Human Telomerase Reverse Transcriptase Gene Expression and the Surgical Management of Suspicious Thyroid Tumors

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ABSTRACT

Purpose: Patients with a preoperative cytologic diagnosis of a suspicious thyroid nodule present a therapeutic dilemma because surgery differs for benign and malignant lesions. To address this issue, several molecular markers, including human telomerase reverse transcriptase (TERT), have been tested as markers of thyroid cancer. Because most studies select cases falling into well-defined categories to test new markers, they may overestimate their discriminatory power when applied to samples that are difficult to classify. Fine-needle aspirates (FNAs) of the thyroid with indeterminate cytology are an example of such cases.

Experimental Design: We examined whether assessing TERT mRNA by reverse transcription-PCR could have improved the surgical management in a cohort of 100 patients undergoing thyroidectomy for indeterminate FNA results.

Results: Ninety percent of 48 cancers were TERT positive, as were 35% of 52 benign lesions. When 10 cases with concomitant lymphocytic thyroiditis were excluded, the overall sensitivity of TERT was 91% (95% confidence interval, 80–98%) and specificity was 79% (64–90%). No clinical or tumor variable contributed to the predictive ability of TERT except for tumor size, which added only marginally. Basing the surgical approach on the TERT assay alone would have reduced lobectomies performed for malignant disease from 11 to 4 cases and reduced total thyroidectomies for benign lesions from 15 to 9, an overall 50% reduction in suboptimal treatment.

Conclusions: The overall performance of preoperative differential diagnosis for thyroid tumors with indeterminate FNA results can be substantially improved by the inclusion of molecular markers such as TERT.

INTRODUCTION

Because the operative management of benign and malignant thyroid tumors differs, and the clinician often cannot distinguish the two by fine-needle aspirate (FNA) cytology, the management of patients with suspicious thyroid nodules is challenging. Thyroid lobectomy is generally preferable for benign lesions and avoids lifelong substitution with thyroid hormone. Total thyroidectomy is generally indicated for malignant tumors because adjuvant radioactive iodine therapy is usually required and residual normal thyroid tissue would preclude efficient delivery to any tumor tissue (1,2). Although the cytopathologic assessment of thyroid FNAs has proven to be an excellent predictor of malignancy when the verdict is clearly benign or malignant, there remains a substantial subset of cases in which the FNA is inconclusive. These include FNAs with findings suspicious but not diagnostic of malignancy, or suggesting a follicular neoplasm, which does not distinguish benign from malignant tumors (3–7). Not only is an indeterminate FNA result uninformative in the management of suspicious thyroid nodules, but intraoperative frozen section is often unhelpful in the distinction of benign from malignant lesions as well (8–14). Therefore, surgical decisions are often based on an aggregate of other information, including age and sex of the patient, clinical presentation, size of the lesion, imaging studies, and intraoperative findings, none of which are reliable predictors of malignancy. As a consequence, other adjuncts, such as molecular markers, are needed in the preoperative distinction of these lesions (15,16).

Telomeres are hexameric nucleotide repeats located at the ends of chromosomes and are necessary for maintaining chromosomal stability and integrity (17). Telomerase is a reverse transcriptase that maintains telomere length, a prerequisite for cellular immortality (18–20). The catalytic subunit of telomerase is human telomerase reverse transcriptase (TERT; refs. 21–26). Its expression is suppressed in most normal cells but is reactivated in the majority of malignant neoplasms. We and others have documented telomerase activity and TERT gene expression in thyroid malignancy, as well as in inflammatory thyroid conditions such as lymphocytic thyroiditis, and its measurement is a potentially useful adjunct in the distinction of benign from malignant thyroid nodules when thyroiditis can be excluded as confounding factor (24–32).

It is commonly observed that promising new diagnostic tests often fail when entering more widespread use, a phenomenon we believe to be due in part to case selection (15). New assays are typically tested on well-defined diagnostic classes and not on the less-defined, harder to diagnose lesions, which
can lead to an optimistic estimate of their clinical usefulness. These new assays, however, are more likely to be used clinically for diagnostic problem cases where current diagnostic modalities are unsatisfactory. We therefore specifically focused this study on thyroid tumors that were suspicious for but not diagnostic of thyroid cancer on FNA. We also examined retrospectively how TERT gene expression results could have improved the clinical management of patients with suspicious thyroid neoplasms.

