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Research Article

Lymph Node Thyroglobulin Measurement in Diagnosis of Neck Metastases of Differentiated Thyroid Carcinoma

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Aim. Enlarged cervical lymph nodes (LNs) in patients with thyroid cancer are usually assessed by fine-needle aspiration cytology (FNAC). Thyroglobulin (Tg) is frequently elevated in malignant FNAC needle wash specimens (FNAC-Tg). The objectives of the study were to (1) determine an appropriate diagnostic cut-off for FNAC-Tg levels (2) compare FNAC and FNAC-Tg results in a group of 108 patients affected by differentiated thyroid carcinoma (DTC). *Methods*. A total of 126 consecutive FNACs were performed on enlarged LNs and the final diagnosis was confirmed by surgical pathology examination or clinical follow-up. The best FNAC-Tg cut-off level was selected by receiver operating curve analysis, and diagnostic performances of FNAC and FNAC-Tg were compared. *Results*. The rate of FNAC samples adequate for cytological examination was 77% in contrast FNAC-Tg available in 100% of aspirates ($P < .01$). The sensitivity, specificity, and accuracy of FNAC were 71%, 80%, 74%, 100%, 80%, and 94%, respectively. The most appropriate cut-off value for the diagnosis of thyroid cancer metastatic LN was 1.1 ng/mL (sensitivity 100%, specificity 100%). *Conclusions*. The diagnostic performance of needle washout FNAC-Tg measurement with a cut-off of 1.1 ng/mL compared favorably with cytology in detecting DTC node metastases.

1. Introduction

The prognosis of patients who receive appropriate treatment for thyroid carcinoma is usually favourable, especially for differentiated thyroid carcinoma (DTC). However, although most patients have a long-term survival rate, 5% to 20% of patients will develop recurrence during the followup, primarily in the cervical lymph nodes (LNs) [1, 2]. These LNs metastases may be detected clinically, but now are most often discovered on ultrasonography (US) [3]. It is of great importance to differentiate accurately LN metastases from benign reactive lymph nodes in order to avoid unnecessary treatment, but also to treat metastatic patients without delay. As consequence, diagnostic procedures must offer good sensitivity, but also high negative predictive value. US criteria distinguishing benign from metastatic or suspicious LNs have been described but they lack accuracy [4]. US-guided fine needle cytology (FNAC) proved to be a reliable method in examining the neck in patients who were previously treated for thyroid cancer [5, 6]. However, sensitivity of FNAC is far from excellent, varying from 75% to 85%, and altered by high rate of nondiagnostic or false-negative samples. To improve the diagnostic yield of FNAC, several authors have proposed measurement of Tg in aspirates (FNAC-Tg), particularly in the cases involving small, partially cystic, lymph nodes [7–12]. On the basis of prior studies, an increased Tg level in the needle washout has been shown to directly reflect the status of metastatic lymph nodes in patients affected by differentiated thyroid carcinoma. However, controversies still persist concerning some issues. First, there are few studies to validate the benefit of FNAC-Tg over FNAC alone, and, second, cut-off values ranging from 0.9 to 39 ng/mL have been suggested for FNAC-Tg, depending on the method used for the measurement [7, 13–15]. As consequence, the exact place for FNAC-Tg in the management of DTC patients is still debated.

This study was then undertaken to (1) determine a diagnostic cut-off value for washout Tg in patients treated by total thyroidectomy for detecting recurrences, and (2) to compare the performance of the Tg cut-off value to US-guided FNAC for detecting DTC recurrences.

2. Materials and Methods

Our institutional review board approved our research study, and all subjects gave written informed consent.

