Accuracy of core needle biopsy compared to fine needle biopsy for the diagnosis of malignancy in patients with suspected head and neck cancers: A systematic review and meta-analysis of diagnostic test accuracy and comparison of adverse effects.

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DECLARATION

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ABSTRACT

Objective

The objective of this review was to compare the diagnostic accuracy of core needle biopsy and fine needle aspiration cytology for patients with a head and neck mass for a diagnosis of malignancy using surgical histopathology as a reference test and to compare the risks and adverse events associated with each technique.

Introduction

A proportion of head and neck neoplasms are malignant which can only be determined by a tissue diagnosis. Options for tissue biopsy include - surgical biopsy, fine needle aspiration (FNA), and core needle biopsy (CNB). Insufficient tissue for a diagnosis results in additional delays in patient management. The diagnostic sensitivity and specificity of each option for tissue biopsy in diagnosing a head and neck malignancy has not been evaluated in a meta-analysis. Our review aimed to compare and review the diagnostic accuracy of FNA and CNB for head and neck lesions and assess the risk and adverse events associated with each technique.

Inclusion criteria

Studies that compared ultrasound guided CNB and/or FNAC to investigate lumps suspicious for head and neck malignancy in thyroid, cervical lymph nodes, or salivary gland in adult patients were included. The comparator test was definitive histology in the form of surgical biopsy/excision.

Methods

MEDLINE, EMCARE, EMBASE, Web of Science, and the Cochrane Database of Systematic Reviews were searched. Studies were critically appraised by two independent reviewers for methodological quality using the modified critical appraisal instrument QUADAS2 using JBI – SUMARI software. Data was extracted from papers included in the review using a modified data extraction tool available in the JBI Reviewer's Manual. Meta-analysis was performed using a random-effects model. Comparison of accuracy of the two techniques was achieved by comparing pooled sensitivity and specificity using a bivariable model. The inadequacy rate and inconclusive rate were also pooled for comparison. Summary receiver operating characteristic (ROC) graphs were created to confirm diagnostic accuracy. Narrative review of adverse effects was conducted.

Results

Majority of the patients in the included studies compared FNA and CNB for thyroid masses. Data on a total of 1229 patients for FNA and 1135 patients for CNB from six studies met the inclusion criteria and were included in the final meta-analysis. The studies were of moderate-low or unknown quality. While CNB and FNA had similar sensitivity and specificity in diagnosing thyroid malignancy, the non-diagnostic and inadequacy rate for CNB was significantly lower: sensitivity 0.91 (95% CI: 0.79 to 0.96) vs 0.75 (95% CI: 0.66 to 0.83) respectively, specificity 1.00 (95% CI: 0.98 to 1.00) vs 1.00 (95% CI: 0.60 to 1.00) respectively, non-diagnostic rate 0.043 (95% CI: 0.016 to 0.07) vs 0.164 (95% CI: 0.083 to 0.245) respectively, inadequacy rate 0.112 (95% CI: 0.087 to 0.137) vs 0.17 (95% CI: 0.106 to 0.233) respectively ($p<0.001$). There were no substantial differences in complication rates noted.

Conclusion

Sensitivity and specificity of FNA and CNB for diagnosis of thyroid malignancy for FNA and CNB are high. The inadequacy rate and inconclusive rate for CNB is lower than FNA for thyroid malignancy. CNB could be used instead of FNA for diagnosis of thyroid nodules if found to be cost effective. These results need to be treated with caution as the methodological quality of included studies was generally poor, introducing a high risk of bias; while substantial differences in study characteristics resulted in significant between study heterogeneity. Further verification of these results with high quality studies is required.

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TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

GLOSSARY OF TERMS

Accuracy – expression of a tests ability to discriminate between people with the target condition and those without it.

Sensitivity - proportion that test positive amongst those having the target condition.

Specificity - proportion that test negative amongst those without the target condition.

Negative likelihood ratio - ratio of the proportion that test positive amongst those that have the target condition compared to the proportion that test positive amongst those who do not have the target condition.

Negative predictive value - proportion that do not have the target condition amongst those that test negative.

Positive likelihood ratio - ratio of the proportion that test positive amongst those that have the target condition compared to the proportion that test positive amongst those who do not have the target condition.

Positive predictive value - proportion that have the target condition amongst those that test positive.

Pre-test probability - proportion with the target condition amongst the group suspected of having the condition.

Receiver characteristic operating (ROC) curve - the sensitivity and specificity of a test vary depending on the threshold value chosen. The ROC curve describes the trade-off between sensitivity and specificity as the threshold changes.

Threshold - the value above or below which a test result is considered positive

Cost-effectiveness – comparison of both costs (resource use) and consequence (outcomes/effects) to determine an intervention's productivity in relation to its cost.

Indeterminate - Cytological results that are unable to differentiate between malignant and benign nodules with confidence

Non-diagnostic - Inadequate sampling that does not allow for microscopic examination

CHAPTER 1 **INTRODUCTION**

1.1 The Historical Context of Systematic Reviews

Literature reviews became popular as a means of bringing together articles in support of a position or argument in the 1960s, or to present a narrative overview of a topic in fields such as psychology, education and the social sciences.[1, 2] Early literature reviews summarised the findings of several studies on the same topic using similar measures, however, concerns with quality, transparency and reliability were compounded by a lack of standardised methodology.[3] Systematic reviews became popular as a field of science in response to the need for increased rigor and reliability, while reducing the risk of bias and systematic error which was considered a limitation of literature reviews. Evidence-based Medicine (EBM) was introduced in the early 1990s to assist clinicians that were increasingly relying on healthcare literature to make management decisions.[1] With the increase in the number of primary studies, it became apparent that all available evidence needed to be synthesised within a particular domain to help clinicians make truly evidence informed decisions. Early review articles lacked systematic and statistical methods to derive reliable estimates of treatment effects and consequently were prone to biased and inaccurate conclusions.[1]

Literature can be reviewed systematically to reduce the risk of bias using a diverse range of methods to serve the demands of various research and policy domains. These methods are guided by the type of evidence being reviewed; quantitative and qualitative methods are common to EBM.[1] Quantitative evidence is produced by the study of natural and social sciences using traditional scientific methods that generate numerical data.[4] Quantitative research includes the use of statistical methods to assess effectiveness, incidence,

prevalence, aetiology of disease, quality of life, satisfaction and care. Quantitative reviews include the synthesis or statistical analysis of primary quantitative studies, preferreably using an established, transparent and rigorous methodology. Alternately, as a contribution to evidence-based healthcare, analysis of human experience and cultural and social phenomena can be studied by qualitative methodologies.[5] Qualitative evidence holistically draws on complex human phenomena in naturalistic (uncontrolled) settings.[6] Examples of qualitative methodology include ethnography, phenomenology, qualitative enquiry, action research, discourse analysis and grounded theory.[7] In the healthcare context, qualitative research seeks a deeper understanding of the experience, attitudes, beliefs and perspectives of clinicians and patients. This evidence is produced by observation (either direct or indirect) or by conducting individual or group interviews. Quantitative and qualitative systematic reviews synthesise the evidence base to help clinicians and policy makers identify feasible, appropriate, meaningful and effective healthcare practices to improve healthcare outcomes.

Within the scientific consensus associated with evidence for healthcare, it is now increasingly recognised that the methodological rigor with which a review is executed is equally pertinent to the strength of evidence provided by the included study designs.[3, 8] The strength, and certainty (or confidence) of conclusions drawn from systematic review results depend on the precision of the review question, the inclusion and exclusion criteria, and the data extraction techniques.[8] To achieve the level of rigour and quality equivalent to primary studies, systematic reviews require an a-priori protocol, a systematic, comprehensive search, appraisal of the internal validity of included studies and transparent methods of synthesising research evidence while adhering to guidelines on the conduct and reporting of the review.[3] Table 1 describes the salient differences between systematic reviews and literature reviews.

Table 1 Differences between systematic review and literature reviews[1, 8]

	Literature review	Systematic review
Aim	Provides current thinking/context of several aspects of a topic without a specific question.	Answers a precise question, using a predetermined method detailed in a study protocol.
Data collection	Search of selected databases unsystematically. Use of grey literature common.	Comprehensive search strategy of several specified databases, search of gray literature may be included.
Data extraction	Subjective interpretation of study's conclusions.	Use of a pre-specified data extraction tool to collect data congruent to outcome measures. 2 researchers usually extract data.
Inclusion criteria	No explicit inclusion criteria.	Criteria for inclusion pre-defined in terms of participants, intervention, comparator and outcome (PICO).
Data analysis	No clear indication of methodological assessment. Often unsystematic compilation of randomly selected studies.	Use of standardised critical appraisal tools/checklists to identify bias and methodological quality and strength of evidence.
Data synthesis and presentation	Typically, narrative using chronological/conceptual or thematic summarisation with no clear explanation regarding how conclusions are drawn.	Use of PRISMA, tabular summarisation of data with statistical pooling where possible or narrative.
Outcome	Recommendation informed by evidence drawn from various included studies.	Actions/directions for practice, identifies gaps in knowledge and uncertainty of findings (if any) and recommendations for future research based on evidence from reviewed papers.

It is important to note at this point that meta-analysis is an analytic technique that statistically combines the results of quantitative studies to provide an augmented numerical analysis of the included studies, it is not a term that is analogous with the term 'systematic review'.[1] Meta-analysis should only be conducted as part of a systematic review if the following criteria are met:[9]

- Clinical homogeneity - Similarity in study participants in terms of age, the disease state that allows for pooling of data and generalisation for the chosen population
- Methodological homogeneity - Similarity in study designs and methods for combining data
- Statistical homogeneity: low heterogeneity as demonstrated by statistical tests of heterogeneity such as the Cochran's Q test and I^2 statistic.

1.2 The Context of this Review

Literature suggests that persistent head and neck masses in adult patients should be considered malignant until proven otherwise.[10] Delay in diagnosis can affect tumour stage and prognosis with poorer functional outcome after treatment and increased mortality.[11] Diagnosis can be complicated as a wide spectrum of non-neoplastic and neoplastic pathology presents as head and neck masses in adult patients. Underlying aetiologies responsible for head and neck masses include infectious, inflammatory, congenital, traumatic, benign or malignant neoplastic processes. Head and neck cancers account for the 9th most common cancer in the world and the 7th most common cancer in Australia, with increasing incidence and mortality in both developed and developing countries.[12, 13] Presence of a persistent head and neck mass prompts urgent investigation and management as this can be the initial or the

only clinically apparent manifestation of head and neck cancers, namely squamous cell carcinoma (HNSCC), lymphoma, skin, thyroid or salivary gland cancer.

History and physical examination findings suggestive of a malignant process include local or referred pain, voice change, neck mass, dysphagia, weight loss, stridor or bleeding. The signs and symptoms prompt imaging with computed tomography (CT), magnetic resonance imaging (MRI) or high-resolution ultrasound.[14] While these imaging modalities can provide useful information about head and neck tumours, they are unable to definitively determine whether a lesion is malignant or benign.[15] Tissue diagnosis is a standard requirement for clinical management as it provides the pathological status of masses. Tissue diagnosis can be achieved with fine-needle aspiration (FNA), core needle biopsy (CNB) or open surgical biopsy.

Timely and standardised assessment of pathology pre-operatively has several advantages. These include triaging of patients in planning the type and timing of operative intervention;, consideration of pre-operative adjuvant/neoadjuvant therapy (if indicated); and prevention of unnecessary surgery in select patients that can be observed and managed conservatively (Warthin's tumour) or those that require non-surgical management (lymphoma).[16] Historically, many head and neck lesions were treated by surgical excision under a general anaesthetic, serving both diagnostic and therapeutic purposes.[16] However, open surgical biopsy or lymph node excision is an invasive option to provide adequate histological information as it often requires a hospital admission, and has a higher risk of complications such as bleeding, incomplete or inadequate excision, and wound infections as compared to FNA and CNB.[17] In the recent guidelines, open surgical biopsy is contraindicated in cases of suspected malignancy due to the increased risk of tumour seeding, reduced survival rates and increased

risk of malignancy recurrence after treatment.[16, 18, 19] Consequently, less invasive methods have evolved to diagnose masses that are indeterminate based on clinical information provided by history, exam, laboratory and imaging modalities.

Fine needle aspiration (FNA) and core needle biopsy (CNB) provide less invasive alternatives to open surgical biopsy for diagnosis of head and neck cancers. Although both FNA and CNB have similar safety profiles, at present FNA is the recommended initial diagnostic technique because it is rapid and cost-effective.[18] CNB provides tissue diagnosis with preserved histological architecture and is the preferred diagnostic test in the diagnosis of lymphoma and in patients that have received previous head and neck irradiation.[18, 20, 21] The main objective of this systematic review was to compare the diagnostic accuracy of FNA and CNB for neoplasia and malignancy and assess the risk of adverse events associated with each technique.

1.3 Studies of Diagnostic Test Accuracy

Health professionals, policymakers and patients depend on effective, appropriate, feasible and meaningful research to make informed, evidence-based decisions.[22] Evidence-based healthcare integrates clinical expertise with the best available evidence while taking into account patient preference.

Clinicians use diagnostic tests to determine if a disease or condition is present or absent, this directly informs management plans. Diagnostic tests encompass signs and symptoms observed while taking a history or examining the patient, psychological investigations, and investigations such as biochemical technologies, pathology, and imaging.[23]

As science advances, a better understanding of the aetiology of diseases and ever progressing technological innovations has resulted in the development of advanced diagnostic tests with improved accuracy, efficiency, safety, and cost-effectiveness. This advancement has been accompanied by research efforts to test the accuracy of new and existing diagnostic tests.[24] Diagnostic test accuracy is defined as a test's capacity to distinguish between people with the the target condition and those without it.[25] Measures of test accuracy include: sensitivity and specificity; positive and negative predictive values; positive and negative likelihood ratios.[25] Evaluation of diagnostic accuracy involves comparing the results of the index test i.e. the novel test with those obtained using a standard reference test, in a population of patients suspected of having the disease.[26]

Summary statistics for test accuracy are conventionally presented in a two by two table that is obtained by comparing the index test (test outcome) with the reference standard (disease state) as shown in Table 2.

Cell 'a' are those patients that the test correctly diagnosed with the disease, these are true positives (TP). Cell 'b' are those patients that have a positive test result but do not have the disease as per the reference standard, these tests are false positives (FP). Cell 'c' are those patients that have the disease but were incorrectly labelled as non-diseased by the index test, these tests are false negatives (FN). Cell 'd' labelled true negatives (TN) are those patients that do not have the disease and appropriately had a negative test result.

Table 2 Classification of test results and disease status in a 2x2 table

Test outcome (index test)	Disease/condition status		
	Diseased	Disease absent	Total
Test positive	True positives (a)	False positives (b)	Test positives (a+b)

Test negative	False negatives (c)	True negatives (d)	Test negatives (c+d)
Total	Disease/condition positives (a+c)	Disease negatives (b+d)	N (a+b+c+d)

Sensitivity is defined as the percentage of patients with positive index test results that have the disease, i.e. the test correctly classifies an individual as 'diseased' (from Table 2 a/a+c). Specificity is defined as the percentage of patients that correctly have a negative index test i.e. the test correctly classifies an individual as disease free (from Table 2 d/b+d).[27] In practice a highly specific test if positive rules the disease in, while a highly sensitive test if negative rules the disease out. It is important to note that measures of test accuracy depend on the threshold that defines the value above or below which a test result is considered positive.[25] Sensitivity and specificity are dependent on the threshold/cut off of the index test. If a test is considered positive above a certain threshold and negative if the result is below the cut-off, decreasing the cut-off decreases the number of false negatives and consequently increases the sensitivity of the test. However, decreasing the cut-off will also result in higher false positives, thus decreasing the specificity. It is therefore important to account for the threshold used when interpreting sensitivity and specificity data. Sensitivity and specificity help us identify the utility of a test in making a diagnosis, but do not indicate whether a positive result truly signifies the presence of the disease. There are other alternatives proposed to assess test accuracy[28] such as predictive values and likelihood ratios[29] that provide this information.

Predictive values provide the probability of the diagnostic value of the result of the test i.e. the proportion of patients who are correctly diagnosed.[30] The positive predictive value is the proportion of individuals with positive test results that are correctly diagnosed (from Table 2 a/a+b). The negative predictive value is the proportion of individuals with negative test results

who are diagnosed correctly (from Table 2 d/c+d). Predictive values are directly related to the prevalence of the disease.[31] Prevalence also referred to as pretest probability is the proportion of the population that has the disease at any given time. populations with higher disease prevalence have higher positive predictive values and lower negative predictive values.[32] Sensitivity and specificity are not mathematically affected by the prevalence of the disease, and therefore the estimated false positive and false negative results remain constant across populations with different disease prevalence.[33]

Likelihood ratios assess the probability that the test result obtained would be expected in a person with the condition, compared to the probability that the same result would be seen in a person without the condition. Positive likelihood ratios express how likely it is that people will receive a positive test compared to those who do not have the condition. Negative likelihood ratios express how many times more likely it is that people with the condition will receive a negative test compared to those who do not have the condition.[23] A likelihood ratio is particularly useful when index test results can be divided into more than two outcomes rather than just positive and negative. For example, a test may be strongly positive, weakly positive, or negative and likelihood ratios for each test result can be calculated.[34] Additionally, the clinical utility of the test can be determined by comparing the pretest to posttest probability of the disease. A test is generally more useful if the pretest to posttest probability of the disease increases or decreases significantly.

Evaluation of diagnostic tests is important for policymakers to determine funding and availability of tests.[35] Clinicians and policymakers require a thorough assessment of the new and upcoming tests and their ability to accurately diagnose the condition of interest. Transition to newer diagnostic tests should be guided by the comparative cost, ease of performance,

patient safety and accuracy of the test.[26] If the new test obviates the need for further investigation without reducing accuracy and results in appropriate and effective therapy in a safe and timely fashion, the new diagnostic test could be preferentially used;[36] ultimately impacting clinical practice and patient outcomes.

