Original Article

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A Comprehensive Cross-sectional Analysis on the Diagnostic Predictors of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration

Internal Medicine Section

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ABSTRACT

Introduction: Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA) is a relatively new and minimally invasive procedure for sampling mediastinal and hilar lymph nodes. Various factors can influence the diagnostic yield of EBUS-TBNA and comprehensive studies evaluating them together are scarce.

Aim: To evaluate the factors predicting the diagnostic yield of EBUS-TBNA in sampling mediastinal and hilar lymph nodes.

Materials and Methods: A cross-sectional study was conducted at Institute of Chest Diseases, Government Medical College, Kozhikode , Kerala, India, from June 2019 to May 2020. The patients with enlarged mediastinal and hilar lymph nodes on Computed Tomography (CT) thorax underwent Fibre Optic Bronchoscopy (FOB) followed by EBUS-TBNA under conscious sedation. Patient and procedure related factors and ultrasonological features of lymph nodes were noted. Their relationships with EBUS-TBNA histopathological results were assessed. Statistical methods like Fisher's exact test with significant p-value as <0.05 were used for analysis.

Results: The mean age was 60.78±13.664 years with 59 (81%) males. Out of 73 lymph node stations sampled, 49.3% were subcarinal, followed by right lower paratracheal (30.1%), left hilar (8.2%), left upper paratracheal (6.9%) and left lower paratracheal (5.5%). EBUS-TBNA Histopathology Report (HPR) came as positive in 68.5% (50/73) cases with squamous cell carcinoma found in 34%, adenocarcinoma in 32%, poorly differentiated carcinoma in 16%, tuberculosis in 14%, and non specific inflammation in 4% cases. Significant association was found with factors like moderate sedation, duration of procedure taking >30 minutes, lymph node size >1 cm and absence of hilar sign, more number of passes per node and use of suction while sampling lymph nodes and diagnostic yield by EBUS-TBNA (p-value <0.05). There was no significant association with lymph node stations, lymph node features like shape, margin, echogenicity, necrosis and Rapid On-Site Evaluation (ROSE) and diagnostic yield; so also is the case with patient related factors like age, sex, co-morbidities, FOB and CT findings.

Conclusion: The duration of the procedure, type of sedation, lymph node size and absence of hilar sign, number of passes per node and use of suction while sampling the node are the main factors predicting the diagnostic yield of EBUS-TBNA in sampling mediastinal and hilar lymph nodes.

Keywords: Bronchoscopy, Diagnostic yield, Histopathology, Lymph node, Sedation

INTRODUCTION

Intrathoracic lymph node enlargement can be due to multiple causes which may either be benign or malignant, or just non specific reactive hyperplasia. The benign causes include common infections like mycobacterial, fungal and viral including Human Immunodeficiency Virus (HIV), rare infections like actinomycosis, anthrax and tularaemia and non infectious inflammatory conditions like sarcoidosis, rheumatological and autoimmune diseases, hypersensitivity pneumonitis, amyloidosis, Whipple disease, Castleman's disease etc. The malignant causes may be either primary like lymphoma, myeloma, leukaemia etc., or secondary due to lymph node metastases from lung, gastrointestinal, breast, testicular or thyroid cancers. Many of these conditions are life threatening prompting early diagnosis for effective management. Traditionally, tissue diagnosis from these nodes was obtained by CT-guided fine needle aspiration/biopsy, mediastinoscopy, or thoracoscopy. These investigations have limitations in the form of invasiveness, specimen yield, safety, and cost.

EBUS-TBNA, first introduced in 2002, is a relatively new and minimally-invasive endobronchial technique that uses ultrasound probe incorporated into the tip of bronchoscope to visualise the airway wall and structures adjacent to it, and allows real-time guidance in the sampling of mediastinal and hilar lymph nodes, and tumours [1]. It is a relatively quick and safe day care procedure and can be performed under conscious sedation.

Using EBUS-TBNA, enough samples can be obtained for histological diagnosis and Immunohistochemistry (IHC). EBUS-TBNA can shorten the duration of diagnosis and staging in lung cancer and can diagnose most of the benign aetiologies of mediastinal lymphadenopathy. In comparison to surgical mediastinoscopy, EBUS-TBNA has an excellent safety profile and cost advantages. Diagnostic sensitivity is often equivalent to surgical mediastinoscopy [2]. EBUS-TBNA may obviate the need of invasive methods [3].

