

Family/Last name

Date of birth

DD – MM – YYYY

Given name(s)

Patient identifiers

Date of request

DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are **CORE**. Elements in **grey text** are **NON-CORE**. indicates multi-select values     indicates single select values

SCOPE OF THIS DATASET

**CLINICAL INFORMATION** (Note 1)

- Information not provided  
 Information provided (select all that apply)

 Previous history of testicular cancer, *specify* Previous therapy, *specify* Other clinical information, *specify***SERUM TUMOUR MARKERS** (Note 2)

- Not provided  
 Provided  
 Serum tumour markers within normal limits

Specify serum tumour markers used, level and date markers were drawn (select all that apply)

Date   AFP  ug/L LDH   b-HcG  IU/L**OPERATIVE PROCEDURE** (Note 3)

- Not specified  
 Orchidectomy, partial  
 Left     Right     Laterality not specified  
 Orchidectomy, radical  
 Left     Right     Laterality not specified  
 Other, *specify*

**TUMOUR FOCALITY** (Note 4)

- Cannot be assessed  
 Unifocal  
 Multifocal

Specify number of tumours

**TUMOUR DIMENSIONS** (Note 5)

- 
- Cannot be assessed

Dimensions (largest tumour)

 mm x  mm x  mm

Dimensions of additional tumour nodules

 mm x  mm x  mm mm x  mm x  mm mm x  mm x  mm**MACROSCOPIC EXTENT OF INVASION** (select all that apply) (Note 6)

- Cannot be assessed  
 Confined to testis  
 Invades epididymis  
 Invades tunica vaginalis  
 Invades hilar structures  
 Invades spermatic cord  
 Invades scrotum  
 Other, *specify*

**BLOCK IDENTIFICATION KEY** (Note 7)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

**HISTOLOGICAL TUMOUR TYPE** (select all that apply) (Note 8)

- 
- Germ cell tumour,
- specify type and percentage*

 →  % →  % →  % →  %

- 
- Other,
- specify*

**MICROSCOPIC EXTENT OF INVASION** (Note 9)**Rete testis of stromal/interstitial type**

- Not submitted  
 Not involved  
 Involved

**Epididymis**

- Not submitted  
 Not involved  
 Involved

**Hilar soft tissue**

- Not submitted  
 Not involved  
 Involved

**Tunica albuginea***(White fibrous capsule around testicular parenchyma)*

- Not submitted  
 Not involved  
 Involved

**Tunica vaginalis***(Either mesothelial layer of the tunica vaginalis)*

- Not submitted  
 Not involved  
 Involved

**Spermatic cord**

- Not submitted  
 Not involved  
 Involved

**Scrotal wall**

- Not submitted  
 Not involved  
 Involved

**LYMPHOVASCULAR INVASION** (Note 10)

- Indeterminate  
 Not identified  
 Present, *specify type*

**IN SITU AND INTRATUBULAR LESIONS** (Note 11)**Germ cell neoplasia in situ**

- Cannot be assessed  
 Not identified  
 Present

**Other intratubular/in situ lesions**

- Not identified  
 Present, *specify type*

**RESPONSE TO ADJUVANT TREATMENT** (Note 12)

- No previous treatment  
 Response absent  
 Response present  
 Cannot be assessed, *explain reasons*

**MARGIN STATUS** (Note 13)**Partial orchidectomy**

- Cannot be assessed  
 Not involved  
 Distance of tumour from closest margin  mm  
 Involved

**Radical orchidectomy** (select all that apply)

- Cannot be assessed  
 Spermatic cord margin not involved  
 Spermatic cord margin involved  
 Other margin involved, *specify*

**COEXISTENT PATHOLOGY** (Note 14)

- None identified  
 Present, *specify*

**ANCILLARY STUDIES** (Note 15)

- Not performed  
 Performed, *record test(s), methodology and results*

**Representative blocks for ancillary studies**, *specify those blocks best representing tumour and/or normal tissue for further study*

**PATHOLOGICAL STAGING (UICC TNM 8<sup>th</sup> edition)<sup>a</sup>** (Note 16)**TNM Descriptors** (only if applicable) (select all that apply)

- m - multiple primary tumours  
 r - recurrent  
 y - post-therapy

**Primary tumour (pT)**

- TX<sup>b</sup> Primary tumour cannot be assessed  
 T0 No evidence of primary tumour  
 Tis Germ cell neoplasia in situ  
 T1 Tumour limited to testis (including rete testis) without vascular/lymphatic invasion and without invasion of the epididymis  
 T2 Tumour limited to testis with vascular/lymphatic invasion, or invading hilar soft tissue or the epididymis or tumour extending through tunica albuginea with involvement of visceral tunica vaginalis  
 T3 Tumour invades spermatic cord with or without vascular/lymphatic invasion  
 T4 Tumour invades scrotum with or without vascular/lymphatic invasion

