



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

Version: Testis 4.0.1.0

Protocol Posting Date: June 2017

Includes pTNM requirements from the 8th Edition, AJCC Staging Manual

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Radical Orchiectomy	Includes specimens designated orchiectomy and orchidectomy
Tumor Type	Description
Germ cell tumors	Includes seminoma and variants, all non-seminomatous germ cell tumors, mixed germ cell tumors, Leydig cell tumors, Sertoli cell tumors, granulosa cell tumors, and placental site trophoblastic tumors
Sex cord-stromal tumors	Includes Leydig cell tumors, Sertoli cell tumors, granulosa cell tumors, and mixed sex cord tumors

This protocol is NOT required for accreditation purposes for the following:

Procedure
Retroperitoneal lymphadenectomy
Biopsy (needle, incisional or wedge)
Primary resection specimen with no residual cancer (eg, following neoadjuvant therapy)
Cytologic specimens

The following tumor types should NOT be reported using this protocol:

Tumor Type
Paratesticular malignancies (consider Soft Tissue protocol)
Non-testis germ cell tumors (consider Extragonadal Germ Cell protocol)
Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)
Sarcoma (consider the Soft Tissue protocol)

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

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Accreditation Requirements

This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- Core data elements are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is “not applicable” or “cannot be determined.”
- Conditional data elements are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- Optional data elements are identified with “+” and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired "Data element: Response" format is NOT considered synoptic.
- The data element must be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including “Cannot be determined” if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
 - Anatomic site or specimen, laterality, and procedure
 - Pathologic Stage Classification (pTNM) elements
 - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e. all required elements must be in the synoptic portion of the report in the format defined above.

CAP Laboratory Accreditation Program Protocol Required Use Date: March 2018*

* Beginning January 1, 2018, the 8th edition AJCC Staging Manual should be used for reporting pTNM.

CAP Testis Protocol Summary of Changes

Version 4.0.1.0 errata:

Size of Largest Metastatic Deposit

- **MODIFIED** Unit of measure from millimeters to centimeters

Tumor Extension

- **MODIFIED** ___ Tumor invades through tunica albuginea and perforates tunica vaginalis (mesothelium)

Primary Tumor

- **MODIFIED** ___ pT3: Tumor directly invades spermatic cord soft tissue with or without lymphovascular invasion

Version 4.0.0.0:

The following data elements were modified:

Pathologic Stage Classification (pTNM, AJCC 8th Edition)

Surgical Pathology Cancer Case Summary

Protocol posting date: June 2017

TESTIS: Radical Orchiectomy**Select a single response unless otherwise indicated.****Specimen Laterality**

- Right
 Left
 Not specified

Tumor Focality

- Unifocal
 Multifocal
 Cannot be determined

Tumor Size

Greatest dimension of main tumor mass (centimeters): ___ cm

+ Additional dimensions: ___ x ___ cm

Greatest dimensions of additional tumor nodules (centimeters) (required only if applicable): ___ cm[#]

___ Cannot be determined (explain): _____

*#Note: Include additional greatest dimensions for additional nodules as necessary***Histologic Type (Notes A, B, and C)**Intratubular Germ Cell Neoplasia

- Germ cell neoplasia in situ (GCNIS)
 Intratubular seminoma
 Intratubular embryonal carcinoma
 Other intratubular germ cell tumor (specify): _____

Seminoma

- Seminoma
 Seminoma with syncytiotrophoblastic cells
 Seminoma with associated scar
- Embryonal carcinoma
 Yolk sac tumor, postpubertal type
 Choriocarcinoma
 Mixed germ cell tumor
- Seminoma (specify percentage): _____%
- Embryonal carcinoma (specify percentage): _____%
- Yolk sac tumor, postpubertal type (specify percentage): _____%
- Choriocarcinoma (specify percentage): _____%
- Teratoma (specify percentage): _____%
- Other (specify type and percentage): _____%

Non-Choriocarcinomatous Trophoblastic Tumor

- Non-choriocarcinomatous trophoblastic tumor, NOS
 Placental site trophoblastic tumor
 Epithelioid trophoblastic tumor
 Cystic trophoblastic tumor

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

- Teratoma, postpubertal type
- Teratoma with somatic-type malignancy (specify type): _____

Testicular Scar/Regressed Germ Cell Tumor

- Scar diagnostic of regressed germ cell tumor
- Scar suspicious for regressed germ cell tumor

