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Fine-needle aspiration biopsy of cervical lymph nodes: factors in predicting malignant diagnosis

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The objective of the study was to determine the predicting factors in malignant diagnosis in ultrasonography guided fine-needle aspiration biopsy of cervical lymph nodes. Design is retrospective follow-up study. Ultrasonography guided fine-needle aspiration biopsies of cervical lymph nodes were performed in 290 patients. The mean age was 45.5±14.4 years (range; 15-85). 207 (71.4%) and 83 (28.6%) were women and men, respectively. Cytopathologist was not present in any biopsy procedure. Factors in predicting malignancy were age, gender, presence of primary malignancy, localization (Level 1-6), hypoechogenicity with loss of echogenic hilum, microcalcification, cystic feature, minimum and maximum sizes, and index value (minimum size/maximum size). Factors were analyzed by univariate and multivariable tests. The mean minimum size and index value of the lymph nodes were 10.4±5.5 mm and 0.58±0.18, respectively. Age, gender, microcalcification, cystic feature, minimum size, and index value were poor predictors in malignancy. Predictors were presence of primary malignancy ($p<0.001$), the level of localization ($p=0.001$), and hypoechogenicity ($p<0.001$) in malignancy. Microcalcification and cystic parts were specific US findings of metastasis of thyroid carcinoma; nevertheless cystic parts were seen more specific finding in the other malignancies. Malignant lymph nodes were often found in the presence of primary malignancy, mid neck and lower neck localizations as Level 3-6, and markedly hypoechoic lymph nodes. In 131 patients with a primary thyroid carcinoma, the predictors for malignancy were localization where the most often regions were Level 3, 4, and 6 and hypoechogenicity. Malignancy rate was relatively low in patients with thyroid malignancy than those with non thyroid malignancies in Level 5. Level 6 was the most difficult area for biopsy due to postoperative changes. Microcalcification was specific only in thyroid carcinoma, whereas cystic parts were more specific in the other malignancies.

Key words: Fine-needle aspiration biopsy; cervical; neck; lymph node; malignancy.

Several studies have shown that ultrasonography (US) has a markedly higher sensitivity than palpation for detecting enlarged lymph node in patients who have suspected cervical lymph node metastases [1]. Additionally, it provides the ability to perform US-guided fine-needle aspiration biopsy (FNAB), which informs us about the nature of the pathologic process [1].

There are no definite US criteria for distinction between benign or malignant cervical lymph nodes in the literature [1-11]. Nevertheless, malignant nodes are described as being more round and of a heterogeneous structure (commonly hypoechoic with a loss of the hilum, sometimes with cystic degeneration or calcifications) [1].

The objective of our study was to determine the predictor factors and their limitations in malignant cervical lymph nodes. These variables were determined as age, gender, presence of primary malignancy, localization (Level 1-6), echogenicity, microcalcification, cystic feature, minimum and maximum sizes, and index value (minimum size/maximum size). We examined the variables in a cohort study of 290 patients having US-guided FNAB of cervical lymph nodes. Surgical definitive diagnosis was performed in 66 patients.

Patients and methods

We retrospectively evaluated US-guided fine-needle aspiration biopsies of cervical lymph nodes performed in 290 patients in our radiology department between February 2007 and October 2009. The mean age was 45.5±14.4 years (range; 15-85). 207 (71.4%) and 83 (28.6%) were women and men, respectively. Age, gender, and presence of any primary malignity were noted. The US characteristics before biopsy

Figure 1. 77-year-old male patient with operated thyroid and colon carcinomas. Ultrasonography (US) shows markedly hypoechoic, round, right Level 3 cervical lymph node (black arrow). Index value=0.90 (9 mm/10 mm). Fine needle biopsy was resulted in metastasis of papillary carcinoma. The levels were Level 1 (submental and submandibular), Level 2 (upper cervical; from skull base to lower body of hyoid bone), Level 3 (middle cervical; between lower levels of hyoid bone and cricoid cartilage), Level 4 (lower cervical; from level of bottom of cricoid cartilage to clavicle), Level 5 (5a-upper and 5b-lower. due to level of bottom of cricoid cartilage in posterior triangle), and Level 6 (midline visceral cervical; between lower hyoid bone and superior manubrium of sternum).

