

The 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer An Expert Panel Discussion

Moderator

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Division of Endocrinology, Metabolism and Diabetes

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Expert Panel



Dr. Bryan R. Haugen (moderator) is Professor of Medicine and Pathology at the University of Colorado School of Medicine, and Chief of the Division of Endocrinology, Metabolism & Diabetes and Director of the Thyroid Tumor Program. His clinical interests include thyroid neoplasms, advanced thyroid cancer, thyroid dysfunction, and other endocrine tumors (parathyroid, adrenal, carcinoid). Dr. Haugen's research interests include molecular studies of thyroid neoplasm diagnosis and pathophysiology, and the study of molecular therapeutic targets. His research group also studies the individual host-tumor interaction in thyroid cancer to develop novel tumor immunology tests and therapies.



Dr. Kenneth Burman is Chief, Endocrine Section, MedStar Washington Hospital Center, and Professor, Department of Medicine, Georgetown University, Washington, DC. His recent research areas of interest focus on the identification of novel agents to treat thyroid cancer and on the mechanism(s) of thyroid cancer cell growth.



Dr. Ronald J. Koenig is Professor of Internal Medicine in the Division of Metabolism, Endocrinology and Diabetes at the University of Michigan Medical Center in Ann Arbor. His clinical and research areas of interest relate to thyroid cancer and span basic and mechanistic aspects of thyroid cancer to clinical trials.



Dr. Susan J. Mandel is Director, Clinical Endocrinology and Diabetes, University of Pennsylvania Health System, and Professor of Medicine and Radiology at the Hospital of the University of Pennsylvania in Philadelphia. Her research interests include the use of sonography in the evaluation of patients with thyroid nodules, the novel introduction of ^{123}I imaging in differentiated thyroid cancer, and thyroid disease during pregnancy.



Dr. Bryan McIver is Program Leader for Endocrine Oncology and Deputy Physician in Chief, Moffitt Cancer Center, and Professor of Oncologic Sciences, Morsani School of Medicine, University of South Florida, in Tampa. His research areas of interest include the genetic regulation of growth, invasion, and spread of thyroid tumors of all types. His primary research focus is the use of genetic and molecular techniques to improve the accuracy of diagnosis of thyroid nodules, more accurately predict outcomes, tailor appropriate treatment to a patient's unique needs, and guide the use of novel therapies for progressive and life-threatening disease.



Dr. Steven Sherman is the Chair and Naguib Samaan Distinguished Professor in Endocrinology in the Department of Endocrine Neoplasia and Hormonal Disorders at The University of Texas MD Anderson Cancer Center, Houston. His clinical practice is limited to the care of patients with any form of thyroid cancer, with a special interest in advanced therapeutics, and he has been the senior investigator on several phase II and III trials of novel systemic therapies that have transformed the treatment of patients with metastatic thyroid cancer.



Dr. Jennifer A. Sipos is an Associate Professor of Medicine and Director of the Benign Thyroid Disorders Program at The Ohio State University, in Columbus. She has developed an interest in the use of ultrasonography for the diagnosis and management of thyroid cancer. Her clinical research focuses on the factors involved in the development of salivary damage after radioiodine therapy, and on clinical trials evaluating multikinase inhibitor therapies in refractory thyroid cancer and the diagnostic use of molecular markers in thyroid nodules.



Dr. Julie Ann Sosa is Professor of Surgery and Medicine (Oncology) at Duke University, and Chief of Endocrine Surgery and Director of Health Services Research in the Department of Surgery and Leader of the Endocrine Neoplasia Diseases Group at the Duke Cancer Institute and the Duke Clinical Research Institute, in Durham. Her clinical interest is in endocrine surgery, with a focus in thyroid cancer, and her research focuses on outcomes, health care delivery, hyperparathyroidism, and thyroid cancer, with an emphasis on clinical trials.

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The 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

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Dr. Haugen: In this roundtable discussion, our main goal is to explore the opportunities and challenges in applying the recently published 2015 American Thyroid Association (ATA) Management Guidelines¹ for adult patients with thyroid nodules and differentiated cancer.

We are fortunate to have a panel of experts in thyroid nodule and cancer management, three of whom were part of the task force—Dr. Julie Ann Sosa, Dr. Susan Mandel, and Dr. Steven Sherman—and four of whom were not members of the task force—Dr. Jennifer Sipos, Dr. Bryan McIver, Dr. Ken Burman, and Dr. Ron Koenig.

Briefly, by way of introduction, I will start by explaining that the ATA issues a charge to update each of its guidelines periodically. This most recent update of these guidelines has been approximately a three-and-a-half-year process. We set up a new task force that rotated some of the members off the previous 2009 guidelines task force and brought on new expertise, particularly in the areas of medical oncology, pathology, molecular pathology, and data and systematic review analysis.

That process has spanned the past three and a half years, during which we surveyed key stakeholders, asking about useful or unhelpful recommendations

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and some management issues that were not addressed in the 2009 guidelines. Since these are question-based guidelines, we clarified the questions, selected a new grading system that is adapted from the American College of Physicians, and then did our literature searches and recommendation revisions.

The manuscript was submitted to the ATA membership for review in July 2014, and subsequently submitted to the journal *Thyroid* in January 2015. Six reviewers read through the guidelines and three different iterations based on the reviews. That gives you a brief background into the process of developing these new guidelines.

Finally, I would like to highlight the new components of the guidelines: we added eight new questions and 21 new recommendations. We also feel that 21 recommendations changed significantly in these guidelines. These are highlighted in table 5 of the guidelines.

With that as a background, I would like to begin with an open-ended question: what do you see as the most helpful and the most challenging recommendations or sections in these new guidelines? I am posing this question to those panelists who were not on the task force, and I would like to begin with Dr. Sipos.

