Transcutaneous biopsy of adrenocortical carcinoma is rarely helpful in diagnosis, potentially harmful, but does not affect patient outcome

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Abstract

Context: Adrenocortical carcinoma (ACC) is a rare malignancy with high recurrence and mortality rates. The utility, sensitivity, and effect on patient outcome of transcutaneous adrenal biopsy (TAB) for single, large, adrenal masses are unclear.

Objective: This study evaluated the utility, diagnostic sensitivity, and effect on patient outcome of TAB in patients with ACC.

Design and setting: We conducted a retrospective review of the electronic medical records of all ACC patients who were evaluated at the University of Michigan Health System from 1991 to 2011. We evaluated the sensitivity of TAB for tumors with the final pathological diagnosis of ACC. We compared the characteristics and survival of patients with stage I–III disease who underwent TAB with those who did not undergo TAB.

Results: A total of 75 ACC patients with TAB were identified. Complications occurred in at least 11% of patients and were mainly associated with bleeding. The maximum sensitivity of the procedure in diagnosing ACC was 70%. For stage I–III patients, baseline characteristics, stage at diagnosis, and adjuvant treatment with mitotane or radiation were not significantly different between the TAB (n = 36) and the non-TAB (n = 254) groups. There was no significant difference in recurrence-free (P = 0.7) or overall survival (P = 0.7) between patients who underwent TAB and those who did not.

Conclusions: TAB of single, large, adrenal masses is usually unnecessary, exposes patients to risk, but does not affect recurrence-free or overall survival.

Introduction

Adrenal tumors are common and incidentally discovered in 1–2% of the population on cross-sectional imaging (1). Only a very small percentage of these are adrenocortical carcinomas (ACCs). An initial study reported a prevalence of ACC among incidentally found adrenal masses of ~4% (2). A more recent review estimates the prevalence to be 1.4% (3). Nonetheless, ACC remains a clinical concern due to its dismal prognosis (4, 5). Symptoms are caused by either hormone excess or mass effect of the tumor. Approximately 60% of patients present with evidence of adrenal steroid hormone excess. Approximately 30–50% of ACCs are considered as ‘non-functional’ because they do not secrete hormones or they secrete mainly steroid hormone precursors. Tumor size is the most significant factor distinguishing benign from malignant adrenal masses. ACC has been identified in 2% of tumors smaller than 4 cm, 6% of tumors of 4.1–6 cm, and 25% of tumors larger than 6 cm (6, 7).
There is a long-standing debate over the use of transcutaneous adrenal biopsy (TAB) in the setting of single, large, adrenal masses. Currently, the only widely accepted indication for an adrenal biopsy is a suspected metastasis from a known primary tumor in a patient for whom the result would change the therapeutic approach, e.g. surgery for limited disease vs chemotherapy for metastatic disease (6, 8). TAB should only be conducted after biochemical exclusion of a pheochromocytoma because of potentially fatal catecholamine surge during TAB (6, 9). Previous studies have shown that TAB is associated with a significant risk of morbidity and mortality (10, 11, 12). Yet some patients with newly diagnosed single, large, adrenal masses without another primary cancer continue to undergo TABs.

It remains unclear whether this practice affects ACC patient outcome. The nature of TAB violates a fundamental principle of surgery on ACC, where en bloc resection is performed to avoid any violation of the tumor capsule (13). Indeed, there are cases in the literature reporting needle-track seeding associated with TAB of ACC and adrenal metastases (14, 15). In light of this, an understanding of the effect of TAB on patient outcome is important because it may shed light on whether TAB should be considered as a risk factor when deciding on adjuvant treatment after complete surgical excision. The two main adjuvant therapies employed are radiation therapy and pharmacotherapy with mitotane. Although most studies regarding adjuvant therapy are small and retrospective in nature, there is good evidence that radiation therapy prevents local recurrence and mitotane prolongs recurrence-free survival (4, 16, 17, 18, 19).

The aim of our study was to evaluate the utility, sensitivity, and, most importantly, effect on patient outcome of TAB in a retrospective study of patients with the diagnosis of ACC and biopsy of an adrenal mass seen at the University of Michigan.

**Subjects and methods**

**Patient identification and review of medical records**

We used ICD-9 billing codes to query the University of Michigan Medical Center electronic medical records system to identify all patients who were evaluated for ACC at our institution over a 20-year period (1991–2011). Patient electronic medical records were reviewed individually and using a natural language processing algorithm for electronic medical records (EMERSE) (20). All cases had a confirmed diagnosis of ACC by pathological reports or in a small number of cases by adrenal hormone excess and a metastasized tumor with a large adrenal primary tumor. Data collected included: demographics, staging, hormone production, reason for biopsy, number of biopsies, institution performing the biopsy, complications associated with biopsy, pathology, adjuvant therapy, follow-up surgery, recurrence-free survival, and overall survival. All patients were staged based on the ENSAT staging system (21). For survival data, in addition to hospital medical records, we reviewed the Social Security Death Index.

