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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}F 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 $\times 150$, 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 | R III 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 | R III 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 | R III 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 | R IV 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

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 | — |

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.

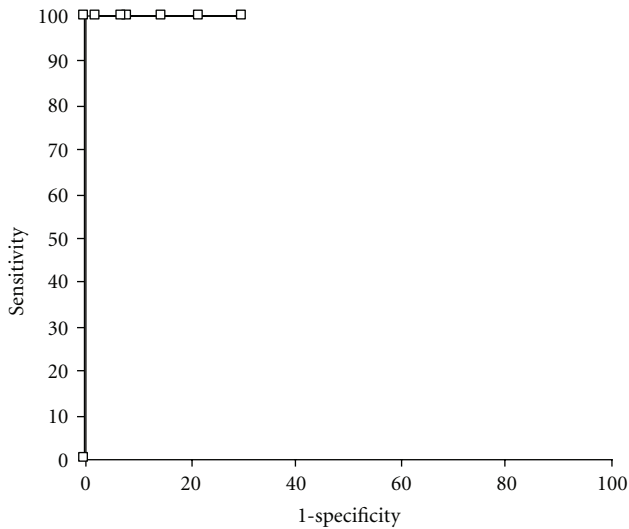


FIGURE 1: FNAC-Tg: ROC curve analysis.

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.

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