Value Considerations for Thyroid Core Needle Biopsy

Value Brief

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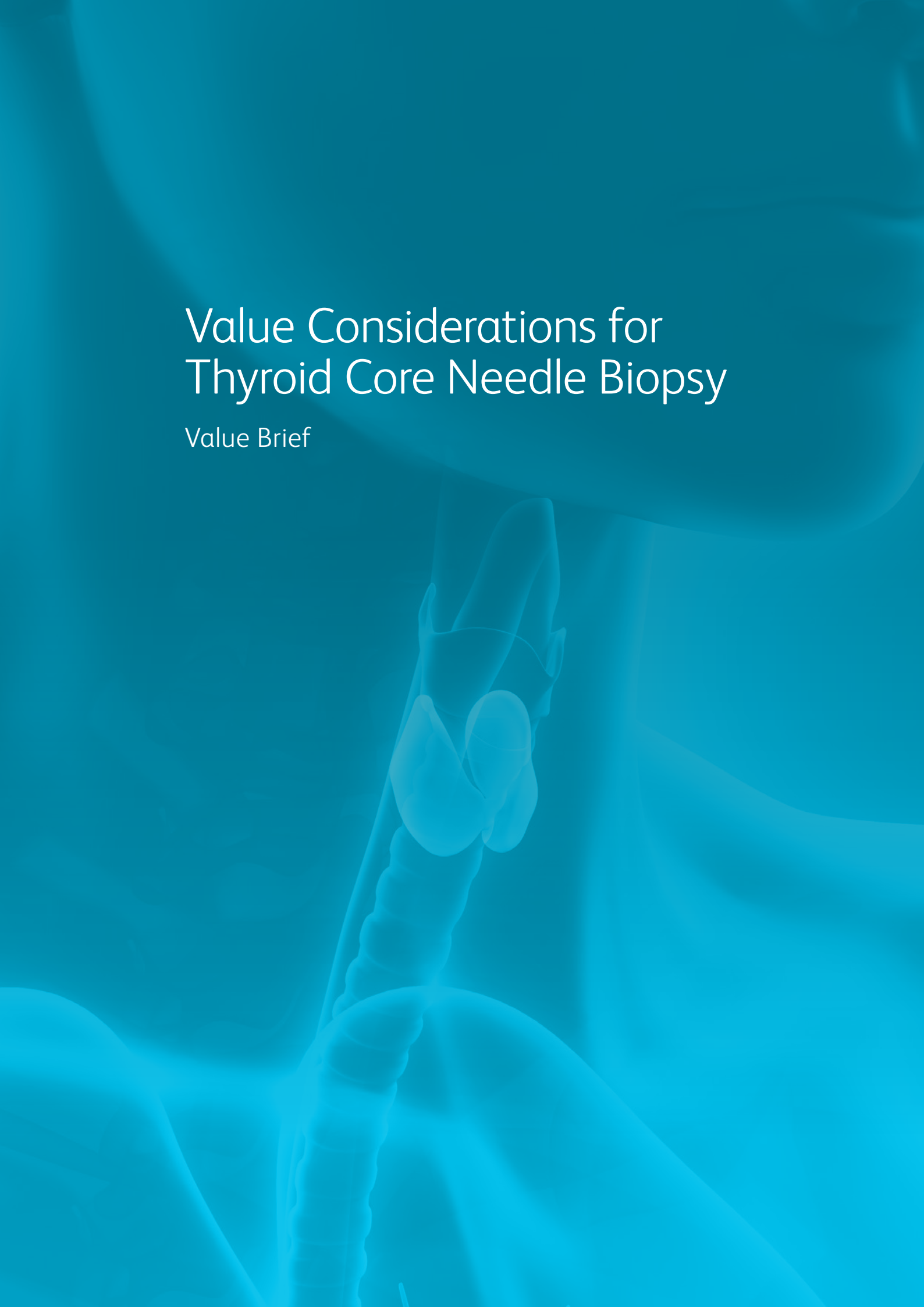


There is a need for accurate diagnostic tools for thyroid cancer

Major Subtypes of Thyroid Cancer [1]

- *Papillary Carcinoma (75-85%)*
- *Follicular Carcinoma (10-20%)*
- *Medullary Carcinoma (5%)*
- *Anaplastic Carcinoma (<5%)*

- Thyroid nodules are common in the American general population, with an occurrence rate of 50% to 60% in healthy people.[2]
- In contrast, thyroid cancer is uncommon, with a lifetime risk of 1.2% in the United States.[3]
- Most nodules are asymptomatic and benign, but the absence of symptoms does not rule out malignancy.[2]
- There is a need to accurately rule out malignancy using a combination of diagnostic imaging and non-invasive biopsy tools.[2]
  - US-guided fine needle aspiration (US-FNA)
  - US-guided core needle biopsy (US-CNB)
- Biopsied samples may also undergo additional immuno-cytochemical/ histochemical or molecular testing to identify molecular markers of specific sub-types of thyroid cancer.[2]
- It is estimated that >1 million thyroid biopsies are performed each year in the United States.[4]

Accuracy of thyroid cancer diagnosis by nodule biopsy influence clinical management

Persistently non-diagnostic, AUS/FLUS, FN or SFN results may lead to repeat biopsies and diagnostic lobectomy. [2; 5]

- After physical examination and US evaluation, US-FNA is often the first-line biopsy tool to differentiate benign from malignant nodules:[2; 6]
- The Bethesda System for Reporting Thyroid Cytopathology* is commonly used to classify thyroid nodule samples collected by US-FNA, and influences the management strategy for thyroid cancer **(Table 1 and Figure 1)**.[5]
- When non-invasive biopsy tools produce inconclusive or indeterminate results, surgical lobectomy is commonly used to provide definitive diagnosis.[2; 5]

