

Unknown primary cancer presenting as an adrenal mass: Frequency and implications for diagnostic evaluation of adrenal incidentalomas

Jeffrey E. Lee, MD, Douglas B. Evans, MD, Robert C. Hickey, MD, Steven I. Sherman, MD, Robert F. Gagel, MD, Marie C. Abbruzzese, MBA, and James L. Abbruzzese, MD, Houston, Tex

Background. Fine-needle aspiration biopsy to identify adrenal metastasis from an occult primary malignancy has been recommended as part of the evaluation of the patient who presents with an incidentally discovered adrenal mass. This recommendation was assessed by examining the frequency of adrenal involvement in patients with suspected unknown primary cancer.

Methods. Data from 1715 patients referred for evaluation of suspected unknown primary cancer were retrospectively reviewed.

Results. Of 1639 patients found to have cancer, the adrenal gland was identified as a site of involvement at presentation in 95 (5.8%). Involvement was limited to the adrenal gland in 4 patients (0.2%). All 4 patients had large (≥ 6 cm) adrenal tumors, 3 of 4 had bilateral involvement, and all had symptoms that otherwise mandated evaluation for an occult malignancy; none had a true adrenal incidentaloma.

Conclusions. Although cancer of an unknown primary site occasionally involves the adrenal gland, metastatic cancer presenting as a true adrenal incidentaloma is extremely rare. Therefore, in the absence of a history of prior malignancy or symptoms, physical examination findings, radiographic findings, or laboratory findings suggestive of an occult malignancy, we do not recommend fine-needle aspiration biopsy as part of the diagnostic evaluation of the patient who presents with a unilateral adrenal mass. (*Surgery* 1998;124:1115-22.)

From the Departments of Surgical Oncology, Medical Specialties, and Gastrointestinal Medical Oncology, The University of Texas, M. D. Anderson Cancer Center, Houston, Tex

INCIDENTALLY DISCOVERED ADRENAL masses are found in up to 4% of individuals undergoing abdominal computed tomography (CT) and in up to 7% of individuals at autopsy.¹ Appropriate evaluation of the patient who presents with an adrenal mass discovered incidentally on abdominal imaging (incidentaloma) must take into consideration the frequencies of diseases that can involve the adrenal gland in the population in which the mass is discovered (Bayesian analysis).² Failure to do so may result at best in unnecessary and expensive tests being performed and at worst in inappropriate and potentially dangerous treatment. Therefore, important considerations to keep in

mind when evaluating a patient with an adrenal incidentaloma include the observations that benign nonfunctioning adrenal cortical adenomas are common, adrenal cortical carcinomas are extremely rare, and metastases to the adrenal glands from malignant solid tumors occur with moderate frequency.³⁻⁸ The evaluation of a patient who presents with an incidental adrenal mass should therefore include assessment of the tumor's functional status and consideration of the likelihood that the tumor represents a primary malignancy or that the tumor represents metastatic disease.^{9,10}

There is a general consensus that determination of the functional status of adrenal incidentalomas should include screening for pheochromocytoma and hypercortisolism.^{2,4} Further, it is generally recognized that large size is the single best clinical indicator of a primary malignancy of the adrenal gland in patients who present with an incidental adrenal mass.^{2,8} Controversy arises, however, regarding the extent of evaluation neces-

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Reprint requests: Jeffrey E. Lee, MD, Department of Surgical Oncology, Box 106, The University of Texas, M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

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sary to exclude the possibility of metastatic malignancy in patients with adrenal incidentalomas. Some authors have recently recommended that all patients who present with an isolated incidental adrenal mass undergo fine-needle aspiration biopsy (FNA) of the mass to exclude metastasis from an occult (unknown) primary malignancy.¹¹ However, before such a recommendation can be accepted it is important to determine the frequency with which patients with unknown primary cancer present with an isolated adrenal metastasis. If the frequency is low then most incidentalomas can be expected to have other causes, and FNA is unlikely to benefit most patients. Therefore we examined the frequency and natural history of adrenal involvement at presentation in patients referred to our Unknown Primary Tumor Clinic with suspected occult (unknown) primary cancer.

