Endoscopic Ultrasound of the Adrenals in Primary Aldosteronism

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Abstract

Background/Aim: It is a major challenge in the diagnosis of primary aldosteronism to identify patients with aldosterone producing adrenal adenoma which may benefit from surgical treatment (adrenalectomy/adenomectomy). Adrenal adenomas may be visualized by endoscopic ultrasound. However, a possible role and relevance of endoscopic ultrasound in the diagnostic process of primary aldosteronism has not been investigated systematically yet.

Methods: We included 112 patients (48 females, 64 males, 54 ± 12 years) between 1997 to 2019 with positive screening test (aldosterone/renin-ratio) and arterial hypertension undergoing endoscopic ultrasound imaging of the adrenals into this study. Final diagnosis of aldosterone producing adenoma based on confirmation tests, imaging, selective blood sampling, histopathology and postsurgical improvement.

Results: In 44 patients, diagnosis of aldosterone producing adrenal adenoma could finally be defined. Endoscopic ultrasound detected and localized 39/44 (89%) correctly (tumor diameter 15.6 ± 5.4 (5.7 to 26.0) mm). Computed tomography (n=26) localized correctly in 81%, magnetic resonance imaging (n=25) in 76%, and conventional sonography (n=19) in 32%. Endoscopic ultrasound was the only method localizing correctly in 8 cases (18%).

Conclusion: Endoscopic ultrasound is a reliable and highly sensitive diagnostic tool in suspected aldosterone producing adrenal adenoma with a high negative predictive value. It can be useful to define patients which benefit from surgical treatment.

Keywords: Adenoma; Aldosterone; Conn’s disease; Endoscopic ultrasound; Imaging

Introduction

It is a major challenge in the diagnostic work-up of Primary Aldosteronism (PA) to distinguish patients with Aldosterone Producing Adrenal adenoma (APA) from those with Idiopathic Hyperaldosteronism (IHA) [1,2]. APA patients may benefit from surgical treatment, i.e. adenomectomy [3]. Besides selective Adrenal Vein Sampling (AVS) [4,5], also a diagnostic approach based on the analysis of adrenal morphology using Computed Tomography (CT) has been shown to achieve appropriate therapeutic decisions [6].

Endoscopic Ultrasound (EUS) enables high resolution imaging of even small adrenal adenomas in cases where CT and Magnetic Resonance Imaging (MRI) remain negative [7-10].

We aimed to study systematically a possible role of EUS in the diagnostic work-up of APA.

Materials and Methods

A total of 112 patients (48 (43%) females, 64 (57%) males, 54 ± 12 years) presenting consecutively for EUS imaging of the adrenals between 1997 and 2019 were included into a retrospective diagnostic study. They fulfilled the following both inclusion criteria:
1. Positive screening/case finding test for PA, i.e. positive Aldosterone/Renin-ratio (A/R) \[11\] and high serum/plasma aldosterone concentration as suggested by Young \[12\]; or in times when the A/R had not been established, an elevated aldosterone level with renin concentration in the low normal range was accepted (Supplemental Material 1).

2. Diagnosis of arterial hypertension, i.e. documented systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg \[13\], or prevalent antihypertensive medication before EUS imaging.

In the further diagnostic workup, confirmation tests (Saline Infusion Test (SIT), Captopril Challenge Test (CCT), aldosterone and aldosterone metabolites in 24 h urine sampling) and localization tests (EUS, CT, MRI, Conventional Sonography (CS), AVS, Posture Stimulation Test (PST) were performed) (Supplemental Material 2).

EUS was carried out according to a standard procedure described previously \[10\] by one single investigator (ph.k).

APAs were defined based on a reassessment of the endocrine parameters, histopathology and criteria of therapeutic success following suggestions by Vorselaars et al. \[21\] (Supplemental Material 3).

**Major study endpoint**

The results of EUS (and the other localization tests) for the patients with APA have been analyzed in terms of correct identification and localization in a descriptive manner.