* See Glossary for the terminology used for thyroid nodule biopsy results.[5]

Abbreviations: AUS/FLN: Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance; FN: Follicular Neoplasm; SFN: Suspicious for a Follicular Neoplasm

Table 1. The Bethesda System for Reporting Thyroid Cytopathology.[5]

Class	Diagnostic Category[5]	Risk of Malignancy (%)[5]	Usual Management[a; 2; 5; 6]
I	Non-diagnostic or Unsatisfactory	1-4	Repeat FNA with ultrasound guidance
II	Benign	0-3	Clinical follow-up
III	Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~5-15[b]	Repeat FNA
IV	Follicular Neoplasm or Suspicious for a Follicular Neoplasm	15-30	Diagnostic surgical lobectomy[d]
V	Suspicious for Malignancy	60-75	Near-total thyroidectomy or surgical lobectomy[c]
VI	Malignant	97-99	Near-total thyroidectomy[c]

[a] Actual management may depend on other factors (e.g., clinical, sonographic) besides FNA interpretation
[b] Estimate extrapolated from histopathologic data from patients with "repeated atypicals."
[c] In the case of "Suspicious for metastatic tumor" or a "Malignant" interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.
[d] Diagnostic surgical lobectomy may involve partial or total removal of one of the two thyroid gland lobes.

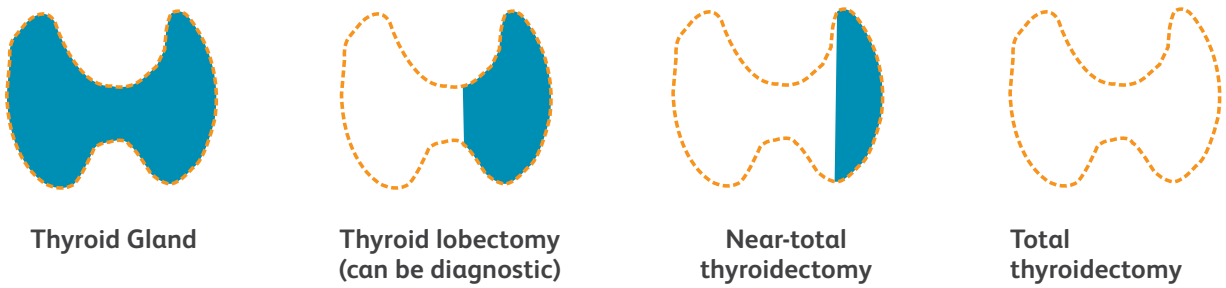


Figure 1. Surgical management of thyroid cancer may involve partial to total removal of the thyroid gland.[2]

Despite its benefits, US-FNA has been found to have certain limitations and may lead to unnecessary diagnostic lobectomy or total thyroidectomy

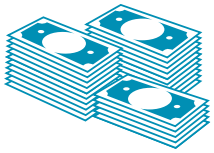
- US-FNA has been found to have non-diagnostic rates ranging from 2% to 27%.[7-9] Persistently non-diagnostic samples may lead to repeat biopsy and diagnostic lobectomy.[2; 5]
- Thyroid nodules with an indeterminate US-FNA cytology have been reported to range from 10% to 25%.[2; 8; 10] These may be referred for diagnostic lobectomy to establish histological diagnosis and definitive tumor removal.[2; 5; 6]
- Thyroid surgery after indeterminate or persistently non-diagnostic thyroid biopsy may result in unnecessary resection of noncancerous tissue.[8; 10-12]
  - Approximately 71% to 75%[8; 10] of indeterminate biopsies, and 30% to 90%[12; 13] of persistently non-diagnostic US-FNA biopsies, led to unnecessary diagnostic lobectomy of benign nodules, in 2 prospective[8; 10] and 2 retrospective[12; 13] studies.
  - Nearly 20% of patients with indeterminate thyroid nodule biopsy underwent an initial total thyroidectomy for benign disease, in a retrospective study of 639 patients.[11]

Lobectomy and total thyroidectomy† may be associated with short- and long-term patient complications

- Common short-term complications after lobectomy or total thyroidectomy may include transient hypocalcemia, recurrent laryngeal nerve (RLN) injury, and post- operative bleeding.[14]
  - Overall short-term complication rates were estimated at 7.4% and 21.8%, for lobectomy and total thyroidectomy, respectively.[15]
  - Surgical site infections are estimated to be rare (~0.4%) but may cause significant patient post-operative complications.[16]
- Chronic complications after lobectomy and total thyroidectomy may include hypocalcemia due to permanent hypoparathyroidism, and RLN paralysis.[14]
  - Overall rates of permanent complications after lobectomy and total thyroidectomy were estimated at 1.4% and 3.9%, respectively.[15]
  - A systematic review of studies that pooled lobectomy and total thyroidectomy complications estimated the rate of permanent hypoparathyroidism at 2 to 6 events per 100 surgeries, and the rate of permanent RLN palsy at 1 or 2 events per 100 surgeries.[17]

- Patients who experience hypoparathyroidism report a large burden of symptoms and impact of their condition on employment, social life and well-being.[18]
  - In one study (n=374), 20% of patients reported that hypoparathyroidism symptoms (e.g., fatigue, inability to concentrate) directly influenced their change in employment status.[18]
  - Symptom management with oral calcium and active vitamin D require close monitoring for long-term complications such as hypercalcemia, hypercalciuria, and kidney disease.[18]

