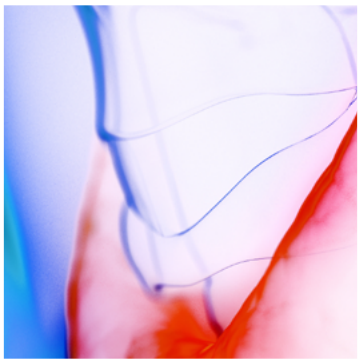
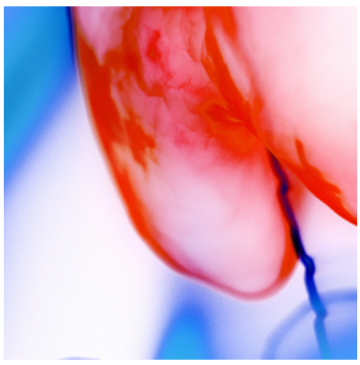
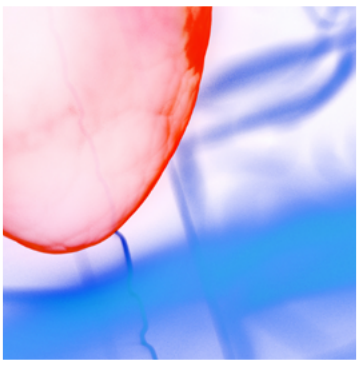
CONGRESS REPORT

Summary of the Latin American Thyroid Society (LATS) XVIII Congress







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SCIENTIFIC SEMINARS
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BIOGRAPHY

GABRIELA BRENTA

Gabriela Brenta is a staff member and thyroid unit coordinator of the Department of Endocrinology and Metabolism at Dr Cesar Milstein Care Unit in Buenos Aires, Argentina. She is also Assistant Professor at the Medical School of the University of Buenos Aires. Her areas of interest in clinical research include the cardiovascular and metabolic effects of thyroid hormones and in particular, the study of thyroid diseases, including nodular disease, in the elderly. She has published original papers and reviews in Thyroid, Nature and JCEM, as well as in other journals, and is a member of the editorial board of Thyroid and the Journal of Endocrinology Investigation. Dr. Brenta is a member of the Argentine Society of Endocrinology and Metabolism, where she actively participates in the thyroid division activities.
In June 2019, Dr. Brenta completed her term as President of the Latin American Thyroid Society (LATS) and in 2020 was engaged, on behalf of LATS, to serve on the Scientific Committee of the 16th International Thyroid Congress and also on the Scientific Committee of the 19th International Congress of Endocrinology.

Although a virtual meeting, the **XVIII Latin American Thyroid Society (LATS) Congress** attracted 1600 attendees, 17 international and 101 regional speakers, and presented two LATS senior awards and 2 Young LATS investigator awards.
The congress held its traditional **Thyroid Ultrasound Course** where the topics of the use of ultrasound for active surveillance (AS) of differentiated thyroid cancer, malignancy risk stratification of thyroid nodules and diverse ablation strategies were discussed by a panel of experts from Latin America, moderated by Dr Rosalinda de Camargo (Brazil) and Dr Eduardo Kiyoshi Tomimori (Brazil).
The **Kocher Conference,** chaired by Dr Erivelto Martinho Volpi (Brazil) and Dr Gregory Randolph (USA), considered new surgical techniques, such as Transoral Robotic Thyroidectomy (TORT), Transoral Endoscopic Thyroidectomy Vestibular Approach (TOETVA), and nonsurgical techniques, such as Radiofrequency Ablation (RFA) in the management of thyroid nodular disease. The recurrent dilemma: lobectomy versus total thyroidectomy (TT) or whether prophylactic neck dissection is indicated was also covered. New alternatives such as parathyroid autofluorescence, neural monitoring and molecular profiling for advanced thyroid cancer were discussed. Local speakers together with leaders in the field from South Korea, the USA and Japan shared their experience in these areas.
This summary covers only a small part of the incredibly rich material from international and local speakers, and poster presentations at this congress. A section is also devoted to those who participated and won the **LATS PRIZES**.

