Utility of Sydney System for Reporting the Neck Lymphadenopathy underwent Real-time Ultrasound Guided Fine-Needle Aspiration

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Introduction:

Cytology reporting relies on established systems, the Bethesda system and Melan system, are used for thyroid and salivary glandular tumor/nodule cytology. Recently, the Sydney system was proposed for reporting lymphadenopathy. Similar to the Bethesda system, the Sydney system categorizes lymphadenopathy five groups: inadequate/insufficient, benign, atypical undetermined significance/atypical lymphoid of uncertain significance (AUS/ALUS), suspicious, and malignant. This classification system was reported to be effective in lymphadenopathy. In this study, we intend to check the performance of the ultrasound scoring system, elastography and Sydney system in reporting neck lymphadenopathy.

Methods:

This is a cross-sectional study and the institutional ethics committee review board approved this study plan. (FEMH-IRB-109074-E). All patients signed written informed consent forms.

1. Patients

The inclusion criteria included patients more than 20 years old who had enlarged neck lymphadenopathy and at least one US characteristic abnormality (i.e., size, shape, hilar echogenicity, margin, or vascular pattern) that permitted US-FNA. Patients with lymph node enlargement identified by the Otolaryngology or Oncology departments at Far-Eastern Memorial Hospital were referred for ultrasound examination. The ultrasound scans were primarily conducted by Dr. Liao (the first author), with a smaller portion performed by Dr. Lo (the fourth author). Informed consent was obtained either by Dr. Liao or a research nurse who explained the study and invited patients to participate. Pathological examinations were mainly conducted by Dr. Wu (the second author) in the Pathology department

2. US Examination

Sonograms were performed with one high-resolution 7- to 18-MHz real-time linear-array transducer (Aplio MX, Toshiba, Tokyo, Japan). We measured the lengths of the short and long axes and the diameter ratio of the short to long axis (S/L ratio) of enlarged LNs. The nodal margin was classified as regular or irregular. Echogenicity compared to the adjacent muscles was speculated and classified as hypoechoic, isoechoic, or hyperechoic. The echogenic hilum was differentiated and classified as its presence or absence. The internal echotexture was examined and classified as a homogenous or heterogeneous pattern. The vascular pattern was evaluated with power Doppler US and grouped into avascular or hilar type versus mixed, spotted, or peripheral type. All the morphological US data were entered into our Marosis PACS system (Marotech Inc., Seoul, South Korea). A predictive scoring scale was proposed as: 0.06 x (age) + 4.76 x (S/L ratio) + 2.15 x (internal echo) + 1.80 x (vascular pattern). Cervical lymphadenopathy was regarded as malignant with a score >or=7.

3. Elastography

For our elastographic technique, real-time elastographic images were demonstrated together with grayscale sonograms in a two-panel format. We further compressed with light pressure followed by decompression, which repeated the cycle until the size and color distribution of the region of interest (ROI) in numerous sequential images appeared nearly identical. Compression was directed along the radiation axis, with a focus on preventing any motions that deviate from the plane. Real-time elastographic visual employed a color-coded graphic format, with emphasis on the selected target area. Stiffness was denoted by blue, intermediate firmness by green and yellow, and softness by red within this representation. We used the 4-point scoring system to evaluate lymphadenopathy as follows: Elastographic score (ES) 1 represents soft (less than 10% of red areas), ES 2 represents moderately soft (10% to 50% of red areas), ES 3 represents moderately stiff (10% to 50% of blue, green, and yellow areas), and ES 4 represents stiff (less than 10% of blue, green, and yellow areas). An LN with RTE of ES 3 or 4 was classified as malignant.

Another elastographic technique employed in this study was shear wave elastography (SWE). Shear wave elastographic images were also displayed along with the grayscale sonograms in two-panel images for comprehensive evaluation. A high-intensity pulse is generated by the ultrasound probe toward the target, where perpendicular shear wave propagation is detected. The shear wave propagation is then converted and recorded as shear velocity (m/s) and Young's modulus (kPa). The mean SWE value of the included lymphadenopathy was used as a cutoff value for evaluation. An LN with SWE higher than the cutoff value of SWE is classified as malignant.