<sup>a</sup> *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8<sup>th</sup> Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 12<sup>th</sup> July 2024).*

<sup>b</sup> *TX should be used only if absolutely necessary.*

## Definitions

### CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence<sup>1</sup>). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

### NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the DAC.

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## Scope

The dataset has been developed for the reporting of both partial and radical orchidectomy specimens from patients of any age with germ cell neoplasia of the testis. The dataset does not apply to sex cord-stromal tumours of the testis or to extra-gonadal germ cell tumours. The former have different criteria for malignancy from germ cell tumours, and the latter have an entirely separate staging system dependent on location. Sex cord stromal tumours are complex, with some types being entirely benign while others can be malignant. They are therefore too complex to include within this germ cell tumour focussed proforma. Paratesticular malignancies are also excluded for similar reasons. This dataset does not include information on the excision of residual metastatic masses after chemotherapy. A separate ICCR dataset is available for the reporting of retroperitoneal lymphadenectomy specimens.<sup>2</sup>

For bilateral tumours, complete a separate dataset for each tumour.

The second edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Tumours, Urinary and Male Genital Tumours, 5<sup>th</sup> edition, 2022.<sup>3</sup> The ICCR dataset includes 5<sup>th</sup> edition Corrigenda, July 2024.<sup>4</sup> In development of this dataset, the DAC considered evidence up until July 2024.

### **General information on the use of macroscopic and microscopic risk factors for recurrence**

A large number of competing risk factors have been previously assessed for the likelihood of relapse in testicular germ cell tumours and how they relate to tumour stage. The clinical importance of these is more important for those tumours which present at Stage I (no distant spread).

Adjuvant treatment reduces the chance of relapse and later need for treatments with higher morbidity. Possible adjuvant therapies may include chemotherapy, radiotherapy (for pure seminomas) or retroperitoneal lymph node dissection (RPLND). Treatment availability and choices vary greatly worldwide and are often based on patient choice as well as risk factors.

Numerous previous studies on this issue have been performed and are referenced in the individual sections. The vast majority assess risk factors by examining stage at presentation as a surrogate for outcome,<sup>5-7</sup> or they examine pathological records and do not perform re-review. Often the pathology has not been assessed to modern standards.<sup>8-10</sup>

A large number of factors have been shown to be prognostic on univariate analysis. However, some are competing variables (for instance rete testis invasion is related to tumour size). Multivariable statistics on these cohorts reveals sometimes divergent results and many studies are underpowered for many factors.

Two recent studies from Denmark have clarified some of these issues for seminoma and non-seminomas as they have both full pathological review on 924 seminomas and 453 non-seminomas, relapse data and an untreated cohort.<sup>11,12</sup>

A list of changes in this dataset edition can be accessed [here](#).

The authors of this dataset can be accessed [here](#).

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## **Note 1 – Clinical information (Core and Non-core)**

This is a recommended rather than a required item as it is the responsibility of the clinician requesting the pathological examination of a specimen to provide information that will have an impact on the diagnostic process or affect its interpretation. The use of a standard pathology requisition/request form including a checklist of important clinical information is strongly encouraged to help ensure that relevant clinical data is provided by the clinicians with the specimen. Occasionally testes are removed as an emergency for torsion and serum markers are not taken.

Relevant past medical history and known risk factors associated with testicular tumours should be provided, including ethnicity, cryptorchidism (and location of testis; intrascrotal, inguinal, intra-abdominal), history of orchidopexy, prior testicular germ cell tumour, family history of testicular tumours and clinical syndromes associated with testicular tumours.

Any recent history of injury or torsion or of previous chemotherapy may cause extensive or complete tumour necrosis which will affect the morphology of the remaining viable tumour.

