Evaluation and surgical resection of adrenal masses in patients with a history of extra-adrenal malignancy

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Background. Adrenal abnormalities are often identified on imaging studies performed during the staging of patients presenting with a new malignancy or restaging of patients with a history of a malignancy.

Methods. We reviewed the records of patients who underwent surgical resection of an adrenal mass identified in the setting of previously or newly diagnosed extra-adrenal malignancy.

Results. Eighty-one patients with an adrenal mass and recently diagnosed malignancy (n = 24) or history of a malignancy (n = 57) underwent adrenalectomy. In 42 patients (52%) the adrenal mass was a metastasis. In 39 patients (48%) the adrenal mass was an additional primary adrenal tumor process: 19 pheochromocytomas, (14 syndrome-associated, 5 sporadic), 13 cortical adenomas, 3 adrenocortical carcinomas, 2 ganglioneuromas, and 2 cases of nodular hyperplasia.

Conclusions. In this series nearly half of the patients with cancer and an adrenal mass had adrenal pathologic condition independent of their primary malignancy. Despite the presence of a newly diagnosed malignancy or history of malignancy, all patients with an adrenal mass should undergo a standard hormone evaluation to confirm that the mass is not a functional neoplasm. An assumption that the adrenal mass is metastatic disease will be wrong in up to 50% of such patients. (Surgery 2001;130:1060-7.)

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Adrenal masses are identified in up to 4% of patients undergoing computed tomography (CT) scanning of the abdomen or chest. Because metastases involving the adrenal gland are frequently seen as a component of the natural history of a number of relatively common malignancies, including renal cell carcinoma, malignant melanoma, and carcinoma of the lung, colon, and rectum, adrenal masses identified during the radiographic staging of a newly diagnosed malignancy or radiographic surveillance after therapy for a previously treated malignancy are often assumed to be metastatic lesions. However, the assumption that an adrenal mass identified in a patient with a concurrent or prior extra-adrenal cancer is a metastasis rather than an independent tumor process may result in unnecessary and inappropriate cancer-directed therapy. In addition, failure to recognize that an adrenal mass identified in a cancer patient may represent a process independent of the index malignancy may result in delayed or incorrect treatment of a primary adrenal pathologic condition. To determine more accurately which patients with relatively limited extra-adrenal cancer are more likely to have metastatic disease versus a primary adrenal mass unrelated to the index cancer, we retrospectively reviewed all patients who underwent resection of an adrenal mass in the setting of a prior or concurrent extra-adrenal malignancy in a tertiary referral cancer center.

PATIENTS AND METHODS
The medical records of 196 patients with tumors involving the adrenal gland who were referred for evaluation and underwent adrenalect-
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Of these patients, 115 had no history of extra-adrenal malignancy; none of these patients had metastasis to the adrenal gland from an unknown primary cancer, confirming the rare nature of this presentation. Eighty-one of the 196 patients had 1 or more previously or synchronously diagnosed extra-adrenal malignancies. The medical records of these 81 patients were retrospectively reviewed to determine the results of laboratory testing, radiographic evaluation, histopathologic diagnosis, and surgery as well as to obtain follow-up and survival information. Because of the retrospective nature of the study representing more than 29 years of clinical experience, extent of evaluation (eg, preoperative hormone screening) and treatment (eg, open vs laparoscopic adrenalectomy) were not necessarily standardized. Estimates of adrenal tumor size were obtained from the surgical pathology report; adrenal tumor size was recorded as the greatest cross-sectional diameter reported on radiographic imaging studies (CT or magnetic resonance imaging [MRI]). Follow-up was current through February 2001. Patient survival duration was measured from the date of adrenalectomy. The survival distribution was estimated with the product-limit method described by Kaplan and Meier, and the survival data of the subgroups were compared with log-rank analysis. Calculations were performed with STATISTICA 5.5 for Windows (StatSoft, Tulsa, Okla).