According to American College of Chest Physicians (ACCP) lung cancer guidelines, the overall median sensitivity and median negative predictive value of EBUS-TBNA in mediastinal staging of lung cancer is 89% and 91%, respectively. This guideline recommends ultrasound-guided, needle-based sampling techniques over surgical staging as the first step in the mediastinal staging of lung cancer [4].

Various questions are often raised about the optimal performance of the procedure and best conditions for a maximal diagnostic yield. Comprehensive studies considering all factors together to predict the diagnostic yield of EBUS-TBNA is lacking especially in Indian population. The present study aimed to evaluate both patient and procedure related factors to predict the diagnostic yield of EBUS-TBNA in sampling mediastinal and hilar lymph nodes.

MATERIALS AND METHODS

This was a cross-sectional study conducted at Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala, India for a period of one year from June 2019 to May 2020. The study protocol was approved by the Institutional Ethics Committee (GMCKKD/RP 2019/IEC/162).

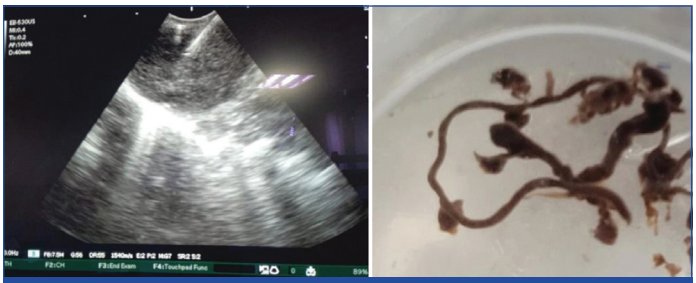
Inclusion criteria: All patients above 18 years of age with enlarged mediastinal and hilar lymph nodes on CT thorax who provided written informed consent within the study duration were included in the study.

Exclusion criteria: Those patients with hypoxia not corrected by supplemental oxygen, bleeding tendency or coagulation dysfunction, recent myocardial infarction or severe cardiac insufficiency, haemodynamic instability or who failed to provide informed consent were excluded from the study.

Patient related factors like age, sex, co-morbidities, vitals, respiratory system examination, pre procedure clinico-radiological diagnosis, CT and FOB findings were recorded.

Study Procedure

The procedures were performed under conscious sedation, using either dexmedetomidine or midazolam and fentanyl. EBUS-TBNA was done using a convex probe ultrasonic bronchoscope EB-530 US (Fujifilm, Tokyo, Japan). Scanning allowed for a penetration of 5 cm at a frequency of 7.5 MHz. TBNA was done by passing a dedicated 22- or 21-G needle (Cook Medical Echo Tip). The needle with central stylet was passed through the working channel of the bronchoscope, and then advanced through the airway wall, and into the lymph nodes under real-time ultrasound guidance. An integrated colour-power Doppler ultrasound (Fujifilm, Tokyo, Japan) was used to exclude vessels prior to needle puncture. After stylet removal, suction was applied using a syringe, while moving the needle back and forth approximately 10-20 times within the lesion. A minimum of three needle passes per lymph node were performed. After the sampling, suction was released slowly and the needle was retracted. Lymph node aspirates and core biopsy specimens were subjected to cytological, histopathological and microbiological examinations [Table/Fig-1,2].



[Table/Fig-1]: EBUS-TBNA from subcarinal lymph node.
[Table/Fig-2]: EBUS-TBNA core biopsy specimen. (Images from left to right)

Procedure related factors like depth of sedation, lymph node characteristics, stations, number of lymph node sampled, number of passes per node, needle type, specimen type, use of suction, duration of procedure, use of ROSE were assessed.

