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The PSGS Evidence-based Clinical Practice Guidelines on the Diagnosis and Initial Management of Cervical Lymphadenopathy

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The presence of cervical lymphadenopathy is a common condition presenting to the surgeon. This may be associated with various diseases such as an acute bacterial infection in the head and neck region, tuberculosis, or malignancy. There is significant variability among clinicians in the approach to its diagnosis and management because of the lack of evidence-based guidelines which are can be applicable to our local setting. Recognizing this need, the Philippine Society of General Surgeons (PSGS), through the Head and Neck Study Group decided to formulate evidence-based clinical practice guidelines on the diagnosis and initial management of cervical lymphadenopathy.

These guidelines are based on the most recent available scientific evidence and the views of local experts on current practices. They are intended to guide surgeons (fellows and resident trainees) and general physicians who encounter such clinical condition in their practice and assist them in clinical decision making. They are merely recommendations and may be modified according to patients' preferences , socio cultural and other factors that may affect the management of actual patients. These statements are not to be used as a basis for court litigations, administrative sanctions or similar situations. This project was funded solely by PSGS.

Executive Summary

The Technical Working Group (TWG) composed of fellows of PSGS and who are also active members of the Philippine Academy for Head and Neck Surgery, Inc., held a meeting on March 18, 2015 to establish the basic framework of the CPG. Clinical questions to be tackled were formulated and literature search using Medline and HERDIN was done. Key words used for the search included Mesh terms : "cervical lymph node", "cervical lymphadenopathy", "diagnosis", "clinical evaluation", "clinical history", "benign", "malignant", "ultrasound", "CT scan", "fine needle biopsy", "trial of antibiotic therapy". The search yielded 269 articles. Out of the 47 articles considered relevant, 43 articles were available with full text. Critical appraisal was conducted from April to June 2015. On July 11, 2015, the group together with PSGS Committee on Research Chair Dr. Cheryl Cucueco held a meeting to evaluate the level of evidence using Oxford Center for Evidence Based Medicine, 2011. The TWG held several meetings from August to December 2015 to propose a recommendation for each clinical question. The draft of the clinical practice guidelines was prepared from January to March 2016. To ensure acceptability of the guidelines by the other specialties, a multidisciplinary

Panel of Experts was convened on April 30, 2016 to discuss and finalize the recommendations. Six additional articles were provided by the experts. The recommendations were then presented in a public forum last August 5, 2016 during the Philippine Society of General Surgeons' Annual Surgical Forum. The technical writing and editing was done by the current Chair of the Research Committee Dr. Joseph Quebral.

Technical Working Group:

1. Fernando L. Lopez, MD (Chairman)
2. Maria Cheryl L. Cucueco, MD (Chair, PSGS Committee on Research , 2015)
3. Alfred Phillip O. de Dios, MD (PSGS, PAHNSI)
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Levels of Evidence

Grade of the Recommendations

A- at least 75 percent agree on the recommendation

B- less than 75 percent agree on the recommendation

C- disagreement among the experts regarding the recommendation

Members of the Expert Panel

Aristotle Peter T. Lee, MD, FPSP, DPSP
Pathologist

Lino S. Pabillo MD, FPCR, FUSP
Radiologist, Past President
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Ma. Antonia O. Yamamoto, MD, FPAFP, FPCOM
Family Physician

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

(OCEBM Table of Evidence Working Group. Oxford Centre for Evidence-based Medicine 2011 Levels of Evidence. Retrieved from http://www.cebm.net)

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Operational Definitions

1. Lymphadenopathy - refers to any condition or disease process involving lymph nodes which are abnormal in size and consistency.

2. Lymphadenitis - lymphadenopathies that are due to inflammatory processes. It is characterized by inflammatory signs: swelling, pain, fever, edema, erythema, and collection of pus.

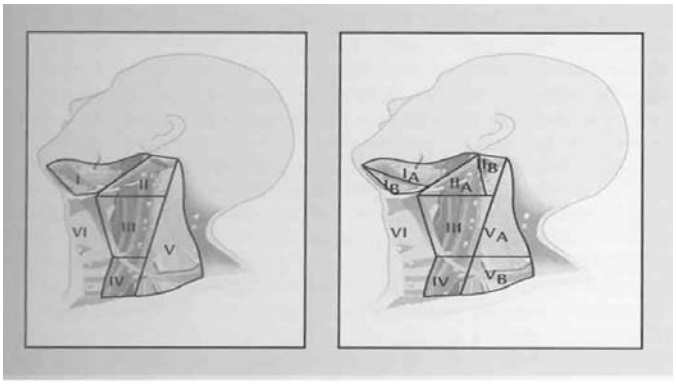
3. Acute lymphadenitis - 2 weeks in duration

4. Sub-acute lymphadenitis - 2 to 6 weeks duration

5. Chronic lymphadenitis- > 6 weeks duration

6. Non-specific reactive hyperplasia of lymph nodes (NSRH) - a benign reversible enlargement of the lymph node resulting from the proliferation of part or all of its cellular components

The American Head and Neck System for leveling of cervical lymph nodes was utilized.