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## Note 2 – Serum tumour markers (Non-core)

The serum tumour markers, alpha-fetoprotein (AFP), beta subunit of human chorionic gonadotropin (b-hCG), and lactate dehydrogenase (LDH), play an essential role in the management of men with testicular tumours and have been included in the staging system for testicular tumours as an ‘S’ stage.<sup>13,14</sup> The ‘S’ stage is usually based on the **post**-orchidectomy serum tumour marker values, which reflect the degree of marker production by the patient’s metastatic disease. In advanced disease, the marker levels closest to the start of chemotherapy should be used to determine the final ‘S’ stage and may significantly differ (higher or lower) than pre-orchidectomy markers. In select cases of advanced disease when orchidectomy is deferred until after chemotherapy, the markers used for staging are not obtained post-orchidectomy. It is important to recognise the half-life of b-hCG (1-3 days) and AFP (5-7 days) when assigning the ‘S’ stage to a patient with declining markers post-orchidectomy. Patients with AFP or b-hCG that decline at or more rapidly than the expected half-life following orchidectomy and have no evidence of metastatic disease on imaging should be followed until marker normalisation or rise in order to differentiate between Stage IA/B and Stage IS disease. The latter implies metastatic disease is present even when not apparent on imaging.

Since the tumour markers obtained prior to orchidectomy are typically what is available to the pathologist, in most cases, the pathologist is not able to assign the ‘S’ stage and notation of ‘SX’ should be used, similar to when nodal and metastasis stages cannot be assigned. Nevertheless, the pre-orchidectomy marker levels are important and should be provided to the pathologist whenever possible. It has been shown that the pre-orchidectomy levels of LDH and b-hCG are independently predictive of recurrence in Stage I seminomas.<sup>11</sup> The occurrence of elevated serum levels of AFP or b-hCG may indicate the need for additional sections of certain specimens if the initial findings do not account for such elevations. For each marker, notation of the level and date it was drawn or the lack of availability should be noted in the pathology report. In addition, for LDH, the upper limit of normal for the assay should be provided when available. Ideally serum makers would be a ‘core’ data item, however there is often difficulty with obtaining these at the time of reporting. There are also occasional testes removed for trauma which have incidental germ cell tumours.

### Anatomic Stage/Prognostic Groups

Group	T	N	M	S
Stage 0	pTis	N0	M0	S0
Stage I	pT1-4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-3
Stage II	Any pT/TX	N1,N2,N3	M0	SX
Stage IIA	Any pT/TX	N1	M0	S0
	Any pT/TX	N1	M0	S1
Stage IIB	Any pT/TX	N2	M0	S0
	Any pT/TX	N2	M0	S1
Stage IIC	Any pT/TX	N3	M0	S0
	Any pT/TX	N3	M0	S1

Stage III	Any pT/TX	Any N	M1	SX
Stage IIIA	Any pT/TX	Any N	M1a	S0
	Any pT/TX	Any N	M1a	S1
Stage IIIB	Any pT/TX	N1,N2,N3	M0	S2
	Any pT/TX	Any N	M1a	S2
Stage IIIC	Any pT/TX	N1,N2,N3	M0	S3
	Any pT/TX	Any N	M1a	S3
	Any pT/TX	Any N	M1b	Any S

### Prognostic Factors

#### Serum Tumour Markers (S)

SX Serum marker studies not available or performed

S0 Serum marker study levels within normal limits

	<u>LDH</u>	<u>hCG (mIU/mL)</u>	<u>AFP (ng/mL)</u>
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

LDH - lactate dehydrogenase

hCG - human chorionic gonadotropin

mIU/mL - milli-international units per millilitre

AFP - alpha-fetoprotein

ng/mL - nanograms per millilitre

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

The Serum Tumour Markers (S) category comprises the following:

- AFP – half-life 5 to 7 days
- hCG – half-life 1 to 3 days
- LDH.

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### Note 3 – Operative procedure (Core)

Whether the surgical procedure is a radical or partial orchidectomy must be stated, as this will influence the assessment of surgical margins. For bilateral tumours, complete a separate dataset for each testis.

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### Note 4 – Tumour focality (Core)

There is no specific paper dealing with multifocality in germ cell tumours. Two papers by Wagner et al (2023 and 2024) on 924 Stage I seminomas and 453 Stage I non-seminomas with relapse data shows it is not a risk factor for relapse.<sup>11,12</sup> However many cases have multifocal tumours which may coalesce together to form a complex multifocal nodule. The noting of multifocality is important, as the separate nodules may contain

different tumour elements which will affect prognosis.<sup>15</sup> Secondly, the determination of maximum tumour diameter depends on whether the tumours are multifocal or unifocal. Rare testicular tumours may be associated with multifocality and suggest a variety of syndromes.<sup>16</sup>

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## Note 5 – Tumour dimensions (Core and Non-Core)

