Abstract: Background. Our aim in this study was to assess the relevance of 99mTc-sestamibi (MIBI) scan in the diagnostic evaluation of thyroid nodules with nondiagnostic cytology.

Methods. In all, 74 patients with a single nodule and repeatedly nondiagnostic ultrasound-guided fine-needle aspiration cytology (US-FNAC) were enrolled. In all cases thyroid nodules were cold in 99mTc-pertechnetate (Tc) scans. Thyroid scans were also acquired 30 and 120 minutes after intravenous administration of MIBI. Nodules that concentrate MIBI were considered as positive (ie, suspicious for malignancy). Histologic findings were obtained after surgery in all patients.

Results. No differences occurred in early and late MIBI images. None of 63 patients with a negative MIBI scan had a final histologic diagnosis of malignancy (ie, no false-negative results). Two patients with a final histologic diagnosis of papillary thyroid carcinoma (PTC) and 1 with follicular thyroid carcinoma (FTC) had a positive MIBI scan. Eight patients with a final histologic diagnosis of benign lesions (3 with follicular adenomas) also had MIBI-positive scans. The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were, respectively, 100%, 88%, 89%, 27%, and 100%.

Conclusions. A negative MIBI scan in a cold nodule accurately excludes malignancy when US-FNAC is reported as nondiagnostic. This avoids the need for more invasive diagnostic procedures (ie, surgery) and positively influences the cost-effectiveness profile. A MIBI scan may be performed by acquiring images 30 minutes after tracer administration alone. Histology is still necessary to distinguish benign from malignant disease in a MIBI-positive nodule but unnecessary surgery could have been reduced from 71 to 8 cases in our series.

Keywords: differentiated thyroid carcinoma; follicular adenoma; fine-needle aspiration cytology; MIBI scan; histology

The evaluation of patients with thyroid nodules typically includes measurement of serum thyrotropin (TSH) and ultrasound-guided fine-needle aspiration cytology (US-FNAC). Patients who have a suppressed TSH are evaluated by iodine-123 or technetium-99m pertechnetate (Tc) scan. Hyperfunctioning nodules show a very low incidence of malignancy and may be treated by radioiodine or lobectomy without undergoing US-FNAC. In other cases, thyroid ultrasound is
used to select nodules; the US-FNAC is done when a hypoechoic nodule ≥10 mm showed ≥1 of these findings: irregular margins, chaotic intranodular vascular spots, round or taller than wider shape, microcalcifications. This approach has proven to be accurate for the detection of thyroid cancer. Although the majority of US-FNAC procedures are adequate for a cytologic diagnosis, 5% to 20% will be nondiagnostic. The algorithm for managing these nondiagnostic cases has not been established, although current opinion suggests that nondiagnostic aspirates should be repeated because such nodules may be malignant. When evaluating an initially nondiagnostic US-FNAC, a repeated procedure provides diagnostic specimens in 50% to 60% of cases; a third aspiration is less likely to be diagnostic and surgery is advocated in these cases. The 99mTc-sestamethoxyisobutylisonitrile (MIBI) has been reported to accumulate in differentiated thyroid carcinoma (DTC) and medullary thyroid carcinoma, respectively. The probability of thyroid malignancy increases in hypofunctioning (ie, cold) and MIBI-positive thyroid nodules, whereas nodules with absent MIBI uptake have generally proved to be benign. The aim of the present study was to prospectively evaluate the role of MIBI scan in the evaluation of thyroid nodules with nondiagnostic US-FNAC.

PATIENTS AND METHODS
Enrolled were 74 patients having a normal TSH (reference range, 0.4–4.00 ng/mL) and a single thyroid nodule fulfilling the following criteria: (1) suspicious in ultrasound examination; (2) maximum diameter of ≥10 mm; (3) having a nondiagnostic US-FNAC; and (4) hypofunctioning in a 99mTc-pertechnetate (Tc) scan.

Ultrasound Examination. In our clinic, thyroid ultrasound was performed by experienced nuclear medicine physicians and was reported in accord with the guidelines established by the American Association of Clinical Endocrinologists. Any hypoechoic nodule ≥10 mm with irregular margins, chaotic intranodular vascular spots, round or taller than wider shape, and/ or microcalcifications was considered suspicious. Patients referred from external centers were also evaluated by thyroid ultrasound and were reported to have a suspicious nodule, although diagnostic criteria were not standardized “a priori,” and diagnostic ultrasound examination was not repeated before US-FNAC.

