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

Protocol applies to adrenal cortical carcinoma only. Cortical adenomas, pheochromocytoma, neuroblastic tumors, and adrenal tumors of childhood are not included.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: October 2009

Procedures
• Biopsy
  - Needle Core
  - Incisional
  - Excisional
• Adrenalectomy

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

ADRENAL GLAND: Biopsy (Core Needle, Incisional, Excisional); Resection

Select a single response unless otherwise indicated.

Specimen
Adrenal gland; received:
___ Fresh
___ In formalin
___ Other (specify): ____________________________

Procedure
___ Needle biopsy (radiographically guided)
___ Adrenalectomy, total
___ Adrenalectomy, partial
___ Other (specify): ____________________________
___ Not specified

Specimen Integrity
___ Intact
___ Fragmented

Specimen Size
Greatest dimensions: ___ x ___ x ___ cm
*Additional dimensions (if more than one part): ___ x ___ x ___ cm

Specimen Laterality
___ Right
___ Left
___ Not specified
___ Other (specify): ____________________________

Tumor Size (Note A)
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined (fragmented specimen)

Tumor Gland Weight (Note B)
Specify: ___ g

* 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.
*Tumor Description (select all that apply)
*___ Hemorrhagic
*___ Necrotic
*___ Invasion:
  *___ Capsule
  *___ Vessels
  *___ Extra-adrenal (specify): ____________________________
*___ Other (specify): __________________________

Histologic Type (Notes C through E)
___ Adrenal cortical carcinoma

*Microscopic Tumor Extension
*Specify: __________________________

Margins
___ Margins uninvolved by tumor
___ Margin(s) involved by tumor
  Distance from closest margin: ___ mm or ___ cm
  Specify margin(s) if possible: ____________________________
___ Cannot be determined
___ Not applicable

*Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy)
*___ Not identified
*___ Present (specify): __________________________
*___ Indeterminate

Lymph-Vascular Invasion (select all that apply) (Note F)
___ Not identified
___ Present
  ___ Large vessel (venous)
  ___ Small vessel (capillary lymphatic)
___ Indeterminate

*Perineural Invasion
*___ Not identified
*___ Present
*___ Indeterminate

*Lymph Nodes, Extranodal Extension
*___ Not identified
*___ Present
*___ Indeterminate

* 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.
Pathologic Staging (pTNM) (Note G)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (post-treatment)

Primary Tumor (pT)
___ pTX: Cannot be determined
___ pT0: No evidence of primary tumor
___ pT1: Tumor 5 cm or less in greatest dimension, no extra-adrenal invasion
___ pT2: Tumor greater than 5 cm, no extra-adrenal invasion
___ pT3: Tumor of any size with local invasion, but not invading adjacent organs#
___ pT4: Tumor of any size with invasion of adjacent organs#

# Adjacent organs include kidney, diaphragm, great vessels, pancreas, and liver.
Note: There is no category of carcinoma in situ (pTis) relative to carcinomas of the adrenal gland.

Regional Lymph Nodes (pN) (Note H)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis
Specify: Number examined: ____
Number involved: ____

Distant Metastasis (pM) (Note I)
___ Not applicable
___ pM1: Distant metastasis
   *Specify site(s), if known: _______________________________

*Additional Pathologic Findings (select all that apply)
* ___ None identified
* ___ Tumor necrosis
* ___ Degenerative changes
   * ___ Calcifications
   * ___ Hemorrhage
   * ___ Cystic change
* ___ Other (specify): __________________________

* Non-Pathology Findings (select all that apply) (Notes J and K)
* ___ Urinary 17-ketosteroids increased (10 mg/g creatinine/24 hours)
* ___ Hormone production
   * ___ Cushing syndrome
   * ___ Conn syndrome
   * ___ Virilization/feminization
* ___ Weight loss
* ___ Other (specify): __________________________
*Ancillary Studies (Note L)
*Specify type(s): _______________________
*Specify result(s): _______________________

*Clinical History (select all that apply)
*___ Neoadjuvant therapy
   *___ Yes (specify type): ____________________________
   *___ No
   *___ Indeterminate
*___ Other (specify): ____________________________

*Comment(s)
Explanatory Notes

A. Primary Site and Laparoscopic Surgery
The adrenal glands sit in a supra renal location (retroperitoneal) surrounded by connective tissue and a layer of adipose tissue. The adrenal glands are intimately associated with the kidneys and are enclosed within the renal fascia (Gerota's). Each gland has an outer cortex, which is lipid rich and on gross examination appears bright yellow, surrounding an inner “gray-white” medullary compartment composed of chromaffin cells. There is a rich vascular supply derived from the aorta, inferior phrenic arteries, and renal arteries. Veins emerge from the hilus of the glands. The shorter right central vein opens into the inferior vena cava and the left central vein opens into the renal vein. A single adrenal vein is present for each gland. The regional lymph nodes include the aortic lymph nodes (para-aortic, peri-aortic) and retroperitoneal lymph nodes.

