Protocol for the Examination of Specimens from Patients with Carcinoma of the Adrenal Gland

Protocol applies to adrenal cortical carcinoma only. This protocol does not apply to tumors of the adrenal medulla (e.g., pheochromocytoma), pediatric adrenal cortical neoplasms (≤18 years), sarcoma, or lymphoma.

Based on:

AJCC/UICC TNM, 8th edition
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Revision History:

None

Summary of Changes:

This protocol is revised to the 8th edition of the AJCC Cancer Staging Manual and the current version of the CAP Cancer Protocol Adrenal Gland 4.0.1.0.

Procedures Covered in this Protocol:

- Biopsy
  - Percutaneous Needle Core
  - Endoscopic Directed Biopsy
- Total Adrenalectomy
- Partial Adrenalectomy

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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.

The AAPA cautions that the use of the Protocols in practice may require the use of additional considerations that are beyond the scope of the Protocols. The AAPA does not offer medical advice or diagnoses, or engage in the practice of medicine. The information provided in the Protocols is not intended or implied to be a substitute for the Laboratory Personnel's own training, professional medical opinion, diagnosis, or treatment advice. All content, including text, graphics, images and information contained in the Protocols are for the above stated purposes only. Laboratory Personnel are encouraged to confirm any information provided in these Protocols with other sources. The inclusion of a product name, organization, or service in an AAPA publication, including without limitation the Protocols, should not be construed as an endorsement of such product, organization, or service, nor is failure to include the name of a product, organization or service to be construed as disapproval.

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Molecular Considerations:

Ki67 expression has been utilized to help differentiate between malignant and benign adrenal tumors. High expression of Ki67 has been associated with poor survival and significantly shortened disease-free interval. Other immunohistochemical studies have been utilized, such as E-cadherin, cyclin E, HER2/neu, N-cadherin, and topoisomerase IIa to aid in diagnoses of adrenal gland carcinomas with limited results.

Mismatch repair proteins may be tested, as adrenal cortical carcinoma is recognized in approximately 3% of patients with Lynch syndrome.

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 the fixation be provided as well.

If special procedures are performed via image analysis, specify the methodology, software, or technique utilized.

PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:

- **Procedures Covered by this Protocol:**

  - Biopsy
    - Percutaneous needle biopsy
    - Endoscopic directed biopsy (specify radiographic technique)
  - Adrenalectomy, total
  - Adrenalectomy, partial

- **Specimen Laterality**

  - Specify right, left, or bilateral

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

  - Total specimen size in three dimensions
  - Total specimen weight (weight includes tumor and the gland) *
  - Identification and dimensions of attached structures
    - Kidney
    - Diaphragm
    - Large blood vessels (renal vein or vena cava)
    - Pancreas
    - Liver
    - Spleen

  *Note: If only a small amount of peri-adrenal soft tissue is present, the entire specimen may be weighed. If there is a large amount of soft tissue present, take sections demonstrating margins and possible soft tissue invasion. Non-involved soft tissue may then be removed prior to weighing.

- **Specimen Integrity and Adequacy:**

  Provide an assessment of the specimen integrity such as intact or fragmented. Laparoscopic adrenalectomies can lead to fragmented specimens that render the margins and tumor dimensions difficult if not impossible to interpret. Identify and describe any defects or disruptions. *

  **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 ("T" of TNM)

- **Tumor Size:**
  - Include three dimensions. *
  - If there are multiple tumors include dimensions for each.
  - If difficult to determine, such as in fragmented specimens, provide the greatest dimension.
  - Adrenal gland / tumor weight. **

    * Tumor size greater than 6.5 cm is likely to be malignant. The risk of malignancy typically increases with tumor exceeding 4 cm.

    **Weight is an important factor and incorporates the total gland weight including the tumor. Adrenal cortical neoplasms weighing less than 50 grams are more frequently associated with benign disease, whereas the weight of malignant tumors is usually greater than 100 grams.

- **Tumor Site(s):**
  - Specimen laterality
  - Tumor(s) confined to the gland or with local / distant extension into surrounding adipose tissue or other structures
  - The tumor is not dissected away from the gland
    - Sections should be taken to demonstrate the relationship of the tumor to the adrenal, to the tumor capsule, and to any associated soft tissues and visceral organs.