- Spermatocytic tumor
- Spermatocytic tumor with a sarcomatous component
- + Prepubertal type teratoma
 - + Dermoid cyst
 - + Epidermoid cyst
 - + Well-differentiated neuroendocrine tumor (monodermal teratoma)
 - + Other (specify): _____
- Mixed germ cell-sex cord stromal tumor, gonadoblastoma

Sex Cord-Stromal Tumor

- Leydig cell tumor
- Malignant Leydig cell tumor
- Sertoli cell tumor, NOS
- Sertoli cell tumor, malignant
- Sertoli cell tumor, large cell calcifying
- Sertoli cell tumor, intratubular large cell hyalinizing
- Granulosa cell tumor, adult type
- Granulosa cell tumor, juvenile type
- Fibroma-thecoma
- Sex cord-stromal tumor, mixed type (specify components and approximate percentages): _____
- Sex cord-stromal tumor type, unclassified
- Other histologic type not listed, (specify): _____

Tumor Extension (select all that apply) (Note D)

- No evidence of primary tumor
- Germ cell neoplasia in situ only
- Tumor limited to testis
- Tumor invades rete testis[#]
- Tumor invades hilar soft tissue
- Tumor invades epididymis
- Tumor invades through tunica albuginea and perforates tunica vaginalis (mesothelium)
- Tumor invades spermatic cord
- Tumor invades scrotum
- Tumor invades other structures (specify): _____
- Cannot be assessed

[#] See Note D for definition of rete testis invasion.

Margins

Spermatic Cord Margin

- Cannot be assessed
- Uninvolved by tumor
- Involved by tumor

Other Margin(s) (required only if applicable)

- Cannot be assessed
- Uninvolved by tumor (specify margin(s)): _____

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

___ Involved by tumor (specify margin(s)): _____

Lymphovascular Invasion (Note E)

- ___ Not identified
 ___ Present
 ___ Cannot be determined

Regional Lymph Nodes

___ No lymph nodes submitted or found

Lymph Node Examination (required only if lymph nodes are present in the specimen)

Number of Lymph Nodes Involved: _____

___ Number cannot be determined (explain): _____
 Specify Site(s) (if applicable)[#]: _____

Sites may include interaortocaval, paraaortic, paracaval, preaortic, precaval, retroaortic, retrocaval, or other lymph nodes.

Number of Lymph Nodes Examined: _____

___ Number cannot be determined (explain): _____

Lymph Node Metastasis (required if any lymph nodes are involved)

Size of Largest Lymph Node (or Nodal Mass) Involved (centimeters): ___ cm

+ Size of Largest Metastatic Deposit (centimeters): ___ cm

+ Specify Site: _____

Extranodal Extension (required only if lymph nodes involved)

- ___ Not identified
 ___ Present
 ___ Cannot be determined

Histologic subtype of germ cell tumor in involved lymph nodes (if applicable, specify): _____

Pathologic Stage Classification (pTNM, AJCC 8th Edition) (Note F)

Note: Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. Only the applicable T, N, or M category is required for reporting; their definitions need not be included in the report. The categories (with modifiers when applicable) can be listed on 1 line or more than 1 line.

TNM Descriptors (required only if applicable) (select all that apply)

- ___ m (multiple)
 ___ r (recurrent)
 ___ y (posttreatment)

Primary Tumor (pT)

- ___ pTX: Primary tumor cannot be assessed
 ___ pT0: No evidence of primary tumor
 ___ pTis: Germ cell neoplasia in situ
 ___ pT1: Tumor limited to testis (including rete testis invasion) without lymphovascular invasion
 ___ pT1a: Tumor smaller than 3 cm in size[#]
 ___ pT1b: Tumor 3 cm or larger in size[#]
 ___ pT2: Tumor limited to testis (including rete testis invasion) with lymphovascular invasion OR
 Tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

- pT3: Tumor directly invades spermatic cord soft tissue with or without lymphovascular invasion
 pT4: Tumor invades scrotum with or without lymphovascular invasion

Subclassification of pT1 applies only to pure seminoma

Regional Lymph Nodes (pN)

- pNX: Regional lymph node 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 tumor
 pN3: Metastasis with a lymph node mass larger than 5 cm in greatest dimension

Distant Metastasis (pM) (required only if confirmed pathologically in this case)

- pM1: Distant metastasis
 pM1a: Nonretroperitoneal nodal or pulmonary metastases
 pM1b: Nonpulmonary visceral metastases
 Specify site(s), if known: _____

