

Protocol for the Examination of Specimens from Patients with Malignant Germ Cell and Sex Cord-Stromal Tumors of the Testis

Protocol applies to all malignant germ cell and sex cord-stromal tumors of the testis. Paratesticular malignancies are excluded.

Based on AJCC/UICC TNM, 7th edition

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Procedures

- Radical Orchiectomy
- Retroperitoneal Lymphadenectomy (RPLND)

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CAP Testis Protocol Revision History

Version Code

The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: Testis 3.0.0.0

Summary of Changes

No changes have been made since the October 2009 release.

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

TESTIS: Radical Orchiectomy

Select a single response unless otherwise indicated.

*Serum Tumor Markers (select all that apply) (Note A)

(see Serum Tumor Markers [S] classification below)

- * Unknown
- * Serum marker studies within normal limits
- * Alpha-fetoprotein (AFP) elevation
- * Beta-subunit of human chorionic gonadotropin (b-hCG) elevation
- * Lactate dehydrogenase (LDH) elevation

Specimen Laterality

- Right
- Left
- Both
- Not specified

Tumor Focality

- Unifocal
- Multifocal

Tumor Size

Greatest dimension of main tumor mass: ___ cm

*Additional dimensions: ___ x ___ cm

Greatest dimensions of additional tumor nodules: ___ cm, ___ cm, etc

Cannot be determined (see Comment)

Macroscopic Extent of Tumor (select all that apply)

- Confined to the testis
- Invades hilar soft tissues
- Invades tunica vaginalis (perforates mesothelium)
- Invades epididymis
- Invades spermatic cord
- Other (specify): _____

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

MarginsSpermatic Cord Margin

- Cannot be assessed
 Uninvolved by tumor
 Involved by tumor

Other Margin(s)

- Cannot be assessed
 Uninvolved by tumor (specify): _____
 Involved by tumor (specify): _____
 Not applicable

Microscopic Tumor Extension (select all that apply) (Note E)

- * Rete testis
 * Epididymis
 * Hilar fat
 Spermatic cord
 Tunica vaginalis (perforates mesothelium)
 Scrotal wall
 None of the above

Lymph-Vascular Invasion (Note F)

- Absent
 Present
 Indeterminate

Pathologic Staging (pTNM) (Note G)TNM Descriptors (required only if applicable) (select all that apply)

- m (multiple)
 r (recurrent)
 y (post-treatment)

Primary Tumor (pT)

- pTX: Cannot be assessed
 pT0: No evidence of primary tumor
 pTis: Intratubular germ cell neoplasia (carcinoma in situ)
 pT1: Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade tunica albuginea but not tunica vaginalis
 pT2: Tumor limited to the testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
 pT3: Tumor invades the spermatic cord with or without vascular/lymphatic invasion
 pT4: Tumor invades the scrotum with or without vascular/lymphatic invasion

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Regional Lymph Nodes (pN)

- pNX: Cannot be assessed
 pN0: No regional lymph node metastasis
 pN1: Metastasis with a lymph node mass 2 cm or less in greatest dimension, or 5 or fewer positive nodes, none more than 2 cm in greatest dimension
 pN2: Metastasis with a lymph node mass greater than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none greater than 5 cm; or evidence of extranodal extension of tumor
 pN3: Metastasis with a lymph node mass greater than 5 cm in greatest dimension
 Specify: Number examined: ____
 Number involved: ____

Distant Metastasis (pM)

- Not applicable
 pM1: Distant metastasis present
 pM1a: Nonregional nodal or pulmonary metastasis
 pM1b: Distant metastasis other than to nonregional lymph nodes and lung
 *Specify site(s), if known: _____

***Serum Tumor Markers (S) (Note A)**

- 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> |
|--------------------------------|-----------------------|-----|---------------------|-----|--------------------|
| * <input type="checkbox"/> S1: | <1.5 X N [#] | and | <5,000 | and | <1,000 |
| * <input type="checkbox"/> S2: | 1.5-10 X N | or | 5,000-50,000 | or | 1,000-10,000 |
| * <input type="checkbox"/> S3: | >10 X N | or | >50,000 | or | >10,000 |

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

***Additional Pathologic Findings (select all that apply) (Note H)**

- None identified
 Intratubular germ cell neoplasia
 Hemosiderin-laden macrophages
 Atrophy
 Other (specify): _____

***Comment(s)**

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

TESTIS: Retroperitoneal Lymphadenectomy (Note B)

Select a single response unless otherwise indicated.