Source: Shah, JP. Head & Neck Surgery& Oncology,2003

For the purpose of this guideline, lymphadenopathies were classified according to the duration of its presentation as a guide to its pathology and recommended management approach.

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Clinical Questions

I. Among patients with cervical lymphadenopathy, what is the role of history taking and physical examination?

Ia. Among patients with cervical lymphadenopathy, what are the clinical manifestations that will support a clinical diagnosis of acute infection?

Ib. Among patients with cervical lymphadenopathy what are the clinical manifestations that will support the clinical diagnosis of tuberculous lymphadenopathy?

Ic. Among patients with cervical lymphadenopathy, what are the clinical manifestations that will support the clinical diagnosis of malignancy?

II. Among patients with cervical lymphadenopathy, what is the role of fine needle aspiration cytology (FNAC)?

IIa. What is the role of FNAC among patients suspected to have acute lymphadenitis?

IIb. What is the role of FNBAC among patients suspected to have TB lymphadenitis?

IIc. What is the role of FNAC among patients suspected to have metastatic lymphadenopathy?

IId. What is the role of FNAC among patients suspected to have lymphoma?

III. Among patients with cervical lymphadenopathy, what is the role of neck ultrasound?

IIIa. What is the role of US among patients suspected to have acute lymphadenitis?

IIIb. What is the role of US among patients suspected to have TB lymphadenitis?

IIIc. What is the role of US among patients suspected to have metastatic lymphadenopathy?

IV. Among patients with cervical lymphadenopathy, what is the role of CT scan of the neck?

V. Among patients with cervical lymphadenopathy, what is the role of trial of antibiotic therapy?

Summary of Recommendations

I. Among patients with cervical lymphadenopathy, what is the role of history taking and physical examination?

A comprehensive history and thorough physical examination should be the initial step in evaluating patients presenting with cervical lymphadenopathy. Clinical evaluation is helpful in coming up with a presumptive diagnosis that can guide further management of the lymphadenopathy.

Level 5 Category A

The important clinical information to obtain include: patient's age, duration and progression of the lymphadenopathy, symptoms of inflammation and systemic manifestations like fever, malaise, and other associated symptoms like difficulty swallowing, voice change, epistaxis including exposure to an infectious source or known carcinogen.

Level 5 Category A

The important physical findings to take note of include: size, number, consistency, tenderness, location of the lymph nodes; other abnormal findings in the head and neck region like infections, masses and non-healing ulcers among others.

Level 5 Category A

A. Among patients with cervical lymphadenopathy, what are the clinical manifestations that will support a clinical diagnosis of acute infection?

Cervical lymphadenopathy of less than two weeks duration, tender, accompanied by fever and symptoms such as nasal discharge or sore throat; dental caries or other infections in the head and neck area point to a septic etiology.

Level 3 Category A

B. Among patients with cervical lymphadenopathy, what are the clinical manifestations that will support the clinical diagnosis of tuberculous lymphadenopathy?

Cervical lymphadenopathy that last for more than two weeks, do not resolve with intake of antibiotics, occurring in a patient from a country endemic for TB or with history of TB and/or exposure to TB, possibly

associated with fever, unintended weight loss, cough with nodes that are usually matted and non-tender, should be suspected as TB lymphadenopathy. In this setting, the presence of a draining sinus is highly suggestive of TB adenitis.

Level 4 Category A

C. Among patients with cervical lymphadenopathy what are the clinical manifestations that will support the clinical diagnosis of malignancy?

Adult patients with risk factors for head and neck cancer, presenting with hard non-tender cervical lymphadenopathy more than 2 cm, more than six weeks duration, should raise the suspicion of malignancy.

Level 5 Category A

Among pediatric patients, an increase in size of the lymph nodes over a period of two weeks or non-resolution within six weeks, becoming firm or matted should raise the suspicion of malignancy.

