BENEFIT OF MEASURING BASAL SERUM CALCITONIN TO DETECT MEDULLARY THYROID CARCINOMA IN A DANISH POPULATION WITH A HIGH PREVALENCE OF THYROID NODULES

Martin Hasselgren, MD,1 Laszlo Hegeduš, MD, DMSc,1 Christian Godballe, MD, PhD,2 Steen Joop Bonnema, MD, PhD1

1Department of Endocrinology and Metabolism, Odense University Hospital, Odense, Denmark. E-mail: steen.bonnema@dadlnet.dk
2Department of Oto-Rhino-Laryngology, Odense University Hospital, Odense, Denmark

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Abstract: Background. Routine measurement of serum calcitonin to detect medullary thyroid carcinoma (MTC) continues to be fiercely debated, although less attention has been paid to the positive predictive value (PPV) of this method. Methods. We collected data from 959 patients with non-toxic nodular goiter; thyroidectomy was performed in 307 of these patients. Results. Thirty-nine patients had elevated serum calcitonin; 6 of these patients had MTC detected by the initial diagnostic setup. No additional patient in the cohort was registered in the Danish Thyroid Cancer Database, reflecting that all patients with MTC were classified correctly initially. The sensitivity of serum calcitonin for detection of MTC was 100%, the specificity was 95.3%, the positive predictive value was 15.4%, and the negative predictive value was 100%.

Conclusion. Serum calcitonin has high sensitivity and specificity for detection of MTC. The low PPV might lead to unnecessary thyroid surgery. Thus, the result of serum calcitonin measurement should always be interpreted in the context of other clinical variables.

Keywords: calcitonin; medullary thyroid carcinoma; nodular goiter; sensitivity; screening

Medullary thyroid carcinoma (MTC), accounting for 5% to 10% of all thyroid malignancies,1–3 is derived from the calcitonin secreting parafollicular C-cells of the thyroid. MTC has a rather poor prognosis, which in turn is intimately related to the stage of the tumor.4–8 Hence, early detection of MTC among patients with nodular goiter is of obvious importance for the prognosis. MTC is either sporadic (75%) or hereditary (25%).1,6,9 The better prognosis of the latter is attributed to early genetic screening of the RET (“rearranged during transfection”) proto-oncogene involved, enabling timely detection of MTC and subsequent early thyroidectomy.3,5,8

Routine measurement of basal serum serum calcitonin in the investigation of nontoxic thyroid nodular disease has been investigated and
frequently discussed during recent years. Serum calcitonin correlates well with the tumor burden in patients with MTC and should be part of the follow-up strategy. There are advantages and disadvantages of routine use of serum calcitonin in the early diagnosis of MTC. An elevated serum calcitonin provides early detection of some cases of MTC, allows subsequent early thyroidectomy, and leads to a better prognosis. However, an elevated serum calcitonin, not associated with MTC, can be seen in C-cell hyperplasia, Hashimoto’s thyroiditis, impaired renal function, small cell lung carcinoma, and some other rare neuroendocrine tumors. Many authors recommend measurement of serum calcitonin routinely in patients referred with nodular goiter, whereas others are more reluctant to follow such a strategy. The controversy is reflected in the existing guidelines. European guidelines recommend serum calcitonin screening, whereas American guidelines cannot advise either for or against.

Most previous studies were performed in patients living in an iodine-sufficient area. In regions with a suboptimal dietary intake of iodine, such as Denmark, benign thyroid nodules are very prevalent, and the role of serum calcitonin measurement in the diagnostic setup is less clear. The aim of our study was to estimate the validity of serum calcitonin for detection of MTC in a consecutive population of patients with nontoxic nodular goiter, living in a mild to moderate iodine-deficient area. Any misclassification at the initial evaluation was ruled out by linkage to our nationwide thyroid cancer database, in which all patients diagnosed with a malignant thyroid disorder are registered.

MATERIALS AND METHODS

Study Design and Study Population. We conducted a retrospective study, based on data from consecutive patients with nontoxic nodular goiter, examined at our secondary/tertiary referral center from 1996 to 2003 inclusive. Patient files from 1060 patients were reviewed; 101 of these were excluded because of missing data or wrongly registered diagnosis. Consequently, 959 patients, all referred with nontoxic nodular goiter, were included. Patient data on clinical findings, cytology, histopathology, biochemistry, and treatment were collected from microfilmed patient files and were registered in a database. Serum calcitonin was measured in 702 of the patients. A flow diagram of the study population is presented in Figure 1.

