—Original Article—

Performance characteristics of EUS-FNA biopsy for adrenal lesions: A meta-analysis

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ABSTRACT

Background and Objective: The role of EUS-FNA biopsy (EUS-FNAB) for detection of metastatic lesions (mets) to adrenals has not been evaluated systematically. Our aim is to systematically evaluate the performance characteristics of EUS-FNAB in detecting metastasis to the adrenal glands. **Materials and Methods:** We performed a systematic search on PubMed and OvidSP from January 1990 to July 2016 using various search terms for EUS and adrenal lesion. Only articles published in English literature were included in the study. Studies with fewer than 10 patients were excluded from the study. Publication bias was assessed using Begg-Mazumdar test and visual inspection of funnel plots. **Results:** Eight studies including 360 adrenal lesions that underwent EUS-FNAB were identified. Of these, 137 FNABs were conclusive for malignancy. Sensitivity of EUS-FNAB in detecting metastasis to the adrenals was 95% (95% confidence interval [CI]: 90%–98%) and specificity was 99% (95% CI: 96%–100%). Pooled positivity of EUS-FNAB in detecting lung cancer metastasis to the adrenals was 44% (95% CI: 31.5%–57.3%). No evidence of publication bias was noted. **Conclusion:** Our study demonstrates that EUS-FNAB is highly sensitive and specific in detecting metastasis to adrenals. It also shows that up to about half of the patients with lung cancer and adrenal lesions on imaging have metastasis, a finding with profound implications on lung cancer staging and treatment.

Key words: Adrenal mass, adrenal metastases in lung cancer, EUS-FNA biopsy

INTRODUCTION

The increasing use of abdominal imaging in the form of an ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and other advanced techniques is resulting in incidental identification of adrenal lesions. While only 2% of all lesions are metastatic,[1] this changes when imaging is done for cancer evaluation. Adrenal lesions identified during staging in patients with cancer can represent metastasis, in as many as 75% of patients.[2] In lung cancer,

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adrenal metastases (mets) incidence ranging from 4.1% to 18%[3] suggests that tissue verification is critical since metastatic involvement of the adrenals determines whether surgery or systemic therapies such as chemoradiation are the appropriate treatments.

Current imaging modalities lack the sensitivity and specificity to differentiate benign from malignant lesions, with 10% false-positive and false-negative rates being reported on CT scans.[4,5] The positive predictive values (PPVs) of CT scan and fluorodeoxyglucose (FDG)-positron emission tomography (PET)-CT for adrenal mets can reach up to 62% and 81%, respectively,[6-8] making tissue acquisition very important for tumor staging. Conventionally, CT-guided adrenal biopsy or laparoscopic/open adrenalectomies have been used; however, image-guided sampling techniques have their own limitations including high rates of nondiagnostic samples (up to 14%) and high complication rates (up to 12%).[9,10]

Endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) is a promising alternative for sampling adrenal lesions due to its relative safety, accuracy, and high diagnostic yield.[11,12] Few studies have attempted to evaluate the safety and diagnostic yield of EUS-FNAB for adrenal lesions, and most were limited by small sample size. In the current meta-analysis, we aim to study the performance characteristics of EUS-FNAB of adrenal lesions in identifying the metastasis in patients with nonadrenal malignancies.

MATERIALS AND METHODS

Study selection/search strategy

We performed a comprehensive systematic literature search in PubMed and OvidSP to identify peer-reviewed articles that evaluated the performance of EUS-FNAB in detecting mets to adrenals. Search period was set from January 1990 to July 2016 without language restriction using the following terms: EUS, EUS-FNAB, Endosonography, Endoscopic ultrasound AND adrenal lesion, adrenal mass, adrenal tumor, and adrenal metastasis. Crosschecking was performed through the reference list of each included study to identify further relevant studies. The process of systematic review was conducted in adherence to standards of quality for reporting meta-analysis.[13] Two reviewers (SP and AD) independently and thoroughly assessed all the articles per predefined inclusion and exclusion criteria. Any disagreements over study selection were resolved by consulting with a third reviewer (KJ).

Inclusion/exclusion criteria

Relevant studies were only included if they met the following criteria: (1) age of study participants >18 years and (2) original article published in English. Exclusion criteria set for the study: (1) Studies where <10 EUS-FNABs were reported. This was done to avoid selection bias for studies with few patients. (2) Case reports. (3) Abstracts.

