Review

A Systematic Review and Meta-Analysis of Palpation Versus Ultrasound-Guided Fine Needle Aspiration of Thyroid Nodules

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Abstract

Background: Thyroid nodules are a common clinical finding. Fine-needle aspiration (FNA) is the most widely accepted diagnostic tool used to differentiate malignant and benign thyroid nodules. FNA can be carried out by manual palpation of the nodule or with ultrasound guidance. Existing clinical practice guidelines give mixed recommendations regarding the use of ultrasound guidance for thyroid FNA. Given the inconsistencies in the guidelines, we performed a systematic review and meta-analysis to compare the diagnostic accuracy of palpation-guided fine needle aspiration (PG-FNA) versus ultrasound-guided fine needle aspiration (USG-FNA).

Methods: Studies comparing PG-FNA and USG-FNA were identified through a search of PubMed, the Cochrane Library, and Embase (1990- December 2011). Titles and abstracts were reviewed and studies were selected for a full text review. Meta-analysis of included studies was performed to estimate the average sensitivity, specificity, and rate of inadequate samples for each technique.

Results: We screened 1934 citations and selected seven studies meeting our predefined inclusion criteria. The pooled sensitivity of USG-FNA was found to be higher than PG-FNA [0.91 (CI=0.82, 1.0) and 0.79 (CI=0.69, 0.85), respectively]. The pooled specificity of USG-FNA was also found to be slightly higher than PG-FNA [0.77 (CI=0.69, 0.85) and 0.73 (CI=0.64, 0.81), respectively]. The mean rate of inadequate samples was higher for PG-FNA at 14.7% versus 8.4% for US-FNA.

Conclusions: Our findings show that USG-FNA has a higher diagnostic accuracy than PG-FNA and a lower rate of inadequate samples. Overall, these findings suggest an advantage to the use of USG-FNA over PG-FNA.

Thyroid nodules are a common clinical finding. The prevalence of thyroid nodules detectable on clinical exam ranges between 4-7%.[1] With the use of ultrasound examination, the prevalence of nodules increases dramatically and ranges from 19%-60%.[2] The vast majority of thyroid nodules are benign. It is therefore important to distinguish which ones are benign from those that are malignant. The malignancy rate of palpable nodules is around 5%.[3] Fine-needle aspiration (FNA) biopsy has been the most widely accepted diagnostic tool used to evaluate thyroid nodules due to its accuracy, ease, safety, and cost-effectiveness.[4,5] The ability of FNA to distinguish benign from malignant nodules has greatly reduced the number of surgeries for nodules that were preoperatively diagnosed as benign.[6,7]

Palpation-guided FNA (PG-FNA) is the traditional method for the evaluation of thyroid nodules. Estimates of the accuracy of the technique vary, with sensitivity ranging between 57-93%[5] and specificity ranging between 50-100%.[5,7-12] The rates of false-positive and false-negative findings are reported to be 3% and 5%, respectively.[5,13] Studies have reported that up to 40% of specimens collected using PG-FNA are inadequate, defined as those that did not contain the minimal adequate material for cytological diagnosis.[8,14,15]

Ultrasound-guided FNA (USG-FNA) allows for the visualization of the needle and the nodule during the biopsy. This technique has the potential of reducing the rate of false-negative and non-diagnostic results. Reports of the sensitivity and specificity of the technique vary and range between 66%-100% and 70%-96%, respectively.[8] The reported false negative rate is 1%-2%.[8] The reported rate of inadequate samples is 4%-21%.[5,8,9]

Currently, recommendations for the assessment of thyroid nodules vary between organizations. Some organizations promote the universal use of ultrasound guidance while others advocate for a more selective approach. The American Thyroid Association (ATA) recommends USG-FNA for nodules that are difficult to palpate or partially cystic.[16] The guidelines offered by the US National Cancer Institute[17] and the British Thyroid Association[18] state that palpation-guided FNA should only be used when the nodule is discrete, readily palpable and is mostly solid. On the other hand, the American Association of Clinical Endocrinologists (AACE), the Associazione Medici Endocrinologi (AME), and the European Thyroid Association (ETA) consensus guidelines state that FNA biopsy should be carried out under ultrasound guidance to reduce the possibility of false-negative diagnoses and decrease the non-diagnostic rate.[19] The guidelines suggested by different organizations are therefore inconsistent on this point.