Figure 2. US shows markedly hypoechoic lymph node with hyperechoic punctuate microcalcifications (white arrows) in a patient with operated differentiated thyroid papillary carcinoma. The node was diagnosed as metastasis of papillary carcinoma in both fine needle aspiration biopsy and operation.

were localization (Level 1-6), hypoechogenicity relating to the adjacent strap muscles (hypoechoic and non hypoechoic), microcalcification, cystic feature, minimum and maximum sizes, and index value (minimum size/maximum size). We used an international cervical lymph node classification for level localization, which was due to the Som et al.'s classification system [2]. Nodes with asymmetric and symmetric cortical thickening and heterogeneous echo with hilum made up non hypoechoic nodes. The loss of hilum was seen in all the hypoechoic lymph nodes (Figure 1). Microcalcifications were seen as hyperechoic punctuate lesions (Figure 2). Cystic parts were defined as marked posterior acoustic enhancement, which often shows early cystic change in malignant lymph nodes (Figure 3). Diameters were measured as described in the literature [1]. All lymph nodes were scanned in the transverse plane, and the largest size was maximum diameter and the least size was minimum diameter. Mean diameter was equal to half of the minimum diameter plus maximum diameter. Index value was accepted minimum diameter/maximum diameter.

Indication for FNAB was request of referring physician in any lymph node. Informed consent was obtained from each patient. Cytopathologist was not present in any biopsy procedure. A 20- or 21-gauge needle was used with an attached 20-mL syringe for aspiration. A freehand biopsy technique was used and FNAB was performed. This procedure was repeated one or two times in the same procedure. The collected material was placed onto glass slides. Air-dried slides were stained with both May-Grünwald-Giemsa stain and Papanicolaou method; alcohol-fixed slides were stained with Hematoxilyn-Eosin.

Ethics considerations, follow-up, and analysis of results

Informed consent was obtained from each patient. All the data were obtained from our files and hospital electronic database system after taking permission of the institutional review board. The node with a marker on its surface skin was surgically removed in 66 patients.

Correlation was made between cytologic and surgical pathologic diagnosis after surgical resection of the node or at least of 8 months follow-up. The diagnosis was classified as benign, indeterminate including atypical cells or suspected malignant, malignant, and nondiagnostic depending on pathologic results. Diagnosis was nondiagnostic if there were no well-visualized lymphoid cells. Malignant and benign cytology which had the same diagnosis on surgery or on follow-up were accepted true positive and true negative; malignant and

Table 1. Demographic features of 290 patients

Characteristics		Value
Age (years)		45.5±14.4 [a]
Gender	Women	207 (71.4%) [b]
	Male	83 (28.6%)
Primary malignity	Negative	122 (42.1%)
	Positive[c]	168 (57.9%)
Location[d]	Level 1	65 (22.4%)
	Level 2	89 (30.7%)
	Level 3	40 (13.8%)
	Level 4	37 (12.8%)
	Level 5[d]	25 (8.6%)
	Level 6	34 (11.7%)
Echogenicity	Non hypoechoic[e]	141 (48.6%)
	Hypoechoic	149 (51.4%)
Microcalcification	Negative	272 (93.8%)
	Positive	18 (6.2%)
Cystic component	Negative	260 (89.7%)
	Positive	30 (10.3%)
Minimum size (mm)		10.4±5.5
Maximum size (mm)		18.6±8.2
Mean size (mm)		14.7±6.3
Index value		0.58±0.18

[a] Mean±2SD
[b] Number (percent)
[c] One primary in 164 nodes and two primaries in 4 nodes
[d] 14 nodes in Level 5a and 11 nodes in Level 5b, the levels were explained in Figure 1.
[e] 72 symmetric and 57 asymmetric cortical thickening, and 12 heterogeneous

Figure 3. US shows markedly hypoechoic lymph node with cystic parts and acoustic enhancement in each one (white arrows). Level 4, cervical lymph node. Fine needle biopsy was resulted in necrosis but surgical diagnosis was metastasis of neuroendocrine carcinoma.

benign cytology which had different diagnosis on surgery or follow-up were accepted false positive and false negative, respectively. We calculated accuracy rates after excluding indeterminate cytology.