1.4 The science of synthesising evidence of diagnostic test accuracy

Systematic reviews of diagnostic test accuracy (DTA) systematically identify, select and critically appraise relevant research to analyse data from primary studies of diagnostic accuracy.[25] Systematic reviews and meta-analyses can provide more valid summary estimates of diagnostic tests[24] than individual DTA studies, that can help guide clinicians and policymakers. Additionally, systematic reviews can provide information on covariates that affect tests' diagnostic accuracy and help identify areas for further research.[24] A well-conducted systematic review of high quality diagnostic studies is the highest level of diagnostic evidence.[37]

A meta-analysis is a component of systematic reviews that integrates the results of primary research studies with specialised statistical methodology.[38] Meta-analysis requires homogeneity between key characteristics of included studies. However, differences in patient populations due to small sample sizes or patient selection, methods, measurement instruments and outcomes contribute to between study heterogeneity.[35] In addition, the results of diagnostic tests can vary at different stages of the disease or with different test interpretations and interpreters.[39]

1.5 Anatomical subsites of Head and Neck Masses

1.5.1 Thyroid nodules

A thyroid nodule is a radiologically distinct lesion within the thyroid gland different from the surrounding thyroid parenchyma.[40] The incidence of palpable thyroid nodules is between 4-7% in the general population.[41] Extensive use of imaging has resulted in more frequent detection of thyroid nodules with up to 67% of adults being diagnosed with 'incidentalomas'.[42]

Table 3 classifies the different types of thyroid nodules. With 7-15% of thyroid nodules being malignant, it is imperative to rule out thyroid cancer when investigating a nodule.[43, 44] In Australia, it is estimated that approximately 3,615 new cases of thyroid cancer would be diagnosed in 2019.[45] Thyroid cancer has the greatest percentage increase in the age-standardised incidence from 3.7 to 13 per 100,000 persons between 1982 and 2019.[13] This may be attributed to increased surveillance and introduction of neck ultrasonography.[46] In 2016, 140 deaths were attributed to thyroid cancer in Australia and the overall 5-year survival rate of thyroid cancer is 97%.[45]

A preoperative diagnosis facilitates informed patient consent in surgical cases and helps provide appropriate treatment of patients at high risk of thyroid cancer mortality and morbidity. It is important to rule out malignancy to avoid unnecessary overtreatment, anxiety, and suffering that diagnostic surgery causes in patients with benign neoplasms. Serum thyroglobulin level, radionuclide and cross-sectional (CT and MRI) imaging and ultrasonography can provide useful information in the differential diagnosis of thyroid nodules. However, these investigations are unable to definitively diagnose the neoplastic nature of the thyroid nodule. FNA or CNB are therefore indicated to guide further management.

Table 3 Histopathological classification of thyroid nodules(67, 70, 71)

	Types	Approximate distributions
Non-neoplastic	Hyperplastic Colloid Colloid nodule Inflammatory Hashimoto thyroiditis Subacute thyroiditis	80% of all thyroid nodules
Thyroid cysts	Simple or haemorrhagic cysts	
Neoplastic		
Benign	Follicular adenoma	10-15% of all thyroid nodules
Malignant		7-15% of all thyroid nodules
	Papillary carcinoma	70-80% of all thyroid cancers
	Follicular carcinoma	15-20% of all thyroid cancers
	Hurthle cell carcinoma	A less common subtype of follicular carcinoma
	Medullary carcinoma	4% of all thyroid cancers
	Anaplastic carcinoma	1% of all thyroid cancers
	Primary thyroid lymphoma	
	Metastatic malignant lesion	

1.5.2 Salivary gland neoplasms

Salivary gland neoplasms are rare and represent a variety of both benign and malignant histological subtypes summarised in Table 4. In 2009 salivary gland cancers accounted for

6.8% of new head and neck cancers.[47] The mortality from salivary gland cancers varies by stage and pathology, with an overall 5-year survival rate of 70.4%.[47]

Amongst salivary gland tumours, 80% arise in the parotid glands, 10-15% arise in the submandibular gland, and the rest arise in sub-lingual and minor salivary glands.[48] Salivary gland tumours present as an enlarging mass and may be associated with neurological signs such as facial nerve paralysis. Clinical features suspicious for malignancy include pain, fixed tumour, ipsilateral facial nerve palsy, and cervical lymphadenopathy.[48, 49] Cross-sectional imaging with CT and MRI scans are useful adjuncts for operative planning but preoperative cytological or histological diagnosis is imperative as the indication for and extent of surgery is determined by the diagnosis.

Table 4 Common salivary neoplasms(114)

	Types	**Parotid incidence**	**Submandibular incidence**
Benign	Pleomorphic adenoma Warthin's tumour (papillary cystadenoma lymphomatosum Oncocytoma Monomorphic	59% 7.3%	36%
Malignant	Mucoepidermoid carcinoma Adenoid cystic carcinoma Acinic cell carcinoma Carcinoma Ex-pleomorphic adenoma Squamous cell carcinoma Adenocarcinoma	7.9% 3.1% 3.5% 4.4% 2%	12% 25% 1% 10% 7% 1%

1.5.3 Cervical lymphadenopathy

An abnormal congenital or acquired lesion that is visible, palpable or seen on imaging below the mandible, above the clavicle and deep to the skin is defined as a neck mass.[18] A variety

of benign and malignant pathologies present as lymphadenopathy or unclear masses of the neck[15] these are summarised in

Table 5. Infectious lymphadenopathy is the most common cause of neck masses in children; however, most persistent masses in adults are due to neoplasms.[18] Presentation with asymptomatic neck mass may be the first manifestation of a malignancy such as squamous cell carcinoma (HNSCC), lymphoma, thyroid or salivary gland cancer.[18] Adults with a persistent neck mass need to be investigated in a timely fashion to rule out malignancy as tumour growth within the regional lymph nodes from metastatic spread can result in a neck mass.[50] Mucosal HNSCC may originate in the nasopharynx, oral cavity, oropharynx, hypopharynx or larynx.[18] A delayed diagnosis can result in a poor prognosis, progression of HNSCC and lymphoma, and poorer functional outcomes.[11, 51-53]

In 2019, the estimated number of new cases of head and neck cancer and lymphoma diagnosed in Australia was predicted to be 5212 and 6423 accounting for the 7th and 6th most common cancers in Australia.[54, 55]

Table 5 Cervical lymph node pathology(14)

Vascular	Carotid body tumour Arteriovenous fistula Pseudoaneurysm
Infectious	Cytomegalovirus Epstein Barr virus Staphylococcus or streptococcal infection Toxoplasmosis Tuberculosis Human immunodeficiency virus Viral upper respiratory tract infection
Neoplastic	Parotid lymphadenopathy Squamous cell carcinoma of the upper aerodigestive tract Hodgkin lymphoma Human papillomavirus-related squamous cell carcinoma Metastatic cancer Non-Hodgkin lymphoma
Inflammatory	Acute sialadenitis
Congenital	Branchial cleft cyst Thyroglossal duct cyst
Auto-immune	Sarcoidosis Sjögren syndrome Amyloidosis
Idiopathic	Castleman disease (angiofollicular lymphoproliferative disease) Kikuchi disease (histiocytic necrotizing lymphadenitis) Kimura disease Rosai-Dorfman disease

1.6 Biopsy Assessment of Head and Neck Pathology

1.6.1 The Use of Fine Needle Aspiration

Fine needle aspiration (FNA) was popularised in Scandinavia and Europe in 1952 to retrieve cellular material for cytological examination.[56] FNA was recognised in North America as the

preferred diagnostic technique for evaluating masses of different sites in the late 1980s.[57, 58] Over the years, FNA has become the recommended test for preoperative cytological assessment of almost all body lesions including head and neck masses.[59] Since the introduction of FNA, the number of unnecessary surgeries has reduced significantly.[60]

Fine needle aspiration is performed using a 21-28-gauge needle through suction or capillary action to draw cellular material that is transferred to a glass slide, which is fixed and dried to allow for microscopic evaluation. FNA can be performed in an outpatient, clinic setting by palpation and insertion of a needle into the tumour and aspiration by the cytopathologist, surgeon, or physician.[61, 62]

1.6.1.1 Thyroid nodules – Fine Needle Aspiration

In 2009, the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was developed to standardise the terminology and morphologic criteria related to thyroid FNA and relay their associated malignancy risks.[63] All thyroid pathological reports are reported according to TBSRTC or British Thyroid Association Guidance, or other country/region specific guidelines. The TBSRTC was updated in 2017, with the revision of malignancy risks based on more recent (post-2010) data and updated evidence-based clinical management recommendations, summarised in Table 6.[64]

Table 6 Recommended diagnostic categories, risk of malignancy, and recommended clinical management(73-75)

Diagnostic category	UK Royal College of pathologists' diagnostic category	Description	Risk of malignancy (%)	Recommended management
Non-diagnostic or Unsatisfactory	Thy1	Cyst fluid only Virtually acellular specimen Other (Obscuring blood, clotting artefact, etc.)	5-10	Repeat FNA with ultrasound guidance
Benign	Thy2	Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.) Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context Consistent with granulomatous (subacute) thyroiditis Other	0-3	Clinical and sonographic follow up
Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)	Thy3a	Atypia	~10-30	Repeat FNA, molecular testing, or lobectomy

Diagnostic category	UK Royal College of pathologists' diagnostic category	Description	Risk of malignancy (%)	Recommended management
Follicular neoplasm or suspicious for follicular neoplasm	Thy3f	Specify if Hurthle cell (oncolytic) type	25-40	Molecular testing, lobectomy
Suspicious for malignancy	Thy4	Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma Other	50-75	Near total thyroidectomy or lobectomy
Malignant	Thy5	Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma Undifferentiated (anaplastic) carcinoma Squamous-cell carcinoma with mixed features Metastatic carcinoma Non-Hodgkin lymphoma Other	97-99	Near total thyroidectomy or lobectomy

Bongiovanni et al in 2012 investigated the validity of Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) through meta-analysis. A total of 6,362 (25%) of 25,445 thyroid

FNAs underwent surgical excision and this subgroup was used to determine the accuracy of TBSRTC.[65] The meta-analysis found the sensitivity, specificity, and accuracy to be 97, 50.7 and 68.8%, respectively. The meta-analysis concluded a high overall accuracy indicating that TBSRTC is a reliable and valid reporting system for thyroid cytology.[65] There are no standardised reporting systems for salivary gland and cervical lympahadenopathy for FNA or CNB.

1.6.1.2 Salivary gland – Fine needle Aspiration

Preoperative tissue diagnosis plays an important role in treatment decisions and patient counseling for salivary gland lesions. A malignant preoperative diagnosis can help prepare the patient in terms of extent of surgery, the need for neck dissection or postoperative radiotherapy. A meta-analysis published in 2011 that analysed 64 studies concluded that FNA had high specificity (97%) but a lower sensitivity (80%) with a relatively high false negative rate (20%) in salivary gland FNA.[66]

1.6.1.3 Cervical lymphadenopathy – Fine needle Aspiration

Current clinical practice guidelines for evaluation of neck masses in adults strongly recommend clinicians perform FNA or refer patients considered to be at increased risk of malignancy to someone who can perform FNA.[18] A meta-analysis of 782 cervical lymph node aspirates reported high sensitivity and specificity with 94.2% and 96.9% respectively. [67]

1.6.2 Optimisation of Fine Needle Aspiration

Fine needle aspiration is widely accepted because of its many advantages including rapid, relatively safe, cost-effective and accurate results. However, it has become increasingly apparent that FNA can be associated with high non-diagnostic rates. The diagnostic yield of FNA can be improved by the use of ultrasound-guidance, rapid onsite evaluation of the

aspirate, and use of ancillary techniques.[68-70] The use of real time image guidance with ultrasound has several advantages including provision of important information regarding the site of origin, the ability to biopsy non-palpable lesions and lesions less than a centimeter, improved accuracy in sampling heterogeneous nodules, and avoidance of adjacent vessels, implants, and other important structures.[71, 72] Ultrasound guided FNA performed by surgeons as well as cytologists have shown higher specificity, negative predictive value and sensitivity in recent studies along with fewer non-diagnostic samples compared to palpation guided FNA.[72-75] A randomised controlled trial performed by head and neck surgeons in an office based setting, reported a significant comparative diagnostic advantage with adequacy rate of 87% for ultrasound guidance versus 60% for standard palpation based biopsy.[73] Conrad et al in 2018 demonstrated significant reduction in nondiagnostic results for cytopathologist using ultrasound guided FNA (6.6%) versus palpation guided FNA (21.2%).[72]

Availability of onsite cytology allows for detection of inadequate samples and re-aspiration of the lesions as indicated, and provision of interim diagnosis.[76-78] Recent advances in liquid fixation allow for multiple thin-layer preparations and enhanced ability to perform immunohistochemistry that may help further refine diagnosis.[67] Molecular testing e.g. BRAFV600E mutation for papillary thyroid cancer is gaining popularity and may assist in determination of benignity in thyroid aspirate samples; however, molecular testing for FNAC is not currently available in Australia.

Shortcomings of Fine Needle Aspiration

1.6.2.1 Non-Diagnostic results

Despite optimisation of fine needle aspiration with ultrasound-guidance, rapid onsite evaluation of the aspirate, and ancillary testing, an ongoing concern with FNA is the non-diagnostic samples. Inadequate sampling results in diagnostic delays and unnecessary surgery in 10-15% of cases.[67] This has been noted as a pitfall across all head and neck subsites. FNA of thyroid nodules has been found to have a high rate of inadequate/unsatisfactory samples resulting in failure to provide a definitive diagnosis. Similarly, a systematic review assessing the diagnostic accuracy of FNA for salivary gland tumours demonstrated an inadequate sample rate of 8.6%. The non-diagnostic rate for cervical lymphadenopathy FNA without ultrasound guidance ranged from 3% to 30% in a systematic review of 782 lymph nodes.[67]

Repeat FNA with ultrasound guidance has been shown to provide a definitive diagnosis in only 50% of the cases for thyroid FNAs with non-diagnostic results.[79] If ultrasound or clinical findings are suspicious for malignancy, diagnostic surgery is recommended for persistently non-diagnostic FNA results.[40] Bongiovanni et al in 2012 conducted a meta-analysis in a pooled population of 25,445 FNA biopsies of thyroid nodules and found that 8.4% of non-diagnostic FNA patients underwent diagnostic surgery, and majority of the cases were ultimately benign that could have been managed conservatively (83.2%).[65]

1.6.2.2 Indeterminate results

Indeterminate samples result in inability to distinguish between non-neoplastic, benign and malignant thyroid follicular lesions.[80, 81] Cytological results that are unable to differentiate between malignant and benign nodules with confidence form the inconclusive category of FNA results for thyroid nodules.[64] Bethesda categories included in this sub-group are

“follicular lesion/atypia of undetermined significance (AUS/FLUS)” and “follicular neoplasm/suspicious for follicular neoplasm (FN/SFN)”. Bongiovanni et al in a meta-analysis reported that 9.6% of all FNAs were AUS/FLUS and FN/SFN contributed to 10.1% of all FNAs. [65]The diagnostic surgery rate for AUS/FLUS was 39.2% and 69.7% for FN/SFN, with a malignancy rate of 15.9% and 26.1% respectively. There appears to be no universal consensus on the management of this subcategory. Some guidelines recommend repeat FNA, while others recommend a hemithyroidectomy, the Korean guidelines recommend core need biopsy.[40, 82 83] Repeat FNAC has been found to provide a definitive cytological diagnosis in some patients but up to 30% of patients continue to have an indeterminate result.[84-86]

FNA has also been found to have indeterminate results for paucicellular cysts or neoplasms of salivary gland lesions with overlapping features such as cellular pleomorphic adenoma, adenoid cystic carcinoma and lesions with minimal cytological atypia (e.g. low-grade mucoepidermoid carcinoma and acinic cell carcinoma) and malignant lymphomas.[87]

A systematic review of 78 studies reported an overall inadequacy rate of 9.3% for patients undergoing head and neck FNAs.[71] The review also concluded that different operators contribute to variation in the inconclusive rate as does the presence of onsite cytology.[71] FNA cytology is also unable to differentiate between subtypes of lymphoma and cannot reliably distinguish between certain salivary and thyroid tumours.[18, 62, 88] A systematic review published in 2008 including 30 studies with 3459 aspirates from all head and neck sites reported that FNA was unable to reliably differentiate between follicular adenoma or benign hyperplastic nodules from carcinoma for thyroid nodules.[67]

1.6.3 An Alternative: Ultrasound guided Core Needle Biopsy

Core needle biopsy is performed under local anaesthetic with semi-automated or fully automated side-cut or end-cut 16-20-gauge needles.[15] Cylindrical intact tissue is harvested, preserving tissue architecture, in turn, reducing the inadequacy rates. The biopsy is formalin-fixed and paraffin-embedded allowing for more reliable immunohistochemical testing than FNA smears and centrifuged preparations. A larger gauge needle provides enough tissue material for immunophenotyping of the tumour allowing for tests like flow cytometry, Human papillomavirus (HPV) testing, and p16 immunohistochemistry. Novoa et al in 2012 published a systematic review including 26 studies and a total of 1291 core needle biopsies demonstrated an overall accuracy of 96% in detection of malignancy.[20] Table 7 compares the diagnostic accuracy of FNA and CNB from systematic reviews assessing FNA and CNB for head and neck masses.

Table 7 Results of previous diagnostic accuracy studies for head and neck masses.