A number of studies have been published in the past two decades addressing the use of PG-FNA and USG-FNA; however, they have not been systematically identified and synthesized. We performed a systematic review and meta-analysis of the existing literature to determine the test accuracy of PG-FNA versus USG-FNA.

Methods

Literature Search

All studies that compared PG-FNA with USG-FNA were identified through an electronic search of PubMed, the Cochrane Library, and EMBASE databases. Professional librarians assisted in conducting a comprehensive search. The search included studies in the English language that were published between January 1990 and December 2011. The following MeSH and keyword search terms were used: "thyroid neoplasms", "thyroid cancer", "thyroid nodule", "needle biopsy", "ultrasonography", and "palpation". As part of the search, bibliographies of included studies and relevant other systematic reviews were manually inspected for relevant articles. The scheme for the search is illustrated in Figure 1.

Study Selection

To be included in our review, studies must have met the following inclusion criteria: had a retrospective or prospective study design comparing USG-FNA versus PG-FNA to diagnose thyroid malignancy; reported the sensitivity, specificity, and inadequacy rate of each diagnostic technique and presented the raw data; used a surgical pathologic specimen as a reference standard

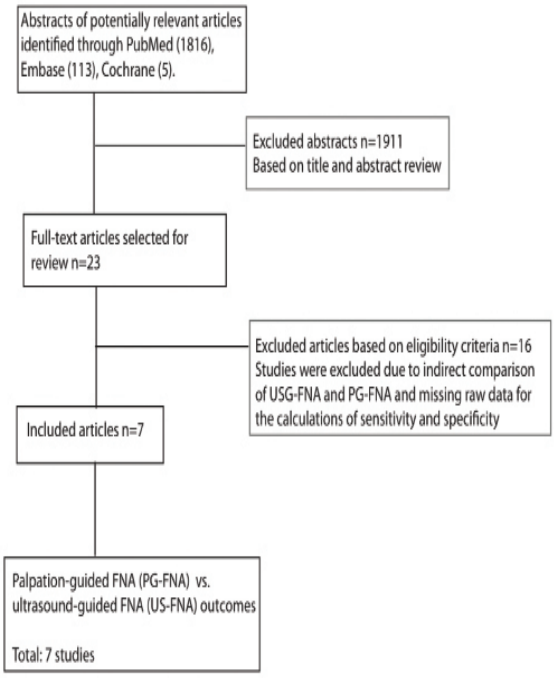

Figure 1. Study selection

and was written in the English language. People of all ages were included in data analysis. Studies that compared the diagnostic techniques in either the same patient population or two different patient populations were included.

Case reports and commentaries were excluded from the analysis. Studies in languages other than English were excluded.

Two reviewers independently read all titles and abstracts and selected articles for a full text review. Full text articles were then read independently. The co-authors (J.M. and J.N.), reached consensus on studies for inclusion and exclusion. Figure 1 shows the flow chart for the search and article selection. All studies that compared PG-FNA and USG-FNA and conformed to selection criteria were included.[5,7-12]

Data Collection

Identifying information, such as the authors' names, the journal name, the year of publication as well as raw data for true-positive, true-negative, false-positive, and false-negative values, was extracted from the included studies. Values for sensitivity and specificity were calculated for each study, using the raw data. The calculated values were compared with those reported in the studies. In cases of discrepancy, calculated values were used for the meta-analyses.

Nodules that were considered benign on cytology were said to be negative. Nodules that were found to be malignant, suspicious, or indeterminate were said to be positive. Inadequate samples, defined as those that did not contain the minimal adequate material for cytological diagnosis, were excluded from the meta-analyses of diagnostic accuracy. These values, however, were used in the analyses exploring the rates of inadequacy. Using the above rules consistently across the studies, true-positives, true-negatives, false-positives, and false-negatives were used to calculate the sensitivity, specificity, and inadequacy rate for each study. The results were compared with the diagnostic values presented in the studies.

The studies selected for the review varied in their classification of indeterminate nodules. The indeterminate category typically includes nodules with a predominantly follicular pattern or a prevalence of Hurthle cells, where a clear-cut cytological diagnosis cannot be made. Some studies included these nodules as positive findings[8], some as suspicious[5], and some as negative.[11] In our analysis, nodules that were deemed to be indeterminate on cytology were classified as a positive finding. The reason for this categorization is that, in practice, such samples would either be assessed with further diagnostic testing, or depending on the clinical context, would be enough to warrant thyroid surgery.