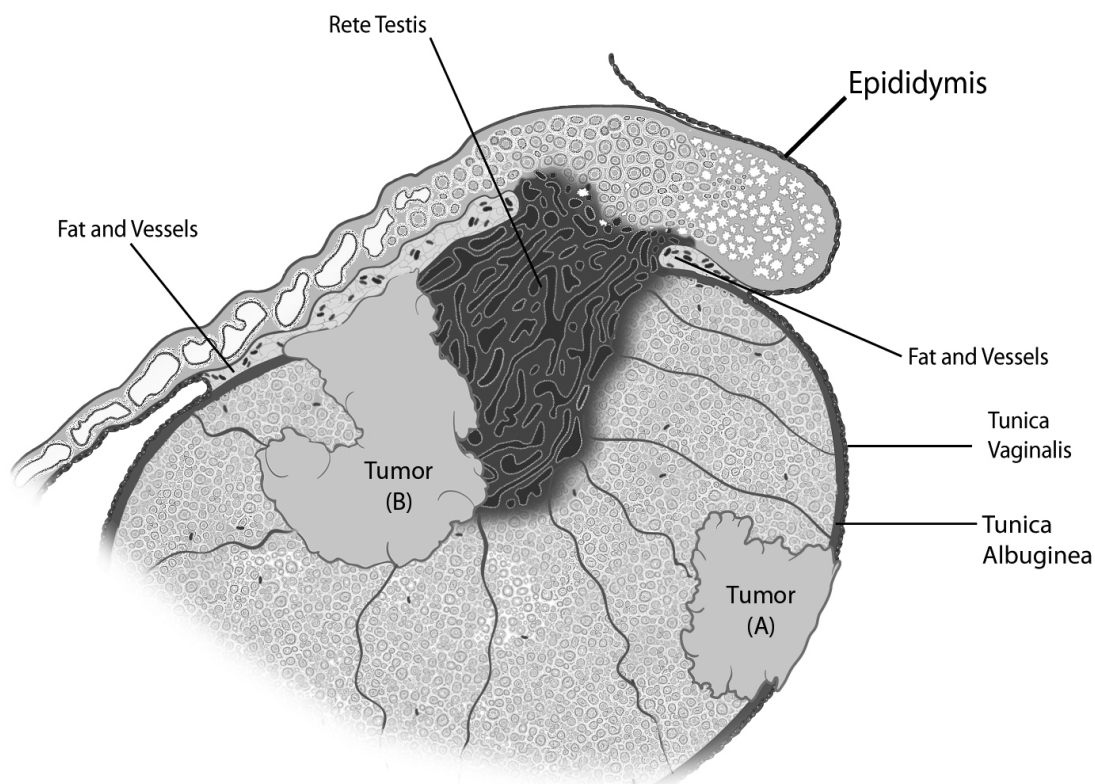
It has been shown in a number of studies that the maximum tumour dimension has prognostic significance, especially in seminomas.<sup>6-8,10,17</sup>

The evidence for the importance of size in non-seminomatous germ cell tumours is less well established but is reported,<sup>5</sup> and was significant for relapse on multivariate analysis in the study by Wagner et al (2024).<sup>12</sup> Therefore, the maximum diameter of the largest tumour is a core measurement. The dataset authors recommend that when there is multifocality, the largest diameter of the largest focus be recorded, and that the maximum diameter of the additional nodules may also be recorded (non-core). Where the nodules coalesce, this may be difficult to calculate. Evidence for the relevance of this is disputed but the DAC also recommend that tumours should be counted as separate if there is intervening parenchyma.

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## Note 6 – Macroscopic extent of invasion (Core)

The macroscopic extent of the disease may be difficult to discern even on close inspection of the testis and hilar structures. The vast majority of radical orchidectomies will not include the scrotum unless the surgeon finds evidence of invasion at surgery. The testis parenchyma is bound by the tunica albuginea except in the region where the rete testis connects with the epididymis and vas deferens. Adjacent to the hilum in this area is a small amount of hilar soft tissue. The tunica albuginea is bound by a double layer of mesothelium, termed the tunica vaginalis (Figure 1). Involvement of the hilar soft tissue, epididymis or tunica vaginalis may be challenging to detect. Also, diffusely infiltrative tumours such as intertubular seminoma which infiltrate between the tubules may not be easy to detect, meaning that the size of the tumour may in fact be larger than that suspected macroscopically. Therefore, all suspected areas of invasion seen macroscopically should be conformed microscopically by appropriate sampling for confirmation.



**Figure 1: Diagrammatic representation of a tumour (Tumour A) invading the tunica vaginalis, perforating through the mesothelium, and another tumour (Tumour B) partly involving the rete testis and invading the hilar soft tissue.** Figure courtesy of Satish K. Tickoo, MD. Source: College of American Pathologists (2023). *Protocol for the examination of radical orchidectomy specimens from patients with malignant germ cell and sex cord-stromal tumours of the testis.*<sup>18</sup>

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## Note 7 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies or clinical trials.

