Assessment of Ultrasound -Guided Core Needle Biopsy as the First-Line Diagnostic Procedure for Cervical Lymphoma

Original Article

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ABSTRACT

Objective: This study was conducted to assess the effectiveness of Ultrasound-guided Core Needle Biopsy (US-CNB) to provide sufficient information for diagnosis and initiation of the treatment for head and neck lymphoma.

Study Design: We carried out the prospective consecutive case series in a single- center study.

Setting: The tertiary medical center setting.

Patients and Methods: Totally, 72 patients were enrolled and the US-CNB of suspicious cervical lymph node was performed. Demographics, imaging and pathological data were collected for each patient and used to identify the factors that shape the diagnostic yield of US-CNB.

Results: We observed among 72 CNBs 52 were fully diagnosed and 20 cases needed Excisional Surgical Biopsy for sub-classification. Then the factors influencing the results of the US-CNB, as the first-line diagnostic procedure for suspected cervical lymphadenopathy were discussed. The CNB results did not differ in terms of BMI, neck circumference and pathological subtype. Fully diagnosis CNB results demonstrated an association with higher mean tumor size and LAP in cervical zones 1 to 4 rather than posterior triangle.

Conclusion: About 30% of the patients in the present study required ESB after US-CNB for fully diagnosis and this delayed their treatment. Therefore, the use of US-CNB as a primary method in assessment of cervical lymphadenopathy still needs more studies to investigate the factors influencing the results and shaping its diagnostic yield.

Key Words: Cervical lymphadenopathy, core needle biopsy, Excisional surgical biopsy, Fine needle aspiration, Neck lymphoma.

INTRODUCTION

Enlargement of head and neck lymph nodes is a common presentation of many pathological processes. The cervical lymphadenopathy is the first presentation in 70–75% of head and neck lymphoid neoplasm cases. In this regard, specific diagnosis and differentiation between benign and malignant diseases is essential.[1,2]

The 2016 World Health Organization (WHO) classification of lymphoid neoplasm represents established guidelines for diagnosis of malignant lymphomas based on clinical, pathological, and genetic or molecular data characteristics.[3,4] Both pathologists and oncologists consider Excisional Surgical Biopsy (ESB) as the gold standard for diagnosis of lymphoma based on sufficient histologic pathological material obtained from surgically excised specimens.

In the recent years, reliance on Fine Needle Aspiration Cytology (FNAC) and Core Needle Biopsy (CNB) in evaluation of cervical lymphadenopathy when lymphoma is highly suspected has increased due to their excellent diagnostic outcomes. Many institutions have performed FNA and CNB as primary diagnostic procedures for the patients with suspected lymphoma.[5-10] CNB is a simple, cost-effective, and outpatient procedure with minimal complications compared to ESB. In addition, CNB unlike FNA provides sufficient lymph node tissue for Immunohistochemistry (IHC) and subgroup diagnosis of lymphoma that allows the clinicians to initiate the treatment. However, the oncologists frequently question whether any image-guided biopsy techniques (FNA and CNB) rather than the ESB are adequate to allow instigation of the treatment.[11,12]

To assess the effectiveness of Ultrasound-guided Core Needle Biopsy (US-CNB) to provide sufficient information for initiation of the treatment of lymphoid neoplasm, we performed the prospective consecutive case series in a

single- center study to address: (1) how frequently US-CNB results provide a specific WHO classification of lymphoma, (2) clinical, radiological, and pathological factors influencing diagnostic accuracy of the US-CNB for head and neck lymphoma.

PATIENTS AND METHODS:

This study was carried out with a prospective consecutive case series design in a tertiary medical center setting catering to both referred patients and the patients from the community. In our center, when the clinicians had diagnostic suspicion to lymphoma, according to history, physical examination, feature of mass imaging and FNA results, the patients referred for excisional biopsy (ESB). In this study, the CNB was performed for the patients before ESB, as an initial investigation. The study protocol was approved by the local Ethics Review Committee of our institution (Approval ID: IR.TUMS.MEDICINE. REC.1397.731) and written informed consent was obtained from all the patients.

