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The Year in Medical Thyroidology Review: Current Challenges and Future Directions

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This is a summary of the American Thyroid Association's Opening Session at the 89th Annual Meeting in October 2019. This review highlights the most clinically impactful articles in medical thyroidology published from January 2018 through September 2019.

Keywords: Hashimoto's, Graves' disease, quality of life, thyroid nodules, thyroid cancer

Introduction

This year, at the 89th American Thyroid Association Annual Meeting, I was honored to be a part of the opening session. I was asked to summarize the most influential and thought-provoking publications in medical thyroidology over the past year. This review summarizes the 89th Annual Opening session presentation on Medical Thyroidology: Year in Review (Table 1).

Methods

Original, peer-reviewed research articles published between January 2018 and September 2019 were included in this review. The articles discussed herein were identified by a thorough review of the available literature, publications reviewed in *Clinical Thyroidology* and a survey of physicians for original research articles in the given time frame that they felt affected the clinical practice of thyroidology. A brief summary of these articles is presented along with its clinical utility or implications. Publications of interest discussed below include the following: Hashimoto's and hypothyroidism, hyperthyroidism and therapy-induced thyroid dysfunction (duration of antithyroid drug [ATD] use, morbidity from radioactive iodine (^{131}I) treatment and ATDs, and immunotherapy-induced thyroid dysfunction), and thyroid nodules and thyroid cancer (active surveillance, quality of life and targeted systemic therapies).

Hashimoto's and Hypothyroidism

Hashimoto's thyroiditis is not a well-understood phenomenon. Despite much research in this arena, there are more questions than answers. There are many euthyroid patients with positive thyroid peroxidase antibodies (+TPO abs) who suffer symptoms or desire for pregnancy, yet the jury is still out on therapeutic next steps. Below I summarize findings from two articles that try to address these issues.

Dhillon-Smith *et al.* investigated effects of levothyroxine replacement in pregnant patients with +TPO abs before conception (1). The authors sought to determine if replacement with levothyroxine 50 mcg improves the live birth rate (after 34 weeks of gestation) in pregnant euthyroid women with +TPO abs. To investigate this, they conducted a multicenter, randomized, placebo-controlled Thyroid Antibodies and Levothyroxine (TABLET) trial evaluating levothyroxine 50 mcg daily versus placebo. Only women who had +TPO abs preconception, had a history of infertility, or more than one miscarriage were enrolled. Women had to be euthyroid with thyrotropin (TSH) in the range of 0.44–3.63 mU/L. A total of 952 women were randomized before conception and equally distributed between the levothyroxine arm and placebo arm. No significant baseline differences were seen. Of those randomized to the thyroid hormone treatment group, 56.6% of them had live births versus 58.3% of those in the placebo group. There were no differences seen in the primary outcome of live birth rates at 34 weeks of gestation between the two groups (37.4% vs. 37.9%, respectively), and similar rates of miscarriage were seen between the groups (28.2% vs. 29.6%).

This article has stimulated much discussion regarding thyroid hormone replacement during pregnancy. While levothyroxine 50 mcg did not improve live birth rates or pregnancy in euthyroid +TPO ab women who had ≥1 miscarriage or infertility, the potential benefits of thyroid supplementation during pregnancy cannot be ruled out. Additional research is required to determine whether higher doses of levothyroxine might yield different results. Similarly, it is possible that a higher risk population with higher recurrent pregnancy losses might yield different results (2).