Quality Assessment

The QUADAS tool for diagnostic studies was used to evaluate the quality of the selected studies.[20] The 14 questions used for quality assessment cover elements such as the patient spectrum, the selection criteria, the adequacy of reference standard, and incorporation bias and verification bias (Table 1).

Meta-Analysis

Random effects models were chosen to enable generalization beyond the observed set of studies to make inferences about the parameters of a larger population of studies that may not be strictly identical to the observed set. Pooled estimates of sensitivity and specificity, with confidence intervals generated by random effects models are more appropriately reflective of the true confidence intervals than those generated from fixed effects models.

The meta package[21] of the R language for statistical computing was used to perform the meta-analyses.[22] The I^2 statistic was used to measure the percentage of

Table 1: Items for quality assessment

Item 1	Was the spectrum of patients representative of the patients who will receive the test in practice?
Item 2	Were the selection criteria clearly described?
Item 3	Is the reference standard likely to classify the target condition?
Item 4	Is the time period between the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the two tests?
Item 5	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
Item 6	Did patients receive the same reference standard regardless of the index test result?
Item 7	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
Item 8	Was the execution of the index test described in sufficient detail to permit replication of the test?
Item 9	Was the execution of the reference standard described in sufficient detail to permit its replication?
Item 10	Were the index test results interpreted without knowledge of the results of the reference standard?
Item 11	Were the reference standard results interpreted without knowledge of the results of the index test?
Item 12	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
Item 13	Were uninterpretable/ intermediate test results reported?
Item 14	Were withdrawals from the study explained?

Table 2. Results of the quality analysis using the QUADAS tool

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14
Can et al.	Y	N	Y	Y	N	N	Y	Y	N	Y	U	Y	Y	Y
Carmeci et al.	Y	N	Y	Y	N	N	Y	Y	N	Y	U	Y	Y	Y
Cesur et al.	Y	Y	Y	Y	N	N	Y	Y	N	Y	U	Y	Y	Y
Danese et al.	Y	Y	Y	Y	N	N	Y	Y	N	Y	U	Y	Y	Y
Hatada et al.	Y	N	U	Y	N	N	Y	Y	N	Y	U	Y	Y	Y
Solymosi et al.	Y	N	Y	Y	N	N	Y	N	N	Y	U	Y	Y	Y
Takashima et al.	Y	Y	Y	Y	N	N	Y	Y	N	Y	U	Y	Y	Y

variation across studies attributable to heterogeneity rather than chance.

Results

The search strategy identified 1934 total unique citations (Figure 1). After a review of the titles and abstracts, 23 studies were selected for a full review. Seven studies met all selection criteria and were included in the meta-analysis. The main reasons for exclusion were evaluation of either US-FNA or PG-FNA, but not both in the same study[4,23] and missing raw data to allow calculations of sensitivity and specificity.[24,25] Overall, data on 2305 nodules was included from the studies: 1108 patients underwent PG- FNA and 1197 were tested with USG-FNA.

The baseline characteristics of the included studies are presented in Table 3. All studies, except for Cesur et al.[5], were retrospective analyses and used two different patient populations for comparison of PG-FNA and USG-FNA. Cesur et al.[5] was a comparative prospective study and used the same patient population for both tests. The numbers of participants varied widely between studies. Two studies[9,11] included more than 350 participants in each group. Two studies included 33-99 participants in each group.[10,12] Finally, three studies[5,7,8] included less than 50 participants in each group. No differences were noted between the studies in terms of patient age or gender.