- Approximately 1 in 5 patients will experience biochemical hypothyroidism after thyroid lobectomy, with clinical hypothyroidism in 1 of 25 patients, as reported in a meta-analysis.[19]
  - Thyroid hormone replacement may be necessary in approximately 14% of patients after lobectomy.[15; 20]
  - Life-long thyroid hormone therapy may be associated with atrial fibrillation, loss of bone calcium resulting in osteopenia/osteoporosis, and reduced psychological well-being.[20; 21]



- The burden of costs associated with thyroid surgery complications may be substantial:
  - From a payer perspective, 2016 costs of initial treatments were estimated at $400 for temporary thyroidectomy complications, $3,280 for permanent thyroidectomy complications, and $5,515 for lobectomy complications.[15]
  - Mean medical costs for hypoparathyroidism cases were approximately three times those of control cases, in a 2011 US population-based study (using provider-linked billing data).[22]
  - Annual medications may cost between $700 and $855 for hormone replacement therapy, supplemental calcium, and vitamin D (assuming daily doses of 100 mcg levothyroxine, 0.25 mcg calcitriol, and 1000 mg/800 IU calcium/vitamin D).[15; 23-25*]

† Performed for definitive diagnosis after persistently non-diagnostic, AUS/FLUS, or FN/SFN biopsy results.

* Average wholesale price (includes markup from wholesale acquisition cost) was acquired from RedBook[24] to calculate medication costs.

US-CNB has advantages that address certain limitations of US-FNA

Advantages of US-CNB compared with US-FNA

- *Greater tissue yield* [26; 27]
- *Fewer samples required (~1 vs. up to 12)* [28]
- *Cytopathologist not required at the procedure*[9]
- *Beneficial for diagnosis of certain nodule types* [29-32]

- US-CNB has been shown to obtain a larger amount of nodule tissue than US-FNA, and provide more information of histologic architectural structures.[26; 27]
- US-CNB doesn't require the presence of a cytopathologist at the procedure, and usually takes less time than US-FNA.[9]
- Sensitivity of US-CNB may be greater than US-FNA for diagnosis of malignancies,[7; 33] which are most commonly papillary thyroid carcinoma.[1]
- Microhistologic diagnoses made using US-CNB specimens in combination with immunohistochemistry are advantageous over cytologic US-FNA for malignant thyroid lymphoma,[29] medullary thyroid carcinoma,[30] and anaplastic thyroid carcinoma.[29]
- US-CNB may help to increase the diagnosis of benign thyroid nodules with isolated macrocalcification,[31] and suspicious US features,[32] thus reducing the need for repeat tests or diagnostic thyroid lobectomy.[31; 32]
- Both US-FNA and US-CNB have a limited role in the diagnosis of follicular carcinoma, which requires evaluation of the entire nodular capsule to detect capsular/vascular invasion.[34]

Several key guidelines recognize the value of US-CNB as a complementary† diagnostic method to US-FNA

- The American Association of Clinical Endocrinologists, American College of Endocrinology, Associazione Medici Endocrinologi (AACE/ACE/AME) and National Cancer Institute (NCI) guidelines recommend US-CNB after persistently non-diagnostic US-FNA,[2; 35] whereas the American Thyroid Association (ATA)[6] does not yet recommend US-CNB for thyroid biopsy.
- Current thyroid guidelines of the British Thyroid Association (BTA),[36] and Korean Society for Thyroid Radiology (KSThR)[37] also recommend US-CNB as a complementary procedure to US-FNA for classification of thyroid nodules.

† As a complementary tool, US-CNB would be used after a first-line or repeat US-FNA, and before performing diagnostic lobectomy.[2]

As a second-line tool, US-CNB may help to reduce non-diagnostic and inconclusive US-FNA results, as well as improve sensitivity

The probability of a non-diagnostic result using US-CNB is almost four times lower than that for US-FNA. [38]

- A meta-analysis of 20 retrospective studies, based on 4,580 patients with 4,746 thyroid nodules, reported on US-CNB and US-FNA biopsy results after an initial non-diagnostic or indeterminate US-FNA findings (see **Table 2** for pooled biopsy results).[33]
  - US-CNB generated lower rates of non-diagnostic and inconclusive biopsy results when compared with repeat US-FNA.[33]
  - Sensitivity of US-CNB was numerically greater than that of repeat US-FNA for detecting malignancy.[33]
  - Specificities of US-CNB (99%) and US-FNA (100%) for malignancy were both very high.[33]

Table 2. Second-line biopsy test results for US-CNB and US-FNA after initial non-diagnostic or indeterminate US-FNA.[33]

Parameter	US-CNB % / # studies	US-FNA % / # studies
Non-diagnostic	5.5 / 17	22.6 / 11
Inconclusive (Non-diagnostic or AUS/FLUS)	8.0 / 11	40.2 / 6
Sensitivity[a] (for malignancy)	91 / 10	74 / 6
Specificity[b] (for malignancy)	99 / 10	100 / 6

[a] Sensitivity: Probability that patient with disease has positive test results (true positive cases among all cases with disease).[39]
[b] Specificity: Probability that patient without disease has negative test results (true negative cases among all cases without disease).[39]

- Other meta-analyses also reported fewer non-diagnostic results for US-CNB after an initial non-diagnostic US-FNA, when compared with repeat US-FNA:[38; 40]
  - The risk of obtaining a non-diagnostic result after a previous non-diagnostic US-FNA was 78%* lower for US-CNB compared with US-FNA.[38]
  - The odds of US-FNA providing a non-diagnostic result after a previous non-diagnostic US-FNA were 19 times† that of US-CNB.[40]

* Relative Risk = 0.22
† Odds Ratio = 19.13

There is a growing body of evidence in support of US-CNB as a standalone or combined US-CNB/US-FNA first-line biopsy tool for thyroid cancer