	Fine needle aspiration[67]	**Core needle biopsy[20]**
Overall accuracy (range)	93.1% (73.3-98%)	96%
Overall sensitivity	89.6%	93%
Specificity	96.5%	99%
Positive predictive value	96.2%	98%
Negative predictive value	90.3%	95%

In the case of repeated indeterminate and AUS/FLUS results for thyroid nodules, an ultrasound-guided CNB is an alternate low morbidity intervention to obtain tissue diagnosis

instead of diagnostic surgical excision.[89] The result of a core biopsy may change further management especially when lymphoma is suspected. Core biopsy provides more sample tissue thus increasing the adequacy rate.[90, 91] It is well tolerated by patients and has minimal reported complications.[92] A systematic review and meta-analysis of 39 studies published by Ha et al in 2018, reported a low pooled complication rate with a core needle biopsy.[92] Core needle biopsy can effectively differentiate between anaplastic thyroid cancer and lymphoma which have a similar presentation of rapidly increasing neck mass.[93] Core needle biopsy has some limitations, including the need for local anaesthesia and local discomfort. Although scarce, there are dated reports (from mid 1900s) in the literature of needle track tumour implantation, haemorrhage and recurrent laryngeal nerve damage but these complications are not specific to CNB and also apply to FNA.[58, 94, 95]

Although many studies have assessed the diagnostic accuracy of FNA and CNB individually for the salivary gland, thyroid gland and cervical lymph nodes, this specific body of literature has not been compared, reviewed and analysed systematically.[20, 67, 71, 96-99]

1.6.4 Risks and complications of fine needle aspiration and core needle biopsy

Fine needle aspiration and core needle biopsy are considered safe sampling procedures that can be performed in the outpatient setting. CNB requires the use of local anaesthesia and is therefore slightly more time-consuming.

A few case studies reported uncontrolled haemorrhage and massive haematomas post palpation guided FNA resulting in acute upper airway obstruction requiring hospital admission and active intervention; however, these were rare case reports from the late 1980s.[100-102]

A systematic review summarised all reported complications post thyroid FNA, noting self-limiting, localized pain and haematoma as the most common complications.[103] Post

procedure infections, transient recurrent laryngeal nerve dysfunction and tumour dissemination were noted to be rare occurrences.[103] The review concluded that in the hands of experienced operators FNA was a safe and effective biopsy technique and awareness of possible complications is important for informed consent.[103] Similarly, Schmidt et al conducted a systematic review assessing diagnostic accuracy of FNA in salivary gland masses in 2011 and reported the haematoma rate to be 1.6% per procedure with no cases of permanent facial nerve injury or tumour seeding in 512 procedures.[66]

Kim and Kim in 2018 reported a haematoma rate of 0.5% for CNB for 1315 procedures confirming the safety of CNB.[97] Ha et al conducted a systematic review and meta-analysis of complications following ultrasound guided core needle biopsy of thyroid nodules and concluded that various complications can occur after ultrasound guided CNB but the pooled complication rate was 1.11%, with major complications accounting for 0.06%.[104]

Nasrollah et al investigated and compared patient comfort and tolerability of FNA and CNB for thyroid nodules.[92] A total of 61 consecutive patients that underwent both biopsies were asked to fill out structured questionnaires to assess their comfort during the procedures. The majority of the patients reported pain during both biopsies (95%), 2 patients reported pain only during CNB, and one reported no pain. Complaints of local pain after FNA were reported in 29% of the patients, while post-CNB pain was reported in 45% of patients. Patients reported comparable tolerability of FNA and CNB, 82% and 83% respectively. Stangierski et al compared pain post core needle biopsy after a failed FNA using a visual analog scale, and the median score for CNB was 4/10.[105] Approximately 60% of the patients thought the pain was similar to the pain experienced during conventional FNA, while 40% reported that the pain was ‘slightly stronger’ than FNA. This shows a discordance in the literature with limited

good quality epidemiological data assessing local pain and discomfort post-FNA and CNB procedures.

The type of tumour and anatomic site contributes to the potential risk of seeding; however, a large study of 11,700 abdominal biopsies performed with FNA demonstrated low rates of tumour seeding (0.017%).[106] This was further confirmed by a study of salivary gland biopsies that demonstrated the presence of salivary adenomas along the needle track (22g needle) but this did not lead to tumour recurrence at five year follow up.[107] A study compared the incidence of post salivary gland biopsy seeding and found only 2 cases of tumour seeding after 14G CNB, with 2 cases also described post FNA.[108] As seeding can present up to 20 years post-biopsy, ongoing close follow up is recommended to identify any long term complications associated with seeding.[109] Another option to avoid seeding is to excise the biopsy tract when surgical excision is performed but there is no evidence to support this routinely.[110] A systematic review conducted by Shah et al assessed 575 studies including 41,468 FNAs and 35 studies including 1803 CNBs of head and neck masses, predominantly case series and case reports due to the extremely low incidence of needle track seeding.[111] The crude estimate for seeding post- procedure was 0.00012% and 0.0011% after FNA and CNB respectively.[111] In context of clinically relevant tumour development/recurrence the risk of seeding was found to be very low.[111] Overall, both FNA and CNB are safe procedures with low complication rates.

1.7 Justification of need for evidence synthesis in this area

Percutaneous biopsy techniques are critical for surgical management of head and neck masses and have become the standard of care in preoperative diagnosis of neoplasms and malignancy. Investigation with imaging modalities such as ultrasound, CT and MRI provides

valuable information to guide treatment planning for these patients. However, in the context of tailoring management, tissue diagnosis helps identify the subset of patients who could potentially be managed conservatively and helps determine the extent of surgical resection. A meta-analysis by de Bondt et al in 2017 including 17 articles concluded that ultrasound guided FNA is more accurate than ultrasound, CT and MRI in detecting cervical lymph node metastases.[112] Ultrasound features of thyroid nodules such as marked hypo-echogenicity, irregular margins, micro-calcifications or 'taller than wide' shape suggest malignancy with sensitivity of up to 87%, specificity of 83.1% and a high negative predictive value of 95.7%.[113] The high specificity reduces the number of unnecessary FNAs performed due to the low false positive rates. These features help identify patients that should undergo further investigation with percutaneous biopsy but cannot replace tissue diagnosis.[40]

Fine needle aspiration of palpable, superficial lesions such as enlarged lymph nodes, thyroid nodules and salivary gland lesions can be performed by different clinicians including endocrinologists, haematologists, cytopathologist, radiologists and surgeons. Traditionally, FNA was performed without any image guidance. However, ultrasound guided FNAs by interventional radiologists has gained popularity in the recent times.[72] The guidelines for investigation and management of thyroid nodules as well as head and neck lesions recommend fine needle aspiration as a first line biopsy technique, and a repeat ultrasound guided fine needle aspiration if inadequate specimen is obtained.[18, 40, 82, 83, 114]

Ultrasound guided FNA has been reported to have high sensitivity and specificity and has been accepted as the preferred preoperative technique for diagnosis of head and neck masses;[18, 40] however, a known pitfall of FNA is its lower diagnostic rate. For thyroid lesions, approximately 14% and 15% of non-diagnostic and indeterminate diagnoses respectively

have been reported for FNA, respectively.[115] This is in keeping with the results of the assessment of salivary gland masses, axillary lymph node metastases, and primary breast tumours.[96, 116, 117]

FNA success is dependent on two vital independent variables: specimen acquisition and specimen interpretation.[118] Acquisition of adequate material is paramount for subsequent diagnostic and ancillary testing to obtain results. As FNA is a technical skill, practice, sufficient procedure volume, and continuing education regarding FNA techniques is critical for high quality specimen acquisition.[118] Operator experience has been found to affect the non-diagnostic rate of FNA.[119, 120] In a study by Ljung et al, 314 aspirates were performed by 69 physicians without formal training with median experience of 2 FNAs a year found a nondiagnostic rate of 36.9% versus 2.2% for 729 aspirates performed by 7 formally trained physicians with at least 100 FNAs per year experience.[119] Ghofrani et al demonstrated that the ultrasound guided FNA non-diagnostic rate was 8.2% in less experienced radiologists and 5.4% in the experienced radiologist group, this difference was not statistically significant.[120] Rapid onsite evaluation (ROSE) of the aspirate by a trained cytologist has been recommended for real-time feedback to ensure adequate specimen acquisition. A meta-analysis conducted by Witt and Schmidt found that adequacy rate without ROSE for salivary gland aspirates was 83% compared to 92% with ROSE.[121] This was found to be dependent on the initial inadequacy rate of the centers, with centers with lower initial adequacy rates benefitting the most from implementation of ROSE.[121] Core needle biopsy being a mechanically operated technique performed by trained interventional radiologists is being explored to curb the inadequate and inconclusive results of FNA. Core needle biopsy provides larger and better architecturally preserved tissue that allows assessment with molecular testing and immunohistochemical staining.

The caveat to the superiority of CNB is the reported higher post procedure complication risk in some studies.[117] CNB being a slightly more invasive technique, has increased theoretical risk of using a larger bore needle. The pertinent risks include vascular or parotid facial/recurrent laryngeal nerve damage, and displaced epithelia and tumour seeding.[109] A systematic review assessing CNB accuracy for salivary tumours reported an overall haematoma rate of 1.7%[96]. A recently published meta-analysis that evaluated types and incidence of complications associated with CNB in diagnosis of thyroid nodules reported a pooled complication rate of 1.11%, with pooled major complication rate being much lower (0.06 %) than minor complications (1.08%).[104] A systematic review of complications post FNA reported a similar risk profile for FNA.[103] Most complications following FNA and CNB are transient, have low morbidity and are self-limited: the overall safety of FNA and CNB appears to be comparable.[104]

It is important to determine the accuracy of ultrasound guided CNB compared to ultrasound guided FNA in its ability to provide adequate tissue to obtain a pathological diagnosis. Timely indentification of malignancy allows for prompt treatment whilst correct identification of benign tumours avoids unnecessary diagnostic surgery and the associated patient anxiety, complications and healthcare costs. The potential advantages and disadvantages of each technique raise questions about the relative roles of each technique in the diagnosis of head and neck masses. Should CNB be used first instead of FNA or should it be reserved for situations when FNA cytology is inadequate or inconclusive? A head to head comparison of diagnostic accuracy of FNA and CNB is necessary to help address these questions. The objective of this systematic review was to compare the diagnostic accuracy of ultrasound guided CNB and ultrasound guided FNA in the diagnosis of malignant and neoplastic head

and neck nodules, through meta-analysis of data from two arm prospective and retrospective studies.

Systematic reviews have become a cornerstone of evidence-based medicine and provide the basis for policy making and clinician and patient decision making. Several studies have attempted to analyse the accuracy of FNA and CNB individually, but a diagnostic assessment by comparison of CNB and FNA has not been summarised in a meta-analysis for head and neck masses. PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the *JBI Database of Systematic Reviews and Implementation Reports* were searched and no current or underway systematic reviews on the topic were identified. The objective of this review was to determine the difference in diagnostic accuracy of CNB and FNA for patients with a head and neck mass using surgical histopathology as a reference test and compare the risks and adverse events associated with each technique.

CHAPTER 2 **METHODOLOGY**

Systematic reviews are at the cornerstone of evidence-based medicine providing an overview of the relevant literature in a systematic and transparent way. Systematic reviews explicitly describe the origin of their study base and the reasons for selection of included studies.[39] A thorough methodological quality assessment is performed, and if appropriate, the results are summarised quantitatively in a meta-analysis. The robust methodology aims to limit and recognise bias, and improve the reliability of conclusions.[2] Additionally, systematic reviews help us verify whether findings are consistent and can be generalised to various situations.[39]

Diagnostic tests help clinicians develop management plans by identifying presence or absence of a condition in a patient.[26] Common diagnostic tests include signs and symptoms observed when taking a history or performing a clinical exam, biochemical and imaging technologies, and psychological interventions.[23] To address the ongoing need for faster, cost-effective tests, that are easy to perform, and are safe and accurate, new tests are being developed continuously.[26] Subsequently, at any given time there are multiple tests available to diagnose a particular condition. This has resulted in a growing demand for high level evidence on accuracy of diagnostic tests to improve patient outcomes. Systematic reviews of effectiveness consider if diagnostic tests improve outcomes. Systematic reviews of diagnostic test accuracy (DTA) investigate the accuracy of diagnostic tests.

Systematic reviews and meta-analyses of diagnostic test accuracy are a relatively new addition to evidence-based medicine. The decision to include this methodologically challenging review type in the Cochrane Group was made in 2003, ten years after The Cochrane Collaboration was founded.[25] The first diagnostic accuracy review was published in October 2008 a year after the Cochrane Library was ready to register DTA reviews.[39] This delay has been mainly attributed to slow methodological development and difficulty synthesising results of diagnostic studies, resulting in narrative summaries as opposed to meta-analyses.[39] At the time of writing seven out of 11 chapters of the Cochrane Handbook for Systematic Review for DTA are incomplete. Low quality of included studies, inadequate reporting resulting in an inability to assess the quality of included studies tarnish many systematic reviews of diagnostic test accuracy.[23, 26, 28, 35]

The objectives, inclusion criteria and methods of analysis for this review were specified in advance and documented in an a priori published protocol.

Soumya, Whitehorn A, Ooi EH, Lockwood C. Accuracy of core needle biopsy compared to fine needle biopsy for the diagnosis of neoplasm in patients with suspected head and neck cancers: a systematic review protocol of diagnostic test accuracy. JBI Database System Rev Implement Rep. 2020.

2.1 Inclusion Criteria

2.1.1 Participants

The review considered adults (above age 18 years) presenting with a head and neck lesion for investigation. All studies with paediatric patients were excluded, as head and neck lumps in children are often of infectious or congenital aetiology[18] and are generally not subjected to

investigation with FNA or CNB. In addition, paediatric patients that do undergo tissue sampling have altered techniques e.g. FNA under local anaesthetic or lack of excisional biopsy as a reference test.[122] Patients of all genders were included. Studies with patients with a suggestive history and physical examination of a head and neck lesion with or without formal imaging were included.

2.1.2 Index test

This review included studies that compared the diagnostic accuracy of ultrasound-guided CNB and ultrasound-guided FNA as the index test of interest. While needle biopsy can be conducted by palpation, studies have demonstrated a higher diagnostic yield for image-guided (ultrasound or CT) biopsy.[68-70] Therefore, studies that did not specifically state the use of ultrasound were excluded.

For categorisation of neoplasm, the results were recorded as positive if the index test diagnosis was neoplastic, malignant, atypical, or suspicious, and recorded non-neoplastic results as negative. For analysis of malignancy, malignant, suspicious results were recorded as positive; benign, atypical and non-neoplastic results were recorded as negative. Indeterminate was defined as atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) or follicular neoplasm or suspicious for follicular neoplasm. Prior to the introduction of the Bethesda, some studies classified indetermediate results as benign increasing the false negative rate while other studies classified them as malignant increasing the false positive rate.[123, 124] In our review, the rate of indeterminate or inadequate results were recorded and compared where possible.

All studies that used 21- 28-gauge needles for FNA and 16-20-gauge needles for CNB were included. Where available methodological description was recorded to assess if diagnostic

accuracy was affected by sample collection method, preparation and interpretation. Needle size, number of passes, clinical background and experience of the person performing the biopsy (radiologist, pathologist, clinician), availability of onsite assessment of adequacy by cytopathologist/pathologist, and experience of pathologist analysing the sample were recorded. In addition, where available, the device used for CNB and use of immunohistochemical and histochemical stains was recorded.

2.1.3 Reference test

The primary reference standard was the final surgical histopathology in the form of neck dissection, parotidectomy, thyroidectomy, or excisional biopsy. The reference test result was deemed positive if found to be neoplastic for neoplasms or malignant for assessing malignancy, and negative if non-neoplastic. Patients that have a negative index test generally do not undergo surgical excision as it is invasive and often unnecessary if the condition is benign. In such cases, where available, long term clinical follow up was used as a reference standard (minimum 1 year).

2.1.4 Diagnosis of interest

Lesions of the head and neck broadly categorised as non-neoplastic, benign and malignant were the target diagnoses of interest. The accuracy of two diagnoses were assessed in this review 1) neoplastic versus non-neoplastic and 2) malignant versus non-malignant.

2.1.5 Types of studies

This review considered two-armed studies that compared the accuracy and/or complications of ultrasound-guided FNA and CNB for the diagnosis of lesions of the head and neck. Included studies had extractable accuracy data including true positives (TP), false positives (FP), false negative (FN) and true negatives (TN) either as group totals, case by case

indexing of diagnoses or provided raw data that allowed for calculation of TP, FP, FN, and TN Table 8 shows an example of classification of TP, FP, FN, TN.

Studies were not limited by publication type, year of publication, language, location or setting. Studies published in English were included. Studies published in foreign languages were excluded at the full-text review stage, but their title pages are presented in the Appendix I of this review. The studies described number of patients that received FNA and CNB, and the number of patients that were referred to the specific type of follow up (medical versus surgical) and the outcomes for each group.

This review considered both experimental and quasi-experimental study designs, including randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies were considered for inclusion. Conference abstracts were excluded as no extractable data was available and not enough information regarding the methodology and patient selection was available to critically appraise the study.

Table 8 Description of patient classification for diagnostic test accuracy of FNA for malignancy

Patient classification	Description of test result
True positive	Positive FNA result Positive final histopathology result
True negative	Negative FNA result Negative final histopathology result
False positive	Positive FNA result Negative final histopathology result
False negative	Negative FNA result Positive final histopathology result

Positive FNA result = suspicious for malignancy/malignancy

Negative FNA result = benign, non-neoplastic, atypical, AUS/FLUS, FN/Suspicious for follicular neoplasm.

2.2 Search strategy

The search strategy aimed to locate both published and unpublished studies. An initial limited search of MEDLINE was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for MEDLINE (see Appendix II). The search strategy, including all identified keywords and index terms, were adapted for each included information source using Polyglot Search Syntax Translator.[125] The reference lists of all studies selected for critical appraisal were screened for additional studies.

2.3 Information sources

The databases that were searched included MEDLINE, EMCARE, EMBASE, Web of Science, Cochrane library. Sources of unpublished studies and grey literature included the TRIP database, the National Institute of Health and Care Excellence (NICE), and Evidence-Based Medicine Reviews (EBMR) to retrieve evidence-based resources relevant to this systematic review, the reference lists of grey literature were also scanned for additional studies.