2.1. Patients. Between January 2006 and February 2009 a total of 126 consecutive US-guided FNACs were performed on enlarged LNs. The samples were obtained from 108 patients (19 males, 89 females; age 42.7 ± 18.2 years; 91 patients with 1, 94 with 2, and 5 with 3 lesions, resp.). All patients had histologically confirmed primary DTC (papillary, $n = 99$, including two tall-cell variants; follicular, $n = 9$, including 2 Hürtle cells carcinomas). The primitive carcinoma was classified pT1 in 34 cases, pT2 in 43 cases, pT3 in 24 cases, and pT4 in 7 cases. Forty-five patients (42%) had LN metastases at diagnosis. All patients underwent (near) total thyroidectomy and subsequent radioiodine ablation (administered activity from 1.85 to 3.70 GBq). The US criteria for possible malignant infiltration of lymph nodes were rounded contour, irregular internal echogenicity, punctate calcifications, fluids components, and abnormal colour Doppler pattern. Patients with positive cytology and/or FNAC-Tg measurement ($n = 86$, 96 lesions) underwent surgery and, if necessary, further radioiodine treatments. The diagnosis was confirmed in all cases by surgical pathology examination. Patients with negative FNAC-Tg measurement and cytology ($n = 22$, 30 lesions) underwent further follow up by serial clinical examinations, serum Tg measurements, neck US, and, whenever necessary, additional imaging procedures (i.e., radioiodine scan, ^{18}FDG-PET/CT). No DTC recurrence was detected among these patients (follow up: mean 36 months, range 15–42 months).

2.2. US-Guided FNAC Procedure. All US-guided FNAC procedures were performed on supine patients with the neck hyperextended under continuous real-time US guidance with a high-resolution transducer (ACUSON ×150, Siemens, Erlangen, Germany). Each lesion was aspirated at least twice by a 21 G needle. The needle was inserted obliquely within the transducer plane of view, and moved back and forth through the nodule to compensate for patient movement and needle deflection. Gradual aspiration was applied by a 20 mL syringe connected to Cameco's device. Contents of needles were expelled onto glass slides and smeared with a second slide to spread fluid across the surface. Slides were fixed in 95% ethanol, papanicolaou stained to identify cellular details, and read by our cytopathologist. Following collection of cytology samples the needles were washed by 1 mL of normal saline in a plain serum tube (Vacutainer Systems, Plymouth, UK) and the washout directly sent to the laboratory [16]. Cytological examinations were performed by experienced cytopathologists and expressed as (1) positive: presence of epithelial cells with atypical cytological characteristics, or with cytological features of papillary carcinoma; (2) negative: reactive lymphadenitis and absence of malignant cells; (3) inadequate or nondiagnostic: absence of cells or presence of blood cells.

2.3. Tg Measurement. Thyroglobulin was measured in fine-needle washouts using an immunoradiometric assay (IRMA) based on coated tubes with monoclonal antibodies directed against distinct epitopes of the molecule of Tg (DYNO test Tg-plus, BRAHMS Diagnostic GmbH, Berlin, Germany). With this measurement, analytic sensitivity, defined as the detectable minimum concentration different from zero (mean value + 2 standard deviation), and functional sensitivity, defined as the lowest value that was measured with the precision of a maximum 20% interassay variance, were 0.08 ng/mL and 0.2 ng/mL, respectively. We did not measure Tg antibodies (FNAC-TgAb) because the clinical performance of FNAC-Tg is unaffected by serum TgAb [17].

2.4. Data Analysis. Diagnostic performance (i.e., sensitivity, specificity, positive predictive value, negative predictive value, and accuracy) of FNAC and FNAC-Tg was evaluated by comparing the results of the two procedures to the status of the patients defined as follows: malignant lymph node from thyroid cancer was proved by histological examination of surgically resected LNs; benign lymph node was proved by negative histological examination of surgically respected LNs, or if disappearance or absence of evolution on imaging modalities was demonstrated at 12 months or more follow up.

The Chi-square (χ^2) test, performed with SAS version 9.1 for Windows (SAS Institute, Cary, NC, US) was employed to compare the diagnostic rate of FNAC and FNAC-Tg. The FNAC-Tg receiver operating characteristic curve was developed using MedCalc 6.1 software (MedCalc Software, Mariakerke, Belgium). The cut-off values which maximise the sum of sensitivity plus specificity were determined as the points in the upper left hand corner. A P value $< .05$ was considered to indicate statistical significance.