STATISTICAL ANALYSIS

Data were entered in Microsoft Excel and analysis was done by Statistical Package for the Social Sciences (SPSS) version 21.0. The categorical variables were expressed in proportion and continuous variables in mean and standard deviation. The appropriate statistical methods like Fisher's-exact test and Chi-square test were used for analysis. The level of significance was estimated with 95% confidence interval. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 73 subjects with enlarged mediastinal and hilar lymphadenopathy on CT Thorax and posted for EBUS were enrolled in the study. The mean age of the patients was 60.78±13.664 years. There were 59 (81%) males and 14 (19%) females in the study group. The baseline characteristics of study subjects are shown in [Table/Fig-3]. Dyspnoea (64.4%) followed by cough (54.8%) were the main symptoms. Other symptoms included haemoptysis (10.66%), hoarseness (8.2%), fever (6.9%) and wheezing (2.7%).

Age (years)	60.78±13.6	Sex: M/F	59/14
Symptoms	**n (%)**	**CT thorax findings**	**n (%)**
Dyspnoea	47 (64.4)	Mediastinal lymph node	30 (41.1)
Cough	40 (54.8)	Mass+Lymph node	42 (57.5)
Haemoptysis	8 (10.66)	Consolidation+Lymph node	1 (1.4)
Hoarseness	6 (8.2)		
Fever	5 (6.9)		
Wheezing	2 (2.7)		
Co-morbidities	**n (%)**	**Fibre optic bronchoscopy findings**	**n (%)**
Diabetes	18 (24.7)	Normal	51 (69.9)
Hypertension	33 (45.2)	Extraluminal compression	18 (24.7)
Old pulmonary tuberculosis	2 (2.7)	Carina blunt	4 (5.5)
Chronic kidney disease	2 (2.7)		

[Table/Fig-3]: Baseline characteristics.

A total of 73 lymph node stations were sampled out of which 36 (49.3%) were subcarinal (station 7), 22 (30.1%) were right lower paratracheal (station 4R), 6 (8.2%) were left hilar (station 10L), 5 (6.9%) were left upper paratracheal (station 2L), and 4 (5.5%) were left lower paratracheal (station 4L). The overall diagnostic yield according to EBUS-TBNA HPR was 68.5% (50/73). Out of this squamous cell carcinoma was found in 17 (34%) cases, adenocarcinoma in 16 (32%) cases, poorly differentiated carcinoma in 8 (16%) cases, tuberculosis in 7 (14%) cases and non-specific inflammation in 2 (4%) cases. In 23 patients, histopathology results came as negative.

The procedure was done under moderate sedation using parenteral dexmedetomidine and fentanyl in 56 patients. Out of these patients, EBUS-TBNA histopathological report was positive in 43 patients (76.8%) compared to a diagnostic yield of 41.2% (7 out of 17) in those who underwent the procedure under mild sedation using parenteral midazolam and fentanyl. The difference in diagnostic yield was statistically significant with a p-value of <0.05. Significant association was not found between patient related factors like age, sex, co-morbidities, CT Thorax findings, FOB findings etc and diagnostic yield [Table/Fig-4].

Patient related factors		EBUS-TBNA HPR		Total	p-value
		Positive	Negative		
Age (years)	≤60	23 (79.3%)	6 (20.7%)	29 (100%)	0.150
	>60	27 (61.4%)	17 (38.6%)	44 (100%)	
Sex	Male	38 (64.4%)	21 (35.6%)	59 (100%)	0.103
	Female	12 (85.7%)	2 (14.3%)	14 (100%)	
Co-morbidities	Diabetes mellitus	12 (66.7%)	6 (33.3%)	18 (100%)	0.315
	Hypertension	20 (60.6%)	13 (39.4%)	33 (100%)	
	Chronic kidney disease	4 (100%)	0 (00)	4 (100%)	
	No co-morbidities	14 (77.8%)	4 (22.2%)	18 (100%)	

CT Thorax findings	Mediastinal LN	22 (73.3%)	8 (26.7%)	30 (100%)	0.489
	Mass+LN	27 (64.2%)	15 (35.7%)	42 (100%)	
	Consolidation +LN	1 (100%)	0 (00)	1 (100%)	
Fibre optic bronchoscopy findings	Normal	33 (64.7%)	18 (35.3%)	51 (100%)	0.225
	Extraluminal compression	15 (83.3%)	3 (16.7%)	18 (100%)	
	Carina blunt	2 (50 %)	2 (50%)	4 (100%)	
Sedation	Mild	7 (41.2%)	10 (58.8%)	17 (100%)	0.006
	Moderate	43 (76.8%)	13 (23.2%)	56 (100%)	

[Table/Fig-4]: EBUS-TBNA Histopathology Report (HPR) versus patient related factors.