Patients with the signs and symptoms of acute febrile illness and upper respiratory infection, apparent benign mass, salivary gland and thyroid tumor (history or clinical diagnostic suspicion), other primary focused head and neck malignancies, known lymphoma, transplant recipients, or those with a history of chemoradiotherapy or HIV were excluded from the study. There were no exclusions based on age, gender, or cervical lymphadenopathy (LAP) size. Totally, 72 patients were enrolled in the study from April 2016 to April 2018.

The US-CNB of cervical lymph node was taken after complete head and neck examinations and color Doppler sonography by an experienced head and neck surgeon. Each specimen was visually inspected, and multiple biopsies were collected until the surgeon was satisfied with the size of retrieved specimen. A coagulation screen was not routinely performed, and if the patient was taking Aspirin (ASA), then it continued before and after the US-CNB without any changes. The US-CNB was performed by a free hand technique using the Super Core™ Semi-Automatic Biopsy Instrument (16G x 10 cm) under local anesthesia with 1% lidocaine in outpatient settings. The patients were monitored for 30 min after the US-CNB, and gentle compression was applied on biopsy site.

All the CNBs were fixed in AFA (75% alcohol, 0.8% formalin, and 5% acetic acid). The CNBs were evaluated by an experienced board-certified pathologist in our institution. When the biopsies were diagnosed as malignant lymphomas, a panel of antibodies and Immunohistochemistry (IHC) was performed to determine histological subtype. A subtype-specific classification of lymphoma was made according to the 2016 revision of the WHO classification of lymphoid neoplasm.[3,4]

The following terminology was used based on the suggestions by Burke *et al* and Skelton *et al* for grading diagnostic quality of the FNA and CNB specimens, which was as follows: Grade 0 (Inadequate): insufficient material for diagnosis, Grade 1 (Equivocal): pathologist was unable to differentiate reactive lymph nodes from lymphoma, Grade 2 (Partially diagnostic): consistent with lymphoma but no sub – classification was determined for the tumor, and Grade 3 (Fully diagnostic): sufficient information obtained for sub classification of lymphoma to allow instigation of the treatment. In this study, Grades 0 and 1 were considered as non-diagnostic. Partially and non-diagnostic patients underwent the ESB for further tissue harvesting ,and fully diagnosed patients referred to a chemotherapist for initiation of the treatment.

Demographic data including age, gender, BMI, neck circumference, and tumor size (the largest LAP diameter obtained by ultrasound examinations), and location, and pathologic data including the results of FNA, CNB, and ESB (if done) were collected for each patient. Sensitivity, specificity, Positive and Negative Predictive Value (PPV, NPV) were calculated for CNBs in diagnosis of lymphoma. In addition, adequacy of CNBs was evaluated for a complete diagnosis and sub -classification of lymphoma and effective factors. The statistical package IBM SPSS software for Windows (version 24.0 Armonk, NY: IBM Corp) was used for data analysis. T -test and Chi -Square test were used to compare the results obtained from assessment of CNBs between the groups in terms of continuous and categorical variables, respectively. P -values of <0.05 were considered as statistically significant.

RESULTS:

Totally, 72 CNBs of cervical LAP were obtained from 72 patients (Table 1). Mean age of the patients including 45 males and 27 females was equal to 48.92 years old with an age range of 11 - 86 years old. Tumor size ranged from 1.5 to 7 cm with a mean of 4.37 cm. FNA results were non-diagnostic in 45 (62.5%) cases and partially - diagnostic in 27 (37.5%) cases.

Among 72 CNBs, six non-diagnostic cases were reported. The ESB results for these six CNBs were two Hodgkin Lymphomas (HL), two Follicular Non-Hodgkin Lymphomas (FNHL), one Diffuse Large B -cell Lymphoma (DLBL), and one Tuberculosis (TB).

There were 59 true positive and seven true negative diagnoses. There were also one false positive and five false negative findings. Therefore, calculated sensitivity for CNB in diagnosis of lymphoma was equal to 92% in clinically suspected patients and the specificity was calculated as 87.5% (Table 2). NPV, PPV, and accuracy for CNB in diagnosis of lymphoma were calculated as 59, 98, and 92%, respectively.