- In a 2016 meta-analysis of 8 studies reporting first-line biopsy results for US-CNB and US-FNA, including 1,900 nodules, US-FNA was numerically 2.4 times more likely to provide a non-diagnostic result compared with US-CNB.[40]
- First-line US-CNB and US-FNA/US-CNB produced lower non-diagnostic and inconclusive rates, and higher sensitivity and accuracy for malignancy when compared with US-FNA, in a large retrospective analysis of 782 thyroid nodule biopsies **(Table 3)**.[7]
- Higher sensitivity and accuracy were reported for first-line US-CNB (86.8% and 92.1%, respectively) or US-FNA/US-CNB (90.6% and 94.2%, respectively compared with US-FNA (68.6% and 82.0%, respectively), in a retrospective analysis of 555 consecutive thyroid nodules with surgically confirmed diagnoses.[26]
- Non-diagnostic rates for first-line US-CNB ranged from 1.3%[41] to 3.2%[8] in prospective studies and from 1.4%[26] to 4.9%[42] in retrospective studies.
- First-line US-CNB has been associated with very low rates of unnecessary thyroid surgery* (0.5% to 0.6%), as reported in two retrospective studies.[41; 42]

Table 3. First-line biopsy results for 782 thyroid nodules using US-CNB, US-FNA and US-FNA/US-CNB.[7]

Parameter	US-FNA %	US-CNB %	US-FNA/US-CNB %
Non-diagnostic	13.2	2.0	1.4
Inconclusive (Non-diagnostic or AUS/FLUS)	23.7	10.2	6.5
Sensitivity[a] (for malignancy)	62.3	89.3	91.1
Specificity[b] (for malignancy)	100	100	100
Diagnostic accuracy[c] (for malignancy)	84.5	95.6	96.4

[a] Sensitivity: Probability that patient with disease has positive test results (true positive cases among all cases with disease).[39]
[b] Specificity: Probability that patient without disease has negative test results (true negative cases among all cases without disease).[39]
[c] Diagnostic accuracy: Proportion of correctly classified cases (true positive and true negatives) among all cases.[39]

* Unnecessary thyroid surgery included nodules reported as malignant or follicular neoplasm by biopsy results and diagnosed as benign after surgery.[41; 42]

US-CNB may reduce the rate of missed cancer diagnoses associated with US-FNA

US-FNA may be associated with more missed malignancy diagnoses than US-CNB. [8; 26; 27; 30; 43; 44]

- In cohort studies, rates of missed malignancy results range between 12%-48% for US-FNA,[8; 26; 27; 30; 43; 44] and 0%-20%[8; 26; 27; 30; 41-45] for US-CNB (**Table 4**), with a consistent trend of increased missed malignancy for US-FNA vs. US-CNB in comparative studies.
- Several studies reported that false-negatives (i.e., malignancies misdiagnosed as benign) resulted from errors in sampling or interpretation, or difficult nodule types with severe calcification or fibrosis.[8; 26; 42; 45]
- In one retrospective study, delayed medullary thyroid cancer diagnosis was reported for 25.7% (44/171) patients who underwent US-FNA, and 0% (0/22) for US-CNB.[30]

Table 4. Missed thyroid cancer diagnoses in US-FNA and US-CNB.

Study	US-FNA % Missed Malignancy[a]	US-CNB % Missed Malignancy[a]	Reasons/Misdiagnoses
Kim et al. 2017[42]	—	10% (40/387)	non-diagnostic (8), benign (8), AUS/FLUS (16), SFN/FN (8)
Paja et al. 2016[45]	—	20% (36/181)	benign (8), follicular and oncocytic neoplasms (28)
Suh et al. 2016[41]	—	9% (19/211)	non-diagnostic (1), benign (7), AUS/FLUS (3), SFN/FN (8)
Ha et al. 2015[30]	44% (75/169)	0% (0/22)	**US-FNA:** non-diagnostic (6), benign (13), AUS/FLUS (44), FN (12)
Yi et al. 2015[43]	28% (9/32)	13% (4/32)	**US-FNA:** non-diagnostic (2), benign (3), AUS/FLUS (4) **US-CNB:** benign (3), AUS/FLUS (1)
Choi et al. 2014[44]	48% (12/25)	4% (2/47)	**Repeat US-FNA:** non-diagnostic (5), benign (1), AUS/FLUS (6) **US-CNB:** non-diagnostic (1), benign (1)
Trimboli et al. 2014[8]	12% (4/34)	0% (0/24)	**US-FNA:** benign (1), indeterminate (2), not adequate (1)
Na et al. 2012[27]	42% (33/79)	18% (14/79)	**US-FNA:** non-diagnostic (3), benign (1) AUS/FLUS (29) **US-CNB:** non-diagnostic (3), AUS/FLUS (10), SFN/FN (1)
Sung et al. 2012[26]	31% (100/318)	13% (42/318)	US-FNA: non-diagnostic (16), benign (5), AUS/FLUS (78), SFN/FN (1) **US-CNB:** non-diagnostic (6), benign (2), AUS/FLUS (30), SFN/FN (4)

[a] **% Missed malignancy:** Proportion of non-diagnostic, benign, AUS/FLUS, and SFN/FN biopsy diagnoses given a final diagnosis of malignancy by surgery among total malignancies (which includes missed malignancies, suspected malignancy and malignancy diagnoses). Note: A higher rate of missed malignancy indicates worse test performance.