PATIENTS AND METHODS

Patients and database. For this retrospective review the patient population consisted of 1715 consecutive patients referred between January 1987 and February 1996 to the Unknown Primary Tumor Clinic at the University of Texas M. D. Anderson Cancer Center for evaluation of a suspected unknown primary cancer. All referred patients were entered into the Unknown Primary Tumor Database^{12,13} at the time of initial registration. Patients with squamous cell carcinoma involving high cervical or midcervical lymph nodes frequently were referred directly to the Department of Head and Neck Surgery and therefore are underrepresented in this series. The medical records of the patients were periodically evaluated for results of laboratory tests, diagnostic studies, pathologic diagnoses, and survival data; these data were entered into the database. Follow-up was current through January 1998.

Diagnostic evaluation. All patients referred to the Unknown Primary Tumor Clinic underwent a standardized diagnostic evaluation¹³ consisting of a history, physical examination (including breast and pelvic examinations in women and testicular and prostate examinations in men), stool examination for occult blood, liver function tests, hemogram, measurement in men of prostate-specific antigen, chest radiography, CT of the abdomen and pelvis, and mammography in women. When indicated by abnormal findings during this initial evaluation, additional directed diagnostic tests were performed. These selectively employed studies included sputum cytology, CT of the chest, breast or pelvic ultrasonography, bronchoscopy, and gastrointestinal endoscopy.

When clinically appropriate, biopsies were performed on suspected sites of metastasis. All available pathologic material was reviewed. No attempt to confirm all metastases pathologically was made.

Identification of primary malignancies. Identification of a primary malignancy was established by determination of a specific histopathologic diagnosis (lymphoma, melanoma, sarcoma, multiple myeloma, leukemia, central nervous system malignancies, and extragonadal germ cell tumors) or, in the case of the common epithelial neoplasms (adenocarcinoma, carcinoma, squamous cell carcinoma), by detection of a primary tumor site. For patients with a history of prior invasive cancer appropriate histopathologic and clinical findings were required for the new tumor to be considered a recurrence.

Treatment. Patients with unknown primary carcinomas were treated according to currently accepted guidelines. Patients whose primary tumors were identified by diagnostic evaluation were treated based on the oncologic principles established for the management of the specific primary tumor type.

Statistical analysis. Patient survival was measured from the time of diagnosis and the survival distribution was estimated using the product-limit method of Kaplan and Meier. Subgroup frequencies were compared with use of chi-square analysis. Survival data were compared with use of the Cox-Mantel log-rank test. All calculations were performed with the Stata statistical software package (release 3; Stata Corp, College Station, Tex).

RESULTS

After evaluation in the Unknown Primary Tumor Clinic 76 of 1715 patients were found to be without evidence of malignancy and were excluded from further analysis. The remaining 1639 patients had malignancies. The adrenal gland was identified as a site of involvement at presentation in 95 (5.8%) of the patients (Fig 1).

Diagnostic evaluation identified the primary tumor site in 24 (25%) of 95 patients with adrenal involvement (Table I). The most common primary tumor site identified in the 95 patients with adrenal involvement was the lung. In contrast, patients referred for evaluation of suspected unknown primary cancer without adrenal involvement had a lower frequency of discovered lung primary tumors (71% vs 33%; $P < .0001$). Only a single patient was found to have primary adrenal cortical carcinoma. The histologic diagnoses in these 24 patients were adenocarcinoma in 13, carcinoma in 7, hepatocellu-

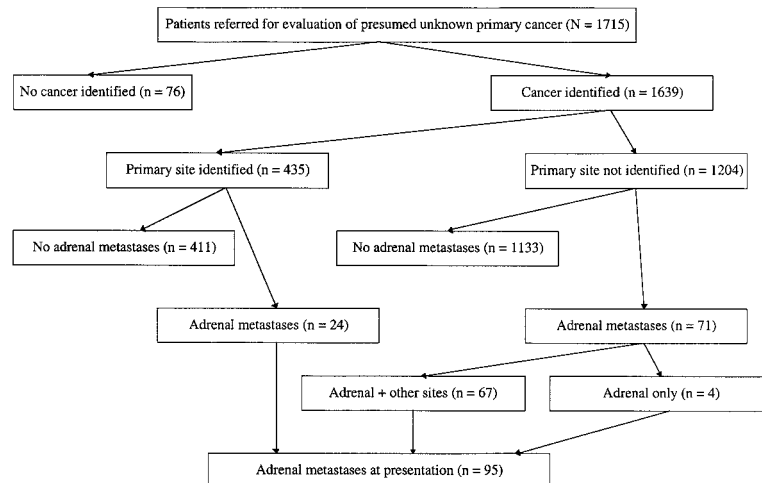


Fig 1. Outcome of evaluation of 1715 patients referred with presumed unknown primary cancer.

lar carcinoma in 2, neuroendocrine carcinoma in 1, and lymphoma in 1.

