Early Diagnosis of Medullary Thyroid Carcinoma: Is Systematic Calcitonin Screening Appropriate in Patients with Nodular Thyroid Disease?

GIUSEPPE COSTANTE, SEBASTIANO FILETTI

Dipartimento di Medicina Sperimentale e Clinica, University Magna Græcia, Catanzaro and Dipartimento di Medicina Interna, University La Sapienza, Rome, Italy

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Compare guideline recommendations regarding the use of routine calcitonin screening to diagnose medullary thyroid carcinoma patients with clinical risk factors.
2. Select patients for whom calcitonin screening for medullary thyroid carcinoma may be an appropriate diagnostic approach.

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ABSTRACT

Because of its poor prognosis and high mortality rate, early diagnosis of medullary thyroid carcinoma (MTC) is a challenge. For almost two decades, routine serum calcitonin (CT) measurement has been used as a tool for early MTC diagnosis, with conflicting results. In 2006, the European Thyroid Association (ETA) recommended serum CT measurement in the initial workup of thyroid nodules, whereas the American Thyroid Association (ATA) declined to recommend for or against this approach.

In late 2009, the revised ATA guidelines were published, and in June 2010 the ETA released new guidelines for the diagnosis and management of thyroid nodules that had been drafted in collaboration with the American Association of Clinical Endocrinologists and with the Associazione Medici Endocrinologi, and the picture became even more complex. The ATA still takes no stand for or against screening but acknowledges that, if testing is done, a CT value >100 pg/ml should be considered suspicious and an indication for treatment. As

Correspondence: Giuseppe Costante, M.D., Dipartimento di Medicina Sperimentale e Clinica, University of Catanzaro Magna Græcia, Viale Europa, Località Germaneto, 88100 Catanzaro, Italy. Telephone: 39-0961-364-7390; Fax: 39-0961-369-4073; e-mail: costante@unicz.it Received October 13, 2010; accepted for publication December 7, 2010; first published online in *The Oncologist Express* on January 6, 2011. ©AlphaMed Press 1083-7159/2011/\$30.00/0 doi: 10.1634/theoncologist.2010-0344

for the ETA, it seems to have taken a step back from its 2006 position, and it now advocates CT screening only in the presence of clinical risk factors. These new positions are more cautious and less straightforward because prospective, randomized, large-scale, long-term

trial data are lacking. Are such studies feasible? Can they solve the CT dilemma? In the absence of adequate evidence, selective aggressive case finding should be pursued to improve MTC prognosis. *The Oncologist* 2011;16:49–52

Medullary thyroid carcinoma (MTC) is derived from the calcitonin (CT)-secreting parafollicular cells (C cells) of the thyroid and represents 4%–10% of all thyroid malignancies [1]. Approximately 25% of all MTCs are hereditary forms that can be detected by molecular screening for *RET* proto-oncogene mutations [1–3]. In families known to harbor a *RET* mutation, carriers can be identified before disease onset and offered preventive care [1]. Three in four MTCs are sporadic tumors [1], which usually present as palpable thyroid nodules. Although several clinical features can raise the suspicion of MTC, diagnosis of these tumors is often a challenge. In fact, in most series, the sensitivity of fine-needle aspiration cytology for presurgical MTC diagnosis is around 40%–50% [4], substantially lower than that reported for thyroid malignancies arising from follicular cells.

When patients present with lymph node involvement or distant metastases, the outcome is usually poor [1], so early diagnosis and radical surgical treatment are the main means for reducing MTC-related morbidity and mortality. The fact that virtually all MTCs are associated with elevated circulating levels of CT at the time of diagnosis led several groups to suggest that routine measurement of serum CT in patients with nodular thyroid disease might improve the early diagnosis of MTC (references in [4]). In 2006, the European Thyroid Association (ETA) published a consensus statement [5] recommending this approach, but in guidelines issued in roughly the same period [6], the American Thyroid Association (ATA) declined to take a stand on this issue, emphasizing instead unresolved questions related to cost/effectiveness. The ATA noted that, in most studies, screening accuracy required confirmation of basal CT elevations with additional assays of pentagastrin-stimulated CT—a problem largely confined to the U.S., where pentagastrin was no longer available. On the basis of the available evidence, several other aspects of the issue also appeared controversial at that time. First, the studies that had been published had used different CT assays that varied widely in sensitivity [4], hindering reliable comparison of the results and making it impossible to draw meaningful conclusions on the diagnostic accuracy of the approach. Furthermore, the studies varied widely in

terms of their false-positivity rates [4], basal CT thresholds that required confirmatory poststimulation testing [4], and cutoffs for distinguishing benign and malignant disease. The latter issue is further complicated by the fact that, although C-cell hyperplasia (CCH) is undeniably a precancerous lesion in familial settings [1, 7], there is no clearcut evidence that sporadic CCH progresses to MTC.