RESULTS

There were 81 patients with an adrenal mass in the setting of a prior or concurrent diagnosis of 1 or more extra-adrenal malignancies who were treated by adrenalectomy. Ten of the patients had 2 extra-adrenal malignancies, resulting in a total of 91 cancer diagnoses (Table I). In 57 patients (70%) the adrenal mass was identified in the setting of a prior diagnosis of malignancy, and in 24 patients (30%) the adrenal mass was identified during evaluation for a newly identified malignancy. Seventy-one patients (88%) had a unilateral adrenal mass,
and 10 (12%) had bilateral adrenal masses. Eighty-four adrenalectomies were performed via open laparotomy; 7 were performed via laparoscopy. Six patients with bilateral tumors underwent a cortical-sparing partial adrenalectomy (5 pheochromocytomas, 1 melanoma). The median size of the resected adrenal lesions was 3.5 cm (mean, 4.3 cm; range, 0.8 to 20.0 cm).

In 42 patients (52%) the adrenal mass was a metastasis from an extra-adrenal malignancy (Table II). The median size of the resected adrenal metastases was 3.8 cm (mean, 4.2 cm; range, 0.0 to 19.5 cm). In these patients the most common source of metastasis to the adrenal gland was renal cell carcinoma (24 patients, 57%) followed by melanoma, colorectal cancer (colon, 3 patients; rectal, 1 patient), prostate cancer, and non-small cell lung cancer. Bilateral metastases to the adrenal gland were seen in 4 patients (10%). Fifteen patients (36%) had extra-adrenal distant metastatic disease identified either concurrently with or before their adrenal metastasis. In contrast, in 27 patients (64%) distant metastatic disease was clinically and radiographically limited to the adrenal gland. In 36 patients (86%) distant metastatic disease was limited to the adrenal gland at the time of resection, whereas in another 3 patients (7%) limited extra-adrenal distant metastatic disease amenable to complete surgical resection at the time of adrenalectomy was present. Finally, in 3 patients complete resection of metastatic disease was not feasible; adrenalectomy was carried out to palliate pain.

Metastatic cancer was identified in the adrenal glands of 24 (89%) of 27 patients with a current or prior history of renal cell carcinoma compared with 40% to 57% of those with a current or prior history of melanoma, colorectal cancer, prostate cancer, or non-small cell lung cancer. In 17 of 18 patients with adrenal metastasis who underwent preoperative hormone evaluation, the results effectively excluded the presence of a functioning adrenal tumor. The remaining patient had a modest elevation in the 24-hour urine level of catecholamines, suggesting the possible presence of a pheochromocytoma; however, metastatic melanoma, not pheochromocytoma, was documented on final histopathologic evaluation of the patient’s resected adrenal gland.

All 42 patients with adrenal metastases underwent preoperative cross-sectional imaging studies of the adrenal glands (CT and/or MRI). These studies showed characteristics suggestive of the presence of an adrenal metastasis rather than a primary adrenal tumor in 17 patients (40%). In the remaining 25 patients these studies could not reliably determine whether the adrenal masses were metastatic cancer or a primary adrenal neoplasm. Preoperative fine-needle aspiration (FNA) biopsy was performed in 18 patients (43%) and supported a diagnosis of metastatic cancer in 16 (89%) of the 18 patients.

In the 42 patients with an adrenal metastasis, the average time from initial cancer diagnosis to the diagnosis of adrenal metastasis was 3.9 years (median, 2.5 years; range, 0.0 to 14.9 years). After a median follow-up of 1.4 years, 19 (45%) of the 42 patients who had died. The median actuarial overall survival duration after adrenalectomy was 3.4 years (Fig 1). This series included 2 patients who were alive more than 5 years after adrenalectomy; one had metastatic renal cell carcinoma, and the other had metastatic choriocarcinoma. There was no difference in survival duration between patients who underwent adrenalectomy for metastatic renal cell carcinoma and those who underwent adrenalectomy for non-renal cell carcinoma metastasis. Similarly, there was no difference in survival duration between patients who underwent adrenalectomy in the setting of prior or current extra-adrenal

<table>
<thead>
<tr>
<th>Cancer diagnosis</th>
<th>No. of patients</th>
<th>No. of patients with bilateral adrenal metastases</th>
<th>No. of patients with metastases limited to the adrenal gland*</th>
<th>No. of patients with synchronous extra-adrenal metastasis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell carcinoma</td>
<td>24</td>
<td>1</td>
<td>20</td>
<td>4</td>
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<tr>
<td>Melanoma</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Non-small cell lung cancer</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Choriocarcinoma</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Unknown primary cancer</td>
<td>1</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total (%)</td>
<td>42</td>
<td>4 (10)</td>
<td>36 (86)</td>
<td>6 (14)</td>
</tr>
</tbody>
</table>

*At the time of surgical resection.
distant metastatic disease and those whose distant metastatic disease was limited to the adrenal gland.