US-CNB for thyroid lesions is associated with low complication rates and is well tolerated by patients

- Before the innovation of modern US-guided and spring-activated CNB, serious complications were reported for large-needle biopsies, including recurrent laryngeal nerve palsy, hemorrhage, and tumor implantation along the biopsy track.[47]
- In a structured questionnaire administered to 61 patients who underwent US-CNB after an inconclusive US-FNA, patients reported similar comfort, tolerability, and pain level for US-CNB and US-FNA.[46]
- A 2016 meta-analysis of 20 studies reported low risk of major or minor complications for both US-CNB and US-FNA (Table 5), as well as low overall complication rates.[33]
  - The pooled proportion of complications was 0.01% for US-CNB (n=3,163 patients) and 0.0% for US-FNA (n=2,572 patients).[33]
- A large 2017 retrospective, single center study of 6,169 patients and 6,687 thyroid nodules, reported a low overall complication rate 0.81%, major complication rate of 0.06%, and minor complication rate of 0.79% for US-CNB (**Table 5**).[47]
- In a 2018 retrospective, single center study of 200 consecutive patients who underwent US-FNA (n=100) or US-CNB (n=100), there were no major complications in either group, and only 3 minor complications in the US-CNB group.[48]
  - US-FNA and US-CNB groups also reported similar median pain levels and procedure tolerability.[48]

Table 5.
Rates of major and minor complications for US-FNA and US-CNB reported in a meta-analysis[33] and large retrospective study.[47]

	US-FNA		US-CNB	
	# studies [# patients]	**Value**	**# studies [# patients]**	**Value**
Major complications[a]	12 [2,572][33]	0%[33]	18 [3,163][33]	0.03%[33]
			1 [6,169][47]	0.06%[47]
Minor complications[b]	12 [2,017][33]	0.15%[33]	18 [2,608][33]	0.58%[33]
			1 [6,169][47]	0.79%[47]

[a] Major complications included bleeding,[33] hematoma, pseudoaneurysm, and voice change > 1 month[47]
[b] Minor complications included hematoma, transient hoarseness, hemoptysis, carotid injury, voice change for < 1 month, tracheal puncture, and dysphagia[33; 47]

U.S. Payer Perspective

US-CNB as a second-line tool for thyroid biopsy was predicted to be a cost saving strategy in comparison with US-FNA, due to avoided diagnostic lobectomies

UP TO
$598,000
OF THYROID DIAGNOSTIC PROCEDURE COSTS MAY BE SAVED
per 1,000 patients, when US-CNB is used as a second-line test instead of FNA.‡

- After an indeterminate US-FNA biopsy result, procedure costs* of using a second-line US-CNB test were estimated to be ~34% lower than that of diagnostic thyroidectomy, in a cost-analysis study.[10]
- Diagnostic lobectomy procedures, often conducted with persistently non-diagnostic or indeterminate thyroid biopsy results, are considerably more costly than repeat biopsy procedures to U.S. payers, with procedure reimbursement rates ranging from **$2,097** to **$10,238** depending on site of service.
- Given reported differences in rates of non-diagnostic and indeterminate results between US-FNA and US-CNB,† an economic model predicted that **$429,277** to **$598,570** could be saved per 1,000 patients if US-CNB was used as a second-line test instead of US-FNA (**Figure 2**).‡
  - Cost savings were primarily driven by avoided thyroidectomy payments. Specifically, second-line CNB was associated with a 59% to 65% reduction in diagnostic lobectomy payments.

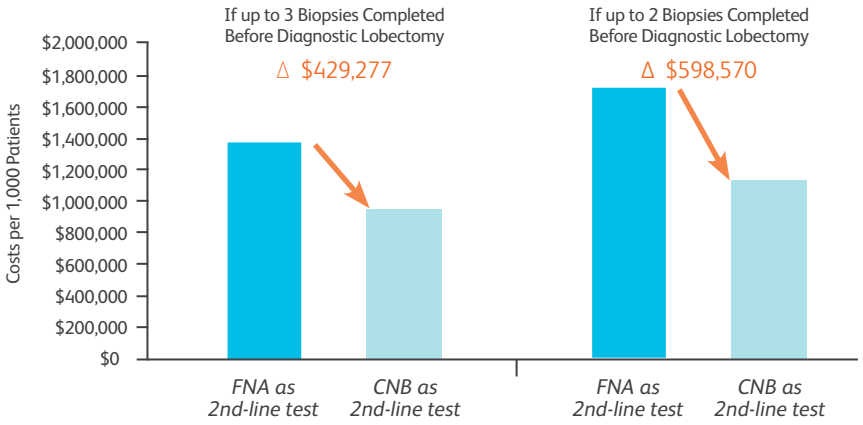


Figure 2. Total thyroid diagnostic procedure costs per 1,000 patients, as predicted by an economic model.

- The model also predicted cost savings with second-line combination FNA and CNB use compared second-line FNA use only.
- There are additional economic benefits to avoiding diagnostic lobectomies that can be relevant for U.S. payers, including lobectomy-related complication costs (e.g., hypoparathyroidism, annual medication for hormone replacement therapy).[15]

* Overall cost for each US-CNB procedure included the price of two cutting needles, other surgical instruments, operating theater, surgical team, and microhistologic examination; Cost of diagnostic surgery included all medical instruments and medications, patient recovery costs, operating theater, surgical team, cost of histologic examination.

† Non-diagnostic, AUS/FLUS, and FN/SFN result rates for US-FNA and US-CNB were obtained from published data.[7-9; 26-28; 33; 41-44; 49; 50]

‡ US-FNA used as first-line biopsy for all patients.

U.S. Provider Perspective

US-CNB as a second-line tool was predicted to provide economic value in comparison with US-FNA, due to avoided diagnostic lobectomies

- An economic model predicted that US-CNB as a second-line tool **avoids 69 to 105 diagnostic lobectomies** per 1,000 patients compared with second-line US-FNA use, depending on whether up to 2 or 3 biopsies are completed prior to diagnostic lobectomy, respectively.*
- A Medicare outpatient study demonstrated that the true procedure cost of a diagnostic lobectomy exceeded the average hospital outpatient APC 5361 payment (i.e., ranged between 107% to 114% of reimbursement, see **Table 6**).