- **Tumor Depth of Invasion and Relationship to Attached Organs / Structures:**
  - Tumor Extension
    - Specify if tumor is confined to the adrenal cortex without invasion through tumor capsule (if present).
    - Specify if tumor invades into or through the adrenal capsule.
    - Specify if tumor invades into extra-adrenal structures.
    - Specify if tumor invades into adjacent organs. *
    - Specify if tumor invades large vessels or the renal vein. **

    * Adjacent organs include: kidney, liver, diaphragm, pancreas, stomach, spleen, and other organs.

    ** Larger-caliber vascular space invasion portends a worse prognosis.

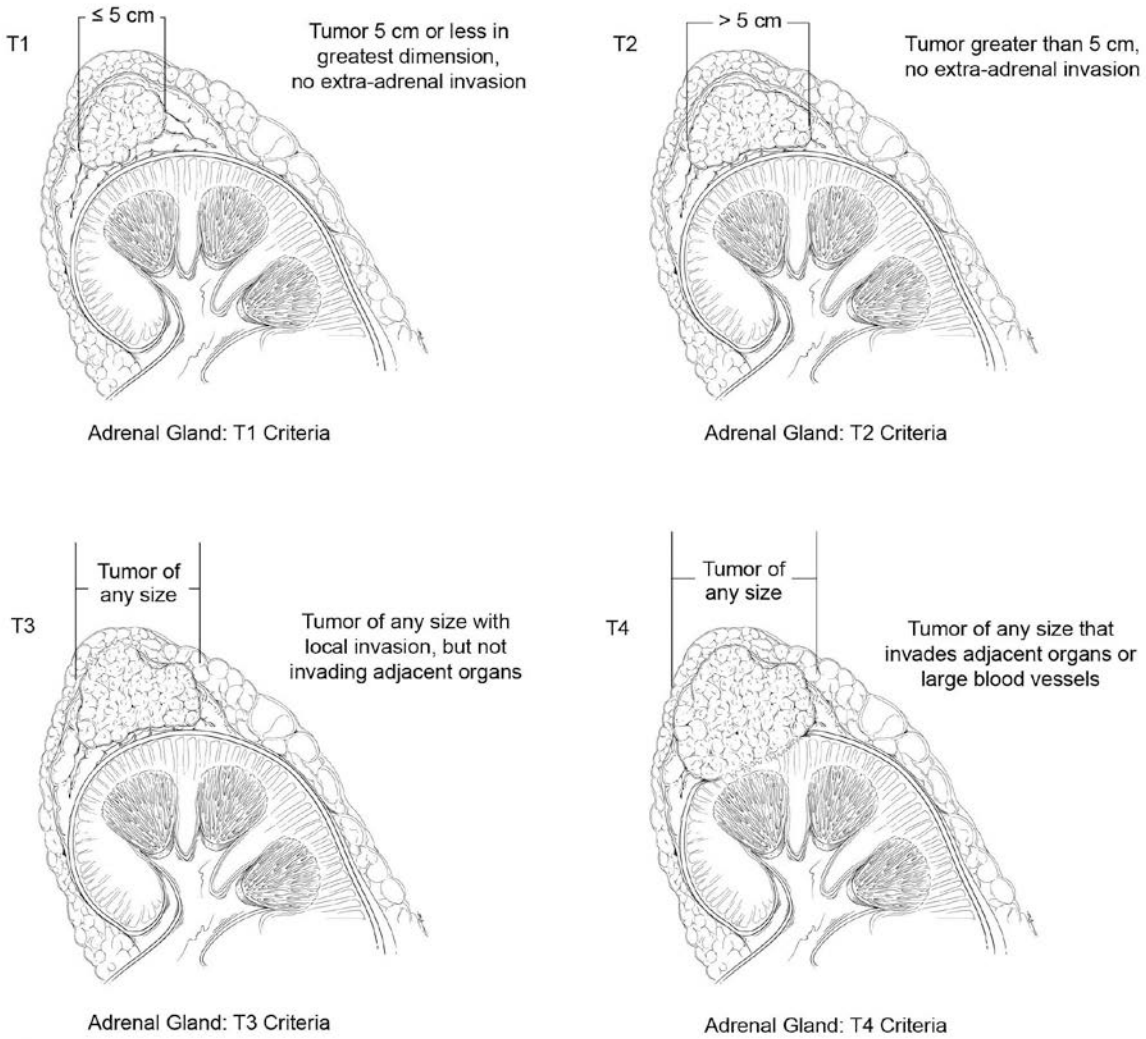

Figure 1: Adrenal Cortical Carcinoma - T1 - T4 Criteria

TNM classification for primary tumors of the adrenal gland

Definition of Primary Tumor (pT)