1) INTERNATIONAL SPEAKERS

A) THYROID NODULAR DISEASE

Dr Lisa Orloff (USA) in **Shifting paradigms in thyroid surgery: Open, remote, ablation or observation?** underscored ultrasonography's increasing relevance to guide decisions on thyroid nodules. Patients now have multiple therapeutic options that may include AS, surgery or minimally invasive techniques to ablate the lesion. Dr Orloff suggested that these new options should be discussed with patients, and she also clarified that although costly, RFA is now starting to be covered by Medicare in the USA.

Dr Marius Stan (USA) described the **Mayo Clinic experience with RFA** which started in 2013 with about 100 benign nodules. The program then included papillary thyroid microcarcinoma (mPTC) <10 mm, divided into low or high risk (lymph nodes (N)+ or metastasis (M)+, located in extrathyroidal areas, high-grade malignancy). The high-risk mPTC was referred to surgery but if low-risk mPTC was found, alternative management was proposed, either AS or RFA.

Dr Stan also described the results of Zhan M, et al,[1] in China, who treated 80 cases of isolated mPTC surgically, and 94 cases with RFA. The number of recurrences was similar in both groups, and there were no lymph node metastasis. The authors concluded that both approaches had the same oncological outcomes, however, the surgery took longer, and was costlier. In addition, there were recurrent laryngeal nerve injuries (2.5% of patients) and cases of hypoparathyroidism (1.2%) after surgery, whereas better quality of life was observed after RFA.

The Mayo Clinic RFA for mPTC pilot study concluded that parenchyma around the lesion is key, but after RFA, the lesion may look much bigger. Dr Stan explained that this was a natural consequence because the ablated area usually includes the surrounding thyroid. Consistent with this idea, according to Cho SJ et al.,[2] who followed 83 patients for 5 years, the buffer zone of normal parenchyma is also ablated, explaining why lesions look larger immediately after RFA.

The persisting questions on RFA, according to Dr Stan, are:

- Which PTC will most likely be cured by RFA?
- How does RFA compare with other ablative therapies?
- What is the inflection point between RFA and surgery?
- Ethanol ablation for thyroid lesions may be an alternative for cystic thyroid nodules, mPTC and adenopathies.

In summary, RFA can achieve nodule shrinkage of >50% by 6 months, symptom control is observed in most patients, all euthyroid patients before RFA remain euthyroid afterwards, toxic nodules respond well to RFA functionally and anatomically. However, RFA for PTC still has an investigational status, mainly for cases of mPTC.

Dr Cosimo Durante (Italy) addressed the intriguing question of **Why stratifying thyroid cancer risk is needed?** by first detailing the well-known epidemic of thyroid cancer, with incidence increasing all over the world. However, Dr Durante countered this by describing the occurrences in South Korea 1993–2011 when a national screening program uncovered more subclinical disease than would normally be found in the population, at the same time as recording stable mortality rates due to thyroid cancer. This overdiagnosis of low-risk thyroid cancer resulted in overtreatment, with an increase in thyroid surgical procedures from 1000 in the year 2000 to 10,000 procedures in 2012. In 2014, screening was stopped in South Korea with a 35% reduction in surgical procedures.
Similarly, in the USA between 2006 and 2011[3], surgery also increased 31%, with TT accounting for 12% per year of this increase. Overtreatment equals a higher rate of complications, even for high-volume surgeons, especially when TT is compared with lobectomy.
According to all these data, more low-risk thyroid cancer cases are being seen in clinical practice. In addition, the outcome of patients is also changing - today, with new, highly sensitive tools, recurrence is being detected earlier.

Dr Durante urged the audience to tailor their practice to the new profile of patients. Old paradigms include TT, radioiodine (RAI), levothyroxine (LT4) suppressive therapy and life-long follow-up for every thyroid cancer patient. New paradigms include identification of low, intermediate and high risk of recurrence patients, according to the American Thyroid Association (ATA), and an individual-based approach is deemed important.