Dr. Sipos: In terms of the most helpful recommendations, I think the ultrasound stratification of thyroid nodules is a wonderful addition to the guidelines. It is admittedly somewhat complicated at first blush, but as one becomes more familiar with it, it is a truly comprehensive and user-friendly assessment of sonographic patterns in thyroid nodules. An advantage of this stratification system is that it not only provides guidance regarding which nodules require fine-needle aspiration (FNA), but it also directs the evaluation of the patient after the diagnostic workup. For example, this current system provides assistance when deciding on the interval for follow-up, the indications for repeat FNA, the use of molecular testing, and the indication for surgery.

I would say the use of molecular testing, as described in recommendation 13, will present the greatest challenge for clinicians in practice. I think that it is left as a somewhat vague guideline rather than a specific indication of when to use this testing and how to use it. I would surmise that this ambiguity is intentional, perhaps because this topic is a bit more controversial from the standpoint of the existing literature.

Dr. Haugen: So one of the challenges you see is the guideline for molecular analysis not being specific enough as far as saying when exactly to use the test and which test to use?

Dr. Sipos: Correct. Leaving it as a vague recommendation may present a challenge for some clinicians

because they may want more guidance as to when it is appropriate to use a molecular test and which particular test to employ, but I also think that this haziness is probably an essential component of the guidelines. The wording of the recommendation is not so binding that we are obligated to use the tests. If they are not applicable in a specific situation, then we should not use them, and if they are appropriate, then we can use them. This ambiguity provides flexibility in deciding when to use molecular tests to give the physician room to use their judgment and patient preference in addition to the clinical scenario to help guide this important decision-making process.

Dr. Haugen: You see that as a challenge?

Dr. Sipos: It is vague, which presents a challenge, but I also think that a certain degree of ambiguity is a necessity for this particular recommendation.

Dr. Haugen: In follow-up, I would ask Dr. Sosa to provide the task force perspective and give us some insight into the thinking behind recommendations 13 through 17. What was the discussion related to bringing molecular testing into the area of indeterminate cytology?

Dr. Sosa: I would preface my comments by saying that this is an entirely new portion of the guidelines. The fact that molecular testing is addressed and discussed, I think, demonstrates the kinetic nature of this process.

Dr. Sipos is correct in saying that the guidelines are not prescriptive with regard to whether to use molecular testing and, if molecular testing is used, which molecular test to use. I think there are several reasons why this was the approach taken.

First, it is important to emphasize that we did not believe that the evidence from the literature yet suggests that molecular analysis is a substitute for, first and foremost, “being a physician,” performing a history and physical examination and using that to drive the clinical suspicion for cancer.

Second, emphasis is placed on using molecular testing, when ordered, to supplement findings of ultrasonography, which I think continues to be a fundamental tool in the evaluation of the indeterminate thyroid nodule. Finally, this is a rapidly evolving field, and I think it is difficult to be prescriptive when the science is changing so quickly.

As a result of this dynamic process, there are still some deficits in our knowledge. For example, we are still missing long-term follow-up for patients who have undergone molecular testing resulting in a reassuring finding and a non-operative surveillance approach. Some on the committee emphasized that we really need to have that kind of robust long-term

data to be able to go “all in” with regard to endorsing molecular testing.

I think a common theme across many sections in these guidelines is an emphasis on the patient playing a role in decision making. Just as that is true in the surgical section, it is definitely also true in the section about molecular testing, in that there are risks and benefits and strengths and limitations to using molecular testing versus not using it. In the end, we as physicians need to counsel our patients. However, patient preference may well be the most critical consideration.

Dr. Haugen: Thank you, Dr. Sosa. Focusing more specifically for a moment on the topic of indeterminate cytology, how do you think the recommendations on approaches to patients with indeterminate cytology will affect practice? And I would like to open this question up to anyone who wants to respond.

Dr. McIver: I am happy to see these recommendations in the guidelines early in the process of developing molecular markers and determining their role in the clinical management of these patients. I believe that this encourages all of us to be involved in the development of the science that underpins their use. Of course, it also encourages insurance carriers to make sure that they are actually offering patients the opportunity to take part in these testing opportunities.

I think that all of us who care for these patients would agree that there is still some uncertainty in the science, and that those patients on whom we are not going to operate on the basis of “negative” molecular markers deserve to have more careful follow-up than that which we might recommend for a patient with a cytologically benign nodule because the residual risk of cancer is likely to be higher. Nonetheless, the guidelines have done a good job of opening up this issue early on in the process so we can continue to gain clinical experience in the field.

Dr. Haugen: Great, thank you. Anyone else?

Dr. Sherman: I think recommendations 13 and 14 are among the more important aspects of the recommendations regarding molecular testing because, even before discussing the actual use of the test, they discuss the really critical role of the physician or the clinician in explaining what the tests do and do not do for the patient.

This is a rather complex area. The types of tests we are talking about and the interpretation of the results are far from black and white. And the recommendations emphasize that the physician has to engage patients in a dialogue so they can understand how the tests might help and what their limitations are.

The recommendations also point out the need for high-quality testing procedures and the fact that some of the molecular testing that might be available in one’s local research laboratory may not be sufficient to provide the quality and assurance that is really necessary for tests that are going to inform clinical decision making.

Finally, I should emphasize that those of us involved with the development of specific tests or with confluence of interests with any of the companies marketing these tests were excluded from formulating the final recommendations regarding molecular testing.

Dr. Mandel: I would like to add my appreciation of Jen’s comments because this is obviously an area of the guidelines that deals with some of the most current research. As a member of the task force, I view this section of the guidelines as setting the bar for which criteria should be met by a test to be used in this clinical situation. What would that test look like in order for it to be clinically applicable for a patient with an indeterminate cytological diagnosis? That said, we understand that over the next months and years, there are probably going to be many developments in this area. We have also introduced what Julie Ann already mentioned—the importance of patient preference and of discussing the tests with patients.