+ Pre-Orchiectomy Serum Tumor Markers (select all that apply) (Notes F and G)

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

+ Post-Orchiectomy Serum Tumor Markers (select all that apply) (Notes F and G)

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

+ Serum Tumor Markers (S) (Note G)

- + 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: | $<1.5 \times N^{\#}$ | and | $<5,000$ | and | $<1,000$ |
| + <input type="checkbox"/> S2: | $1.5-10 \times N$ | or | $5,000-50,000$ | or | $1,000-10,000$ |
| + <input type="checkbox"/> S3: | $>10 \times N$ | 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
 + Germ cell neoplasia in situ (GCNIS)
 + Microlith
 + Sertoli cell nodule (Pick's adenoma)
 + Atrophy
 + Other (specify): _____

+ Comment(s)

Surgical Pathology Cancer Case Summary

Protocol posting date: June 2017

TESTIS: Retroperitoneal Lymphadenectomy**Note: This case summary is recommended for reporting retroperitoneal lymphadenectomy specimens, but is not required for accreditation purposes.****Select a single response unless otherwise indicated.****+ Specimen Site(s) (Note A)**

+ Specify: _____

+ Prelymphadenectomy Treatment

- + ___ Chemo/radiation therapy
- + ___ No chemo/radiation therapy
- + ___ Unknown

+ Number of Nodal Groups Present

- + Specify: ___
- + ___ Cannot be determined

Histologic Viability of Tumor (if applicable) (select all that apply)

- ___ Viable teratoma present
- ___ Viable nonteratomatous tumor present
- ___ No viable tumor present

Histologic Type of Metastatic Tumor (Note B)

- ___ Seminoma
- ___ Seminoma with syncytiotrophoblastic cells
- ___ Embryonal carcinoma
- ___ Yolk sac tumor, postpubertal type
- ___ Choriocarcinoma
- ___ Mixed germ cell tumor, specify components and approximate percentages: _____
- ___ Non-choriocarcinomatous trophoblastic tumor, NOS
- ___ Placental site trophoblastic tumor
- ___ Epithelioid trophoblastic tumor
- ___ Cystic trophoblastic tumor
- ___ Teratoma, postpubertal type
- ___ Teratoma with somatic-type malignancy (specify type): _____
- ___ Spermatocytic tumor
- ___ Spermatocytic tumor with a sarcomatous component
- ___ Well-differentiated neuroendocrine tumor (monodermal teratoma)
- ___ Other histologic type not listed(specify): _____

Regional Lymph Nodes

Number of Lymph Nodes Involved: _____
 ___ Number cannot be determined (explain): _____
 Specify Site(s): _____

Note: Sites may include interaortocaval, paraaortic, paracaval, preaortic, precaval, retroaortic, retrocaval, or other lymph nodes.

Number of Lymph Nodes Examined: _____

+ Data elements preceded by this symbol are not required for accreditation purposes. These optional elements may be clinically important but are not yet validated or regularly used in patient management.

___ Number cannot be determined (explain): _____

Size of Largest Lymph Node (or Nodal Mass) Involved (centimeters): ___ cm

+ Size of Largest Metastatic Deposit (centimeters): ___ cm
+ Specify Site: _____

Extranodal Extension (ENE)

___ Not identified
___ Present
___ Cannot be determined

Histologic subtype of germ cell tumor in involved lymph nodes (if applicable, specify): _____

Nonregional Lymph Node Metastasis (M1a, AJCC 8th Edition) (Note I)

___ Not applicable
___ Not identified
___ Present
+ Number of Lymph Nodes Involved: _____
+ ___ Number cannot be determined (explain): _____
+ Specify site(s): _____

+ Number of Lymph Nodes Examined: _____
+ ___ Number cannot be determined (explain): _____

Regional Lymph Nodes (pN, AJCC 8th Edition) (Note I)

Note: Reporting of pN category is based on information available to the pathologist at the time the report is issued.

___ 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 tumor
___ pN3: Metastasis with a lymph node mass larger than 5 cm in greatest dimension

+ Comment(s)

Explanatory Notes

A. 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 nontumorous 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. When there are multifocal tumors (with ≥ 2 separate tumor nodules), additional tumor nodule(s) should also be sampled. 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 that have obliterated individual nodes, 1 section for every centimeter of maximum tumor dimension, including grossly different looking areas, is recommended.