Table 6. Estimated true cost of thyroid lobectomy procedures expressed as a % of hospital outpatient Medicare payments.

CPT codes	Description	Hospital Outpatient Estimated True Cost as % of Reimbursement [a,b]
60210	Partial thyroid lobectomy, unilateral; with or without isthmusectomy	108%
60212	Partial thyroid lobectomy, unilateral; with contralateral subtotal lobectomy, including isthmusectomy	114%
60220	Total thyroid lobectomy, unilateral; with or without isthmusectomy	107%
60225	Total thyroid lobectomy, unilateral; with contralateral subtotal lobectomy, including isthmusectomy	111%

[a] 2018 Medicare Notice of Final Rulemaking Addendum B.10.27.17 Final, APC 5361
[b] 2017 Medicare Hospital Outpatient Geometric Mean Costs of CPT procedures

UP TO
$404,000
OF OUTPATIENT DIAGNOSTIC LOBECTOMY PROCEDURE COSTS MAY BE SAVED
per 1,000 patients with second-line US-CNB compared with US-FNA

- An economic model predicted that second-line US-CNB avoids approximately **$266,016 to $404,190** per 1,000 patients in diagnostic lobectomy outpatient procedure costs compared with second-line FNA.
- Across sites of service, device costs (i.e., FNA needles and CNB) as a proportion of thyroid biopsy reimbursement are very comparable irrespective of whether US-FNA (i.e., 3%) or US-CNB (i.e., 4%) are used as the second-line test.†
- If >1 FNA needle is used per procedure compared with 1 CNB needle, second-line US-CNB may become a more economically favorable strategy for providers when the cost of additional FNA devices is considered in proportion to thyroid biopsy reimbursement.

* US-FNA used as first-line biopsy for all patients.
† The economic model assumed 1 FNA or CNB needle was used per procedure.

Glossary

Table 7. Terminology used for thyroid nodule biopsy results.[5]

Term	Description
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)	Microfollicles exclude FN/SFN, predominance of Hürthle cells, nuclear atypia in otherwise benign-appearing sample
Benign	Consistent with a benign follicular nodule, multimodal goiter, follicular adenoma, lymphocytic thyroiditis, granulomatous (subacute thyroiditis)
Follicular Neoplasm or Suspicious for a Follicular Neoplasm (FN/FSN)	Probable follicular carcinoma, disturbed cytoarchitecture but cannot be distinguished from follicular adenoma by cytopathology
Indeterminate	AUS/FLUS (low risk indeterminate) or FN/SFN (high risk indeterminate)
Malignant	Characteristics of thyroid carcinoma (papillary, poorly differentiated, medullary, undifferentiated (anaplastic)
Non-diagnostic	Inadequate sample due to too few follicular cells, blood/clotting artifact, cyst fluid, or drying of smear
Suspicious for Malignancy	Subtle or focal nuclear and architectural changes, only 1 or 2 features of papillary thyroid carcinoma, sparsely cellular

Assumptions for calculations: For a cohort of 1,000 patients, up to 2 or 3 biopsy tests were allowed before a diagnostic lobectomy could be performed. One FNA or CNB needle was assumed per procedure. A non-diagnostic or AUS/FLUS result led to a repeat biopsy test, whereas an FN/SFN result led to a diagnostic lobectomy. Non-diagnostic, AUS/FLUS, and FN/SFN result rates for US-FNA and US-CNB were obtained from published data.[7-9; 26-28; 33; 41-44; 49; 50] All patients underwent an US-FNA as first test, then US-FNA or US-CNB as the following tests. Overall costs for the payer perspective included reimbursement costs of US-FNA, US-CNB, and diagnostic lobectomy; costs were considered across care settings.

Sample Payer overall reimbursement cost calculation:
Inputs: A = cost of first US-FNA test for total cohort, B = % patients with non-diagnostic or AUS/FLUS result (first biopsy test result), C = cost of second biopsy test (and beyond), D = % patients with FN/SFN result (first biopsy test result), E = cost of diagnostic lobectomy, F = % patients with non-diagnostic or AUS/FLUS result after a first non-diagnostic or AUS/FLUS test result (second biopsy test result), G = % patients with FN/SFN result after a first non-diagnostic or AUS/FLUS test result (second biopsy test result), H = % patients with non-diagnostic, AUS/FLUS or FN/SFN after a second non-diagnostic or AUS/FLUS test result (third biopsy test result). **Overall reimbursement cost = A + C(B+F) + E(D+G+H)**

Sample Provider cost calculations:
Inputs: A = % patients with FN/SFN result from first, second, or third biopsy test result, B = % patients with non-diagnostic or AUS/FLUS after a second non-diagnostic or AUS/FLUS test result (third biopsy test result). **Total thyroid lobectomies per 1,000 patients** = 1000 X (A + B). Avoided thyroid lobectomies = Total thyroid lobectomies for FNA scenario – Total thyroid lobectomies for US-CNB scenario (i.e., as second test and beyond). **Avoided thyroidectomy costs** = Estimated thyroid lobectomy hospital outpatient true cost for US-FNA scenario - Estimated thyroid lobectomy hospital outpatient true cost for US-CNB scenario (i.e., as second test and beyond). **Device cost as % reimbursement** = Total scenario device costs / Total scenario device reimbursement payments