Level 5 Category A

II. Among patients with cervical lymphadenopathy, what is the role of fine needle aspiration cytology (FNAC)?

IIa. What is the role of FNA/FNAC among patients suspected to have acute lymphadenitis

Fine needle aspiration cytology is not indicated in acute lymphadenitis. However, needle aspiration for culture and sensitivity studies is indicated in patients who fail to improve within 48 to 72 hours of antibiotic therapy signifying the possibility of antimicrobial resistance.

Level 5 Category A

IIb. What is the role of FNAC among patients suspected to have TB lymphadenitis?

In the absence of evidence of pulmonary TB (PTB) FNAC may be used as a diagnostic procedure in support of TB adenitis.

Level 2 Category A

IIc. What is the role of FNAC among patients suspected to have metastatic lymphadenopathy?

FNAC is a useful procedure to confirm metastasis. However, a negative FNAC result warrants further diagnostic procedures.

Level 2 Category A

IId. What is the role of FNAC among patients suspected to have lymphoma?

For patients in whom there is a strong clinical consideration of lymphoma, fine needle aspiration cytology is not adequate, hence a tissue biopsy is recommended.

Level 3 Category A

III. Among patients with cervical lymphadenopathies, what is the role of neck ultrasound?

Among patients with equivocal clinical findings, high resolution grey scale ultrasound with power Doppler is useful in determining the characteristics of the lymph nodes to help in its diagnosis.

Level 2 Category A

IV. Among patients with cervical lymphadenopathies, what is the role of neck CT scan?

Neck CT scan is not recommended as a first line diagnostic test but is useful in staging patients with head and neck cancer.

Level 2 Category A

V. Among patients with cervical lymphadenopathies, what is the role of trial of antibiotic therapy?

Trial of antibiotic therapy should be given only to patients suspected of having bacterial cervical lymphadenitis.

Antimicrobials given to patients with bacterial cervical lymphadenitis should cover for gram-positive microorganisms.

Re-assessment is performed if there is no improvement or there is worsening of the symptoms.

Level 4 Category A

Summary of Evidence

I. Among patients with cervical lymphadenopathy, what is the role of history taking and physical examination?

A comprehensive history and thorough physical examination should be the initial step in evaluating patients presenting with cervical lymphadenopathy. Clinical evaluation is helpful in coming up with a presumptive diagnosis that can guide further management of the lymphadenopathy.

Level 5 Category A

The important clinical information to obtain include: patient's age, duration and progression of the lymphadenopathy, symptoms of inflammation, and systemic manifestations like fever, malaise, and other associated symptoms like difficulty swallowing, voice change, epistaxis including exposure to an infectious source or known carcinogen.

Level 5 Category A

The important physical finding to take note of include: size, number, consistency, tenderness, location of the lymph nodes; other abnormal findings in the head and neck region like infections, masses and non-healing ulcers among others.

Level 5 Category A

A. Among patients with cervical lymphadenopathy, what are the clinical manifestations that will support a clinical diagnosis of acute infection?

Recommendation

Cervical lymphadenopathy of less than two weeks duration, tender, accompanied by fever and symptoms such as nasal discharge or sore throat; dental caries or other infections in the head and neck area point to an infectious cause.

Level 3 Category A

B. Among patients with cervical lymphadenopathy , what are the clinical manifestations that will support the clinical diagnosis of tuberculous lymphadenopathy?

Recommendation

Cervical lymphadenopathy that last for more than two weeks, do not resolve with intake of antibiotics, occurring in a patient from a country endemic for TB or with history of TB and/or exposure to TB, possibly associated with fever, unintended weight loss, cough with nodes that are usually matted and non-tender, should be suspected as TB lymphadenopathy. In this setting, the presence of a draining sinus is highly suggestive of TB adenitis.

Level 4 Category A

C. Among patients with cervical lymphadenopathy what are the clinical manifestations that will support the clinical diagnosis of malignancy?

Adult patients with risk factors for head and neck cancer, presenting with hard non-tender cervical lymphadenopathy more than 2 cm, more than six weeks duration, should raise the suspicion of malignancy.

Level 5 Category A

Among pediatric patients, an increase in size of the lymph nodes over a period of two weeks or non-resolution within six weeks, becoming firm or matted should raise the suspicion of malignancy.

Level 5 Category A

Summary of Evidence

The etiology of cervical lymphadenopathy is varied. It may be an acute infection in the head and neck area, tuberculosis or metastasis either from a known or unknown primary in the head and neck region. It can be categorized as inflammatory/reactive or neoplastic. A thorough history and comprehensive physical examination should always be the first step to help the clinician obtain relevant data to determine the possible etiology and thereby assist in the decision-making regarding the use of diagnostic tests or treatment options to offer.[1-5]

Among the information which can be gathered, the age of the patient, duration of the symptoms, progression of the lymphadenopathy, as well as symptoms of either inflammation with or without systemic manifestations like fever, malaise, or other associated symptoms like difficulty swallowing, voice change, epistaxis can point to its possible cause.