2.4 Study selection

Following the search, all identified citations were collated and uploaded into EndNote X9 (Clarivate Analytics, PA, USA) and duplicates removed.[126] Covidence was used to screen titles and abstracts by two independent reviewers for assessment against the inclusion criteria for the review.[127] Potentially relevant studies were retrieved in full and their citation details

imported into the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI) (Joanna Briggs Institute, Adelaide, Australia).[128] The full text of selected citations was assessed in detail against the inclusion criteria by two independent reviewers. Reasons for exclusion of full text studies that did not meet the inclusion criteria were recorded and reported in the systematic review. Any disagreements that arose between the reviewers at each stage of the study selection process were resolved through discussion. The results of the search were reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[129, 130]

2.5 Assessment of methodological quality

Studies that met the inclusion criteria were critically appraised by two independent reviewers for methodological quality using the signaling questions from the standardized critical appraisal instrument QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool.[131] The QUADAS-2 tool incorporates reviewers concerns regarding the applicability of included studies, this element of QUADAS-2 was not included in this review as research studies that did not meet the inclusion criteria or studies that did not answer the research question did not proceed to the critical appraisal stage. Any disagreements that arose were resolved through discussion.

2.6 Data extraction

Data was extracted from papers included in the review using the standardized data extraction tool available on JBI Reviewers Manual: JBI Diagnostic Accuracy Test Assessment and Review Instrument by two independent reviewers (Appendix IV).[132] The data extracted

included specific details about the tests, populations, study methods and outcomes of significance to the review question and specific objectives. Test accuracy results were recorded in a 2x2 table (Table 9) adapted from Macaskill et al[133] Any disagreements that arose between the reviewers were resolved through discussion.

Table 9 An example for 2x2 data extraction table to classify test results and disease status

Test outcome (CNB results)	**Disease/condition status (final histopathology results)**		
	Malignancy positive	**Malignancy negative**	**Total**
CNB positive	True positives (a)	False positives (b)	Test positives (a+b)
CNB negative	False negatives (c)	True negatives (d)	Test negatives (c+d)
Total	Disease/condition positives (a+c)	Malignancy negatives (b+d)	N (a+b+c+d)

The sensitivity and specificity were calculated using the data from Table 9.

$$Sensitivity = a \div (a + c)$$

$$Specificity = d \div (b + d)$$

2.7 Data synthesis

Analyses were performed using a meta-analysis of diagnostic accuracy by fitting a bivariate mixed-effects logistic regression model. All systematic reviews of diagnostic accuracy inherently have significant heterogeneity in between studies. Pooled proportions for non-diagnostic and inconclusive specimens were determined using a random-effects model, which incorporates an estimate of between study variation (heterogeneity) in the weighting for

calculation of summary statistics.[133] The random effects model describes the variability in test accuracy across studies and estimates the average accuracy of the tests.

Results are presented as Summary Receiver Operating Characteristics (SROC) curves, forest plots and estimated summary sensitivity, specificity, positive and negative likelihood ratios, and area under the SROC curve with 95% confidence intervals (CI). Heterogeneity among the studies was assessed by the Cochran Q and the I_2 statistics. The Q statistic was defined as the weighted sum of squared deviations of the estimates of all studies; $p < 0.05$ was considered statistically significant for heterogeneity. An I_2 statistic >50% indicated heterogeneity.

All analyses were performed using Stata v15 (College Station, TX, USA)[134]. Diagnostic accuracy meta-analyses were performed using the user-written package *midas*.[135] Pooled estimates for non-diagnostic and inconclusive specimens were performed using the Stata package *metan*.[136]

2.8 Assessing confidence

A 'summary of findings' table was created using GRADEPro GDT software. The GRADE approach for grading the quality of evidence for diagnostic test accuracy was followed.[137] The following outcomes were included in the 'Summary of Findings' table: index test outcomes: non-neoplastic, inadequate, indeterminate, benign, suspicious/atypical, malignant; reference test outcomes: benign, malignant.

CHAPTER 3 **RESULTS**

3.1 Search results

The search for relevant studies was conducted in May-June 2019 with assistance from an experienced research librarian. The search strategy detailed in Appendix II was tailored and used to search the databases mentioned in 'Methodology' section 2.3. A total of 3999 potentially relevant titles were identified by the primary author. The number of duplicates excluded were 1426. Duplicates were identified and removed using EndNote[126] and Covidence[127] followed by manual searching and removal of remaining duplicates. Titles, keywords and abstracts of 2575 potentially relevant articles were screened in Covidence (108) against the inclusion criteria by two independent reviewers (AW and SS), any disagreements were resolved through discussion.(144) At the title/abstract search stage, 2422 papers were excluded as they were irrelevant or did not meet inclusion criteria , and 149 were retrieved for full text examination to assess eligibility for inclusion. Following full text review, 140 studies were excluded by two independent reviewers (AW and SS), any disagreements were resolved by discussion and involvement of third reviewer (CL). Figure 1 details the study identification process. Finally, nine studies were included in the systematic review of which six studies were included in the meta-analysis.

The most common reasons for exclusion at the full text review stage included (Appendix V):

- The study focused on sensitivity/specificity data of one of the tests only, for example fine needle aspiration with no comparison to core needle aspiration (n=30)

- Conference abstracts were excluded due to lack of adequate demographic data to assess for eligibility or lack of index test details to assess methodological quality or lack of extractable data (n=23)
- Literature reviews/editorials discussing diagnostic accuracy of core needle biopsy and fine needle aspiration (n=16)
- The study did not have a histopathological surgical comparator i.e. study reference test (n=15)
- Unclear or lack of ultrasound guidance for fine needle aspiration (n=13)
- Inclusion of paediatric patients in analysis (n=13)
- Many studies of lymph nodes did not report data specific for head and neck region, e.g. studies of lymphoma that combined data from axillary, inguinal, and the head and neck regions. (n=10)

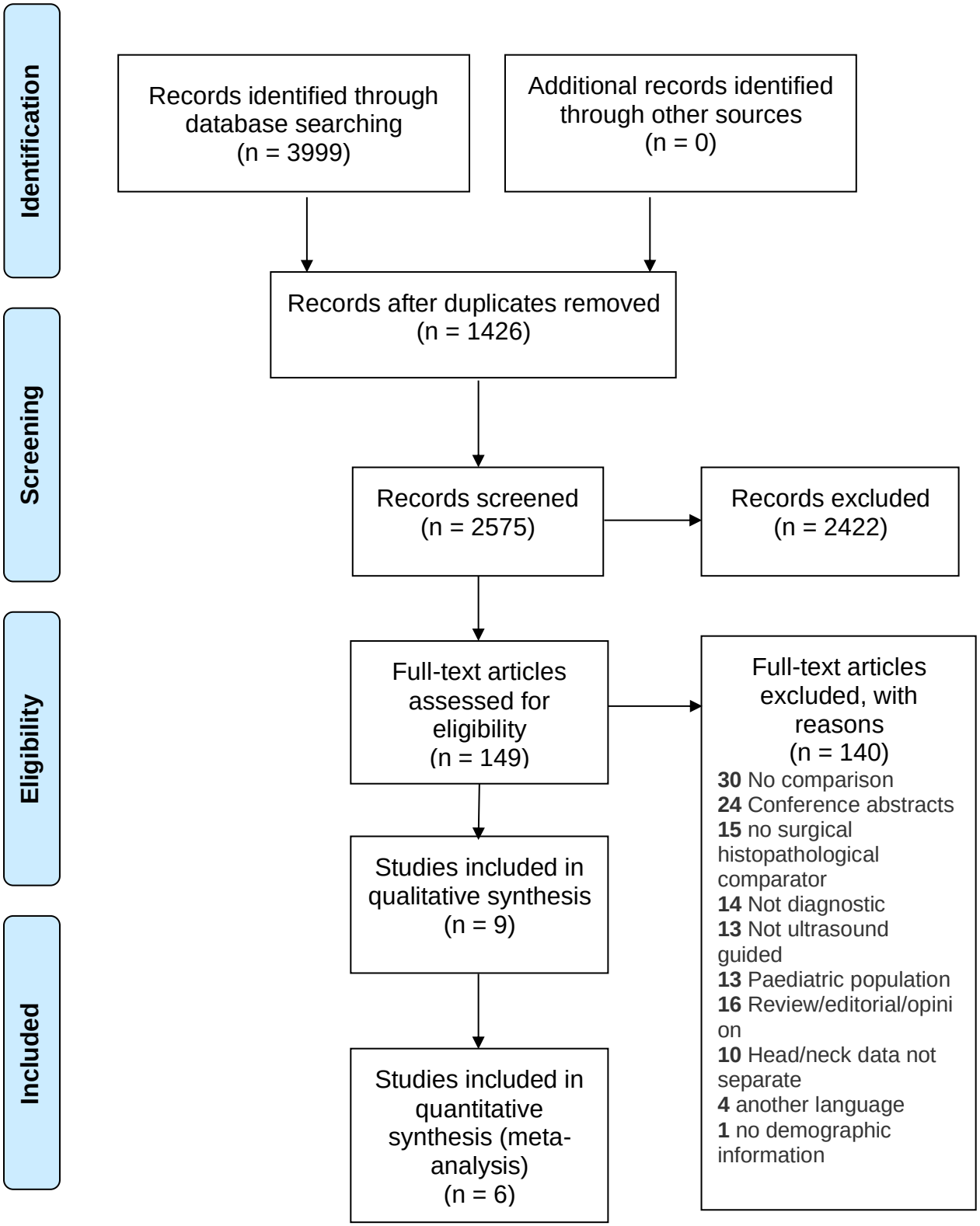

Figure 1 Study selection process(140)

3.2 Methodological quality

Assessment of the quality of the included studies was performed using the JBI modified QUADAS-2 tool (Table 10). The QUADAS-2 work group have identified two important components that constitute quality of a diagnostic study a) avoidance of 'risk of bias', as well as b) concerns regarding 'applicability'.[131] JBI recommends the use of QUADAS-2 and includes the signaling questions in the appended checklist (Appendix III).[138] However, concerns regarding applicability are omitted in this checklist as a primary study should not proceed to critical appraisal if there was concern regarding its inclusion criteria or research question.[138] Four key domains are assessed in the QUADAS-2 tool - patient selection, index test, reference standard, and patient flow through the study and the timing of the index test and reference standard.

Table 10 JBI Critical Appraisal Checklist for Diagnostic Test Accuracy Studies(115)

Q1 Was a consecutive or random sample of patients enrolled?
Q2 Was a case control design avoided?
Q3 Did the study avoid inappropriate exclusions?
Q4 Were the index test results interpreted without knowledge of the results of the reference standard?
Q5 If a threshold was used, was it pre-specified?
Q6 Is the reference standard likely to correctly classify the target condition?
Q7 Were the reference standard results interpreted without knowledge of the results of the index test?
Q8 Was there an appropriate interval between index test and the reference standard?
Q9 Did all patients receive the same reference standard?
Q10 Were all patients included in the analysis?

The overall quality of the included studies was moderate. The results of the critical appraisal are summarised in Table 11 andTable 12 and Figure 2. No studies were assessed to be at low risk of bias in all four domains. Two studies were at high risk of bias in the patient selection domain. Bias associated with domains of index test and reference test could not be assessed due to inadequate reporting in the included primary studies. Flow and timing was the domain most susceptible to bias.

Table 11 Methodological quality assessment using QUADAS-2

	Patient selection			**Index test**		**Reference test**		**Flow and timing**		
Study	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**
Choi 2014	Y	Y	Y	U	NA	Y	U	U	N	N
Harvey 2005	U	Y	Y	Y	NA	Y	U	U	N	Y
Karstrup 2000	Y	Y	Y	Y	NA	Y	U	U	N	N
Novoa 2015	U	Y	U	Y	NA	Y	Y	U	N	Y
Pisani 2000	N	Y	Y	Y	NA	Y	U	U	N	N
Sung 2012	Y	Y	Y	U	NA	Y	U	U	N	Y
Trimboli 2014	N	Y	Y	Y	NA	Y	U	U	Y	Y
Yi 2015	U	Y	Y	Y	NA	Y	Y	U	N	N

Table 12 Summary of Risk of Bias Assessment

Study	RISK OF BIAS			
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Harvey 2005	?	☺	?	☺
Karstrup 2000	☺	☺	?	☹
Yi 2015	☺	☺	☺	☹
Novoa 2015	?	☺	☺	☺
Pisani 2000	☹	☺	?	☹
Trimboli 2014	☹	☺	?	☺
Sung 2012	☺	?	?	☺
Choi 2014	?	?	?	☹

☺Low Risk ☹High Risk ? Unclear Risk

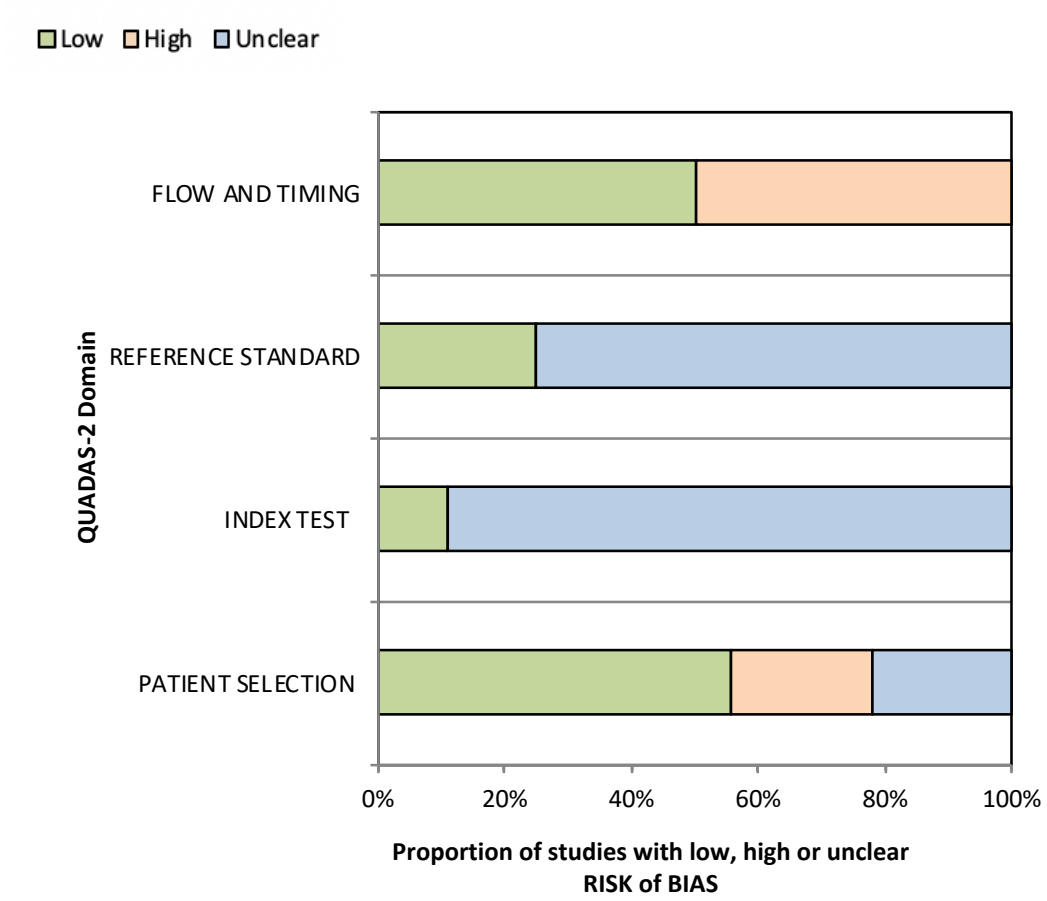

Figure 2 Risk of bias

3.2.1 Patient Selection

Most studies described that the patients were enrolled consecutively or that all cases within a particular period were included (7/9).[123, 124, 139-143] However, the selection criteria for allocation of patients to CNB versus FNA was not clearly described in Harvey et al, Pisani et al, Trimboli et al, and Choi et al.[123, 140, 141, 143] It is difficult to ascertain if the patients selected for CNB in these studies are representative of all patients with neck masses that may have ordinarily been selected for FNA as there was no randomised allocation of participants to receive CNB versus FNA in these studies.

In Yi et al[144], it seemed likely that consecutive cases were included; however, it was not clearly stated. In Novoa et al[88], the selection criteria were not clear.

All the included studies avoided a case-control study design. All studies avoided inappropriate exclusions. The overall risk of bias was assessed to be low for patient selection in most studies 8/9.[123, 124, 139-144] Novoa et al reported patient selection poorly, adequate methodological assessment of patient selection was not possible, and risk of bias could not be assessed.

3.2.2 Index Test

None of the studies explicitly stated that the cytologist/histopathologist interpreting FNA and CNB were blinded or unaware of the reference standard except Yi et al.[144] However, the index test (FNA or CNB) is generally the predictor of the reference standard (surgical histopathology/follow up), one could assume that FNA and CNB results were interpreted without knowledge of the results of the reference standard. As the majority of the studies were retrospective the risk of bias could not be assessed for question 4 for the index test domain. In one retrospective study, the cytology/histopathology results of FNA and CNB were 're-classified' according to the Bethesda 2009 system.[142] There was no mention of blinding of the pathologists to the reference standard when this reclassification was conducted. This introduces a potential for bias if the pathologist interpreting the index test was aware of the reference standard result.

There was no pre-specified threshold used in any of the included studies, this component was therefore not applicable to the methodological quality assessment

3.2.3 Reference Standard

Histopathological examination of the surgical specimen was the reference standard used to correctly classify malignancy for all included studies. A positive FNA or CNB result is an indication for surgical excision, the specimen is then stained for confirmation of diagnosis and staging.[66] This reference standard may be imperfect and may give rise to misclassification errors, but there is no literature on the error rate of histopathological diagnosis.

