Limited Value of Adrenal Biopsy in the Evaluation of Adrenal Neoplasm

A Decade of Experience

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Objective: To determine the value of percutaneous adrenal biopsy in the evaluation of adrenal neoplasm.

Design: Retrospective review.

Setting: Tertiary referral center.

Patients: All adult patients undergoing image-guided adrenal biopsy from 1997 to 2007.

Main Outcome Measure: Biopsy sensitivity for malignancy.

Results: There were 163 biopsies performed on 154 patients. Mean (SD) age was 66 (12.5) years. Eighty-eight biopsies (53.4%) were performed in patients with a prior diagnosis of cancer. Forty-five (26.4%) were performed when imaging study results suggested previously undiagnosed cancer with a simultaneous adrenal metastasis. Thirty (20.2%) were performed for isolated adrenal incidentalomas. Rates of positive biopsy results in these 3 groups were 70.6%, 69.0%, and 16.7%, respectively. Prebiopsy evaluation for pheochromocytoma was performed in less than 5% of patients with established or suspected nonadrenal malignancies and 32% of patients with incidentalomas. In patients with isolated adrenal incidentaloma, a radiology report recommended biopsy 33% of the time for characteristics inconsistent with benign adenoma. Benign incidentalomas measured mean (SD) 4.2 (2.1) cm (range, 1.4-10.7 cm), and malignancies measured mean (SD) 9.3 (3.3) cm (range, 5.3-14 cm) (P < .05). All incidentalomas 5 cm or less (n = 18) were benign. There were 4 false-negative biopsy results: 3 adrenocortical carcinomas and 1 pheochromocytoma.

Conclusions: Biopsy is unhelpful in patients with isolated adrenal incidentaloma. Despite atypical radiographic findings, all nonfunctioning nodules 5 cm or less were benign. The negative predictive value is unacceptably low and cannot be relied on to rule out malignancy. The value of biopsy remains the diagnosis of metastatic carcinoma in patients with a nonadrenal primary malignancy, proven by the more than 70% positive rate in this group.


ADRENAL INCIDENTALOMAS are defined as adrenal neoplasms 1 cm or more in diameter identified on a radiologic examination performed for indications other than adrenal disease. The traditional definition of incidentaloma excludes patients undergoing imaging procedures as part of staging and workup for cancer, as well as those in whom the diagnosis of a symptomatic adrenal-dependent syndrome was missed because of insufficient suspicion or investigation.1,2 The incidence of incidentaloma is rising because of the increased use of cross-sectional imaging, and studies show that an adrenal incidentaloma will be identified in 1.3% to 3.4% of abdominal and chest computed tomographic examinations (CTs) performed.3 A recent review of more than 2000 incidentalomas identified nonfunctioning adenoma to be the most likely diagnosis at 82%, followed by subclinical Cushing’s syndrome (5.3%), pheochromocytoma (5.1%), adrenocortical carcinoma (4.7%), metastatic disease (2.5%), and aldosteronoma (1.0%).4

Once discovered, incidentalomas should be assessed for biochemical function and malignant potential, as it is generally agreed that all functioning and potentially malignant lesions should be removed.2,5,6 The complexities of this investigation for some lesions cannot be overstated, and they demand the expertise of multiple specialists, including surgery, endocrinology, and radiology. Unfortunately, because of the growing volume of such patients, many incidentalomas are often managed without appropriate endocrine evaluation. Some who have sub-
clinical Cushing’s syndrome or pheochromocytoma are being subjected to inappropriate and potentially dangerous adrenal biopsy, when biochemical testing would have established the diagnosis.

Some investigators have strongly advocated a role for adrenal biopsy in the workup of adrenal incidentaloma to distinguish malignant from benign cortical lesions. However, the ability of adrenal biopsy to differentiate benign cortical neoplasms from adrenocortical carcinoma remains limited at best, and in general, its accuracy cannot be relied on to safely recommend observation over surgery. In patients with a known extra-adrenal malignancy who have undergone disease-appropriate treatment, a new adrenal lesion should not be considered an incidentaloma, but instead should raise the specter of metastatic disease. Studies show that 40% to 75% of adrenal neoplasms in this patient population represent metastatic disease. Because of this high prevalence, both the accuracy and effectiveness of adrenal biopsy to firmly establish the diagnosis of metastatic cancer has been well established in these patients.

This study reviews all adrenal biopsies performed at a single institution over 10 years to determine patient selection criteria, evaluation for hormonal function, and value of biopsy in patients with incidentaloma vs those with a known or suspected extra-adrenal malignancy.

