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: November 2011

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

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The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the "Surgical Pathology Cancer Case Summary" portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the required data elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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CAP Adrenal Gland Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: AdrenalGland 3.1.0.1

Summary of Changes
The following changes have been made since the February 2011 release.

Biopsy (Core Needle, Incisional, Excisional); Resection

Margins
Reporting elements have been changed to the following:

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

Surgical Pathology Cancer Case Summary

Protocol web posting date: November 2011

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

+ 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
    Distance from closest margin: ___ mm *or* ___ cm
    Specify margin if possible: _____
___ Margin(s) involved by tumor
    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

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

___ 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) **(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 lymh pnodes (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
Other Adrenal Tumors
- Adenomatoid tumor
- Hematolymphoid malignancies
- Sex cord-stromal tumor

Soft tissue tumors and Tumor-like lesions
Myelolipoma
Teratoma
Schwannoma
Angiosarcoma
Miscellaneous, including adrenal pseudotumor

[#] Covered in protocol.

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 (eg, highly atypical nuclei, trabecular growth, necrosis, and many mitoses), the risk of distant metastases is increased.[2,5-7] 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.[1,6] 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.[7]

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 (eg, 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[8]; another study found that tumor weight was the only reliable predictor of behavior, with tumors weighing over 500 g being malignant[9]; and another study correlated tumor volume of greater than 200 cm^3 and weight greater than 80 g associated with an adverse outcome.[10] 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[11]; 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 MacFarlane[16] and modified by Sullivan et al[17] and Henley et al[18] 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]

Stage	Extent	Size
Stage I	Confined to gland	5 cm or less
Stage II	Confined to gland	Greater than 5 cm
Stage III	Extends out of gland without involving adjacent organs	Any
Stage IV	Distant metastasis or involvement of adjacent organs	Any

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.

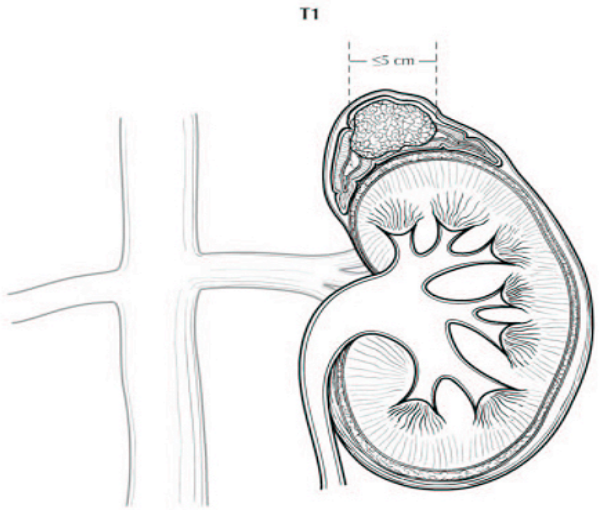

Figure 1. T1: Tumor 5 cm or less in greatest dimension, no extra-adrenal invasion. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual,* 7th ed (2009) published by Springer Science and Business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

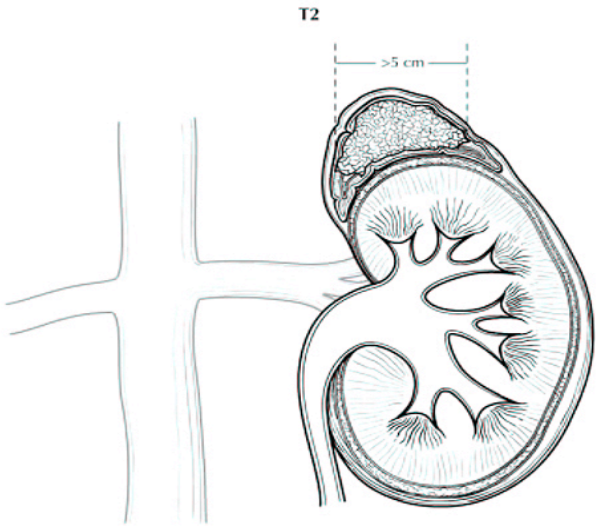

Figure 2. T2: Tumor greater than 5 cm, no extra-adrenal invasion. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual,* 7th ed (2009) published by Springer Science and Business Media LLC, www.springerlink.com.

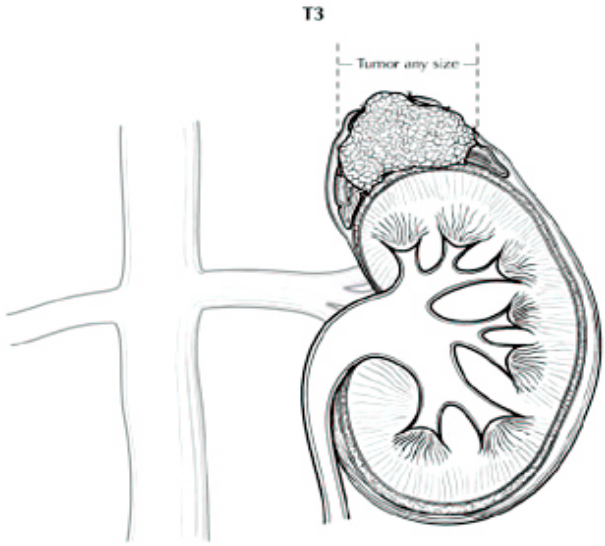

Figure 3. T3: Tumor of any size with local invasion, but not invading adjacent organs. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual,* 7th ed (2009) published by Springer Science and Business Media LLC, www.springerlink.com.

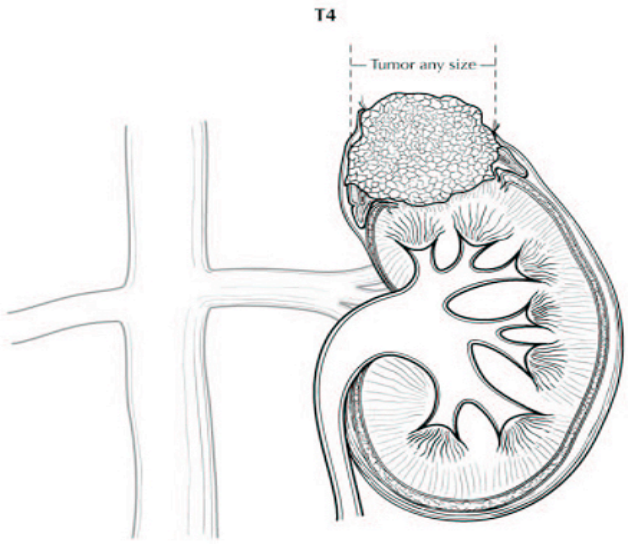

Figure 4. T4: Tumor of any size with invasion of adjacent organs. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual,* 7th ed (2009) published by Springer Science and Business Media LLC, www.springerlink.com.

Regional Lymph Nodes (pN)

pN0	Negative regional nodes
pN1	Positive regional nodes

Distant Metastasis (pM)

pM0	No distant metastasis
pM1	Distant metastasis

Stage Definitions

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
Stage IV	T3	N1	M0
	T4	N0	M0
	Any T	Any N	M1

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 (**s**arcoma; **b**reast and **b**rain tumors; **l**eukemia, **l**aryngeal carcinoma and **l**ung cancer; and **a**drenal cortical carcinoma) syndrome[20] 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.

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