**Minor study endpoints**

a) The applicability of typical morphological criteria for adrenal adenomas (non-functioning and subclinical Cushing’s syndrome) \[22\] on APA was studied.

b) Further patients that underwent surgery for suspected APA, but in our post hoc analysis did not fulfill the APA criteria, were analyzed in a descriptive manner.

**Ethics**

Our local ethical committee certified on July 1st, 2016 that this retrospective scientific study of anonymized patient data obtained in clinical routine diagnostic procedures does not require formal evaluation by the ethical committee.

**Results**

Out of the total cohort of 112 patients included into the study, 44 patients were defined as APA.

**Major study endpoint**

EUS detected and localized 39/44 (89%) of APAs correctly. Their largest diameter determined by EUS was 15.6 ± 5.4 mm (range 5.7 mm to 23.0 mm), or prevalent antihypertensive medication before EUS imaging.

In four cases bilateral adenomas were detected by EUS. In one case, EUS was the only imaging performed; AVS documented a slight thickening of the organ considered unspecific (Supplemental Material 4).

In our study, EUS was the only method localizing the APA correctly in 8 cases (18%). Their largest diameter determined by EUS was 14.9 ± 4.6 mm (range 8.0 mm to 23.0 mm). Here, CT was performed in three, MRI in four and CS in two cases and did not reveal complications were observed.

**Table 1:** Lateralization of 44 aldosterone producing adenomas.

<table>
<thead>
<tr>
<th>Lateralization</th>
<th>Absolute</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left</td>
<td>27</td>
<td>61</td>
</tr>
<tr>
<td>Right</td>
<td>17</td>
<td>39</td>
</tr>
</tbody>
</table>

**Table 2:** Correct localization of aldosterone producing adenomas in 44 patients as obtained by endoscopic ultrasound and other localization methods.

<table>
<thead>
<tr>
<th>Correct/Total%</th>
<th>Annotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUS 39/44 89%</td>
<td>In four cases bilateral adenomas detected</td>
</tr>
<tr>
<td>CT 21/26 81%</td>
<td></td>
</tr>
<tr>
<td>MRI 19/25 76%</td>
<td>+1 False localized in the contralateral adrenal</td>
</tr>
<tr>
<td>CS 6/19 32%</td>
<td>+2 False localized in the contralateral adrenal</td>
</tr>
<tr>
<td>AVS 5/14 36%</td>
<td>selectivity index &lt;2 in 9 cases</td>
</tr>
<tr>
<td>PST 5/21 24%</td>
<td>Referring to correct differentiation APA vs. IHA</td>
</tr>
</tbody>
</table>

APA: Aldosterone Secreting Adenoma; EUS: Endoscopic Ultrasound; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; CS: Conventional Sonography; AVS: Selective Adrenal Venous Sampling; PST: Posture Stimulation Test

**Table 3:** Morphological characteristics of 44 aldosterone producing adenomas by endoscopic ultrasound.

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Number/total* %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoechoic echogenicity</td>
<td>36/44 82%</td>
</tr>
<tr>
<td>Hyperechoic capsular tumor margin</td>
<td>41/44 93%</td>
</tr>
<tr>
<td>Termination of medullary echo at tumor margin</td>
<td>38/39 97%</td>
</tr>
<tr>
<td>Largest diameter ≤2 cm</td>
<td>34/44 77%</td>
</tr>
<tr>
<td>No/only discrete hyperperfusion (duplex)</td>
<td>32/34 94%</td>
</tr>
</tbody>
</table>

*Referring to the number of tumors where this parameter has been assessed/ documented

**Minor study endpoints**

(a) For this analysis, the 39 EUS findings of adenomas as well as the 5 findings considered unspecific, post hoc classified as APA, were analyzed. Typical morphological criteria by EUS of APA were:

- hypoechoic echogenicity
- largely homogenous echo structure
- capsular tumor margin
- termination of medullary echo at tumor margin
- largest diameter ≤2 cm
- missing or just slight hyperperfusion by duplex ultrasound

Table 3, Figure 1 and 2. Of the APAs analyzed in this study, 91% (n=40) fulfilled at least 5, 7% (n=3) at least four of these criteria. APAs tended to be more homogenous hypoechoic and smaller compared to non-functioning adrenal adenomas and those causing subclinical Cushing’s syndrome \[22\].