4. US-FNA Procedure

In US-guided FNA procedure, each patient underwent the process by placing the array probe parallel to the needle for guidance and with a 22-G needle within the node that was the most suspicious to be malignant.

5. Sydney System

The cases were classified according to the Sydney system[4] into five groups, denoted as L1 to L5: L1: Inadequate/Insufficient; L2: Benign; L3: Atypical (cells) Undetermined Significance/Atypical Lymphoid (Cells) of Uncertain Significance (AUS/ALUS); L4: Suspicious and L5: Malignant. The categories L3 to L5 were classified as malignant, and calculate the sensitivity, specificity, and overall accuracy for the malignancy classification. This comprehensive approach allowed for a thorough assessment of diagnostic performance.

6. Statistical Analysis

Mann–Whitney U tests and chi-squared tests were used to determine the differences in clinical parameters. The optimal cutoff point of ES in share wave elastography was determined at the point of highest accuracy for malignancy. The diagnostic accuracy was expressed as the sensitivity, specificity and area under the ROC curve (AUC). A p value < 0.05 was interpreted as statistically significant. All statistical analyses were accomplished using Stata software, version 12.0 (StataCorp. LP, College Station, TX).

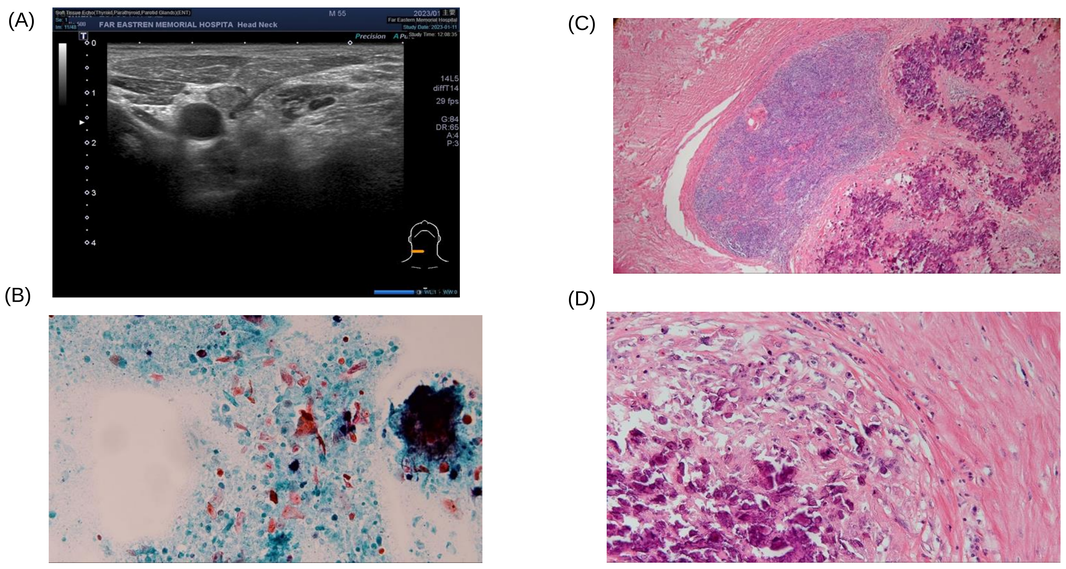

Figure 1. There was one false-positive case in our study. Preoperative ultrasound found lymph nodes with heterogeneous echo texture overriding the common carotid artery (A). On cytology, the smear showed a tumor necrotic debris background with some keratinocyte-like cells (in orange color) and some cell shadows with enlarged nuclei (in green color). This finding was comparable to malignancy in cytology according to the Sydney system (B). In the final pathology with H&E staining, calcifications, histiocytes, and necrotic debris with necrotic keratinocyte-like cells were observed (C: low power & D: high power). Because there were no viable carcinoma cells, the final diagnosis was no metastatic carcinoma.