History of environmental exposures can also strengthen one's clinical suspicion like living in an endemic area for TB or exposure to person with TB or exposure to risk factors for head and neck cancer such as smoking and alcohol and provide a good starting point to help the physician in the step by step work-up when required, including laboratory tests, imaging modalities, and tissue diagnosis to reach an appropriate diagnosis.

Physical examination findings which include the size, number, consistency, location of the lymph nodes; and other abnormal findings in the head and neck area like dental caries, inflamed tonsillopharyngeal area or the presence of a mass or non-healing ulcer are also useful in determining the etiology of the lymphadenopathy.

Age

Malignancy as a cause of lymphadenopathy is not common among children but increases with age.[6] Among the benign causes, only 39% can be attributed to a specific etiology while 61% are of unknown origin.[7] In a review by Mohsen, the prevalence of malignancy was 0.4% in patients under 40 years old and 4% in those over 40 years old in the primary care setting, with increasing prevalence to 17% in referral centers and further increases to 40-60% in highly suspicious patients.

Duration of Symptoms

A lymph node which is only less than two weeks in duration or already a year long but with a stable size has a low probability of being malignant.[6] Acute lymphadenopathy in the pediatric age group are usually benign (98.2%). Malignancy and tuberculosis usually present as chronic lymphadenopathy.[7]

Related Symptoms and Signs

A recent upper respiratory tract infection, fever, or pharyngitis points to an infectious cause of the lymphadenopathy. Significant fever, night sweats, and unexplained weight loss are the "B" symptoms of lymphomas but may also be associated with TB or collagen vascular diseases.[6,7] Patients with a known diagnosis of head and neck cancer or those with dysphagia, change in voice quality or hoarseness should increase the suspicion of metastatic lymphadenopathy.

Exposure

TB is a common cause of lymphadenopathy in adults and children living in tropical and endemic areas.[8-10] A history of exposure to tobacco, alcohol and ultraviolet radiation should make the clinician suspect the possibility of head and neck, and skin cancer.[6]

Location

Lymphadenopathy in the supraclavicular area has been noted to be associated with a higher risk for malignancy[6,11] especially in older age groups: 90% in patients more than 40 years old and 25% in those under 40 years old.[2] The same high association between a supraclavicular location of a node and malignancy has been noted in pediatric patients ($p = 0.008$).[7,12]

Size

Based on several studies, there is no uniform nodal size at which one should suspect malignancy but there are some useful guides. A lymph node larger than 1 cm is considered a lymphadenopathy although this varies by lymphatic region. Cervical nodes more than 1.5 cm in diameter are considered abnormal except if they are in the submental or submandibular area.[2,13] Palpable supraclavicular nodes of any size are considered abnormal. Maximum diameters of more than 1.5 cm to 2 cm, has been recommended by Bazemore as an appropriate starting point for high suspicion of malignant or granulomatous disease. However, a more important basis to consider malignancy is the increase in size or persistence over time rather than a specific degree of nodal enlargement.[6] In the series by Oguz, the size associated with malignancy was more than 3 cm (p=0.001).[7]

Tuberculous Lymphadenopathy

Tuberculous lymphadenopathy should be among the considerations in a cervical node which has been present for more than two weeks in duration and especially if it happens in an endemic region.[9,10,14] In the study by Jha, the 11 30 year old age group was commonly involved. Majority of the patients were from the lower socioeconomic group. For the physical finding, most of the patients had matted nodes. The nodal groups commonly involved were the upper deep jugular, jugulodigastric and jugulo-omohyoid groups.[10]

Cervical Lymphadenopathy Due to Malignancy

Even when there are no other clinical signs of malignancy, the possibility of malignancy can be as high as 38%. In a review of 95 patients who underwent open lymph node biopsy clinical factors such as age, sex, history of alcohol and tobacco use, location of the mass, number, size and duration of the mass were analyzed on their ability to predict the presence of neoplasia and malignancy using logistic regression analysis. There were 30 cases of new growth (31.6%) and 12 cases of cancer (12.6%).[15] Statistically significant predictors for neoplasia were patient age, duration and size of the mass with estimated odds ratios as follows: an increase in odds of 1.42 (95% CI 1.05-1.90) for each 10-year increase in age, 1.08 (95% CI, 0.99-1.17) for each 10-week increase in duration, and 1.50 (95% CI 1.11-2.02) for each centimeter increase in size.