Statistics

Clinical and radiological factors in predicting malignancy were statistically analyzed by univariate test and binary logistic regression analysis. These were age, gender, presence of primary malignancy, localization (Level 1-6), hypoechogenicity, microcalcification, cystic feature, minimum and maximum sizes, and index value (minimum size/maximum size). Similarly, these tests except for presence of primary malignancy were also performed in 131 patients with primary thyroid cancer. Predicting values were obtained after multivariable analysis. Significant scale variables were examined by receiver operating characteristic curve (ROC) analysis. Cut-off values were determined, and groups were divided by these values. Sensitivities and specificities were calculated as in the literature [3]. Significance was accepted at $p<0.05$.

Results

Features of 290 patients are summarized in Table 1. Table 2 and Table 3 show biopsy and surgical diagnosis of nodes, respectively.

The nondiagnostic cytology was detected in 36 of 260 nodules (12.4%). The most frequent site of them was Level 6 with 35.3% (12/34) where thyroidectomy was previously

Table 2. Diagnostic correlation of lymph nodes in biopsy cohort

Cytological results	Diagnosis		Total
	Benign	Malignant	
Benign	182 (96.3%)[a]	7 (3.7%)	189 (65.2%)
Indeterminate[b]	4 (50.0%)	4 (50.0%)	8 (2.8%)
Malignancy	1 (1.8%)	56 (98.2%)	57 (19.7%)
Nondiagnostic	33 (91.7%)	3 (8.3%)	36 (12.4%)
Total	220 (75.9%)	70 (24.1%)	290 (100%)

[a] Number (percent)
[b] Atypical lymphoid cells or suspected malignant

Table 3. Surgical correlation of lymph nodes in biopsy cohort

Cytological results	Surgical diagnosis		Total
	Benign	Malignant	
Benign	14 (66.7%)[a]	7 (33.3%)	21 (31.8%)
Indeterminate[b]	1 (100%)	0 (0%)	1 (1.5%)
Malignancy	0 (0%)	37 (100%)	37 (56.1%)
Nondiagnostic	4 (57.1%)	3 (42.9%)	7 (10.6%)
Total	19 (28.8%)	47 (71.2%)	66 (100%)

[a] Number (percent)
[b] Atypical lymphoid cells or suspected malignant

performed in all for thyroid cancer. Malignancy was detected in 3 of 36 biopsies with nondiagnostic cytology, which were metastasis of papillary thyroid carcinoma, metastasis of neuroendocrine carcinoma, and Hodgkin lymphoma nodular sclerosing type each one. Eleven of 36 nondiagnostic biopsies (30.6%) were repeated; 6 were successful and 5 were failure. Nondiagnostic yield was decreased to 10.3% (30/290) after the repeat biopsy. There were 55 true positive, 182 true negative, 43 false negative, and 2 false positive results. Among 43 false negatives excluding nondiagnostic cytology, 5 false negatives (71.4%) were due to lymphoma (B-cell in 2, Hodgkin lymphoma in 2, and T-cell in one) as definitive diagnosis.

Table 4. Variables effecting malignancy in 290 patients

Variable		Benign	Malignant	p value[a] p value[b]
Age (years)		44.1±13.8[c]	49.9±15.3	0.003[a] 0.794[b]
Gender	Women	164 (79.2%)[d]	43 (20.8%)	0.034[a]
	Male	56 (67.5%)	27 (32.5%)	0.420[b]
Primary malignity	Negative	106 (86.9%)	16 (13.1%)	<0.001[a]
	Positive	114 (67.9%)	54 (32.1%)	<0.001[b]
Location	Level 1	63 (96.9%)	2 (3.1%)	
	Level 2	78 (87.6%)	11 (12.4%)	
	Level 3	24 (60.0%)	16 (40.0%)	<0.001[a]
	Level 4	21 (56.8%)	16 (43.2%)	0.001[b]
	Level 5	11 (44.0%)	14 (56.0%)	
	Level 6	23 (67.6%)	11 (32.4%)	
Echogenicity	Non hypoechoic	134 (95.0%)	7 (5.0%)	<0.001[a]
	Hypoechoic	86 (57.7%)	63 (42.3%)	<0.001[b]
Microcalcification	Negative	213 (78.3%)	59 (21.7%)	<0.001[a]
	Positive	7 (38.9%)	11 (61.1%)	0.157[b]
Cystic component	Negative	207 (79.6%)	53 (20.4%)	<0.001[a]
	Positive	13 (43.3%)	17 (56.7%)	0.986[b]
Minimum size (mm)		9.3±4.6	13.9±6.8	<0.001[a] 0.305[b]
Maximum size (mm)		18.3±8.1	19.4±8.3	0.318[a] 0.578[b]
Index value		0.54±0.17	0.72±0.16	<0.001[a] 0.128[b]