3. Results

Patients characteristics and cytological, pathological, and biochemical data are displayed in Table 1. Of the 126 lymph node lesions assessed for postoperative recurrences by US-guided FNAC and FNAC-Tg, 86 (68%) lesions were finally diagnosed as malignant and the remaining 40 (32%) lesions were diagnosed as benign LNs, respectively. The final diagnosis of the 86 malignant and 8 benign LN was established by surgical pathology; the remaining 32 benign lesions were diagnosed based on imaging follow up after at least 1 year. The time from thyroid ablation to US-FNAC was 19.5 ± 14.31 and 19.4 ± 13.76 months in patients with benign and malignant lesions, respectively (P not significant). Serum Tg levels were higher in patients with malignant lesions (median 4.20 ng/mL, range <0.2–27.10 ng/mL) than those with benign lesions (median .80 ng/mL, range <0.2–2.70 ng/mL; $P < .0001$). Serum TgAb were positive in 11

Table 1: Patients characteristics and cytological, pathological, and biochemical data.

Patients	Histology	pTNM	Duration (months)	Tg (ng/mL)	TgAb (IU/mL)	Lesions	Sites	FNA		Final diagnosis
								Cytology	Tg (ng/mL)	
1	PTC	pT1N1Mx	6	1.0	<60	1	R II	ND	<0.2	B
2	PTC	pT1NxMx	15	4.6	<60	1	L III	Negative	435.2	M
3	PTC	pT1NxMx	18	1.7	<60	1	R IV	CTM	85.3	M
4	PTC	pT1NxMx	30	0.4	<60	1	R III	ND	<0.2	B
5	PTC	pT1N0Mx	6	3.1	<60	1	L II	ND	97.2	M
6	PTC	pT2N0Mx	19	9.1	<60	2	R IV, VI	CTM	118.5	M
7	PTC	pT2NxMx	47	<0.2	334	1	L IV	CTM	879.4	M
8	PTC	pT2N1Mx	6	0.9	78	1	VI	Negative	1.1	B
9	PTC	pT1N1Mx	9	9.8	<60	1	L II	ND	1348.6	M
10	PTC	pT2N0Mx	14	1.5	<60	1	L III	CTM	358.5	M
11	PTC	pT1NxMx	8	12.6	<60	3	R II	CTM	2387.4	M
12	PTC	pT2NxMx	16	9.7	<60	1	R III	CTM	875.9	M
13	PTC	pT1NxMx	9	6.3	<60	1	R II	CTM	958.6	M
14	PTC	pT1N0Mx	11	1.0	<60	1	L III	Negative	48.7	M
15	PTC	pT2N1Mx	39	9.5	<60	1	L IV	CTM	>3000	M
16	PTC	pT1NxMx	12	0.8	<60	1	L III	CTM	107.5	M
17	PTC	pT2NxMx	19	2.7	<60	3	R III-IV	ND, CTM	541.6	RIII B, IV M
18	PTC	pT4N1Mx	6	1.6	<60	1	L III	CTM	31.8	M
19	PTC	pT1N1Mx	15	0.5	289	1	R IV	ND	<0.2	B
20	PTC	pT2N1Mx	3	2.3	<60	1	L III	ND	540.7	M
21	PTC	pT1NxMx	34	4.1	<60	1	L III	CTM	650.6	M
22	PTC	pT2N1Mx	8	<0.2	98	1	L II	ND	5.8	M
23	PTC	pT1NxMx	9	0.8	<60	2	R II, R III	CTM	87.5	M
24	PTC	pT4N0Mx	10	1.4	755	1	R II	CTM	196.4	M
25	PTC	pT2NxMx	21	11	<60	1	R III	ND	585.3	M
26	PTC	pT1NxMx	9	<0.2	<60	1	R III	Negative	<0.2	B
27	PTC	pT4N1M	12	1.1	160	1	L III	Negative	0.3	B
28	PTC	pT1N0Mx	23	5.3	<60	1	R III	CTM	784.2	M
29	PTC	pT2N1Mx	5	<0.2	>1000	1	R III	ND	<0.2	B
30	PTC	pT2N0Mx	22	4.9	<60	1	R III	CTM	641.5	M
31	PTC	pT1NxMx	36	0.3	367	1	R IV	Negative	<0.2	B
32	PTC	pT1NxMx	15	7.1	<60	1	R III	ND	665.4	M
33	PTC	pT2N0Mx	41	<0.2	<60	1	L II	Negative	<0.2	B
34	PTC	pT1NxMx	24	2.6	<60	1	R III	CTM	570.6	M
35	PTC	pT4N0Mx	31	1.4	>1000	3	L IV, VI	CTM	96.7	M
36	PTC	pT4N1M	12	27.1	<60	1	R II	CTM	2987.3	M
37	PTC	pT1N1Mx	54	6.8	<60	1	L III	CTM	875.6	M
38	PTC	pT2NxMx	12	<0.2	149	1	R IV	Negative	<0.2	B
39	PTC	pT2N0Mx	9	0.9	<60	1	R II	Negative	<0.2	B
40	PTC	pT1N0Mx	34	2.4	89	1	L III	ND	347.4	M
41	PTC	pT2NxMx	14	5.1	<60	1	L IV	ND	1655.7	M
42	PTC	pT4N1M	8	7.7	<60	1	L III	Negative	2076.5	M
43	PTC	pT1NxMx	61	1.1	<60	1	VI	Negative	<0.2	B
44	PTC	pT2N0Mx	22	1.0	<60	1	L II	CTM	90.6	M

