Neoplasia of the Testis - Retroperitoneal Lymphadenectomy Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are REQUIRED. Elements in **grey text** are RECOMMENDED.

CLINICAL INFORMATION (Note 1)

- ○ Not provided
- ☐ Previous history of testicular cancer, *specify*
- ☐ Previous therapy, *specify*
- ☐ Other, *specify*

PRE-PROCEDURE SERUM TUMOUR MARKERS (select all that apply) (Note 2)

- ○ Not provided
- ○ Provided
  - ☐ Serum tumour markers within normal limits
    OR
    Specify serum tumour markers used, level and date markers were drawn
    - Date
    - ☐ AFP ug/L
    - ☐ LDH IU/L
    - ☐ b-HcG IU/L

SPECIMEN(S) SUBMITTED (select all that apply) (Note 3)

- ○ Not specified
- ☐ Retroperitoneal lymphadenectomy, *specify nodal site*
  - ○ No disease ○ Necrosis ○ Viable tumour
  - ○ No disease ○ Necrosis ○ Viable tumour
  - ○ No disease ○ Necrosis ○ Viable tumour
  - ○ No disease ○ Necrosis ○ Viable tumour
- ☐ Brain
- ☐ Lung
- ☐ Liver
- ☐ Other, *specify*

SIZE OF LARGEST NODAL METASTASIS (select all that apply) (Note 4)

- ○ Cannot be assessed
- ☐ Maximum dimension ..... mm
- ☐ Additional dimensions ..... mm X ..... mm

BLOCK IDENTIFICATION KEY (Note 5)

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

HISTOLOGICAL TUMOUR TYPE (Note 6)

(Value list from the World Health Organisation Classification of tumours. Pathology and genetics of urinary system and male genital organs (2016))

- ☐ Viable tumour
  - ○ Present ○ Absent
  - ⇩ %
- ☐ Germ cell tumour, *specify type and percentage*
  - ⇨ %
  - ⇨ %
  - ⇨ %
  - ⇨ %
- ☐ Other, *specify*

MARGIN STATUS (Note 7)

- ○ Cannot be assessed
- ○ Not involved
  - ⇩ Closest margin
  - Distance of tumour from closest margin mm
- ○ Involved, *specify*

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EXTRANODAL EXTENSION (Note 8)

◯ Not identified ◯ Present ◯ Indeterminate

PATHOLOGIC STAGING (TNM 8th edition)## ^(Note 9)

Regional lymph nodes (pN)

◯ NX	Regional lymph nodes cannot be assessed
◯ N0	No regional lymph node metastasis
◯ N1	Metastasis with a lymph node mass 2 cm or smaller in greatest dimension and less than or equal to five nodes positive, none larger than 2 cm in greatest dimension
◯ N2	Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension; or more than five nodes positive, none larger than 5 cm; or evidence of extranodal extension of tumour
◯ N3	Metastasis with a lymph node mass larger than 5 cm in greatest dimension

Distant metastasis (pM) (if resected)

◯	No distant metastases
◯ M1	Distant metastasis
◯ M1a	Non-retroperitoneal nodal or pulmonary metastases
◯ M1b	Non-pulmonary visceral metastases

Used with the permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2016) published by Springer Science+Business Media.

^ Please note that implementation of AJCC TNM 8th edition has been deferred until January 2018 in some jurisdictions. UICC 7th edition or AJCC 7th edition may be useful in the interim.

Scope

The dataset has been developed for the reporting of retroperitoneal and other lymphadenectomy specimens as well as visceral metastasis excision specimens from patients with malignant tumours of the testis. The protocol applies to all malignant germ cell and sex cord-stromal tumours of the testis. Paratesticular malignancies are excluded.

Note 1 - Clinical information (Recommended)

Reason/Evidentiary Support

Retroperitoneal lymphadenectomies (RPLNDs) may be performed at the time of diagnosis of a testicular tumour, or may be performed after chemotherapy, and this will affect the likely pathological changes seen. Although the majority of excisions will be for germ cell tumours, primary prophylactic excisions for malignant sex cord- stromal tumours are also occasionally performed.[1]

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Note 2 - Pre-procedure serum tumour markers (Recommended)

Reason/Evidentiary Support

Serum marker studies play a key role in the clinical management of patients with testicular germ cell tumours and in the monitoring of recurrent disease.[2-4] Most patients who undergo post chemotherapy RPLND will have negative markers following orchiectomy as those with positive markers will be treated with further chemotherapy or radiotherapy. The occurrence of elevated serum levels of alpha-fetoprotein (AFP) or the beta subunit of human chorionic gonadotropin (b-hCG) may indicate the need for additional sections of certain specimens if the initial findings do not account for such elevations.