For patients that were found to have a benign result or were not surgical candidates, most studies considered clinical and sonographic follow up as the reference standard. Both these reference standards were deemed appropriate for all studies. The differential verification introduces a partial verification bias, as the two reference standards probably have a varying error rate. However, there is no suitable reference test that can be applied to both groups.[145]

Generally, the pathologist is aware of the FNAC and CNB findings when interpreting surgical specimens, but the histopathological specimens are weighted more than FNA and CNB findings. Although the results of FNA and CNB influence the final diagnosis, this influence is not likely to be significant enough to alter the histopathological diagnosis. There was an unclear risk of bias for the conduct of index tests. Novoa et al and Yi et al clearly stated that the pathologist was blinded to reduce information bias while interpreting the reference test and were scored positively.

3.2.4 Flow and Timing

No studies specifically mentioned the time interval between FNA/CNB and histological evaluation, possibly leading to timing bias. Generally, if surgery is indicated, it is performed

relatively soon after the index test, we believe that the interval between the index tests and examination of the surgical specimen is unlikely to be long enough for the tumour to significantly change and produce false negative results. This item for time interval between the index test and reference test was marked unknown for all studies

The patients did not receive the same reference standard in most of the studies as it is not standard practice for all patients with benign index test results to have surgical intervention (7/8).[88, 123, 124, 140, 142-144] Only Trimboli et al used final histological exam as the reference standard for all patients.[141] In all included studies, histological verification was used for malignant FNA and CNB results. Varying proportions of patients with benign pathology were followed up sonographically and clinically across the included studies. Differential verification of FNA and CNB also poses a problem as generally reference standards differ in accuracy (histopathology of a nodule vs follow-up for detection of malignancy) and this affects the diagnostic test accuracy introducing a risk of bias.

Not all studies included all patients in the analysis. Karstrup et al compared FNA and CNB results to the histological surgical diagnosis for 41 patients but did not describe the follow up/results for the remaining 36 patients.[124] Yi et al did not account for 59 patients that were not included in the final analysis due to lack of final diagnosis.[144] Pisani et al did not describe any follow up details for 95/136 patients that did not have a histological diagnosis.[140] Choi et. al did not verify results for 52/180 patients for CNB and 40/180 patients for FNA.[143] Exclusion of patients at the analysis stage without an explanation introduces a partial verification bias as test results for patients' that did not have surgery/follow up did not receive any form of verification.

3.3 Description of studies

Data collected included setting (outpatient vs inpatient), period of study, location (country), study design (prospective vs retrospective), study type (cross-sectional case-study vs cross-sectional cohort) population characteristics (age, gender), method (experience of pathologist, availability of onsite cytology, details of person performing the procedure, needles and devices used, number of passes), and the reference standard used. The detailed characteristics of the included studies are summarised in Table 13. The majority of the studies were conducted in South Korea (4 of 9). There were six retrospective and three prospective studies. The studies were generally unclear on the setting of the FNA and CNB.

Of the nine included studies eight focused on the diagnostic accuracy of FNA and CNB for thyroid nodules[123, 124, 139-144], the remaining study assessed salivary gland masses.[88] The study by Novoa et al was not included in the meta-analysis as it would be inappropriate to pool sensitivity of one study assessing salivary gland pathology with eight studies focusing on thyroid nodules. A total of six studies had diagnostic accuracy data related to thyroid malignancy. There was not adequate raw data available for pooling of sensitivity and specificity for thyroid neoplasm.

Table 13 Characteristics of included studies

Study	Location	Study Period	Anatomical subsite	Clinical features	Design and setting	Participant recruitment	Methodology
Choi 2014[143]	South Korea	2008-2011	Thyroid	Initial FNA non-diagnostic	All nodules that underwent repeat FNA or CNB in patients with non-diagnostic initial FNA	Consecutive	Retrospective
Harvey 2005[123]	UK	1994-2001	Thyroid	All reports for thyroid samples subjected to cytologic or histopathologic analysis.	CNB in random patients that had failed FNA; some patients had FNA without sonographic guidance. FNA and CNB performed in the outpatient setting	Consecutive	Retrospective
Jeong 2018[139]	South Korea	2013	Thyroid	Not recorded	Patients completed a visual analogue scale to rate their pain immediately and 10 minutes post procedure.	Consecutive	Retrospective
Karstrup 2001[124]	Denmark	1997-1999	Thyroid	Euthyroid patients with palpable dominant thyroid nodule which were cold on scintiscan.	FNAB and CNB simultaneously in outpatient setting;	Consecutive	Retrospective
Novoa 2015[88]	Switzerland	Not recorded	Salivary glands	Patients with a salivary gland lesion that underwent uss guided CNB and FNA	CNB performed under general anaesthetic before surgical excision of salivary gland	Not recorded	Prospective

Study	Location	Study Period	Anatomical subsite	Clinical features	Design and setting	Participant recruitment	Methodology
Pisani 2000[140]	Italy	1996	Thyroid	Ultrasonographically diagnosed as having thyroid nodules. Physical exam TFT, and 131 scinitigraph performed prior	FNA performed on all patients and 40 of them were also referred for CNB. CNB was performed on 32 patients with dominant/solitary hypo functioning nodules, ultrasonographically hypoechoic and larger than 1 cm.	Consecutive	Prospective
Sung 2012[142]	South Korea	2008-2009	Thyroid	All patients that had simultaneous FNA and CNB for thyroid nodules (538 patients excluded as final diagnosis not obtained.)	FNAB and CNB simultaneously	Consecutive	Retrospective
Trimboli 2014[141]	Italy	2012-2013	Thyroid	All patients with recently discovered suspicious thyroid nodule. Hot lesions excluded	All patients were offered CNB, those that refused CNB had FNA	Consecutive	Prospective
Yi 2015[144]	South Korea	2010-2012	Thyroid	All patients with macrocalcifications	Simultaneous FNA and CNB	Not recorded	Retrospective

Patient demographics and index test characteristics are summarised in Table 14. The studies recruited a total of 2061 patients, with mean (or median) age ranging from 44.4 to 54.4 years. The proportion of male patients ranged from 13.7 to 23% for all studies except Novoa et al where salivary gland nodules were more common in men (54%).

All nine studies used ultrasound guidance for both FNA and CNB.[20, 123, 124, 139-144] Harvey et al included 266 patients that underwent FNA, only 59 of these patients underwent aspiration under ultrasound guidance.[123] Only the ultrasound guided results were included in the meta-analysis. FNA was performed using 21 - 25 gage needles in one to three passes. For CNB, the biopsy procedures were generally performed using 18 - 21 gauge (G) core needles, with the majority of the studies using 18G needles[123, 124, 139, 142-144] with one to four passes. Five studies specified that the sample was obtained by a radiologist[124, 139, 142-144], one study indicated that specimens were obtained from non-pathologists (surgeons, endocrinologist, or radiologist)[123], one study specified that the sample was obtained by a surgeon[141], one study had two experienced sonographers obtaining specimens[88] and one study did not specify who obtained the sample.[140] The experience of radiologists ranged from 5-17 years and was well documented in four studies.[124, 142-144] Only two studies reported the experience of the pathologist in years.[142, 144]

Novoa et al had onsite cytology available for FNA.[88] The accuracy rate and non-diagnostic rate of FNA for these participants may be higher due to this provision. Choi et al assessed sample adequacy crudely by visual inspection and re-aspirated nodules with less than six particles.[143] The use of immunohistochemistry is likely to improve the inconclusive and non-diagnostic percentage of FNA and CNB.[121] Only Novoa et al and Trimboli et al explicitly reported the use of immunohistochemistry.[88, 146]

Table 14 Characteristics of participants and index tests of included studies

Study	Age (range/SD)	Gender M: F	Number of patients	Needle size		Passes		Performed by.	Assessed by
				FNA	CNB	FNA	CNB		
Choi 2014[143]	54.4 (20-79)	83:277	360	21-23G	18G	1-3	Not recorded	2 Radiologists – 11- and 16-year experience	Experienced pathologist
Harvey 2005[123]	(20-91)	58:364	422	21-25G	18G	1-3	2	Endocrinologist/general surgeons/ENT surgeons/radiologists	Histopathology department
Jeong 2018[139]	Mean 50.5 (26-78)	30:180	200	23G	18G	1-3	1-3	Radiologist	Not recorded
Karstrup 2001[124]	Median 51 (33-81)	13:64	77	21G	18G	2	2	Radiologist – 15-year experience	Department of pathology, same person assessed both samples; aspirates interpreted 1-2 days before histological biopsies
Novoa 2015[88]	54 (19-90)	60:51	111	24G	20G	NR	NR	2 Sonographers – 15-year experience	Not recorded
Pisani 2000[140]	NR	NR	136	23-25G	20-21G	NR	NR	Not recorded	Cytologist/Pathologist
Sung 2012[142]	44.32 (+/-11.86)	85:453	538	23G	18G	>2	1-2	3 radiologists – 6-13-year experience	2 pathologists with >10-year experience
Trimboli 2014[141]	50 (+/- 13.7)	12:60	72	23G	21G	2	2	Surgeon	Expert cytopathologist and experienced pathologist

Study	Age (range/SD)	Gender M: F	Number of patients	Needle size		Passes		Performed by.	Assessed by
				FNA	CNB	FNA	CNB		
Yi 2015[144]	53.27 (28-78)	33:112	145	21-25G	18G	1-4	1-3	4 radiologists - 5-17-year experience	Staff pathologist with nine years of experience

Table 15 describes the characteristics of the nodules and the reference standard details. The mean nodule size ranged from 12.8 – 16.2 mm in diameter with the majority of the nodules being solid. Jeong et al[139] Pisani et al[140], Novoa et al[88] and Yi et al[144] did not describe the characteristics of the nodules. Karstrup et al[124], Yi et al[144] and Choi et al [143] failed to account for patients lost to follow up/ that did not have a final diagnosis.

Table 15 Characteristics of target condition and reference standard(s)

Study	Samples collected		Nodule size	Characteristics of the nodules	Target condition	Final diagnosis (n)	Reference standard
	FNA	CNB					
Choi 2014[143]	180	180	CNB 13.9, FNA 12.8	321 solid, 30 predominantly solid, nine predominantly cystic nodules	Malignancy	268 (FNA - 140; CNB – 128)	Malignant final diagnosis based on the surgical specimen (n=72,26.9 %). A final diagnosis of benign nodule was made in196 nodules (73.1 %) surgical (n=14, 5.2 %); repeated benign readings on FNA/CNB (at least 2) (repeat FNA n=21, 7.8 %/CNB n=93, 34.7 %)); stable in size for at least one year (n=68,25.4 %)
Harvey 2005[123]	59	79	10–33 (range)	61 cystic lesions - FNA	Malignancy	FNA - 35 CNB - 69	Final diagnosis obtained from histopathology or by follow-up.
Jeong 2018[139]	100	100	NR	NR	NA		NA
Karstrup 2001[124]	77	77	8-80 mm (median 30)	48 homogeneous solid, 29 complex with cystic and solid nodule structures	Neoplasm	41	Final diagnosis obtained from histopathology (surgery) (n=41)
Novoa 2015[88]	111	111	NR	NR	Malignancy Neoplasm	111	Histological verification was performed on 103 cases, eight patients that were not surgical candidates had clinical follow up.

Study	Samples collected		Nodule size	Characteristics of the nodules	Target condition	Final diagnosis (n)	Reference standard
	FNA	CNB					
Pisani 2000[140]	136	32	NR	NR	Malignancy Neoplasm	42 (FNA-42; CNB-29	42 patients underwent surgery; all the patients with benign result were followed up clinically and sonographically and did not demonstrate increase in nodule size. No clear indication of how follicular neoplasms were managed.
Sung 2012[142]	555	555	3-80 mm (Mean 16.2)	526 solid, 26 predominantly solid and 3 cystic	Malignancy	555	Final diagnosis of malignant nodules was determined by surgical resections (318); benign diagnosis (237) surgical (n=41,17.3%) repeated benign readings on FNA/CNB (at least 2) (n=35,14.8%) benign FNA/CNB and decrease in maximal diameter of >50% at follow up (n=6, 2.5%) concordant FNA and CNB and clinical follow up of at least 1 year (n=155, 65.4).
Trimboli 2014[141]	41	31	11.5	All nodules were solid	Malignancy	72 (FNA-41; CNB – 31)	Final histological examination (FNA n=41 and CNB n = 31)
Yi 2015[144]	147	147	NR	NR	Malignancy	86	Histopathological results after surgery (n=32) or a benign diagnosis based on: repeated benign readings on FNA (at least 2) (n=11, 20.4%) benign FNA/CNB and stable size at follow up >1 year (n=13, 24.1%) concordant benign FNA and CNB (n=30, 50.6%)

3.4 Findings of the review

3.4.1 Diagnostic accuracy of CNB and FNA for diagnosing salivary gland lesions - Novoa et al[88]

Only one study comparing the accuracy of FNA and CNB for salivary gland tumours met this systematic review's inclusion criteria. A total of 108 patients listed for salivary gland surgery based on FNA were prospectively recruited and CNB was performed under general anaesthetic immediately before surgical excision for 100 patients. Novoa et al found that CNB detected malignancy and true neoplasms in salivary gland lesions with a sensitivity of 95% and 98% respectively as compared to 64% and 94% for FNA.[88] Table 16 describes the results of the study.

Table 16 Diagnostic accuracy of CNB and FNA for diagnosing salivary gland lesions - Novoa 2016[88]

Study	Method	Tissue type	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	Non-diagnostic (%)
Novoa 2016[88]	FNA	Malignancy Neoplasm	14 89	5 3	8 6	74 3	64 94	94 50	2.8
	CNB	Malignancy Neoplasm	19 87	0 0	1 0	76 7	95 98	100 100	6

3.4.2 Complications for salivary gland lesions – Novoa et al[88]

Novoa et al was the only study to include salivary gland lesions and did not note any bleeding, major hematomas, local infections, or nerve injuries in their study. Participants in this study ceased antiplatelets and anticoagulants for one week prior to the biopsy where possible. CNB and FNA was performed on three patients that could not cease antiplatelets. Six patients had FNA with bridging unfractionated heparin ceased four hours prior to the procedure, one patient was on low-molecular weight heparin while FNA was performed.

Novoa et al examined needle tracks in the surgical specimen for all the patients that underwent surgical excision, no tumour seeding was noted in 63% of the cases, and the needle track could not be identified in 37% of the patients. All patients were followed up clinically and sonographically for up to six years and did not demonstrate tumour recurrence.

3.4.3 Diagnostic accuracy of CNB and FNA for diagnosing thyroid malignancy

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was used to classify nodules from category 5 (suspicious for malignancy) and category 6 (malignancy) as

malignant. Category 1 (non-diagnostic) results were not included in the analysis of malignancy. Six studies compared the diagnostic accuracy of 1118 patients for FNA and 1024 patients for CNB (Table 17)

Table 17 Details of the studies included in meta-analyses

Study	Method	Tissue type	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	Non-diagnostic (%)	Inconclusive (%)	Prevalence %
Choi 2014[143]	FNA	Malignancy	13	2	7	62	65	97	40	33	23
	CNB	Malignancy	45	0	1	80	98	100	1	8	36
Harvey 2005[123]	FNA	Malignancy	3	0	1	31	75	100	41	8	11
	CNB	Malignancy	4	0	2	63	67	100	13	11	8.7
Karstrup 2000[124]	FNA	Neoplasm	15	5	3	17	83	77	3		45
	CNB	Neoplasm	14	1	4	17	78	94	12		48
Pisani 2000[140]	FNA	Neoplasm	22	3	1	16	96	84	4	10	54
	CNB	Neoplasm	6	0	0	10	100	100	41	13	35
	FNA	Malignancy	10	0	3	29	77	100	4	10	31
	CNB	Malignancy	3	0	2	11	60	100	41	13	31
Sung 2012[142]	FNA	Malignancy	218	0	84	219	72	100	6	19	58
	CNB	Malignancy	276	2	36	233	88	99	1	13	57
Trimboli 2014[141]	FNA	Malignancy	30	0	3	7	91	100	2	17	82
	CNB	Malignancy	24	0	0	6	100	100	3	0	80
Yi 2015[144]	FNA	Malignancy	23	0	7	43	77	100	27	16	41
	CNB	Malignancy	28	0	4	53	88	100	1	12	37

Table 17 shows the performance data for the diagnosis of thyroid malignancy from included studies. Table 18 shows the accuracy estimates for each diagnosis method. The SROC curve for diagnosis of malignancy is shown in Figure 3a and 3b. The area under the SROC curve was larger in CNB than in FNA (1.00; 95% CI 0.99 to 1.00 vs. 0.88; 95% CI 0.85 to 0.91) (Figure 3).

Figures 4 and 5 show the forest plots for the sensitivity and specificity for FNA and CNB. CNB demonstrated a summary sensitivity of 91% (95% confidence interval [CI] 79% to 96%) and specificity of 99% (95% CI 98% to 100%); and FNA demonstrated a summary sensitivity of 75% (95% CI 66% to 83%) and specificity 100% (95% CI 60% to 100%). There was no significant difference between the summary estimates of sensitivity (p = 0.125) or specificity (p = 0.806). There was more variability in sensitivity than specificity.