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.

B. 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.¹⁻¹² For hematolymphoid neoplasms involving the testis, refer to the corresponding CAP protocols.

World Health Organization (WHO) Histologic Classification of Testicular Tumors (2016)¹³

Germ Cell Tumors Derived From Germ Cell Neoplasia In Situ

Noninvasive germ cell neoplasia

Germ cell neoplasia in situ

Specific forms of intratubular germ cell neoplasia

Tumors of a single histologic type (pure forms)

Seminoma

Seminoma with syncytiotrophoblastic cells

Nonseminomatous germ cell tumors

Embryonal carcinoma

Yolk sac tumor, postpubertal type

Trophoblastic tumors

Choriocarcinoma

Nonchoriocarcinomatous trophoblastic tumors

Placental site trophoblastic tumor

Epidermoid trophoblastic tumor

Cystic trophoblastic tumor

Teratoma, postpubertal type

Teratoma with somatic-type malignancy

Nonseminomatous germ cell tumors of more than one histologic type

Mixed germ cell tumor

Germ cell tumors of unknown type

Regressed germ cell tumor

Germ Cell Tumors Unrelated to Germ Cell Neoplasia In Situ

Spermatocytic tumor
Teratoma, prepubertal type
 Dermoid cyst
 Epidermoid cyst
 Well-differentiated neuroendocrine tumor (monodermal teratoma)
 Yolk sac tumor, prepubertal type
Mixed teratoma and yolk sac tumor, prepubertal type
York sac tumor, prepubertal type

Sex Cord-Stromal Tumors

Pure tumors
Leydig cell tumor
 Malignant Leydig cell tumor
Sertoli cell tumor
 Malignant Sertoli cell tumor
 Large cell calcifying Sertoli cell tumor
 Intratubular large cell hyalinizing Sertoli cell neoplasia
Granulosa cell tumor
 Adult granulosa cell tumor
 Juvenile granulosa cell tumor
Tumors in the fibroma-thecoma group
Mixed and unclassified sex cord stromal tumor
 Mixed sex cord-stromal tumor
 Unclassified sex cord-stromal tumor

Tumor Containing Both Germ Cell and Sex Cord-Stromal Elements

Gonadoblastoma

Miscellaneous

Ovarian epithelial-type tumors
 Serous cystadenoma
 Serous tumor of borderline malignancy
 Serous cystadenocarcinoma
 Mucinous cystadenoma
 Mucinous borderline tumor
 Mucinous cuystadenocarcinoma
 Endometrioid adenocarcinoma
 Clear cell adenocarcinoma
 Brenner tumor
Juvenile xanthogranuloma
Hemangioma

Hematolymphoid Tumors

Diffuse large B-cell lymphoma
Follicular lymphoma
Extranodal NI/T-cell lymphoma, nasal type
Plasmacytoma
Myeloid sarcoma
Rosai-Dorfman disease

Tumors of Collecting Duct and Rete Testis

Adenoma
Adenocarcinoma

Tumors of Paratesticular Structures

Adenomatoid tumor

Mesothelioma

Well-differentiated papillary mesothelioma

Epididymal tumors

Cystadenoma of the epididymis

Papillary cystadenoma

Adenocarcinoma of the epididymis

Squamous cell carcinoma

Melanotic neuroectodermal tumor

Nephroblastoma

Paranglioma

Mesenchymal Tumors of the Spermatic Cord and Testicular Adnexa

Apipocytic tumors

Lipoma

Well-differentiated liposarcoma

Dedifferentiated liposarcoma

Myxoid liposarcoma

Pleomorphic liposarcoma

C. Scar

Testicular scars, particularly in patients presenting with metastatic disease and clinically inapparent testicular primaries, may represent regressed, “burnt-out” testicular germ cell tumors. There are 2 established criteria to indicate a scar is diagnostic of a regressed germ cell tumor (GCT): a scar with associated germ cell neoplasia in situ (GCNIS) or a scar that contains coarse intratubular calcifications within expanded tubular profiles, which correspond to dystrophic calcifications that occurred in completely necrotic intratubular embryonal carcinoma. Features that are suspicious for, although not diagnostic of, regressed germ cell tumors include testicular atrophy, microlithiasis, and, in the scar, lymphoplasmacytic infiltrates and prominent vascularity.¹⁴ 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 nonseminomatous germ cell tumor component of the tumor.