The major strength of this article is that it is a large, randomized-controlled, placebo-controlled trial of more

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Table 1. Summary of Advances in Medical Thyroidology 2018–2019

Fixed low dose of thyroid hormone may not increase live birth rate in euthyroid women with +TPO abs
Surgery improves quality of life in patients with Hashimoto's thyroiditis
ATDs may need to be continued for longer than 18–24 months to decrease the rate of relapse in Graves' disease
Hyperthyroidism should be treated rapidly and remain controlled to improve total and cardiovascular mortality
Treatments for hyperthyroidism with RAI and ATDs but not surgery may be associated with increased cancer mortality
Pediatric thyroid nodules are at higher risk of malignancy compared with adults but perhaps not as high as previously thought
Low-risk thyroid cancer patients worry about harm, death, and recurrence from thyroid cancer and its therapies
Patients perceive they do not have choice in RAI treatment of their thyroid cancer
Therapeutic options for systemic therapy for metastatic thyroid cancer have advanced, increased, and become more personalized

ATD, antithyroid drug; RAI, radioactive iodine therapy; +TPO abs, positive antithyroid perixodase antibodies.

than 900 individuals. It is unclear what the compliance of this group was, if age or +TPO ab titers mattered, but nonetheless a provocative article.

Another important article in patients with Hashimoto's thyroiditis compared thyroidectomy versus medical management in euthyroid patients with Hashimoto disease and persistent symptoms. This study by Guldvog *et al.* randomized patients with symptomatic Hashimoto's thyroiditis to surgery versus medical management (3,4). The authors found that in Hashimoto's patients who met their strict entry criteria, quality-of-life health scores, including fatigue at 18 months, improved in all areas in the group randomized to surgery compared with expectant medical management (no sham surgery group).

Hyperthyroidism and Therapy-Induced Thyroid Dysfunction

Several articles came out this year having an impact in the field of Graves' disease (GD) and hyperthyroidism. Here I highlight articles dealing with the choice of therapy for hyperthyroidism, length of therapy, and potential morbidities associated with the treatment of hyperthyroidism. All of these studies may affect future guidelines on treatment of hyperthyroidism (4).

Length of therapy for hyperthyroidism

Azizi *et al.* set out to determine whether longer use of ATDs is associated with higher remission rates from GD (5). They designed a prospective, single-center, randomized parallel-group trial between October 2001 and March 2017 in an iodine-sufficient area of Iran. The primary endpoint was overt hyperthyroidism. The secondary endpoint was subclinical thyroid dysfunction. There were 258 patients who, after 18–24 months of methimazole (MMI) treatment, were randomized to continue on long-term MMI (36–102 more months) versus discontinuation of MMI. Study participants were followed for 48 months. The baseline characteristics were similar in both groups with a trend toward older patients in the long-term treatment group and higher goiter grade in the discontinuation group. The duration of MMI treatment was 95 + 22 months in the long-term treatment group versus 19 + 3 months in the discontinuation group. The relapse rates of GD at 48 months were 18/119 (15%) in the long-term group versus 65/123 (53%) of those in the discontinuation group. Interestingly, factors that were associated with relapse included older age (trend toward a bias in the long-term group) and higher thyroid receptor antibody levels. They also found that single-nucleotide polymorphism, rs1879877 CD28 or DQB1-05 HLA, was associated with relapse. In the multivariate analysis only, lower TSH and higher triiodothyronine (T3) levels were also associated with higher rates of relapse. The study concluded that longer term ATDs may be associated with lower relapse rates than the conventional 18–24 months, and this translated to 3 times lower relapse in a 4-year period. Some important caveats are this study differed from other studies as relapse was defined as development of overt hyperthyroidism rather than subclinical hyperthyroidism and that the multivariate analysis included variables that were nonsignificant in the univariate analysis as they were felt to be clinically significant.

Current guidelines on the recommended duration of ATDs state that ATDs may not be helpful beyond 18–24 months (4). This new evidence may cause this treatment recommendation to be modified. As always, patient preference on treatment options of GD will need to be taken into consideration.

Morbidity of therapies

Several articles published in the past year describe morbidities from therapies for hyperthyroidism (radioactive iodine and ATDs) and immunotherapy-induced thyroid dysfunction.