The overall model for neoplasia had positive and negative predictive values of 63.6% and 78.1%, respectively, and an overall accuracy of 74.7%. However, for prediction of malignancy, age turned out to be the only statistically significant factor. Logistic regression analysis for malignancy of the neck mass found only patient age and a constant to be significant ($p < 0.05$ for significance of log-rank model improvement).

The estimated odds ratio increased by 1.66 (95% CI 1.15-2.41) times for each 10-year increase in age.

Table 1. Descriptive statistics for independent variables.

Clinical Variable	Finding	Univariate Significance* for Neoplasia	Univariate Significance* for Malignant Neoplasm
Categorical, No. (%)			
Sex†		.38	.82
Male	29 (30.5)		
Female	66 (69.5)		
Ever smoked†	29 (30.5)	.58	.66
Never smoked	66 (69.5)		
Smoking at time of biopsy	16 (16.8)		
Heavy alcohol use	4 (4.2)		
Location†		.14	.76
Regions II-IV and VI	52 (54.7)		
Region V	10 (10.5)		
Region I	33 (34.7)		
Bilateral masses	14 (14.7)		
Continuous, mean (range)			
Age, y†	42.2 (2.0-85.0)	.002	.01
Duration of mass, wk†	38.4 (0.5-572.0)	.06	.63
No. of masses†	1.45 (1.0-5.0)	.53	.52
Size, cm†	2.81 (0.5-10.0)	<.001	.04

**For categorical variables, significance corresponds to significance of Pearson χ^2 statistics; for continuous variables, to significance of Student t test.*

†Variable analyzed in the regression model.

Reference: Bhattacharyya N. , 1999

In another retrospective study by Aribas using ultrasound guided FNAC result as the reference standard, associated predictors for the presence of malignancy in

lymph nodes include the presence of primary malignancy ($p < 0.001$), mid neck and lower neck localizations as Level 3-6 ($p = 0.001$), and markedly hypoechoic lymph nodes ($p<0.001$). Age, gender, microcalcification, cystic feature, minimum size, and index value seem to be poor predictors in malignancy.[16] Another study among pediatric patients identified these factors predictive of malignancy: lymph node size greater than 2cm, multiple levels of adenopathy and supraclavicular location. In these cases, biopsy should be performed.[17]

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II. Among patients with cervical lymphadenopathy, what is the role of FNAC?

IIa. What is the role of FNA/FNAC among patients suspected to have acute lymphadenitis?

Fine needle aspiration cytology is not indicated in acute lymphadenitis. However, needle aspiration for culture and sensitivity studies is indicated in patients who fail to improve within 48 to 72 hours of antibiotic therapy signifying the possibility of antimicrobial resistance.

Level 5 Category A

IIb. What is the role of FNAC among patients suspected to have TB lymphadenitis?

In the absence of pulmonary TB (PTB) FNAC may be used as a diagnostic procedure in support of TB adenitis.

Level 2 Category A

IIc. What is the role of FNAC among patients suspected to have metastatic lymphadenopathy?

FNAC is a useful procedure to confirm metastasis. However, a negative FNAC result warrants further diagnostic procedures.

Level 2 Category A

IId. What is the role of FNAC among patients suspected to have lymphoma?

For patients in whom there is a strong clinical consideration of lymphoma, fine needle aspiration cytology is not adequate, hence a tissue biopsy is recommended.

Level 3 Category A

Summary of Evidence

An eEmpiric antimicrobial therapy is usually initiated for patients suspected to have acute lymphadenitis. Needle aspiration for culture and sensitivity studies is indicated for patients who have failedfail to improve within 48 to 72 hours, which may signify a resistant organism.[1] Needle aspiration may also be an effective and safe method of draining suppurative cervical lymphadenitis and avoid open drainage.[2]

Fine needle aspiration cytology (FNAC) may be used as an initial diagnostic procedure in detecting tuberculosis. Although it has a high specificity, its disadvantage is the variable sensitivity in different studies. Studies have shown statistically significant differences in the sensitivity when compared to core needle and excision biopsies ($p = 0.0003$ and $p < 0.0001$, respectively).[4] Performing different stains, such as the Romanowsky's method (Wright's stain) for cytological diagnosis and Ziehl Nielsen (hot method) for the identification of acid-fast bacilli increases the diagnostic accuracy. Submitting some material for culture can further increase the diagnostic accuracy.[5]