**RESULTS**

A total of 163 biopsies were performed in 154 patients. There were 95 men and 59 women. Mean (SD) age was 66 (12.5), and age did not differ among the 3 categories of patients. The mean (SD) tumor size was 3.9 (2.2) cm. In group 1, 84 patients had a prior diagnosis of nonadrenal cancer. The most common malignancies in this group were lung (44), renal cell (12), and colorectal (4). Group 2, 42 patients had imaging results that suggested the diagnosis of a nonadrenal malignancy with a synchronous adrenal metastasis. In group 3, 28 patients had an adrenal incidentaloma. The percentage of total patients in each group was 54%, 26%, and 20%, respectively. The average ages were similar across groups. Men accounted for 67% and 64% of patients in groups 1 and 2 and 43% in group 3. The mean (SD) size of all biopsied lesions was 3.9 (2.2) cm, but it differed significantly among the 3 groups. Lesions in group 1, presumed adrenal metastases, measured mean (SD) 3.3 (1.6) cm. Suspected adrenal metastases (group 2) measured mean (SD) 4.4 (2.4) cm and incidentalomas measured mean (SD) 4.6 (2.5) cm. The total number of adrenal biopsies performed per year ranged from 10 to 21. The number of incidentalomas biopsied ranged from 1 to 4 per year until 2006 but jumped to 8 in 2007.

The probability that an adrenal biopsy specimen would be positive for malignancy was 70.6% in group 1, 69.0% in group 2, and 16.7% in group 3 (Table 1). In group 1, patients with a primary lung cancer had the highest likelihood (90.7%) of a positive biopsy result, followed by patients with renal cell cancer (80.0%). The remaining patients in this group had a 33.3% likelihood of identifying adrenal metastases at the time of biopsy. In group 2, where 69% of biopsy specimens showed metastatic disease, 39 of 42 patients had imaging results suggestive of lung cancer with a synchronous adrenal metastasis.

**Table 2** details the size, indication for biopsy, biopsy result, biochemical screen, and surgical pathology result for the 30 biopsies performed on incidentalomas. In group 3 incidentalomas, 3 biopsy specimens (10%) were interpreted by cytopathology to be adrenocortical cancer. Additional malignancies were identified by biopsy in 2 patients, 1 lymphoma and 1 sarcoma. Two of the biopsy specimens revealed pheochromocytoma, 1 in a patient whose prior biochemical testing predicted this

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**Table 1. Probability of Biopsy Results Being Positive for Malignancy**

<table>
<thead>
<tr>
<th>Patient’s Prebiopsy Malignancy Status</th>
<th>Site of Primary Malignancy</th>
<th>No. (%) of Biopsy Results Positive for Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established nonadrenal cancer</td>
<td>Lung</td>
<td>43 (90.7)</td>
</tr>
<tr>
<td></td>
<td>Renal cell</td>
<td>15 (80.0)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>27 (33.3)</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>85 (70.6)</td>
</tr>
<tr>
<td>Suspected nonadrenal cancer</td>
<td>Lung suspected</td>
<td>39 (69.2)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>3 (66.6)</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>42 (68.0)</td>
</tr>
<tr>
<td>Incidentaloma</td>
<td></td>
<td>30 (16.7)</td>
</tr>
</tbody>
</table>

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**METHODS**

After obtaining appropriate institutional review board approval, the pathology database at Rhode Island Hospital was queried for the word “adrenal,” using a natural language search, for the period from October 1997 to October 2007. The results were reviewed to select only patients who had undergone percutaneous image-guided adrenal biopsy. These biopsies included either fine-needle aspiration for cytology or core needle biopsy for histopathology; however, they are both referred to as “biopsy” for the purposes of this study. These patients’ computerized records and hospital medical records were retrospectively reviewed. Patients were placed into 1 of 3 biopsy categories: (1) patients with an established nonadrenal malignancy, (2) patients without a cancer diagnosis but imaging suggestive of a nonadrenal primary malignancy with a simultaneous adrenal metastasis, and (3) patients with adrenal lesions discovered on imaging performed for unrelated reasons (adrenal incidentaloma). The maximum diameter of the adrenal lesion was obtained from the radiology report. The pathology results from the percutaneous image-guided biopsy were categorized as (1) positive for metastatic disease, (2) benign (cortical neoplasm without malignant features), (3) adrenocortical cancer, (4) other (ie, lymphoma, sarcoma, ganglioneuroma), or (5) nondiagnostic. The accuracy of each biopsy was established for the 3 categories of patients based on long-term clinical follow-up documented in hospital and clinic computerized records and/or surgical pathology in the patients who underwent adrenalectomy. Records for patients who were not operated on were examined from the time of biopsy through 2006 for all documentation regarding the status of their adrenal tumors. Statistical analysis was performed using χ² and t tests.
diagnosis. The other patient was not screened for catecholamine excess. Three benign nonadrenal tumors were biopsied: a ganglioneuroma, a benign spindle cell tumor, and a nerve sheath tumor. There was also 1 myelolipoma. Sixty-three percent (19 of 30) of the biopsy specimens in group 3 were interpreted as either benign cortical tissue (17) or a nondiagnostic specimen (2). Three of these 19 biopsy specimens were false negatives, 1 confirmed at the time of operation and 2 based on clinical progression of disease. Six of the total 28 patients with incidentaloma in group 3 underwent adrenalectomy, and their final surgical pathology results did confirm the prior biopsy diagnoses: 2 pheochromocytomas, 1 adrenocortical carcinoma, 1 cortical adenoma, 1 macronodular hyperplasia, and 1 sarcoma.