Diagnostic Setup and Indication for Surgery. The diagnostic setup included clinical evaluation, thyroid scintigraphy and sonography, fine-needle aspiration biopsy (FNAB), thyroid function tests, antithyroid antibodies, and serum calcitonin measurement. Not all patients underwent FNAB and serum calcitonin measurement. Thus, patients with multinodular goiter without a dominant or ultrasonically suspicious tumor most frequently were not biopsied. In addition, serum calcitonin was not measured consistently in all patients because the inclusion of this test to some extent relied on the clinical judgment of the physician.

Ultrasound-guided fine-needle aspiration biopsy (US-FNAB) was performed in dominant and/or scintigraphically cold nodules. Indication for surgery was based on the composition of the following variables: (1) clinical evaluation
including age, comorbidity, thyroid size, suspicion of malignancy; (2) sonographic appearance; (3) result of FNAB; (4) result of serum calcitonin measurement (cases with a borderline increased level might be treated nonsurgically, based on the other findings); and (5) patient preference.

The diagnoses of both cytologic and histologic specimens were established by experienced pathologists at the Department of Pathology, Odense University Hospital. RET proto-oncogene analysis was performed in patients with histopathologically confirmed MTC.

The postoperative histopathologic diagnosis was considered the true diagnosis. However, congruent with other studies, only a fraction ($n = 307, 32.0\%$) of our study population underwent thyroidectomy. To ensure long-term follow-up of the study population, we performed cross-linkage with the Danish Thyroid Cancer Database (DATHYRCA). All patients who have surgery in Denmark and have a histologically confirmed diagnosis of thyroid malignancy are included in this database, starting in 1996. Thus, any patient with MTC not initially diagnosed at our center would eventually, as the disease progresses, become registered in DATHYRCA, irrespective of whether followed in our clinic. In this way, the true number of MTC cases in the study population was established.

### Statistical Analysis.
All statistical analyses were performed using SPSS 10.0 (SPSS Inc, Chicago, IL). Results were presented as frequencies, medians, and in cross tables. The essential analyses were sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of serum calcitonin for detection of MTC. Three different serum calcitonin cutoff levels ($>0.10, >0.20, \text{and} >0.50 \mu g/L$) were assessed at the most suitable level in this context.

### RESULTS
The total number of patients was 959: 811 female patients (84.6\%) and 148 male patients (15.4\%). The median age at examination was 49 years (13–93 years). The distribution of the final diagnoses is presented in Table 1: 307 patients were treated surgically (32.0\%), 84 (27.4\%) of whom were suspected of thyroid malignancy. Twenty-five patients (2.6\%, of whom 84\% were women) had thyroid malignancy confirmed by a histopathologic examination of the surgical specimen.

Serum calcitonin was measured in 702 patients (73.2\%): 39 patients (33 women and 6
men) had elevated serum calcitonin (>0.10 μg/L), ranging from 0.11 to 34 μg/L. Sixteen of the patients (41.0%) with elevated serum calcitonin, ranging from 0.11 to 1.0 μg/L, were not treated surgically; 67.5% of the patients with multinodular goiter without a dominant nodule were screened with serum calcitonin, compared with 79.2% of the patients with a solitary nodule or a cyst (p < .001, Fisher’s exact test).

Six patients (5 women and 1 man; median age, 42 years; range, 22–73 years) had histopathologically confirmed MTC (Table 2), corresponding to a prevalence of 0.63% (24% of all thyroid malignancies). All 6 patients had elevated serum calcitonin and negative analysis for the RET proto-oncogene indicating sporadic MTC. Two of the 6 patients with MTC had a false-negative (benign) cytology by FNAB.

By the end of 2006, after a median follow-up period of 7 years (range, 3–10 years), no additional patient from the study population was registered in DATHYRCA. Importantly, this includes those in whom serum calcitonin was not measured at the initial examination. Thus, with great probability, no patient with MTC seems to have been overlooked at the initial evaluation.

Using a cutoff level of 0.10 μg/L, the sensitivity of serum calcitonin for detection of MTC was 100%, whereas the specificity was 95.3%, the PPV was 15.4%, and the NPV was 100%. The sensitivity, specificity, PPV, and NPV using different serum calcitonin cutoff values are presented in Table 3.