MATERIALS AND METHODS

Subjects. We selected 100 patients who underwent surgical resection for a cytologically suspicious thyroid tumor from 1991 to 2001 at the Johns Hopkins Hospital (Baltimore, MD) and the Mayo Clinic (Jacksonville, FL) for whom both the original FNA was available for review and an additional FNA or frozen tumor sample was available for RNA extraction. Medical records of confirmed cases were then reviewed for demographic data, including age, race, and gender; clinical presentation, including history of radiation exposure and symptoms; imaging studies; intraoperative findings, including frozen section results; and pathology and cytopathology reports. The original FNA was reviewed by the senior cytopathologist (D. P. C.) for confirmation of any of the following FNA diagnoses: (a) suspicious for papillary thyroid cancer; (b) suspicious for follicular variant of papillary thyroid carcinoma; (c) follicular neoplasm; (d) Hürthle cell neoplasm; and (e) suspicious for thyroid neoplasm, otherwise specified. The FNA diagnoses were categorized as showing either a follicular cytology (see FOLLICULAR FNA in Fig. 2) when the report suggested follicular or Hürthle cell tumors, or as showing a nonfollicular cytology (NONFOLLICULAR FNA) when the report indicated papillary thyroid carcinoma, follicular variant of papillary thyroid carcinoma, or thyroid neoplasm, otherwise specified. Presence or absence of lymphocytic infiltrates was scored independent of cytologic category. Specimens were collected under respective Institutional Review Board approvals.

Tissue Samples. Frozen tissue samples were used when the FNA material was unavailable (e.g., only one clinical reference slide available) or did not yield sufficient thyroid-specific mRNA. Overall, 55 assays were performed on FNA material and 45 assays on frozen tissue.

Reverse Transcription-PCR. RNA was extracted from either frozen thyroid tissue or ethanol-fixed FNA samples by use of Trizol reagent (Invitrogen Life Technologies, Inc., Carlsbad, CA) as described previously (24, 33). We reverse-transcribed 400 ng to 1 µg of total RNA in a 20-µL reaction containing 5 mmol/L MgCl₂, 50 mmol/L KCl, 10 mmol/L Tris-HCl (pH 8.3), 5 µmol/L random hexamers, 1 µmol/L deoxyribonucleoside triphosphates, 1 unit/L RNase inhibitor; and 2.5 units/L reverse transcriptase for 15 minutes at 42°C. The reaction was heat-inactivated at 95°C for 5 minutes, and then 10 µL of the reverse transcription reaction and 40 µL of PCR mixture (final concentrations, 2.5 mmol/L MgCl₂, 60 mmol/L Tris-HCl (pH 8.5), 15 mmol/L ammonium sulfate, 1 unit of Taq polymerase, and 0.2 µmol/L specific primers) were mixed and amplified with 35 cycles at 95°C for 1 minute, 60°C for 1 minute, and 72°C for 2 minutes. PCR products were electrophoresed on a 1.5% agarose gel containing ethidium bromide and then visualized on a gel imager (Bio-Rad, Hercules, CA; see Fig. 1), scoring for the presence or absence of 183-bp (TERT) and 350-bp thyroglobulin (TG) bands.

The sequences of the PCR primers for TERT were as follows: 5’-AGA GTG TCT GGA GCA AGT TGCC-3’ (forward) and 5’-CGT AGT CCA TGT TCA CAA TG-3’ (reverse; ref. 33). TG gene expression served as load control for the presence of thyroid cells, and reverse transcriptase-negative reactions served as negative control. TG was chosen because the use of β-actin or glyceraldehyde-3-phosphate dehydrogenase (GAPDH) would also reflect the number of white blood cells present in the FNA samples (34). Only samples showing evidence of TG gene expression were included in the study. The sequences of the primers for TG were as follows: 5’-TGT GAG CTG CAG AGG GAA ACG GCC-3’ (forward) and 5’-ATA CAC CTC CAT CCC CTC TGC GTC CAC ACA-3’ (reverse; ref. 34). The TERT gene expression or telomerase enzyme activity results of 58 of these cases were reported previously as part of pilot studies on the role of telomerase assays in thyroid tumors (24, 33).