***Prelymphadenectomy Treatment**

- * Chemo/radiation therapy
- * No chemo/radiation therapy
- * Unknown

***Serum Tumor Markers (select all that apply) (Note A)**

- * Unknown
- * Serum marker studies within normal limits
- * Alpha-fetoprotein (AFP) elevation
- * Beta subunit of human chorionic gonadotropin (b-hCG) elevation
- * Lactate dehydrogenase (LDH) elevation

***Specimen Site(s)**

*Specify: _____

***Number of Nodal Groups Present**

- *Specify:
- * Cannot be determined

Size of Largest Metastatic Deposit in Lymph Node

Greatest dimension: cm

*Additional dimensions: x cm

Histologic Viability of Tumor (if applicable)

- Viable teratoma present
- Viable non-teratomatous tumor present
- No viable tumor present

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Histologic Type of Metastatic Tumor (Note C)

- Seminoma, classic type
- Seminoma with syncytiotrophoblastic cells
- Mixed germ cell tumor (specify components and approximate percentages):

- Embryonal carcinoma
- Yolk sac tumor
- Choriocarcinoma, biphasic
- Choriocarcinoma, monophasic
- Cystic trophoblastic tumor
- Placental site trophoblastic tumor
- Teratoma
- Teratoma with a secondary somatic-type malignant component
(specify type): _____
- Monodermal teratoma (specify type): _____
- Spermatocytic seminoma
- Spermatocytic seminoma with a sarcomatous component
- Malignant neoplasm, type cannot be determined
- Other (specify): _____

Regional Lymph Nodes (pN) (Note I)

- pNX: Cannot be assessed
 - pN0: No regional lymph node metastasis
 - pN1: Metastasis with a lymph node mass less than 2 cm in greatest dimension, or 5 or fewer positive nodes, none greater than 2 cm in greatest dimension
 - pN2: Metastasis with a lymph node mass greater than 2 cm but no more than 5 cm in greatest dimension, or more than 5 nodes positive, none greater than 5 cm; or evidence of extranodal extension of tumor
 - pN3: Metastasis in a lymph node greater than 5 cm in greatest dimension
- Specify: Total number examined: ____
Total number involved: ____

Nonregional Lymph Node Metastasis (M1a) (Note I)

- Not applicable
- Not identified
- Present

***Comment(s)**

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Explanatory Notes

A. Serum Markers

The protocol emphasizes the importance of relevant clinical information in the pathologic evaluation of specimens. Serum marker studies play a key role in the clinical management of patients with testicular germ cell tumors.¹⁻³ 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. Information regarding pre-orchietomy serum marker status (lactate dehydrogenase [LDH], AFP, and b-hCG) is also important in the “S” categorization of the tumor for stage groupings.

B. Tissues Submitted for Microscopic Evaluation

The entire testicular tumor may be blocked if it requires 10 blocks or less (tissue may be retained for special studies); 10 blocks of larger tumors may be taken, unless the tumor is greater than 10 cm, in which case 1 block may be submitted for every 1 cm of maximum tumor dimension. Blocks must contain the interface with non-tumorous testis, as well as the tunica albuginea, even away from the tumor, because lymphatic invasion is best appreciated in the peritumoral tissue, as well as in the vessels within and under/parallel to the tunica. Tissues to be sampled include:

- Tumor, including interface with surrounding testis, and tunica albuginea
- All of the grossly different appearing areas in the tumor
- Testicular hilum/mediastinum testis
- Uninvolved testis, including tunica albuginea
- Epididymis
- Spermatic cord, including cord margin
- Other lesion(s)
- All identifiable lymph nodes[#]
- Other tissue(s) submitted with specimen

[#] For large masses which have obliterated individual nodes, 1 section for every centimeter of maximum tumor dimension, including grossly different looking areas, should be taken.

The margins in a specimen resected for a malignant tumor of the testis, depending on the extent of the surgery, include spermatic cord margin, the parietal layer of tunica vaginalis, and scrotal skin.