Table 1: Continued.

Patients	Histology	pTNM	Duration (months)	Tg (ng/mL)	TgAb (IU/mL)	Lesions	Sites	FNA		Final diagnosis
								Cytology	Tg (ng/mL)	
45	PTC	pT2N1Mx	12	6.4	<60	2	R III-IV	CTM, ND	458.6	RIII M, IV B
46	PTC	pT1NxMx	45	0.6	<60	1	R IV	Negative	<0.2	B
47	PTC	pT4N0Mx	36	4.3	<60	1	R III	CTM	766.4	M
48	PTC	pT2NxMx	11	1.9	<60	1	L II	ND	306.5	M
49	PTC	pT3NxMx	18	7.0	<60	1	R III	CTM	955.6	M
50	PTC	pT2NxMx	10	1.2	<60	1	L III	Negative	<0.2	B
51	PTC	pT1N1Mx	12	3.9	<60	1	R III	CTM	564.7	M
52	PTC	pT3N0Mx	25	6.4	190	1	R III	ND	1078.6	M
53	PTC	pT2N1Mx	16	9.5	<60	1	L IV	CTM	759.4	M
54	PTC	pT1NxMx	9	0.6	<60	1	R III	Negative	<0.2	B
55	PTC	pT3N1Mx	60	<0.2	107	2	L II-III	CTM	137.5	M
56	PTC	pT1N0Mx	11	5.3	<60	1	R II	CTM	654.8	M
57	PTC	pT2N1Mx	18	1.1	860	1	L III	ND	<0.2	B
58	PTC	pT1NxMx	9	0.9	<60	1	R IV	Negative	<0.2	B
59	PTC	pT2NxMx	28	1.1	<60	1	R III	ND	99.6	M
60	PTC-TCV	pT3NxMx	13	4.6	<60	1	L II	CTM	436.8	M
61	PTC	pT1NxMx	2	2.7	<60	1	R II	CTM	194.5	M
62	PTC	pT3NxMx	7	21.9	<60	3	R III, L II	Neg., CTM	>3000	RIII B, LII M
63	PTC	pT1NxMx	18	1.1	<60	1	R III	CTM	27.4	M
64	PTC	pT3NxMx	10	3.5	<60	1	VI	CTM	147.4	M
65	PTC	pT2N0Mx	29	<0.2	>1000	1	R IV	Negative	<0.2	B
66	PTC	pT3N1Mx	6	5.6	<60	1	L III	CTM	<0.2	M
67	PTC	pT1N1Mx	11	2.1	<60	1	R III	ND	<0.2	M
68	PTC	pT3N0Mx	18	0.7	<60	1	R III	ND	<0.2	B
69	PTC	pT2N0Mx	23	1.7	<60	1	L IV	CTM	75.6	M
70	PTC	pT1NxMx	9	3.5	<60	1	L II	ND	72.6	M
71	PTC	pT3N0Mx	18	7.1	<60	2	R IV, VI	CTM	386.2	RIV B, VI M
72	PTC	pT1NxMx	7	1.8		1	L II	Negative	<0.2	B
73	PTC	pT2NxMx	11	3.6	<60	1	R III	ND	245.7	M
74	PTC	pT2NxMx	29	2.2	<60	2	L III-IV	CTM	67.4	IV M, III B
75	PTC	pT2N1Mx	14	5.7	<60	1	L II	CTM	198.7	M
76	PTC	pT1N0Mx	8	1.5	<60	1	R IV	CTM	26.1	M
77	PTC	pT2NxMx	10	2.1	<60	1	VI	CTM	59.7	M
78	PTC	pT1NxMx	18	0.7	<60	1	R IV	Negative	<0.2	B
79	PTC	pT3N1Mx	34	12.3	<60	1	R III	ND	678.4	M
80	PTC	pT1N1Mx	16	1.8	<60	1	L II	Negative	<0.2	B
81	PTC	pT2N0Mx	52	0.9	<60	1	R III	Negative	<0.2	B
82	PTC	pT2N1Mx	25	9.4	<60	1	L III	ND	563.6	M
83	PTC	pT1NxMx	9	4.1	<60	1	VI	CTM	64.7	M
84	PTC	pT2N1Mx	18	3.1	<60	1	R IV	CTM	116.4	M
85	PTC-TCV	pT2NxMx	20	15.5	<60	3	R IV-L III	CTM	432.9	M
86	PTC	pT3N0Mx	8	<0.2	56	1	VI	ND	<0.2	B
87	PTC	pT1N0Mx	31	2.9	<60	1	R IV	CTM	39.3	M
88	PTC	pT2NxMx	11	1.7	<60	1	R III	Negative	<0.2	B
89	PTC	pT2NxMx	54	6.5	<60	1	L IV	ND	467.7	M
90	PTC	pT1N1Mx	28	0.3	651	1	R II	Negative	<0.2	B
91	PTC	pT2NxMx	12	2.1	<60	1	L III	CTM	88.6	M