Statistical Analysis. Statistical calculations were performed using the SAS system (35) or the JMP software package (SAS Institute, Cary, NC). The primary relationship under study was the association of TERT gene expression with the final histopathologic diagnosis. Cross-tabulations were analyzed using χ² or Fisher’s exact tests where appropriate (36). Logistic regression was used to assess the effects of multiple variables on
final pathology. Race was coded as Caucasian and non-Caucasian. The predictive ability of the resulting multivariate model was described with a classification table, calculated using a “bias-corrected” leave-one-out algorithm to adjust for optimism inherent in using the same data to both fit the model and predict. The “leave-one-out” algorithm, which is used in SAS, examines the prediction of a subject’s outcome probability from a logistic model that is developed without that subject in the dataset. Thus, for N subjects, N slightly different logistic models are used, each fit on N – 1 subjects, although the final reported model is fit on everyone. The logistic model was developed only to see if it could materially improve on a classification tree (Fig. 2), whose data splits (i.e., 3 cm in tumor size) were chosen a priori. Sensitivity, specificity, positive and negative predictive values, and related statistics were used to evaluate TERT predictions in all patients and the follicular FNA subset. All confidence intervals are at the 95% level.

RESULTS

Patients. The ages of the patients ranged from 12 to 79 years with a mean of 48 years. Twenty-three patients were male, and 77 were female; 80 were Caucasian, 13 were African American, 5 were Asian, and 2 were Hispanic. There were 20 patients with associated symptoms, 16 with bilateral nodules, 5 with ipsilateral multiple nodules, 5 with Graves’ disease, and 2 with a history of head-and-neck irradiation.

Pathology and Management of Thyroid Tumors. There were 48 malignant neoplasms, including 11 follicular carcinomas, 6 Hürthle cell carcinomas, 15 papillary thyroid carcinomas, and 16 follicular variant of papillary thyroid carcinomas (see Table 1). The cancers ranged in size from 1.2 to 12 cm with a median of 2.8 cm. There were 52 benign lesions, including 19 follicular adenomas, 15 Hürthle cell adenomas, 13 hyperplastic nodules, and 5 Hashimoto’s thyroiditis lesions (Table 1). These lesions ranged in size from 0.5 to 5.5 cm with a median of 2.3 cm. A total of 10 cases, including 1 cancer, showed substantial lymphocytic infiltrates consistent with Hashimoto’s thyroiditis as primary or secondary diagnosis.

Thirty-seven (77%) of 48 patients with thyroid cancer underwent total thyroidectomy, and 11 (23%) underwent thyroid lobectomy and isthmusectomy at the initial operation. Nine of these 11 patients underwent a second operation for a completion thyroidectomy once the final histopathology confirmed a malignancy. Thirty-three (64%) of 52 patients with benign lesions underwent a thyroid lobectomy and isthmusectomy, whereas 19 (37%) patients underwent a total thyroidectomy (Table 2).

Predictors of Malignancy. On the basis of the FNA, samples were initially classified into follicular (n = 68), non-follicular (n = 22), and inflammatory (n = 10) pathologic patterns. Because TERT is likely to be positive in the presence of infiltrating inflammatory cells regardless of underlying pathology, subsequent analyses considered the inflammatory group separately.

The frequencies of malignancies, according to a variety of potential clinical, tumor, and demographic risk factors overall and stratified by the initial FNA result, are shown in Table 3. Only TERT and tumor size showed univariate relationships with malignancy, with TERT being by far the most powerful predictor. TERT was a perfect predictor of malignancy in the nonfollicular group, although the small sample sizes made the confidence intervals wide [sensitivity = 100% (15 of 15; lower 95%
Subjects had malignancy (5%; 95% confidence interval, 0.1–3%). Those with tumors >3 cm and positive TERT assay had an 81% chance of malignancy (13 of 16; 95% confidence interval, 54–96%). However, those with tumors <3 cm who were TERT positive still had a 71% chance of malignancy, and TERT-negative patients with large tumors had a 33% chance (based on only nine patients).

The classification tree suggested that tumor size was not a strong enough predictor to affect surgical management after obtaining the TERT result. However, the 3-cm split was not chosen to maximize the predictive power of the combination of TERT and tumor size. To find what weighted combination of TERT and tumor size would maximize predictive power and to see whether the exact tumor size conveyed more valuable information, we used these terms in a logistic regression model along with the other clinical variables. As expected, no clinical variable statistically contributed to the prediction except for tumor size, which was marginal (P = 0.03). Even when the exact tumor size in an optimal combination with TERT was used, we could not modify the probabilities seen in Fig. 2 to a clinically relevant extent, i.e., knowing that the tumor was <2 cm in TERT-positive patients or >4 cm in TERT-negative patients would not lead to probabilities of malignancy that would change a clinical decision made on the basis of TERT alone.