C. Histologic Type

The protocol mainly applies to malignant tumors of the testis, the vast majority of which are of germ cell origin. It may also be applied to other malignant or potentially malignant tumors of the testis included in the classification shown below.⁴⁻¹⁵ For lymphomas and plasmacytomas of the testis, refer to the CAP non-Hodgkin lymphoma protocol.

Modified Armed Forces Institute of Pathology (AFIP) and World Health Organization (WHO) Histologic Classification of Testicular Tumors

Germ Cell Tumors

Precursor lesion

Intratubular germ cell neoplasm, unclassified

Intratubular germ cell neoplasm, specific type

Tumors of 1 histologic type

Seminoma

Variant: Seminoma with syncytiotrophoblastic cells

Partially regressed tumor showing seminoma with scar

Spermatocytic seminoma

Variant: Spermatocytic seminoma with a sarcomatous component

Embryonal carcinoma

Yolk sac tumor

Choriocarcinoma

Variant: "Monophasic" type

Placental site trophoblastic tumor

Trophoblastic tumor, unclassified

Teratoma

With a secondary somatic-type malignant component

Monodermal variants

Carcinoid

Primitive neuroectodermal tumor

Others

Tumors of more than 1 histologic type

Mixed germ cell tumor (specify components; estimate approximate percentage of each)

Testicular scar, consistent with regressed tumor

Scar only

Scar with intratubular germ cell neoplasia

Partially regressed tumor with scar and residual germ cell tumor (specify type)

Sex Cord-Stromal Tumors

Leydig cell tumor

Sertoli cell tumor

Variant: Large cell calcifying Sertoli cell tumor

Variant: Sclerosing Sertoli cell tumor

Granulosa cell tumor

Adult type

Juvenile type

Mixed and indeterminate (unclassified) sex cord stromal tumor

Mixed Germ Cell- Sex Cord-Stromal Tumors

Gonadoblastoma

Unclassified

Miscellaneous

Sarcoma (specify type)

Plasmacytoma

Lymphoma (specify type)

Granulocytic sarcoma or leukemic infiltrates

Adenocarcinoma of rete testis

Carcinomas and borderline tumors of ovarian type

Malignant mesothelioma

D. Scar

Testicular scars, particularly in patients presenting with metastatic disease and clinically inapparent testicular primaries, may represent regressed, “burnt-out” testicular germ cell tumors. Features that further favor such a diagnosis include associated intratubular calcifications, intratubular germ cell neoplasia unclassified (IGCNU), a lymphoplasmacytic infiltrate, hemosiderin-containing macrophages, and testicular atrophy. Scars with residual invasive tumors most likely represent partial regression of the tumor. In otherwise pure seminoma, such partial regression may have clinically important implications, since it is possible that some of these scars may represent regression of a non-seminomatous germ cell tumor component of the tumor.

E. Invasion of the Rete Testis, Hilar/Mediastinal Soft Tissue, Epididymis or Tunica Vaginalis

Tumors invading the tunica vaginalis (perforating the mesothelial lining) (Figure 1, Tumor A) are considered as stage pT2 by the American Joint Committee on Cancer (AJCC) TNM staging system. Invasion of rete testis or epididymis is not assigned a higher pT stage than that for a tumor limited to the testis. Rete testis invasion has been reported by some to be associated with higher risk of relapse in clinical stage I seminoma.¹⁶ Hilar soft tissue invasion (Figure 1, Tumor B) is the predominant pathway of extratesticular extension for testicular tumors.¹⁷ However, the issue of hilar soft tissue invasion has not been addressed by AJCC TNM, and its clinical significance also has not been studied well.