Tumour sampling should be generous to ensure documentation of all tumour types present. Germ cell tumours should, as a minimum be sampled at 1 block per centimetre (cm) (10 millimetres (mm)) of tumour. However while this may be adequate for a non-seminomatous germ cell tumour, to represent different elements, it has been recommended that seminomas are more generously sampled than this, as small foci of non-seminoma will change patient management; if the tumour is small (less than 2 cm) it can be completely sampled.<sup>19</sup> Pure seminomas should be sampled especially thoroughly to exclude small areas on non-



seminomatous germ cell tumour. It is important that blocks include the adjacent testicular parenchyma to allow for the assessment of lymphovascular invasion (LVI) and germ cell neoplasia in situ (GCNIS).

Different areas of the tumour must be sampled, particularly including haemorrhagic and necrotic areas and solid/fleshy areas. All of the haemorrhagic tumour must be blocked, as choriocarcinoma is often haemorrhagic with little residual viable tumour.

Sections of tumour should include at least one section showing the relation of the tumour to the testicular hilum. If the tumour is well away from the hilum, there should be a separate section of the hilum clearly showing this region is free of tumour.

Sections of tumour should include the adjacent tunica albuginea and vaginalis and adjacent testicular parenchyma. Sections of uninvolved testicular parenchyma should be included. A block from the cord resection margin should be taken as well as the cord base to assess for direct cord invasion above the level of insertion of the tunica vaginalis. Some suggest that this block should be taken prior to incision of the tumour to avoid contamination,<sup>20</sup> while others suggest that this is unnecessary as it does not avoid contamination of tumour blocks and that good fixation of the testis is more important for staging and diagnosis. Delaying this may compromise tumour typing. More important is the careful distinction between artifactual spread and vascular invasion/stromal invasion.<sup>19</sup>

### **Orchidectomy specimens for clinically localised disease**

Blocks are selected to represent:

- the cord resection margin and base of cord (further cord blocks depending on macroscopy)
- the relationship of the tumour(s) to the rete testis, epididymis and cord
- the minimum distance of the tumour to the nearest inked resection margin for partial orchidectomies
- all areas of the tumour(s) with different macroscopic appearances (solid, cystic, pale or haemorrhagic)
- adjacent testis including the tunica albuginea (and vaginalis), a common site for vascular invasion
- uninvolved testis.

It is recommended that a record is kept of a good representative paraffin block of tumour and whether frozen tissue has been stored.

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## **Note 8 – Histological tumour type (Core)**

The classification of testicular tumours is taken from the WHO Classification of Tumours, Urinary and Male Genital Tumours, 5th edition, 2022 (Table 1).<sup>3</sup> The ICCR dataset includes 5<sup>th</sup> edition Corrigenda, July 2024.<sup>4</sup> Note that some of these entities do not metastasize but the entire classification is given here for completeness.

**Table 1: World Health Organization classification of tumours of the testis and paratesticular tissue.<sup>3</sup>**

Descriptor	ICD-O codes <sup>a</sup>
<b>Germ cell tumours derived from germ cell neoplasia in situ (GCNIS)</b>	
<i>Non-invasive germ cell neoplasia</i>	
Germ cell neoplasia in situ	9064/2
Specific forms of intratubular germ cell neoplasia	
Gonadoblastoma	9073/1
<i>The germinoma family of tumours</i>	
Seminoma	9061/3
<i>Non-seminomatous germ cell tumours</i>	
Embryonal carcinoma	9070/3
Yolk sac tumour, postpubertal-type	9071/3
Choriocarcinoma	9100/3
Placental site trophoblastic tumour	9104/3
Epithelioid trophoblastic tumour	9105/3
Cystic trophoblastic tumour	
Teratoma, postpubertal-type	9080/3
Teratoma with somatic-type malignancies	9084/3
<i>Mixed germ cell tumours of the testis</i>	
Mixed germ cell tumours	9085/3
<i>Germ cell tumours of unknown type</i>	
Regressed germ cell tumours	9080/1
<b>Germ cell tumours unrelated to germ cell neoplasia in situ</b>	
Spermatocytic tumour	9063/3
Teratoma, prepubertal type	9084/0
Yolk sac tumour, prepubertal-type	9071/3
Testicular neuroendocrine tumour, prepubertal-type	8240/3
Mixed teratoma and yolk sac tumour, prepubertal-type	9085/3