An entire adrenal tumor may be removed laparoscopically, but with this technique, the gland may become fragmented. This anatomic information, including maximal diameter of the resected tumor, should be provided by the surgeon. A recent study\(^1\) demonstrates a tumor size greater than 6.5 cm is likely to be malignant.

B. Weight
Accurate weights of adrenal cortical neoplasms are important.\(^2\) Although tumor mass cannot be used as the sole criterion for malignancy, adrenal cortical neoplasms weighing less than 50 g are almost always benign, whereas the weight of malignant tumors is usually greater than 100 g. Weight is a reflection of gland weight rather than tumor weight because, in actuality, following surgically excision, the tumor is not dissected from the gland proper and weighed separately.

C. Histologic Type
The following histologic classification of adrenal tumors has been modified from Page et al\(^3\) and from the World Health Organization (WHO) classification of tumors of the adrenal gland.\(^4\) This list may not be complete. This protocol applies only to adrenal cortical carcinoma and does not apply to other tumor types.

**Histologic Classification of Adrenal Tumors**

**Cortical Tumors**
- Adenoma
- Oncocytic adrenocortical neoplasm
- Carcinoma\(^#\)

**Medullary Tumors**
- Pheochromocytoma (benign and malignant)
- Neuroblastoma
- Ganglioneuroblastoma
- Ganglioneuroma

**Composite Tumors**
- Composite corticomedullary tumor
- Composite pheochromocytoma (Composite paraganglioma)
  - Pheochromocytoma-ganglioneuroblastoma
  - Pheochromocytoma-ganglioneuroma

Extra-Adrenal Paragangliomas
D. Histologic Grade

Adrenal cortical carcinomas are not usually graded on histologic grounds. Severe nuclear atypia, high mitotic count, vascular invasion, tumor necrosis, and other microscopic features may, in combination, support a diagnosis of adrenal cortical carcinoma and should be recorded. When several malignant features are present together (e.g., highly atypical nuclei, trabecular growth, necrosis, and many mitoses), the risk of distant metastases is increased. In some studies, specific combinations of features, such as mitotic rates of >5 per 50 high-power fields (HPF) along with atypical mitosis and venous invasion, have been found to correlate with metastasis or recurrence of adrenal cortical carcinomas. Other studies have shown that mitotic rates greater than 20 per 50 HPF are associated with decreased survival, suggesting that a high mitotic index may be an important adverse prognostic factor.

The criteria used in adults to separate benign from malignant cortical tumors are not entirely applicable to adrenocortical tumors in pediatric age groups. Further, pediatric adrenocortical neoplasms showing histologic features worrisome for malignancy in adults (e.g., capsular invasion, vascular invasion, increased mitotic activity, atypical mitoses, necrosis) may not be predictive of biologic behavior; such a pediatric adrenocortical neoplasm exhibiting such histologic features may have a clinically benign course. A number of classification schemes attempting to separate benign from malignant pediatric adrenocortical tumors have been proposed. One of these studies is based on the presence (carcinoma) or absence (adenoma) of 4 histologic features (modified Weiss system) including high nuclear grade, necrosis, mitotic rate greater than 5 per 50 HPF, and atypical mitoses; another study found that tumor weight was the only reliable predictor of behavior, with tumors weighing over 500 g being malignant; and another study correlated tumor volume of greater than 200 cm³ and weight greater than 80 g associated with an adverse outcome. Subsequent to these studies, another study proposed classifying pediatric adrenocortical neoplasms based on a series of 9 criteria including tumor weight greater than 400 g, tumor size greater than 1.5 cm, extension into periadrenal soft tissues and/or adjacent organs, invasion into the vena cava, venous invasion, capsular invasion, presence of tumor necrosis, mitotic rate greater than 15 per 20 HPF, and the presence of atypical mitoses; based on this study, the presence of up to 2 of these criteria was associated with a benign outcome, 3 criteria were considered indeterminate for malignancy, and 4 or more criteria were associated with malignant behavior.

Although this protocol does not cover medullary tumors, it should be noted that pheochromocytoma is usually diagnosed preoperatively by clinical and laboratory
means. Metastatic disease is considered the standard proof of malignancy, but recently
a constellation of histologic features that can be used to predict malignant has been
proposed.12,13

E. Adrenal Incidentalomas
With the technical advancement and availability of radiographic imaging, many
asymptomatic adrenal neoplasms are coming to clinical attention at much smaller limits.
Such asymptomatic neoplasms are referred to as “adrenal incidentalomas.” Adrenal
incidentalomas can present clinical dilemmas to the treating physician. A consensus
statement on how to manage adrenal incidentalomas was proposed in 2002.14,15 Follow-
up and treatment decisions are based on a combination of clinical/laboratory parameters
and tumor size (<4 cm, 4-6 cm, >6 cm).