**DISCUSSION**

The vast majority of previous studies support the use of serum calcitonin screening in patients with nontoxic nodular goiter, referring to the high sensitivity and specificity of the method.16–19,21,22,24–28,30 Our study is the first of its kind performed in Denmark, a region with mild to moderate iodine deficiency. MTC is a rare disease that is no more prevalent in Denmark than it is in other parts of Europe. However, thyroid nodules and goiter are very common in Denmark and <5% of patients referred with nodular goiter harbor thyroid malignancy, and only 0.5% to 1% have MTC.1,16,21 This makes it very difficult for the clinician to diagnose the few patients with MTC, comparing the situation with “finding a needle in the haystack.” Although serum calcitonin measurement shows a high sensitivity and specificity, some false-positive results will nonetheless occur as a result of the very low prevalence of the disease. Thus, the PPV becomes very important in a clinical setting.

In our study, the PPV was only 15.4% for a serum calcitonin cutoff value of >0.10 μg/L, whereas the sensitivity was 100%, the specificity was 95.3%, and the NPV was 100%. Only few previous studies focused on PPV. Niccoli et al24 found a PPV of 41.1%, higher than that in the present study, probably because only patients treated surgically were included in that study. Had we used >0.20 μg/L as a cutoff value, the PPV would have increased to 27.8%, but at the expense of a decreased sensitivity. With an even

<p>| Table 2. Clinical features of the patients diagnosed with medullary thyroid carcinoma. |
|---------------------------------|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Serum calcitonin, μg/L</th>
<th>Cytology, FNAB</th>
<th>Histology</th>
<th>Thyroid scintigraphy</th>
<th>Sonography</th>
<th>Nodule diameter, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>F</td>
<td>34.00</td>
<td>Benign</td>
<td>MTC#</td>
<td>Solitary hypofunctioning nodule</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>F</td>
<td>0.47</td>
<td>Malignant</td>
<td>MTC#</td>
<td>Solitary hypofunctioning nodule</td>
<td>Dominant nodule</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>M</td>
<td>0.15</td>
<td>Malignant</td>
<td>MTC#,*</td>
<td>—</td>
<td>Dominant nodule</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>F</td>
<td>0.38</td>
<td>Malignant</td>
<td>MTC</td>
<td>Solitary hypofunctioning nodule</td>
<td>Dominant nodule</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>F</td>
<td>23.00</td>
<td>Malignant</td>
<td>MTC</td>
<td>Solitary hypofunctioning nodule</td>
<td>Solitary cyst-adenoma</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>F</td>
<td>0.41</td>
<td>Benign</td>
<td>MTC</td>
<td>Solitary hypofunctioning nodule</td>
<td>Dominant cyst-adenoma</td>
<td>24</td>
</tr>
</tbody>
</table>

Abbreviations: FNAB, fine-needle aspiration biopsy; F, female; M, male; MTC, medullary thyroid carcinoma.

#Metastases at diagnosis.

*Low grade of differentiation.

<p>| Table 3. Sensitivity, specificity, PPV, and NPV at different basal serum calcitonin cutoff levels. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Serum calcitonin, μg/L</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.10</td>
<td>100.0</td>
<td>95.3</td>
<td>15.4</td>
<td>100.0</td>
</tr>
<tr>
<td>&gt;0.20</td>
<td>83.3</td>
<td>98.1</td>
<td>27.8</td>
<td>99.9</td>
</tr>
<tr>
<td>&gt;0.50</td>
<td>33.3</td>
<td>99.3</td>
<td>28.6</td>
<td>99.4</td>
</tr>
</tbody>
</table>

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.
higher cutoff value (>0.50 μg/L) the PPV would be virtually unaffected, whereas the sensitivity would have declined to 33%. In the latter situation, 4 of 6 patients with MTC would not have been correctly diagnosed, if based only on serum calcitonin.

A low PPV has the consequence that some patients are referred inappropriately to thyroidectomy. On the other hand, having the knowledge that a significant fraction of the serum calcitonin results may be falsely elevated, the clinician might be tempted to disregard a marginally increased serum calcitonin—a potentially wrong decision. In our study, 41% of the patients with a borderline increased serum calcitonin were not treated surgically because the indication for surgery was based on other clinical and paraclinical variables, and not exclusively on the result of the serum calcitonin. A patient with nodular goiter, few symptoms, no clinical suspicion of malignancy, a benign FNAB, and only a marginally elevated serum calcitonin may likely be treated conservatively at our center. We are very confident that none of our patients with MTC was overlooked at the initial investigation, given that we cross-checked our data with our nationwide database, which includes all cases with thyroid malignancy diagnosed at Danish hospitals. A patient with MTC not diagnosed initially at our center would eventually have been admitted to surgery (or autopsy) as the disease progresses. In most previous studies only a fraction of patients underwent thyroidectomy, resulting in a histologic confirmation of the diagnosis. The true status of most patients in those studies was thus to some extent uncertain—a problem we believe to be excluded with our design. Although we cannot exclude that some patients still have undiagnosed MTC, the median follow-up period of 7 years certainly limits the likelihood.