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

A "y" prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., chemotherapy, radiation therapy, or both chemotherapy and radiation therapy).

Prognostic Factors

Serum Tumour Markers (S)

SX Serum marker studies not available or performed

S0 Serum marker study levels within normal limits

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

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

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

- AFP – half-life 5 to 7 days
- hCG – half-life 1 to 3 days
- Lactate dehydrogenase (LDH)

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Note 3 - Specimens submitted (Required)

Reason/Evidentiary Support

The type of retroperitoneal surgery performed is dependent on which testis was affected by tumour and a number of different surgical approaches are possible. Although there are exceptions, right-sided tumours metastasize to the interaortocaval lymph nodes first followed by the precaval and paracaval lymph nodes. Left-sided testicular tumours metastasize to the para- and preaortic areas. Contralateral involvement is more frequent in right-sided tumours as well as in bulky disease. The practice of specimen submission differs greatly, but often surgeons will resect separate nodal sites in separate containers.

After chemotherapy, it is common practice to excise other remaining sites of disease, apart from RPLNDs and these should be identified.

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Note 4 - Size of largest nodal metastasis (Required)

Reason/Evidentiary Support

A number of studies have shown that the size of the retroperitoneal nodes is associated with the presence of tumour (teratoma and also of viable malignant elements). Nodal size may be difficult to measure when nodes are confluent. We suggest that where separate nodes are not readily identifiable then the largest diameter of the overall tumour be taken on macroscopy.[5,6] The other two dimensions are recommended.

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Note 5 - Block identification key (Recommended)

Reason/Evidentiary Support

The origin/designation of all tissue blocks should be recorded and it is preferable to document this information in the final pathology report. This 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.

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

Comprehensive sampling is essential for residual masses, as the identification of even a small area of a different subtype can alter patient management and impact on prognosis. Although the recommendation of one block per centimetre of tumour is usual, more may be required to adequately represent all the macroscopically different areas of tumour. The number of nodes harvested has been shown to impact on prognosis.[7,8]

Blocks are selected to represent:

- all areas of the positive node(s) with different macroscopic appearances (solid, cystic, pale or haemorrhagic)
- the minimum distance of the tumour to the nearest resection margin (which may be inked)
- all macroscopically negative nodes to search for micrometastatic disease
- total number of nodes resected.

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

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Note 6 - Histological tumour type (Required)

Reason/Evidentiary Support

In concordance with the dataset for Orchidectomy specimens, the World Health Organisation (WHO) 2016 classification of testicular tumours should be used.[9]

RPLND before treatment
The type of tumour identified in an RPLND is crucial information to determine further treatment. The tumour in prechemotherapy RPLNDs (also referred to as primary RPLNDs) generally (but not always) show similar findings to that in the orchidectomy specimen. In primary setting, pathologic N staging is more commonly used to determine the need for adjuvant chemotherapy with pN0 and pN1 leading to surveillance and pN2 and pN3 (rare) leading to adjuvant chemotherapy.

RPLND after treatment
After chemotherapy, and especially in late relapses, the pathology may be substantially different from that seen in primary RPLND.[10] In general terms, after chemotherapy, 40-50% of germ cell tumour cases show pure necrosis with no viable tissue seen. A further 40% show teratoma, while the remaining 10% show a mixture of 'malignant' germ cell elements such as embryonal carcinoma, or yolk sac tumour, and a small number may show somatic transformation. Pure teratomatous metastasis is generally treated by surgical excision alone, whereas patients who have other residual germ cell tumour components are usually treated with additional chemotherapy. Metastatic sex cord-stromal tumours are also occasionally operated upon.[1] Even the type of tumour seen substantially affects the prognostic and therapeutic implications[11] with, for example, certain variants

being associated with a good outcome[12] while others are associated with an intermediate[13] or more aggressive course.[14] Diagnosis of these variants may be challenging and require expert consultation. The percentage of 'viable malignant cells' has also shown to be a determinant of prognosis in a number of studies.[15-18] 10% is the most common cut-off used to determine the need for further treatment.