In the remaining 71 patients (75%) with adrenal involvement a primary site was not identified (Tables II and III). Of these patients 67 also had extra-adrenal sites of metastasis; the presence of an underlying malignant process was therefore obvious. A histologic diagnosis was established in 67 of 71 patients; in the remaining 4 patients biopsies were nondiagnostic (2), revealed an unclassified malignant neoplasm (1), or were refused by the patient (1). Of the 71 patients with adrenal involvement and unknown primary cancer, 4 had a history of neoplasm (1 each chronic lymphocytic leukemia, papillary thyroid cancer, breast cancer, and gestational trophoblastic neoplasm) not believed to be the source of the presenting unknown primary tumor.

Only 4 (0.2%) of 1639 patients with cancer had disease limited to the adrenal glands at presentation (Tables III and IV). All 4 patients with adrenal-only disease had large (≥ 6 cm) adrenal tumors. Three of the 4 patients had bilateral adrenal involvement. The demographic distribution of patients with unknown primary cancer limited to the adrenal gland was similar to that of patients with unknown primary cancer and adrenal involvement who also had other sites of disease (Table III). None of the 4 patients with adrenal-only disease had a history of cancer. None of the 4 patients had a primary tumor identified. FNA biopsy revealed that 3 of the 4 patients had adenocarcinomas (moderately differentiated in 1, differentiation not specified in 2); the fourth had an unclassified malignant neoplasm. All 4 patients were symptomatic (abdominal pain in 4; anorexia in 3; weakness in 2). None of the 4 patients underwent surgical resection of the adrenal tumors.

Patients with unknown primary cancer and adrenal involvement had a median overall survival of 7 months; this was shorter than the median overall survival of patients with unknown primary cancer without adrenal involvement (11 months; $P = .0001$; Fig 2).

DISCUSSION

In this study the adrenal gland was an occasional site of involvement in patients presenting with unknown primary cancer (5.8%), but isolated adrenal involvement was extremely rare (0.2%). Further, the 4 patients with adrenal-only disease had large (≥ 6 cm) tumors and were symptomatic, and 3 had bilateral adrenal involvement; therefore no patient in this series had a true adrenal incidentaloma. We thus found no compelling evidence to support the recommendation that all patients with an isolated adrenal incidentaloma undergo FNA to exclude occult metastatic cancer from an unknown primary tumor site.

The established Unknown Primary Tumor Clinic database at the University of Texas M. D. Anderson Cancer Center provided us with a unique opportunity to investigate the natural history of unknown primary cancer involving the adrenal glands, as well as the frequency with which patients with unknown primary cancer present with incidental adrenal masses. Overall, 5.8% of patients in this series had involvement of the adrenal gland at presentation. The adrenal gland was involved in 24 (5.5%) of 435 patients in whom a primary tumor site was identified (Table I) and in 71 (5.9%) of 1204 patients in whom a primary tumor site was not identified (Table II).

The most common primary tumor site identified in the patients with metastases to the adrenal gland

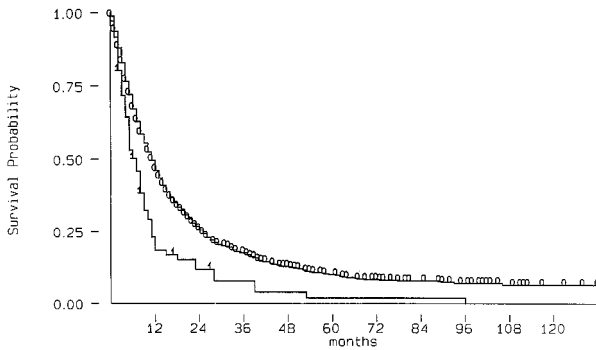


Fig 2. Kaplan-Meier survival curves for patients with unknown primary cancer with adrenal involvement (“1,” n = 71; median survival, 7 months) and without adrenal involvement (“0,” n = 1133; median survival, 11 months; log-rank *P* = .0001). Median follow-up was 9 months; for those patients alive at the end of follow-up, median follow-up was 16 months.