[a] Univariate p value (upper value)
[b] Multivariable p value (lower value)
[c] Mean±2SD
[d] Number (percent)

Among 2 false positives, one was Hodgkin lymphoma at cytology which was diagnosed as reactive lymphoid hyperplasia and the other was non Hodgkin lymphoma at cytology which was definitively diagnosed as metastasis of small cell lung carcinoma. Positive and negative predictive values, sensitivity, specificity, and accuracy rates were detected 96.5%, 80.9%, 56.1%, 98.9%, and 84.0%, respectively. Also, false negative and false positive rates were 43.9% and 1.1%, respectively.

220 (75.9%) and 70 (24.1%) patients had no malignancy and malignancy, respectively. Malignancy rate was low in non hypoechoic nodules (5.0%) relating to hypoechoic (42.3%) nodes. Also, this rate was 7.0% and 0% in asymmetric and symmetric cortical thickening, respectively. Age, gender, microcalcification, cystic feature, minimum size, and index value were poor predictors in malignancy, which were significant in only univariate analysis. Predictors were presence of any primary malignity ($p<0.001$), the level of localization ($p=0.001$), and hypoechogenicity ($p<0.001$) in malignancy (Table 4). Malignant lymph nodes were often found in the presence of primary malignity (32.1% vs. 13.1%), in the Level 3-6 (40.0% in Level 3, 43.2% in Level 4, 56.0% in Level 5, and 32.4% in Level 6 vs. 3.1% in Level 1 and 12.4% in Level 2), in markedly hypoechoic nodes with loss of hilum. Also, index value and minimum size were significant in univariate analysis ($p<0.001$) but not in multivariable analysis. Cut-off values were 11 mm for minimum size and 0.61 for index value (Figure 4). Minimum node size ≥ 11 mm was found more frequently malignant regarding to node size < 11 mm, 44.7% vs. 15.6% (univariate $p<0.001$). Index value ≥ 0.61 was found more frequently malignant regarding to index value < 0.61, 40.9% vs. 11.0% (univariate $p<0.001$). Area under curve (AUC) was higher for index value relating to minimum size.

Primary thyroid carcinoma was seen in 131 patients (45.2%). Types were papillary in 123, medullary in 6, Hurthle cell in one, and follicular in one. Localization ($p<0.001$), hypoechogenicity ($p<0.001$), microcalcification ($p=0.002$), cystic component ($p=0.006$), minimum size ($p=0.001$), and index value ($p<0.001$) were significant for malignancy in univariate analysis of patients with thyroid carcinoma. Microcalcifications and cystic parts were specific US findings of 94.4% and 95.6% rates, but not sensitive of 24.4% and 19.5% rates, respectively. Conversely, hypoechogenicity was sensitive of 82.9% rate, but not specific of 57.8%. Localization ($p=0.001$) and hypoechogenicity ($p=0.025$) were found significant by multivariable analysis in presence of any thyroid malignity. Malignancy rates were 3.7% in Level 1, 20.5% in Level 2, 76.5% in Level 3, 85.7% in Level 4, 28.6% in Level 5, and 32.4% in Level 6. Unlike the other primary malignancies, Level 5 was relatively low frequent region for metastasis of thyroid cancer.

Compared with non thyroid malignancies, cystic change in malignant diagnosis was not specific to only metastasis of thyroid carcinoma, 19.5% (8 of 41 nodes) with it vs. 31.0% (9 of 29 nodes) with non thyroid malignancies. Microcalcification in malignant diagnosis was only specific to metastasis of thyroid carcinoma, 24.4% (10 of 41 nodes) with it vs. 3.4% (one of 29 nodes) with non-thyroid malignancies.