All ATA risk of recurrence disease stages have been validated in retrospective cohort studies or referral centers. So, is the system performing well in a real-world setting? The experience of the Italian Thyroid Cancer Observatory (ITCO) was used to answer this question. ITCO created a web-based database to prospectively collect data on nearly 10,000 patients with thyroid cancer. The current network includes 48 centers in Italy that input cases to the database at the time of treatment. Dr Durante mentioned a paper (Grani G, et al. 2021)[4] containing initial results from ITCO, evaluating the performance of the 2015 ATA risk stratification system in 40 centers in Italy, and predicting the response to treatment in 12 months according to the 2015 ATA response to therapy. Of 2071 patients, Grani et al showed that the ATA risk of persistent/recurrent disease was classified as *low* in 1109 patients (53.6%), *intermediate* in 796 (38.4%), and *high* in 166 (8.0%). Structural incomplete responses were documented in only 86 (4.2%) patients: 1.5% in the low-risk, 5.7% in the intermediate-risk group and 14.5% in the high-risk group. Baseline ATA risk class proved to be a significant predictor of structural persistent disease, both for intermediate-risk and high-risk groups in real-world clinical settings.

The ATA tool has proved to be highly effective, but are we using it in clinical practice? If the extent of surgery is adapted to the extent of the tumor within the thyroid or the presence of spread outside the thyroid, according to ATA guidelines for those with low-risk cancer, the vast majority of patients should be lobectomized.
Since the publication of ATA guidelines, lobectomy has increased from 3% to 11% from 2015 to 2020 in the ITCO database. Yet, diagnostic lobectomy for indeterminate Bethesda categories still counts for almost half of the whole lobectomy group, suggesting lobectomy is still to be encouraged among low-risk thyroid cancer patients.
In addition, according to ATA, RAI therapy should be considered in T3 or N1 patients, indicating that the vast majority of patients should not receive RAI. In the real world ITCO study, RAI was used in 47% of patients before 2016 when the ATA guidelines were published and is still being used in 39% of low-risk patients. In the intermediate category, the numbers are 87% versus 77% after 2016. In ITCO, the unifocal mPTC RAI indication was found to be 15%, and the multifocal mPTC RAI, 46%; all other intrathyroidal PTC were 62–72%, and for T3 microscopic extrathyroidal extension (ETE) it was 72% RAI.

In summary, in Italy, many low-risk tumors still receive TT and RAI, suggesting most colleagues are not following the 2015 ATA guidelines.

In a separate presentation, **Dr Durante** covered the topic of **^{131}I refractory (RAIR) differentiated thyroid cancer (DTC)** disease in several scenarios.
RAIR can be defined as 1) No ^{131}I uptake at all, 2) ^{131}I only present in some tumor foci, 3) metastasis progresses despite ^{131}I uptake. Patients in categories 1), 2) and 3) all have a 29% chance of 10-year survival. Also, 4) 18FDG-PET scan positive lesions have a similar outcome. Disease progression can be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) or doubling time.
To decide upon treatment, one possible strategy is to evaluate if significant disease progression is present or if there are symptoms. If appropriate, either localized or systemic therapy may be started.
To the question - Is it too late or the right time to start multi-kinase inhibitors (MKI)? Dr Durante cited the paper by Tahara M, et al.[5] describing the results of the phase 3 Select study. Patients with lung metastases >1 cm were initiated on lenvantinib vs placebo. Placebo-treated patients could crossover to open-label lenvatinib following progression. Lenvatinib treatment resulted in longer overall survival (OS) in patients with lung metastases of ≥1 cm versus placebo (even with the 89% crossover rate). It was found that the larger the size of the lung metastasis the lower the OS, perhaps indicating that it is better to start on a low burden of disease. Lenvatinib may cause serious adverse effects, which might limit its use.

In conclusion, Dr Durante suggested that once patients are classified as RAIR, disease progression, symptoms, tumor burden and location need to be evaluated to inform the patient´s treatment, to provide clarity on when an early or delayed treatment is preferable. The presence of an experienced and multidisciplinary team can be helpful in clarifying these issues.

Dr Sophie Leboulleux (France) addressed the question **Why do we give radioactive iodine**? She explained the concepts of ablation, adjuvancy, and therapy and talked about evolutionary changes in thyroid cancer management. In the 1990s a patient with a 3 cm PTC with minimal external thyroid extension (mETE) and pT3N1a would have received 100 mCi of ^{131}I. If thyroglobulin (Tg) was 8 ng/mL and 2 foci outside the thyroid bed were found, the patient would have required a second ^{131}I dose. Several diagnostic whole-body scans with LT4 withdrawal would have been performed. However, in 2005, human recombinant thyroid stimulating hormone (rhTSH) was approved, and in 2007, the

technique of ablation or destruction of the remaining tissue was approved. This is one of the first changes to treatment: no need to withdraw LT4 and induce overt hypothyroidism with rhTSH. Other major changes were observed such as improvement of the spatial resolution of neck ultrasound, the development of ultra-specific Tg, SPECT Ct, the 2006 European Consensus, the 2009 and 2015 new ATA guideline recommendations, and the ATA response to treatment classification.