Reference standard for verification of biopsy observations

Various studies used variable criteria for establishing the final pathological diagnosis of adrenal lesions. These included surgical resection, death from progression of disease, repeat radiological imaging, and clinical follow-up. Studies relying on prolonged clinical follow-up considered patient longevity at 6–24 months as proof of benignancy of adrenal lesion since adrenal mets are often associated with poor survival.[14]

Data extraction

After careful review of each study, the following data were extracted: publication data (including first author's last name and first initial, year of publication, and country of origin), sample size, demographics of participants, type of study, primary source of malignancy, laterality of adrenal involvement (right or left or both), prior imaging workup, follow-up duration, and availability of a conclusive pathology source.

Assessment of methodological quality

At present, there are no defined criteria to evaluate the quality of studies without a control arm.[15] We used Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria to evaluate the quality of included studies.[16]

Statistical analysis

We calculated pooled sensitivity, specificity, likelihood ratios (LRs), and odds ratio to assess the performance of EUS-FNA in identifying metastatic lesions to adrenal glands. Pooling was performed using the random-effects model. We also constructed forest plots to compare the point estimates of each individual study with pooled summary results. Weight of each study is depicted by the width of point estimates in the forest plots. We used Chi-square, I^2, and Cochran's Q test to assess heterogeneity. We also prepared

a plot representing area under receiver operating characteristic (ROC) curve to summarize the evidence. The closer the ROC curve was to 1, the higher the diagnostic accuracy of a test was.

For the final analysis, only those studies that provided sufficient data for construction of 2 × 2 contingency tables were considered. Publication bias was assessed using the Begg-Mazumdar test.[17] We used Meta-Disc version 1.4 (Unit of Clinical Biostatistics, Ramon y Cajal Hospital, Madrid, Spain)[18] to calculate pooled sensitivity, specificity, positive LR, negative LR, and the summary ROC curve. We used comprehensive meta-analysis version 3.0 (Biostat, Englewood, New Jersey, USA)[19] to calculate pooled positivity of EUS-FNAB in detecting lung cancer metastasis to adrenals and pooled technical success rates of EUS-FNAB. Since this study does not compare the outcomes of two different tests, we have not reported *P* values for summary effects.

Sensitivity analysis

In a meta-analysis, individual studies can disproportionately influence the results if they incur undue weight. To avoid this bias, we performed sensitivity analysis by removing each individual study data from the pooled results one at a time and evaluated the summary outcomes for the remaining studies to assess if that led to any major change in outcomes.

RESULTS

A total of 126 titles were identified after an initial literature search that matched our predefined criteria. After careful review, we excluded 101 titles and selected 25 relevant titles for full article review. After excluding further irrelevant studies, eight studies were selected for the current analysis. Figure 1 demonstrates the study selection algorithm. Characteristics of each of these included studies are shown in Table 1, and individual study data including sample size, number of EUS-FNAB examinations in each, patients with known or suspected malignancy, number of positive EUS-FNABs, EUS-FNAB conclusive for lung cancer metastasis, methods of follow-up after EUS-FNAB, and adverse events associated with FNAB, if any, are presented in Table 2.

QUADAS-2 criteria were used to assess the quality of studies included, as summarized in Figure 2. In most of the studies, the risk of selection bias was low. There were no applicability concerns regarding patient selection. There was no risk of bias regarding index test or its applicability. However, studies where only clinical follow-up was used as reference standard raised concerns about risk of bias and its applicability. Based on the above, eight studies were included in the analysis[1,4,7,12,20-23] of technical success rate in acquiring a diagnostic sample with EUS-FNAB [Figure 3]. While analyzing the performance characteristics of EUS-FNAB, two studies[4,22] were excluded: the first by Stelow *et al.* where no follow-up data after EUS-FNAB were provided and the second by Bodtger *et al.* where clinical follow-up and longevity at 2 years were considered signs of benignancy of a lesion.