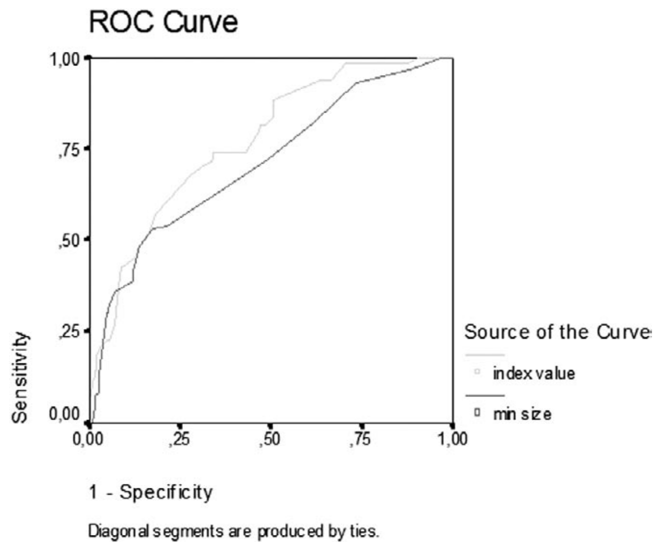

Figure 4. Graph shows receiver operating characteristic curve (ROC) analysis. Cut-off values were found 11 mm for minimum size and 0.61 for index value. Area under curve (AUC) was 0.714 for minimum size and 0.774 for index value.

Discussion

The investigation of potential metastatic disease is the most frequent clinical impetus for FNAB of a cervical node [4]. The diagnostic accuracy of FNAB for metastatic disease is variable with reported sensitivities ranging from 76% to 97% [3, 4]. Similarly, diagnostic specificities for FNAB of metastatic disease have ranged from 91% to 100% [4]. Our sensitivity rate was a low rate of 56.1% relating to the literature, whereas specificity rate was 98.9% in agreement with it. This low sensitivity rate has been mainly caused by nondiagnostic cytology of 12.4% in our series. This could be caused from that cytopathologist was not present in any biopsy procedure. Also, this was the lowest rate in Level 6 due to limitations of US in thyroidectomy region.

Also, diagnosing low-grade lymphoma, particularly the small cell and mixed cell subgroups, solely on cytology is often difficult, and in some cases impossible [5]. Cytology has high sensitivity for detecting metastatic nodal disease, though it is less useful for lymphomas and tuberculous lymphadenitis [5, 6]. Likewise, our false negatives excluding nondiagnostic cytology were mostly due to lymphoma. In recent years the use of ancillary techniques which include immunocytochemistry, immunophenotyping, and molecular techniques to aid in the diagnosis of lymphoma has been well recognized. Similarly, thyroglobulin analysis could have increased accuracy if it had been performed in thyroid cancer. Sensitively, nodal status in the papillary thyroid cancer has been examined with reverse transcription – polymerase chain reaction [12]. We did not use these additional techniques in the study, so false negatives increased.

The probability that cervical adenopathy is due to a malignant process increases with patient age [4]. The diagnosis of reactive lymph nodes is most accurate in patients under 50 year of age [4]. Nevertheless, age was found poor predictor of malignancy in our study.

US criteria for differentiating normal from abnormal cervical lymph nodes have been well established. Among these different US criteria, size and shape are the most commonly used to assess lymph nodes, and they are important criteria for diagnosis [7]. The minimum diameter appears to be the most accurate size criterion, compared to the maximum diameter [8].

A spherical lymph node larger than 10 mm is an indicator for a malignant node, whereas an oval shape and/or a fatty hilus are more benign signs [9]. Although we found minimum diameter to be poor predictor, minimum node diameter ≥ 11 mm was found more frequently malignant regarding to node diameter < 11 mm in our study. To some extent we consider as accurate the routine where many institutions still use minimum size of 10 mm as a cut-off value for the differentiation between benign and malignant nodes [9].

The shape of the lymph nodes is commonly assessed by an index value (minimum diameter/maximum diameter) or short axis to long axis ratio [7]. In previous studies, a cut-off value of 0.5 for the short axis to long axis ratio has usually been used to differentiate benign from malignant nodes [7]. The shape of the node might be important, but some authors doubt its value [8].

Also, some studies have shown that the size and index value criteria may differ depending on the level of the neck being examined, and different cut-off points have been suggested in various levels [7, 9]. Similar to minimum size, index value with 0.61 cut-off was significant ($p<0.001$) in only univariate test of our study. We propose that cervical lymph nodes with index value ≥ 0.61 and minimum size ≥ 11 mm should be examined further. Nevertheless, area under curve (AUC) in ROC analysis of index value was higher than that of minimum size, so, we consider index value more significant than minimum size in malignancy.