**Categories of pathological diagnosis**

Pathological diagnoses of biopsy specimens were divided into five groups – ‘ACC’, ‘benign’, ‘malignant’, ‘indeterminate’, and ‘nondiagnostic’. ‘ACC’ group signifies the pathological diagnosis of ACC. ‘Benign’ specimens include tissue interpreted as adrenal cortical adenoma, specimens containing normal or benign-appearing adrenal cortical cells, and specimens suggesting a cyst or myelolipoma. ‘Malignant’ group consists of specimens containing malignant cells not otherwise specified. ‘Indeterminate’ group consists of specimens interpreted as tissue of adrenal origin that could not be identified as benign or malignant. ‘Nondiagnostic’ group includes all other specimens deemed to be insufficient for a pathological diagnosis.

**Statistical analysis**

The endpoints selected for analysis were recurrence-free survival and overall survival. Recurrence-free survival was defined as the time from the date of surgical resection to the date of the earliest clinical evidence of recurrence of disease. Overall survival was defined as the time from the date of diagnosis to the date of death. In cases where patients did not reach the endpoint of survival times, they were censored according to the last follow-up date. Survival curves were plotted using the Kaplan–Meier method. Patients with a follow-up period less than the first event in a group were not included in analysis (<5%). Differences between subgroups were tested using the log-rank test. Survival was also analyzed using the univariable and multivariable Cox proportional hazards model, adjusting for age at diagnosis, sex, cortisol secretion, and adjuvant therapies. Multivariable analysis was then performed to look for independent predictors of survival. The P values are reported and for interpretation a P value of <0.05 was considered significant. Demographic and tumor characteristics were compared using the χ² test or t-test for non-parametric and parametric parameters respectively.
All data were analyzed using the Statistical Package for Social Sciences software, version 19.0 (SPSS, Inc.).

Human subjects research approval
All studies were approved by the University of Michigan Institutional Review Board (IRB). Initial data collection was carried out under an IRB application aiming to determine risk factors for ACC (HUM00045835). All participants of the study are part of the Michigan Endocrine Oncology Repository (HUM00024461).

Results
Characteristics of patients with adrenal biopsy
A total of 81 TABs were performed on 75 patients. Out of 75 patients, 69 had a single biopsy and six had two. There were 35 males (47%) and 40 females (53%). The median age at diagnosis was 51.9 years. The stage distribution was as follows: stage I, 3 (4%); stage II, 22 (29%); stage III, 11 (15%); and stage IV, 39 (52%). A total of 34 patients (45%) had functional tumors based on clinical evaluation, and 29 patients (39%) had cortisol-secreting tumors. All patients with stage I-III disease had a follow-up adrenalectomy, whereas 16 stage IV patients (41%) underwent a follow-up adrenalectomy. The demographic and clinical characteristics of these patients are summarized in Table 1.

Complications of adrenal tumor biopsies
Of the total number of patients, eight (11%) suffered TAB-related complications. However, documentation was not complete on all patients. Most complications were associated with bleeding during or after the procedure. One patient presented to the emergency department complaining of severe pain at the TAB site. One patient had a hemorrhage within the biopsied mass and became anemic. Four patients developed hematomas secondary to organ puncture: one in the lung, one in the left kidney, and two in the liver. In one case, puncture of the liver was associated with needle-track metastasis, which was diagnosed 2 years later. The patient underwent repeat surgery and is alive without evidence of disease. This patient was part of a previous study at our institution (14). One patient suffered a saddle pulmonary embolism shortly after undergoing biopsy and could not be anticoagulated due to the risk of bleeding from biopsy site. Subsequently, this patient died.

Pathology diagnosis of adrenal tumor biopsies
The histopathological findings for 75 biopsies are listed in Table 2. Of them, 66 (88%) biopsies were performed at other institutions and nine (14%) were nondiagnostic, not revealing a distinct pathological diagnosis. Of the biopsies where an adequate specimen was collected, 28 (42%) were read as ACC, six (9%) as malignant, six (9%) as benign, and 17 (26%) as indeterminate, meaning that they were deemed to be of adrenal origin, but no diagnosis regarding biological behavior could be made. Of the total 75 biopsies, 50 (67%) were obtained at or available for review at the University of Michigan Pathology Department. The final diagnoses for biopsies read at the University of Michigan, including specimens from referred patients and specimens obtained at our institution, were as follows: ACC, 35 (70%); malignant, seven (14%); benign, one (2%); indeterminate, one (2%); and nondiagnostic, six (12%).