<sup>a</sup> The morphology codes are from the International Classification of Diseases for Oncology (ICD-O).<sup>21</sup> Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries. Subtype labels are indented. Incorporates all relevant changes from the 5<sup>th</sup> edition Corrigenda, July 2024.<sup>4</sup>

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### Percentage of different tumour components in mixed germ cell tumours

The percentage of the different tumour elements has been shown to be predictive of the relapse risk in non-seminomatous germ cell tumours (NSGCT), especially the percentage of embryonal carcinoma.<sup>12</sup> As well as the percentage of embryonal carcinoma as a core data item, the approximate percentages of other tumour elements should also be given. A second study showed that 25 out of 85 men who had predominantly embryonal carcinoma histology relapsed.<sup>22</sup>

Giving 'exact' percentages in a mixed non-seminomatous germ cell tumour may be challenging, as some elements may be extremely small, and it may occasionally be difficult to distinguish closely intermingled elements (such as yolk sac tumour and embryonal carcinoma). The dataset authors' suggest that only basic 'eyeball' style quantitation is required. For example, the difference between 10% embryonal carcinoma and 90% embryonal carcinoma may be important in determining the need to adjuvant therapy. However, a difference of 5 or 10% is likely insignificant. For NSGCTs which are of pure type, then the percentage of the pure type should be listed as 100%.<sup>23</sup>

Mention of areas of scarring is helpful, particularly in pure seminoma or teratoma cases as they may indicate areas of regression, which might have represented other tumour types. These findings can explain the occasional discordance between the orchidectomy tumour type and that seen in metastatic deposits.

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## **Note 9 – Microscopic extent of invasion (Core and Non-core)**

### **Rete testis invasion**

Rete testis invasion is the direct invasion of tumour into the stroma of the rete testis and does not include pagetoid spread of GCNIS into the tubules of the rete.<sup>17</sup>

In older studies there remains doubt as to whether rete testis stromal or pagetoid invasion was being assessed.<sup>24</sup> While many studies have therefore shown rete testis invasion to be an independent risk factor,<sup>10,17,25</sup> other studies do not,<sup>8,26</sup> especially when compared with tumour size. However, these latter studies were not pathologically reviewed to modern standards and therefore may include cases of pagetoid rete invasion. The study by Wagner et al (2023)<sup>11</sup> shows that stromal rete invasion to be an independent risk factor for recurrence while pagetoid invasion is not significant even univariately.

For NSGCTs, there is also evidence that rete testis invasion is an important prognostic factor.<sup>5,12,27</sup>

Rete testis and tumour size were not part of the TNM 7<sup>th</sup> edition.<sup>28,29</sup> However, tumour size using a cut off of 30 mm (3 cm) has now been incorporated into the American Joint Committee on Cancer (AJCC) 8<sup>th</sup> edition<sup>14</sup> for pure seminomas only, separating the pT1 stage into pT1a and pT1b. However, it has not been incorporated into Union for International Cancer Control (UICC).<sup>13</sup> Both rete testis invasion and size are used by many clinicians to determine adjuvant chemotherapy and are part of existing European clinical guidelines.<sup>30,31</sup> Recent data show that these two factors are not optimal for predicting recurrence in stage I seminoma patients.<sup>11</sup> The most recent data suggests that size is less important than knowledge of serum levels of LDH and b-hCG pre-orchidectomy.<sup>11,12</sup>

### **Epididymal invasion**

There is little evidence on the prognostic significance of epididymal invasion. It is rare and studies are underpowered, though some show univariate significance.<sup>6,11</sup> Although in previous editions of AJCC<sup>28</sup> and UICC<sup>29</sup> Cancer Staging Manuals (7<sup>th</sup> editions) it has been designated as pT1, the evidence and consensus for pT2 staging of soft tissue has necessitated a redesignation of epididymal invasion as pT2 in the AJCC and updated UICC 8<sup>th</sup> editions<sup>13,14</sup> as it is normally secondary to hilar invasion.

### **Hilar soft tissue invasion**

Invasion of the hilar soft tissues is a common mode of extratesticular spread.<sup>32</sup> However, there has been previously no consensus on the correct way to stage hilar soft tissue invasion.<sup>24</sup> Following a consultation conference by the International Society of Urological Pathologists (ISUP)<sup>33</sup> and adoption by the AJCC 8<sup>th</sup>

edition<sup>14</sup> it has been decided to stage soft tissue invasion as pT2. This has also been adopted now by the UICC 8<sup>th</sup> edition.<sup>13</sup> Soft tissue invasion has been defined as “invasion of the adipose tissue and soft fibrous connective tissue present...beyond the boundaries of the rete testis”.<sup>14</sup>

Using this definition, all of the latest studies have shown soft tissue to be indicative of higher stage,<sup>5-7,27</sup> and the studies by Wagner et al (2023 and 2024) have shown it to be a strong independent factor for relapse in stage I disease.<sup>11,12</sup>

### **Tunica albuginea**

Invasion of the tunica albuginea is often seen. It is designated non-core as it has no role in the TNM staging. The most recent studies to assess its significance in predicting metastasis<sup>11,12</sup> suggest it is also non significant on multivariate analysis.