Table 18 Comparison of accuracy data for CNB Vs FNA for diagnosis of malignancy

	Sensitivity (%)					**Specificity (%)**				
	CNB	***I*²%**	**FNA**	***I*²%**	***P* value**	**CNB**	***I*² %**	**FNA**	***I*²%**	***P* value**
All studies	91 (79 - 96) (*n* = 6)	73.0	75 (66 – 83) (*n* = 6)	29.6	0.125	100 (98 – 100) (*n* = 6)	0.0	100 (60 – 100) (*n* = 6)	56.0	0.806

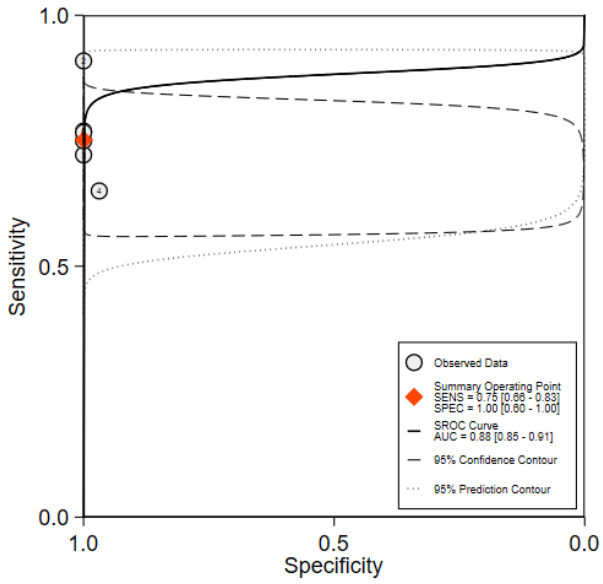

Figure 3a

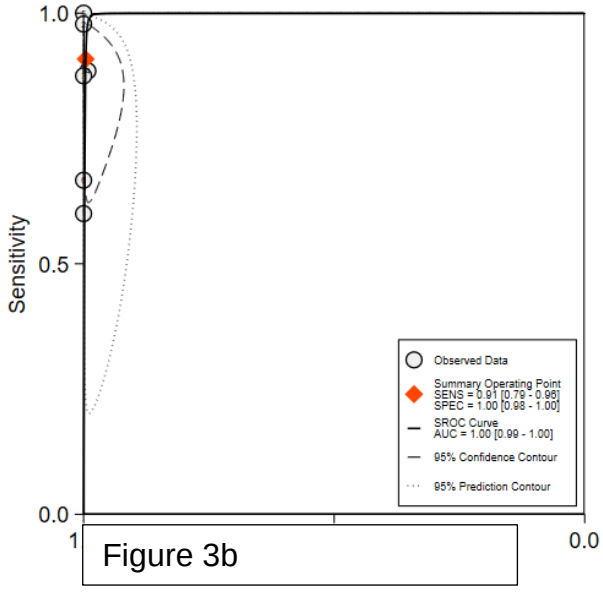

Figure 3b

Figure 3 Summary ROC curves with confidence and prediction regions around mean operating sensitivity and specificity points

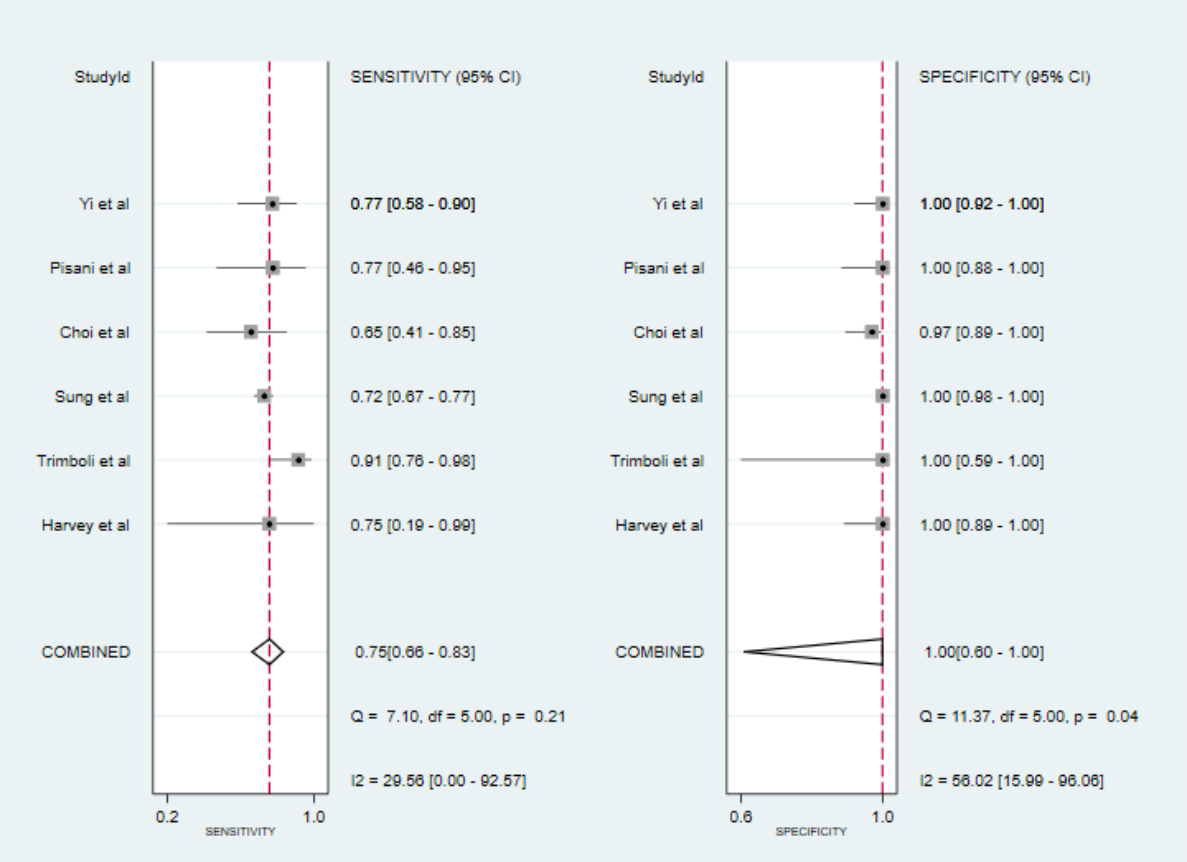

Figure 4 Forest plot study specific and mean sensitivity and specificity with heterogeneity statistics for FNA

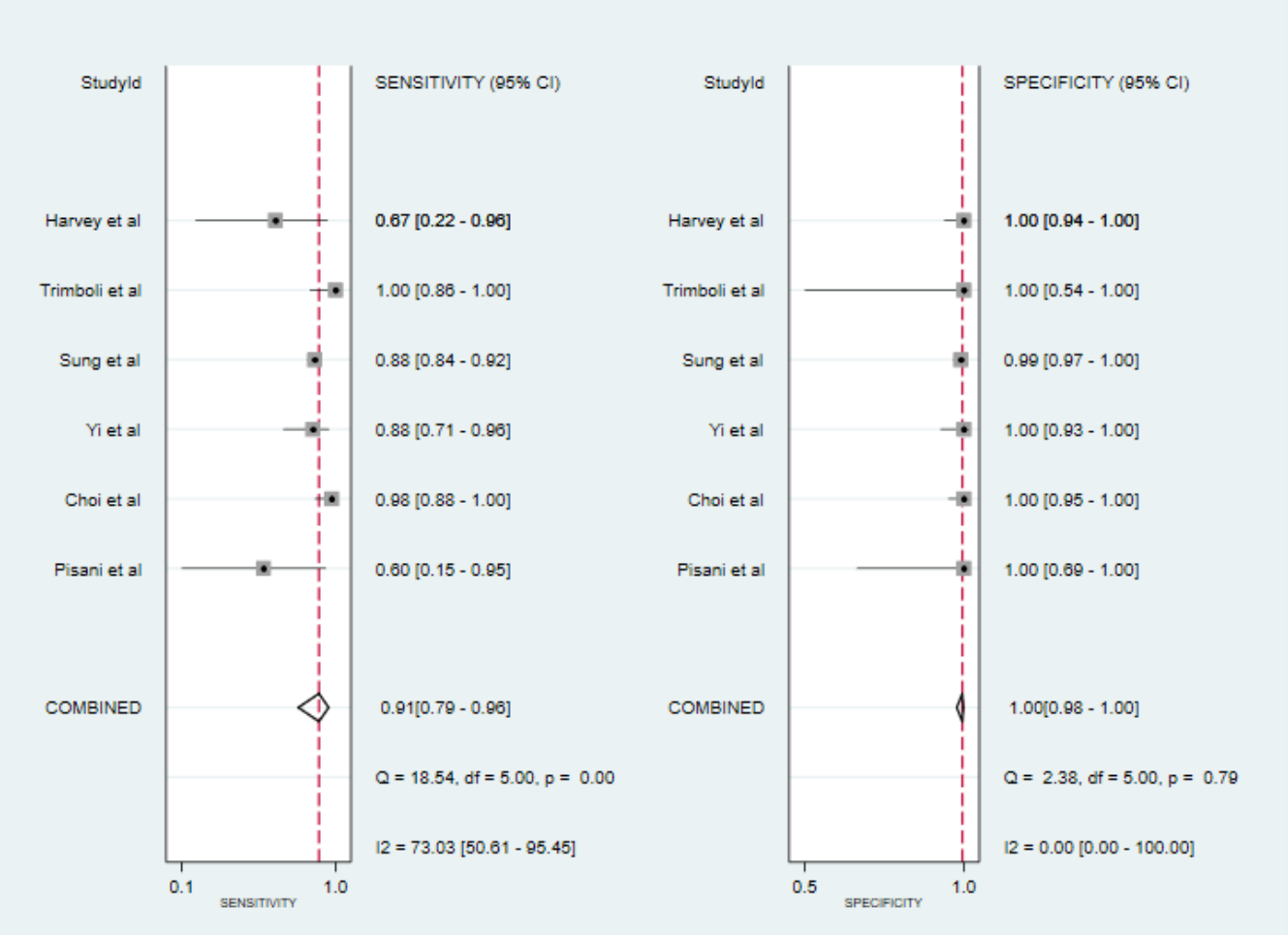

Figure 5 Forest plot study specific and mean sensitivity and specificity with heterogeneity statistics for CNB

A wide range of heterogeneities were found in the summary sensitivity and specificity: Sensitivity: CNB I_2 = 73.0 (Q = 18.5; df = 5; p < 0.001), FNA I_2 = 29.6 (Q = 7.10; df = 5; p = 0.210); Specificity: CNB I_2 = 0.0 (Q = 2.38; df = 5; p = 0.790), FNA I2 = 56.0 (Q = 11.37; df = 5; p = 0.04). Tests for study heterogeneity were not significant for either FNA (Q = 1.95; df = 2; p = 0.189) or CNB (Q = 0.09; df = 2; p = 0.477).

3.4.4 Incidence of the non-diagnostic and inconclusive CNB and FNA results

Table 19 shows the summary of the pooled proportions of the non-diagnostic and inconclusive CNB and FNA results. The non-diagnostic CNB results demonstrated a pooled proportion of 4.3% (95% CI 1.6 to 7.0%), and the non-diagnostic FNA results demonstrated a pooled proportion of 16.4% (95% CI 8.3 to 24.5%). The inconclusive CNB results demonstrated a pooled proportion of 11.2% (95% CI 8.7 to 13.7%), and the inconclusive FNA results demonstrated a pooled proportion of 17.0% (95% CI 10.6 to 23.3%). These results demonstrate that the proportion of non-diagnostic and inconclusive CNB results was significantly lower than FNA ($p < 0.001$). Considerable heterogeneity was found in the pooled proportion of non-diagnostic and inconclusive CNB and FNA results (I_2 = 57.9 to 96.6%). Figure 6 shows the forest plots for the non-diagnostic and inconclusive CNB and FNA results.

Table 19 Summary of the pooled proportions of the non-diagnostic and inconclusive CNB and FNA results

	Non-diagnostic results (%)					Inconclusive results (%)				
	CNB	***I*2 %**	**FNA**	***I*2 %**	***P* value**	**CNB**	***I*2 %**	**FNA**	***I*2 %**	***P* value**
All studies	4.3 (1.6 – 7.0) (*n* = 7)	83.9%	16.4 (8.3 – 24.5) (*n* = 7)	96.0%	<0.001	11.2 (8.7 – 13.7) (*n* = 5)	25.3%	17.0 (10.6 – 23.3) (*n* = 6)	86.1%	<0.001

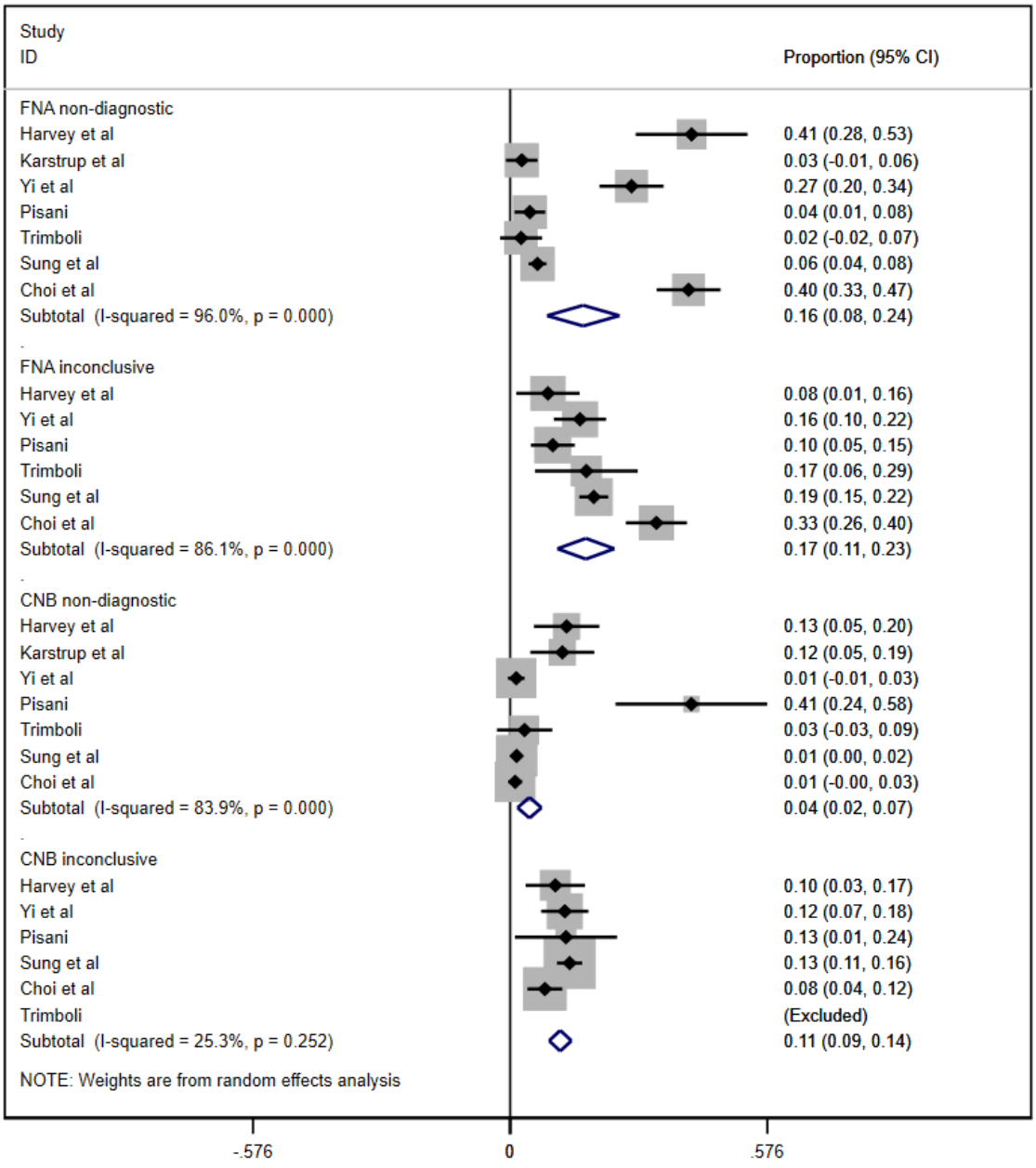

Figure 6 Forest plots for the non-diagnostic and inconclusive CNB and FNA results

3.4.5 Complications

No major complications were reported in any of the included studies. Out of eight studies, three studies described one postoperative haematoma (Table 20), two episodes of haemorrhage and one incident of parenchymal oedema were reported after CNB. Only one patient required hospitalisation for overnight monitoring post a perithyroidal haemorrhage. No complications were reported for FNA in these studies. As patients of four included studies had simultaneous FNA and CNB procedures the complications could not be attributed to a single procedure.[124, 142, 144] In these studies, 19 cases of perithyroidal haematoma and 13 cases of parenchymal oedema were reported. Sung et al did not note any cases of infection or needle track seeding during the follow up period.[124, 142, 144]

Table 20 Complications of FNA and CNB

	FNA	CNB	Simultaneous FNA and CNB
Perithyroidal haemorrhage	Nil reported	2	Nil reported
Perithyroidal haematoma	Nil reported	1	19
Parenchymal oedema	Nil reported	1	13

Six studies described manual compression of the biopsy site after FNA/CNB procedures.[88, 124, 139, 142-144] The time for manual compression ranged from 5 minutes to 30 minutes. Trimboli et al and Sung et al ceased antiplatelets and anticoagulants for one week prior to the biopsy where possible.[141, 142] The remaining studies did not describe antiplatelet/anticoagulation management in their methods.

Jeong et al did not find a statistically significant difference in pain scores during and at 20 minutes after FNA and CNB (3.7 vs. 3.6, P= 0.454; 0.9 vs. 1.1, P = 0.296, respectively).[139]

The study did not demonstrate any difference in tolerability and complications between the two groups.[139]

CHAPTER 4 **DISCUSSION**

4.1 Summary of main results

The main results of this systematic review are presented in summary of findings tables (Table 20 and 21). The objective of this review was to systematically identify and review two arm prospective and retrospective studies to report and compare the complications and accuracy of ultrasound guided CNB and FNA in the diagnosis of malignant and neoplastic head and neck masses. Nine studies conducted in five different countries reporting on the diagnostic accuracy and/or complications of FNA and CNB met our inclusion criteria.