In 39 (48%) of the 81 patients the adrenal mass was a primary adrenal neoplasm (Table III). The median size of the resected primary adrenal tumors was 3.3 cm (mean, 4.4 cm; range, 0.8 to 20.0 cm). In this series the most common primary adrenal tumor was pheochromocytoma (19 patients, 49%); adrenal cortical adenoma was also frequently identified (13 patients, 33%). Fourteen of the 19 pheochromocytomas were identified in patients with multiple tumor syndromes, and the remaining 5 were sporadic. Bilateral pheochromocytoma was identified in 5 patients (all syndrome-associated). Primary cancer diagnoses associated with the presence of pheochromocytoma included medullary thyroid cancer (MTC) (11 patients, all with multiple endocrine neoplasia type 2 [MEN 2]) and melanoma (2 patients). Adrenal cortical adenoma was identified in patients with colorectal cancer, gastrointestinal stromal tumors, melanoma, non-small cell lung cancer, and cervical cancer (2 patients each). Two of 3 patients with adrenal cortical carcinoma had non-small cell lung cancer. The 2 cases of ganglioneuroma were identified in patients with melanoma.

Twenty-nine (74%) of the 39 patients with a history of cancer and an additional primary adrenal tumor process underwent preoperative CT scanning and/or MRI. These studies showed characteristics suggestive of a primary adrenal tumor rather than a metastasis in 10 patients (26%). Four patients with pheochromocytoma and 3 patients with adrenal cortical adenoma underwent confirmatory MRI, and 3 additional patients with pheochromocytoma underwent confirmatory metaiodobenzylguanidine imaging (MIBG). Preoperative FNA biopsy was performed in 11 patients (28%) but established a diagnosis of an additional primary adrenal tumor in only 3 (27%).

**Case histories.** The 4 case histories described below illustrate potential pitfalls in the evaluation of patients with an adrenal mass in the setting of a history of an extra-adrenal malignancy.
Patient 1. A 42-year-old man with a history of regional nodal metastases from malignant melanoma was found to have a 3.9-cm left adrenal mass. Preoperative screening for hormone production was not performed. FNA biopsy of the mass was performed; a Fontana-Masson stain identified the presence of melanin; the biopsy findings were therefore believed to be consistent with metastatic melanoma. The patient underwent systemic therapy for metastatic melanoma without any change in the size of the mass; he subsequently underwent a left adrenalectomy. Intraoperative blood pressure lability suggested that the adrenal mass was a pheochromocytoma rather than metastatic melanoma. The final histopathologic analysis confirmed the diagnosis of a melanin-positive pheochromocytoma.

Patient 2. A 56-year-old man with a history of MTC and MEN 2 presented with a left adrenal mass. He had undergone a total thyroidectomy 10 years before referral. An evaluation for increasing carcinoembryonic antigen and calcitonin levels documented cervical nodal recurrence of MTC with associated hepatic metastases and a 3.5-cm left adrenal mass. Preoperative imaging studies, including CT scanning and MRI, were nonspecific regarding the nature of the adrenal mass. The patient had no symptoms suggesting an excess level of catecholamines, and preoperative 24-hour urine collection showed that his level of total and fractionated catecholamines was normal. Given the high probability that the patient's tumor was a pheochromocytoma rather than metastatic MTC despite the normal catecholamine levels, adrenergic blockade was instituted. The patient subsequently underwent an uneventful laparoscopic left adrenalectomy. Final histopathologic analysis revealed that the adrenal tumor was indeed a pheochromocytoma.