Dr. Haugen: That was a good discussion, and I would like to return to this topic a bit later. I would now again like to pose the more open-ended question about what you consider to be the most helpful and most challenging recommendations in the guidelines, and to ask Dr. Bryan McIver to respond.

Dr. McIver: Extrapolating from the discussion we just had about molecular markers, there is a broad range of new or modified recommendations in this version of the guidelines. It speaks to a change in the philosophy that we now take in dealing with thyroid cancer and thyroid nodules. What these guidelines have done is to start focusing much more extensively on what we know about the biology of the disease, nuancing or adapting our approach to managing patients based on that understanding of the biology and on the genetics and other features that underpin that biology.

I have tremendous respect for the authors. Bryan, you as the chair deserve great respect for the work you have done on this. It is a massive undertaking, and it swings the pendulum dramatically away from our previous approach to thyroid cancer as recently as 10–15 years ago, when essentially the standard of care was a routine total thyroidectomy, central neck dissection, radioactive iodine for everyone, and then a cookie-cutter follow-up strategy. The committee deserves tremendous credit for having shifted the pendulum so far in the other direction.

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Where the challenge may come in throughout these guidelines is in the risk that the pendulum may have swung too far for many people's comfort. We are now talking about doing a less than total thyroidectomy for patients with a papillary tumor ≤ 4 cm. That would have been unheard of 10 years ago. We are talking about not using radioactive iodine in at least a substantial minority of patients, if not even a majority of patients who present with thyroid cancer. We are talking about follow-up that no longer depends on the use of stimulated thyroglobulin and stimulated whole-body scans.

These are seismic shifts in our approach to managing thyroid cancer. I think the hardest part of these guidelines will be in the day-to-day implementation by endocrinologists trying to do their best to practice at the highest levels, but having to shift from one polar extreme to the other, because nearly every step of these guidelines asks our colleagues to do exactly that.

This represents a significant challenge. I hope it is a challenge we are up to, but I think it is going to be very important for academic leaders to lead by example, to educate our colleagues, and to reassure our colleagues that these guidelines are truly based on decades of information and knowledge that is finally being construed in a way that, I believe, is productive, outcomes oriented, and patient centric.

Dr. Haugen: Thank you. I will come back with a follow-up to you, Dr. McIver, on your assertion that this is a challenge of potentially swinging too far. I think one of the things we did, and I will have others talk about this, is that in each area, we worked hard first to ensure that the guidelines are evidence-based, and we will talk more about that in a follow-up question.

Also, for example, in the case of a less than total thyroidectomy for a tumor ≤ 4 cm, we tried to be very careful to say that either a thyroidectomy or a lobectomy is appropriate. Not that we are necessarily pushing a lobectomy or less use of radioiodine, or maybe lower-administered activities. In many of the cases in which there was low-quality evidence, we again tried to say that clinicians could either use this lower dose or not use it, or they have the opportunity to use a higher dose if they are more concerned.

Regarding follow-up of thyroglobulin not being stimulated, even then we tried to say that if it is in a very sensitive assay—down to a sensitivity of 0.1 or 0.2 ng/mL—maybe it does not need to be stimulated, whereas if the sensitivity is lower, you may still need stimulation.

I think we tried, based on the level of evidence, to leave some room for the physician to make a choice for each individual patient. Dr. McIver, did you have any concerns in this area, as far as the recommendation not lining up with the evidence?

Dr. McIver: No, quite the reverse. I think that you have done a better job of hewing to the evidence than perhaps we were able to do in the previous two iterations of the guidelines. Where the challenge comes, of course, is in recognizing that the quality of our evidence in so many areas in thyroid cancer is less than optimal.

There are very few randomized, prospective, double-blinded clinical trials available, except in the field perhaps of the tyrosine kinase inhibitors. But everything else is based on our retrospective experiential reviews. There is clearly poor-quality evidence across the board.

As a result, the challenge remains that the guidelines cease to be very “guiding.” They are no longer explicit about doing a total thyroidectomy; they now say that a lobectomy *might* be adequate. They no longer say “thou shalt use radioactive iodine;” they say that you *could* use radioactive iodine.

In terms of molecular markers, as we were just discussing, they say that molecular markers need to fit certain criteria to be useful. A number of options exist. However, the recommendations do not really tell us which option is optimal in any one circumstance.

Again, this reflects the quality of the data that we have to live with and the uncertainty with which we as endocrine oncologists need to be comfortable. It is perhaps easier for those of us who sit in our ivory towers to be comfortable with that uncertainty. It is much harder, however, for practicing community endocrinologists trying to make the appropriate decision for the patients sitting in front of them.

Dr. Haugen: Yes, point well taken, thank you. I would like to bring Dr. Steven Sherman in for comments on that point.

Dr. Sherman: Dr. McIver has appropriately described the swinging pendulum. In fact, regarding surgical management, this brings us back to the guidelines of the National Comprehensive Cancer Network from 10–15 years ago, where the balance in patients with low-risk papillary thyroid cancer was one of equipoise between total thyroidectomy and lobectomy. They were considered equivalent choices.

This is perhaps not quite as dramatic and unprecedented a shift as going back to recognizing that, in total, the evidence across the literature fails to make a very strong case for either one or the other leading to superior outcomes. Therefore, it is a matter of clinician decision making and involvement of the patient in the choices, as Dr. Sosa referred to—that very critical patient input requirement for informed decision making.

Dr. Haugen: Turning to Dr. Burman, what do you see as the most helpful and most challenging recommendations in these new guidelines?

Dr. Burman: Thank you. I would like to echo the comments that Dr. Haugen and the committee deserve accolades for a tremendous job. When I review the guidelines, one area in particular that seems most helpful regarding metastatic disease is the new risk-stratification system to guide long-term follow-up and therapy.