The results of the meta-analysis suggest that CNB appears to be superior to FNA as it is associated with significantly fewer non-diagnostic results (4.3% vs us FNA 16.4%) and inconclusive results (11.2% versus us-FNA 17%) with similar sensitivity and specificity. (Table 21)

Table 21 Summary of findings table - Thyroid

What is the diagnostic accuracy of ultrasound guided fine needle aspiration compared to core needle biopsy for thyroid malignancy?						
Patients/Population	Adult patients with thyroid nodules suspected to have thyroid malignancy					
Prior testing	Patients found to have a suspicious thyroid nodule on history or physical examination, euthyroid, 131 scintigraph proven cold nodules with baseline ultrasound performed prior					
Index test	Fine needle aspiration					
Comparator test	Core-needle biopsy					
Reference standard	Surgical histopathology would be the gold standard but is not routinely performed for benign lesions. Reference used: clinical follow up and surgical histopathology					
Studies	Cross-sectional cohort studies including equally suspected patient sample (no case control studies)					
Methodological concerns	The methodological quality was generally poor, particularly with respect to the patient selection and the flow and timing domains. For these domains, few studies were at low risk of bias. Differential verification was used in most studies because most of the participants with benign aspiration/biopsy results did not have surgery. Clinical follow-up for these participants was inadequate, incomplete, or poorly described in most studies. Uninterpretable results and withdrawals poorly reported. Inconsistent reporting of inconclusive and non-diagnostic results. Inconclusive results often included in summary accuracy calculation					
Test	Summary accuracy	P value	No of participants (studies)	Prevalence Median (range)	Implication	Test accuracy CoE
Fine needle aspiration	Sensitivity 0.75 (95% CI: 0.66 to 0.83) Specificity	Sensitivity 0.125 Specificity 0.806	1118 (6)	36 (11-82)	With a pre-test probability of 36%, 36 out of 100 people will have thyroid cancer. Of these nine people will be missed by FNA	⊕⊕◯◯ LOW

	1.00 (95% CI: 0.60 to 1.00)					
Core needle biopsy	Sensitivity 0.91 (95% CI: 0.79 to 0.96) Specificity 1.00 (95% CI: 0.98 to 1.00)		1024 (6)	36.5 (8.7-80)	Out of 100 people with a 36.5% probability of having thyroid cancer there would 33 people will be correctly identified as having thyroid cancer and three people with thyroid cancer will remain undetected with CNB.	

What is the diagnostic adequacy of ultrasound guided fine needle aspiration compared to core needle biopsy for thyroid malignancy and neoplasm?

Test	Summary adequacy	P value	No of participants (studies)	Implication	Test accuracy CoE
Fine needle aspiration	Non-diagnostic rate 0.164 (95% CI: 0.083 to 0.245) Inconclusive rate 0.17 (95% CI: 0.106 to 0.233)	Non-diagnostic <0.001 Inconclusive <0.001	1195 (7) 1118 (6)	Out of 100 people that have an FNA 16 patients will have a non-diagnostic result and 17 patients will have an inconclusive result	⊕⊕◯◯ LOW
Core needle biopsy	Non-diagnostic rate 0.043 (95% CI: 0.016 to 0.07) Inconclusive rate 0.112 (95% CI: 0.087 to 0.137)		1102 (7) 992 (5)	Out of 100 people that have a CNB 4 patients will have a non-diagnostic result and 11 patients will have an inconclusive result	

Conclusion: Sensitivity and specificity of FNA and CNB for diagnosis of thyroid malignancy for FNA and CNB are high. The inadequacy rate and inconclusive rate for CNB is lower than FNA for thyroid malignancy.

The results on this table should not be interpreted in isolation from the results of the individual included studies contributing to each summary test accuracy measure. These are reported in the main body of the text of the review

The results describe the absolute impact of FNA and CNB in a population with a pretest probability of 36% (derived from the median prevalence of the included studies). If applied in a setting with a lower prevalence, the absolute number of false positives will increase, and the false negatives will decrease.

Table 22 Summary of findings table - salivary malignancy

What is the diagnostic accuracy of ultrasound guided fine needle aspiration compared to core needle biopsy for salivary gland malignancy?					
Patients/Population	Adult patients with salivary tumours suspected to have a malignancy listed for a parotidectomy				
Prior testing	Patients found to have a suspicious salivary gland on history or physical examination, ultrasound performed prior				
Index test	Fine needle aspiration				
Comparator test	Core-needle biopsy prior to surgery under general anaesthetic				
Reference standard	Surgical histopathology is be the gold standard. Reference used: surgical histopathology for majority of the patients (100), patients not fit for surgery were followed up clinically (8)				
Studies	Cross-sectional cohort study including, patient selection somewhat biased as prospective recruitment via surgical listing				
Methodological concerns	The methodological quality was generally poor, particularly with respect to the patient selection and the flow and timing domains.				
Test	Summary accuracy	No of participants (studies)	Prevalence Median (range)	Implication	Test accuracy CoE

Fine needle aspiration	Sensitivity 0.64 (95% CI: 0.41 to 0.83) Specificity 0.94 (95% CI: 0.86 to 0.98)	108 (1)	23%	23 people (out of 100 people) have (as yet undetected) malignancy. Of the 100 people who take FNA test: - 15 people will be correctly identified as having malignancy (true positives) - However, eight people with malignancy will remain undetected; their “negative” test results will be incorrect (false negatives). - 72 of these people will be correctly identified as not having malignancy (true negatives) - However, 5 people will be incorrectly identified; their “positive” test results will suggest they have malignancy (false positives).	⊕◯◯◯ LOW
Core needle biopsy	Sensitivity 0.91 (95% CI: 0.79 to 0.96) Specificity 1.00 (95% CI: 0.98 to 1.00)			Of the 100 people who take CNB test: - 21 people will be correctly identified as having malignancy (true positives) - However, two people with malignancy will remain undetected; their “negative” test results will be incorrect (false negatives). - 77 of these people will be correctly identified as not having malignancy (true negatives) - However, 0 people will be incorrectly identified; their “positive” test results will suggest they have malignancy (false positives).	

In our review, complication rates for both FNA and CNB were low. CNB was associated with perithyroidal haemorrhage, haematoma and oedema in two studies, and these were all managed conservatively and resolved spontaneously. A systematic review assessing CNB accuracy for salivary tumours reported an overall haematoma rate of 1.7%.[96] A recently published meta-analysis that evaluated types and incidence of complications associated with CNB in diagnosis of thyroid nodules reported a

pooled complication rate of 1.11%, with pooled major complication rate being much lower (0.06%) than minor complications (1.08%).[104] A systematic review of complications post FNA reported a similar risk profile for FNA.[103] Most complications following FNA and CNB are transient, have low morbidity and are self-limited and the overall safety of FNA and CNB is comparable.[104]

4.2 Strengths and Weaknesses

The stregths of this review included a thourough and transparent conduct by following the methodology of Joanna Briggs Institute.[27] A protocol detailing the objectives, methodology for conduct of the review, including the inclusion and exclusion criteria was published.[147] Comprehensive all-inclusive searches were run with no filters to target diagnostic test accuracy studies or language or publication date. To ensure comparison of the index tests in the same study population, we only included studies that made direct comparisons, either by testing all patients using both tests and by randomising patients to different tests. Two review authors independently selected studies for inclusion and assessed methodological quality of the included studies using QUADAS - 2, as recommended by the Joanna Briggs review manual.[138]

It is important to note some of the limitations of this review. Our review focused on the accuracy and safety of FNA and CNB and not their impact on patient outcomes. The primary advantage of FNA and CNB is early identification of malignant and neoplastic conditions requiring surgical intervention to reduce treatment delay and to avoid unnecessary surgery. Therefore, the choice of FNA and CNB will depend on the type of tumour/patients with malignancy or a neoplastic condition requiring surgery that are missed (false negatives), and the proportion of false positives or inconclusive/indeterminate results that if too high will result in patients having unnecessary surgery and associated morbidity, added to the burden of healthcare and block resources needed for patients that actually require surgical intervention. Future studies should be designed as end to end studies i.e. studies that examine the impact of accuracy on patient outcomes and include an economic evaluation. A study with this

design is more likely to identify the biopsy technique that maximises the use of these interventions and leads to better patient outcomes.

The review process was limited by our inability to translate articles in languages other than English due to limited time and resources. In addition to the aforementioned weaknesses, there were limitations related to the available evidence.

4.2.1 Paucity of evidence

The majority of the included studies used retrospective data collection from registries or hospital records which may not contain the necessary information, like patients presenting with procedure complications to other hospitals or primary care providers. Overall there were not enough good quality primary studies that compared ultrasound guided FNA and CNB for the proposed head and neck subsites precluding pooling of results or investigation of heterogeneity for two subsites (salivary gland and cervical nodes). Thyroid malignancy was evaluated in six studies in similar settings. Salivary gland masses were evaluated in only one study. None of the included studies evaluated cervical lymph nodes. Complications were generally poorly recorded and consequently difficult to pool and analyse.

Studies published as conference abstracts were excluded from this review as it was not possible to ascertain the eligibility and methodological quality of these studies, the authors were not contacted for further details due to limitations of time and resources. Of the studies presented as summaries or abstracts at meetings, only half of all studies and a third of randomised trials fail to be published in full.[148] Studies with positive findings, studies from native English-speaking countries, with larger sample sizes are more likely to be published in literature introducing a publication bias.[148] As this review relies on published literature, it is likely affected by publication bias.

4.2.2 Methodological quality of studies

Most of the studies had unclear or moderate methodological concerns indicating high risk of bias.Given this high risk of bias the reported accuracy estimates may not accurately reflect the actual performance of the tests. Patient selection and patient flow posed the most significant concerns.

Two prospective studies were at a high risk of selection bias because they failed to randomise CNB and FNA and did not clearly describe the selection process. Generally, sensitivity and specificity is not affected by prevalence if the spectrum of diseased and non-diseased remains constant. Large variations in populations and patient selection can present as large variation in prevalence and this likely affects accuracy.[149] In this systematic review study samples varied considerably in terms of prevalence suggesting differences in the spectrum of included participants.

With respect to patient flow through the studies and the timing of the index test and reference standard, half the studies were at high risk of bias (4/8).[124, 140, 143, 144] This was largely because of an unexplained difference in the number of patients recruited and the number of patients finally analysed in the two x two tables, introducing a partial verification bias.

Risk of bias regarding conduct of index tests and reference tests and the interpretation of the results could not be assessed due to failure of primary studies to provide sufficient information. The reference standard (surgical histopathology after excision vs clinical follow up) for diagnosis was poorly defined or only applied to an unspecified subset of cases in two studies.[124, 140]

The same reference standard was not applied to all patients. Varying proportion of patients with benign pathology were followed up sonographically and clinically. Differential verification

of FNA and CNB poses a problem as reference standards differ in accuracy (histopathology of a nodule vs follow-up for detection of malignancy) and this affects the diagnostic test accuracy in turn introducing a risk of bias.

Overall the studies were assessed to be at serious risk of bias and as such the summary accuracy data needs to be interpreted with awareness of these limitations.

4.2.3 Sources of heterogeneity

Heterogeneity secondary to variation in operators performing the test and their experience, the variety of needle sizes used for both techniques, the number of needle passes, the reference standards used were contributing variables identified in this study. These factors affect the sensitivity and post-procedure complication rates as well as non-diagnostic rates. It is therefore important to interpret the results of this review in the context of heterogeneity of data.

Subgroup analysis of the different anatomical sites as planned was not possible due to inadequate number of published studies meeting our inclusion criteria. Post-hoc the following additional possible subgroup analyses were identified:

- operator characteristics
- nodule characteristics (solid vs cystic; macrocalcification vs no macrocalcifications)
- Diagnostic accuracy for first line aspiration and core needle biopsy
- Diagnostic accuracy of repeated fine needle aspiration and core needle biopsy in patients with prior nondiagnostic/indeterminate FNA results

4.3 Previously published meta-analyses compared to this review

The results of this meta-analysis are consistent with the results from previous meta-analyses presented in Table 23. Only one meta-analysis systematically compared accuracy of FNA and CNB;[98] however, this review was limited to thyroid nodules, made indirect comparisons between FNA and CNB and included studies that had patients <18 and non-ultrasound guided FNA. All the studies had similar methodological issues associated with diagnostic accuracy reviews, poor reporting, unclear patient flow and timing of index and reference tests, between study variation and heterogeneity and biased patient selection.

The results of this meta-analysis are comparable with the results of other studies investigating the diagnostic accuracy of FNA and CNB in salivary gland masses, axillary lymph node metastases, and primary breast tumours.[96, 116, 117] A meta-analysis that compared FNA and CNB for diagnosis of axillary lymph node metastases included 1353 patients from six studies. The findings suggested that CNB was a superior diagnostic technique with sensitivity of CNB (88%) being higher than sensitivity of FNA (75%) with a high specificity of 100%. The repeat diagnostic procedure rate for FNA was 4% vs 0.5% of CNB.

Table 23 Previous meta-analyses - head and neck masses

Author and publication year	Number of participants (included studies)	Focus of review	Summary sensitivity (95% CI)	Summary specificity (95% CI)	Summary adequacy (95% CI)
Cao (2016)[98]	2942 (12)	(1) compare the accuracy of C.N.B. and F.N.A. in the detection of thyroid malignancy; (2) evaluate the accuracy of C.N.B. in nodules with prior non-diagnostic F.N.A. results.	FNA – 0.747 (0.655, 0.822)	FNA – 0.956 (0.855, 0.988)	OR 4.983 (Range 2.17 – 11.19) favoring CNB
			CNB – 0.808 (0.747, 0.857)	CNB – 0.955 (0.880, 0.984)	
Suh (2017)[150]	2240 (9)	to evaluate the efficacy and safety of core needle biopsy for the examination of thyroid nodules with initially indeterminate results on fine-needle aspiration.	Not pooled CNB – range (0.447 – 0.85)	Not pooled CNB – 1.00	Non diagnostic 0.018 (0.004 –0.032),
					Inconclusive 0.251 (0.154–0.349).
Liu (2016)[151]	5647 (63)	(1) to analyze the sensitivity and specificity of fine-needle aspiration (FNA) in distinguishing	FNA - 0.882 (0.509–0.982)	FNA - 0.995 (0.960–0.999)	Non diagnostic 0.053 (0.030–0.075)

Author and publication year	Number of participants (included studies)	Focus of review	Summary sensitivity (95% CI)	Summary specificity (95% CI)	Summary adequacy (95% CI)
		benign from malignant parotid disease. (2) To determine the anticipated posttest probability of malignancy and probability of non-diagnostic and indeterminate cytology with parotid FNA			
Schmidt (2011)[66]	6169 (64)	to summarize the evidence on the diagnostic accuracy of FNAC for parotid gland tumors	FNA - 0.80 (0.76-0.83)	FNA - 0.97 (95% CI, 0.96-0.98)	Not pooled – 8.6% inadequate/indeterminate
Schmidt (2011) [152]	403 (5)	to obtain improved estimates of the diagnostic accuracy of CNB	CNB - 0.92 (0.77-0.98)	CNB – 1.00 (0.99 – 1.00)	Not pooled – 1.2% Difference in adequacy rate calculated between above study and this study. 0.069 (0.042-0.096); statistically significant p=0.001
Witt (2014)[96]	512 (5)	To obtain summary estimates of the sensitivity and specificity of core needle biopsy for assessment of	CNB – 0.96 (0.87–0.99)	CNB – 1.00 (0.84–1.00)	Not pooled 1.6%

Author and publication year	Number of participants (included studies)	Focus of review	Summary sensitivity (95% CI)	Summary specificity (95% CI)	Summary adequacy (95% CI)
		salivary gland lesions			
Kim (2018)[24]	1315 (10)	to provide an updated meta-analysis and systematic review of core needle biopsy in the salivary glands.	CNB - 0.94 (0.92-0.96)	CNB - 0.98 (0.97-0.99)	Not pooled - 3.26%
Tandon (2008) [67]	3459 (30)	to assess the effectiveness of FNAC in the diagnosis of masses presenting in the head and neck by way of a systematic review of the literature and subsequent meta-analysis of the raw data extracted from studies that fulfilled the inclusion criteria of the review	FNA – 89.6 (CI not reported)	FNA – 96.5 (CI not reported	Not reported
Novoa (2012) [20]	1291 (16)	to determine the role of CNB in the assessment of head and neck lesions	CNB – 93% (CI not reported)	CNB 99% (CI not reported)	Not pooled (5% inadequacy rate)

CHAPTER 5 **CONCLUSION**

5.1 Implications for practice

Percutaneous biopsy techniques are critical for surgical management of head and neck masses and have become the standard of care in preoperative diagnosis of neoplasms and malignancy. A correct diagnosis allows for prompt treatment in turn avoiding progression of disease. Diagnostic delays can lead to poorer prognosis and outcomes in some patients due to progression of the disease to an advanced stage.[18] Sensitivity is key for a diagnostic biopsy test in order to avoid incorrectly clearing a patient that has a malignancy (false negative). However, in addition to high sensitivity, an ideal test will ensure that no patients undergo the risk of morbidity associated with unecessary surgery. The prime metric for determining a 'superior' biopsy technique in addition to high sensitivity and specificity in our opinion is the inadequacy rate.

This review's findings suggest that core needle biopsy has consistently lower non-diagnostic and inconclusive rate with comparable sensitivity and specificity and similar risk profile to FNA for thyroid nodules.

This review suggests that due to its high sensitivity and specificity, and low inadequacy and inconclusive rate CNB is certainly an appropriate test to triage individuals that need to undergo more invasive surgical management for thyroid nodules. Considering this and the similar safety profile, cost permitting, CNB could replace FNA in the clinical pathway in diagnosis of thyroid nodules, if not all head and neck masses.

Overall, the number of included studies was small, and most studies were at high risk of bias and there were substantial differences in study characteristics and large between-study heterogeneity in the reported accuracy estimates. Consequently, these findings should be treated with caution. Better designed studies are required to verify our provisional hypotheses.

5.2 Implications for research

Good quality primary diagnostic accuracy studies that make direct comparisons between ultrasound guided FNA and CNB either in a paired or a randomised unpaired methodology and present standardised reporting of core accuracy data following the STARD (Standards for the Reporting of Diagnostic Accuracy)[153] statement are required to further assess the adequacy, accuracy and complications associated with each procedure. The accuracy of CNB should be compared with that of FNA to assess if CNB should replace FNA as a diagnostic test, or alternatively be used only in patients with non-diagnostic/inconclusive results.