In this study, the diagnostic yield was 80% (48/60) when the lymph node size was >1 cm. EBUS-TBNA HPR came positive only in 15.4% (2/13) cases when the lymph node size was <1 cm.The difference was significant with a p-value of <0.05. Significant association was also found with absence of Central Hilar Structure (CHS) and a diagnosis of malignancy (74.2%). There was no significant association with lymph node station and lymph node features like shape, margin, echogenicity, necrosis etc., and diagnostic rate [Table/Fig-5].

Ultrasonological features		EBUS-TBNA HPR Positive	EBUS-TBNA HPR Negative	Total	p-value (Fisher's-exact test)
Lymph node station	2L	2 (40%)	3 (60%)	5 (100%)	0.57
	4R	16 (72.7%)	6 (27.3%)	22 (100%)	
	4L	2 (50%)	2 (50%)	4 (100%)	
	7	26 (72.2%)	10 (27.8%)	36 (100%)	
	10L	4 (66.7%)	2 (33.3%)	6 (100%)	
Lymph node size	<1 cm	2 (15.4%)	11 (84.6%)	13 (100%)	0.0001
	>1 cm	48 (80%)	12 (20%)	60 (100%)	
Lymph node shape	Oval	37 (67.3%)	18 (32.7%)	55 (100%)	0.695
	Round	13 (72.2%)	5 (27.8%)	18 (100%)	
Lymph node margin	Distinct	12 (63.2%)	7 (36.8%)	19 (100%)	0.561
	Indistinct	38 (70.4%)	16 (29.6%)	54 (100%)	
Lymph node ECHO	Homogenous	8 (57.1%)	6 (42.9%)	14 (100%)	0.319
	Heterogeneous	42 (71.2%)	17 (28.8%)	59 (100%)	
Necrosis	Present	11 (61.1%)	7 (38.9%)	18 (100%)	0.437
	Absent	39 (71%)	16 (29%)	55 (100%)	
Hilar sign	Present	4 (36.3%)	7 (63.6%)	11 (100%)	0.017
	Absent	46 (74.2%)	16 (25.8%)	62 (100%)	

[Table/Fig-5]: EBUS-TBNA Histopathology Report (HPR) versus ultrasonological features.

EBUS-TBNA HPR was positive in 18.2%, 28.6%, 81.6%, 100% following 3 passes, 4 passes, 5 passes, 6 passes per node, respectively with a significant value (p-value <0.05). Suction was used in 60 cases in which 48 (80%) cases yielded positive HPR (p-value <0.05). In this study, there was no association between ROSE and diagnostic yield (p=0.763). The procedure took more than 30 minutes in 55 cases. Out of these, HPR came positive in 44 (80%) cases compared to procedures which took <30 minutes (33.3%) with a significant difference (p-value <0.05) [Table/Fig-6].

DISCUSSION

The overall diagnostic yield according to EBUS-TBNA HPR was 68.5% (50/73). Out of the 23 negative cases, 13 reports came as reactive mature lymphocytes, five reports came as sparsely cellular aspirate, three reports came as inconclusive and the remaining two reports came as clusters of spindle cells and fibroblasts. Most of the

		EBUS-TBNA HPR Positive	EBUS-TBNA HPR Negative	Total	p-value (Fisher's-exact test)
Needle	22 Gauge	45 (73.8%)	16 (26.2%)	61 (100%)	0.035
	21 Gauge	5 (41.7%)	7 (58.3%)	12 (100%)	
Number of passes per node	3 passes	2 (18.2%)	9 (81.8%)	11 (100%)	0.0001
	4 passes	2 (28.6%)	5 (71.4%)	7 (100%)	
	5 passes	40 (81.6%)	9 (18.4%)	49 (100%)	
	6 passes	6 (100%)	0 (00)	6 (100%)	
Suction	Present	48 (80%)	12 (20%)	60 (100%)	0.0001
	Absent	2 (15.4%)	11 (84.6%)	13 (100%)	
Rapid Onsite Evaluation (ROSE)	Present	17 (70.8%)	7 (29.2%)	24 (100%)	0.763
	Absent	33 (67.3%)	16 (32.7%)	49 (100%)	
Duration	<30 minutes	6 (33.3%)	12 (66.7%)	18 (100%)	0.0001
	>30 minutes	44 (80%)	11 (20%)	55 (100%)	