Results:

From July 2020 to April 2023, this study enrolled 208 patients presenting with neck lymphadenopathy, comprising 68 cases with malignancy and 140 with benign condition. The prevalence of malignant LNs was 33% (68/208). Of the enrolled patients, 117 were males, accounting for 56% of the patients, while 91 were females, constituting the remaining 44%. The mean age of the participants was 46 years old, with ages spanning a range from 20 to 82 years. The patients' final diagnoses are summarized in **Table 1**.

Table 2 presents the rate of malignancy based on the Sydney system classification. We found that the specimen inadequate rate of US-FNA was 2% (4/208). The malignancy rates varied across different Sydney system categories with rates of 2%, 89%, 100% and 98% for the L2 to L5 groups, respectively. Moving from L1 to L5, the probability of malignancy increases.

Table 3 demonstrates the patient and US characteristics for benign and malignant lymphadenopathies. In patients with malignant lymphadenopathies, there is a higher proportion of males, and the average age is comparatively older (55.9 yeas vs. 41.4 years) when compared to the benign group. However, there is no significant difference observed between the left and right sides of the lymph nodes. Malignant lymph nodes frequently tend to be larger in size, rounder in size (S/L ratio), and greater stiffness in both RTE and SWE. We also found that the LN score was notably higher in malignant lesions as compared to benign lesions, with respective mean scores (±SD) of 9.2±2.6 versus 5.9±1.8(p value <0.01).

A comparison of the diagnostic performance of elastography, share wave elastography, the US scoring system and the Sydney system in reporting neck lymphadenopathy is demonstrated in **Table 4**. The real-time elastography (ES 3&4) demonstrated a sensitivity of 62.7%, specificity of 58.2% and an overall accuracy of 59.8%. For shar wave elastography (>44 kPa), the sensitivity was 63.9%, specificity was 62.0%, and the accuracy reached 62.6%. When utilizing the US scoring system, we observed a sensitivity of 81%, specificity of 77%, and an accuracy of 78%. Conversely, the Sydney system exhibited remarkable performance, with a sensitivity of 97%, specificity of 99% and a high accuracy of 99%.

Table 1. Final diagnosis of patients

Item		Numbers (%)
Malignant nodal disease	NPC	14 (7)
	Hypopharyngeal cancer	10 (5)
	Oral cancer	8 (4)
	Thyroid cancer	8 (4)
	Esophageal cancer	6 (3)
	Oropharyngeal cancer	5 (2)
	Lung cancer	5 (2)
	Unknown primary carcinoma	5 (2)
	Laryngeal cancer	2 (1)
	Other cancer	6 (3)
	B cell lymphoma	2 (32)
	Prostate cancer	1 (17)
	Pancreas cancer	1 (17)
	Endometrial cancer	1 (17)
	Breast cancer	1 (17)
Benign nodal disease	Reactive lymphoid hyperplasia	122 (58)
	Tuberculosis	1 (1)
	Kikuchi disease	1 (1)
	Negative follow-up	15 (7)

Table 2. Risk of malignancy according to the Sydney system classification.

Sydney system/Final diagnosis	N (%)	Benign (%)	Malignant (%)
Inadequate/Insufficient	4 (2%)	4 (100%)	0/4 (0%)
Benign	137 (65%)	135 (98%)	2/137 (2%)
AUS/ALUS	9 (4%)	1 (11%)	8/9 (89%)
Suspicious	2 (1%)	0 (0%)	2/2 (100%)
Malignant	56 (27%)	0 (0%)	56/57 (98%)

Table 4. Comparison of the diagnostic performance by the RTE/SWE/LN scoring system and the Sydney system

Items	sensitivity	specificity	overall accuracy
RTE (3+4)	62.71%	58.18%	59.76%
SWE (>44kPa)	63.93%	61.98%	62.64%
SWE(>3.8m/s)	54.10%	68.33%	63.54%
LN Score (>7)	80.60%	77.37%	78.43%
Sydney system(L3-5)	97.06%	99.26%	98.53%

Table 3. demonstrate the patients and US characteristics for benign and malignant lymphadenopathy.

