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REVIEW ARTICLE

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Recommendations for the reporting of tumors of the adrenal cortex and medulla

Association of Directors of Anatomic and Surgical Pathology

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Abstract The Association of Directors of Anatomic and Surgical Pathology has developed recommendations for the surgical pathology report for common malignant tumors. The recommendations for tumors of the adrenal cortex and medulla are reported herein.

Key words Adrenal gland · Cortex · Medulla · Tumor

Introduction

The Association of Directors of Anatomic and Surgical Pathology (ADASP) has named several committees to develop recommendations regarding the content of the surgical pathology report for common tumors. A committee of individuals with special interest and expertise write the recommendations, and they are reviewed and approved by the council of ADASP, and subsequently by the entire membership.

The recommendations have been divided into four major areas: (1) items that provide an informative gross description; (2) additional diagnostic features that are recommended and included in every report, if possible; (3) optional features that may be included in the final report; and (4) a checklist.

The purpose of these recommendations is to provide an informative report for the clinician. The recommendations are intended as suggestions, and adherence to them is completely voluntary. In special clinical circumstances, direct recommendations may not be applicable. The recommendations are intended as an educational resource, rather than a mandate.

These recommendations were developed by an ad hoc committee composed of Ernest E. Lack (Chair), Frederic B. Askin, Louis P. Dehner, David L. Page, and Lawrence M. Weiss

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Guidelines

Tumors of adrenal cortex and medulla are uncommon in general surgical pathology practice, and may be broadly grouped into mostly endocrine and some nonendocrine tumors. The following guidelines are offered for a general, more inclusive, approach for generating a complete surgical pathology report, realizing of course that minor or major modifications are appropriate depending upon the type (or subtype) of tumor received. Explanatory notes are appended.

1. Clinical data. Information should include patient identification (name, medical record number, age, date of birth, and gender), attending physician, date of surgery and date of receipt of specimen, clinical history and/or endocrinologic data and both pre- and postoperative diagnoses (see explanatory note A).
2. Topography. The precise anatomic location should be stated.
3. Surgical procedure. The report should indicate whether the surgical procedure was a complete adrenalectomy or a more extended surgical procedure, whether a biopsy or subtotal excision was done or whether resection was done by laparoscopy (which has been possible for some smaller adrenal tumors, even pheochromocytomas).
4. Specimen processing. The report should indicate whether the specimen was received fresh or in fixative (specify type of fixative). It may be desirable to have some indication in the report of approximate time that had elapsed between surgical removal of specimen and its arrival for examination in surgical pathology.
5. Gross examination
   a) Orientation of specimen should be indicated if pertinent (see explanatory note B).
   b) Record size of adrenal tumor in three dimensions.
   c) Specify any other organs or tissues if pertinent.
   d) Weigh specimen, preferably intact. Special specimen preparation may be indicated (see note C).

e) Accurate and complete description of adrenal tumor on external examination and in representative cross section. Record color of tumor and necrosis or hemorrhage if present.
f) Describe appearance of adrenal remnant (cortex and/or medulla) where appropriate (see note D).
g) Record results of intraoperative consultation.
h) Note the following if done: gross photography, tissue processed for electron microscopy or frozen for special studies, any ancillary procedures (e.g. gross chromaffin reaction, frozen sections for lipid stain).

6. Microscopic examination and diagnosis.
   a) Histologic type or subtype of tumor with brief reference to clinical and/or endocrinologic data if pertinent (see note E).
   b) Histologic grade if pertinent (see note F).
   c) Descriptive diagnosis if pertinent (see note G).
   d) Descriptive features as appropriate (e.g. necrosis, extra-adrenal extension, invasion of adjacent tissues or organs, presence of vascular/lymphatic invasion).
   e) Margins of surgical resection where pertinent.
   f) Status of regional lymph nodes where pertinent (i.e., total number identified, location if possible and number with metastatic tumor [see note H for information regarding staging of specific tumors]).
   g) Add comment or note as appropriate (e.g., correlation with other specimens such as submitted material (cytology or surgical), correlation with clinical and/or endocrinologic data, and correlation with intraoperative consultation). Record whether special studies (e.g. electron microscopy, immunohistochemistry, DNA quantitation, cytogenetics or other) are to be done (specify outside reference laboratory), whether outside consultation is requested or desired, and indicate source of consultation. Record whether portion of tumor submitted for tumor bank.

Appendix A. Explanatory notes

A. Clinical and/or endocrinologic data

Clinical and endocrinologic information is often very important in evaluation of adrenal cortical or medullary tumors. Information such as change in body habitus, hypertension or endocrine syndromes such as virilization or feminization may be helpful. The adrenal gland(s) are rarely encountered as surgical specimen(s) resected for ACTH or pituitary-dependent Cushing's disease, but if this occurs and the glands are only mildly stimulated one may mistakenly regard them as "normal." Incidentally discovered nonfunctional adrenal cortical nodule or adenoma can mimic an adenoma associated with a known endocrine syndrome (e.g. Cushing's syndrome), and correlation can help here. Also of potential importance are family history (e.g. multiple endocrine neoplasia [MEN] syndrome type 2) when an adrenal gland may need to be evaluated for adrenal medullary hyperplasia or early pheochromocytoma(s). A history of previous surgery may be important, particularly tumors of other endocrine organs.