[Table/Fig-6]: EBUS-TBNA Histopathology Report (HPR) versus procedural factors.

negative results came from small oval nodes <1 cm in size which usually favours benign aetiology sonologically. Thus, in this study, there were 68 (93.15%) adequate samples, with adequacy being defined as finding granuloma, atypical cells, reactive lymphoid tissue etc. The diagnostic yield and sample adequacy are consistent with real world data from the AQUIRE registry [5].

EBUS-TBNA histopathological report was positive in 76.8% patients (43 out of 56) who underwent the procedure under moderate sedation compared to a diagnostic yield of 41.2% (7 out of 17) in those who underwent the procedure under mild sedation. The difference was statistically significant with a p-value of <0.05. This may be due to patient comfort, stabilisation of airways and ease of doing the procedure under moderate sedation. But no difference was found overall between sedation groups according to studies done by Dal T et al., and Casal RF et al., [6,7]. According to Yarmus L et al., statistically significant association was found in employing deep sedation during EBUS with regard to diagnostic yield [Table/Fig-7] [6-8]. So, it is prudent to consider moderate sedation employing parenteral dexmedetomidine and fentanyl during the procedure ideal for enhancing diagnostic yield.

Study	Type and number of patients	Sedation	Outcome
Dal T et al., (2014) [6]	Prospective (n=60)	Deep v/s moderate	Comparable
Casal RF et al., (2015) [7]	Prospective RCT (n=149)	General anesthesia v/s moderate	Comparable
Yarmus L et al., (2013) [8]	Retrospective (n=209)	Deep v/s moderate	Deep superior
This study, 2023	Prospective (n=73)	Mild v/s moderate	Moderate superior

[Table/Fig-7]: Comparison of present study result with previous study on sedation [6-8].

In this study, the diagnostic yield was 80% (48/60) with lymph node size >1 cm as opposed to 15.4% (2/13) when the lymph node size was <1 cm with a significant p-value of <0.05. According to Memoli JS et al., a statistically significant increase in presence of malignancy in a lymph node occurred as the size increased [9]. They also confirmed that round shaped lymph nodes were more likely malignant than triangular or draping lymph nodes. But such an association between lymph node shape and diagnosis rate could not be demonstrated in this study. Fujiwara T et al., found that a round shape, distinct margins, heterogeneous echogenicity, and a central necrosis sign were independently predictive of malignancy. When all four factors were absent, 96% of the lymph nodes were benign [10].

There was significant association with absence of CHS and diagnosis of malignancy in this study (p-value=0.017), but not with

lymph node echogenicity and necrosis. According to Jhun BW et al., absence of CHS was predictive of lymph node metastasis [11]. Schmid-Bindert G et al., also reported ultrasound criteria for predicting nodal metastasis. According to this study nodal size >10 mm, round shape, heterogeneous echogenicity and absence of CHS could be predictive factors for metastasis [12].

According to Nakajima T et al., there was no statistically significant difference in diagnostic yield with the size of the needle used [13]. The authors also found that the 21-gauge needle provided better histological structure with an increased number of tumour cells in the specimen, but it was associated with more blood contamination. Yarmus LB et al., could not find significant difference in sample adequacy or diagnostic yield. The use of the 21-gauge needle, when combined with the presence of ROSE, was associated with fewer needle passes per lymph node (3.5 versus 4.2; p-value <0.01), suggesting improved quality of specimen [14]. 22 gauge needles performed better than 21 gauge needle in this study (73.8% versus 41.7%, p-value 0.035). 21 gauge needles were used in 12 patients only, mainly in those with small lymph nodes (<1 cm) to enhance tissue content in the samples. This along with a large difference in the sample size between the two groups may be the reasons for such an outcome.

According to a prospective study done by Wolters C et al., use of the 19-gauge needle resulted in significantly more tissue and tumour cells per slide with a safety profile similar to 22-G needles, but the diagnostic yield was similar in both groups [15]. A randomised trial was done by Oki M et al., in 60 patients with hilar/mediastinal adenopathy or tumour adjacent to a central airway [16]. There was no difference between needle gauges in outcome measure. This study also showed trend of inadequate samples with 21 gauge needles. [Table/Fig-8] shows the comparison of present study with previous studies done [4,13-16].