So where do we stand in 2021? Individualized treatment is mandatory, but practice still varies in different parts of the world, such as Europe versus America.

In the USA, low-risk patients do not generally receive RAI; in Europe, RAI is the preferred treatment in selected patients. For intermediate-risk patient, the USA recommends RAI in selected patients, while most European patients receive it. There is general agreement for RAI use in high-risk patients in both areas of the world.
In low-risk patients, three randomized controlled trials (RCT): ESTIMABL, HILO, and ESTIMABL 2 showed the advantages of lower 30 mCi doses of iodine and also of rhTSH for ablation. In the follow-up of ESTIMABL, no relapses were observed, and it was found that postoperative stimulated Tg levels before RAI administration >10 ng/ml were a predictor of recurrence. In the long-term follow-up of 6.5 years in HILO, again, no differences between 30 and 100 mCi or rhTSH or withdrawal were observed in recurrence or survival rates.
But a question remains regarding the impact of RAI on low-risk patients with stage I disease. How is Tg going to be assessed in the absence of RAI ablation? After 9 months, it was <1 ng/ml in 91% of the TT patients, shown by Nascimento C, et al, 2013[6] and Durante C, et al, 2012[7], who also showed that it declines with time. If the Tg level is shown to be <0.3 ng/ml, disease recurrence is unlikely (Mourao GF, et al, 2016[8]).
In the ongoing long-term follow-up prospective study, ESTIMABL 2, in low-risk DTC (which represents 50% of most thyroid cancers), Dr Leboulleux anticipated promising results showing a low rate of recurrence (4.2%), no cancer-related deaths, and non-inferiority between follow-up (no RAI) versus RAI 30 mCi after 3 years. Tg/rhTSH >5 ng/ml in the ablation group or Tg/LT4 >5 ng/ml in both groups was a useful marker of relapse.

Mostly retrospective studies are available for intermediate risk patients, but not yet any prospective studies. In high-risk patients, RAI is mandatory, but this will eventually evolve to depend on the molecular profile of the tumor for RAI uptake. Dr Leboulleux remarked that in the future, RAI will probably not be given without first genotyping the tumor.
In another presentation, Dr Leboulleux also addressed **Redifferentiation in BRAF and RAS mutated patients.**
In general, distant metastasis occurs in <10% of patients. Two-thirds retain RAI uptake and a complete response might be obtained in up to 40% of patients. This means that 2/3 of patients are not cured with RAI.

Dr Leboulleux introduced the subject of redifferentiation by mentioning how The Cancer Genome Atlas Network (TCGA Network)[9] is expanding the somatic genetic landscape of PTC into a molecular classification. The results derived from a comprehensive multiplatform analysis of 496 PTCs, while excluding clinically aggressive thyroid cancers (poorly and undifferentiated carcinomas) to maximally develop the compendium of tumor-initiating alterations. The BRAF-RAS score obtained showed that BRAF tumors are less differentiated and RAI sensitive, and RAS-mutated tumors have better prognosis. The differentiation score is correlated to the MAPK output which is higher in BRAF-mutated tumors. Landa, et al, 2016[10] further characterized genomically poorly differentiated thyroid

cancer (PDTC) and anaplastic thyroid cancer (ATC) leading to the conclusion that they arise from well-differentiated tumors through the accumulation of key additional genetic abnormalities, many of which have prognostic and possible therapeutic relevance.
Redifferentiation can overcome insensitivity to RAI. Some drugs, such as trametinib and dabrafenib tried in 95% of RAIR thyroid cancers with BRAF mutations, have shown detectable RAI uptake after these drugs were combined. A new phase 2 redifferentiation trial currently ongoing by Dr Leboulleux has shown a 38% partial response at 6 months.

After the conference, a discussion among panelists revealed that in Europe most RAIR tumors are genotyped, but this is not yet as widely available in LATAM.