Table 1: Continued.

Patients	Histology	pTNM	Duration (months)	Tg (ng/mL)	TgAb (IU/mL)	Lesions	Sites	FNA		Final diagnosis
								Cytology	Tg (ng/mL)	
92	PTC	pT3N0Mx	17	9.4	<60	2	R IV, VI	CTM	156.2	IV M, VI B
93	PTC	pT1NxMx	22	1.0	<60	1	L IV	Negative	<0.2	B
94	PTC	pT2N1Mx	9	4.3	<60	1	VI	Negative	53.8	M
95	PTC	pT2N0Mx	26	<0.2	<60	1	R IV	Negative	<0.2	B
96	PTC	pT1N0Mx	12	0.9	<60	1	R III	ND	2.7	M
97	PTC	pT2NxMx	17	8.1	<60	1	L II	ND	356.4	M
98	PTC	pT2NxMx	9	0.9	<60	1	R III	CTM	19.6	M
99	PTC	pT3N1Mx	12	1.1	<60	1	L III	ND	0.6	B
100	FTC	pT1N1Mx	45	4.9	<60	1	R III	CTM	117.5	M
101	FTC	pT3N0Mx	36	1.4	<60	1	R III	Negative	<0.2	B
102	FTC	pT2N1Mx	11	<0.2	>1000	2	R III-IV	Negative	<0.2	B
103	FTC (HC)	pT1NxMx	72	10.4	<60	1	R IV	ND	278.9	M
104	FTC	pT2N1Mx	11	0.7	<60	1	R III	Negative	<0.2	B
105	FTC	pT1N0Mx	18	2.1	<60	1	R IV	CTM	74.4	M
106	FTC (HC)	pT1N0Mx	6	1.9	<60	1	L III	Negative	0.8	B
107	FTC	pT2N1Mx	25	7.8	<60	1	R II	ND	116.4	M
108	FTC	pT1NxMx	19	4.6	<60	2	L II-III	CTM	89.5	M

FNA, fine-needle aspiration; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; TCV, tall-cell variant; HC Hürtle cell; R, right, L, left; duration, time from thyroid ablation to FNA; II-III-IV, upper, middle, lower neck lateral compartment, IV, central neck compartment.

Table 2: Diagnostic performance of FNAC cytology as compared to final diagnosis.

FNAC	Final diagnosis	
	Malignant LNs ($n = 86$)	Benign LNs ($n = 40$)
Positive	61	0
Negative	4	32
Inadequate	21	8

Table 3: Diagnostic performance of FNAC-Tg as compared to final diagnosis.