One thought provoking article that received a lot of press was an article by Kitahara *et al.* where they evaluated the association of radioactive iodine treatment with cancer mortality (6). The objective of this article was to determine if the absorbed dose of radioactive iodine is associated with overall and site-specific cancer mortality in patients with hyperthyroidism. The data were derived from an older study entitled cohort study ''(Cooperative Thyrotoxicosis Therapy Follow-up Study).'' It is a follow-up of the original study of more than 35,000 subjects treated between 1946 and 1964 and this was the 24 plus year follow-up (7). They used organ-based ^{131}I exposure to determine association of ^{131}I therapy with cancer risk. They report data on 197 subjects who had three or more measures of blood, thyroid, and urine kinetics from the original 18,805 subjects. Body mass index, height, and sex were used to calculate plasma volume and other patient-specific variables. The number of ^{131}I disintegrations in the various tissue compartment models was estimated. In addition, the organ-specific ^{131}I exposure was estimated from the administered ^{131}I dose and the compartmental model through a series of assumptions. As an example the amount of ^{131}I organ exposure correlates with the fraction of body water space occupied by the organ. The authors then obtained the background age- and cause-specific death rates from the U.S. 2014 Surveillance, Epidemiology, and End Results data.

The majority of these patients were females being treated for GD. One-third of the patients received more than one dose of ^{131}I and some could have received more than one type of treatment for hyperthyroidism. The mean dose of ^{131}I for GD was 10.1 mCi. There was a positive association with organ dose absorbed and all solid cancer mortality [RR 1.05 (1.01–1.10)], including breast cancer [RR 1.12 (1.003–1.32)]. They attribute 7% of all solid cancer deaths and 14% of breast cancer deaths to ^{131}I exposure. The authors state that for every 1000 hyperthyroid patients receiving radioactive iodine at typical doses to the stomach, an estimated lifetime excess of solid cancer deaths could occur. Based on their findings, the authors conclude that treatment with ^{131}I for hyperthyroidism was associated with increased mortality from solid cancers. There was no identified increased mortality related due to leukemia, non-Hodgkin lymphoma, multiple myeloma, or thyroid cancer.

The strengths of this study are that it is a large cohort study with extended follow-up, which the authors are to be commended for. They used an elegant ^{131}I biokinetic model with estimates of exposure of 26 organs. However, that very model may be their limitation as well. What was a little unclear from the article was when calculating risk of all solid cancers from ^{131}I exposure, why was the stomach exposure dose chosen to be used in the model rather than the sum of all organs exposed or respective organ dose exposure? Further validation of this model is needed. The model included significant assumptions with lack of controls for other treatments of hyperthyroidism (surgery and ATD—reported in their 1998 study) and for known risk factors for cancer, including smoking, obesity, and estrogen among others.

A companion commentary was published in the *Journal of Nuclear Medicine* in October 2019 by two of the coauthors of the article described above (8). This is not an original study, but a commentary with additional data. This article shows a table of previously unpublished data of long-term follow-up from the same cooperative TTFU study by Kitahara *et al.* described above. This table shows observed mortality and standardized mortality ratio from radioactive iodine-treated patients but also included was this same mortality data for ATD-treated patients and patients who underwent surgery. The data showed ATDs are associated with higher risk of cancer deaths, with higher relative risks than that shown for radioactive iodine therapy (RAI), while surgery is not. While the Kitahara article estimated 19–32 excess deaths per 1000 hyperthyroid patients treated with ^{131}I, these data suggest a prediction of 62–231 excess solid cancer deaths per 1000 hyperthyroid patients treated with ATDs. This article raises question in the age-old controversy of increased cancers from ATDs and ^{131}I and leaves food for thought for us as to what the true associated risk of malignancy and deaths is and how this should change our therapeutic options for our patients with hyperthyroidism.