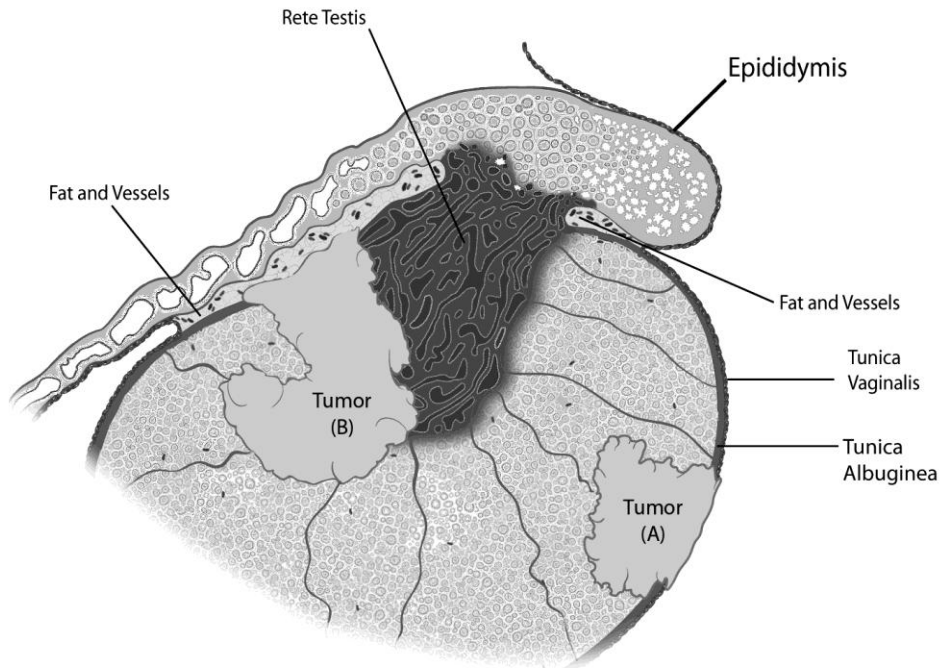


Figure 1. Diagrammatic representation of a tumor (Tumor A) invading tunica vaginalis, perforating through the mesothelium, and another tumor (Tumor B) partly involving the rete testis and invading the hilar soft tissue. Figure courtesy of Satish K. Tickoo, MD.

F. Venous/Lymphatic Vessel Invasion

In several studies, the presence of vascular space invasion (usually lymphatic but possibly also capillary or venous invasion) has been correlated with a significantly elevated risk for distant metastasis.¹⁸⁻²⁴ This observation, therefore, is most pertinent for patients who have clinical stage I disease, ie, those who have no evidence of spread beyond the testis by clinical examination (including radiographic and serum marker studies). Some clinicians manage the patients with clinical stage I disease who lack evidence of lymphatic or vascular invasion in their orchiectomy specimens (with possibly other favorable prognostic features, such as relatively small amounts of embryonal carcinoma) by close follow-up examinations rather than intervention.

The AJCC TNM staging system does not specifically address the issue of vascular invasion in the spermatic cord. While invasion of the cord is considered a pT3 stage, it would be logical to regard vascular invasion in the cord as pT2 stage, unless the tumor penetrates through the vessel wall into perivascular soft tissues of the cord.

G. Staging

The protocol recommends staging according to the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) TNM staging system.^{25,26} Additional criteria for staging seminomas according to a modification of the Royal Marsden system are also recommended.²⁷ Some studies suggest that the staging of patients with seminoma by the TNM system is less meaningful therapeutically than staging by a modification of the Royal Marsden method.²⁵⁻²⁷ Also, the data from a large

Danish study of seminomas clinically limited to the testis do not support the conclusion that local staging of the primary tumor, as performed in the TNM system, provides useful prognostic information; rather, the most valuable prognostic indicator was the size of the seminoma.²⁸ This protocol, therefore, encourages the use of the TNM system with optional use of the modified Royal Marsden staging system for patients with seminoma.

AJCC/UICC TNM and Stage Groupings

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

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 (post-orchietomy)
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 T	Any N	M1b	Any S

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

The “a” prefix designates the stage determined at autopsy: aTNM.

Additional DescriptorsResidual Tumor (R)

Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

Modified Royal Marsden Staging System

Stage I	Tumor 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

H. Additional Pathologic Findings

Important findings include Leydig cell-hyperplasia, which may be correlated with b-hCG elevation; scarring, the presence of hemosiderin-laden macrophages, and intratubular calcification, which may indicate regression of a tumor; testicular atrophy; and abnormal testicular development (eg, dysgenesis or androgen-insensitivity syndrome).^{29,30}

I. Metastatic Tumor

Often the most important distinction in patients with metastatic testicular germ cell tumor following initial chemotherapy is the differentiation of metastatic residual teratoma from nonteratomatous types of germ cell tumor. Pure teratomatous metastasis is generally treated by surgical excision alone, whereas patients who have other residual germ cell tumor components are usually treated with additional chemotherapy.

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