Impact of TERT Results on Surgical Management. Basing the surgical decision on the TERT result alone in the 90 patients without evidence of thyroiditis would have led to a substantial reduction of both unnecessary thyroidectomies and insufficient partial resections. Of the 53 patients with benign disease, 15 had total resections, whereas only 9 would have had resections if only TERT-positive patients underwent this procedure (Table 5). Conversely, of the 47 with malignant disease, of whom 11 underwent partial resection, only 4 would have had this procedure if it had been limited to TERT-negative patients. In total, the 26 suboptimal procedures (26 of 90; 29%) would have been halved to 13 (13 of 90; 14%) if the surgical decision had been based solely on the TERT result. Interestingly, the total number of both kinds of procedures would have been almost identical under both approaches (51 total thyroidectomies with clinical decision only; 52 with TERT-based decision only); the difference is that they would have been performed on a more optimal selection of patients.

### Table 2 Summary of surgical management of suspicious thyroid tumors

<table>
<thead>
<tr>
<th>Operation</th>
<th>Malignant (n)</th>
<th>Benign (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total thyroidectomy</td>
<td>37</td>
<td>19</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>11</td>
<td>33</td>
</tr>
<tr>
<td>Lobectomy followed by completion</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

Reasons for total thyroidectomy

- Bilateral nodules: 7/9
- Dyspnea: 1/0
- FNA highly suspicious: 3/0
- Frozen section: 11/0
- Graves' disease: 2/3
- Head-and-neck irradiation: 0/2
- Intraoperative gross findings: 2/1
- Multiple ipsilateral nodules: 5/0
- Patient preference: 0/3
- Pregnancy: 1/0
- Size of lesion: 3/0
- Thyrotoxicosis: 0/1
- Unknown: 2/0

### Table 3 Frequency of malignancy according to potential risk factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Nonfollicular, % (n)</th>
<th>Follicular, % (n)</th>
<th>Inflammatory, % (n)</th>
<th>Overall, % (n)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TERT</td>
<td>Negative</td>
<td>0 (7)</td>
<td>13 (31)</td>
<td>100 (1)</td>
<td>13 (39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>100 (15)</td>
<td>76 (37)</td>
<td>0 (9)</td>
<td>70 (61)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>83 (6)</td>
<td>63 (16)</td>
<td>0 (1)</td>
<td>65 (23)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>63 (16)</td>
<td>42 (52)</td>
<td>11 (9)</td>
<td>43 (49)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;48 yrs</td>
<td>70 (10)</td>
<td>50 (34)</td>
<td>20 (5)</td>
<td>51 (49)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥48 yrs</td>
<td>67 (12)</td>
<td>44 (34)</td>
<td>0 (5)</td>
<td>45 (51)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Symptoms</td>
<td>No</td>
<td>71 (17)</td>
<td>48 (44)</td>
<td>0 (6)</td>
<td>49 (67)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>67 (3)</td>
<td>33 (15)</td>
<td>50 (2)</td>
<td>40 (20)</td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>&lt;3 cm</td>
<td>57 (14)</td>
<td>37 (43)</td>
<td>0 (9)</td>
<td>36 (66)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>≥3 cm</td>
<td>88 (8)</td>
<td>64 (25)</td>
<td>100 (1)</td>
<td>71 (34)</td>
<td></td>
</tr>
<tr>
<td>Multiple nodules</td>
<td>No</td>
<td>69 (16)</td>
<td>45 (51)</td>
<td>0 (6)</td>
<td>47 (73)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>67 (6)</td>
<td>53 (17)</td>
<td>25 (4)</td>
<td>52 (27)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>Non-Caucasian</td>
<td>83 (6)</td>
<td>45 (11)</td>
<td>33 (3)</td>
<td>55 (20)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td></td>
<td>Caucasian</td>
<td>63 (16)</td>
<td>47 (57)</td>
<td>0 (7)</td>
<td>46 (80)</td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

Although the surgical management of thyroid cancer is debated, most agree that with the exception of low-risk patients, the majority are best treated with total thyroidectomy followed by radioiodine ablation (1, 2, 37–39). The management of thyroid nodules classified as suspicious on FNA, however, presents a dilemma because at the time of surgery the best management is often unclear. Some patients with malignant neoplasms may therefore be treated in a less than ideal fashion with lobectomy and isthmusectomy and later require a completion thyroidectomy with its additional surgical risks. Conversely, some patients with benign lesions may undergo total thyroidectomy even in the absence of compelling reasons and will then require lifelong thyroid hormone replacement.