	Malignant LNs ($n = 86$)	Benign LNs ($n = 40$)
FNAC-Tg >1.1 ng/mL	86	0
FNAC-Tg ≤1.1 ng/mL	0	40

Table 4: Figures of merits of FNAC cytology and FNAC Tg.

FNAC	Sensitivity	Specificity	PPV	NPV	Accuracy
Cytology	71%	80%	88%	56%	74%
Tg	100%	100%	100%	100%	100%

of 40 patients with benign lesions and 7 of 67 patients with malignant lesions ($P < .001$). The rate of FNAC samples adequate for cytological examination was 77% (97 samples) in contrast FNAC-Tg available in 100% of aspirates ($P < .01$). As shown in Table 2 cytological examination correctly identified 61 malignant LNs, was negative in 4, and inadequate in 21. For benign LNs, FNAC was negative in 32 and inadequate in 8. It showed no false-positive results. Thus, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of FNAC were 71%, 80%, 88%, 56%, and 74%, respectively. The ROC curve analysis demonstrated that the most appropriate cut-off value for the diagnosis of thyroid cancer metastatic lesions was 1.1 ng/mL (sensitivity 100%, specificity 100%, PPV 100%, NPV 100%, accuracy 100%; Figure 1, Tables 3, and 4). Basing on this cut-off level, the FNAC-Tg results correctly concluded all 25 malignant (100%) and 8 benign (100%) cases with false-negative ($n = 4$) and nondiagnostic ($n = 29$) FNAC results, respectively (Table 5). The FNAC-Tg levels were significantly higher in malignant (median 513.8 ng/mL, range 1.7-> 3000 ng/mL) than benign (median <0.2 ng/mL, range <0.2–1.1 ng/mL) lesions, respectively ($P < .0000001$). Particularly, specimen Tg levels were undetectable (i.e., <0.2 ng/mL) in 36 cases and were 0.3, 0.6, 0.8, and 1.1 ng/mL in remaining 4 cases with benign lesions.

Table 5: Rate of positive FNAC-Tg values (i.e., >1.1 ng/mL) in patients with inadequate or misdiagnosed FNAC-cytology.

Final status	FNAC inadequate ($n = 29$)	FNAC false-negative ($n = 4$)
Malignant LNs ($n = 25$)	21/21	4/4
Benign LNs ($n = 8$)	0/8	—

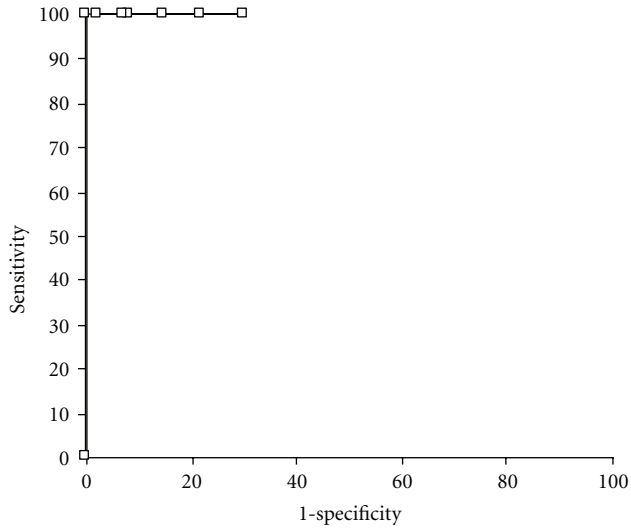

Figure 1: FNAC-Tg: ROC curve analysis.