Reference List

1. Kumar V, Abbas AK, Aster JC (2018). Robbins Basic Pathology
2. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM et al. (2016) American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical practice for the diagnosis and management of thyroid nodules–2016 update. Endocrine practice 22 (s1): 1-60.
3. National Cancer Institute (Web Page) Surveillance, Epidemiology, and End Results Program (SEER) Cancer Stat Facts: Thyroid Cancer. Based on 2012-2014 data. Updated Available online at: http://seer.cancer.gov/statfacts/html/thyro.html. Accessed: January 26, 2018.
4. GlobalData (2014) Biopsy Devices - Global Analysis and Market Forecasts. GDME0188MAR
5. Cibas ES, Ali SZ (2009) The Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol 132 (5): 658-665.
6. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ et al. (2016) 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 26 (1): 1-133.
7. Hong MJ, Na DG, Kim SJ, Kim DS (2017) Role of core needle biopsy as a first-line diagnostic tool for thyroid nodules: a retrospective cohort study. Ultrasonography
8. Trimboli P, Nasrollah N, Guidobaldi L, Taccogna S, Cicciarella Modica DD et al. (2014) The use of core needle biopsy as first-line in diagnosis of thyroid nodules reduces false negative and inconclusive data reported by fine-needle aspiration. World J Surg Oncol 12 61.
9. Chen BT, Jain AB, Dagis A, Chu P, Vora L et al. (2015) Comparison of the efficacy and safety of ultrasound-guided core needle biopsy versus fine-needle aspiration for evaluating thyroid nodules. Endocr Pract 21 (2): 128-135.
10. Trimboli P, Nasrollah N, Amendola S, Crescenzi A, Guidobaldi L et al. (2015) A cost analysis of thyroid core needle biopsy vs. diagnostic surgery. Gland Surg 4 (4): 307-311.
11. Schneider DF, Cherney Stafford LM, Brys N, Greenberg CC, Balentine CJ et al. (2017) Gauging the Extent of Thyroidectomy for Indeterminate Thyroid Nodules: An Oncologic Perspective. Endocr Pract 23 (4): 442-450.
12. Anderson TJ, Atalay MK, Grand DJ, Baird GL, Cronan JJ et al. (2014) Management of nodules with initially nondiagnostic results of thyroid fine-needle aspiration: can we avoid repeat biopsy? Radiology 272 (3): 777-784.
13. Eun NL, Yoo MR, Gweon HM, Park AY, Kim J-A et al. (2016) Thyroid nodules with nondiagnostic results on repeat fine-needle aspiration biopsy: which nodules should be considered for repeat biopsy or surgery rather than follow-up? Ultrasonography 35 (3): 234-243.
14. Kandil E, Krishnan B, Noureldine SI, Yao L, Tufano RP (2013) Hemithyroidectomy: a meta-analysis of postoperative need for hormone replacement and complications. ORL J Otorhinolaryngol Relat Spec 75 (1): 6-17.
15. Balentine CJ, Vanness DJ, Schneider DF (2018) Cost-effectiveness of lobectomy versus genetic testing (Afirma(R)) for indeterminate thyroid nodules: Considering the costs of surveillance. Surgery 163 (1): 88-96.
16. Elfenbein DM, Schneider DF, Chen H, Sippel RS (2014) Surgical site infection after thyroidectomy: a rare but significant complication. J Surg Res 190 (1): 170-176.
17. Lin JS, Aiello Bowles EJ, Williams SB, Morrison CC (2017). U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. eds). Agency for Healthcare Research and Quality (US): Rockville (MD).
18. Hadker N, Egan J, Sanders J, Lagast H, Clarke BL (2014) Understanding the burden of illness associated with hypoparathyroidism reported among patients in the PARADOX study. Endocr Pract 20 (7): 671-679.
19. Verloop H, Louwerens M, Schoones JW, Kievit J, Smit JW et al. (2012) Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. J Clin Endocrinol Metab 97 (7): 2243-2255.
20. Stoll SJ, Pitt SC, Liu J, Schaefer S, Sippel RS et al. (2009) Thyroid hormone replacement after thyroid lobectomy. Surgery 146 (4): 554-558; discussion 558-560.
21. Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R et al. (2002) Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf) 57 (5): 577-585.
22. Leibson C, Clarke B, Ransom J, Lagast H (2011) Medical care costs for persons with and without prevalent hypoparathyroidism: a population-based study. J Bone Miner Res 26 S183.
23. Lee L, Mitmaker EJ, Chabot JA, Lee JA, Kuo JH (2016) Cost-Effectiveness of Diagnostic Lobectomy Versus Observation for Thyroid Nodules >4 cm. Thyroid 26 (2): 271-279.
24. Truven Health Analytics LLC (2018) RED BOOK Online(R). Average wholesale price
25. Stack Bc, Jr., Bimston Dn, Bodenner Dl, Brett Em, Dralle H Et Al. (2015) American Association Of Clinical Endocrinologists And American College Of Endocrinology Disease State Clinical Review: Postoperative Hypoparathyroidism–Definitions And Management. Endocr Pract 21 (6): 674-685.
26. Sung JY, Na DG, Kim KS, Yoo H, Lee H et al. (2012) Diagnostic accuracy of fine-needle aspiration versus core-needle biopsy for the diagnosis of thyroid malignancy in a clinical cohort. Eur Radiol 22 (7): 1564-1572.