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pT1	Tumor ≤5 cm in greatest dimension, no extra-adrenal invasion
pT2	Tumor >5 cm, no extra-adrenal invasion
pT3	Tumor of any size with local invasion but not invading adjacent organs
pT4	Tumor of any size that invades adjacent organs (kidney, diaphragm, pancreas, spleen, or liver) or large blood vessels (renal vein or vena cava)

Note: There is no pTis (carcinoma in situ) category relative to adrenal gland carcinomas.

Note: The most significant prognostic factors are extent of invasion into surrounding tissues and metastatic spread.

TNM Descriptors:

pT(m)NM: For multiple primary tumors, the T score is modified, with the suffix "(m)" recorded in parentheses following the pT indicator (pT indicating primary tumor). Each tumor should be assessed independently of the others. Variability in histologic features should be considered with adequate sampling performed to either ensure or exclude histologic variability. With regard to the T score, for staging purposes, the pT score is established based on the primary tumor showing the greatest degree of invasion.

ypTMN: If neoadjuvant therapy has been utilized the T score will be modified with the prefix "y". The "y" categorization is not an estimate of tumor prior to multimodality therapy (i.e., before initiation of neoadjuvant therapy). Rather, the extent of tumor actually present at the time of examination must be disclosed. If neoadjuvant therapy renders macroscopic examination of tumor involvement inconclusive, dissection methods should be considered, which allow for mapping of the treated area, emphasizing the areas of potential greatest degree of invasion.

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

rTNM: The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval.

- **Margins:**

Give distance of tumor to surgical margins:
- Adipose resection margin
- Gerota's fascia, if received
- Adjacent organs

If margins are ***macroscopically negative***:
- For uninvolved margins, unit of measure for distance is millimeters.
- Document distance from closest margin in millimeters.
- Submit a section for microscopic demonstration of tumor at closest approach to the margin, including ink, if used.

If margins are ***macroscopically positive***:
- Document the involved margin.
- Submit a section for microscopic demonstration of involved margin; include ink, if used.

- **Explanatory Notes:**

Adequate sampling of the tumor is important. Histologic criteria are used in differentiating small adrenal cortical adenomas from carcinomas. The Weiss system, developed in 1984, utilizes nine histologic features to determine malignancy. If the tumor cells meet three or more of these histologic features, then the tumor is likely to metastasize or recur. The three most important criteria are venous invasion, atypical mitoses, and mitotic activity >5 per 50 HPF.

LYMPH NODES ("N" of TNM)

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

Definition of Regional Lymph Node (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in regional lymph node(s)

Regional lymph nodes include retroperitoneal (peri-nephric and peri-adrenal) lymph nodes and aortic (para-aortic and peri-aortic) lymph nodes.

Specify the number of lymph nodes examined and the number of lymph nodes involved. If only a single lymph node is identified, provide three dimensions of the lymph node. If multiple lymph nodes are identified, provide a range of sizes (i.e., 0.3 up to 1.1 cm).

Macroscopically positive lymph nodes

The highest N category is reached with one positive node.

- Count and submit one representative section of positive nodes.
- Include sections of extranodal extension, if present.
- Note anatomic location if known.
- 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.

Macroscopically negative lymph nodes

All lymph nodes must be evaluated microscopically.

- Count and submit all macroscopically negative lymph nodes.
- Note anatomic location if known.
- Submit small lymph nodes in toto.
- Bivalve or serially section large lymph nodes and submit entirely.
- 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.

METASTASIS ("M" of TNM)

- **Metastasis:**

Definition of Distant Metastasis (pM) (required only if confirmed pathologically)

M0	No distant metastasis
pM1	Distant metastasis

Common metastatic sites include the retroperitoneum, lung, and liver. Rare sites include the brain and skin. Cutaneous involvement of the scalp can simulate angiosarcoma.

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