4. Discussion

An accurate discrimination between metastatic and reactive LNs is essential in the management of thyroid cancer. Cytological examination of FNAC samples disclosed by US has been the most accurate method to diagnose a cervical LN. However, as showed also in our study, its sensitivity is negatively impacted by the rate of nondiagnostic samples although FNAC procedures are performed by US-experienced physicians and dedicated cytopathologists [5, 6, 15]. In the present study 23% of samples were nondiagnostic; this perfectly conforms with previously reported data [18]. Cystic metastasis and partial LN involvement comprise most of the inadequate/nondiagnostic FNAC-cytology cases and could be misinterpreted as a benign cervical cystic mass or branchial cleft cysts and could therefore delay the correct diagnosis and a further radical neck lymphadenectomy. The immunocytochemical Tg staining on FNAC samples from of neck nodes was previously evaluated in patients with DTC. Because an adequate FNAC sample is required, however, the practical impact of this technique is limited in clinical practice [19]. Recently, the FNAC-Tg measurement has been proposed to be a useful diagnostic technique in the management of patients with thyroid cancer. Because Tg is produced only by follicular thyrocyte-derived cells, measurement of Tg in FNAC specimens of nonthyroidal tissues enables the detection of persistence, recurrence, or metastasis of differentiated thyroid carcinoma. In our study FNAC-Tg analysis was more sensitive for detecting metastasis when compared with FNAC alone, and allows the accurate diagnosis in samples with inconclusive cytology. Our results perfectly conforms those recently reported by Bournaud and colleagues [18]. By contrast Tg could be determined in all aspirates and a sensitivity of 100% was achieved in our series, that is at the higher end of previously reported data (81%–100%) [7, 9, 14, 17, 18]. Although the performance of FNAC-Tg is well established, the Tg threshold value remains controversial. The Tg assays employed and methods for determining the cut-off value differed from one study to another, resulting in a large range, from 0.9 ng/mL to values as high as 39 ng/mL, proposed in the literature.

In our study the best Tg threshold was determined at 1.1 ng/mL by ROC curve analysis. Using a threshold of 1.1 ng/mL we observe neither false-positive results in non-malignant LNs nor false-negative results in malignant LNs at final diagnosis. Additionally, FNAC-Tg results correctly classified as malignant 4 lesions that tested negatively in cytological examination. All in all, our results are in accordance with those of Snozek and colleagues that used a Tg assay with a functional sensitivity at 0.1 ng/mL and proposed a cut-off level of 1.00 ng/mL: basing on their results these authors suggested that FNAC-Tg should be substituted for FNAC in many cases [7]. Of importance, our samples were obtained in a population of well-differentiated thyroid carcinomas (i.e., only two Hürtle cell and two tall-cell variants among 108 DTC cases). Several authors reported, however, that FNAC-Tg levels could be undetectable in some types of thyroid cancers (i.e., poorly differentiated thyroid carcinomas) [13, 17]. This correspond to the fact that amount and intensity of Tg expression parallel with differentiation of the tumor and could produce false-negative results. As a consequence, caution is needed, and a combination of FNAC and FNAC-Tg should remain the standard, especially in patients harboring less differentiated thyroid carcinomas.

5. Conclusions

The diagnostic performance of needle washout FNAC-Tg measurement with a cut-off of 1.1 ng/mL compared favourably with cytology and allowed accurate diagnosis in all cases in whom cytology was nondiagnostic.

Conflict of Interests

The author report that there are no conflicts of interests.

References

[1] L. Davies and H. G. Welch, "Increasing incidence of thyroid cancer in the United States, 1973–2002," *Journal of the American Medical Association*, vol. 295, no. 18, pp. 2164–2167, 2006.

[2] M. J. Schlumberger, "Papillary and follicular thyroid carcinoma," *The New England Journal of Medicine*, vol. 338, no. 5, pp. 297–306, 1998.

[3] N. A. Johnson and M. E. Tublin, "Postoperative surveillance of differentiated thyroid carcinoma: rationale, techniques, and controversies," *Radiology*, vol. 249, no. 2, pp. 429–444, 2008.

[4] A. Frasoldati and R. Valcavi, "Challenges in neck ultrasonography: lymphadenopathy and parathyroid glands," *Endocrine Practice*, vol. 10, no. 3, pp. 261–268, 2004.

[5] M. O. Bernier, C. Moisan, G. Mansour, A. Aurengo, F. Ménégaux, and L. Leenhardt, "Usefulness of fine needle aspiration cytology in the diagnosis of loco-regional recurrence of differentiated thyroid carcinoma," *European Journal of Surgical Oncology*, vol. 31, no. 3, pp. 288–293, 2005.

[6] G. W. Boland, M. J. Lee, P. R. Mueller, W. Mayo-Smith, S. L. Dawson, and J. F. Simeone, "Efficacy of sonographically

guided biopsy of thyroid masses and cervical lymph nodes," *American Journal of Roentgenology*, vol. 161, no. 5, pp. 1053–1056, 1993.