### **Tunica vaginalis**

In keeping with previously used definitions, only invasion of the single celled mesothelial layer of the tunica vaginalis is considered to represent invasion.

### **Direct invasion of the spermatic cord**

Spermatic cord invasion is a core data item as it is required for TNM staging, but evidence on its prognostic significance in seminoma is lacking. Spermatic cord invasion has been better defined and separated as a prognostic factor from hilar soft tissue invasion as ‘tumour extending beyond the angle between the epididymis and spermatic cord proper or tumour surrounding the vas deferens’.<sup>14</sup>

As so defined there are few studies examining this, and it is uncommon. The most recent studies on seminoma and non-seminoma by Wagner et al (2023 and 2024) show univariate but not multivariate significance.<sup>11,12</sup> Older studies have mixed findings but generally are univariately significant.<sup>20,25,34</sup>

Lymphovascular invasion (LVI) in the cord should not be staged as pT3, but pT2. However, it does appear to portend a higher degree of relapse than when confined to the cord.<sup>35</sup>

A further issue is the designation of discontinuous tumour deposits in the cord. According to the AJCC staging system<sup>14</sup> (not yet covered by UICC), these should be regarded as M1 deposits if invading stromal tissue. Of the two studies into this issue, although one found little difference between pure pT3 and pT3 M1 (cord) tumours,<sup>36</sup> a second showed it was associated with more advanced clinical presentation.<sup>37</sup>

### **Scrotal wall**

The invasion of the scrotal wall is a core part of the dataset and part of TNM staging.<sup>13,14</sup> However it is extremely rare and because of this there are no studies that can fully assess its prognostic import.

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## **Note 10 – Lymphovascular invasion (Core and Non-core)**

In several studies, the presence of LVI has been correlated with a significantly elevated risk for distant metastasis, particularly in NSGCTs.<sup>12</sup>

Most of the previous studies on LVI appear not to use immunochemistry routinely in its diagnosis. Although one study suggests that the routine use of immunochemistry to identify LVI may be helpful, further studies

are needed and at present the DAC recommend that diagnosis should be made on haematoxylin-eosin (H&E) backed up by immunochemistry for lymphovascular vessels in challenging cases.<sup>38</sup>

The dataset authors' recommend that vascular invasion be called either present or 'not identified' as equivocation in the report is unhelpful to the clinician. The DAC advise restricting the definition of vascular invasion so that those cases which are equivocal are assigned as 'not identified'. Vascular invasion is much more likely to be seen at the periphery of the tumour than within the centre of solid tumour masses. It is often seen in fibrous bands surrounding or intersecting the main tumour mass, as well as in the region of rete testis. LVI may be seen in the tunica albuginea, spermatic cord vessels or the parenchyma of the testis. All warrant a stage of pT2.

In seminoma, the most recent studies use strict criteria to exclude artifactual smearing. In addition, they do not rely on data pooled from previous pathology reports.<sup>17,25</sup> The recent papers all show the strong significance for vascular invasion to predict high stage disease.<sup>6,7</sup> Also vascular invasion when carefully assessed is an extremely strong predictor in multivariate analysis of recurrence in stage I disease.<sup>11</sup>

For NSGCTs, LVI has been shown in multiple studies to be a powerful predictor of metastatic disease and recurrence.<sup>5,39-46</sup>

If LVI is present in a mixed or combined germ cell tumour, it is good practice to state which subtype of tumour is showing the LVI as this may alter clinical management if it was an embryonal carcinoma component showing LVI versus classical seminoma. Indicating that a case is 'uncertain' for vascular invasion is unhelpful for the treatment of patients with germ cell tumours.

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## **Note 11 – In situ and intratubular lesions (Core and Non-core)**

The term GCNIS has replaced the previous terms, carcinoma in situ (CIS), intratubular germ cell neoplasia, unclassified (IGCNU) and testicular intraepithelial neoplasia (TIN). None of the previous terms was entirely correct and led to much confusion in the literature.

In fact, the true in situ area for the development of germ cell tumours is in a specific intratubular location, the 'spermatogonial niche' between the basement membrane and the tight junctions between adjacent Sertoli cells.