In cases where FNAC results are non-diagnostic, excision biopsy should be performed.[6,7]

Fine needle aspiration cytology (FNAC) is very specific, but sensitivity varies in among different studies to the extent such that it cannot yet be relied upon to exclude malignancy. The overall diagnostic sensitivity, specificity, positive predictive value and negative predictive value of FNAC of cervical lymph nodes were 90.9%, 67.2%, 82.6% and 81.3%, respectively. If any of the clinical, radiological or laboratory findings is suspicious, then further investigation is justified.[8] In case of malignancies, the histopathologic correlation is 100%.[9] Due to its high specificity, FNAC has proven to be a good first line method in identifying malignancy in lymph nodes. However, a negative result may not automatically exclude malignancy and may warrant further investigation, such as excision biopsy. For patients in whom there is a strong clinical consideration of lymphoma, fine needle aspiration cytology alone is not sufficient in classifying the different subtypes of lymphoma and significantly delays obtaining the definitive diagnosis as compared to doing an excision biopsy at the onset.[10]

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III. Among patients with cervical lymphadenopathy, what is the role of neck ultrasound?

Among patients with equivocal clinical findings, high resolution grey scale ultrasound with power Doppler is useful in determining the characteristics of the lymph nodes to help in its diagnosis.

Level 2 Category A

Summary of Evidence

Conventional ultrasound is presently being used as an adjunct in the evaluation of patient's presenting with cervical lymphadenopathy. This is especially useful when the clinical findings are expected to result in a definitive

diagnosis. Although the use of ultrasonography is now accepted as one of the techniques in the routine evaluation of cervical lymph nodes one drawback is that reporting is not usually standardized and the results are dependent on the user's experience.[1]

A cross-sectional study involving 50 patients who underwent CT examination and subsequent extended field-of-view (EFOV-US) showed that this technique of ultrasonography is comparable to CT scan in detecting the presence of cervical lymphadenopathy. The sensitivity increases the more caudal to the carotid bifurcation (Tables 1 & 2) and there is a strong linear correlation between rates of detection of CT and EFOV-US (Pearson's coefficient = 0.98, $p < 0.001$).[1]

Table 1. Detection rate of enlarged cervical lymph node by CT and parallel scanned EFOV-US sequences (Beissert, 2000).

	CT	EFOV-US
Caudal to carotid bifurcation	79	78
Cranial to carotid bifurcation	166	160
Total	245	238

* data is about number of lymph nodes

Table 2. False positive and false negative lymph nodes in parallel scanned EFOV-US sequences (Beissert, 2000).

	CT	EFOV-US
Caudal to carotid bifurcation	1	2
Cranial to carotid bifurcation	9	15
Total	10	17

* data is about number of lymph nodes

Compared to palpation, ultrasonography has a higher sensitivity (97% to 73%) as shown in one non-systematic review.[2,3] Shown below are the different features differentiating a benign from a malignant lymph node as presented in this non-systematic review.[2]

Several considerations were emphasized by the review. No consensus on the cut-off point for size has been established. The articles advocated the use of comparative increase in size during serial examination. This however, would become a problem if an immediate diagnosis is needed. Shape should not be used as a single criterion since normal submandibular and parotid nodes are round. Half of metastatic nodes may have an echogenic hilus.[2] The evaluation of the vascular pattern

Table 3. Sonographic features of benign and malignant neck nodes (Ying, 2013).

Sonographic features	Benign nodes	Malignant nodes
Size	Persistent or slight changes in serial examinations	Increase in serial examinations
Shape	Elliptical (S/L <0.5)	Round (S/L >0.5)
Nodal border	Unsharp	Sharp, Proven malignant nodes with unsharp borders indicate extracapsular spread
Echogenic hilus	Present	Absent
Echogenicity	Hypoechoic	Hyperechoic in metastatic nodes from papillary thyroid carcinoma. Other malignant nodes tend to be hypoechoic
Intranodal reticulation	Absent	Common in lymphomatous nodes
Intranodal calcification	Absent	Punctate and peripherally located calcification is common in metastatic nodes from papillary thyroid carcinoma
Intranodal cystic necrosis	Common in tuberculous nodes	Common in metastatic nodes from papillary thyroid carcinoma and squamous cell
Matting	Common in tuberculous nodes	May be found in patients with previous neck radiation therapy
Adjacent soft tissue edema	Common in tuberculous nodes	May be found in patients with previous neck radiation therapy. May be found in malignant nodes with extracapsular spread
Intranodal vascular pattern	Hilar vascularity or apparently avascular	Peripheral or mixed vascularity
Stiffness	Soft	Hard

can help differentiate metastatic from reactive nodes (sensitivity: 83-89%; specificity: 87-100%). It is also effective in differentiating lymphomatous and reactive nodes (sensitivity: 67%; specificity: 100%). This then could increase the diagnostic accuracy for those with equivocal ultrasound findings.[2]