Quality Assessment

The results of the quality assessment are presented in Table 2. All studies selectively used verification with the reference standard (QUADAS Item 5) and the index test result was verified only in a subset of the sample (Item 6), subsequently being scored as "no." No studies provided an explanation of the surgical technique (Item 9). Studies varied in the extent of the description of the selection criteria (Item 2). No studies stated whether the

Table 3: Baseline Characteristics of the Selected Studies

Study	Procedure	Number of patients/nodules	Benign	Malignant	Indeterminate[1]	Inadequate[2]
Can, 2008	PG-FNA	18	12	2	1	3
	US-FNA	23	11	5	6	1
Carmerci, 1998	PG-FNA	47	13	21	7	6
	US-FNA	17	1	10	4	2
Cesur 06	PG-FNA	26	11	4	3	8
	US-FNA	26	14	4	4	4
Danese 98	PG-FNA	535	307	55	160	13
	US-FNA	540	310	70	155	5
Hatada 98	PG-FNA	94	42	24	0	28
	US-FNA	72	37	23	0	12
Solymosi 00	PG-FNA	354	197	120	0	37
	US-FNA	420	302	78	0	40
Takashima 94	PG-FNA	34	12	22	0	0
	US-FNA	99	32	67	0	0

[1] The indeterminate category included nodules with a predominantly follicular pattern or a prevalence of Hurthle cells, where a clear-cut cytological diagnosis cannot be made. In our analysis, samples indeterminate on cytology were classified as a positive finding.
[2] Inadequate samples were defined as those that did not contain the minimal adequate material for cytological diagnosis. Inadequate FNA samples were excluded from the meta-analysis and later used separately for calculations of inadequacy rate.

Table 4. Diagnostic Results from the Studies

Study	Technique	Number of Patients	True Positives	False Positives	False Negatives	True Negatives
Can 08	PG-FNA	18	2	1	0	12
	US-FNA	23	8	3	0	11
Carmeci 98	PG-FNA	47	17	11	2	11
	US-FNA	17	10	4	0	1
Cesur 06	PG-FNA	26	4	3	2	9
	USFNA	26	6	2	1	13
Danese 98	PGFNA	535	76	136	7	300
	USFNA	540	99	126	3	307
Hatada 98	PGFNA	94	23	1	19	23
	USFNA	72	22	1	11	26
Solymosi 00	PGFNA	354	19	101	6	191
	USFNA	420	35	102	3	240
Takashima 94	PGFNA	34	21	1	3	9
	USFNA	99	64	3	3	29

results of the FNA were known during the histological interpretation of the sample. (Item 11)

Results of PG-FNA versus USG-FNA

The diagnostic accuracy values of the included studies are presented in Table 4. For USG-FNA, the pooled sensitivity and specificity, using the random effects model (with 95% confidence intervals), were 0.906 (0.816, 0.996) and 0.769 (0. 686, 0. 853), respectively (Figures 2 and 3). The sensitivity and specificity values for PG-FNA using the random effects model (with 95% confidence intervals) were 0.794 (0. 659, 0.928) and 0.727 (0.644, 0.810) (Figures 4 and 5). These results were also plotted on a receiver operating characteristic (ROC) curve (Figure 6) demonstrating the corresponding sensitivity and specificity values along with the 95% confidence intervals.

The rates of inadequacy varied between the two techniques. In PG-FNA, the mean rate of inadequate samples was 14.7%. For USG-FNA, the mean rate of inadequate samples was 8.4%.

Discussion

A number of studies over the last two decades have investigated the sensitivity and specificity of PG-FNA and USG-FNA. The sensitivity and specificity of PG-FNA has been reported to be anywhere between 57%-98% and 72%-100%, respectively.[13,26-29] The sensitivity and specificity of USG-FNA is reported to be between 66%-100% and 70%-96%.[8]

This meta-analysis showed that the pooled sensitivity of USG-FNA was found to be higher than PG-FNA (0.906 and 0.769, respectively). The pooled specificity