For post-chemotherapy residual masses, particularly in the absence of a biopsy diagnosis prior to treatment, it is often useful to examine areas of necrosis, as ghost outlines of the tumour often remain and allow the distinction between seminoma and non-seminomatous germ cell tumour. The reporting of number and location of lymph nodes involved by necrosis, fibrosis, xanthomatous and fibroxanthomatous reaction is important to the treating physician to evaluate the extent and distribution of tumour in different lymph nodes. There is evidence that fibrosis often represents neoplastic stroma originating from teratoma or yolk sac tumor. The spindle cells in the areas of fibrosis are often reactive to cytokeratin and display allelic loss (85%) and 12p anomalies (33%) characteristic of germ cell tumours. Xanthomatous and fibroxanthomatous reaction may sometimes pose a diagnostic challenge and immunohistochemical staining for evaluation of residual tumour is deemed necessary in occasional cases. It is important to recognise that residual viable malignancy (embryonal carcinoma, yolk sac tumour, classical seminoma or choriocarcinoma) may trigger further chemotherapy and therefore it is important to only report viable elements along with percentage of viable tumour and not semi-viable or non-viable tumour. Necrosis and post-chemotherapy teratoma would not usually trigger further therapy, unless the clinical situation dictates otherwise. In the case of cystic trophoblastic tumour (CTT), an explanatory note should be provided to caution the physicians against further chemotherapy. Data for CTT are limited but the largest study of 15 patients with follow-up showed that 11 did not recur, three showed late recurrences of possibly unrelated yolk sac tumour and the one patient who did recur with a rise in hCG had unresected residual masses.[12] For post-chemotherapy RPLND, it may be desirable to embed more of the specimen if it is found to contain necrosis or non-viable tumour to exclude small foci of viable tumour.

Secondary somatic malignancy is rare and challenging to diagnose. The tumour typically consists of a pure population of atypical mesenchymal or epithelial cells and occupies at least one low-power field (×4 objective, 5 mm in diameter).[9] Sarcomas are the most common type, though some post-chemotherapy sarcoma-like tumours may be sarcomatoid yolk sac tumours.[19] Primitive neuroectodermal tumour (PNET) is another relatively common somatic-type malignancy which behaves aggressively.[20,21] Most carcinomas are adenocarcinomas, usually Not Otherwise Specified (NOS) type. Occasionally, patients may develop nephroblastoma.[22]

A somatic malignancy in a metastasis increases likelihood of dying from the disease and if it is localized, surgical resection is the optimal treatment.[14] Patients usually respond poorly to the treatment for conventional germ cell malignancy.[23] Some somatic malignancies may respond to a specific chemotherapy that is effective for the specific subtype, so accurate subtyping of the somatic transformation is important.

WHO classification of tumours of the testis and paratesticular tissue[a9]

Descriptor	ICD-O codes
Germ cell tumours derived from germ cell neoplasia in situ (GCNIS)	
Non-invasive germ cell neoplasia	
Germ cell neoplasia in situ	9064/2
Specific forms of intratubular germ cell neoplasia *Tumours of one histological type (pure tumours)*	
Seminoma	9061/3
Seminoma with syncytiotrophoblast cells	
Non-seminomatous germ cell tumours	
Embryonal carcinoma	9070/3
Yolk sac tumour, postpubertal-type	9071/3
Trophoblastic tumours	
Choriocarcinoma	9100/3
Non-choriocarcinomatous trophoblastic tumours	
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
Non-seminomatous germ cell tumours of more than one histological type	
Mixed germ cell tumours	9085/3
Germ cell tumours of unknown type	
Regressed germ cell tumours	9080/1
Germ cell tumours unrelated to germ cell neoplasia in situ	
Spermatocytic tumour	9063/3
Teratoma, prepubertal type	9084/0
Dermoid cyst	
Epidermoid cyst	
Well-differentiated neuroendocrine tumour (monodermal teratoma)	8240/3
Mixed teratoma and yolk sac tumour, prepubertal-type	9085/3
Yolk sac tumour, prepubertal-type	9071/3
Sex cord-stromal tumours	
Pure tumours	
Leydig cell tumour	8650/1
Malignant Leydig cell tumour	8650/3
Sertoli cell tumour	8640/1
Malignant Sertoli cell tumour	8640/3
Large cell calcifying Sertoli cell tumour	8642/1
Intratubular large cell hyalinizing Sertoli cell tumour	8643/1
Granulosa cell tumour	
Adult granulosa cell tumour	8620/1
Juvenile granulosa cell tumour	8622/0
Tumours in the fibroma-thecoma group	8600/0
Mixed and unclassified sex cord-stromal tumours	

Descriptor	ICD-O codes
Mixed sex cord-stromal tumour	8592/1
Unclassified sex cord-stromal tumour	8591/1
Tumour containing both germ cell and sex cord-stromal elements	
Gonadoblastoma	9073/1

a The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours.