Study	Type and number of patients	Needle size	Outcome
Wahidi MM et al., (2016) [4]	Systematic review	21 v/s 22 G	Comparable
Nakajima T et al., (2011) [13]	Prospective (n=45)	21 v/s 22 G	Comparable
Yarmus LB et al., (2013) [14]	Retrospective (n=1235)	21 v/s 22 G	Comparable
Wolters C et al., (2019) [15]	Prospective (n=107)	19 v/s 22 G	Comparable
Oki M et al., (2011) [16]	Prospective RCT (n=60)	21 v/s 22 G	Comparable
This study, 2023	Prospective (n=73)	21 v/s 22 G	22 G superior

[Table/Fig-8]: Comparison of present study result with previous study on needle size [4,13-16].

A randomised prospective trial conducted by Casal RF et al., comparing EBUS-TBNA with suction referred to as transbronchial needle capillary sampling (EBUS-TBNCS) versus EBUS-TBNA without the use of suction, found no significant differences between the two groups in specimen adequacy, diagnosis rate, or specimen quality regardless of node size. Concordance rates between the techniques were high for adequacy, diagnostic yield, and specimen quality ranging from 83.3-95.8% [17]. In the prospective study by Mohan A et al., the addition of suction has not been shown to improve the diagnostic yield or sample adequacy when compared with either lower suction of 10 cm or higher suction of 20 cm or no suction at all [18]. Using suction increased the tissue-core acquisition rate compared with the no suction group even though the difference in diagnostic yield was not statistically significant in a randomised controlled trial by Lin X et al., [Table/Fig-9] [19]. This study showed significant association with suction use and diagnostic yield (p-value <0.05).

Study	Type and number of patients	Suction	Outcome
Casal RF et al., (2012) [17]	Prospective RCT (n=115)	Yes/No	Comparable
Mohan A et al., (2021) [18]	Prospective RCT (n=323)	Yes/No	Comparable
Lin X et al., (2018) [19]	Prospective RCT (n=97)	Yes/No	Suction increased core tissue
This study, (2023)	Prospective (n=73)	Yes/No	Suction superior

[Table/Fig-9]: Comparison of present study result with previous study on suction [17-19].

Sample adequacy was 90.1% after the first pass, 98.1% after two passes, and 100% after three passes. The sensitivity for differentiating malignant from benign lymph node stations was 69.8%, 83.7%, 95.3%, and 95.3% for one, two, three, and four passes, respectively according to Lee HS et al., study [20]. This study demonstrated significant association between the number of needle passes and diagnosis yield (p-value <0.05). Such a relationship was also found between procedure duration and diagnosis rate (p-value <0.05) which was indirectly influenced by excess time spent for more needle passes per node.

Murakami Y et al., study showed that ROSE did not have any impact on the diagnostic yield (99% with ROSE versus 90% without ROSE; p-value <0.1), rather it reduced the number of aspirates per procedure (mean 2.3 with ROSE versus 4.0 without ROSE; p<0.01) [21]. The systematic review by Sehgal IS et al., also maintained that the use of ROSE neither improved the diagnostic yield nor reduced the procedure time during TBNA [22]. ROSE did not influence diagnostic rate in this study.

Limitation(s)

The main drawback of this study was that the procedure was done by different operators and their operator skill varies which indirectly affected the diagnostic yield. Only 15 out of 23 patients with negative HPR could be followed-up for six months who improved clinico-radiologically thus avoiding further procedures in them. The results were also not compared with gold standard surgical biopsy.

CONCLUSION(S)

EBUS-TBNA is a highly efficacious, first line diagnostic procedure in characterising mediastinal and hilar lymphadenopathy with results as good as gold standard surgical biopsy and significantly improved safety profile. Administration of moderate sedation, systematic analysis of nodal stations consuming sufficient time, lymph node size >1 cm and absence of hilar sign, five or more number of passes per node and use of suction while sampling lymph nodes, all can significantly increase the diagnostic yield of the procedure.

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