Historically, we would determine a stage of disease at the beginning of treatment, or at the time of the initial diagnosis, and maintain that stage regardless of how the patient responded to the therapy. It is more reasonable to have an individualized, personalized approach, which these guidelines emphasize. Now, we stratify the patients based on their risk initially and also following their response to therapy. A patient is considered to have an “excellent response” when there is no evidence of residual thyroid cancer assessed clinically, biochemically (e.g., serum thyroglobulin level), or structurally, based on imaging studies. A “biochemically incomplete response” is considered when there is no definitive evidence of structural disease remaining, but there is an abnormal serum thyroglobulin level or increasing antithyroglobulin antibodies. A “structurally incomplete response” is designated when imaging studies demonstrate persistent or new locoregional neck disease or distant metastases. Lastly, there are some patients who have nonspecific biochemical or structural findings, and it is not clear that these represent persistent or recurrent thyroid cancer. These patients would be classified as having an “indeterminate response.”

I think the recommendation to reassess and re-stage patients following therapy is an important advance and will allow more appropriate therapy over the long term. For example, why consider a patient with differentiated thyroid cancer who had lung metastases that responded totally to radioactive iodine therapy as still having stage 4 disease if there is biochemical and structural evidence the disease has resolved?

Dr. Haugen: What do you see as challenging or controversial in the guidelines?

Dr. Burman: I note a particularly challenging area that relates to recommendation 91, regarding radioactive iodine refractory disease. Obviously, the committee spent a great deal of time and effort considering this issue and formulated a specific identification of conditions that typically represents iodine refractory disease. These conditions apply in the context of an appropriately elevated serum thyrotropin (TSH) and after adherence to a low-iodine diet: (i) malignant metastatic tissue (usually detected by cross-sectional imaging) that has not ever concentrated radioactive iodine; (ii) malignant tissue that has lost its ability to

concentrate radioactive iodine; (iii) radioactive iodine concentrated in some, but not all, lesions; and (iv) metastatic disease that continues to progress despite the patient having received significant concentrations of radioactive iodine therapy. However, in practice, it is frequently challenging to identify individual thyroid cancer that may be radioactive iodine refractory.

If a patient’s known lesions do not trap radioactive iodine in any of these areas—for example, in the lung, bone, or abdomen—and there are cross-sectional imaging studies and perhaps even a biopsy that demonstrate it is metastatic differentiated thyroid carcinoma, I think we could agree that this represents radioactive iodine refractory disease.

However, certain technical factors need to be considered that may alter the apparent uptake of radioactive iodine in lesions that may make it appear as though there is radioactive iodine refractory disease. For example, the dose of radioactive iodine given for the scan, time of scanning, the equipment, and the assiduousness of the nuclear medicine team may make it difficult to know with certainty that a lesion does not trap radioactive iodine.

We are concerned about the urine iodine values and what represents an optimal urine iodine level to allow maximal radioactive iodine uptake into residual thyroid tissue. If the patient’s urine iodine level is inappropriately elevated at the time of the radioactive iodine scan, then the disease may be misinterpreted as relative radioactive iodine refractory. Another potential issue is whether radioactive iodine avidity in many, but not all, known lesions actually represents radioactive iodine refractory disease.

In addition, the guidelines note that if a patient shows progressive disease following radioactive iodine therapy, this may indicate refractory disease. Such a conclusion depends on many factors, including how many rads were actually administered with a given dose of ^{131}I and the time period of analysis.

Finally, what percent uptake does a given lesion need to have to be radioactive iodine refractory? In summary, the concept of radioactive iodine refractory disease is important, and identifying patients as being in this category will likely reduce their exposure to additional radioactive iodine treatments and the possible adverse consequences. I agree with the guidelines that the healthcare provider should assess each patient individually to identify optimally those that may or may not benefit from further radioactive iodine therapy treatment(s).

Dr. Haugen: Thank you, Dr. Burman. I agree that this aspect of the guidelines is controversial and involved lengthy discussion not only within the task force, but also among reviewers for the journal *Thyroid*. This was one of the last issues we dealt with, in an effort to use the best language possible.

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It is important to strike a balance between using radioiodine when it is useful, but to realize when it is no longer useful to continue, especially when treating patients with large doses of radioiodine. I also agree that this was one of the challenges—especially when you refer to multiple lesions—that some take up iodine and some do not. And how do you decide what is radioiodine refractory and what is not?

That is a bit of a challenge. Dr. Sherman, would you like to add to this discussion?

Dr. Sherman: I completely agree with Dr. Burman that a tremendous amount of detail was not included in this, in part because it is based on very unsettled science. I think the value of this recommendation is in providing a thought construct for physicians to begin to allow them to characterize their patients as radioiodine refractory or not.

In particular, it takes on the very practical recognition that, at the end of the day, patients who die from thyroid cancer tend to die because of disease that is radioiodine refractory and not because of disease that is radioiodine sensitive and responsive. Thus, this errs on the side of saying that the patient who has disease that is not likely to benefit from further radioiodine therapy can be spared the additional toxicity of what is not likely to be beneficial treatment.

At the same time, it then follows with a fairly extensive discussion of the options for treatment beyond radioactive iodine. This includes a sobering dose of reality about the toxicities and the limited benefit of those treatment options. It is not that we are moving from treating everybody *ad nauseam* with radioiodine to treating everyone *ad nauseam* with systemic therapy, but rather recognizing the limitation of all of these treatment options in those patients who have progressive radioiodine refractory disease.

Dr. Haugen: I would now like to turn to Dr. Ron Koenig and again ask the question, “What do you see as the most helpful and most challenging recommendations in these new guidelines?”

Dr. Koenig: In terms of what is most helpful, I would point to the overall goals presented in section [B2] regarding the initial management. I really liked that because it sets the stage and gives a low-power view of what the goals should be that really influence all of the more specific things that follow. I also really liked the discussion of prophylactic central neck dissection in clinically node negative patients because it is quite scholarly and addresses the pros and cons in a very nice way.