Among 72 patients, eight cases were reactive lymphoma or Tuberculosis, and 64 patients were finally diagnosed with lymphoma (CNBs or ESBs). Forty-five CNB cases were fully diagnosed as 22 HLs, 21 DLBLs, and 2 Burkitt lymphomas. Fourteen and five cases were partially and non-diagnostic, respectively. Their ESB results were compatible with 11 HLs, 4 DLBLs, and 4 FNHLs (Chart 1).

Following analysis of the results, CNB cases were divided into two subgroups as positive for initiation of the treatment (fully diagnosis) and negative for initiation of the treatment (partially and non-diagnostic) that referred to the surgery. Two subgroups were compared according to BMI, neck circumference, pathological lymphoma subtype, tumor size, and Lymph Node (LN) location (Table 3). The CNB cases did not differ in terms of BMI (*p-value=0.46*) and neck circumference (*p-value=0.37*). Regarding pathological lymphoma subtype, the two subgroups did not demonstrate any statistically difference (*p-value=0.35*). The positive subgroup demonstrated a higher mean tumor size than the negative subgroup (4.65 vs. 3.54 cm, *p-value=0.004*). More negative CNB results in the subgroups belonged to LAP in cervical zone 5 (posterior triangle) rather than zones 1 to 4, (*p-value<0.001*).

Table 1: Demographic parameters of the study population

Gender	Male % (n)	62.5 % (45
	Female % (n)	37.5 % (27)
Age (year)		48.92 (11-86)
BMI (Kg/m^2)		24.05 (19.38-33.29
Neck circumference (cm)		34.4 (31.7-38.6)
Mass size (cm)		4.37 (1.50-7.00)
		29.2% (21)
FNA % (n)		33.3% (24)
		37.5% (27)
		0 % (0)

Data were presented as mean (range) or percent (number).

Table 2: seventy-two lesions identified as positive or negative for lymphoma by core needle biopsy (CNB) pathology with subsequent comparison with surgical excision pathology or improvement after treatment as a diagnostic gold standard standard.

		diagnostic gold standard		
		positive	negative	total
CNB	Positive	59	1	60
	Negative	5	7	12
	Total	64	8	72

Sensitivity = true malignant needle biopsy results/total malignant surgical results = 92%
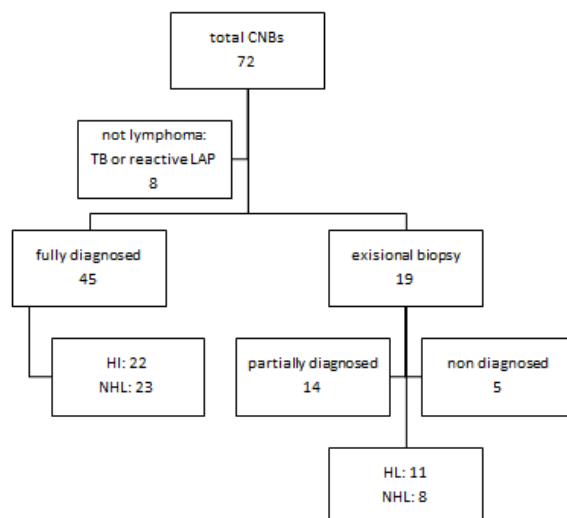Specificity = true benign needle biopsy results/total benign surgical results = 87.5%

Chart 1: Core needle biopsy chart's result.
CNB: Core needle biopsy, TB: tuberculosis, LAP: lymphadenopathy, HL: Hodgkin lymphoma, NHL: non Hodgkin lymphoma.

Table 3: Core needle biopsy result according to BMI, Neck circumference, pathological lymphoma subtype, tumor size, and lymph node (LN) location

		Core needle biopsy result		
		Fully diagnosed	Partially or non diagnosed	P-value
BMI		24.29	23.71	0.46
Neck circumference (cm)		34.2	34.7	0.37
lymphoma subtype	Hodgkin lymphoma	22	11	0.35
	Non Hodgkin lymphoma	23	8	
Tumor size (cm)		4.65	3.54	0.004
LN location	Zone 1	16	2	
	Zone 2 to 4	29	11	*<0.001*
	Zone 5	0	6	

DISCUSSION

Selection of image -guided techniques (FNA and CNB) or ESB for cervical lymphadenopathy tissue sampling is influenced by numerous considerations, such as reliability, accuracy, morbidity, and cost-effectiveness.[14]