(b) Another 6 patients underwent surgery for confirmed PA and preoperatively diagnosed APA, however did not fulfill the post hoc definition criteria of APA in our analysis, either due to missing diagnostic criteria (n=3, histologically confirmed adenomas) or due to missing histopathological verification of an adenoma (n=3, histological examination showing nodular-hyperplastic changes in the adrenals) (Supplemental Material 6). No EUS-associated complications were observed.
Discussion

EUS improves the quality of conventional sonographic adrenal imaging [24,25] dramatically. Its use has been suggested in diagnosing and localizing APAs [7,8].

The major challenge in diagnostic process of suspected PA is to identify the patients that may benefit from minimal invasive surgery, i.e. adrenalectomy or partial adrenal adenomectomy - which may be facilitated by EUS which enables to identify morphologically normal parts of the affected adrenal - with respect to cure or at least improve arterial hypertension and - in case - hypokalemia [11,26,27]. All the other patients receive medical treatment based on aldosterone antagonism in order to avoid deleterious effects, amongst others to myocardial structure and function [11,28-30].

To the best of our knowledge, this study on a total of 112 patients is the first ever addressing systematically a possible role of EUS to identify and localize APAs. Our results appear to be encouraging. In a relevant number of patients, EUS was the key to detect the APA and to indicate surgical treatment. In this study, these were eight cases (18%) illustrating the high sensitivity of EUS in detecting and localizing APA associated with a high negative predictive value, i.e. if EUS does not detect an APA-typical finding, the presence of an APA may be considered unlikely.

Nevertheless, some limitations need to be discussed: This is a retrospective study. All EUS examinations have been performed by one ambitious investigator. Data from other methods and tests included in our study were derived from more or less standardized procedures. Concerning CT, MRI, AVS and confirmation tests, we had to deal with incomplete data sets. EUS has not been performed blinded to other test results.

Thus, based on our study it cannot be concluded that EUS is superior to any other method in detecting APAs and this was even not the aim of our study. However, it seems to be legit to state that EUS can be a useful tool to detect and localize APAs and also to define the contralateral adrenal to be morphologically normal, i.e. tumor free. In our institution, in a case of clearly confirmed PA, evidence for APA in one adrenal and completely normal morphology of the other adrenal by EUS, we tend to take this as sufficient information to define an indication for surgery without any other localization test. This also refers to the so called SPARTACUS trial which revealed that patients’ outcome seems to be equivalent comparing decision making based on AVS to high resolution imaging in the SPARTACUS trial an imaging method accompanied by radiation exposure, i.e. CT [6], which furthermore seems to be maybe less sensitive than EUS, the latter however only being an assumption and not definitively proven by our study.

In this context, it deserves attention that especially AVS is accompanied by a relevant radiation exposure [31] which is rarely addressed in literature, and that AVS may be afflicted with a relevant rate of technical failure even under optimized conditions [5] and probably even more in normal clinical routine. It may be a matter of debate to assess the risk of considering a hormone inactive adenoma as APA by EUS vs. to strain the patient with AVS and receiving diagnostic worthless results.

Conclusion

EUS in experienced hands has been found to be a useful and reliable diagnostic tool in suspected APA with a high sensitivity and negative predictive value. If available, it may be offered to patients where EUS might yield a contribution to a finally correct diagnosis to enable planning the appropriate therapeutic strategy, especially to define patients which benefit from a minimal invasive surgical treatment.

Acknowledgment

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References