In terms of challenges, I want to point out that in a global sense, it is confusing to me how the committee

can make a strong recommendation with low-quality evidence. That occurs in quite a few places. I am sure you had good reasons, but I am not sure that the general reader of these guidelines will pay attention to the fact that the quality of the evidence is low. Thus, I consider that to be an overview challenge.

In terms of a specific challenge, I would refer to the initial risk-stratification system, which is in section [B23]. I have a couple of issues with this. Looking at figure 4, which relates to this, I can definitely understand the need to increase complexity. However, on the right side of figure 4, as things get to be really complex, they also became harder to use.

I would have liked the committee to say something about how strong the data are for all of these things with regard to structural recurrence, because I do not think there were good data in the Surveillance, Epidemiology, and End Results (SEER) or the National Cancer Database (NCDB) about this. I am guessing that a lot of these data are from single institutional studies, and, for example, the specific institution and who the surgeon was could substantially influence the risk of recurrence. Overall, I have some uncertainty about the modifications of the initial risk-stratification system.

Dr. Haugen: Thank you, Dr. Koenig. I think, in reverse order, I will briefly comment on those points and then open it up to my colleagues on the task force. With the initial risk stratification, you are right. Using figure 4 as an example, on the left-hand side, we still do have the general high, intermediate, and low risk for persistent/recurrent disease, which have been a bit modified because you can see patients with cancer-involved lymph nodes included in all three of them.

In my mind, the lymph node disease drove us a lot in that if you have a single microscopic lymph node, you likely could be a low-risk patient. If you have multiple lymph nodes that are not terribly enlarged, you may be at intermediate risk. And if you have very large or extranodal extension, you are at high risk.

Then what we tried to do, which can be both confusing and, hopefully in the end, helpful, is on the right side of figure 4 to get into more of those details. For each one that has percentages associated with it, there are related studies in the literature. We put the approximate lines in many of these because for a lot of them, you are right, Dr. Koenig, there are only single studies.

Therefore, in this section, when we say that one should consider using this risk stratification, we do so as a weak recommendation based on low-quality evidence. We need to have more evidence to help either to modify this or to strengthen what we have

already recommended. Would my colleagues on the task force like to comment further on the initial risk stratification?

Dr. Mandel: Ron, I really appreciate your comments. This was an area that generated a lot of discussion, especially the idea of having a continuum on one side of the figure, the right, and then a more discrete categorization on the left.

Understanding that not all lymph node metastases mean the same thing for recurrence allows for more precise risk stratification, even in the presence of the pathologic diagnosis of lymph node metastases. Although, especially for the micromets, the data are based on single-institution studies, a number of those studies consistently demonstrate differences in recurrence rates based on the volume and size of metastatic involvement. The available data are reviewed in the text, and reference is made to a paper written by the ATA Surgical Committee, led by Greg Randolph and Mike Tuttle, which extensively reviewed all of the retrospective studies that have tried to analyze risk of recurrence based on size, number, and location of lymph node metastases.

The other point that is really an addition to this guideline is the inclusion of follicular thyroid cancer, which you can see on the right side of figure 4. Specifically, it separates minimally invasive follicular thyroid cancer with its very low risk of recurrence versus follicular cancer with extensive vascular invasion and high recurrence risk.

This is probably the most comprehensive compilation of available data to predict risk, but again, based on the quality of the studies, I would label it as weak evidence. Our goal was to present what we know while at the same time focusing on when not to overtreat, such as in small-volume lymph node metastases and patients with minimally invasive follicular cancer.

Dr. Haugen: Thank you, Dr. Mandel. Unfortunately, in our field right now, we do have a lot of low-quality evidence. We were very careful, and we debated quite a bit whenever we would have a strong recommendation based on low-quality evidence.

In the end, as a task force comprised of, hopefully, a broad group of experts, when we felt that this is something that either should or should not be done, even though the quality of evidence was low, we pushed that up to a strong recommendation. Even in the broader discussion of the field of guidelines and of grading evidence and assessing guidelines, there is a lot of debate on when to consider making a strong recommendation based on low-quality evidence.

Dr. Sosa: A good example of just such a recommendation can be seen in the section pertaining to surgery, where we felt for the first time that it was important

to articulate the importance of communication and transition of care between the surgeon and the endocrinologist or nuclear medicine physician in the post-operative setting regarding intraoperative findings and postoperative complications.

We were concerned that these transitions of care often are characterized by a paucity of data and, therefore, the person accepting the patient for the next phase of treatment was often ill-equipped to do so. The call for explicit communication around such transitions of care was a strong recommendation with low-quality evidence in the new guidelines. We felt strongly that these transitions of care are important but, sadly, no one has really studied them in a meaningful fashion, so the quality of evidence was low. Indeed, a study probably would be very hard to do.

Dr. McIver: I agree wholeheartedly with Dr. Sosa's comments. Those transitions of care have traditionally been a major problem for us in the field of thyroid cancer because what the endocrinologist believes the surgeon may have done is often not actually what the surgeon has done.

This is sometimes made more complicated by the use of terms that are not familiar to both parties. I think that the more multidisciplinary we become in the field of thyroid cancer, the more important it will be to have very clear use of language—to fall back onto formal oncologic principles in the use of language, but where the communication is very, very clear.

One of the big challenges for the guidelines relates to the fact that it opens up such a variety of opportunities—for example, the extent of surgery for tumors ≤ 4 cm, as we have mentioned. One could easily envision a situation in which an endocrinologist believes that the appropriate treatment for a papillary thyroid cancer is a total thyroidectomy, whereas the surgeon reading the same set of guidelines believes that the appropriate management is a thyroid lobectomy. The patient would return to the endocrinologist with the endocrinologist anticipating that the patient is going to get radioactive iodine, whereas the surgeon never felt that was going to be necessary.