US-FNAC. In all, 445 US-FNAC procedures were done in our clinic between January 2007 and December 2008. A total of 326 patients were first examined in our center: 25 (8%) had nondiagnostic results and thus US-FNAC was repeated. Additionally, US-FNAC was done in 119 patients referred from external centers after 1 (n = 85) or 2 (n = 34) nondiagnostic procedures. Globally, 144 patients repeated US-FNAC after nondiagnostic procedures. The US-FNAC procedures were performed on patients with the neck hyperextended. The needle (23–25 G) was inserted obliquely within the transducer plane of view, and was 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 a Cameco syringe holder (Belpro Medical, Anjou, Quebec, Canada). Two to 4 separate passes were performed for each nodule. 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, Papnicolaou-stained (Sigma-Aldrich, St. Louis, MO) to identify cellular details. All samples were evaluated by the same experienced cytopathologist, blinded to ultimate histologic diagnosis, and reported in accord with British Thyroid Association guidelines: Thy1—nondiagnostic; Thy2—benign; Thy3—indeterminate; Thy4—susicious; Thy5—carcinoma. A sample containing <6 groups of ≥10 cells each or with technical artifacts was considered nondiagnostic (Thy1). Among 144 patients, 74 still had a Thy1 classification in repeated US-FNAC and were enrolled in the present study (56 women, 18 men; mean age, 42.7 ± 12.96 years; range, 17–76).

Thyroid Scans. A thyroid scan was first obtained after intravenous (IV) administration of 74 MBq of 99mTc-pertechnetate to rule out patients with hyperfunctioning (ie, hot) nodules. Subsequently, MIBI scans were obtained 30 and 120 minutes after IV administration of 370 MBq of 99mTc-MIBI (Cardiolite, Bristol-Meyers-Squibb, North Billerica, MA). All scans were obtained in the anterior projection of the neck with a gamma-camera (E-Cam, Siemens Electronics, Erlangen, Germany) equipped with an
ultra-high resolution, parallel-hole, low-energy collimator. Images were obtained in a 128 × 128 matrix using a digital zoom of 2 (pixel dimension, 2.4 mm). The acquisition time was set to 600 seconds with a 20% window centered at 140 keV in all cases. A scan was reported as negative when the thyroid nodule showed no MIBI uptake (ie, MIBI uptake ≤99mTc-pertechnetate uptake). A positive MIBI scan was reported when the nodule showed MIBI uptake (ie, any MIBI uptake >99mTc-pertechnetate uptake).

**Surgery and Histologic Examination.** Lobectomy was done in all patients and final histologic diagnosis was obtained after examination of permanent sections of the surgical specimens. Tissue specimens were fixed in 10% formaldehyde, treated by conventional techniques, and imbibed in paraffin wax; 3- to 5-μm sections were then cut and stained with hematoxylin and eosin. The final histologic diagnosis served as the reference standard to establish either the presence or the absence of thyroid tumors.

**Statistics.** Statistical analysis was performed with the use of the SPSS Conjoint software (version 11; Aspire Software International, Ashburn, VA). Sensitivity, specificity, accuracy, predictive values, and likelihood ratios were calculated for each MIBI scan.

**Ethics.** Patients were informed of the diagnostic and therapeutic procedures that would be performed, which included Tc/MIBI thyroid scan and surgery and histologic analysis of the surgical specimens. Upon explanation of all diagnostic and therapeutic procedures, all patients gave written consent for all procedures, in accord with the guidelines of our Institutional Review Board and Ethic Committee.

**RESULTS**

A total of 74 patients with nondiagnostic US-FNAC procedures (Thy1) were evaluated. MIBI scan, lobectomy, and histologic analysis of the surgical specimens were performed in the specified order in all patients.

**Final Histologic Diagnosis.** Final histologic diagnosis of the surgical specimens found 3 patients (5%) with malignant lesions (2 with papillary thyroid carcinoma [PTC]; 1 with follicular thyroid carcinoma [FTC]). Among 71 patients with benign lesions 7 patients had hyperplastic goiters, 43 had colloid goiters, 3 had follicular adenoma, 15 had autoimmune thyroiditis, and 3 had subacute thyroiditis (Table 1).

**Table 1.** Final histologic diagnosis in 74 patients with thyroid nodule and nondiagnostic cytology (Thy1).

<table>
<thead>
<tr>
<th>Histologic diagnosis</th>
<th>Benign (n = 71, 95%)</th>
<th>Malignant (n = 3, 5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colloid goiter</td>
<td>43</td>
<td>—</td>
</tr>
<tr>
<td>Hyperplastic goiter</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>Follicular adenoma</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
<td>15</td>
<td>—</td>
</tr>
<tr>
<td>Subacute thyroiditis</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>—</td>
<td>1</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Nondiagnostic thyroid FNAC remains a significant problem and, despite ultrasound guidance, there is a 5% to 15% risk of initial nondiagnostic specimens. Thyroid ultrasound is widely used to select nodules for cytologic examination and has reduced the need for US-FNAC to one third of nodules. Even if ultrasound criteria were not standardized among patients referred from external centers only suspicious nodule in ultrasound were enrolled, and consequently repeated
US-FNAC cannot be ruled out by using ultrasound findings in our series. Repeated US-FNAC often provides an adequate specimen in up to 60% of patients, although management of the remaining patients is still challenging, given their risk to have thyroid malignancy.4,5 Thyroid MIBI scans have been studied by several groups searching for differences between benign and malignant hypofunctioning thyroid nodules. Both semiquantitative and visual methods proved to have a suboptimal negative predictive value (mean, 65%; range, 44% to 92%) when nodules with higher MIBI uptake than that of surrounding thyroid tissue were considered as malignant.7,9,11–17 Consequently, MIBI scans scored with these criteria are not sufficient for definitive preoperative differentiation of nodules and cannot be used to rule out surgery.18,19 Vice versa, if MIBI uptake is read as absent (ie, negative) or present (ie, positive) with respect to Tc uptake, negative studies always indicated that nodules are benign, as first shown by Hurtado-Lopez and colleagues20 in a group of 130 histologically controlled patients.