[7] C. L. H. Snozek, E. P. Chambers, C. C. Reading et al., "Serum thyroglobulin, high-resolution ultrasound, and lymph node thyroglobulin in diagnosis of differentiated thyroid carcinoma nodal metastases," *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 11, pp. 4278–4281, 2007.

[8] S. J. Jeon, E. Kim, J. S. Park et al., "Diagnostic benefit of thyroglobulin measurement in fine-needle aspiration for diagnosing metastatic cervical lymph nodes from papillary thyroid cancer: correlations with US features," *Korean Journal of Radiology*, vol. 10, no. 2, pp. 106–111, 2009.

[9] M. J. Kim, E. K. Kim, B. M. Kim et al., "Thyroglobulin measurement in fine-needle aspirate washouts: the criteria for neck node dissection for patients with thyroid cancer," *Clinical Endocrinology*, vol. 70, no. 1, pp. 145–151, 2009.

[10] T. Uruno, A. Miyauchi, K. Shimizu et al., "Usefulness of thyroglobulin measurement in fine-needle aspiration biopsy specimens for diagnosing cervical lymph node metastasis in patients with papillary thyroid cancer," *World Journal of Surgery*, vol. 29, no. 4, pp. 483–485, 2005.

[11] Z. W. Baloch, J. E. Barroeta, J. Walsh et al., "Utility of thyroglobulin measurement in fine-needle aspiration biopsy specimens of lymph nodes in the diagnosis of recurrent thyroid carcinoma," *CytoJournal*, vol. 5, article 1, 2008.

[12] E. Sigstad, A. Heilo, E. Paus et al., "The usefulness of detecting thyroglobulin in fine-needle aspirates from patients with neck lesions using a sensitive thyroglobulin assay," *Diagnostic Cytopathology*, vol. 35, no. 12, pp. 761–767, 2007.

[13] A. L. Borel, R. Boizel, P. Faure et al., "Significance of low levels of thyroglobulin in fine needle aspirates from cervical lymph nodes of patients with a history of differentiated thyroid cancer," *European Journal of Endocrinology*, vol. 158, no. 5, pp. 691–698, 2008.

[14] N. Cunha, F. Rodrigues, F. Curado et al., "Thyroglobulin detection in fine-needle aspirates of cervical lymph nodes: a technique for the diagnosis of metastatic differentiated thyroid cancer," *European Journal of Endocrinology*, vol. 157, no. 1, pp. 101–107, 2007.

[15] A. Frasoldati, E. Toschi, M. Zini et al., "Role of thyroglobulin measurement in fine-needle aspiration biopsies of cervical lymph nodes in patients with differentiated thyroid cancer," *Thyroid*, vol. 9, no. 2, pp. 105–111, 1999.

[16] L. Giovanella, L. Ceriani, S. Suriano, and S. Crippa, "Thyroglobulin measurement on fine-needle washout fluids: influence of sample collection methods," *Diagnostic Cytopathology*, vol. 37, no. 1, pp. 42–44, 2009.

[17] F. Boi, G. Baghino, F. Atzeni, M. L. Lai, G. Faa, and S. Mariotti, "The diagnostic value for differentiated thyroid carcinoma metastases of thyroglobulin (Tg) measurement in washout fluid from fine-needle aspiration biopsy of neck lymph nodes is maintained in the presence of circulating anti-Tg antibodies," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 4, pp. 1364–1369, 2006.

[18] C. Bournaud, A. Charrié, C. Nozières et al., "Thyroglobulin measurement in fine-needle aspirates of lymph nodes in patients with differentiated thyroid cancer: a simple definition of the threshold value, with emphasis on potential pitfalls of the method," *Clinical Chemistry and Laboratory Medicine*, vol. 48, no. 8, pp. 1171–1177, 2010.

[19] T. Pisani, A. Vecchione, N. T. Sinopoli, A. Drusco, C. Valli, and M. R. Giovagnoli, "Cytological and immunocytochemical analysis of laterocervical lymph nodes in patients with previous thyroid carcinoma," *Anticancer Research*, vol. 19, no. 4, pp. 3527–3530, 1999.