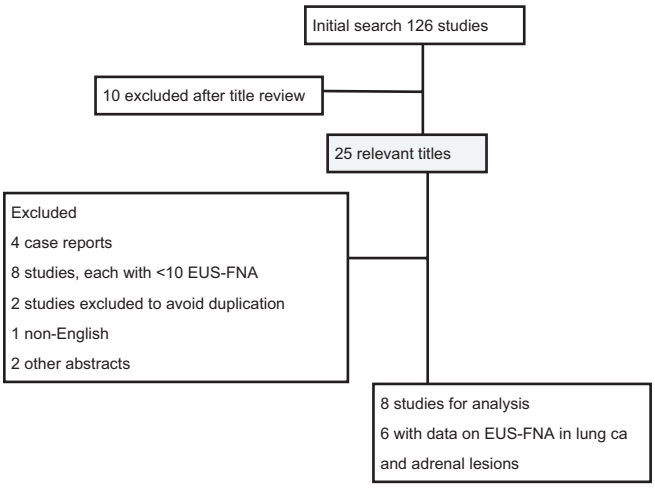

Figure 1. Study selection chart

A total of 360 EUS-FNABs of adrenal glands were performed in the 8 studies included. Of these, 322 (89%) had suspected or known malignancy elsewhere. One of the selected studies was multicenter[7] and three were prospective.[12,20,21] Two of the studies only sampled the left adrenal gland[4,7] while the rest sampled either the right or the left. On-site cytopathology was available in most studies except two,[21,23] while one study[4] did not report this data. Included studies used various available needles for obtaining the sample. Four studies[4,7,12,21] used 22 gauge, one study[23] used 19 gauge, while one study[20] did not report on needle size. Stelow *et al.*[22] used either 22- or 25-gauge needles while Martinez *et al.*[1] used 19-, 22-, or 25-gauge needles.

Among 322 patients with suspected or known malignancy anywhere, 137 had malignant cytology on EUS-FNAB of an adrenal lesion. Similarly, among 221 patients with suspected or known lung cancer,

Table 1. Study characteristics

Study name	Year	Country	Retrospective versus prospective	Number of patients who had EUS-FNAB	Male:female	Age range of participants in years	Right adrenal sampling success
Jhala *et al.*[20]	2004	USA	Prospective	24	18:6	48-81	1 of 1
Stelow *et al.*[22]	2005	USA	Retrospective	22	13:9	37-86	1 of 1
Bodtger *et al.*[4]	2009	Denmark	Retrospective	40	20:20	38-79	Only left
Eloubeidi *et al.*[12]	2010	USA	Prospective	59	37:22	47-79	5 of 5
Schuurbiers *et al.*[7]	2010	Netherlands	Retrospective	85	51:34	37-86	Only left
Uemura *et al.*[23]	2012	Japan	Retrospective	12	NR*	43-86	5 of 5
Martinez *et al.*[1]	2014	USA	Retrospective	94	50:44	32-86	5 of 5
Puri *et al.*[21]	2015	India	Prospective	21	14:7	44-68	3 of 3

*NR: Not reported

Table 2. Individual study data

Study name	Number of EUS-FNAB	Number of known or suspected malignancy/mass	Known or suspected lung cancer/mass	FNAB consistent with malignancy	FNAB consistent with lung metastases	Method of follow-up	Adverse events
Jhala *et al.*[20]	24	21	14	7	6	Resected specimen and/or clinical follow-up 0-24 months	None
Stelow *et al.*[22]	24	19	3	4	NR*	NR*	NR
Bodtger *et al.*[4]	40	40	40	11	10	Clinical	None
Eloubeidi *et al.*[12]	59	55	41	22	17	Clinical and/or imaging	None
Schuurbiers *et al.*[7]	85	85	85	55	53	Clinical and imaging 2-40 months' follow-up	None
Uemura *et al.*[23]	13	11	11	6	6	Surgery and clinical follow-up 6-12 months	None
Martinez *et al.*[1]	94	82	24	25	10	Resected specimen or clinical follow-up 4-96 months	None
Puri *et al.*[21]	21	9	6	7	6	Imaging	None

*NR: Not reported, FNAB: Fine-needle aspiration biopsy

Figure 2. Quality of eligible studies as assessed by the QUADAS-2 criteria

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
1.Jhala *et al.*[20]	☺	☺	☺	☺	☺	☺	☺
2. Stelow *et al.*[22]	☺	☺	?	☺	☺	☺	?
3. Bodtger *et al.*[4]	☺	☺	☹	?	☺	☺	☹
4. Eloubeidi *et al.*[12]	☺	☺	☺	☺	☺	☺	☺
5. Schuurbiers *et al.*[20]	☺	☺	☺	?	☺	☺	☺
6. Uemura *et al.*[20]	☺	☺	☺	?	☺	☺	☺
7. Martinez *et al.*[20]	☺	☺	☺	?	☺	☺	☺
8. Puri *et al.*[20]	☺	☺	☺	☺	☺	☺	☺

☺: Low risk, ☹: High risk, ?: Unclear risk

108 had malignant cytology on EUS-FNAB of an adrenal lesion; however, the study by Stelow *et al.* was excluded from this calculation as required details were not provided by the authors. The pooled sensitivity and specificity of EUS-FNAB in detecting metastasis to the adrenals were 95% (95% confidence interval [CI]:

90%–98%) and 99% (95% CI: 96%–100%), respectively [Figures 4 and 5]. The pooled positive LR (+LR) was 29.60 (95% CI: 10.57–82.90) and pooled negative LR (−LR) was 0.08 (95% CI: 0.04–0.16). An ROC curve is shown in Figure 6. The overall pooled technical success rate in obtaining diagnostic tissue was 94% (95% CI: 90%–96%) [Figure 3]. The pooled positivity in identifying lung cancer metastasis to the adrenals was 44% (95% CI: 31.5%–57.3%) [Figure 7].

Sensitivity analysis

To ascertain that no one study incurred undue weight leading to profound impact on the results of the analysis, we performed sensitivity analysis by removing one study at a time from cumulative analysis and recalculating performance characteristics. We concluded that no one study had enough weight to alter the results of the analysis.

DISCUSSION

To our knowledge, this is the first meta-analysis on the diagnostic yield and performance characteristics of EUS-FNAB of adrenal glands. Our meta-analysis clearly demonstrates that EUS-FNAB of the adrenal glands is highly sensitive (pooled sensitivity 95% with 95% CI: 90%–98%) and specific (pooled specificity 99% with 95% CI: 96%–100%) at diagnosing malignant lesions which is superior to other imaging-guided sampling techniques.[4-8] In addition, pooled negative LR of 0.08 indicates that it can be used as a single test alone to exclude malignancy from adrenal lesions noted on prior imaging workup. If EUS-FNAB is negative for malignancy, patients can probably be followed clinically without requiring any further invasive workup. In addition, EUS-FNAB is highly accurate at differentiating malignant lesions from benign ones as shown in Figure 6.

Furthermore, EUS is more effective at obtaining diagnostic samples compared to other modalities. As demonstrated in Figure 3, the pooled technical success rate of EUS for obtaining diagnostic sample from adrenal lesion is about 94% (95% CI: 90%–96%). This is likely due to the fact that the left adrenal gland lies in close proximity to the

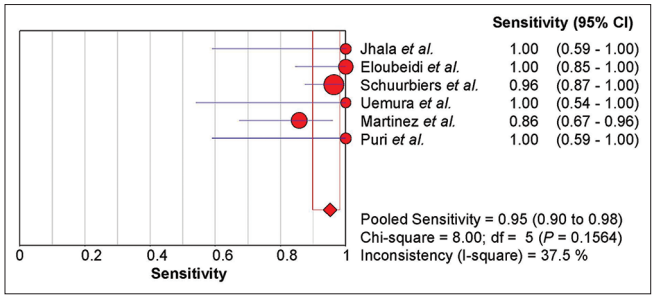

Figure 3. Forest plot of studies reporting outcomes of EUS-FNAB in detecting metastases to adrenals: Pooled sensitivity

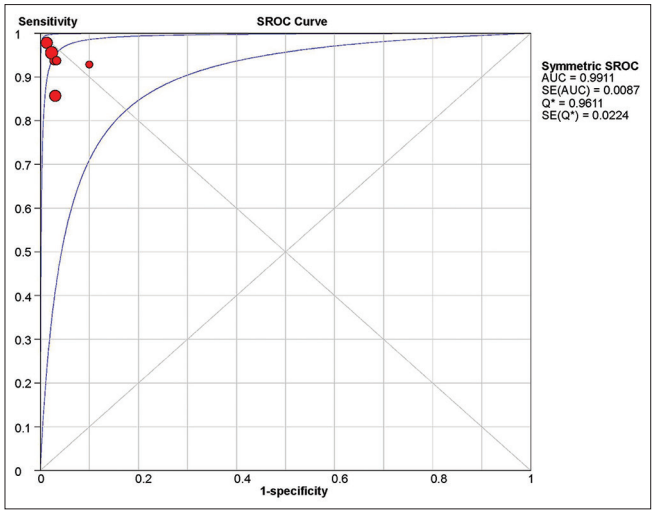

Figure 5. Receiver operating characteristic curve

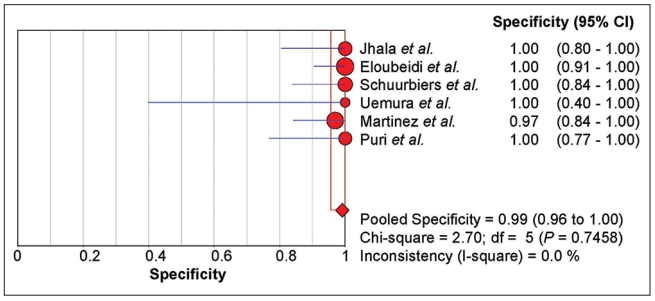

Figure 4. Forest plot of studies reporting outcomes of EUS-FNAB in detecting metastases to adrenals: Pooled specificity