D. 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 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.¹⁵ Rete testis invasion is that the invasive tumor involves the rete testis stroma, with or without luminal involvement. Pagetoid extension of GCNIS into the rete testis should not be considered rete testis invasion. Hilar soft tissue invasion (Figure 1, Tumor B) is the predominant pathway of extratesticular extension for testicular tumors.^{16,17} There is evidence beginning to accumulate that rete testis and hilar soft tissue invasion have predictive value for metastatic disease in patients with nonseminomatous GCTs.¹⁷ *Invasion of epididymis and hilar soft tissue is staged as pT2 by the 8th edition of AJCC TNM.*²⁶

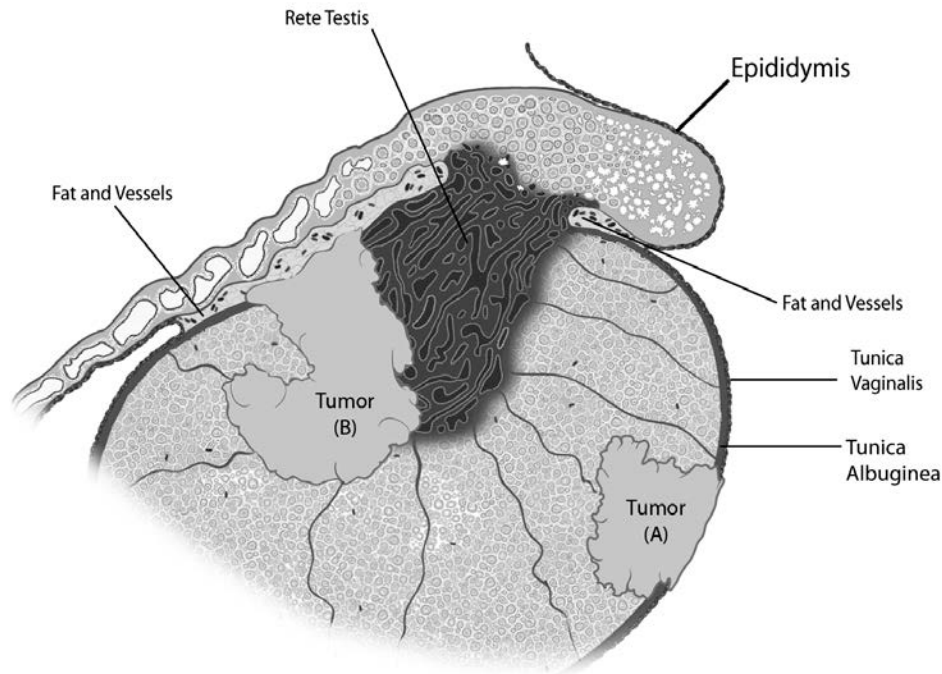


Figure 1. Diagrammatic representation of a tumor (Tumor A) invading tunica vaginalis, perforating through the mesothelium, and another tumor (Tumor B) partly involving the rete testis and invading the hilar soft tissue. Figure courtesy of Satish K. Tickoo, MD.

E. 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.

According to the 8th edition AJCC TNM staging system, discontinuous involvement of the spermatic cord soft tissue via a vascular thrombus is better regarded as a metastatic deposit (pM1). Presence of only an intravascular tumor in the spermatic cord in the absence of parenchymal invasion is considered pT2.²⁶

F. Staging

The protocol recommends staging according to the AJCC TNM staging system.²⁵ 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 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.

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 Descriptors

Residual 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

G. 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.²⁹⁻³¹

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 preorchietomy serum marker status (lactate dehydrogenase [LDH], AFP, and b-hCG) is also important in the “S” categorization of the tumor for stage groupings. Postorchietomy serum markers are important for the assignment of stage IS only.

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 (measured 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

Prognostic Factors**Serum Tumor 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

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

The serum tumor markers (S) category comprises the following:

- Alpha fetoprotein (AFP) – half-life 5 to 7 days
- Human chorionic gonadotropin (hCG) – half-life 1 to 3 days
- Lactate dehydrogenase (LDH)

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 coarse intratubular calcifications in expanded tubular profiles (distinct from microlithiasis), which may indicate regression of a tumor; testicular atrophy; sertoli cell nodules

(Pick's adenoma), which most often are associated with undescended testes, and abnormal testicular development (eg, dysgenesis or androgen-insensitivity syndrome).^{32,33}

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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