B. Orientation of adrenal gland(s)

Sectioning of the gland(s) in the transverse plane at narrow intervals (2–3 mm) may provide valuable information regarding cortical or medullary hyperplasia. It may be necessary to evaluate the gland(s) for adrenal medullary abnormalities, and in that case it will be informative on gross examination to orient and section the gland(s) through the head and body, where most of the medullary or chromaffin tissue is concentrated, and also to section through the tail of the gland. Morphometric techniques may be used to document hyperplasia.

C. Weight of resected adrenal gland

Accurate weighing of adrenal neoplasms is important; adrenal cortical adenomas are usually less than 50 g in weight, while carcinomas are characteristically over 100 g. Special effort may be required in the smaller tumors (e.g. 80–120 g) to remove as much extraneous connective tissue and fat as possible to obtain accurate adrenal weights. It must be acknowledged and noted whether tissue has been harvested in the operating room for investigative purposes. The preferred practice is for the intact fresh specimen to be submitted to surgical pathology, where essential weights and dimensions can be obtained before tissue is procured for other nondiagnostic purposes.

D. Gross examination of cortex and/or medulla

In cases of primary adrenal hypercortisolism (Cushing's syndrome) examination of the attached cortex in the case of an adenoma or carcinoma may show atrophy. In familial cases of pheochromocytoma (e.g. MEN syndrome type 2) examination of the nonneoplastic medulla may show gross evidence of diffuse and/or nodular medullary hyperplasia; the pheochromocytoma(s) in this setting may be bilateral and multinodular.

E. Histological classification of adrenal tumors

Histologic classification of adrenal tumors can be complex, given the wide variety of tumors and tumor-like lesions and sometimes confusing clinical and/or imaging characteristics. A relatively simplified classification is shown here, which is based upon that published in the 3rd series fascicle *Tumors of the Adrenal Gland and Extra-adrenal Paraganglia* of the *Atlas of Tumor Pathology* [1]. Several studies have identified important histologic factors in the diagnosis of adrenal cortical carcinoma, and among them are high mitotic count (particularly atypical mitotic figures), vascular invasion and tumor necrosis; a combination of adverse histologic findings is

Table 1 Pathologic features in the grading of neuroblastic tumors[a]

Differentiation of neuroblasts	Undifferentiated Poorly differentiated Differentiating
Mitotis-karyorrhexis index	Low (2% or less of cells) Intermediate (2% to 4% of cells) High (4% or greater of cells)
Stroma (neuroma-like, not neurofibrillary)	Poor Rich
Calcifications	Present Absent

[a] The pathologic assessment of a neuroblastic tumor for purposes of grading should be done on a suitable, pretreatment specimen with areas of well-preserved tumor cells and in the absence of extensive necrosis and hemorrhage. The primary tumor is the ideal specimen for tumor grading, but a lymph node metastasis is satisfactory. However, liver or bone marrow biopsy, a small crushed biopsy, posttreatment tumor and recurrent disease are not satisfactory for pathologic grading. Details of the definitions of these various features are available elsewhere

most useful in making a diagnosis of adrenal cortical carcinoma [1–4]. The approach to classification of childhood adrenal cortical tumors may be slightly different from that used in adults, since some are more likely to be clinically benign than had previously been thought [1].

Histological classification of neoplasms or tumor-like lesions of adrenal cortex and medulla

I. Adrenal cortical tumors
   - Adenoma
   - Carcinoma
   - Myelolipoma
   - Tumor–like adrenal cortical nodule(s)
   - Other

II. Adrenal medullary tumors
   - Pheochromocytoma
   - Neuroblastoma, Ganglioneuroblastoma
   - Ganglioneuroma
   - Other

III. Miscellaneous neoplasms and tumor–like lesions
   - Adrenal cyst
   - Primary mesenchymal or neural tumors (benign and malignant)
   - Metastatic tumors
   - Other

F. Histologic grading and other prognostic factors

Grading has been applied to adrenal cortical carcinoma (high grade and low grade) in adults on the basis of mitotic activity [2], but there is currently no uniformity in the application of these criteria, whether for carcinomas in the adult or the pediatric age group. There is no grading system for pheochromocytoma, and prediction of their biologic behavior can be notoriously difficult.

