Protocol for the Examination of Specimens from Patients with Extragonadal Germ Cell Tumors

Protocol applies to pediatric and adult patients with germ cell tumors located in the mediastinum, sacrococcygeal area, retroperitoneum, neck, and intracranial sites. This protocol does not include ovarian germ cell tumors or testicular germ cell tumors.

No AJCC/UICC TNM Staging System
The Children's Oncology Group Staging recommendations are included.

Based on:

CAP Cancer Protocol version: GermCell 3.1.0.2
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Revision History:

None

Summary of Changes:

This protocol is revised to the current version of the CAP Cancer Protocol GermCell 3.1.0.2.

Procedures Covered in this Protocol:

- Biopsy
- Resection

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None

The purpose of the Protocols is to support Laboratory Personnel engaged in the macroscopic examination of cancer resection specimens. The Protocols are based on specified relevant source documents, drafted by pathologists' assistant experts, and supported by information provided by the College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC). These Protocols are intended to serve patients by ensuring that the macroscopic examination of cancer resection specimens is compliant with CAP Cancer Protocols, the AJCC Cancer Staging Manual, and provide optimization of the pre-analytic steps necessary to promote appropriate molecular studies.

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Molecular Considerations:

Molecular studies are becoming increasingly valuable with respect to extragonadal germ cell tumors (EGCTs).

- When possible, procure at least 100 mg of grossly viable tumor to be snap frozen and submitted for molecular studies.

Cytogenetics:

- Submit a sample of tumor in alpha MEM or other suitable transport media for cytogenetic analysis.

Cytogenetic studies can be of use, as many mediastinal germ cell tumors exhibit increased incidence of trisomy 8 and are seen in patients with Klinefelter syndrome and Down syndrome. The most common karyotypic abnormality for adult germ cell tumors is isochromosome 12p, but this aberration is very rare in children younger than 10 years. The presence of these abnormalities helps identify midline germ cell tumors presenting as poorly differentiated carcinomas with atypical features. Serum testing should also be considered as many tumors demonstrate elevated AFP, hCG, HPL, LDH and PLAP.

Many of the mediastinal germ cell tumors also have shown a clonal relation to some hematopoietic malignancies such as AML (megakaryocytic or monocytic differentiation; i.e., M7, M4, and M5). These diseases also frequently share the i(12p) isochromosome but may also yield translocations more typical of the specific morphologic phenotype; e.g., del (5q), trisomy 8. The germ cell component is typically yolk sac tumor, but immature teratomas and other nonseminomatous germ cell tumors are also described.

Immunohistochemistry:

EGCTs typically show immunoreactivity patterns identical to their gonadal counterparts. In general, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and the epithelial elements of teratoma all show cytokeratin AE1/AE3 reactivity. A dot-like paranuclear reactivity pattern to low-molecular-weight cytokeratin (i.e., CAM 5.2) is seen in up to 80% of mediastinal seminomas.

Newer markers show better specificity for germ cells tumors. Nearly 100% of seminomas and embryonal carcinomas show nuclear reactivity for OCT4. OCT4 is rapidly becoming the marker of choice for documenting germ cell origin (i.e., seminoma or embryonal carcinoma) in the work-up of an undifferentiated neoplasm. Yolk sac tumors and choriocarcinoma show cytoplasmic and membranous reactivity for the oncofetal protein glypican-3, with no significant reactivity in embryonal carcinoma or germinoma. Most recently, SALL4 has been shown to demonstrate strong nuclear staining in germinoma, embryonal carcinoma, and yolk sac tumors. If vascular invasion is suspected, blood vessels can be highlighted with immunoperoxidase staining for factor VIII, CD31, and CD34. Lymphatic markers, D2-40 (podoplanin) or LYVE1 may confirm lymphatic invasion.

These tests can be performed on formalin fixed paraffin embedded tissue sections. The macroscopic description should provide the fixative used. 10% neutral buffered formalin is the preferred fixative. It is recommended that the duration of fixation be provided as well.

PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:

- **Procedures Covered by this Protocol**:

  - Biopsy
    - Core needle biopsy
    - Incisional biopsy
    - Excisional biopsy
  - Resection
    - Marginal resection
    - Wide resection
  - Other (specify)

- **Specimen Size and Extent of Resection:**

  - Provide three dimensions in cm.
  - Identify and provide dimensions of attached structures.

- **Specimen Integrity and Adequacy:**

  - Intact
  - Fragmented

  Provide an assessment of specimen integrity and adequacy:

  - If the specimen is fragmented, state the number of pieces included and/or provide an aggregate measurement.
  - State if a tumor capsule is present and if the capsule is intact, ruptured, or fragmented.
    - *Completeness of excision is an important prognostic factor.*
  - Photograph the specimen for additional documentation.

  Definitive statements about specimen integrity should be provided, including positive (definitive statement that the specimen in intact) or negative (definitive statements that the specimen is not intact) statements. If not intact, statements should include, with as much clarity as can be provided, the anatomic location of the defects or disruptions, and should also incorporate statements which assess the relationship of any defects or disruptions to the tumor and final surgical margin. If defects or disruptions involve the tumor or margins and serve to hinder assessment of the final surgical margin, this must be stated. Consultation with the surgeon for clarification should be considered, as well as differentially inking the margin in areas affected by defects or disruptions. Completely fragmented tumors, which cannot be reasonably measured, should be accompanied with a maximal tumor dimension on the requisition sheet or through consultation with the surgeon.

TUMOR

- **Tumor Size:**

  - Provide measurement of tumor in three dimensions.
  - Provide the weight of the tumor.
  - Submit at least one section per centimeter of the tumor's greatest dimension.

- **Explanatory Notes:**

  The number of sections submitted varies with the size and character of the specimen and the nature of the underlying neoplastic process. At least one section per centimeter of the tumor's greatest dimension is recommended if the tumor is a germ cell neoplasm because diverse elements may only be found with extensive sampling and may impact the tumor classification. The identification and quantity of neuroepithelial components is important for assessing immature and malignant elements.

- **Tumor Site(s):**

  - Intracranial
  - Head and neck region (including thyroid)
  - Mediastinum (pericardium, heart, thymus and lung)
  - Retroperitoneum/abdomen
  - Sacrococcygeal
  - Other (specify)

  Extragonadal germ cell tumors may represent a variety of tumor types and generally occur along the midline of the body. They can be benign (teratomas) or malignant. The malignant types can be either seminomas or non-seminomas (embryonal carcinoma, immature teratoma, yolk sac tumor, choriocarcinoma, or mixed germ cell tumors). Malignant mediastinal masses carry a poor prognosis with studies demonstrating over 70% mortality within 36 months, despite aggressive treatment.

- **Tumor Site Age Divisions:**

  - Congenital/Neonatal (birth to 6 months) *
    - Sacrococcygeal (most common GCT of the neonate)
    - Intracranial (large size may obliterate landmarks and obscure site origin)
    - Mediastinal (pericardium, heart, thymus, and lung)
    - Head and neck region (including thyroid)
    - Retroperitoneal/abdominal

  **Neonatal teratomas may occur anywhere along the body midline, following the course of the embryonic germ cell ridge. These tumors have a similar morphology at each site.*

  - Prepubertal/Child (7 months to 11 years)
    - Sacrococcygeal (presacral and pelvic)
    - Mediastinal (rare in this age group)
    - Retroperitoneal/abdominal (rare in this age group)
    - Intracranial

- Postpubertal/Adult (≥12 years) *
    - Mediastinal (most common in this age group)
    - Sacrococcygeal (considered to have been present since birth)
    - Head and Neck (frequent involvement of the thyroid)
    - Retroperitoneal (usually a metastatic site from an occult primary in the testicle or ovary)
    - Intracranial (uncommon in this age group)

**EGCT is one of the few tumor types where age affects prognosis, therefore conscientious and diligent documentation and sampling is imperative. Studies have suggested that age 12 years or older carries a significant adverse prognostic factor, especially for thoracic tumors, and thus may represent the transition point to adult type tumors*.

- **Tumor Macroscopic Features and Relationship to Attached Organs / Structures:**

    - Identify any areas of necrosis, fibrosis, hemorrhage, or cystic structures.
    - The coccyx must be identified in resection of sacrococcygeal teratomas.

