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
Protocol web posting date: February 1, 2011

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 3.1.0.0

Summary of Changes
The following changes have been made since the October 2009 release.

Radical Orchiectomy Checklist and Retroperitoneal Lymphadenectomy Checklist

Regional Lymph Nodes (pN)
Specify: Number examined / Number involved, has been changed to:

___ No nodes submitted or found

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

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

Explanatory Notes

Note G. Staging
The words “(post-orchiectomy)” were deleted from the definition of Stage IS.
Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: February 1, 2011

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.
Histologic Type (select all that apply) (Note B, Note C)

- Intratubular germ cell neoplasia, unclassified only
- Seminoma, classic type
- Seminoma with associated scar (Note D)
- Seminoma with syncytiotrophoblastic cells
- Mixed germ cell tumor (specify components and approximate percentages):
  __________________________________________________
  __________________________________________________
- Embryonal carcinoma
- Yolk sac tumor
- Choriocarcinoma, biphasic
- Choriocarcinoma, monophasic
- Placental site trophoblastic tumor
- Teratoma
- Teratoma with a secondary somatic-type malignant component
  (specify type):
  __________________________________________________
  Monodermal teratoma, carcinoid
- Monodermal teratoma, primitive neuroectodermal tumor
- Monodermal teratoma, other (specify):
  __________________________________________________
- Spermatocytic seminoma
- Spermatocytic seminoma with a sarcomatous component
- Mixed germ cell-sex cord-stromal tumor, gonadoblastoma
- Mixed germ cell-sex cord-stromal tumor, others
  (specify):
  __________________________________________________
- Testicular scar (Note D)
  - Scar only
  - Scar with intratubular germ cell neoplasia
- Sex cord-stromal tumor
  - Leydig cell tumor
  - Sertoli cell tumor
    - Classic
    - Sclerosing
    - Large cell calcifying
  - Granulosa cell tumor
    - Adult-type
    - Juvenile-type
  - Mixed, with components (specify components and approximate percentages):
  __________________________________________________
- Unclassified
- Malignant neoplasm, type cannot be determined
- Other (specify):

Margins

Spermatic Cord Margin
- Cannot be assessed
- Uninvolved by tumor
- Involved by tumor

* 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.
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

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

* 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.
__ No nodes submitted or found

*Number of Lymph Nodes Examined*
Specify: _____
____ Number cannot be determined (explain): __________________________

*Number of Lymph Nodes Involved*
Specify: _____
____ Number cannot be determined (explain): __________________________

*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

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<th>AFP (ng/mL)</th>
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<tr>
<td>*___ S2:</td>
<td>1.5-10 X N or 5,000-50,000 or 1,000-10,000</td>
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</tr>
<tr>
<td>*___ S3:</td>
<td>&gt;10 X N or &gt;50,000 or &gt;10,000</td>
<td></td>
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</tr>
</tbody>
</table>

# 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: February 1, 2011

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
___ No nodes submitted or found

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

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

Nonregional Lymph Node Metastasis (M1a) (Note I)

___ Not applicable
___ Not identified
___ Present

*Comment(s)
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-orchiectomy 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
Background Documentation
Genitourinary • Testis
Testis 3.1.0.0

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**

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<th>T</th>
<th>N</th>
<th>M</th>
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<td>M0</td>
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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
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.

References