27. Na DG, Kim JH, Sung JY, Baek JH, Jung KC et al. (2012) Core-needle biopsy is more useful than repeat fine-needle aspiration in thyroid nodules read as nondiagnostic or atypia of undetermined significance by the Bethesda system for reporting thyroid cytopathology. Thyroid 22 (5): 468-475.
28. Renshaw AA, Pinnar N (2007) Comparison of thyroid fine-needle aspiration and core needle biopsy. Am J Clin Pathol 128 (3): 370-374.
29. Ha EJ, Baek JH, Lee JH, Kim JK, Song DE et al. (2016) Core needle biopsy could reduce diagnostic surgery in patients with anaplastic thyroid cancer or thyroid lymphoma. Eur Radiol 26 (4): 1031-1036.
30. Ha EJ, Baek JH, Na DG, Kim JH, Kim JK et al. (2015) The Role of Core Needle Biopsy and Its Impact on Surgical Management in Patients with Medullary Thyroid Cancer: Clinical Experience at 3 Medical Institutions. AJNR Am J Neuroradiol 36 (8): 1512-1517.
31. Na DG, Kim DS, Kim SJ, Ryoo JW, Jung SL (2016) Thyroid nodules with isolated macrocalcification: malignancy risk and diagnostic efficacy of fine-needle aspiration and core needle biopsy. Ultrasonography 35 (3): 212-219.
32. Ha EJ, Baek JH, Lee JH, Song DE, Kim JK et al. (2013) Sonographically suspicious thyroid nodules with initially benign cytologic results: the role of a core needle biopsy. Thyroid 23 (6): 703-708.
33. Suh CH, Baek JH, Lee JH, Choi YJ, Kim KW et al. (2016) The role of core-needle biopsy in the diagnosis of thyroid malignancy in 4580 patients with 4746 thyroid nodules: a systematic review and meta-analysis. Endocrine 54 (2): 315-328.
34. Yoon JH, Kim EK, Kwak JY, Moon HJ (2015) Effectiveness and limitations of core needle biopsy in the diagnosis of thyroid nodules: review of current literature. J Pathol Transl Med 49 (3): 230-235.
35. Baloch ZW, Cibas ES, Clark DP, Layfield LJ, Ljung BM et al. (2008) The National Cancer Institute Thyroid fine needle aspiration state of the science conference: a summation. Cytojournal 5 6.
36. Perros P, Boelaert K, Colley S, Evans C, Evans RM et al. (2014) Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf) 81 Suppl 1 1-122.
37. Na DG, Baek JH, Jung SL, Kim JH, Sung JY et al. (2017) Core Needle Biopsy of the Thyroid: 2016 Consensus Statement and Recommendations from Korean Society of Thyroid Radiology. Korean J Radiol 18 (1): 217-237.
38. Wolinski K, Stangierski A, Ruchala M (2017) Comparison of diagnostic yield of core-needle and fine-needle aspiration biopsies of thyroid lesions: Systematic review and meta-analysis. Eur Radiol 27 (1): 431-436.
39. Šimundić A-M (2009) Measures of Diagnostic Accuracy: Basic Definitions. EJIFCC 19 (4): 203-211.
40. Cao H, Kao RH, Hsieh MC (2016) Comparison of core-needle biopsy and fine-needle aspiration in screening for thyroid malignancy: a systematic review and meta-analysis. Curr Med Res Opin 32 (7): 1291-1301.
41. Suh CH, Baek JH, Lee JH, Choi YJ, Kim JK et al. (2016) The Role of Core-Needle Biopsy as a First-Line Diagnostic Tool for Initially Detected Thyroid Nodules. Thyroid 26 (3): 395-403.
42. Kim HC, Kim YJ, Han HY, Yi JM, Baek JH et al. (2017) First-Line Use of Core Needle Biopsy for High-Yield Preliminary Diagnosis of Thyroid Nodules. AJNR Am J Neuroradiol 38 (2): 357-363.
43. Yi KS, Kim JH, Na DG, Seo H, Min HS et al. (2015) Usefulness of core needle biopsy for thyroid nodules with macrocalcifications: comparison with fine-needle aspiration. Thyroid 25 (6): 657-664.
44. Choi SH, Baek JH, Lee JH, Choi YJ, Hong MJ et al. (2014) Thyroid nodules with initially non-diagnostic, fine-needle aspiration results: comparison of core-needle biopsy and repeated fine-needle aspiration. Eur Radiol 24 (11): 2819-2826.
45. Paja M, del Cura JL, Zabala R, Corta I, Lizarraga A et al. (2016) Ultrasound-guided core-needle biopsy in thyroid nodules. A study of 676 consecutive cases with surgical correlation. Eur Radiol 26 (1): 1-8.
46. Nasrollah N, Trimboli P, Rossi F, Amendola S, Guidobaldi L et al. (2014) Patient's comfort with and tolerability of thyroid core needle biopsy. Endocrine 45 (1): 79-83.
47. Ha EJ, Baek JH, Lee JH, Kim JK, Choi YJ et al. (2017) Complications following US-guided core-needle biopsy for thyroid lesions: a retrospective study of 6,169 consecutive patients with 6,687 thyroid nodules. Eur Radiol 27 (3): 1186-1194.
48. Jeong, EJ, Chung, SR, Baek, JH, et al. (2018) A Comparison of Ultrasound-Guided Fine Needle Aspiration versus Core Needle Biopsy for Thyroid Nodules: Pain, Tolerability, and Complications. Endocrinol Metab (Seoul) 33(1): 114-120.
49. Lee, SH, Kim, MH, Bae, JS, et al. (2014) Clinical outcomes in patients with non-diagnostic thyroid fine needle aspiration cytology: usefulness of the thyroid core needle biopsy. Ann Surg Oncol 21(6): 1870-7.
50. Samir, AE, Vij, A, Seale, MK, et al. (2012) Ultrasound-guided percutaneous thyroid nodule core biopsy: clinical utility in patients with prior nondiagnostic fine-needle aspirate. Thyroid 22(5): 461-7.

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