There are limited or no studies diagnostic accuracy studies addressing salivary gland masses and cervical lymphadenopathy resulting in an inability to analyse and compare ultrasound guided FNA and CNB for these subsites. This needs to be addressed by further studies that assess and compare the safety and efficacy of the use of FNA and CNB for these sub sites to guide further management.

The majority of the primary studies were of unclear or moderate risk of bias due incomplete reporting. Future studies need to address this by being transparent in their methodology and

ensuring that guidelines such as STARD are adhered to, and complete reporting of patients enrolled, patients lost to follow up, and patients undergoing the intervention arerecorded

There is a paucity of cost-effectiveness data comparing ultrasound guided FNA and CNB for head and neck masses. The utility of CNB as a primary diagnostic test versus an ad hoc add on test with FNA will be affected by the cost factor. Primary studies of cost-effectiveness for each technique are critical for policy makers and clinicians to help make informed, cost-effective decisions.

An ideal cytological/histological test for identification of neoplasms and malignancy will have binary results neoplastic/non-neoplastic or malignant or non-malignant. However, inadequate samples or indeterminate results are a common finding that add variability to the results of diagnostic test accuracy studies. The Bethesda system for reporting thyroid cytology was established in 2009 to define intermediate cytology findings and to report risk of malignancy associated with each category. In our study, prior to the introduction of the Bethesda, some studies classified indetermediate results as benign increasing the false negative rate while other studies classified them as malignant increasing the false positive rate.[123, 124] This inconsistency creates confusion in interpretation of data.[66] Haematological malignancies have the French-American-British and World Health Organisation classification systems that assist in interpretation of bone marrow aspirates, similarly breast FNA has diagnostic categories.[117, 152] The standardisation of classification has helped researchers and clinicians in analysing, reporting and interpreting fine needle aspirates of thyroid nodules, breast nodules and bone marrow aspirates respectively. There is a need for standardisation of cytopathology reporting for salivary gland lesions and lymph node masses. Core needle biopsy also needs classification systems for histopathological analysis of head and neck lesions.

The diagnostic yield of addition of CNB as a diagnostic test for all patients undergoing FNA for investigation of head and neck masses was not investigated in this study and should be considered in future studies. Additionaly, the role of CNB in the diagnostic ladder as a test that is used as a triaging tool versus an add on test or whether it can replace FNA was not established in this study and needs to be assessed by future studies.

Appendix I Studies in other languages

ANA PAULA CANDIDO DOS SANTOS

Análise comparativa da Punção Aspirativa por Agulha Fina (PAAF) em relação a biópsia em cavidade oral e região de cabeça e pescoço

·甲状腺外科·

超声引导下穿刺粗针病理学和细胞学及细针细胞学在甲状腺微小结节中的诊断价值

张少航 牛丽娟

【摘要】 **目的** 研究超声引导下粗针病理学检查(ultrasound-guided core-needle biopsy, US-CNB)、粗针细胞学检查(ultrasound-guided core-needle aspiration, US-CNA)及细针细胞学检查(ultrasound-guided fine-needle aspiration, US-FNA)在甲状腺微小结节诊断中的价值。**方法** 对 92 例超声诊断为可疑恶性的甲状腺微小结节患者的 92 个结节进行穿刺。所有病例经手术治疗有病理证实。其中 52 例行 US-CNB 及 US-FNA;另外 40 例行 US-CNA 及 US-FNA。**结果** 52 例行 US-CNB 和 US-FNA 患者中,41 例 US-CNB 取材不满意,11 例取材满意,且诊断与术后病理符合;52 例 US-FNA 取材均满意,均有明确诊断,6 例与术后病理不符,46 例与术后病理符合。40 例行 US-CNA、US-FNA 的患者中,26 例 US-CNA 取材成功,14 例取材失败或欠满意;36 例 US-FNA 取材成功,4 例取材失败或欠满意。92 例 US-FNA 对于鉴别甲状腺微小良、恶性结节的敏感度、特异度、阳性预测值、阴性预测值、符合率分别为 93.4%、86.7%、97.3%、72.2%、92.3%。**结论** US-FNA 是甲状腺微小结节的术前穿刺最有价值的活检方式。

【关键词】 甲状腺结节; 活组织检查,细针; 活组织检查,粗针

Evaluation of the efficacy and the limitation of ultrasound-guided core-needle biopsy, core-needle aspiration and fine-needle aspiration in micro-nodules of thyroid

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【**Abstract**】 **Objective** To evaluate the efficacy and the limitation of ultrasound-guided core-needle biopsy, ultrasound-guided core-needle aspiration and ultrasound-guided fine-needle aspiration in micro-nodules of thyroid. **Methods** A retrospective was performed in 92 patients with suspectable malignent micro-nodules in thyroid. Of them, 52 patients underwent US-CNB and US-FNA and 40 patients underwent US-CNA and US-FNA. The diagnoses for the micro-nodules were identified by histopathlogical examination after surgery. **Result** Among 52 cases with both US-CNB and US-FNA, 41 got nondiagnostic US-CNB and 11 cases successfully got the correct diagnoses of US-CNB; 6 cases got the incorrect diagnosis of US-FNA and 46 cases got the correct diagnosis of US-FNA. Of 40 cases with US-CNA and US-FNA, unsatisfactory specimen of US-CNA occurred in 14 cases and satisfactory specimen of US-CNA were got in 26 cases; unsatisfactory specimen of US-FNA occurred in 4 cases and satisfactory specimen of US-FNA. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of US-FNA in 92 cases for the diagnosis of malignancy were 93.4%, 86.7%, 97.3%, 72.2% and 92.3%, respectively. **Conclusions** US-FNA is the most valuable method for the diagnosis of suspectable malignent micro-nodules in thyroid before operation.

【**Key words**】 Thyroid nodule; Biopsy, fine-needle; Biopsy, large-core needle

甲状腺结节在人群中多见,成人中可触及甲状腺结节的患病率约为 5%[1],通过高分辨率超声检查甲状腺结节的患病率约为 19% ~67%[2]。绝大多数甲状腺结节是良性病变[3-4],恶性病例仅占 5%[5-6]。恶性的甲状腺结节大多需要手术治疗,而无症状的良性甲状腺结节一般定期随诊[7-8]。如何使恶性结节病例得到早期诊治,使良性结节病例免

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Stellenwert der Feinnadelaspirationszytologie und Stanzbiopsie im Kopf-Hals-Bereich

Value of Fine Needle Aspiration Cytology and Core Needle Biopsy in the Head and Neck Region

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Schlüsselwörter
- Feinnadelaspirations-zytologie
- Grobnadelpunktion
- Kopf-Hals-Karzinome
- FNAC
- GNP
- Stanzbiopsie

Key words
- core needle biopsy
- fine needle aspiration cytology
- head and neck cancer
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Editor's-Choice

Zusammenfassung

Hintergrund: Mit der Feinnadelaspirationszytologie (FNAC) und der Stanzbiopsie (auch: Grobnadelpunktion, GNP) existieren 2 wenig invasive Methoden zur Dignitätsklärung von klinisch oder bildgebungstechnisch auffälligen Veränderungen im Kopf-Hals-Bereich. Zum Vergleich beider Techniken liegen bisher wenige Daten vor. Das Ziel dieser retrospektiven Studie ist es, den diagnostischen Stellenwert sowie die Sensitivität und Spezifität der FNAC und der Stanzbiopsie zu vergleichen.

Material und Methoden: Im definierten Zeitraum wurde bei 86 Patienten eine Stanzbiopsie und bei 408 Patienten eine FNAC durchgeführt. Aufgrund der Ergebnisse aus FNAC oder Stanzbiopsie wurden 52 Patienten der Stanzbiopsie-Gruppe und 224 Patienten der FNAC-Gruppe anschließend operiert, sodass die Ergebnisse mit der endgültigen Histopathologie verglichen werden konnten.

Ergebnisse: Die Sensitivität der FNAC lag mit 85 % höher als die der Stanzbiopsie (80 %), die Spezifität (87 vs. 94 %) und der positiv prädiktive Wert (64 vs. 97 %) waren geringer. Überlegen war die FNAC beim negativ prädiktiven (92 vs. 71 %) und dem falsch-negativen Wert (5 vs. 13 %). Bei der Berechnung des falsch-positiven Wertes schnitt die Stanzbiopsie besser ab (2 vs. 15 %).

Schlussfolgerungen: Beide Methoden sind gut geeignet, die Dignität von Raumforderungen im Kopf-Hals-Bereich zu klären. Die FNAC eignet sich besonders zur Diagnostik von hämatologischen Erkrankungen und zum Ausschluss von Malignomen bei suspekten Lymphknoten. Die Stanzbiopsie hat sich als besonders valide bei der Erkennung von Rezidiven in bereits bestrahltem oder operiertem Gewebe erwiesen. Zudem hat sie den Vorteil einer Histologiegewinnung zur definitiven Therapieplanung.

Einleitung

Im klinischen Alltag sieht sich der HNO-Facharzt häufig mit unklaren Raumforderungen im Kopf-Hals-Bereich konfrontiert. Von der einfachen Palpation, über die Sonografie, bis hin zum MRT steht ein breites Spektrum an diagnostischen Untersuchungen zur Verfügung, um die Dignität weiter abzuklären.

Mit der Feinnadelaspirationszytologie (FNAC) und der Stanzbiopsie (auch: Grobnadelpunktion, GNP) existieren 2 wenig invasive Methoden zur Dignitätsklärung von klinisch oder sonografisch auffälligen tumorösen Veränderungen im Kopf-Hals-Bereich. Zum Vergleich der beiden Techniken liegen bisher wenige publizierte Daten vor [1].

Bisherige Studien fokussieren sich auf eine der beiden Techniken, oder auf lediglich Teilaspekte des Kopf-Hals-Bereichs wie z. B. ausschließlich die Glandula parotis [2] oder die Schilddrüse.

Beide Techniken bieten gegenüber einer unmittelbaren Exstirpation suspekter Raumforderungen folgende Vorteile: Bei sicherem Malignitätsausschluss kann, z. B. im Falle von vergrößerten Halslymphknoten, eine nicht zwingend erforderliche Operation mit verschiedenen Risiken und Narbenbildung vermieden werden. Bei sicherem Malignitätsnachweis kann eine definitive onkologische Operation mit konsequenter Tumorresektion bzw. Neck dissektion durchgeführt werden [3, 14, 15].

Das Ziel dieser retrospektiven Studie ist es, den diagnostischen Stellenwert anhand von Sensitivität, Spezifität und positiv prädiktivem sowie negativ prädiktivem Wert dieser beiden Untersuchungen zu vergleichen.

Mit der Erstellung eines diagnostischen Pfades wurde die Anwendung der beiden Techniken im klinischen Alltag eingeordnet.

·短篇论著·

超声造影后颈部淋巴结粗针与细针穿刺活检的结果比较

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【摘要】 **目的** 探讨超声造影后颈部淋巴结粗针与细针穿刺活检的优劣势。**方法** 用掷硬币法将患者随机分为 A、B 两组，均于穿刺术前超声造影后选择目标淋巴结及穿刺点，A 组行粗针穿刺活检，取出组织用 10% 甲醛固定；B 组行细针穿刺活检，取出物涂片后 95% 乙醇固定，两组均送病理学检查。**结果** A 组：49 枚颈部淋巴结肉眼取材成功率 100.0%，病理诊断阳性率 97.9%；B 组：56 枚颈部淋巴结肉眼取材成功率 96.4%，病理诊断阳性率 82.1%；A 组病理诊断阳性率较 B 组高（χ^2 = 6.97，P < 0.05）。**结论** 超声造影后颈部淋巴结粗针穿刺活检病理诊断阳性率较细针高。

【关键词】 超声检查，多普勒； 结核，淋巴结； 活组织检查，针吸

基金项目：浙江省医药卫生计划（2014KY183）；杭州市医药卫生科技计划（2013A39）；杭州科技计划发展项目（20120633B10）

Comparative study of core needle biopsy and fine needle aspiration cytology in the diagnosis of neck lymph node diseases with contrast-enhanced ultrasound *Zhang Wenzhi, Yang Gaoyi, Xu Jianping, Zhang Lin, Li Jun, Zhao Dan*

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【**Abstract**】 **Objective** To compare the efficacies of core needle biopsy and fine needle aspiration cytology in the diagnosis of neck lymph node diseases with contrast-enhanced ultrasound. **Methods** A total of 105 patients with enlargement cervical lymph nodes were randomly divided into two groups, 49 in group A and 56 in group B. All patients were firstly examined with contrast-enhanced ultrasound to determine the targeted lymph node and the puncture point. Core needle biopsy was performed in Group A and tissues were fixed by with 10% formaldehyde; Fine needle aspiration cytology was performed in Group B and extracts were smeared and fixed with 95% alcohol. **Results** The success rates of sampling were 100.0% in group A and 96.4% in group B. The positive rates of pathological examinations were 97.9% in group A; and 82.1% in group B, with a significant difference between two groups (χ^2 = 6.97, P < 0.05). **Conclusion** The pathologically positive rates of core needle biopsy is higher than that of fine needle aspiration cytology for the diagnosis of neck lymph node diseases with contrast-enhanced ultrasound.

【**Key words**】 Ultrasonography, Doppler; Tuberculosis, lymph node; Biopsy, needle

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穿刺活检是诊断浅表淋巴结肿大病因的重要途径，超声造影能显示淋巴结内部微循环灌注[1-2]。将淋巴结内微循环灌注与穿刺活检相结合，能弥补常规超声的识别能力有限、穿刺取材不满意或所取标本区域不具针对性等缺点。本文旨在探讨超声造影后颈部淋巴结粗针与细针穿刺活检的优劣势，优化颈部淋巴结穿刺活检的方法。

资料与方法

一、一般资料

2012 年 1 月—2015 年 8 月入住杭州市红十字会医院结核科的颈部淋巴结肿大患者 105 例，掷硬币法将患者随机分为 A 组和 B 组。A 组 49 例：其中男 18 例，女 31 例，年龄 18～61 岁，平均年龄 35 岁；B 组 56 例：其中男 23 例，女 33 例，年龄 18～60 岁，平均年龄 33 岁。共活检肿大淋巴结数 105 例，105 枚（大小：长径 > 1.0 cm，横径 > 0.5 cm，纵横比均 < 2），其中 63 例为单侧多发，9 例为单侧单发，33 例为双侧多发。所有淋巴结病变性质均经穿刺活检证实或经手术证实。

二、方法

本研究经医院伦理委员会批准，所有患者在术前均知情

Appendix II Search strategy

Search strategy for PubMed

(((((head[tiab] OR neck*[tiab] OR parathyroid[tiab] OR thyroid[tiab] OR cervical [tiab] OR salivary[tiab] OR parotid[tiab] OR sublingual[tiab] OR submandibular[tiab] OR lymphadenopath*[tiab] OR Lymph Node*[tiab] OR occipital[tiab] OR mastoid[tiab] OR maxillary[tiab] OR parotid[tiab] OR supramandibular[tiab] OR submandibular[tiab] OR submental[tiab] OR pre-auricular[tiab] OR preauricular[tiab] OR parathyroid[tiab] OR thyroid[tiab]))))) OR (("head and neck neoplasms"[mh] OR Salivary Glands[mh] OR parathyroid glands[mh] OR thyroid gland[mh] OR thyroid nodule[mh] OR lymphadenopathy[mh] OR immunoblastic lymphadenopathy[mh] OR Lymph Nodes[mh]))))) AND (((biopsy, fine-needle[mh] OR FNA[tiab] OR FNAB[tiab] OR FNAC OR fine needle*[tiab] OR fine-needle*[tiab] OR needle aspiration[tiab] OR UGFNAB[tiab] OR F.N.A[tiab] OR F.N.A.C[tiab])) AND (biopsy, large-core needle[mh] OR core needle*[tiab] OR CNB[tiab] OR NCB[tiab] OR cutting needle*[tiab] OR core biops*[tiab] OR core-needle*[tiab] OR needle core[tiab]))

PubMed (Medline) Search conducted on 2 March 2019 – 595 article hits

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Appendix III JBI Critical Appraisal Checklist for Diagnostic Test Accuracy Studies

JBI Critical Appraisal Checklist for Diagnostic Test Accuracy Studies

Reviewer_____Date_____

Author _____Year_____Record Number _____

	Yes	No	Unclear	Not applicable
1. Was a consecutive or random sample of patients enrolled?	☐	☐	☐	☐
2. Was a case-control design avoided?	☐	☐	☐	☐
3. Did the study avoid inappropriate exclusions?	☐	☐	☐	☐
4. Were the index test results interpreted without knowledge of the results of the reference standard?	☐	☐	☐	☐
5. If a threshold was used, was it pre-specified?	☐	☐	☐	☐
6. Is the reference standard likely to correctly classify the target condition?	☐	☐	☐	☐
7. Were the reference standard results interpreted without knowledge of the results of the index test?	☐	☐	☐	☐
8. Was there an appropriate interval between index test and reference standard?	☐	☐	☐	☐
9. Did all patients receive the same reference standard?	☐	☐	☐	☐
10. Were all patients included in the analysis?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

Appendix IIV JBI Data extraction tool

Author/Date	
Inclusion/exclusion criteria: i.e. presenting symptoms, results from previous tests	Inclusion: Exclusion:
Sample size	
Participant demographics (i.e. age, sex, spectrum of presenting symptoms, comorbidity, current treatments, recruitment centers)	
Study methodology (consecutive or random; retrospective or prospective)	
Period that study was carried out (beginning and end date)	
Index test description (including criteria for positive test)	
Reference test description (including criteria for positive test)	
Geographical location of data collection	
Setting of data collection	
Persons executing and interpreting index tests (numbers, training, and expertise)	
Persons executing and interpreting reference test	
Index/reference time interval (and treatments carried out in between)	
Distribution of severity of disease in those with target condition	

Other diagnoses in those without target condition	
Adverse events from index test	
Adverse events from reference test	

Index test results Threshold=	Condition positive	Condition negative	Total
Index test positive (T+)			
Index test negative (T-)			
Total			

Appendix V Excluded studies and reason for exclusion

Another language

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