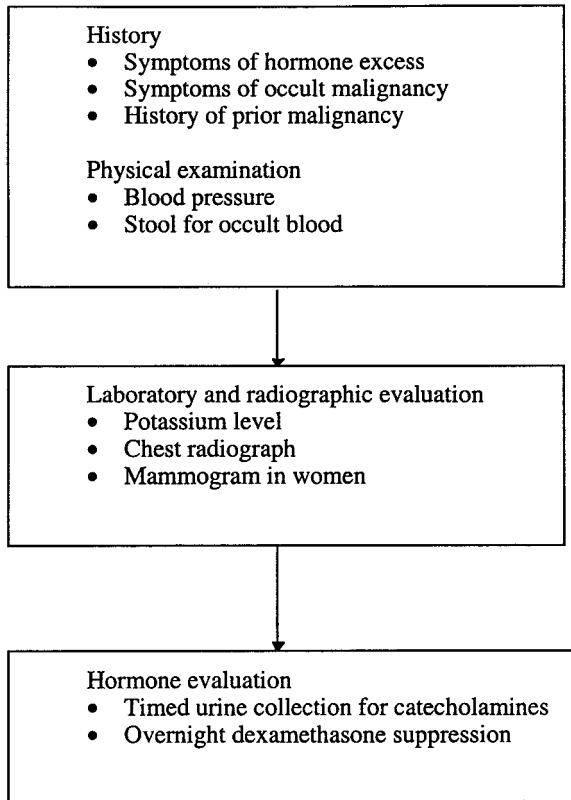


Fig 3. Recommended evaluation of the patient presenting with an incidental adrenal mass.

was the lung. Patients with adrenal involvement had a higher frequency of discovered lung primary tumors than patients without adrenal involvement (*P* < .0001). Therefore patients—particularly smokers—with an adrenal mass suspicious for metastatic

cancer should undergo a screening chest radiograph to evaluate for occult lung cancer.

The most common histologic type identified in this series was adenocarcinoma, both in the subset of patients in whom a primary tumor site was identified (13 of 24, 54%) and in those with true unknown primary cancer (45 of 71, 63%). Adenocarcinoma was also the most common histologic diagnosis in reported series of patients with metastatic cancer undergoing FNA¹⁴ or surgical resection¹⁵ of involved adrenal glands (Table II).

Patients with unknown primary cancer and adrenal involvement had a poor overall prognosis, with a median survival of only 7 months. This survival duration was demonstrably shorter than that for patients with unknown primary cancer without adrenal involvement (Fig 2). These findings corroborate the previously reported poor prognosis in patients with metastatic cancer involving the adrenal glands can include occult or overt adrenal insufficiency, particularly among patients with metastatic lung cancer. Adrenocorticotropic (ACTH) stimulation testing is useful because it may document an Addisonian state in such patients, who may benefit from exogenous steroid hormone replacement.^{16,17}

True incidentalomas of the adrenal gland are defined as a serendipitous finding unrelated to the clinical presentation. Most clinicians would further restrict incidentalomas to adrenal masses smaller than 4 to 6 cm. In our series we found isolated adrenal involvement at presentation in only 4 (0.2%) of 1639 patients with suspected unknown primary cancer. All 4 patients with adrenal-only disease had large tumors (≥6 cm); this finding in itself should mandate evaluation for malignancy (Table IV). Further, 3 of 4 had bilateral adrenal involvement, and all were symptomatic. Thus no patient in this series fulfilled the criteria for a true adrenal incidentaloma.

Although it may be argued that referral bias could account—at least in part—for the absence of small, unilateral, asymptomatic adrenal tumors in this patient population, examination of the reported experiences of others supports our findings. Whereas an adrenal mass in a patient with a history of prior invasive malignancy frequently represents metastatic cancer (Table V), isolated metastases to a unilateral adrenal gland in an asymptomatic patient without a history of malignancy are quite uncommon (Table VI). There is no compelling evidence therefore to indicate that all patients with an adrenal incidentaloma (as defined above) and normal findings from a hormonal evaluation require FNA to exclude an occult primary malignancy.