Many pathologic grading systems of neuroblastic tumors have been introduced in the past 30–40 years. Three basic types of neuroblastic tumors are widely recognized, with an assumption that they represent biologic stages in differentiation and maturation from a primitive neuroblast of the neuroblastoma to a ganglion cell of the ganglioneuroblastoma and ganglioneuroma [5, 6]. It is possible in most cases to assign a particular neuroblastic tumor into one of three pathologic subtypes, but for purposes of histologic grading and prognostic assessment, recent studies have shown the significance of several morphologic features in the clinical outcome (Table 1) [7]. In addition, there are several other important cytogenetic and molecular markers of prognostic importance (Table 2) [8]. An age-linked classification of childhood neuroblastoma and ganglioneuroblastoma stratifies tumors into favorable and unfavorable groups [9]. Useful guidelines for determination of the mitotis-karyorrhexis index (MKI) have been reported, which require less time and are readily usable by surgical pathologists [10]. Another modified grading system of neuroblastoma has also been reported with age as a prognostic factor [11], and results indicate similar subgroups (low risk versus high risk) in terms of prognosis.

The profile for a prognostically unfavorable neuroblastic tumor is an undifferentiated or poorly differentiated neuroblastoma which is stroma-poor, has a high MKI and lacks calcifications. This same tumor is likely to be near diploid and to have deletions in chromosomes 1p and 14q, amplified MYCN and low expression of TRK-A and TRK-C [8]. The patient with this unfavorable neuroblastoma is typically older than 1 year of age at diagnosis, has an adrenal-based primary tumor, and has stage III or IV disease at presentation. Another unfavorable pathologic type of neuroblastic tumor is the stroma-rich, nodular ganglioneuroblastoma or composite ganglioneuroblastoma, which should be differentiated from the favorable histology intermixed or diffuse ganglioneuroblastoma.

Table 2 Cytogenetic and molecular markers in the prognostic assessment of neuroblastomas (*LOH* loss of heterozygosity; *MYCN* N-*myc* oncogene; *TRK* tyrosine kinase (receptor) nerve growth factor)

DNA ploidy	Favorable	Unfavorable
	Hyperdiploid or near triploid	Near diploid
1p LOH	Absent	Present
14q LOH	Absent	Present
MYCN	Normal	Amplified
TRK-A	High expression	Low or absent expression
TRK-B	Low expression	High expression
TRK-C	High expression	Low or absent expression

Table 3 Staging of adrenal cortical carcinoma

Percent		Stage		Staging criteria
2.8	I	T1N0M0	T1	Tumor less than or equal to 5 cm, no invasion
			T2	Tumor greater than 5 cm, no invasion
29.0	II	T2N0M0	T3	Tumor any size, locally invasive but not involving adjacent organs
			T4	Tumor of any size with invasion of adjacent organs
19.3	III	T1N1M0	N0	Negative regional node(s)
		T2N1M0	N1	Positive regional node(s)
		T3N0M0	M0	No distant metastases
			M1	Distant metastases
48.9	IV	Any T, any N, M1		
		T3 N1		
		T4		

Table 4 Neuroblastoma staging system proposed by the International Staging System Working Party

Stage	Staging criteria	Incidence	Survival at 5 years
Stage I	Local tumor confined to the area of origin, complete gross excision, with or without microscopic residual disease; identifiable ipsilateral and contralateral lymph nodes negative microscopically	5%	90% or greater
Stage IIa	Unilateral tumor with incomplete, gross excision; identifiable ipsilateral and contralateral lymph nodes negative microscopically	10%	70–80%
Stage IIb	Unilateral tumor with complete or incomplete gross excision; with positive ipsilateral regional lymph nodes; identifiable contralateral lymph nodes negative microscopically		
Stage III	Tumor infiltrating across the midline with or without regional lymph node involvement; or midline tumor with bilateral regional lymph node involvement	25%	40–70% (depending on completeness of surgical resection)
Stage IV	Dissemination of the tumor to distant lymph nodes, bone, bone marrow, liver and/or other organs (except as defined under stage IV-S)	60%	More than 60% if age at diagnosis is younger than 1 year; 20% if age at diagnosis is older than 1 year and under 2 years; 10% if age at diagnosis is over 2 years
Stage IVS	Localized primary tumor as defined for stage I or II with dissemination limited to liver, skin, and/or bone marrow	5%	More than 80%

Some modification of conventional terminology and criteria for neuroblastic tumors has also been been suggested [12]. A recent review summarizes various classifications of neuroblastic tumors [13].

G. Descriptive diagnosis

On occasion it may be extremely difficult to predict the biologic behavior of an adrenal cortical neoplasm, and use of descriptive terminology such as “adrenal cortical tumor of indeterminate malignant potential” may be appropriate.

H. Staging of adrenal tumors

The American Joint Committee on Cancer currently has no staging system for adrenal cortical carcinoma. The staging criteria proposed by MacFarlane [14] and modified by Sullivan et al. [15] are shown in Table 3. The proportion of patients in each stage at diagnosis is based upon a recent review by Wooten and King [16].

The staging system for neuroblastoma proposed by The International Staging System Working Party is presented in Table 4 along with incidence and survival at 5 years [17].

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