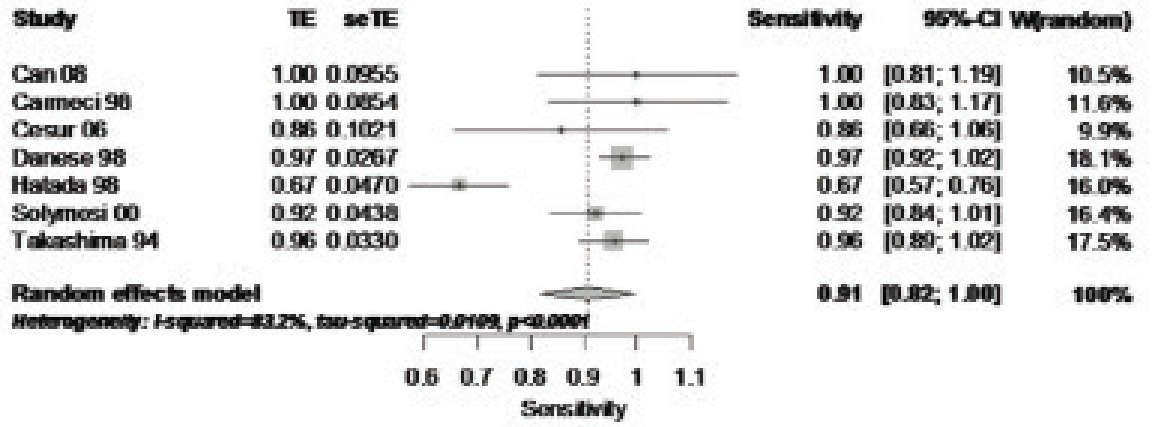

Figure 2. A Forest plot summarizing the meta analysis of sensitivity of USG-FNA.

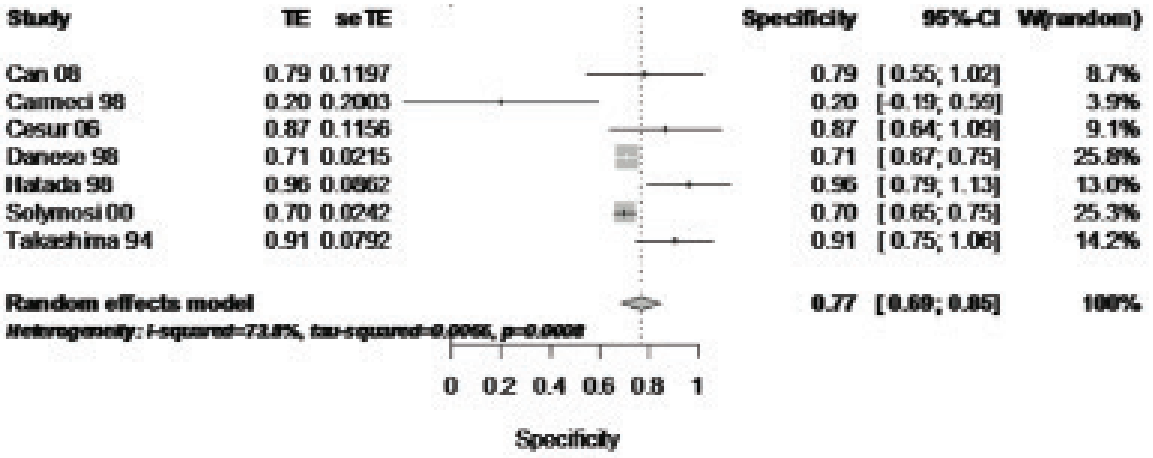

Figure 3. A Forest plot summarizing the meta analysis of specificity of USG-FNA.

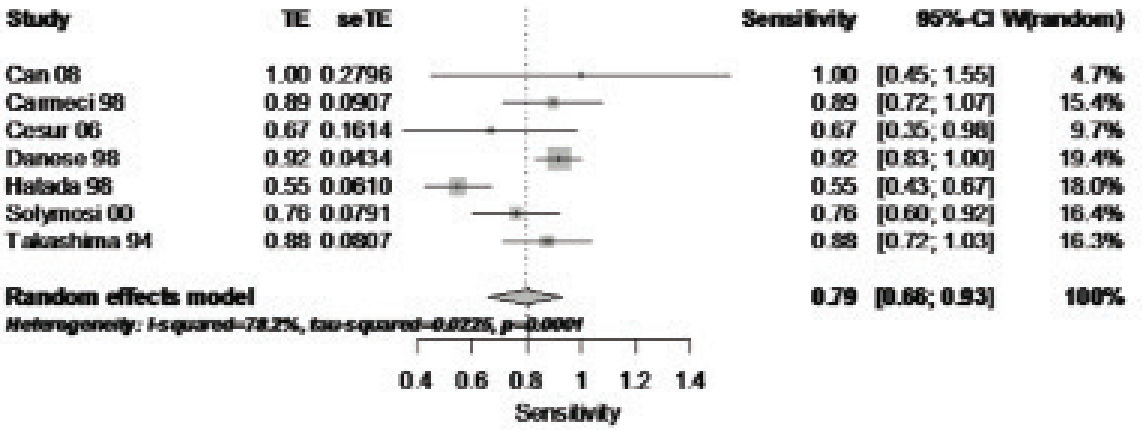

Figure 4. A Forest plot summarizing the meta analysis of the sensitivity of PG-FNA.