MTC is found in 0.5% to 1.4% of patients with a nodular goiter,11 and the prevalence of MTC of 0.6% in the present study is thus well in accord with previous series. However, it is important to realize that any selection bias in the study population—for example, by including patients with a diffuse goiter—will have a negative impact on the PPV. Increasing the PPV could be done by restricting serum calcitonin measurement to a subgroup of patients known to have a higher prevalence of MTC. Confining serum calcitonin screening to patients >40 years old was suggested by Papi et al,32 demonstrating hypercalcitonemia in 23 of 1425 patients, 9 of whom, all >40 years, had MTC. In our population, in which 3 of 6 patients with MTC were younger than 40 years, application of such an age limit would clearly not be advisable. Nevertheless, we consequently did not measure serum calcitonin in all patients included in our study. Serum calcitonin measurement was omitted in a fraction of patients with a very low a priori risk of having thyroid cancer. The fact that no patient with thyroid malignancy seems to have been overlooked supports our diagnostic setup. At our center, clinicians were more prone to measure serum calcitonin in patients with a solitary nodule than in patients with a multinodular goiter. Indeed, all our patients with MTC suffered from a solitary lesion or a dominant nodule. Therefore, restricting serum calcitonin screening to such patients could be contemplated. Nevertheless, more studies including larger cohorts are needed before any final conclusion can be drawn.

To improve the PPV of serum calcitonin measurement, pentagastrin stimulation is performed at some centers. Costante et al22 included 5817 patients with thyroid nodules and found a PPV of 23.1% with determination of unstimulated serum calcitonin (cutoff level, 20 pg/mL). Using pentagastrin stimulated serum calcitonin in patients with elevated basal serum calcitonin increased the PPV to 40%, when a stimulated serum calcitonin cutoff level of 100 pg/mL was applied. Still, the presence of C-cell hyperplasia in a number of patients led to falsely elevated results and a PPV well below 100%. Furthermore, serum calcitonin measurement after pentagastrin stimulation is cumbersome and may not be worthwhile in a routine setting, compared with a basal serum calcitonin measurement. Our present study, in which pentagastrin testing was not included, supports this view.

Analysis of the survival in MTC was performed by Elisei et al16 in 2004. They compared the outcome in a historical group of 45 patients diagnosed before the introduction of serum calcitonin screening (1970–1990) with the outcome in 44 MTC patients diagnosed with the routine use of serum calcitonin (1991–1998). Ten years after diagnosis, only 43.7% of the patients who were not serum calcitonin screened were alive compared with 86.8% in the serum calcitonin screened group, suggesting a positive impact of routine serum calcitonin measurement on survival rates in MTC. However, the fact that the 2
groups were diagnosed during different time periods raises the questions of how much of this difference can be attributed to the CT screening alone, and to what extent other factors are involved, such as the availability of other investigations and surgical techniques.

Normal or only marginally elevated serum calcitonin values occasionally occur if the MTC has a very low grade of differentiation. This will adversely affect the NPV. In our study 1 patient had MTC with low grade of differentiation, and in this individual the serum calcitonin level was the lowest among the 6 patients diagnosed with MTC. The extent of this problem and whether serum calcitonin measurement after pentagastrin stimulation improves the diagnosis of such low-grade differentiated MTC remains to be clarified.

CONCLUSION
In conclusion, our study confirms that measurement of serum calcitonin is useful in the initial investigation of patients with thyroid nodules, and also in a region with borderline iodine deficiency. However, the results of serum calcitonin measurement should always be interpreted in the context of other important variables. The sensitivity of serum calcitonin for detection of MTC is substantially higher than that of FNAB. Nevertheless, a low PPV, reflecting many false-positive results, is a disadvantage and might lead to unnecessary surgery and complications in some patients. Future studies focusing on issues such as cost–benefit and cost-effectiveness analyses and quality of life are needed. In favor of screening, a recent American study argued that the benefit from serum calcitonin screening in thyroid nodular disease is comparable to that of mammography screening.

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REFERENCES


29. Hodak SP, Burman KD. The calcitonin conundrum—is it time for routine measurement of serum calcitonin in patients with thyroid nodules? J Clin Endocrinol Metab 2004;89:511–514.