Table I. Distribution of primary sites identified in patients referred with suspected unknown primary cancer with and without adrenal involvement compared to literature series of patients with adrenal metastases who underwent FNA or surgical resection of involved adrenal glands

<i>Primary site</i>	<i>No. of patients (%)</i>			
	<i>Adrenal involved— current series</i>	<i>Adrenal uninvolved— current series</i>	<i>Adrenal involved— FNA series¹⁴</i>	<i>Adrenal involved— surgical series¹⁵</i>
Lung	17 (71)	142 (33)	55 (69)	11 (21)
Liver	2 (8)	14 (3)	0 (0)	0 (0)
Colon	1 (4)	25 (6)	1 (1)	7 (13)
Pancreas	1 (4)	31 (7)	1 (1)	0 (0)
Adrenal	1 (4)	0 (0)	0 (0)	0 (0)
Lymphoma	1 (4)	22 (5)	3 (4)	0 (0)
Uterus	1 (4)	3 (1)	1 (1)	2 (4)
Breast	0 (0)	32 (7)	1 (1)	1 (2)
Melanoma	0 (0)	19 (4)	5 (6)	3 (6)
Sarcoma	0 (0)	17 (4)	1 (1)	1 (2)
Kidney	0 (0)	17 (4)	7 (9)	15 (29)
Stomach	0 (0)	13 (3)	1 (1)	3 (6)
Central nervous system	0 (0)	12 (3)	0 (0)	0 (0)
Prostate	0 (0)	8 (2)	0 (0)	1 (2)
Esophagus	0 (0)	7 (2)	1 (1)	0 (0)
Other	0 (0)	73 (17)	3 (4)	3 (6)
Unknown	—	—	0 (0)	5 (10)
Total	24	435	80	52

Table II. Histologic diagnoses in patients with unknown primary cancer with and without adrenal involvement compared to literature series of patients with adrenal metastases who underwent FNA or surgical resection of involved adrenal glands

<i>Histologic diagnosis</i>	<i>No. of patients (%)</i>			
	<i>Adrenal involved— current series</i>	<i>Adrenal uninvolved— current series</i>	<i>Adrenal involved— FNA series¹⁴</i>	<i>Adrenal involved— surgical series¹⁵</i>
Adenocarcinoma	45 (63)	666 (59)	52 (65)	36 (69)
Carcinoma	16 (23)	322 (28)	7 (9)	7 (13)
Neuroendocrine carcinoma	3 (4)	51 (5)	0 (0)	0 (0)
Squamous carcinoma	3 (4)	72 (6)	3 (4)	1 (2)
Melanoma	0 (0)	0 (0)	5 (6)	3 (6)
Sarcoma	0 (0)	0 (0)	1 (1)	3 (6)
Transitional cell carcinoma	0 (0)	0 (0)	1 (1)	2 (4)
Lymphoma	0 (0)	0 (0)	3 (4)	0 (0)
Renal cell carcinoma	0 (0)	0 (0)	7 (9)	0 (0)
Other	0 (0)	22 (2)	1 (1)	0 (0)
Unclassified/unknown	4 (6)	4 (0)	0 (0)	0 (0)
Total	71	1133	80	52

Evaluation of patients with an incidental adrenal mass should include a history designed to elicit symptoms caused by a functioning tumor or an underlying malignancy (eg, weight loss, abdominal pain, or rectal bleeding), a physical examination (blood pressure; breast, lymph node, pelvic, and rectal examinations; and stool examination for occult blood), a laboratory evaluation (measurement of serum potassium), a chest radiograph, and a mammogram in adult women. Patients with an

incidental adrenal mass should also undergo a biochemical evaluation, including a timed urine collection to measure catecholamines and testing for cortisol overproduction (Fig 3). Overnight dexamethasone (1 mg) suppression is probably the least expensive, most convenient, and most sensitive screening test for hypercortisolism in patients with an incidental adrenal mass; timed urine collection to measure cortisol can be reserved for patients with abnormal responses to overnight dexamethasone

Table III. Demographics of 71 patients with unknown primary cancer and adrenal involvement

Characteristic	No. of patients (%)	
	Adrenal disease only	Adrenal with other disease sites
Total	4	67
Sex		
Female	1 (25)	18 (27)
Male	3 (75)	49 (73)
Age (y)		
0-39	0 (0)	5 (7)
40-49	0 (0)	15 (22)
50-59	2 (50)	15 (22)
60-69	2 (50)	23 (34)
70-79	0 (0)	8 (12)
≥80	0 (0)	1 (1)
Race		
White	3 (75)	56 (84)
Hispanic	1 (25)	6 (9)
Black	0 (0)	4 (6)
Other	0 (0)	1 (1)

