The 2009 American Thyroid Association Guidelines for Management of Thyroid Nodules and Differentiated Thyroid Cancer: Progress on the Road from Consensus- to Evidence-Based Practice

Efisio Puxeddu, M.D., Ph.D.1 and Sebastiano Filetti, M.D.2

In the current issue of *Thyroid*, the American Thyroid Association (ATA) offers us its “Revised Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer” (1). The first edition of these guidelines appeared in 1996 (2), and the revised version was published a decade later (3). That was only 3 years ago, so many of us are likely to wonder: “Is it already time for a new guidelines?”

In our opinion, the answer is a resounding “Yes!” Clinical practice guidelines—in general—are a controversial issue (4), and there has been ample discussion of their limitations and the potential risks associated with their use. This discussion is appropriate and often productive, but the fact remains that clinical guidelines are here to stay. The task forces that elaborate them provide an enormous service to busy clinicians by systematically and scrupulously sifting through the massive amount of scientific evidence that accumulates each year, weighing the evidence, and offering their recommendations. Who among us would be willing to take on this task alone? And is there any assurance that the individual approach would guarantee greater objectivity? The ATA’s decision to update its recommendations earlier, rather than later, is clearly laudable, as is the decision to broaden the base of the task force to include experts from outside the United States, as well as those who are involved in activities not exclusively related to the thyroid disease. A closer look at the 2009 guidelines shows that this approach has produced concrete results.

In the updated guidelines for the management of thyroid nodules, two important aspects have been reconsidered and dealt with more extensively. The first involves the clinical and ultrasound criteria for performing fine-needle aspiration biopsy (FNAB). Great effort has gone into the development of recommendations regarding the size of thyroid nodules that require FNAB (along with their sonographic and clinical features). Information has been meticulously extracted from the literature and organized into a table that shows each recommendation with its strength-of-evidence rating. There are also important updates on the interpretation of FNAB findings. Here, along with the traditional, four-category classification system (nondiagnostic, malignant, indeterminate, and benign)—which continues to be the preferred approach—the task force also presents the expanded classification that emerged in 2008 from the National Cancer Institute’s Thyroid Fine-Needle Aspiration State of the Science Conference, which included six categories: nondiagnostic or unsatisfactory, benign, follicular lesion of undetermined significance, suspicious for a follicular neoplasm, suspicious for malignancy, and malignant (5). No recommendation for or against this new system is made, but—interestingly—in the new algorithm for the work-up of patients with one or more nodules (Fig. 1), the four-category classification has been expanded to include a “suspicious for malignancy” category. This approach is in keeping with the British classification (6), which is currently the most widely used in Europe.

As for the initial management of differentiated thyroid carcinoma, important additions have been made to the sections on optimal surgical management and radioiodine (RAI) remnant ablation. In the former, greater emphasis has been placed on the importance of neck ultrasound in preoperative staging. The sonographic features suggestive of metastatic lymph nodes in the neck are presented in detail, and the authors note that preoperative ultrasound identifies suspicious cervical lymphadenopathy in about 20–31% of patients and furnishes information that changes the surgical strategy in up to 20% of cases. As for initial treatment, effort has been dedicated to defining an optimal surgical strategy. For nodules with biopsy-proven malignancy, total thyroidectomy is recommended, and the indications for lobectomy have been restricted to small (<1 cm), unifocal lesions. In accordance, completion thyroidectomy is recommended for all incidentally discovered thyroid malignancies (except those described above). All this brings the ATA’s approach closer into line with practices in Europe (7).

There is also very important news on surgical approaches to loco-regional lymph node disease. An ad hoc committee composed of endocrinologists, head and neck surgeons, and endocrine surgeons specifically reviewed the topic and

---

1Department of Internal Medicine, University of Perugia, Perugia, Italy.
2Department of Clinical Science, University of Roma “La Sapienza”, Rome, Italy.
developed four key recommendations. The committee advocates central compartment neck dissection for all patients with clinical involvement of central or lateral neck nodes and lateral compartment dissection for those with biopsy-proven metastatic lateral lymphadenopathy. They are more cautious on the subject of prophylactic central compartment neck dissection: its use should be considered in patients with T3 and T4 diseases, but can be avoided in lower-risk patients (those with T1 and T2 diseases). The committee acknowledges that prophylactic dissection is still a controversial issue and the approach they advocate for the central compartment could increase the risk of loco-regional recurrence, but note that, on the whole, it is a safer strategy for less experienced surgical hands. Qualifiers of this sort provide useful keys to interpreting and applying the task force’s recommendations, processes that require active participation by individual clinicians and adaptation to specific settings.