		N (%) / mean ± SD			
Item		Total N=208	Benign N=140	Malignant N=68	P-value
Gender	Male	117 (56)	68 (58)	49 (42)	0.001
	Female	91 (44)	72 (79)	19 (21)	
Age		46.2±14.3	41.4±13.5	55.9±10.7	<0.001
Side	L	109 (52)	73 (67)	36 (33)	0.914
	R	99 (48	67 (68)	32 (32)	
Level	I	34 (16)	29 (85)	5 (15	0.024
	II	74 (36)	43 (58)	31 (42)	
	III	15 (7)	12 (80)	3 (20)	
	IV	15 (7)	7 (47)	8 (53)	
	V	55(27)	40 (73)	15 (27)	
	VI	15 (7)	9 (60)	6 (40)	
Boundary	Clear	179 (86)	138 (77)	41 (23)	<0.001
	Vague	29 (14)	2 (7)	27 (93)	
Internal echo	Homogenous	142 (68)	125 (88)	17 (12)	<0.001
	Heterogenous	66 (32)	15 (23)	51 (77)	
Echogenicity	Hypoechoic	206 (99)	139 (67)	67 (33)	0.600
	Isoechoic	2 (1)	1 (50)	1 (50)	
Calcification	Absent	200 (96)	139 (70)	61 (30)	0.001
	Present	8 (4)	1 (12)	7 (88)	
Architecture	Solid	205 (99)	139(68)	66 (32)	0.206
	Cystic<50%	3 (1)	1 (33)	2 (67)	
Hilar echo	Absent	129 (62)	65 (50)	64 (50)	<0.001
	Linear/Oval	79 (38)	75 (95)	4 (5)	
Vascular pattern	Avascular/Hilar	181 (87)	131 (72)	50 (28)	<0.001
	Other	27 (13)	9 (33)	18 (67)	
Size(short) cm		0.94±0.55	0.7±0.3	1.4±0.6	<0.001
Size(long) cm		1.71±0.89	1.4±0.6	2.3±1.1	<0.001
S/L ratio		0.56±0.18	0.50±0.14	0.68±0.20	<0.001
SWE(kPa)	SWE(kPa)	44.6±24.3	40.4±22.8	52.8±25.2	0.001
	SWE SD(kPa)	23.2±13.9	19.8±12.6	29.9±13.9	<0.001
SWE(m/s)	SWE(m/s)	3.8±2.5	3.4±1.04	4.5±4.0	0.008
	SWE SD(m/s)	1.2±0.7	1.0±.6	1.5±0.7	<0.001
RTE	1	23 (13)	14 (61)	9 (39)	0.008
	2	73 (40)	59 (81)	14 (19)	
	3	80 (43)	45 (56)	35 (44)	
	4	8(5)	4 (50)	4 (50)	
Score LN		7.0±2.6	5.9±1.8	9.2±2.6	<0.001

Discussion:

It is difficult to diagnose LNs after radiation therapy. Figure 1 demonstrates another case of a false-positive result; this is a hypopharyngeal cancer patient. He received an US exam 3 months after concurrent chemoradiotherapy. On US, multiple heterogeneous LNs above the carotid artery were found. US-FNA with the Sydney system was positive for malignancy. Preoperative US found lymph nodes with heterogeneous echo texture overriding the common carotid artery (Figure 1 (A)). On cytology, the smear showed a tumor necrotic debris background with some keratinocyte-like cells (in orange color) and some cell shadows with enlarged nuclei (in green color). This finding was comparable to malignancy in cytology according to the Sydney system (Figure 1 (B)). In the final pathology with H&E staining, calcifications, histiocytes, and necrotic debris with necrotic keratinocyte-like cells were observed (C: low power & D: high power). Because there were no viable carcinoma cells, the final diagnosis was no metastatic carcinoma.

Conclusions:

In conclusion, this study provides valuable insights into the characteristics of neck lymphadenopathy and the diagnostic capabilities of various US methods. Specifically, the Sydney System demonstrated superior performance with higher sensitivity, specificity, and overall accuracy compared to the conventional US scoring system and elastography. Our findings observed that the Sydney System is very effective for reporting neck lymphadenopathy.