A cross-sectional study, involving 158 neck masses in 100 patients, evaluated six ultrasound features and correlated each individually and in combination to the histopathological report. Features included the following: 1) echogenicity; 2) border; 3) size; 4) necrosis; 5) shape; and 6) vascular pattern. Hypoechoic echogenicity, a sharply demarcated border, size > 1 cm, round contour, presence of necrosis and abnormal vascular pattern were considered features of a malignant cervical lymph node.[3]

Assessed individually, each feature was found to give significant results in differentiating between a benign and malignant cervical nodes as seen in Table 4 below. Their combination increases the sensitivity, specificity, PPV and NPV significantly.

Another cross-sectional study (4) involving 192 patients undergoing ultrasound examination and subsequent confirmation by fine needle aspiration cytology further enumerated features that could help establish the diagnosis (TB, metastatic, lymphoma and reactive). This is shown in Table5.

Although average L/S ratio showed significant difference, the use of this feature may not be that accurate as seen from the range of findings that one could obtain. As can be seen from the table the absence of fusion tendency, peripheral halo and internal echoes can help in ruling out a reactive node. Aside from this the following features have also been shown to have low incidence in reactive nodes: irregular margins, hypoechoic center, and absent hilus.

To differentiate lymphoma from TB or metastatic nodes, the following features can be used: presence of a peripheral halo and internal echoes. As can be seen from the table, the incidence of these findings in lymphoma is less than 10%.

Table 4. Morphological characteristics compared to pathologic results/biopsy (Genes, 2014).

%	Echogenicity	Border	Shape	Size	Necrosis	Vascular pattern	Six features
Sensitivity	78.07	39.47	84.21	73.68	35.96	97.37	95.24
Specificity	77.27	54.47	52.47	68.86	100	47.73	100
PPV	69.9	82.05	82.05	85.71	100	82.84	100
NPV	57.63	56.1	56.1	50	37.61	87.5	95.24

PPV – Positive predictive value; NPV – Negative predictive value.

Table 5. Ultrasonographic findings correlated with tissue diagnosis in cervical lymph Nodes of 192 patients (Khanna, 2011).

Characteristics	Tubercular (n = 62)	Metastatic (n = 18)	Lymphoma (n = 14)	Reactive (n = 98)	p value
L/S Ratio	1.8 ± 0.6	1.2 ± 0.3	1.5 ± 0.4	2.2 ± 0.9	<0.01
Irregular margins	41 (66%)	10 (55%)	3 (21%)	7(7%)	>0.01
Hypoechoic center	48 (77%)	11 (61%)	3 (21%)	8(8%)	>0.01
Fusion tendency	50 (81%)	12 (66%)	2 (14%)	Nil	>0.01
Peripheral halo	52 (84%)	10 (55%)	1 (7%)	Nil	<0.01
Internal echoe	52 (84%)	2 (11%)	Nil	Nil	<0.001
Absent hilus	16 (26%)	15 (83%)	4 (28%)	9(9%)	<0.01

The 'p values' compare the significance of difference between metastatic and lymphomatous nodes considered together versus the tubercular lymph nodes.

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IV. Among patients with cervical lymphadenopathies, what is the role of neck CT scan?

Neck CT scan is not recommended as a first line diagnostic test but is useful in staging patients with head and neck cancer.

Level 2 Category A

Summary of Evidence

Most of the articles which came out in the search utilized CT scan in the management of diagnosed cases of head and neck cancer to evaluate the extent of the tumor and regional nodes which is quite different from our scenario of a clinical presentation of lymphadenopathy and diagnosis is not certain yet. One cross sectional study by Sarvanan involving patients with head and neck malignancy and palpable lymph nodes (N = 26 (neck sides) set the following criteria to label the node as metastatic: 1) size- 11mm or greater in transverse plane; 2) central hypodensity with peripheral rim enhancement; 3) conglomeration of nodes in the drainage of the primary; and 4) loss of fat plane between nodes and carotid artery was considered as carotid artery invasion.