Metastatic lymph nodes tend to be large, round, hypoechoic, and hypervascularized with a loss of hilar architecture [10]. We detected markedly hypoechogenity with absence of hilum as predictor of malignancy. Several studies have mentioned hypoechogenicity as a finding suggestive of malignancy, although others have not found [1, 10]. Our result suggests to be a reliable indicator of malignancy.

In addition to these morphologic criteria, the position of nodes in the neck also seems to be important in predicting possible malignancy. Reactively enlarged nodes occur more frequently in submental and submandibular as well as in subdigastric and high jugular regions [10]. In Kuna et al.'s series, 66.5% of the metastatic nodules were situated in the lower third of the neck whereas benign lymph nodes were found more often in the superior (45.9%) and middle (39.5%) third of the neck [1]. The location of the lymph nodes should also be taken into account because most of the metastases are found in the lower compartments [10]. Similarly, we found more malignancy in mid and lower neck regions (Level 3-6) than upper neck regions (Level 1 and 2).

Detection of nodal necrosis in patients with a primary head and neck cancer is the most reliable imaging sign of a metastatic node, which has shown overall 75% sensitivity, 83.3% specificity, and 82.3% accuracy with this criterion on US [3]. However, we found this with high specificity of 95.6% but low sensitivity of 19.5%, as poor predictor likewise microcalcification.

In differentiated thyroid cancer, metastatic lymph nodes may be also demonstrated specific features such as hyperechoic punctuations or microcalcifications and cystic appearance [10]. Thyroid papillary carcinoma most commonly has showed cystic formation in lymph node metastasis, and the incidence of cystic change of lymph nodes in thyroid cancer has been reported in 10–25% of cases [11]. We also found this rate of 19.5%, and microcalcification and cystic parts were specific US findings of metastasis of thyroid carcinoma. Nevertheless, cystic parts were seen less specific in metastasis of thyroid carcinoma than that the other malignancies.

In accordance with previous studies, Leboulleux et al. found a very high specificity (100%) and a low sensitivity (46% and 11%, respectively) for hyperechoic punctuations and cystic appearance. Hyperechoic punctuations or microcalcifications in lymph nodes are characteristic for differentiated thyroid cancer because they seldom exist in metastatic lymph nodes from other cancers [10]. Similarly, microcalcification was specific to thyroid carcinoma, 24.4% with it vs. 3.4% with the other malignancies of our series. We found node localization as predictor; Level 3, 4, and Level 6 were the most malignant regions in thyroid cancer whereas Level 1 was the least malignant region followed by Level 2. Malignancy rate was relatively low in patients with thyroid malignancy than those with non thyroid malignancies in Level 5.

Patients with a history of malignancy were more than twice as likely to show malignancy on lymph node by FNAB compared to those without such a history (87% vs. 41%) in Schafernak et al.'s series [5]. Similarly, we found these rates 32.1% in patients with a malignancy vs. 13.1% in those without any malignancy in multivariable analysis ($p<0.001$). Knowing whether a patient has a history of malignancy provides the appropriate level of suspicion for ordering ancillary investigations or even recommending excision biopsy for further evaluation [5].

One of our restrictions is that retrospective nature of study has potential limitations due to some deficiencies. Among them, Doppler US finding could not be investigated so peripheral and central vascular pattern could not be evaluated. Also, thyroglobulin could not be tested which could have lowered false negative diagnosis rate of the series in presence of thyroid cancer. US positive nodes were removed surgically, whereas US negative nodes went undissected most of the time. This may have produced detection bias, overestimating the specificity and positive predictive value; otherwise, they could be relatively in lower rates.

In conclusion, the lymph node status is one of the most important predictors of cervical lymph nodes; e.g., N-stage has been predictive in overall, disease-specific and disease-free survivals in a series of nasopharyngeal carcinomas [13]. Therefore this status of cervical lymph node is to be verified.

Malignant lymph nodes were often found in the presence of primary malignancy, mid-lower neck localization as Level 3-6, and markedly hypoechoic lymph nodes with loss of echogenic hilum. In patients with a primary thyroid carcinoma, the predictors for malignancy were localization where the most frequent regions were Level 3, 4, and 6 and hypoechogenicity. Malignancy rate was relatively low in patients with thyroid malignancy than those with non thyroid malignancies in Level 5. Also, the most difficult region was Level 6 for biopsy due to postoperative changes which limit the success of lymph node biopsy. Microcalcification was specific in only thyroid carcinoma, whereas cystic parts were more specific in the other malignancies.

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