Even more so than in the past, these guidelines highlight the importance of clear communication, perioperatively in particular, but throughout the continuum of care for these patients and between all of the specialists involved. Having a multidisciplinary team-based approach to managing these patients is ultimately going to be the only rational way forward.

Dr. Haugen: Thank you, Dr. McIver. That is a very good point. To add to that, in the area of communication and discussion related to surgical pathology, we had Dr. Yuri Nikiforov lead this section, and together with a group of other task force members, they developed a new section in the guidelines

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about the types of information we are expecting from our pathologists for information so we can appropriately risk stratify our patients. This reinforces the emphasis on having open communication, the right type of communication, and speaking the same language.

I would now like to delve a little more deeply into how the new recommendations on the choice of radioiodine for remnant ablation, adjuvant therapy, and therapy, and the choice of preparation, might affect practice. I would like to pose this question to one of our colleagues who was not on the task force.

Dr. Burman: I will be glad to make some brief comments. I think that this is a very important addition to the guidelines and, again, the committee should be congratulated. For many decades, endocrinologists and nuclear medicine specialists have used “radioactive iodine” and related terms in a varied and general manner.

The present ATA guidelines, which now recommend more specific detail for dividing radioactive iodine administration into categories of remnant ablation, adjuvantive therapy, and treatment, make a lot of sense. This categorization individualizes the treatment. It decreases the likelihood of side effects for people who do not need larger doses of radioactive iodine. Yet, it enhances the likelihood of the radioactive iodine to be effective in patients who would benefit from its use.

In general, a remnant ablation ^{131}I dose would be approximately 30 mCi. Adjuvantive therapy would be perhaps 30–100 mCi, and a treatment dose would be 100–200 mCi.

Dr. McIver: I would agree entirely with Dr. Burman on this topic. One of the most important advances in the area of radionuclide use in thyroid cancer is exactly what you have done here, which is to recognize that there are three different purposes to the use of radioactive iodine, which we have traditionally called radioactive iodine ablation.

We have ablation of the normal thyroid remnant, treatment of what we assume might be microscopically residual disease, and treatment of anatomically evident disease. Those three different treatment purposes require us to have three different thought processes and perhaps three different approaches to achieving our goals.

Dr. Haugen: Thank you, Dr. McIver. Let’s return now in more detail to the idea that Dr. Sipos brought up earlier about the usefulness of the sonographic pattern approach. We have definitely threaded this throughout our discussion, not only in regard to choice of nodule biopsy, but also decision

making in interpreting the cytology or in follow-up of these patients and how often we monitor them based on the sonographic risk categories.

I would like to focus on how you see this influencing practice. Will it be relatively easy to put into practice or do you see potential challenges?

Dr. Koenig: I actually think it is harder to do in reality than it comes across in the guidelines, although the guidelines do have very thorough discussions and caveats. I would first like to make two specific points. One, there is subjectivity to a number of these ultrasound criteria. Not only is there user dependence, but also equipment dependence. In addition, some of these criteria are really continuous variables. For example, irregular margins would have to be converted into a binary variable—they are either present or absent.

This makes it more difficult to use these guidelines. An example of where I am not totally sure I agree with the recommendations is recommendation 23, which says that nodules with a high suspicion ultrasound pattern and a benign cytology should have a repeat FNA within 12 months.

I am honestly not sure I agree with that. Suppose it is a 1.1 cm nodule that remains 1.1 cm and the high suspicion features are kind of iffy. I totally agree that the criteria you discussed in the reviews are really important, and we should always look for them, but I think in practice it can be more difficult than it sounds on paper.

Dr. Haugen: I will open this up for discussion, but first I would ask you, Dr. Koenig, what you think of figure 2? One of the goals was not just to say what the criteria were, but to show a series of examples. One thing I have been recommending to people, and we do it here, is to take figure 2, laminate it, and put it up in the ultrasound room so you can compare these patterns. Do you think that could be helpful to get around some of the verbiage—to express it more pictorially?

Dr. Koenig: Yes, I really like figure 2.

Dr. Haugen: Good, thank you.

Dr. Mandel: Ron, I truly appreciate the challenges of sonography, and when we were sitting down to discuss ultrasound, a certain distinction between two concepts was vital. These were ultrasound features—the individual ultrasound characteristics we have been trained to identify (e.g., echogenicity, microcalcifications) versus ultrasound patterns—the composite ultrasound image of a nodule.

You mentioned that the features can be really difficult for people to identify accurately. We know that bright reflectors in a nodule are probably the feature

most commonly misinterpreted as microcalcifications when actually they are not. And, identification of margins can be challenging, especially in smaller nodules or cystic nodules.

It turns out that the ultrasound features do not occur independently in a nodule, but instead they are correlated with one another; certain features are more likely to be present together than others. Thus, rather than counting the number of individual “suspicious” features, we want to focus on the constellation of those features together.

If you see bright reflectors in a mixed cystic-solid nodule, those are not going to be microcalcifications. Moreover, if you look at figure 2, you will see examples of small bright reflectors in mixed cystic-solid nodule; these denote a very low suspicion pattern. However, if you see similar appearing bright in a hypoechoic solid nodule, these are microcalcifications and are associated with a high suspicion pattern.

For a nodule to fall into that pattern it has to display a set of features. So I would ask our readers, who are so used to focusing on these individual features, to step back. We are not looking for the absence or presence of an individual feature, but instead how the pattern occurs and how that feature then appears in a pattern with hypoechogenicity and irregular margins, or how the bright reflectors occur in a mixed cystic-solid nodule.

We know that the interobserver variability is so much better when you are identifying patterns, which include a constellation of individual ultrasound features, rather than a single feature, say the presence of an irregular margin without taking into account other sonographic aspects of the nodule. The identification of patterns is much more robust.

We are building upon the literature that was initiated by our colleagues in Europe with TIRADS, the Thyroid Image and Reporting Data System, and trying to develop something accessible using a picture that a physician could look at (figure 2) and say, “Does the nodule I am imaging look like that?” For example, even if the margin looks a little irregular, if it lacks all of the other imaging qualities present in a high-suspicion pattern, it is not then high risk for malignancy.