| Table 2 | Pathological diagnosis for biopsies (read at other institutions or University of Michigan). |
|---------|------------------------------------------------------------------------------------------|
|         | Other (66) | University of Michigan (50) |
|         | n   | %  | n   | %  |
| ACC     | 28  | 42 | 35  | 70 |
| Malignant | 6   | 9  | 7   | 14 |
| Benign  | 6   | 9  | 1   | 2  |
| Indeterminate | 17 | 26 | 1   | 2  |
| Nondiagnostic | 9  | 14 | 6   | 12 |

Table 1 Characteristics of all patients with adrenal tumor biopsies.

| Characteristics      | n = 75 | %  |
|----------------------|--------|----|
| Gender               |        |    |
| Male                 | 35     | 47 |
| Female               | 40     | 53 |
| Age at diagnosis     |        |    |
| Median (years)       | 51.9   |    |
| Range (years)        | 17.1–77.3 |    |
| Race                 |        |    |
| Caucasian            | 63     | 84 |
| African American     | 6      | 8  |
| Asian                | 2      | 3  |
| Unknown              | 4      | 5  |
| Stage at diagnosis   |        |    |
| I                    | 3      | 4  |
| II                   | 22     | 29 |
| III                  | 11     | 15 |
| IV                   | 39     | 52 |
| Hormone production   |        |    |
| Any                  | 34     | 45 |
| Cortisol             | 29     | 39 |
| Follow-up adrenalectomy | 56 | 75 |
In order to evaluate the effect of TAB on patient outcome, we analyzed all patients with non-metastasized ACC separately, excluding all stage IV patients. We compared patients with stage I–III disease who underwent TAB (36 patients) with patients with stage I–III disease who did not undergo TAB (242 patients). Patient characteristics are summarized in Table 3. The only significant differences were observed regarding hormone production. In the TAB group, ten patients (28%) had functional tumors, of whom nine secreted cortisol (25%), as opposed to 150 patients (59%) with functional tumors, of whom 108 patients (43%) had cortisol-secreting tumors.

There was no significant difference in overall survival between patients who underwent TAB as part of their diagnostic work-up at any institution and those who did not (Kaplan–Meier, log-rank P=0.7; Fig. 1A). The median recurrence-free survival time for those who underwent TAB was 14.9 months (S.E.M., 2.2), compared with 15.0 months (S.E.M., 1.7) for patients who did not undergo TAB (Kaplan–Meier, log-rank P=0.6; Fig. 1B). In addition, in univariable and multivariable analysis, adjusting for age at diagnosis, cortisol secretion, tumor stage, and adjuvant therapy, a history of a TAB did not show significant differences regarding overall survival or recurrence-free survival (Table 4).

| Characteristics       | Biopsy n=36 | No biopsy n=254 | P   |
|-----------------------|-------------|-----------------|-----|
| Gender                |             |                 |     |
| Male                  | 13          | 94              | 37  |
| Female                | 23          | 160             | 63  |
| Age at diagnosis      |             |                 |     |
| Median (years)        | 53          | 46.4            |     |
| Range (years)         | 18.9–74.6   | 16–83.0         |     |
| Race                  |             |                 |     |
| Caucasian             | 31          | 223             | 88  |
| African American      | 2           | 6               | 4   |
| Asian                 | 0           | 7               | 3   |
| Unknown               | 3           | 15              | 6   |
| Stage at diagnosis    |             |                 |     |
| I                     | 3           | 8               | 4   |
| II                    | 22          | 147             | 58  |
| III                   | 11          | 98              | 39  |
| Hormone production    |             |                 |     |
| Any                   | 10          | 150             | 59  |
| Cortisol              | 9           | 108             | 43  |
| Adjuvant mitotane     |             |                 |     |
| Yes                   | 10          | 95              | 37  |
| No                    | 23          | 136             | 54  |
| Unknown               | 1           | 3               | 1   |
| Recommended\*         |             |                 |     |
| Yes                   | 7           | 52              | 21  |
| No                    | 27          | 189             | 74  |
| Unknown               | 2           | 6               | 1   |

\*Treatment recommended but not documented in patient’s chart.