F. Lymph-Vascular Invasion
According to the Weiss classification,6 distinguishing between large vessel (venous) and
small vessel (capillary/lymphatic) invasion may have an impact on prognosis, with large
caliber vascular space invasion portending a worse prognosis.

G. Staging
The staging system proposed by MacFarlane16 and modified by Sullivan et al17 and
Henley et al18 is most commonly used for adrenal cortical carcinomas. The American
Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC)
have accepted this initial TNM staging system for adrenal cortical carcinoma to be
published in their 7th editions.19

<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent</th>
<th>Size</th>
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<tbody>
<tr>
<td>Stage I</td>
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<tr>
<td>Stage II</td>
<td>Confined to gland</td>
<td>Greater than 5 cm</td>
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<td>Stage III</td>
<td>Extends out of gland without involving adjacent organs</td>
<td>Any</td>
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<tr>
<td>Stage IV</td>
<td>Distant metastasis or involvement of adjacent organs</td>
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</table>

*Tumors of the Adrenal Gland and Extra-Adrenal Paraganglia*20 proposes the following
staging system:

**Primary Tumor (pT)** (Figures 1 through 4)

- pTX: Primary tumor cannot be assessed
- pT0: No evidence of primary tumor
- pT1: Tumor 5 cm or less in greatest dimension, no extra-adrenal invasion
- pT2: Tumor greater than 5 cm, no extra-adrenal invasion
- pT3: Tumor of any size with local invasion, but not invading adjacent organs
- pT4: Tumor of any size with invasion of adjacent organs

*Note: Adjacent organs include kidney, diaphragm, great vessels, pancreas, and liver.*
Figure 1. T1: Tumor 5 cm or less in greatest dimension, no extra-adrenal invasion. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual, 7th ed* (2009) published by Springer Science and Business Media LLC, www.springerlink.com.

Figure 2. T2: Tumor greater than 5 cm, no extra-adrenal invasion. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual, 7th ed* (2009) published by Springer Science and Business Media LLC, www.springerlink.com.
Figure 3. T3: Tumor of any size with local invasion, but not invading adjacent organs. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual, 7th ed* (2009) published by Springer Science and Business Media LLC, www.springerlink.com.


**Regional Lymph Nodes (pN)**

<table>
<thead>
<tr>
<th>pN0</th>
<th>Negative regional nodes</th>
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<tbody>
<tr>
<td>pN1</td>
<td>Positive regional nodes</td>
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**Distant Metastasis (pM)**
P\(M_0\) No distant metastasis  
P\(M_1\) Distant metastasis

**Stage Definitions**

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**H. Regional Lymph Nodes**
Regional lymph nodes include aortic (para-aortic and peri-aortic) and retroperitoneal (peri-nephric and peri-adrenal).

**I. Metastatic Sites**
Common metastatic sites include liver, lung, and retroperitoneum. Metastases to brain and skin are uncommon although cutaneous involvement of the scalp can simulate angiosarcoma.20

**J. Relevant History**
Endocrine manifestations, such as hypertension, change in body habitus, feminization, or virilism, are important, as is the knowledge of whether the patient suffers from an adrenal-related disease or syndrome (eg, Cushing disease, Conn syndrome). Also of import are family history, previous surgery for adrenal tumors (both benign and malignant) or other endocrine organs, other tumors that may metastasize to the adrenal gland, and endocrine or other therapies. In addition, while the majority of adrenal cortical carcinomas occur sporadically, occasionally adrenal cortical carcinoma may be associated with hereditary cancer syndromes.4,20 Such hereditary cancer syndromes include Li-Fraumeni syndrome or SBLA (sarcoma; breast and brain tumors; leukemia, laryngeal carcinoma and lung cancer; and adrenal cortical carcinoma) syndrome20 and Beckwith-Weidmann syndrome.4 Hyperplastic adrenal tissue may re-grow if previously excised incompletely.

**K. Endocrine Status**
Laboratory findings are important in the evaluation of an adrenal mass. Tumors that are functional, ie, secrete cortisol, aldosterone, or sex hormones, tend to be discovered at an earlier stage than non-functional tumors. Non-functional tumors come to attention due to mass effect and are usually larger.

**L. Ancillary Studies**
Special procedures may include frozen sections, cytologic imprints, immunohistochemical stains, histochemical stains, electron microscopy, flow cytometry, molecular studies, and cytogenetic studies. If such studies are performed in another laboratory, either extra-institutional or intra-institutional, the laboratory should be identified.
References