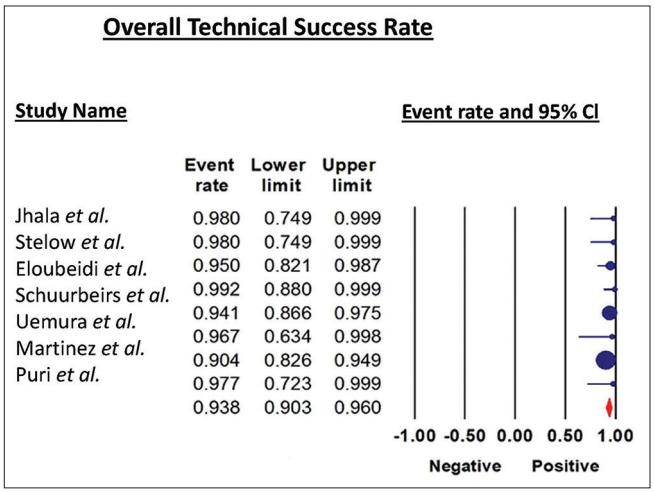

Figure 6. Pooled technical success rate in obtaining diagnostic sample

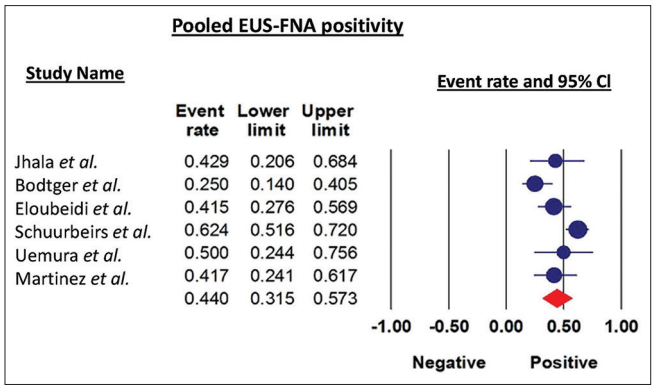

Figure 7. Pooled positivity in detecting lung cancer metastases to adrenals

stomach and is easily accessible through a transgastric approach. In general, visualizing the right adrenal gland can more difficult compared to left, as it requires duodenal maneuvering of the EUS scope. In a retrospective study by Uemura *et al.*,[23] visualization of the right adrenal gland was attempted in 150 patients with potentially resectable lung cancer and was feasible in 131 of 150 patients (87.3%). Subgroup analysis including studies that sampled the right adrenal gland in the current meta-analysis showed 100% diagnostic yield; however, the sample size was very small [Table 2].

Since the adrenal gland is a site of predilection for lung cancer metastasis, EUS-FNAB can be particularly useful in evaluating suspected metastatic adrenal lesions in patients with known or suspected lung cancer. As shown in Figure 7, the pooled sensitivity of EUS-FNAB from an adrenal lesion was about 44% (95% CI: 31.5%–57.3%) in patients with known or suspected lung cancer. This demonstrates that about half of the patients with known or suspected lung cancer presenting with an adrenal lesion have metastatic disease, making it unresectable Stage 4 disease. Confirming adrenal metastatic disease in lung cancer profoundly impacts subsequent management decisions and practically excludes surgery in this case. The study by Bodtger *et al.*[4] specifically evaluated the impact of EUS-FNAB on the clinical decision-making in such patients. There were forty patients with known or suspected lung cancer in whom the impact of EUS on the overall treatment plan was assessed. In this study, the authors identified left adrenal metastasis by EUS-FNAB in two out of four patients who had a normal left adrenal gland reported on prior CT scan. Thus, EUS-FNAB avoided futile surgery in these two patients who were upstaged to Stage IV disease. On the other hand, 28% (10 out of 36) became surgical candidates because of negative EUS-FNAB of a left adrenal lesion in whom prior CT scan was abnormal. In a subsequent study, Eloubeidi *et al.*[12] evaluated 59 consecutive patients, where EUS-FNAB confirmed malignancy in 22. The same study assessed the correlation between size of the adrenal lesion and likelihood of malignancy. Although the malignant lesions were more likely to be larger (3.1 cm) compared to benign lesions (2.3 cm), EUS imaging had an accuracy of 68% for differentiating malignant from benign lesions based on a size threshold of 3 cm. Therefore, size alone is not reliable for differentiating malignant from benign lesions, and tissue acquisition is still needed. The importance of EUS-guided tissue acquisition is further emphasized by the fact that imaging characteristics alone are unreliable in differentiating malignant from benign lesions. Porte *et al.*[9] reported a false-positive rate of malignancy of 21% and false-negative rate of 11% by CT scan based on imaging characteristics only. Another study showed the false-positive rate to be as high as 67% with MRI.[24]