The results of the study by Sarvanan showed that clinical examination had a comparable sensitivity of 92.3% compared to ultrasound (94.44%) and CT scan (94.11 %) in determining whether a lymph node is metastatic. The specificity of clinical exam is slightly better at 79.17% compared with CT (66.66%) but less specific than ultrasound (100%). Based on these results, clinical examination should still be the primary method of evaluating the possible presence of metastatic nodes.

Table 6. Sensitivity and specificity of CT scan criteria for metastatic lymph node. (Sarvanan, 2002)

Criteria	Sensitivity	Specificity
Size 11 mm or greater	88.3	66.67
Presence of lymph node mass/ conglomeration	100	100
Central necrosis	94.11	100
Carotid artery invasion	75	100

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V. Among patients with cervical lymphadenopathies, what is the role of trial of antibiotic treatment?

Trial of antibiotic therapy should be given only to patients suspected of having bacterial cervical lymphadenitis.

Antimicrobials given to patients with bacterial cervical lymphadenitis should cover for gram-positive microorganisms.

Re-assessment is performed if there is no improvement or there is worsening of the symptoms.

Level 4 Category A

Summary of Evidence

Fifteen papers were appraised and reviewed for this section. These included two systematic reviews, one

cohort study, three cross-sectional studies, two case series and seven non-systematic reviews. Several of the papers had patients less than 18 years of age as their subjects. These included both systematic reviews, one cross-sectional study, one case series and three non-systematic reviews.

Generally, the initial management of cervical lymphadenitis is based on an accurate clinical diagnosis. All the articles reviewed stated that the treatment of cervical lymphadenitis varies depending on the etiology and clinical presentation of the patients.

In one review involving subjects of all ages that were seen by a primary care physician, most patients presenting with a neck mass were caused by inflammatory disorders. These masses usually resolved by themselves or disappeared following a course of antibiotics.[1]

It is therefore important to determine the underlying cause. This was supported by two reviews, one involving patient of all ages and other involving children.[2,3] A viral etiology is considered in patients presenting with bilateral cervical lymphadenitis. This is usually associated with an upper respiratory infection.[4] This is especially true in children as shown in the review of Brook[5] and Gosche.[2,5] In such conditions specific therapy is not indicated as most of these cases are self-limited and resolve with no treatment.[2,3,5,6] Most of these cases can be safely monitored but require close observation.[1,7] Treatment is supportive, directed at relieving the symptoms associated with the viral illness.

If the presenting symptom is a unilateral cervical lymphadenitis, the primary cause is a gram-positive bacterium. Most authors agree that this is the only condition where initial empiric antimicrobial therapy is acceptable.[2-6,8-11] Giving empiric antibiotic therapy will prevent abscess formation.[2] The most common organisms involved in bacterial cervical lymphadenitis without any known primary source are Staphylococcus aureus and group A beta-hemolytic Streptococci. For this reason, empiric antibiotic therapy for these patients should provide adequate coverage for gram-positive microorganisms. In one systematic review, a single antimicrobial agent given orally should be sufficient in immunocompetent patients.[7] Treatment is administered for a minimum of 10 days to a maximum of 14 days.[5-7,11] In most observed cases, symptomatic improvement was noted 2 to 3 days after the initiation of treatment. It is then recommended that patients are followed up within 48 to 72 hours to assess clinical response. Immediate resolution of nodal enlargement is not expected until 4 to 6 weeks after treatment.[5,11]

When a primary source of infection has been identified, empiric antimicrobial therapy has to be adjusted.[2,3] Cultures from the primary site should be obtained and antimicrobial treatment adjusted according to the results of the culture and sensitivity test.[2,5,11] If the primary site is in the oral cavity, specifically, periodontal disease, coverage should include anaerobes. A referral to a dental specialist is warranted.[3-5,11] For patients presenting with moderate or severe symptoms, empiric antibiotic treatment is given parenterally and adjusted once culture and sensitivity results are in.[2,5,6,8]

Lack of clinical improvement or worsening of the patient's condition after initial evaluation should prompt re-assessment.[3,5,6] Several ancillary tests should be considered, including aspiration and culture of the node or a diagnostic biopsy.[3,5,6,11] Failure to improve may indicate infection with a resistant or a rare organism and possible noninfectious cause of cervical lymphadenitis.[11] For general practitioners or primary care physicians it is recommended that a referral to an appropriate specialist be made.[1]

In patients where tuberculous cervical lymphadenitis is suspected there is no role for empiric therapy. All the papers reviewed recommend confirmation of the diagnosis before starting definitive treatment.[12-14]

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Algorithm for the initial Diagnosis of Cervical Lymphadenopathy