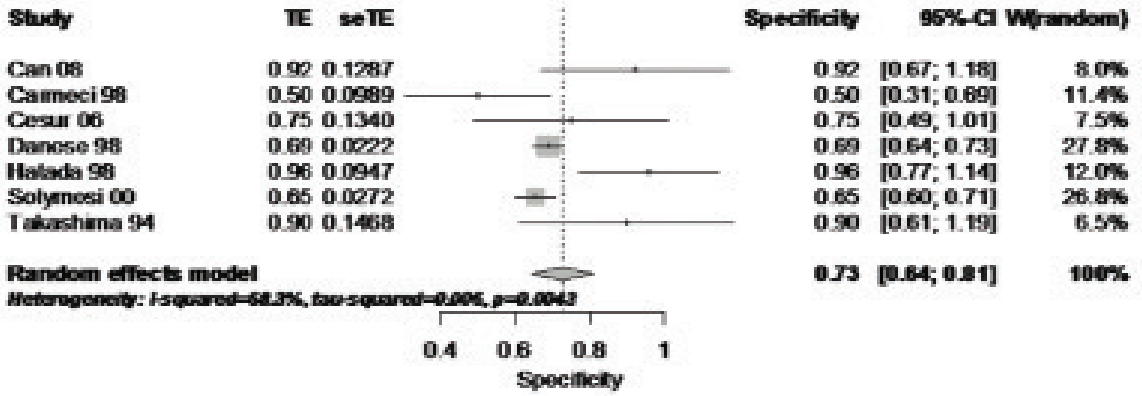

Figure 5. A Forest plot summarizing the meta analysis of the specificity of PG-FNA.

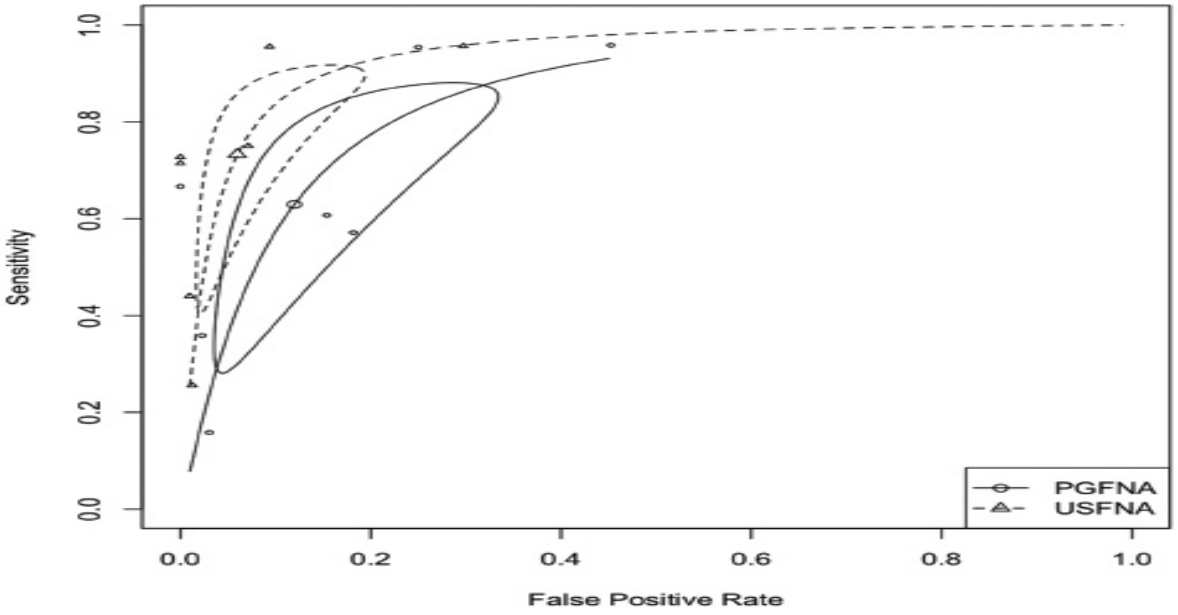

Figure 6. Summary ROC curve showing the comparison of USG-FNA and PG-FNA.