Outcome of patients with stage I–III ACC and adrenal tumor biopsy

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Figure 1
Kaplan–Meier plots for overall survival (A) and recurrence-free survival (B).
of TAB samples obtained via an ex vivo approach. The sensitivity in that study was 76.2%. This is in accordance with the maximum sensitivity of 79.5% for the pathological diagnosis of ACC in our study, when taking into account only samples reviewed at the University of Michigan and disregarding inadequate samples. It is worthwhile to point out that this number clearly indicates the ‘best-case scenario’. There is a clear limitation of a retrospective study conducted at a referral center, where biopsy and final specimen are often reviewed at the same time. The sensitivity of TAB is significantly lower in clinical practice taking into account that the review of samples was conducted after the final surgical or biochemical diagnosis of ACC had been established. We found that the sensitivity of TAB, which is often incomplete in ACC patients (43). Recent studies using urine steroid metabolite analysis may even further increase the sensitivity and specificity of non-invasive biochemical diagnostics (44). Furthermore, TAB in the setting of adrenal tumors with suspicion for malignancy due to size or imaging criteria is seldom helpful as these lesions are almost invariably treated surgically. The only

| Adjustment | Overall survival | Recurrence-free survival |
|------------|------------------|-------------------------|
|            | HR               | P           | HR               | P           |
| Univariable| 1.1 (0.7–1.8)    | 0.6         | 0.9 (0.6–1.4)    | 0.7         |
| Age, sex, cortisol, stage | 1.2 (0.8–2.0) | 0.4 | 1.1 (0.7–1.7) | 0.7 |
| + mitotane | 1.2 (0.7–1.9) | 0.5 | 1.0 (0.7–1.7) | 0.7 |
| + XRT      | 1.2 (0.8–1.9) | 0.4 | 1.1 (0.7–1.7) | 0.7 |
| + mitotane/XRT | 1.2 (0.7–1.9) | 0.5 | 1.1 (0.7–1.7) | 0.7 |

**Discussion**

In summary, our data indicate that TAB has a low diagnostic sensitivity, is often unnecessary, exposes the patients to unnecessary risk, but does not change overall or recurrence-free survival.

There are serious risks associated with TAB. Multiple studies have investigated the complications stemming from this procedure (14, 15, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37). Complication rates ranged from 0 to 12%. Most of these studies involved small numbers of patients, making it difficult to assess the true complication rate. However, there are three studies that examined larger numbers of patients. Welch et al. (36) reviewed the results of 277 TABs and reported a rate of major complications of 2.8%. The other two studies, with 83 and 97 patients, included all complications and described rates of 8.4 and 9% respectively (14, 33). These rates are slightly lower, but comparable with our results, which showed a complication rate of at most 11%.

These rates are significant given the severity of the complications involved. The most frequently reported complications associated with TAB are hemorrhage (23, 31, 33, 35), pneumothorax (24, 28, 33), pancreatitis (27), and isolated reports of adrenal abscess (29), bacteremia (23), and needle-track metastasis (15). We identified one case of needle-track metastasis, which has previously been reported (15). This occurred in a case where the adrenal was biopsied via an unusual transhepatic approach. While we were unable to review follow-up imaging for needle-track seeding in all patients, the overall risk of needle-track metastasis seems to be low, but present. Moreover, in our study, TAB indirectly led to the death of one patient.

A feasibility study demonstrated that a high degree of accuracy is possible in the pathological evaluation of TAB samples obtained via an ex vivo approach (38).
very rare exception to this rule is when an adrenal tumor is clinically strongly suspected to be a non-adrenocortical tumor that requires a therapy other than surgery, such as an adrenal lymphoma. In these cases, biopsy and specimen staining for adrenocortical-specific markers, such as SF1 or inhibin A, might be particularly helpful (45).

However, TAB does not change recurrence-free or overall survival. This is particularly important when assessing a patient’s risk of recurrence and deciding on adjuvant treatment. In this study, no significant differences were found in overall or recurrence-free survival between patient groups with stage I–III disease with and without a history of biopsy. The use of adjuvant treatments in both groups was not significantly different nor were the survival parameters even after adjusting for the main risk factors and post-surgical therapies. Therefore, TAB does not significantly impact survival and should not be a major consideration when planning adjuvant therapies, such as mitotane or radiation.

Overall, we conclude that TAB may be useful in the setting of a metastasis from an unknown primary tumor for diagnosing ACC with sufficient sensitivity. However, in cases of single, large, adrenal masses, TAB should be avoided. TAB might be regarded as relatively safe if used in the right setting, but it still poses an unnecessary risk to the patient considering its paltry diagnostic gain and irrelevance in making future therapeutic decisions. Thorough biochemical work-up can identify the majority of these tumors as adrenocortical in origin. Moreover, surgery is the mainstay of therapy for any tumor with suspicion for malignancy confined to the adrenal gland. However, TAB does not significantly affect patient outcome and the history of a TAB should not majorly affect adjuvant therapeutic decisions.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
T Else was sponsored by the National Institutes of Health (grant number T32-DK007245).

Author contribution statement
A Williams conducted data gathering, data analysis, interpretation, and manuscript writing and participated in study design. G D Hammer participated in study design, result interpretation, and manuscript writing. T Else participated in data gathering, and conducted data analysis, result interpretation, manuscript writing, and study design.

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