Pathologic Staging

As there is not an accepted officially recognized American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TMN staging protocol for EGCTs, the CAP encourages clinicians to use the Children's Oncology Group (COG) 4-tiered staging system. The WHO recommends using modified AJCC TNM staging. Keep the following criteria in mind when macroscopically examining all EGCTs.

Children's Oncology Group Staging for any Malignant Extragonadal Germ Cell Tumors

- Stage I: Complete resection at any site; coccygectomy for sacrococcygeal site; negative tumor margins;
- Stage II: Microscopic residual; lymph nodes negative
- Stage III: Lymph nodes involved by metastatic disease. Gross residual or biopsy only, retroperitoneal nodes negative or positive
- Stage IV: Distant metastases, including liver

Anatomic Classification of Sacrococcygeal Germ Cell Tumors

- Type I: Posterior extension (externalized) with no presacral involvement
- Type II: Externalized with pelvic extension
- Type III: Externalized with intra-abdominal extension
- Type IV: Entirely presacral (no externalization*)

**Externalization is posterior growth. Internalization is anterior or presacral extension.*

Moran and Suster Proposed Clinical Staging for Mediastinal Germ Cell Tumors*

- Stage I: Well-circumscribed tumor with or without focal adhesions to the pleura or pericardium but without microscopic evidence of invasion into adjacent structures
- Stage II: Tumor confined to the mediastinum with macroscopic and/or microscopic evidence of infiltration into adjacent structures (i.e., pleura, pericardium, and great vessels)
- Stage III: Tumor with metastases
    - Stage IIIA: With metastases to intrathoracic organs (lymph nodes, lung, etc)
    - Stage IIIB: With extrathoracic metastases

**Applies to adult (postpubertal) extragonadal germ cell tumors*.

- **Margins:**

  - Apply ink to the external surface of the excision specimen.
  - Assess the margin status; include orientation if provided by the surgeon.
    - State the distance of tumor from the closest margin in cm; specify margin.
    - State if the resection margin is involved by invasive tumor; specify margin.
  - Note the adherence of the mass to adjacent structures, including nerve, vascular structures, bone, and other organs. *
  - Describe the gross extent of infiltration with pertinent negatives when applicable.

  **The presence of these structures and their relationship to the mass may be used to either upstage the tumor or demonstrate lack of spread beyond the primary lesion.*

- **Explanatory Notes:**

  Incomplete resection of a neonatal mature teratoma has been reported to recur in adulthood as adenocarcinoma. The presence of a non-germ cell malignancy in a sacrococcygeal germ cell tumor (SGCT) is a poor prognostic feature and requires complete surgical excision (this includes the coccyx) and consideration of chemotherapy or radiation therapy. The most common malignancy in a neonatal SGCT is yolk sac tumor, and correlation with serum AFP studies may be useful.

LYMPH NODES

- **Lymph Nodes: (if applicable)**

  Depending on the location of the resection, lymph nodes may or may not accompany the specimen.

  - Count the number of lymph nodes identified.
  - Specify the site of the lymph nodes, if identifiable.
  - Measure lymph nodes in three dimensions.
  - Describe the cut surface of the identified lymph nodes.
  - Submit small lymph nodes in toto.
  - Serially section and entirely submit larger lymph nodes.
  - If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
  - Take steps to ensure that an accurate lymph node count can be rendered.

  A rare finding in extragonadal teratomas of very young children is the occurrence of nodal gliomatosis in regional lymph nodes draining the teratoma. It is thought that this phenomenon is similar to peritoneal gliomatosis in ovarian teratomas. This finding seems to have no effect on the patient's clinical course and does not seem to warrant a designation of a "metastasis" upstaging the patient.

METASTASIS

- **Metastasis:**
  - If metastasis is present, specify site if known.
  - Specify the size of largest metastasis.
  - The most common sites of distant metastasis are liver and lungs. Relapses are most common at the site of the primary tumor.
  - Metastases of EGCTs are disseminated by both lymphatic and hematogenous spread and by their infiltrative growth pattern. Intraabdominal and intracranial tumors can also spread via ascites and cerebrospinal fluid, respectively.

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