Patient 3. A 43-year-old man with regional nodal metastases from melanoma was found to have a 3.2-cm left adrenal mass. He had undergone a total thyroidectomy 10 years before referral. An evaluation for increasing carcinoembryonic antigen and calcitonin levels documented cervical nodal recurrence of MTC with associated hepatic metastases and a 3.5-cm left adrenal mass. Preoperative imaging studies, including CT scanning and MRI, were nonspecific regarding the nature of the adrenal mass. The patient had no symptoms suggesting an excess level of catecholamines, and preoperative 24-hour urine collection revealed elevated levels of dopamine (974 µg per 24 hours; normal, 100 to 440 µg per 24 hours) and total catecholamines (1006 µg per 24 hours; normal, < 540 µg per 24 hours). Although metastatic melanoma was still
considered a likely diagnosis, the patient underwent preoperative adrenergic blockade and subsequently underwent an uneventful laparoscopic left adrenalectomy. Final histopathologic analysis revealed that the mass was metastatic melanoma.

**Patient 4.** A 33-year-old man with a local recurrence of melanoma was found to have a 5.0-cm left adrenal mass. Preoperative screening evaluation revealed no evidence of a hormonally functioning adrenal tumor. CT characteristics of the mass were atypical for an adrenal cortical adenoma; because of the possibility that this represented metastatic melanoma, FNA was performed; this showed only cortical cells. The patient underwent surgical resection of his adrenal mass followed by that of his locally recurrent melanoma. The final histopathologic analysis of the adrenal mass revealed that it was a ganglioneuroma.

**DISCUSSION**

Relatively few studies have addressed the issue of appropriate evaluation and surgical treatment of adrenal masses in patients with a history of malignancy. Reports of adrenal incidentaloma often specifically exclude patients with synchronous or metachronous extra-adrenal malignancies, whereas most reports of adrenalectomy for metastatic cancer exclude those with primary adrenal tumors. Table IV compares the present series with prior series that included patients with adrenal metastases from an extra-adrenal malignancy as well as those with unrelated primary adrenal tumors in the setting of a history of an extra-adrenal malignancy. These studies showed that the prevalence of primary adrenal tumors in patients with a history of extra-adrenal malignancy ranged from 27% to 50%. In the current series 48% of the patients found to have an adrenal mass in the setting of a previously or newly diagnosed extra-adrenal malignancy had a primary adrenal tumor. When patients with syndrome-associated pheochromocytoma were excluded, primary adrenal tumors were still identified in 37% of the patients (25 of 67).

In the current series, malignancies that metastasized to the adrenal gland included renal cell carcinoma, melanoma, colorectal cancer, prostate cancer, and non-small cell lung cancer. Metastasis to the adrenal gland is a more likely cause of an adrenal mass in patients with a history of these malignancies. However, not all patients with these malignancies will have adrenal metastases. Patient 1 illustrates this concept; an FNA biopsy of the adrenal mass in this patient was erroneously interpreted as demonstrating metastatic melanoma rather than pheochromocytoma. As occurred in this patient, pheochromocytoma may express melanin and therefore be confused with metastatic melanoma on cytologic evaluation of an FNA specimen. Patients with an extra-adrenal malignancy and adrenal mass should undergo a standard hormone evaluation, including a timed urine collection for measuring the level of catecholamines, before FNA biopsy or surgical resection.

Although the overall prognosis for patients with metastatic cancer in the adrenal glands is poor, the survival duration in highly selected patients who undergo adrenalectomy for metastatic cancer is similar to that in patients who undergo resection of metastases in other visceral sites, such as the liver and lung. It seems reasonable to apply similar criteria for selecting patients for resection of adrenal metastases, including control of extra-adrenal disease, a reasonably long disease-free interval, an acceptable patient performance status, and the absence of significant comorbidity. Recommendations regarding evaluation and treatment of patients presenting with an adrenal mass in the setting of extra-adrenal cancer are summarized in Fig 2.

Although a screening hormone evaluation is an essential part of the evaluation for all patients with an adrenal mass, the limitations of this screening must be recognized. As illustrated by patient 2, urinary catecholamine levels may occasionally be normal in MEN 2 patients with small pheochromocytomas. MIBG may assist in confirming the diagnosis in such patients. Alternatively, as seen in patient 2, adrenergic blockade followed by surgical resection can be performed without MIBG confir-
mation if cross-sectional imaging studies suggest the
diagnosis of pheochromocytoma.