As far as postoperative staging is concerned, the task force acknowledges the importance of the American Joint Committee on Cancer–Union Internationale Contre le Cancer TNM system, as well as the potential advantages offered by other staging systems, but for estimating the risk of recurrence—the weak point of all these systems—it proposes a new three-level system that stratifies cases into low-, intermediate-, and high-risk categories. Low-risk patients include those with no local or distant metastases, no macroscopic tumor left, no sign of tumor invasion, and nonaggressive histology. The high-risk category comprises those with macroscopic tumor invasion, incomplete tumor resection, or distant metastases. The intermediate-risk patients are those with in-between clinical features like microscopic extra-thyroidal invasion, lymph node metastases, aggressive histology, and vascular invasion. The prognostic stratification proposed by the task force members is an interesting tool that deserves to be validated in additional prospective studies. As the members note, the risks of recurrence and disease-specific death are dynamic variables that evolve over time, depending on the course of disease and responses to therapy; hence, the suggestion that appropriate management of thyroid cancer patients requires ongoing reassessment of these risks as new data are obtained during follow-up.

The section dedicated to the ablation of tumor remnants has also been thoroughly reworked. A meticulous review of the available literature has been skillfully summarized in a table that shows the expected benefits (reduced risk of death or of recurrence, facilitation of initial staging and follow-up) and recommendations for the use (no ablation, selective use, ablation recommended) of RAI ablation—each with its own strength-of-evidence rating. In essence, the task force concludes that RAI ablation should be used for patients with distant metastases and/or tumors that are grossly invasive or greater than 4 cm, even in the absence of high-risk features, but it is not recommended for patients with unifocal tumors measuring less than 1 cm or multifocal cancer with all foci measuring less than 1 cm unless they have other features indicative of other high risk. Selective use of RAI ablation is recommended for patients with intermediate-sized thyroid cancers (1–4 cm) that are confined to the thyroid, documented lymph node metastases, or other higher risk features when the combination of age, tumor size, lymph node status, and individual histology predicts an intermediate to high risk of recurrence or death from thyroid cancer.

Updates have also been made regarding the long-term management of differentiated thyroid cancer, in particular surveillance for recurrent disease and management of recurrent or persistent loco-regional and metastatic disease. The importance of neck ultrasound in detecting recurrence is heavily stressed—as it was in the original version—but clear indications (including a size cut-off) have now been added on when to perform FNAB of suspicious lymph nodes and on the method that should be used (cytology with thyroglobulin measurement in the needle washout fluid).

The usefulness of 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography in the follow-up of patients with thyroid cancer is highlighted with a special section that includes a list of the recently expanded indications for this imaging technique. In the section on 131I treatment of loco-regional or distant metastatic disease, the new edition presents the three possible approaches for dose selection (empirc fixed amounts, therapy determined by the upper bound limit of blood and body dosimetry, and quantitative tumor dosimetry) but refrains from indicating the best of the three due to insufficient data. However, greater emphasis has been placed on the side effects of RAI treatment and the risk of exceeding the maximum tolerated radiation absorbed dose (particularly in older individuals) when empiric fixed doses are used. Considering these risks, the task force recommends limiting the 131I dose to 200 mCi or less in patients over 70 years of age.

The new guidelines also place greater emphasis on novel targeted therapies, with a review of the promising data that has recently emerged from phase II trials with anti-angiogenic tyrosine kinase inhibitors for progressive or symptomatic metastatic disease that is unresponsive to RAI. There is also a summary of the benefits, duration of experienced efficacy, and side effects of the new drugs. The significant impact of these treatment modalities in comparison with traditional cytotoxic chemotherapy or radiotherapy resulted in the recommendation that patients with advanced RAI refractory disease should be considered for enrollment in clinical trials (most of which are testing new tyrosine kinase inhibitors), or in the absence of such trials, for treatment with one of the available kinase inhibitors, by-passing the use of cytotoxic chemotherapy.

In short, the new guidelines bring us several steps closer to the goal of evidence-based clinical practice. Compared with its predecessor, the 2009 version contains an additional 38 recommendations with strength-of-evidence ratings—an increase of close to 50%. Of the 124 evidence-rated recommendations, 16% are A-level, 32% are B-level, 33% are C-level, 2% are D-level, 4% are E-level, 3% are F-level, and 9% are I. These figures reflect increases not only in the quantity but above all in the quality of research now being conducted in the area of thyroid disease, but at the same time they highlight the urgent need for new prospective studies and for clear definition of outcomes in research focusing on critically controversial topics. The concluding section of the guidelines is dedicated to future research, and it defines many of the areas that still need to be completely explored. In the meantime, the 2009 “Revised Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer” appears to be the best instrument available for improving clinical decision-making processes. Complete objectivity is an elusive goal, but the broad-based, multidisciplinary task force that has authored this year’s guidelines has produced a document that can and
should be endorsed by thyroid associations throughout the world, and there is little doubt that it will serve as a reference point for physicians far beyond the borders of the United States. Hopefully, the ATA will consider publishing an easy-to-access online version of the 2009 guidelines on its official web site, a small but important step toward greater worldwide awareness of the principles and practice of evidence-based management of thyroid disease.

References