Germ cell neoplasia in situ (GCNIS) is the precursor lesion for the most common variants of invasive germ cell tumours. Although not a prognostic factor, it should be a core item, as its absence may raise the suspicion of a non-GCNIS associated tumour, which have differing prognosis and treatments, as well as the possibility that the tumour is a non-germ cell tumour mimic of a germ cell tumour (notably some Sertoli cell tumours).

'Pagetoid' invasion of the rete testis occurs when GCNIS-like cells infiltrate the epithelial cells of the rete but do not invade the rete stroma. Pagetoid type rete invasion is generally accepted to represent infiltration of GCNIS rather than invasive seminoma and showed no significance in one study to predict recurrence.<sup>11</sup>

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## Note 12 – Response to adjuvant treatment (Non-core)

Occasionally patients with advanced disease and raised tumour markers are treated with chemotherapy prior to orchidectomy. When the orchidectomy is performed it may show evidence of residual disease. The prefix 'y' is used when staging cases after treatment.

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## Note 13 – Margin status (Core and Non-core)

Whether the surgical procedure is a radical or partial orchidectomy must be stated, as this will influence the assessment of surgical margins. Specifically, in the case of partial orchidectomy specimens, it is important that the intratesticular surgical margin is carefully evaluated to ensure that no residual tumour is present in the remaining testis.

For radical orchidectomies there is little evidence that surgical margin status has been studied as an independent prognostic factor separately from stage and other known indicators. The only true surgical margin is the spermatic cord margin in a usual radical orchidectomy and involvement with stromal invasion is rare. Very rarely in a widely invasive tumour, scrotal skin may be included. This should be easily apparent in such cases, and it would be appropriate to state whether the scrotal skin margin was invaded by tumour.

Occasionally the spermatic cord margin may include vessels showing vascular invasion by tumour. This is vascular invasion and does not represent a positive margin.

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## Note 14 – Coexistent pathology (Non-core)

'Burnt out' germ cell tumours may present as scarring, with the presence of hemosiderin-laden macrophages, and intratubular calcification, with surrounding GCNIS and must be carefully evaluated. Signs of testicular dysgenesis, androgen insensitivity, Klinefelter's syndrome or other intersex conditions may be identified or suggested by close examination of the testicular parenchyma. These might include residual gonadoblastoma or ovarian type tissue for intersex conditions. Leydig cell hyperplasia which may be correlated with b-hCG elevation and testicular atrophy may also be seen in dysgenetic gonads (e.g., dysgenesis or androgen-insensitivity syndrome).<sup>47,48</sup>

A history of cryptorchidism has been associated with a higher relapse rates for clinical Stage I testicular non-seminomatous germ cell tumours.<sup>49</sup>

It may be helpful to give the status of the surrounding parenchyma to the tumour, especially the amount of spermatogenesis present and degree of atrophy. The status of the parenchyma is of great importance in some types of testicular neoplasm (prepubertal type teratoma in particular) and also may indicate the functioning status of the contralateral testis.

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## Note 15 – Ancillary studies (Non-core)

Most testicular tumours can be identified on histological examination, though some difficulties may be encountered in differentiating between some types. Immunohistochemistry may be extremely helpful in distinguishing between tumour types and may be helpful in some cases.<sup>50</sup>

Isochromosome i(12p) FISH testing which, although not entirely specific, may be a useful additional test in confirming a tumour as a germ cell tumour related to GCNIS as opposed to a type unrelated to GCNIS such as prepubertal type teratomas and prepubertal type yolk sac tumours.<sup>51</sup>

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## Note 16 – Pathological staging (Core)

This dataset includes the updated UICC 8<sup>th</sup> edition definitions,<sup>13</sup> which now are optimally aligned with the AJCC 8<sup>th</sup> edition definitions.<sup>14</sup> The TNM classification applies only to germ cell tumours of the testis.

Primary testicular germ cell tumours are occasionally removed after chemotherapy, especially when patients present with widespread metastases. In these cases, the DAC suggest filling out the Orchidectomy dataset and adding 'y' as a prefix to the TNM classification.

Except for pTis and pT4, extent of primary tumour is classified by radical orchidectomy, and for this reason a *pathologic* stage is assigned. Tx may be used for other categories in the absence of radical orchidectomy.

Reporting of pathological staging categories (pT,pN,pM) is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC TNM8 and AJCC TNM8,<sup>13,14</sup> the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

The reference document TNM Supplement: A commentary on uniform use, 5<sup>th</sup> edition (C Wittekind et al. editors) may be of assistance when staging.<sup>52</sup>

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