Additionally, when MIBI scans of 448 patients from 13 studies were reviewed by applying these criteria, negative scans again excluded DTC and medullary thyroid carcinoma, confirming a 100% NPV.21 Here US-FNAC was repeated in 144 patients with thyroid nodules and adequate specimens were obtained from 70 patients (48%). Seventy-four patients (52%) remained undiagnosed and were referred to surgery to obtain a definitive histologic diagnosis. Frozen-section assessment of thyroid nodules was not done because of its low accuracy in many cases (ie, follicular tumor).22 Globally, 3 (5%) thyroid carcinomas and 71 (95%) benign nodules were found. Similar data were previously reported in other series, although a higher incidence of colloid goiters (58% vs 45%) was found in our patients.3–5 Demographic differences and diagnostic criteria may account for these differences; additionally, an increase in colloid goiter occurrence (particularly in the age group >40 years) is still reported in formerly iodine-deficient areas such as Switzerland.23 Before surgery a Tc/MIBI scan was performed and scored as negative (MIBI uptake absent) or positive (MIBI uptake present) with respect to a Tc scan.20,21 By comparing Tc/MIBI scan results with definitive histologic diagnosis a 100% NPV was found, confirming data previously obtained by Hurtado-Lopez and colleagues.20 Although these authors did not select nodules by ultrasound and did not exclude those with diagnostic cytology examination, we enrolled only patients with suspicious ultrasound and Thy1 cytology to specifically evaluate the performance of MIBI scan in a high-risk group. Remarkably, a negative MIBI scan excluded thyroid carcinoma with a 100% NPV, even in this challenging clinical setting. Eight patients with benign disease had a (false) positive MIBI scan (specificity, 88%). On the other hand, it is well known that either malignant or benign lesions might be responsible for the MIBI uptake within thyroid nodules, and consequently a positive MIBI scan should be regarded as “indeterminate.”7–9,11–19 Additionally, 3 of 8 MIBI-positive benign lesions were follicular adenomas in our series. Follicular lesions still require definitive histologic confirmation because neither ultrasound, cytology, nor frozen section are able to discriminate a benign follicular adenoma from a malignant thyroid carcinoma.1 As shown here, this is also true for MIBI scans and 1 of 4 MIBI-positive follicular lesions was a carcinoma. Interestingly, this perfectly agrees with data from Mihai and colleagues24 that found a 25% incidence of thyroid carcinoma among patients with follicular (ie, Thy3) cytology. However, nodules with follicular cytology, but hot in an iodine-123 scan or negative in a MIBI scan, always proved to be benign.18,25,26 As a consequence, even if a positive MIBI scan cannot differentiate benign and malignant follicular lesions, a negative one is more effective than other procedures in ruling out surgery.

**CONCLUSION**

In conclusion, a negative MIBI scan rules out malignancies among cold nodules with nondiagnostic cytology, thus avoiding invasive procedures...

**Table 2. Diagnostic performance of the Tc/MIBI scan.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>MIBI scan (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>63</td>
</tr>
<tr>
<td>Positive</td>
<td>11</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>88%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>89.50%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>27%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>100%</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>1.7</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0</td>
</tr>
<tr>
<td>False-positive results</td>
<td>6</td>
</tr>
<tr>
<td>False-negative results</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: Tc/MIBI, technetium-99m-2-methoxyisobutylisonitrile.
(ie, surgery). Histology is still necessary to distinguish benign from malignant diseases in a MIBI-positive nodule, although unnecessary surgery could have been reduced from 71 to 8 cases in our series. Finally, because no differences were found in MIBI images acquired 30 or 120 minutes after tracer injection, late images may be safely omitted, and examination time may be significantly shortened. Based on these results we now perform a combined $^{99m}$Tc-pertechnetate/$^{99m}$Tc-MIBI scan to evaluate all nodules with Thy1 cytology in a US-FNAC procedure (8% of cases in our center).

Patients with a negative scan are followed up periodically, whereas those with positive scans underwent immediate surgery. Even if a detailed cost analysis was not one of our primary aims, this enhanced optimization of our resources and positively influenced a cost-effectiveness profile.

Acknowledgments. The authors thank Stefano Crippa, MD (Cantonal Institute of Pathology, Locarno, Switzerland) and Diego De Palma, MD (Division of Nuclear Medicine, University Hospital, Varese, Italy) for their invaluable support and criticisms.

REFERENCES