In this study, 11 of 48 patients with malignant neoplasms were treated initially with lobectomy and isthmusectomy, and 9 of these underwent a second operation for completion thyroidectomy. Nineteen patients who underwent total thyroidectomy for a variety of reasons (see Table 2) had benign disease on final pathology. Whether the surgeon performed a thyroid lobectomy and isthmusectomy or a total thyroidectomy was dependent on the multidisciplinary approach, gross findings, and frozen section results. A sonographic estimate of nodule size, e.g., could be combined to improve the surgical management of these patients. Given the relatively small number of cases in some of the decision branches, this represents a rough guide only, but it highlights some circumstances in which the treatment option could be made with increased confidence, e.g., a small tumor with a negative TERT result.

The perceived relative seriousness of an unnecessary thyroidectomy versus an inadequate subtotal procedure would be critical in choosing an optimal decision rule. Because patients are likely to have different views of those consequences, there is probably not a single rule that can be applied to all, but the numbers here can help provide input into that decision. For the

### Table 4  TERT gene expression as predictor of thyroid cancer on final histopathology

<table>
<thead>
<tr>
<th>Decision strategy</th>
<th>Surgery</th>
<th>Pathology (n)</th>
<th>Cases with suboptimal outcomes (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Malignant</td>
<td>Benign</td>
</tr>
<tr>
<td>TERT</td>
<td>Total thyroidectomy (n = 51)</td>
<td>36</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Partial thyroidectomy (n = 38)</td>
<td>4</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Total thyroidectomy (n = 52)</td>
<td>43</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Partial thyroidectomy (n = 39)</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Total thyroidectomy (n = 51)</td>
<td>36</td>
<td>15</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

(27, 41, 42). Another theoretical explanation for the false-positive results is the possibility that some follicular adenomas may actually be premalignant without showing pathologic evidence of invasion and therefore have a tendency to express TERT (27, 43).

Notably, when the FNA report was suspicious for a non-follicular neoplasm, TERT results performed very well and correctly classified all tumors when samples with lymphocytic infiltration were excluded (Table 4). On the other hand, when the FNA was suggestive of a follicular neoplasm, TERT was more useful as a negative predictor (87%; Table 4), particularly when the tumor was less than 3.0 cm in size (see Fig. 2). Taking only the TERT result into account would have led to 13 cases of suboptimal surgical management, defined as lobectomy for cancer and thyroidectomy for benign disease, compared with the 26 observed in our cohort. This is obviously a simplification because there are reasons other than malignancy to opt for a thyroidectomy (see Table 2), but it illustrates how additional data might improve therapeutic management.

The decision tree in Fig. 2 shows an example of how the combination of cytology, molecular assay, and a clinical test result, e.g., a sonographic estimate of nodule size, could be combined to improve the surgical management of these patients. Given the relatively small number of cases in some of the decision branches, this represents a rough guide only, but it highlights some circumstances in which the treatment option could be made with increased confidence, e.g., a small tumor with a negative TERT result.

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### Table 5  Comparison of clinical decision strategy versus hypothetical TERT-based strategy

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<td></td>
<td>43</td>
<td>9</td>
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</tbody>
</table>
decision to perform a thyroidectomy, using TERT alone seems to correspond to a reasonable balance, although tumor size might be relevant in those cases in which there was a great premium placed on avoiding one of the two errors. The exact role of tumor size in the clinical decision might still be regarded as an open question.

All of these numbers, however, including the perfect prediction seen in the nonfollicular group, are based on relatively small numbers of patients, and the confidence intervals on almost all of these predictions are quite wide. The guide suggested here must therefore be regarded as preliminary, needing confirmation in larger cohorts of patients.

In conclusion, TERT gene expression results are potentially useful in that, in our series, TERT had higher sensitivity and specificity than the de facto clinical criteria, although the surgical decisions may have been based on considerations other than just the probability of malignancy. When samples with lymphocytic infiltration were excluded, TERT was an excellent predictor of malignancy for nonfollicular cytologies, with the caveat that our confidence intervals are wide in this subset. The differential diagnosis of such cases can now also be aided by detecting the presence of BRAF mutations, which are present in a significant proportion of papillary thyroid carcinomas (44, 45). When the FNA suggests a follicular neoplasm, the TERT result had a false-positive rate or 24% in this series, although it increases the likelihood of malignancy considerably, and the estimated tumor size may be useful in further guiding therapeutic choices. Clearly, additional markers of malignant follicular neoplasms are needed to improve the surgical management of the patient who presents with a suspicious thyroid lesion, but this study shows that even the use of this one marker could substantially reduce the number of suboptimal procedures currently performed on the basis of informal clinical criteria.

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