This is our first attempt at presenting this pictorial “atlas” of patterns, and I hope it will be a stimulus for many studies, just as occurred after prior guidelines. For example, those studies helped us better refine the classifications of Initial Risk of Recurrence for thyroid cancer.

Dr. Haugen: Thank you, Dr. Mandel.

Dr. Sherman: If I can interject, I think that figures 2 and 4 are incredibly important and instructive, not only for all the details that have already been mentioned in the previous discussions, but also because they em-

phasize that what we do when we take care of patients with cancer is a matter of managing risk, from risk for diagnosis to risk for death and everything in between. And risk is a continuum at all times.

And that is why this publication is not entitled “rules” for management of patients with thyroid cancer—it is “guidelines.” We are emphasizing that, yes, for research purposes it is useful to put patients into specific categories with boundaries and silos. In clinical management, though, it is a continuous spectrum of issues we have to deal with, perhaps in a multidisciplinary fashion.

That message keeps coming through these guidelines in a far stronger way than for any document we have prepared before. And these figures really represent that.

Dr. Haugen: Thank you, Dr. Sherman. I would like to return to the topic of radioiodine refractory disease, but rather than talking about its definition, focus instead on the subsequent recommendations related to things such as monitoring, directed therapy, clinical trials, systemic therapy, and all the issues that are brought up in tables 16 and 17.

How do you envision that these may change our approach to patients, or perhaps be helpful to endocrinologists, medical oncologists, or surgeons, who may be treating more advanced patients? I would like to start with Dr. McIver.

Dr. McIver: These tables are tremendously useful and important. Some of the hardest decisions we have to make in this field are not related to the low-level aggression, standard papillary thyroid cancer, where we have argued for decades about the need for extensive surgery and whether to use radioactive iodine.

The key questions that are now coming up with these newer targeted agents are to whom should they be applied and what should be the criteria we use to make that determination.

Those decisions are fundamentally important in our day-to-day clinical practice in a cancer center. Therefore, we have got to understand the toxicity of these drugs to be able to balance that against their efficacy. The risk–benefit ratio has to be carefully thought through.

As a whole, endocrine oncology is finally entering the era of true oncologic care, where we take into account the risk–benefit ratio and understand the appropriate balance between “maximal tolerated therapy,” on the one hand, and “minimal effective therapy,” on the other. These tables start the process of engaging endocrine oncologists in that thought process.

Dr. Sipos: I would echo what Bryan just said and also highlight the importance of this table in making us

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aware that it is okay sometimes to follow these patients with iodine refractory disease. This table introduces the idea of simply following patients with asymptomatic disease and a low tumor burden. Whereas previously we may have felt like we had to act, now we understand that even though we have drugs available, it is not always appropriate to use them.

This is one of the most challenging aspects of treating these patients—making decisions about when to act and when to watch. Now, we can feel more comfortable in an active surveillance mode rather than feeling like we need to be doing something because we recognize that these treatments have toxicities, and we recognize the limitations of the expected outcomes with these therapies.

Dr. Burman: I agree with the comments just noted, specifically with the difficulty in deciding when to initiate therapy with oral chemotherapeutic agents, such as a multikinase inhibitor. In each case, we have to balance the potential toxicities against evident disease progression. I also would like to comment on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, which physicians have used to assess disease regression, progression, or stability. This system does not take into account lesions in the bone, for example, and only assesses a small number of lesions (e.g., five lesions). Also, the relative percent changes required for designation into a specific category are subjective, and it is important that the radiologist be very careful in measuring changes in lesions.

Dr. Haugen: Returning now to the topic of indeterminate cytology, and the overall question of how you approach that—whether you monitor, whether you repeat biopsy, whether you send a patient to surgery and what type of surgery, whether we choose molecular markers, etc.

You have said that there are some definite challenges with the recommendations, but you also provided some explanations for why they need to be written this way. How do you envision that the recommendations regarding indeterminate cytology are going to affect practice? Do you see them as helping to guide practice or are they too diffuse to provide real guidance?

Dr. McIver: Bryan, I think that one of the great benefits of the infusion of molecular information into the field of cytopathology has come from the unexpected recognition that this should not be a sleepy backwater of thyroid oncology. It should be front and center, and vibrant.

In our institution, it has forced us to take a very hard look at the quality of our cytopathology reporting. It has forced us to understand the in-house rates of ma-

lignancy that we see in patients with various Bethesda categories. These are issues that in the past often went unnoticed by the clinicians, when we simply trusted the cytopathologist to direct us.

Now though, in this new era of molecular markers, recognizing that pretest probability influences very dramatically the performance of the molecular assays has really transformed this field in ways that we could never have imagined just a few years ago.

Independent of the actual tests we order has been this recognition that we have to know what cytopathologists mean when they call a Bethesda 3, a Bethesda 4, or a Bethesda 5 diagnostic category. We have to understand what is the probability of that nodule being cancer within these subcategories.

What I am trying to emphasize is that cytopathology has traditionally been more of an art form than a science, and that the categories we have used for years are not solid, discrete silos. There is a gradation of risk from the almost certainly benign to the almost certainly malignant, but “almost” is the operative word here. We have a lot more to learn about the molecular testing, but we have already learned a huge amount about cytopathology from that very exercise.

Dr. Haugen: Yes, thank you, and I would even add that I think in doing some of these studies and tests, a multicenter group that we were part of also brought forward the challenge of intra- and inter-observer variability in indeterminate cytology and in those Bethesda categories. It can even be challenging for experienced cytopathologists to categorize indeterminate cytology reproducibly.

Would anyone else like to comment about the recommendations and whether they will help people make decisions about which patients to send to surgery, when to consider molecular markers, and which patients to monitor?