of USG-FNA was also found to be slightly higher than PG-FNA (0.769 and 0.727, respectively). The summary ROC curves and the 95% confidence regions for both PG-FNA and USG-FNA pooled study estimates are well above the line of no discrimination. The summary ROC plot shows the curve for USG-FNA to consistently lie above the curve for PG-FNA, providing evidence of superior accuracy of USG-FNA. In addition, the USG-FNA pooled study estimate is superior to the PG-FNA pooled study estimate, albeit with some overlap in their 95% confidence regions. In comparison to previous studies[8,13,26-29], the diagnostic accuracy values that we found in our meta-analysis is at the upper range of the estimates for both techniques. Reasons for variability between studies may include differences in the operator's experience with the technique, as well as differences in the criteria used for histological interpretation.

Current published guidelines by the ATA, NCI, BTA, and AACE/AME/ETA are in agreement that USG-FNA should be used for nodules that are non-palpable, difficult to palpate, or partially cystic nodules. The inconsistency in the recommendations pertains to the use of USG-FNA for palpable nodules. We found that studies differed with respect to the type of nodules allocated to PG-FNA and USG-FNA. Three of the studies[7,11,12] preferentially allocated nodules that were non-palpable, difficult to palpate, or nodules that failed PG-FNA to cytology by USG-FNA. The remaining four studies[5,8-10] did not actively triage patients to a specific technique. It is possible that by allocating more "challenging" nodules to USG-FNA, the sensitivity and specificity of USG-FNA may be underestimated or alternatively, the diagnostic accuracy of PG-FNA improved. This is a potential source of bias.

The cost of a diagnostic technique is an important factor that needs to be taken into consideration relative to the potential benefits that the technique offers. PG-FNA is a simple technique that can be easily implemented in the office setting, and most clinicians are familiar with it. USG-FNA requires more specialized equipment, requires additional training, and may be more costly. Indeed, several studies have shown that USG-FNA is less cost effective than PG-FNA.[5,30] On the other hand, Can et al.[31] found that although USG-FNA is more expensive than PG-FNA, the increased diagnostic accuracy and decreased inadequacy rate that USG-FNA offers make it into a more cost-effective strategy. The rates of inadequacy found in our meta-analysis are comparable to those reported in the studies that were reviewed and confirm that USG-FNA, on average, has a lower rate of inadequacy (14.7% versus 8.4%).

Our meta-analysis has a number of limitations. In most of the included studies, the same patients did not undergo both PG-FNA and USG-FNA, which would allow a direct comparison. Cesur et al.[5] was the only study where the entire patient population underwent a PG-FNA that was followed immediately by an USG-FNA. Having the patients undergo both diagnostic techniques reduces the possibility of a selection bias. An additional limitation is that in some of the studies, more than one person performed the aspirations. This leaves room for heterogeneity in the results due to operator experience. Furthermore, not all studies used the same number of passes in the thyroid nodule. It is possible that the number of passes may affect the diagnostic accuracy of the technique, leading to inconsistency across the studies. A final limitation is that the included studies varied in their classification of indeterminate nodules. In our analysis, nodules that were deemed to be indeterminate on cytology were classified as a positive finding. Notably, the risk of categorizing the indeterminate results as positive is increasing the false positive rate of cytological diagnosis. However, since this adjustment is applied across all studies, this increase is uniform and was not expected to bias the relative diagnostic accuracy of each technique. An additional discrepancy between the studies was the classification of inadequate samples. Some of the studies included the inadequate samples in their calculations of sensitivity and specificity[8], while other studies excluded inadequate samples entirely from their calculations.[9] Only diagnostic and indeterminate FNA samples were included in our meta-analyses. Inadequate FNA samples were excluded and later used separately for calculations of the average inadequacy rate.

Conclusions

The purpose of this meta-analysis was to compare USG-FNA with PG-FNA in order to determine which diagnostic technique is superior in terms of sensitivity, specificity, and inadequacy rates. USG-FNA was found to have higher sensitivity than PG-FNA in the diagnosis of thyroid nodules. USG-FNA was also found to have a slightly higher specificity than PG-FNA. Inadequacy rates were, on average, lower with USG-FNA than with PG-FNA. These findings suggest that US-FNA is the more accurate technique. Therefore, there appears to be an advantage to the use of USG-FNA over PG-FNA of thyroid nodules.

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