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Note 7 - Margin status (Required)

Reason/Evidentiary Support

Complete resection of viable 'malignant' germ cell elements is an important prognostic factor in RPLND and therefore is a required element. It is therefore important to liaise with the surgeon to ensure that all margins are true margins, especially when adjacent lymph nodes/tissue is removed individually. Use of marking sutures may be useful in these circumstances to indicate orientation.[17,18,24-26]

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Note 8 - Extranodal extension (Required)

Reason/Evidentiary Support

The detection of extranodal extension of disease has been studied in a number of publications, and although some have shown it to be a poor prognostic indicator, this may not be independently significant of other prognostic parameters such as tumour size, incomplete excision and type of tumour. However, in the TNM staging it upstages from pN1 to pN2 and is utilised as a cut off point for the decision on further chemotherapy.[27,28]

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Note 9 - Pathologic staging (Required)

Reason/Evidentiary Support

This dataset includes the American Joint Committee on Cancer (AJCC) TNM 8th edition definitions.[29] The implementation of AJCC TNM 8th edition has been deferred until January 2018 in some jurisdictions. AJCC 7th edition[30] and UICC 7th edition[31] may be useful in the interim. Although significant differences exist between the AJCC and UICC 8th editions for primary testicular tumours, there are no such differences for pre or post treatment metastasis resections.

These required elements will depend on the nature of the resected specimens. Although most post-chemotherapy resections are of lymph node groups, usually in the retroperitoneum, there are occasional resections of other post-chemotherapy specimens from the lung, brain, liver or other sites. Most, but not all of these specimens will either be of teratoma or show necrosis. All non-lymphoid sites should be classified under M.

An alternative method of staging which may be used is the Royal Marsden method (see below), which has been suggested in some studies to be more prognostically significant and helpful in guiding further therapy than TNM and it is included below as it is requested by some oncological centres.[30-32]

TNM8 Descriptors for RPLNDs and other metastatic resections of primary testicular neoplasms[29]

Regional lymph nodes (pN)
The regional lymph nodes are the abdominal para-aortic (peri-aortic), pre-aortic, interaortocaval precaval, paracaval, retrocaval, and retro-aortic nodes. Nodes along the spermatic vein should be considered regional.
Laterality does not affect the N classification.
The intrapelvic and the inguinal nodes are considered regional after scrotal or inguinal surgery.

pNx Regional lymph nodes cannot be assessed.
pN0 No regional lymph node metastasis.
pN1 Metastasis with a lymph node mass 2 cm or smaller in greatest dimension and less than or equal to five nodes positive, none larger than 2 cm in greatest dimension.
pN2 Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension; or more than five nodes positive, none larger than 5 cm; or evidence of extranodal extension of tumour.
pN3 Metastasis with a lymph node mass larger than 5 cm in greatest dimension.

Distant metastasis (pM) (if resected)
No distant metastases
pM1 Distant metastasis.
pM1a Non-retroperitoneal nodal or pulmonary metastases.
pM1b Non-pulmonary visceral metastases.
A “y” prefix indicates those cases in which classification is performed during or following initial

multimodality therapy (i.e., chemotherapy, radiation therapy, or both chemotherapy and radiation therapy).

Modified Royal Marsden Staging System

Stage I	Tumour confined to the testis
Stage II	Infradiaphragmatic nodal involvement
	IIA greatest dimension of involved nodes less than 2 cm
	IIB greatest dimension of involved nodes 2 cm or more but less than 5 cm
	IIC greatest dimension of involved nodes 5 cm or more but less than 10 cm
	IID greatest dimension of involved nodes 10 cm or more
Stage III	Supraclavicular or mediastinal involvement
Stage IV	Extranodal metastases

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