In contemplating best therapies for our hyperthyroid patients, one must think about other morbidities as well. Previously, there have been questions as to whether there was an association between various therapies for hyperthyroidism and cardiovascular outcomes. In the United Kingdom, Okosieme *et al*. performed a case/control study to answer this very question (9). An impressively large number ($N = 4189$) of patients with GD were analyzed and matched to controls in a 1:4 manner. The primary outcome measure was all-cause mortality with secondary outcomes of cardiovascular events one year after diagnosis. As would be expected for most studies on GD in the United Kingdom, most patients were female, 73.9% of therapies were ATDs, 19.8% were radioactive iodine, and 6.3% underwent surgery. These patients were followed for a minimum of 6 months and a maximum of 16.8 years. The study found an increased total mortality [HR 1.23 (1.06–1.42, $p = 0.08$)] and cardiovascular-related events [HR 2.47 (2.16–2.81, $p = 0.001$)] in patients treated for their GD. Compared with population controls, GD patients had a 23% increased risk for all-cause mortality and greater than two times the risk of a major cardiovascular event. In further analyses, this increased mortality appeared to be consistent independent of and across all treatment types if hyperthyroidism was not resolved and TSH remained low at one year. What we have learned is that no matter what the therapy for GD, rapid, early, and sustained, effective control of hyperthyroidism is associated with improved survival. This study was a large longitudinal sample with good data linkage and regression approach. Longer term prospective studies will be needed to evaluate confounding factors such as patient and physician preferences, and compliance with thionamides and thyroid hormone, to better understand the true risks of morbidity from therapies for hyperthyroidism.

Therapy-induced thyroid dysfunction

Use of immunotherapy for cancer is gaining popularity, and the range of approved indications is increasing at a rapid rate. Endocrinologists, oncologists, and primary care physicians need to be well aware of the thyroid dysfunction that can be seen with these therapies. We highlight, below, a study published by Iyer *et al.* (10). This was a retrospective study aimed at delineating the natural clinical course of immunotherapy-induced thyroid dysfunction. Forty-four subjects on immunotherapy, who were referred to the endocrine clinic for thyroid dysfunction, were evaluated. The median age in this study was 57 years with patients with a variety of cancers and on single-agent antiprogrammed cell death 1 (antiPD-1) or combination of anti PD-1 with anticytotoxic lymphocyte-associated protein 4 (anti-CTLA4) therapies.

The authors found that these patients develop a thyroiditis-type picture with suppression of their TSH rapidly and early within the first 31.5 days (4–173) of therapy and then rapid transition to hypothyroidism, with initial normalization and then elevation of TSH $\sim$41.5 days (18–217) later. A minority of patients develop GD, but these patients were excluded from this study. Of these 44 patients who developed thyroiditis, 73% of patients were asymptomatic during the thyrotoxic phase (i.e., painless thyroiditis). The vast majority (82%) developed hypothyroidism afterward necessitating long-term thyroid hormone replacement. Conservative therapy during the thyrotoxic phase of thyroiditis was sufficient. They showed that immunotherapy-induced thyroiditis was more commonly associated with anti-PD1 drugs used either alone or in combination with anti-CTLA4 therapy. Other studies provide additional information on the clinical course of immunotherapy-induced thyroiditis and when to treat such a clinical scenario. However, larger prospective studies are needed to study the incidence and natural history of thyroiditis, to help predict who will develop it

and best ways to treat and/or prevent it. Thyrotoxicosis guidelines should include immunotherapy-induced thyroiditis as an additional etiology of drug-induced thyroiditis in the future (4).

Thyroid Nodules

There are many studies published this past year that better define the incidence and distribution of thyroid nodules that are indeterminate on fine-needle aspiration cytology. Two of these studies are discussed in detail in this same issue of *Thyroid*, *Surgical Thyroidology*: Year in Review (11,12). An additional study on this topic was published by Wang *et al.* and focused on pediatric thyroid nodules (13). The authors sought to assess the overall malignancy rates for indeterminate thyroid nodules in children, as they felt these nodules are rare in children and that current guidelines may be too aggressive for patients younger than 21. This was a retrospective single-center study over a 17-year period. A total of 302 fine-needle aspiration cytologies were reviewed and 14% were indeterminate. One hundred four thyroid nodules were surgically resected, and 31% were malignant on histology. They divided their indeterminate nodules into Bethesda categories of indeterminate nodules: atypical cells of undetermined significance/follicular lesion of undetermined significance, follicular neoplasm/suspicious for follicular neoplasm, and suspicious for follicular neoplasm.