Three years later, in 2009, the ATA issued specific guidelines for MTC management [7] and revised their recommendations for thyroid nodules and differentiated thyroid cancer [8]. Shortly thereafter, the ETA also released updated guidelines [9], which had been drawn up in collaboration with the American Association of Clinical Endocrinologists (AACE) and the Italian Associazione Medici Endocrinologi (AME). Once again, the ATA declined to take a stand for or against CT screening in patients with thyroid nodules but specified that, if testing was undertaken, a basal CT value >100 pg/ml should be regarded as suspicious, prompting further evaluation and appropriate treatment [8]. As for the ETA, its straightforward support of screening in 2006 was attenuated in the new AACE–AME–ETA recommendations, which call for mandatory measurement of CT levels only when MTC is specifically suspected and/or there is a family history of MTC [9].

In short, the issue seemed to have become paradoxically less clear. To some extent, the distance between the ATA and AACE–AME–ETA positions had shrunk: both groups acknowledged that CT assays may be of help in the preoperative diagnosis of MTC. However, the task forces behind these guidelines obviously felt that the available evidence was still not strong enough to support *systematic* CT screening in all patients with thyroid nodules. An effective diagnostic screening procedure should meet certain criteria: it should be high in sensitivity as well as specificity. It should also allow early detection of the disease that translates into lower morbidity and mortality rates. And last but not least, it needs to be cost-effective. Based on the evidence at hand, routine CT screening for MTC certainly did not meet all these criteria.

However, several enlightening reports appeared on this subject between 2006 and 2009 [10–15]. They confirmed, first of all, that CT screening in patients with nodular thy-

roid disease is a highly sensitive tool for the presurgical diagnosis of MTC [10–12], far more sensitive than cytology [10]. Second, they strengthened the claim that CT screening allows earlier diagnosis of MTC than the classical approach [15], with data showing higher rates of tumors diagnosed during the pT1 stage [12] and better postsurgical outcomes in settings where CT is routinely measured (particularly in patients with basal CT levels <100 pg/ml) [10, 12]. In addition, two recent independent reports—one from Europe and the other from the U.S.—suggested that CT screening is actually cost-effective [13, 14], but unfortunately the conclusions in both cases were based on an analysis of hypothetical data that may or may not reflect real-life scenarios.

Other issues have also remained unresolved. Even with screening, for example, a substantial proportion of MTCs are still being diagnosed late, when surgical eradication is no longer possible [10], and a significant number of the MTCs are incidentally discovered microcarcinomas [10–12], which have never been shown conclusively to progress toward more advanced disease. Finally, even with the most recent ultrasensitive assays, false-positivity rates for basal CT testing remain high (and positive predictive values [PPVs] remain low) [10–12]. In clinical epidemiology, the prevalence of the disease in the study population is generally regarded as the major determinant of the PPV. For an uncommon disease like MTC, the majority of positive results in screening will inevitably be false positives, no matter how sensitive and specific the assay. Basal CT assays alone will not be sufficient: a two-level approach that includes stimulated CT measurement is needed to improve the PPV. It is important to note, at this point, that the limited availability of pentagastrin should no longer be considered an obstacle to this approach because recent studies have convincingly demonstrated that CT stimulation can be achieved equally well with calcium injections [16].

Whether routine CT screening should or should not be adopted and its impact on MTC-related morbidity and mortality are questions that can be answered only in large, long-term, prospective, randomized multicenter initiatives, with standard enrollment criteria, CT assay techniques, and breakpoints for interpreting the results. An effort of this

type might finally provide answers to the questions that continue to be debated in connection with MTC diagnosis and outcome.

In the meantime, how can our currently available knowledge be translated into clinical practice? The only reasonable approach is selective aggressive case finding. Attention should be focused on clinical risk factors for MTC. In affected families with documented *RET* mutations, basal and stimulated CT assays play pivotal roles in decisions regarding the timing of prophylactic surgery for mutation carriers (whereas individuals who test negative for the mutation need no further workup or surveillance) [7]. Periodic CT assays are also indicated for relatives of MTC patients belonging to the rare kindreds that are negative for *RET* mutations but still meet the clinical criteria for multiple endocrine neoplasia (MEN) 2A or MEN 2B [7]. As for the relatives of patients whose MTCs are not associated with *RET* mutations and clearly sporadic, their risk for MTC is <1% [17], so they do not require CT surveillance [7]. More aggressive workup is needed, however, when thyroid nodules present clinical features that are suggestive of MTC (location in the upper third of a lobe, pain on palpation, hypoechogenicity with microcalcifications, lymph node abnormalities, and association with flushing and/or diarrhea). In these cases, fine-needle aspiration biopsy (FNAB) should be supplemented with serum CT assays. CT measurement should also be considered and discussed with patients whose FNAB is indeterminate/nondiagnostic and those with multinodular goiters characterized by cytology-negative dominant nodule(s). And in all these cases, the results of testing have to be interpreted with an eye to the wide range of other conditions that can cause minimal or mild non-C cell related elevations in serum CT, including smoking, renal failure, autoimmune thyroiditis, non-thyroidal neuroendocrine neoplasms, and heterophilic antibodies [4].

AUTHOR CONTRIBUTIONS

Conception/Design: Giuseppe Costante, Sebastiano Filetti
Provision of study material or patients: Giuseppe Costante
Collection and/or assembly of data: Giuseppe Costante
Data analysis and interpretation: Giuseppe Costante, Sebastiano Filetti
Manuscript writing: Giuseppe Costante, Sebastiano Filetti
Final approval of manuscript: Giuseppe Costante, Sebastiano Filetti

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