In all 3 groups, adrenal tumor size was a significant predictor of malignancy. In group 1, mean (SD) size was 2.4 (1.2) cm for benign lesions and 3.6 (1.6) cm for malignant lesions (P = .02). In group 2, benign lesions were mean (SD) 2.6 (0.6) cm and malignant were 5.2 (2.5) cm (P = .003), and in group 3, benign lesions measured mean (SD) 4.2 (2.1) cm and malignant lesions were 9.3 (3.3) cm (P < .001).

In the 30 biopsies performed for incidentaloma (group 3), there were 13 lesions less than 4 cm, 9 lesions 4 to 6 cm, and 8 lesions more than 6 cm. All lesions less than 5 cm in diameter (18 of 30) had a nonmalignant pathology report (Figure). However, one of these patient’s lesions was discovered on follow-up CT to have doubled in size from 3.5 cm to 7 cm. A second biopsy was per-
malignancy have a high likelihood (70%) of harboring the 84 patients in group 1 with a known extra-adrenal lesion. It is clear that adrenal lesions developing in patients like this require careful evaluation. At our large tertiary care medical center, it was observed that 39 adrenal biopsies were performed on patients who ultimately were shown to have adrenocortical carcinoma were interpreted as such.

Thirty-three percent of the patients with incidentaloma (10 of 30) had a biopsy recommended within the text of the radiology report, and none of those 10 patients had a malignant tumor. Nine were for lesions 4.0 cm or less in diameter. Indications included “atypical adenoma,” “enlarging lesion,” and “rule out malignancy.” Of 9 patients whose radiology reports contained references to “lesion characteristics atypical for a benign adenoma,” only 1 turned out to have adrenocortical cancer.

Prebiopsy evaluation for pheochromocytoma was performed in less than 5% of patients with established or suspected nonadrenal primary malignancies and in 32.1% of patients with incidentaloma. Therefore, 19 of the 28 patients with adrenal incidentalomas had an unclear biochemical status at the time of biopsy. Of the 9 patients who were screened for pheochromocytoma prebiopsy, 2 actually had positive biochemical testing results. At surgery, 1 was confirmed to have a pheochromocytoma and the other had a cortical adenoma. Fortunately, neither these nor any others were reported to have hypertensive crises. Overall, there were few reported complications of adrenal biopsy, the most significant being an adrenal hemorrhage causing pain that resolved without intervention. There were no reports of hemodynamic instability.

In this 10-year review of all image-guided percutaneous adrenal biopsies at a large tertiary care medical center, it is clear that adrenal lesions developing in patients like the 84 patients in group 1 with a known extra-adrenal malignancy have a high likelihood (70%) of harboring metastatic cancer. A second group of patients, with a similar 69% yield for metastatic cancer, were those 42 patients in group 2, who were not previously known to have cancer but had imaging study results that suggested a non-adrenal primary cancer with a simultaneous adrenal metastasis. In group 1, making the diagnosis of metastatic cancer in the adrenal lesion was important both prognostically and in directing further therapy. In group 2 patients, percutaneous adrenal biopsy offered a relatively low-risk means of establishing a cancer diagnosis and avoided the potential hazards of biopsying a primary lung lesion.

These results compare favorably with previously published studies. In 1994, Welch et al11 published the Mayo Clinic experience with 277 adrenal biopsies, all but 5 of which were performed in patients with extra-adrenal cancer and presumed metastatic disease. More than half had a primary pulmonary malignancy, and the probability of identifying metastatic disease was 53.1%. Sensitivity and specificity were 81% and 99%, respectively. In 2002, Harisinghani et al11 reviewed 225 patients with extra-adrenal cancer who subsequently had image-guided biopsy of indeterminate adrenal lesions. Only 41 (18%) had biopsy specimens that were negative for metastatic disease, and long-term follow-up confirmed the high specificity of a benign biopsy. Data compiled by the National Institutes of Health revealed that 75% of adrenal lesions found in patients with a known extra-adrenal malignancy are metastases.7 Certainly this high pretest probability improves the biopsy accuracy in this population. Recent advances in the use of chemical shift magnetic resonance imaging to differentiate adrenal adenomas from metastases may help decrease the need for adrenal biopsy to establish the diagnosis of metastatic cancer in such patients.14