With improving technology, FDG-PET or FDG-PET/CT may seem like a reliable noninvasive option for evaluating adrenal lesions. A study by Schuurbiers *et al.*[7] evaluated the correlation between FDG-PET results and EUS-FNAB outcomes. The study included 46 patients referred for EUS-FNAB due to positive FDG-PET scan. In 32 of 46 patients (70%), EUS-FNAB confirmed malignancy. Considering a cytologically conclusive EUS-FNAB as the reference standard, FDG-PET had a PPV of 74%. A study by Erasmus *et al.*[25] showed FDG-PET specificity of 80% at detecting malignancy in patients with lung cancer and adrenal lesions. Finally, a review by Stone *et al.*[26] showed that the FDG-PET/CT had a high sensitivity of 94%, but due to specificity being <90%, tissue acquisition for confirmation of malignancy is recommended.

In addition to its very high diagnostic accuracy, EUS-FNAB offers a safe alternative to image-guided sampling and is associated with fewer adverse events. Since the left adrenal gland is easily accessible through a transgastric approach with no intervening organs, the likelihood of adverse events remains very low. In comparison, a percutaneous approach can be associated with up to 12% adverse events[27] including hemorrhage, pneumothorax, pain, pancreatitis, and rarely, needle track

seeding,[28] with hemorrhage and pneumothorax being the most common ones. No major EUS-FNAB-related adverse events were reported in any of the studies included in this meta-analysis. EUS also offers other advantages such as the lack of radiation exposure, elimination of contrast administration, needle insertion under real-time US guidance, and the ability to perform sampling during the same EUS session when a lesion is detected.

One important consideration not to be ignored is the potential to be sampling a pheochromocytoma. Typically, these patients have no extra-adrenal malignancy on imaging and more typically present with hypertension, palpitations, sweating, and anxiety episodes. Therefore, if an adrenal lesion is identified without concerns for extra-adrenal malignancy, appropriate workup should be performed to rule out possibility of pheochromocytoma before sampling any adrenal lesion. In a case series of four patients (with unsuspected pheochromocytoma) who underwent percutaneous biopsies of the adrenal gland, one patient experienced alteration in blood pressure during procedure while another developed severe hypertensive crisis during percutaneous sampling.[29] Case reports of hypertensive crisis after EUS-FNAB of adrenal lesion in patients with lung cancer have been published.[30] Using a smaller size needle (25 gauge, for example), limiting the number of passes and employing onsite cytopathology review can minimize trauma to a potential pheochromocytoma.

Our meta-analysis has some limitations. The most important one being the unavailability of surgical specimen for a final pathologic diagnosis in many of the studies included. In almost all studies, biopsies confirmatory of malignancy were treated as "definitive evidence of malignancy," and hence, no surgical management was offered. This is consistent with most EUS literature, where a confirmatory cytology is treated as a reference standard for malignancy. Moreover, these patients were noted to have poor outcomes on follow-up which further supports the FNAB diagnosis. It should be noted also that there was no surgical pathology confirmation of benign lesions which could have introduced bias by considering all those biopsies as true negatives and missing some false negatives. In our analyses, we only included patients for whom appropriate follow-up information was available. The lack of uniformity between these studies in terms of follow-up duration and methods is another limitation worthy of mention.

CONCLUSION

In summary, our meta-analysis demonstrates that the EUS-FNAB is highly sensitive and specific for diagnosing malignant adrenal lesions and is extremely accurate at differentiating malignant from benign lesions. We strongly recommend performing EUS-FNAB in patients with known or suspected lung cancer and imaging evidence of an adrenal lesion since only half of these patients have adrenal metastasis. This information can be a key determinant with respect to surgical treatment or chemotherapy focused on the treatment of metastatic disease.

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Conflicts of interest
There are no conflicts of interest.

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