suppression.¹⁰ Screening for androgen or estrogen excess is unnecessary in the absence of specific signs or symptoms suggestive of overproduction of these hormones. Further, because late-onset congenital adrenal hyperplasia and adrenal insufficiency are uncommon causes of asymptomatic adrenal masses, ACTH stimulation testing¹¹ of patients with incidentalomas is unnecessary in the absence of symptoms, physical examination findings, or abnormal laboratory results suggestive of adrenal insufficiency. Finally, because the presence of normal blood pressure and a normal serum potassium level make the diagnosis of aldosteronoma unlikely, determination of plasma aldosterone levels or renin values in patients with incidentalomas is unnecessary in the absence of hypertension or hypokalemia.²

The size of the incidental adrenal mass remains the single best indicator of whether it is a primary malignancy. Although adrenal cortical carcinomas are rare, nonfunctioning adrenal adenomas 6 cm or larger are also rare. A nonfunctioning adrenal mass larger than 6 cm has a 35% to 98% potential to be cancer.² Because large, unilateral adrenal masses have a high probability of being primary adrenal cancers they should be resected; complete surgical resection carries with it a reasonable expectation of cure, and surgical resection is safe in low-risk individuals.⁸ Following large adrenal masses with serial abdominal imaging studies¹¹ is potentially hazardous and is most emphatically not recommended. In patients with intermediate masses (those between 3 and 6 cm) further imaging studies, such as magnetic reso-

nance imaging that includes T₁-weighted chemical-shift analysis, may be helpful.¹⁸

We advocate FNA of isolated adrenal masses only in selected circumstances—for example, in patients with a history of a prior malignancy that commonly metastasizes to the adrenal gland (lung, breast, stomach, kidney, colon, melanoma, lymphoma)¹⁹ or if there are symptoms, physical examination findings, or biochemical or radiographic evidence of an underlying malignancy. Because adrenal incidentalomas are common and occult metastatic cancer presenting as a small, unilateral, asymptomatic adrenal mass is rare, adoption of the recommendation that all patients with hormonally inactive small incidental masses of the adrenal gland undergo FNA to detect occult metastatic cancer would result in the performance of a large number of unnecessary biopsies, with both the small but real risk of complications from that procedure and the significant associated cost.²⁰ It seems much more reasonable to follow patients with small, hormonally inactive isolated adrenal masses by serial clinical examinations and abdominal imaging. FNA may be helpful in differentiating between metastatic cancer and adrenal cortical adenoma in selected patients with a history of malignancy but no other evidence of malignant disease.⁷

Surgery for metastases to the adrenal gland may be considered in low-risk individuals without extra-adrenal disease who have histories of favorable tumor biology (eg, a significant progression-free interval, a response to systemic therapy, or a history of isolated metachronous metastases, or some combination of the three).^{15,21-23} Selected pathologic types that may be considered for resection include metastases from melanoma, renal cell carcinoma, and colorectal cancer. Preoperative evaluation of patients who have an adrenal mass and a history of malignancy should include an evaluation for hormone production before FNA because some of these patients will have pheochromocytomas. In addition, patients with known or suspected adrenal metastases for whom surgical resection is being contemplated should undergo ACTH stimulation testing to document adequate adrenal cortical reserve before adrenalectomy.^{16,17} FNA may be helpful in selected cases to confirm the diagnosis of metastasis before operation.⁷ Alternatively, surgical therapy can be planned based solely on noninvasive imaging studies in patients with a history of a malignancy that commonly metastasizes to the adrenal glands, favorable tumor biology, negative biochemical screening for hormone production, and a mass that either fulfills size criteria for surgi-

Table IV. Clinical characteristics at presentation of 4 patients with unknown primary cancer limited to adrenal gland

Patient	Age	Sex	Symptoms	Size of adrenal tumor(s) in cm	Histopathology	Outcome
1	68	M	Anorexia, weight loss, back pain, right-sided abdominal pain	11.0 (R), 4.0 (L)	Adenocarcinoma	DOD, 1 month
2	54	F	Right-sided abdominal pain	6.4 (R)	Adenocarcinoma	DOD, 6 months
3	51	M	Left leg pain, fatigue, abdominal pain, weakness, anorexia	3.0 (R), 8.0 (L)	Adenocarcinoma	DOD, 7 months
4	60	M	Fever, abdominal pain, weakness, anorexia	6.0 (R), 5.0 (L)	Malignant neoplasm (unknown type)	DOD, 2 months

R, Right; L, left; DOD, dead of disease.