In sharp contrast to the nearly 70% biopsy specimen positivity rate in groups 1 and 2 in this review, the likelihood of identifying a primary adrenal malignancy in group 3 was only 30% (3 of 30). Two of these 3 patients were deemed inoperable, and the third underwent open adrenalectomy. Management was not impacted by the biopsy results, as the third patient met standard criteria for adrenalectomy for a lesion that had doubled in size from 3.5 to 7 cm over several weeks.3 In fact, a CT performed 8 months previously had shown a “normal” adrenal gland, and the adrenalectomy should have been scheduled on identification of the new 3.5-cm adrenal mass. Instead, the 3.5-cm mass was inappropriately biopsied and was interpreted to be benign. When a follow-up CT showed the mass to have doubled in size, a second unnecessary biopsy was performed, again increasing the risk for seeding the biopsy tract with malignant cells.15

Numerous reviews have substantiated the fact that needle biopsy specimens are inadequate for distinguishing benign from malignant adrenocortical tissue; therefore, percutaneous biopsy of adrenal incidentaloma should not be performed.5,9,16 However, in this study alone, 30 biopsies were performed on adrenal incidentalomas, at least 11 of which were recommended within the text of the radiology report. Not only does the pathology literature not support this practice, but there is also an abundance of evidence in the radiology literature to discour-
age this type of recommendation. While certain CT characteristics such as heterogeneity and Hounsfield unit density greater than 18 are more commonly seen with adrenocortical cancer, their positive predictive value remains less than 50% for adrenal incidentalomas. Two recent studies by Song et al\textsuperscript{17,18} demonstrated a 0% rate of malignancy in 973 cancer-free patients who presented with adrenal incidentaloma, including all those with a Hounsfield unit density greater than 10.

Initial studies of adrenal lesions showed a strong positive correlation between lesion size and probability of malignancy.\textsuperscript{19} Herrera et al\textsuperscript{20} demonstrated a benign to malignant correlation between lesion size and probability of malignancy in 973 cancer-free patients who presented with adrenal incidentaloma, including all those with a Hounsfield unit density greater than 10.

Our study findings for patients with incidentaloma demonstrate that tumor size remains the strongest predictor of malignancy.\textsuperscript{10} No lesion less than 5 cm had biopsy results positive for adrenocortical carcinoma; however, there was a false-negative biopsy result of a 3.5-cm lesion as described earlier. Benign lesions in group 3 patients averaged 4.2 cm, in stark contrast to the 9.3-cm average diameter of malignancies.

Three other patients were placed at potential risk for hemodynamic instability when undergoing biopsy, the 2 who eventually had pheochromocytoma resected and a third with prebiopsy laboratory values consistent with pheochromocytoma. All patients considered for adrenal biopsy should undergo an evaluation for excess catecholamine production to prevent adverse outcomes.\textsuperscript{21} Any indication that the tumor is hormone-secretory, be it cortisol, catecholamine, aldosterone, or sex steroids, becomes an automatic indication for surgery and eliminates any indication for biopsy.\textsuperscript{6} Screening for functionality was performed in only a third of patients with incidentaloma and in a small minority of patients in groups 1 and 2. As this and other series demonstrate, the frequency of pheochromocytoma among patients presenting with incidentaloma ranges from 5\% to 10\%.\textsuperscript{5,20} These not inconsequential numbers mandate biochemical screening, which can be accomplished expeditiously by testing serum metanephrine levels. If elevated, the patient should undergo formal evaluation by an endocrinologist or endocrine surgeon prior to any further management decisions. Similarly, 5\% or more will test positive for cortisol hypersecretion, and evaluation for such with an overnight dexamethasone suppression test is necessary. Very few patients in this study were screened for Cushing’s syndrome. Unfortunately, it is clear that these deficiencies in the evaluation of adrenal incidentalomas are not institution specific. A recent review of patients from a major center for endocrine surgery referral illustrates a similar pattern of inappropriate biopsy and inadequate hormonal evaluation.\textsuperscript{27}

Despite the inability of needle biopsy to accurately differentiate benign from malignant adrenal neoplasms, physicians continue to recommend this procedure in some patients with adrenal incidentaloma. This series confirms that lesions less than 4 cm have a very low risk for being carcinoma, even when atypical radiographic findings are present. Therefore, the vast majority of these should be assessed for hormonal production, and if nonfunctioning, they should be observed with annual imaging and assessment for hormone production. If radiographic characteristics are especially concerning, more frequent imaging is reasonable; however, resection may be warranted. Currently, biopsy should only be considered for making the diagnosis of metastatic disease in patients with known or suspected nonadrenal cancer.

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REFERENCES