Dr. Koenig: I think the guidelines for this are really terrific for a couple of reasons. One is what Julie Ann talked about earlier: the importance of engaging the patient and the patient’s preference in the management decision, which I feel is very important. What has been described as the vagueness or diffuseness of the recommendations I think is perfect because molecular testing is not the gold standard. There are uncertainties, as everybody has said, at both ends of the risk spectrum, for the chance of a lesion being malignant or benign.

Therefore, when you are going to use these molecular tools will really depend on each individual case. I think the way it is constructed in the guidelines is extremely helpful and right on target for the current state of the art.

Dr. Haugen: I would add that another issue we dealt with was the rapidly evolving nature of this field. We are writing guidelines that will hopefully be around for a number of years, and we did not want them to become immediately outdated.

Dr. Sipos: I think the guidelines will provide a useful framework from which clinicians can make decisions regarding the management of patients with indeterminate thyroid nodules. One of the really nice things that was done in discussing indeterminate nodules was taking a multifaceted approach, if you will, in that no single feature should be looked at individually, but rather the whole picture should be evaluated. This comprehensive approach involves incorporation of the sonographic assessment of the nodule, the risk of malignancy in a given patient population, and the cytologic changes to decide when to use molecular testing, when to observe the patient, and when to go straight to surgery.

Because the cytologic diagnosis of atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) can encompass such a broad range of nodules, with a wide risk of malignancy, I appreciate how the guidelines discuss atypia in terms of why a nodule may be labeled as indeterminate, or preparation artifact. The authors did a really nice job of describing how these individual features may impact the risk of malignancy in a given nodule. Patient characteristics should be considered as well—their comorbid conditions, radiation exposure, and family history. Additionally, ultrasound features, as discussed earlier, impose a risk of malignancy that may alter our decision making. So I think the guidelines do a nice job of outlining the factors that impact the risk of malignancy in an indeterminate thyroid nodule, rather than taking the view that only one individual feature is going to incur a risk.

Dr. Sosa: There are a lot of moving parts in the new guidelines, and as each part moves, it has a downstream effect that can make other parts move differently. One of the ways we encountered this was the intersection between molecular testing and our evolving recommendations about appropriate extent of surgery for low and low-intermediate risk differentiated thyroid cancers.

For example, in the 2009 guidelines, total thyroidectomy was recommended for all tumors > 1 cm. As a result, some clinicians were using a rule-in molecular test to determine the appropriate extent of surgery; if the molecular test demonstrated a high risk for cancer, they would perform a total thyroidectomy, but if not, a diagnostic thyroid lobectomy would be pursued.

However, now that potentially either lobectomy or total thyroidectomy may be the appropriate oncologic

operation for low-risk thyroid cancers in the 2015 guidelines, how we use molecular testing is cast in a different light. This is just an example, but it will likely have a domino effect. How we change one thing can affect how we think about another, and it will be very interesting over the next several years to see how practice evolves.

Dr. McIver: I agree with the points Dr. Sosa just elucidated that the change in the recommendations, or at least the options for management of especially the low-risk cancers, really has to change how we interpret and use the molecular markers. It also increases the importance of understanding the granular meaning of the molecular markers themselves.

Some specific mutations, for example, confer a low probability of malignancy; others confer a high probability of a low-risk malignancy. I suspect, in the future, we will be seeing that those are present in the subset of tumors that can safely be managed with minimal intervention. Other mutations or genetic abnormalities confer much higher risk—of a more aggressive type of tumor—and even though these might be present in a smaller tumor, those patients perhaps deserve a total thyroidectomy, or other more aggressive intervention.

This is an area of future research, which obviously needs to evolve over the next few years, but it is one of the reasons I am happy that the guidelines were not expressly explicit in which tests we should use. They provide the option to use a variety of these different tests. I think the future is a very exciting one in this field.

Dr. Sherman: Dr. McIver is correct in pointing out that these are important areas for future research. The guidelines do not currently make a recommendation for total thyroidectomy based on a specific molecular profile independent of the usual clinicopathologic parameters.

Dr. Haugen: Thank you. As we approach the end of our discussion, I would like to open it up for comments or thoughts about topics or issues we may not yet have discussed.

Dr. Sherman: I would like to underscore your comment, Bryan Haugen, about how we spent several years trying to create a document that would have some durability in its recommendations, and recognizing that it may be picked apart piece by piece as new information comes out, changing some of the diagnostic classifications, for example, for different subtypes of what has been called thyroid cancer, or as new data emerge from ongoing clinical trials and studies, particularly about the use of systemic therapies.

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I would like to emphasize the importance of viewing this document as a guideline, and as the best possible effort as of the end of 2015. That said, work on the next set of guidelines probably needs to start in January, as this is a rapidly evolving field and the state of the knowledge will dictate that people need to continue to stay current with new information as it becomes available.

Dr. Mandel: To circle back to the beginning of our discussion for just a moment, I would like to reiterate Bryan's introductory comments about what was very helpful to the task force in its efforts to make the guidelines as relevant as possible with the existing literature. We relied extensively on the feedback that we received from the clinicians who use these guidelines.

We will keep this dialogue open because this document will be revised. Critical to those revisions will be the comments that we receive back from our colleagues who use these guidelines over the next couple of years.

Dr. Haugen: Yes, certainly, thank you. In closing, I would mention one section that we do not talk much about: the final section of directions for future research. That is an area in which we say again that we do not yet have enough information to guide our patients' care, where we think and hope the field is going, and in what areas we are seeing encouraging research.

I would like to thank all of the panelists for participating today, contributing to an excellent and broad discussion, and helping to identify some of the most valuable aspects of the new guidelines for clinicians caring for patients with thyroid nod-

ules and cancer. I appreciate, too, your insights into some of the challenges that we see in practice, whether in an academic medical center or in a community practice.

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Dr. Sipos is a Consultant and Speaker for Genzyme.

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