Table V. Frequency of metastasis to adrenal gland in patients presenting with adrenal mass and history of invasive malignancy

First author	Institution/location	Year	Total No. of patients	No. of patients with adrenal metastasis (%)	Size of metastases in cm
Abecassis ¹	Toronto, Canada	1985	44	20 (45)	—
Belldegrun ³	Brigham and Women's	1986	33	24 (73)	1-10*
Penn ⁴	Univ. Cincinnati	1988	34	20 (59)	4.8†
Saboorian ⁷	M. D. Anderson	1995	188	80 (43)	5.0†
Total			299	144 (48%)	

*Range.

†Mean.

Table VI. Frequency of metastasis to adrenal gland in patients presenting with adrenal mass without history of invasive malignancy

First author	Institution/location	Year	Total no. of patients	No. of patients with metastatic cancer (%)	Size of metastases (cm)
Belldegrun ³	Brigham and Women's	1986	28	6 (21)*	—
Herrera ⁵	Mayo Clinic	1991	259	1 (0.4)†	5.5
Sirén ⁶	Helsinki, Finland	1998	36	0 (0)	—
Total			323	7 (2%)	

*Bilateral involvement in 2 of 6; lung cancer identified on initial evaluation in 2 of 6; pancreatic cancer identified on initial evaluation in 1 of 6; unknown primary cancer present in 3 of 6.

†Unknown primary cancer; died of disease progression 2 years after presentation.

cal excision or is radiographically suspect for metastasis.^{9,10} We would consider a laparoscopic approach to resection of adrenal metastases in highly selected patients.^{24,25}

In summary, although cancer of an unknown primary site occasionally involves the adrenal gland at presentation, metastatic cancer presenting as a true adrenal incidentaloma is extremely rare: 0 of 1639 consecutive patients in this study. Therefore, in the absence of a history of prior malignancy or symptoms, physical examination findings, radiographic findings, or laboratory findings suggestive of an occult malignancy, we do not

recommend FNA as a routine part of the diagnostic evaluation of the patient who presents with a unilateral adrenal mass.

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DISCUSSION

Dr Ashok R. Shaha (New York, NY). Does your study include metastatic head and neck carcinomas, or metastatic adenocarcinomas? What would be your workup for a patient with metastatic adenocarcinoma to the cervical lymph nodes?

Dr Lee. There is a potential for referral bias in this series against patients with head and neck involvement. Patients presenting with unknown primary cancer involving the head and neck region who were referred to the University of Texas M. D. Anderson Cancer Center were often sent directly to our Head and Neck Surgical Service, therefore bypassing our Unknown Primary Tumor Clinic. It is conceivable that a referral bias against patients with head and neck involvement would have led us to miss a small number of such patients with metastatic cancer involving the adrenal gland. However, in the needle biopsy and surgical series I presented, head and neck primaries were not a frequent source of metastasis to the adrenal gland. It seems unlikely, therefore, that such a referral bias would fundamentally alter our conclusions. With regard to the extent of evaluation necessary to exclude an occult head and neck primary site in patients presenting with unknown primary cancer, while we do perform a complete general physical examination on our patients, we do not, for example, routinely perform direct or indirect laryngoscopy in the absence of suggestive symptoms or physical examination findings. An exception, of course, would be a patient presenting with squamous carcinoma (rather than adenocarcinoma) involving cervical lymph nodes.

Dr Robert Udelsman (Baltimore, Md). You presented compelling data on an important topic. We see far too many patients with fine-needle biopsies of adrenal masses that are absolutely worthless. My question is, where are the melanomas?

Dr Lee. It is well recognized that melanoma occasionally metastasizes to the adrenal glands. Furthermore, adrenal involvement in patients with metastatic melanoma can be clinically and radiographically unilateral. Metastatic melanoma will occasionally present without a cutaneous primary lesion being identified, therefore fulfilling the definition of an unknown primary cancer. However, I personally know of no single case or case report in which a patient has presented with a unilateral adrenal metastasis from melanoma without either a history of primary melanoma or additional melanoma metastases being present. Such a clinical scenario must be extremely rare. I have personally resected isolated adrenal melanoma metastases in carefully selected patients, as have others. I would consider a carefully selected patient with an isolated unilateral adrenal melanoma metastasis arising from a known or unknown primary site for surgical resection.