In this issue of *Mayo Clinic Proceedings*, Hay et al. present their analysis of the impact of radioactive iodine remnant ablation (RRA) in low-risk adult papillary thyroid carcinoma (PTC). With a median follow-up of 13.8 years and a total of over 50,000 patient-years of follow-up, they found that RRA did not reduce either cause-specific mortality or recurrence rate, and therefore, they do not recommend RRA in low-risk adult patients with PTC who undergo bilateral lobar resection with curative intent.

As the group eloquently describe, the role of RRA in the management of low-risk patients with PTC has been controversial for decades. Early reports of improved outcome following RRA predated the modern-day concept of risk stratification and were based on approaches at significant variance with contemporary practice in the 21st century. Many groups remained skeptical of the overall benefit of RRA in low-risk patients, despite growing support from international guidelines based on further evidence from high-volume national database studies. Continued pressure from these groups has resulted in recent recognition of the uncertainty of benefit associated with RRA in the majority of patients and as a result, a change in the guidelines to reflect this uncertainty.

The challenge for researchers with an interest in low-risk thyroid cancers is the low event rate. With a cause-specific mortality rate of under 5% and recurrence rates between 10% and 20% at 20 years, it is extremely difficult to study questions relating to the impact that management has on oncological outcome. This problem highlights the importance of studies drawn from resources such as the Mayo Clinic Rochester papillary thyroid carcinoma database (MRPD).

When trying to answer a question like “What is the role of RRA in the management of low-risk thyroid cancer?” there are a number of ways that researchers can approach the problem. Clearly, the purest approach is to design a prospective randomized controlled trial. The problem with that approach is the huge numbers of patients required and the duration of follow-up. When the American Thyroid Association considered the feasibility of such an approach, they estimated that almost 6000 patients would have to be enrolled to achieve 80% statistical power. Clearly, this approach is impractical. Recent attempts to analyze outcomes of randomized controlled trials have relied on a noninferiority approach and confirm that low-dose RRA is not inferior to high-dose RRA. These same groups are using similar designs to analyze the outcomes in the low-dose vs no-dose setting, but conclusions again will be limited by the constraints of low patient number and limited follow-up.

Another approach is to use information drawn from large databases on a regional or national scale. Such resources provide powerful tools to capture data on a huge cohort of patients but have significant limitations. Some lack critical information on staging or recurrence details, and information accuracy has been criticized in others. A third way, and the method used by Hay et al., involves the analysis of a single institutional data set over a long time period. The MRPD is a prime example of this approach. Decades of hard work have resulted in one of the most significant thyroid cancer databases in the world. Such resources present highly accurate clinico-pathologic details, comprehensive recurrence recording, and a relatively standardized approach to management within a single institution. However, work
resulting from analysis of such databases is not without its own limitations. Cohort numbers are smaller than those available from national-scale databases, local biases in management are impossible to control for in retrospective analysis, and basic approaches to diagnosis, pathologic classifications, management, and follow-up have evolved during the life of the work. However, with decades of experience in the analysis and presentation of their work, Hay et al have structured their report to address as many of these limitations as possible. Specifically, these authors not only present an overall analysis but also used subgroup analysis to address these issues, and they meticulously highlight how this data source addressed limitations pointed out by other experts in the field who have approached this controversial topic. The MRPD has not only contributed to the very way that all thyroid cancers are now risk-assessed with the MACIS (metastasis, age, completeness of resection, invasion, size) system, still employed internationally decades after it was first described, but also continues to provide insight regarding outcomes for the spectrum of papillary thyroid carcinomas encountered in clinical practice.

Because of the aforementioned challenges, it is most likely that the question of whether RRA is beneficial in patients with low-risk PTC will remain definitively unanswered forever. However, it is increasingly evident that if vast cohorts of low-risk patients are required to make a definitive judgment on statistical benefit, then the chance that there is clinical benefit to the individual patient is extremely low.

How then does the practicing clinician incorporate these findings into their own practice? For a small minority of patients, aggressive treatment (ie, total thyroidectomy, neck dissection, and RRA) is entirely justified. Such patients are easy to recognize preoperatively as they have bulky nodal disease and may have distant metastases. However, the vast majority of patients have lower-risk disease. Such patients have increasingly been found to not benefit from RRA, as demonstrated again by Hay et al in this issue of Mayo Clinic Proceedings. Clinicians must therefore carefully weigh the pros and cons before making treatment recommendations.

The rate of significant pathology in the thyroid lobes contralateral to index malignant pathology is vanishingly low. “Completing" the thyroidectomy is thus performed only to enable the patient to receive radioactive iodine. Therefore, in low-risk patients, one must first decide whether there is an indication for RRA. If that indication is lacking, a second decision is whether there is an indication for contralateral thyroid lobectomy at all. Total thyroidectomy is often recommended for patients with contralateral nodules because such nodules would require lifelong follow-up. However, small-volume benign nodules can be accurately identified using modern ultrasonography and safely monitored without the need for resection in most cases.

With a nonsuspicious contralateral lobe and no clinical evidence of regional or distant disease, thyroid lobectomy alone will achieve an accurate histologic diagnosis, eradicate macroscopic disease, and minimize morbidity from treatment. All of these aims are achieved without the risk of permanent hypocalcemia or tracheotomy, which are uniquely associated with bilateral rather than unilateral thyroid surgery.

The importance, then, of the article by Hay et al can be seen in a variety of lights. First and foremost, it demonstrates that RRA is moving from a treatment that was recommended in almost all patients with differentiated thyroid cancer 10 years ago to one that is indicated only in high-risk disease. In addition, against the backdrop of an increasing number of prospective clinical trials and articles based on information from national database resources, the work of Hay et al highlights the importance of clinicians investing time and effort in producing high-quality, long-term, reliable data sources for scrutiny decades after their design and inception. Finally, and perhaps most importantly, this highly experienced group has yet again demonstrated that in thyroid cancer, as in so many other malignancies, it is the biology of disease rather than the extent of treatment that is crucial to
outcome. Outcomes for patients with more aggressive disease lag behind those for patients with less aggressive disease, irrespective of the approach to therapy adopted. The same cannot be said for treatment-related morbidity, which is directly related to the decisions made by disease management teams across the globe. Hay et al., who have contributed so much to our understanding of the biology of this disease, should once again be commended for their ongoing commitment and efforts to optimize patient outcomes with hard work and careful scrutiny of their practice.

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