In contrast to the false-negative urinary screen-
ing result obtained in patient 2, patient 3 illustrates
that modest elevations of urinary catecholamine
levels can be a nonspecific finding. Patients with
metastatic melanoma in particular may have elevat-
ed urinary dopamine levels, most likely because of
increased conversion of tyrosine to the dopamine
precursor L-dopa by tyrosinase in melanoma tumor
cells. Although MIBG imaging might be consid-
ered in the evaluation of such patients, results from
MIBG imaging must be interpreted with caution in
patients with possible adrenal metastases from
tumors of neural crest origin, such as melanoma,
because these tumors may accumulate MIBG. An
appropriate treatment strategy for these patients
may include preoperative adrenergic blockade,
even if the clinical scenario suggests that the likeli-
hood of pheochromocytoma is relatively low.

Finally, patient 4 illustrates the complex man-
gement issues often faced by patients with extra-
adrenal malignancy and an adrenal mass. This
patient underwent pretreatment screening for
hormone production. After documentation of
normal hormone levels, treatment planning for
his recurrent melanoma required FNA biopsy of
his adrenal mass to determine whether distant
metastatic disease was present. These biopsy find-
ings revealed only cortical cells and were therefore
nondiagnostic; CT findings were not typical of
adrenal cortical adenoma. Therefore, surgery
was recommended. First, an adrenalectomy was
performed. When this procedure identified a sec-
donary primary tumor (ganglioneuroma) rather than
metastatic melanoma, aggressive surgical treat-
ment of the patient’s locally recurrent melanoma
was performed. This procedure consisted of wide
local excision of the melanoma site with myocuta-
neous free-flap coverage as well as intraoperative
lymphatic mapping and sentinel lymph node biop-
sy to provide surgical staging of the patient’s
regional nodal basin.

In summary, patients with extra-adrenal cancer
and an adrenal mass frequently have an adrenal
pathologic condition independent of their primary
malignancy. Despite the presence of a newly diag-
nosed malignancy or the history of a malignancy,
all patients with an adrenal mass should undergo
a standard hormone evaluation to confirm that the
mass is not a functional neoplasm. An assumption
that the adrenal mass is metastatic disease will be
wrong in up to half of such patients.

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Dr Lenert. You are correct in that the majority of patients in the current series underwent adrenalectomy before the availability of selective laparoscopic adrenal resection. Currently we would consider a laparoscopic approach for patients in whom benign histology is expected (based on tumor size and anatomic considerations) and for patients with suspected metastases to the adrenal gland with modestly sized tumors that do not show radiographic evidence for local-regional invasion.

Dr Michael McLeod (Kalamazoo, Mich). This will take you maybe just a little bit off your main theme. I agree with you that it is important to evaluate these adrenal lesions hormonally before excising them in the context of the concern about potentially missing subclinical hyperfunction or subclinical Cushing’s. This allows you to make a decision about whether you have to cover the patient with perioperative cortisol. Would you share with me what is your minimal workup for ruling out an occult hyperfunctioning cortisol-producing tumor that clinically is not apparent but may be associated with suppression of the contralateral gland? In summary, what would be your minimal workup to rule out abnormal cortisol function in these lesions?

Dr Lenert. We recommend that hormone screening for patients presenting with an isolated adrenal mass in the setting of prior or concurrent extra-adrenal cancer consist of a 24-hour urine collection for vanillylmandelic acid, metanephrines, and catecholamines, a 1-mg overnight dexamethasone suppression test, and a serum potassium level.

Dr Charles Proye (Lille, France). I think that in such cases, for diagnosis or exclusion of diagnosis of pheochromocytoma, rather than free catecholamine measurement, I would advocate measurement of urinary and plasma methoxyderivatives, which are much more sensitive tests.

Dr Janice Pasieka (Calgary, Alberta, Canada). The surgical dogma would say that bilaterality is something that we should be looking for when looking at metastatic disease. Could you tell us whether bilaterality at all predicted in these patients whether mass was metastatic or nonmetastatic?

Dr Lenert. There were 10 patients in this series who had bilateral disease. Four had bilateral adrenal metastases. The other 6 patients had benign histology: 5 had bilateral pheochromocytomas and 1 had bilateral nodular hyperplasia.