Some studies have suggested the use of US-CNB as the first-line diagnostic procedure for identified and differentiated malignant lymphoma from other lymphadenopathy etiologies with an overall accuracy more than 85%. This suggestion has been supported in a Randomized Clinical Trial (RCT) conducted by N. Pugliese *et al* (2017) who compared power Doppler US-CNB with ESB in terms of the ability to diagnose lymphoma. They showed that sensitivity of US-CNB for detection of lymphoma was equal to 98.8% (95% CI = 95.9–99.9%). They also estimated that cost per biopsy for the US-CNB was 24-fold lower compared to standard ESB.[15] Adding these observations to the fact that, US-CNB reduces the patients' psychological and physical pain as well as risk of surgery and hospitalization, the use of US-CNB is recommended under optimal study conditions for both superficial and deep lymphadenopathy as the first-line diagnostic procedure for patients with a suspected lymphoma.

Despite the results of the recent studies, US-CNB seems a safe and efficient procedure for diagnosing the cause of cervical lymphadenopathy; and clinical guidelines (European Society of Medical Oncologists (ESMO) and the National Comprehensive Cancer Network (NCCN)) recommend the use of ESB for an initial diagnosis and classification of hematolymphoid neoplasm due to the fact that FNAB or CNB may lack histological architecture that is necessary for fully diagnosis and to allow instigation of the treatment.[16-20]

Several studies such as a systematic review by Frederickson *et al* (2015)[6] and a recent retrospective single-center cohort study in Korea[21] show that the median rate at which CNBs yielded a subtype-fully diagnosis of lymphoma was about 70%. Therefore, 30% of CNBs must be followed by administration of ESB to sub classify lymphoma and provide optimal diagnostic information for the oncologist's therapeutic options that can delay initiation of the treatment. In HL and FNHL, this rate may be worse and there may be higher need for performing the ESB to harvest sufficient material for fully diagnosis.

The results of our study are almost similar to previous studies. In our study, sensitivity, specificity, and accuracy for CNB in detecting lymphoma were calculated as 92, 87.5, and 92%, respectively. Moreover, 70% (45/64) of CNB cases were fully diagnosed.

In the following, the factors influencing the results of the US-CNB, as the first-line diagnostic procedure for suspected cervical lymphadenopathy were identified. The CNB results were statistically different in terms of tumor size and LN location. The fully diagnosed cases demonstrated a higher mean tumor size (4.65 vs. 3.54 cm) and more information was obtained from LAP in cervical zones 1 to 4 rather than zone 5 (posterior triangle) while, there were a small number of specimens at the cervical zone 5 (6 vs. 58 specimens).

In our study, the CNB results did not differ in terms of BMI and neck circumference. Confirmed and deferred results were also compared in terms of their pathological subgroups. However, DLBL was fully diagnosed more by performing CNB than other pathological subtypes (77% vs. 65%) but it was not statistically significant.

CONCLUSION

US-CNB is an inexpensive, safe, and accurate procedure for diagnosis of neck lymphoma. However, about 30% of the patients in the present study

required ESB after US-CNB for fully diagnosis and this delayed their treatment. Therefore, the use of US-CNB as a primary method in assessment of cervical lymphadenopathy still needs more studies to investigate the factors influencing the results and shaping its diagnostic yield. These factors can increase efficiency of the results and identify suspected patients who benefit more from administration of US-CNB as the first-line diagnostic procedure.

LIST OF ABBREVIATION

Ultrasound-guided Core Needle Biopsy (US-CNB), Lymphadenopathy (LAP), Core Needle Biopsy (CNB), Excisional Surgical Biopsy (ESB), Fine Needle Aspiration Cytology (FNAC), Fine Needle Aspiration (FNA), Immunohistochemistry (IHC), Human Immunodeficiency Viruses (HIV), Positive Predictive Value (PPV), Negative Predictive Value (NPV), Hodgkin Lymphomas (HL), Follicular Non-Hodgkin Lymphomas (FNHL), Diffuse Large B -cell Lymphoma (DLBL), Tuberculosis (TB), Randomized Clinical Trial (RCT).

CONFLICT OF INTEREST

There are no conflicts of interest.

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