This study, the largest cohort of pediatric thyroid nodules, highlights that the risk of malignancy in cytologically indeterminate thyroid nodules in children may be lower than previously reported, but is still higher than in adults (Table 2). Larger studies that are designed to include more indeterminate nodules in the pediatric population, including evaluation of molecular markers, are needed to strengthen these findings.

Thyroid Cancer

The thyroid cancer literature has exploded in recent years, including articles regarding the utility of surgery, improvements in diagnostic capability, active surveillance, or need for radioactive iodine. Some areas have limited data, including patient quality-of-life studies and research advances in systemic therapy. Thus, I highlight studies focused on these two areas below.

Table 2. The Estimated Malignancy Rate of Each Subcategory of Indeterminate Nodules

Cytology	*Malignancy rate (%)*
Wang *et al*. cohort	
AUS/FLUS (Bethesda III)	20
FN/SFN (Bethesda IV)	25
SFM (Bethesda V)	100
Wang *et al*. pooled with other studies	
AUS/FLUS (Bethesda III)	19–26
FN/SFN (Bethesda IV)	41–48
SFM (Bethesda V)	67–81

AUS/FLUS, atypical cells of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for follicular neoplasm; SFM, suspicious for follicular neoplasm.

Table 3. Food and Drug Administration-Approved Drugs That Can Be Used in Patients with Thyroid Cancer Who Fail Conventional Therapy

Agent	*Type of genetic alteration*	*Year approved*
Immunotherapy		
Pembrolizumab	MSI-H	2017
NTRKi		
Larotrectinib	NTRK alterations	2018
Entrectinib		2019

MSI-H, mismatch repair instability high tumors; NTRK, NTRKi, neurotrophic receptor kinase; NTRKi, neurotrophic receptor kinase inhibitors.

Quality of life and prognosis

Quality of life and emotional stress in cancer patients are areas that are grossly understudied in the thyroid cancer population. Two important articles were published this past year by Papaleontiou *et al.* (14) and Wallner *et al.* (15).

Papaleontiou *et al*. published an article about worry in thyroid cancer survivors with favorable prognosis (14). The authors performed a survey of patients with newly diagnosed thyroid cancer between 2014 and 2015, using two SEER registry regions (Los Angeles and Georgia) to determine cancer-related worry in thyroid cancer survivors with a favorable prognosis. No patients with recurrent or metastatic disease were included. A total of 2215 patients (most with T1N0 TNM stage disease) who responded to an extensively piloted, systematically developed survey were analyzed. The response rate was 63% and most of the patients were women and white, with almost half having a college degree or higher. Factors associated with more worry included women, those younger than 44 years, those in lower socioeconomic groups, and ethnic minorities. What was surprising was of this group at low risk for recurrence, 41–63% worried about death, recurrence of thyroid cancer, or harm from treatment at 2–4 years after diagnosis. Furthermore, almost one-fourth of them had substantial worry about these factors. Worry was common among those with otherwise excellent prognosis.

In trying to understand patient perspectives regarding treatment decisions, Wallner and associates conducted a

Table 4. RET Inhibitors and Type of Thyroid Cancer Where Oncologic Responses Have Been Observed

Agent	*Cancer type*	*Oncologic response (ORR) (%)*
Blu-667	DTC	83%
	MTC	56% (38–74)
Loxo-292	DTC	78% (40–97)
	MTC	59% (39–77)

RECIST criteria reported: ORR = objective response rate (partial response + complete response).
DTC; MTC.

population-based survey to understand patient decision-making when it comes to RAI (16). Of the 1319 patients surveyed and analyzed, the majority received RAI (75.9%) and a majority (55.8%) perceived they did not have a choice in that decision. The treating physician's strong recommendation for a patient to get RAI was more associated with perception of lack of choice in the matter, odds ratio (OR) = 1.56 [95% confidence interval = 1.13–2.17]. Those who felt they did not have choice in the decision-making were more likely to receive the treatment, OR = 2.50 [95% confidence interval = 1.64–3.82].

