td>Teratoma, differentiated</td>
</tr>
<tr>
<td>Dermoid cyst</td>
<td></td>
</tr>
<tr>
<td>Monodermal teratoma</td>
<td></td>
</tr>
<tr>
<td>Teratoma with somatic transformation</td>
<td></td>
</tr>
<tr>
<td>Tumours of more than one histological type</td>
<td></td>
</tr>
<tr>
<td>Embryonal carcinoma/yolk sac and teratoma</td>
<td>Malignant teratoma, intermediate</td>
</tr>
<tr>
<td>Choriocarcinoma and other non-seminoma</td>
<td>Malignant teratoma, trophoblastic</td>
</tr>
<tr>
<td>Seminoma and non-seminoma</td>
<td>Combined tumour seminoma/non-seminoma</td>
</tr>
</tbody>
</table>

pathologists to adopt the WHO classification, as a minimum, in parallel with the BTTP.

It is essential, however, that the treating clinicians fully understand the reports that are issued. Clarity of understanding is vital, and worth repeated discussions within the multidisciplinary team to ensure that all team members are on the same wavelength. An unfortunate complication of two systems being used is the fact that comparison of pathology results and treatment results is extremely difficult with two classifications in use. This will be avoided if the WHO classification becomes universal.

There are a number of crucial differences between the two classifications. The WHO classification is based around the identification of different germ cell tumour elements; the BTTP system tries to concentrate on entities. Use of the term “teratoma” is especially confusing and misinterpretation of this may lead to severe consequences. The BTTP system recognised at an early stage that all teratomas in adult males were potentially malignant. They used the term for the whole spectrum of non-seminomas: the highly aggressive malignant teratoma undifferentiated (MTU) to teratoma differentiated (TD). The WHO uses embryonal carcinoma for the former and “teratoma” for the latter, still recognising its malignant potential. It has recently abandoned the term malignant teratoma immature (MTI), which is probably the most misused term in testicular pathology, confused with malignant teratoma, intermediate in the BTTP. It used to be used for mixed germ cell tumours with embryonal and teratomatous elements. However, it is also been used for teratomas with focal atypia of the glandular or stromal components and for tumours showing transformation, such as those with prominent neuroectodermal elements. Lumping all these tumours into a “catch all” category is dangerous, as they require entirely different treatment and follow-up. Teratomas with focal atypia are now lumped with the teratomas as they behave in a similar way. It is advised that the individual elements are reported carefully in the report and that the very rare somatic transformations should only be reported by a specialist testicular pathologist.

The teratoma group of WHO has been complicated recently by the inclusion of an allegedly benign entity. The dermoid cyst may contain the typical elements of a mature teratoma, but does not show any IGCNU on exhaustive sampling. Interestingly, it has been recently suggested that these entities may be the equivalent of well known prepubescent teratomas, which have persisted subclinically into adulthood, explaining their benign behaviour. However, relatively few of these have been described, and the differences in potential follow-up between a mature teratoma and a dermoid cyst, means that this group should be treated with caution to avoid undertreatment of a potentially malignant disease.

Vascular invasion

All pathology reports should state the presence or absence of vascular invasion, as it is an important prognostic factor and is often used to decide whether adjuvant chemotherapy is administrated in germ cell tumours. The most common error in pathological material in referral is overcalling vascular invasion.

Single cells within vessels are usually the result of artificial smearing (fig 1). To be true vascular invasion, the presence of associated blood constituents and attachment of the tumour to the vessel wall are helpful features (fig 2). The edge of seminomas is a useful area to search. Invasion of vessels by embryonal carcinoma is common and is often seen in the stroma surrounding the tumour. Embryonal carcinomas are associated with vascular invasion much more frequently than seminoma.

Invasion of local structures

The microscopic examination will be closely informed by the macroscopic appearances, as mentioned above. Rete testis invasion may be of two types. Firstly, there may be a pagetoid type of invasion (fig 3), usually of seminoma, along the epithelial ling of the rete testis. Secondly, there may be interstitial invasion of the parenchyma which is associated with infiltration of tumour between the tubules. In fact, there have been few studies to differentiate the clinical importance of these two phenomena, but in general it is an important prognostic factor.

Figure 1  Seminoma showing artifactual smearing of single cells mimicking vascular invasion.
invasion seen is from IGCNU tracking down seminiferous tubules while the interstitial sort represents true invasion of any tumour subtype. It seems reasonable to distinguish between the two on any thorough report. Tunica vaginalis invasion is seen macroscopically, though invasion up to the tunica albuginea margin, or close to it, is frequent. Invasion of the epididymis and cord should also be assessed. It is important to distinguish true invasion, either as direct spread, or as a “satellite” metastasis, from vascular invasion. Tumour within vessels in the cord does not equate to cord invasion, but to vascular invasion and should be reported as such. Much attention has been placed in the past on taking the cord margin. However, in the real world, if the cord margin is involved, it is usually obvious macroscopically. Sampling down the cord may be more helpful in identifying tumour spread. It is also very important to distinguish tumour from more commonly seen benign nodules in the cord. Paraganglia, adrenal rests, Leydig cell nodules and adenomatoid tumours are only some of the lesions that can be mistaken for germ cell tumours in the cord. 60–63

**Take-home messages**

- Careful macroscopic assessment is vital.
- A multidisciplinary team approach is advocated.
- Use of the revised WHO classification is recommended.
- Caution is necessary in vascular invasion interpretation.

**Intratubular neoplasia**

It is usual to examine the testis to report the presence of IGCNU in the seminiferous tubules adjacent to the tumour. IGCNU has been proven by morphology and genetics to be the precursor lesion of GCTs. 64, 65 This is essential in organ sparing surgery, at the margins, but it is also extremely helpful to identify IGCNU in radical specimens. This is because it is present in a very high percentage of germ cell tumours, and its absence may lead a pathologist to correctly question whether the invasive component is of germ cell origin. A number of lesions, including Leydig cell tumours, may mimic seminoma. 66–69

Other forms of intratubular germ cell tumour have also been described; however they are of interest only in pathogenetic terms, and almost never seen without IGCNU. 34–37

**DEVELOPMENTS IN STAGING AND TYPING FOR TREATMENT**

Staging of testicular tumours can be achieved from interpretation of the pathological data described above. Although a number of systems are in use, we, along with other authors, advocate adoption of the TNM staging system to achieve a degree of institutional uniformity. 7 The IGCCC prognostic index is based on clinical data, serum levels of markers and the presence of visceral metastases. 70

Patient choice now plays an increasing part in GCT treatment and a less interventional approach may be used if it is known that the patient can be monitored closely. Radiotherapy has been standard seminoma treatment for many years. 79–80 However, some centres now offer a single dose of carboplatin. There is recent evidence that this may be as efficacious as radiotherapy and be associated with fewer recurrences in the contralateral testis. 81 Studies in new drugs have concentrated on drug-resistant tumours. DNA topoisomerase I inhibitors are one such drug class and may be of use in treating patients, after conventional agents have failed. 52 Accurate staging and typing is essential if clinical developments are to be meaningful; it also enables easy comparison between institutions.

Germ cell tumours present unique challenges to the histopathologist, who plays a major part in treatment decisions in a large multidisciplinary team. The knowledge that sustained cures and remissions are possible in young men with metastatic disease makes this unusual area not just challenging, but very rewarding.

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**Competing interests**

None declared.

**REFERENCES**


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