While both of these studies were large survey studies with good response rate, they highlight the fact that as physicians and health care providers we need to talk to our patients more, with in-depth discussion of treatment choices, impact of therapy, or lack thereof, and prognosis.

As health care providers, to explain to our patients their prognosis, we need to first understand overall and individual risks and the natural history of the disease. Banerjee *et al.* sought to determine predictors of poor treatment-free survival in treated thyroid cancer patients and to define prognostic groups for treatment-free survival (17). Using a population-based study design, the SEER cohort ($N = 9273$ patients), the authors were able to identify five distinct prognostic groups for treatment-free survival of differentiated thyroid cancer. They showed that the most important factors for predicting treatment-free survival were stage, tumor size, and having radioactive iodine treatment. While all these predictive factors may not be new information, they translate this to create an easy-to-understand treatment-free survival tree where there are clear percent estimates of treatment and corresponding disease-specific survivals. Although there is some missing treatment and response data inherent to population-based studies, it adds to the information to help health care providers prognosticate and discuss options with their patients. The next iteration of the differentiated thyroid cancer guidelines (16) should consider incorporating these studies to highlight the need for more involved discussions with patients and their caregivers regarding treatment options and prognosis.

Systemic therapies

There have been rapid advances in the treatment of thyroid cancer in the last decade, and even more so in the last two years. There has also been a move toward more personalized medicine. Nowhere has this been more evident than in the treatment of cancer. An increasing number of therapeutic trials are designed to enroll patients with multiple cancer types that have a common oncologic driver, otherwise known as ''basket trials.'' The idea is to increase patient access to targeted therapies that may work across tumor types, rather than design individual trials for each cancer subtype. If a response signal is only seen in one or two tumor types, further studies will proceed in those cancers that respond; however, if a signal is seen across tumor types, these drugs may then be approved regardless of cancer type for the specific driver genetic alteration that is present in the cancer.

Three therapies have been approved in the last two years by the U.S. Food and Drug Administration (FDA) for treatment of cancers based simply on the biomarker (somatic alteration) found in the tumor agnostic of cancer or tumor tissue type. These trials enrolled patients of various tumor types and saw oncologic responses across a variety of cancers (18–21). While we do not have published data for thyroid cancer patients specifically at this time, thyroid cancers were included in some of these trials with responses observed.

The approved drugs for the treatment of cancers based on oncologic biomarker agnostic of tumor type and available to our thyroid cancer patients are summarized in Table 3.

This past year also saw publications of ongoing therapeutic trials specifically for advancing thyroid cancer (Table 4). *RET* alterations are considered to be important oncologic drivers in thyroid cancer. Approximately half of all medullary thyroid cancer patients have somatic *RET* mutations, and a small percentage of follicular-derived thyroid cancers have *RET* fusions. Several agents have been discovered to inhibit the RET tyrosine kinase receptor (RET inhibitor) and hence are of potential therapeutic value in thyroid cancer. RET inhibitors have shown promise and are well tolerated with few adverse events in patients with differentiated and anaplastic thyroid cancers with *RET* fusions, as well as medullary thyroid cancer patients with *RET* mutations with some shrinkage in intracranial lesions reported (22–25).

Future Challenges That Are Opportunities

While the above studies help to advance medical thyroidology, there are always new challenges and opportunities to continue to improve and further the field. We need to do better at predictive medicine. Perhaps utilizing machine learning we will be able to predict from the outset the ideal preventative and therapeutic options in our thyroid patients. For example, what is the best thyroid hormone replacement regimen for a particular patient and whether combination replacement is likely to result in improved outcomes, including quality of life. Which thyroid nodule and cancer patients can be safely observed and do not need thyroid surgery? Who will develop thyroid dysfunction from the various immunotherapies being used in clinical practice for a variety of cancers? Which systemic therapies are ideal for the advanced thyroid cancer patient in the adjuvant or metastatic setting? And finally we need to improve our ways to be able to deliver excellent care to more widespread audiences, including utilization of telehealth to access areas of those underserved.

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