Dr Lori Wirth (USA) described her experience with the new RET selective inhibitors pralsetinib in the phase 1–2 ARROW trial[11] and selpercatinib in the phase 1–2 LIBRETTO-001 trial[12], both for RET-mutated medullary cancer and RET-fusion thyroid cancer. They both proved a high overall response rate of about 70% in medullary thyroid cancer patients. She also introduced the new LIBRETTO-531 phase 3 trial that will compare selpercatinib with vandetanib or cabozantinib in unresectable or metastatic RET+ medullary cancer. Similarly, as future directions, she introduced the AcceleRET-MTC pralsetinib phase 3 trial comparing its efficacy with the standard of care for RET-mutated medullary thyroid cancer.

Dr Wirth explained that in the current gene-specific treatment era, the pendulum might be shifting back to starting therapy early. She concluded that molecular testing should always be considered when possible.

Dr Di Cristofano (USA) introduced his presentation, **New insights into the role of phosphoinositide 3-kinase (PI3K) signaling in thyroid cancer** by explaining that mutations in members of the PI3K pathway, such as *PTEN*, *PIK3CA*, and *AKT1*, have been reported at low frequency in PTC. However, they are more frequent in follicular thyroid cancer or ATC and can also be identified in several thyroid cancers by immunohistochemistry as a loss of PTEN - a major controller of this pathway.[13,14]
To further understand this pathway, Dr Di Cristofano undertook a systematic *in vivo* genetic approach that revealed that activation of the PI3K pathway induces proliferation of thyroid epithelial cells but is not sufficient to transform cells. He found that loss of *PTEN* is more potent than PI3K activation in driving proliferation, but for early neoplastic transformation, AKT2 needs to be compromised. However, AKT1 is the main driver of anaplastic lesions.
His *in vivo* models showed that if the proto-oncogene NRAS is introduced in rats together with PTEN or *PIK3CA* plus p53 mutations, tumor lesions are rapidly observed (triple mutant) demonstrating that NRAS proliferation potentially needs these other mutations to be unleashed. In these PI3K/RAS-driven ATC tumors, the presence of stem cells was observed, which may be responsible for such aggressiveness.
As regards potential therapies, unfortunately, resistance to PI3K inhibition occurs rapidly, and several growth factor receptors are overexpressed in resistant cells. Combination therapies for ATC using PI3K inhibitors with Polo-like kinase (PLK1) inhibitors have demonstrated arrested tumor growth. Similar results were observed by the combination of PI3K inhibitors and a CDK4/6 inhibitor (palbociclib) independently of identification of driver mutation.
Despite a common AKT-centric vision of PI3K signaling, serine/threonine-protein kinase (SGK1) was also found to be important during neoplastic transformation. SGK1 appears to play a critical role in sustaining PI3K transforming activity and its inhibition cooperated with AKT inhibitors in suppressing cell growth.

Based on genetic data from SGK-mutant mice, SGK inhibitors are likely to be well-tolerated and may improve the efficacy of AKT-targeted inhibition. According to Dr Di Cristofano´s research, hitting AKT and SGK1 together may provide effective and durable tumor growth suppression.

B) THYROID HORMONE (TH) ACTION

Dr David Cooper (USA) delivered an excellent and thorough review: **Individualized therapy for hypothyroidism: Is T4 enough for everyone?** based on the scenario of a patient with LT4 monotherapy who complains of fatigue, cold intolerance and brain fogginess and asks for LT4/LT3 combination therapy.

Although LT4 monotherapy has been endorsed by most Guidelines, there is still a small proportion of patients who are dissatisfied with treatment, despite attaining normal TSH values - mostly observed in thyroid cancer patients. However, the many other potential causes of the symptoms troubling this patient with normal TSH values should be ruled out first.

In addition, although commonly used, TSH might not be the gold standard for the peripheral action of thyroid hormones, as shown by several hypothyroid-associated parameters that do not objectively improve despite TSH normalization. Peterson SJ, et al, 2016[15] showed that patients on monotherapy used more statins, antidepressants and beta-blockers and had higher body mass index (BMI) measurements than euthyroid individuals.

While combining T3 with T4 might restore normal thyroid status, several RCT on LT4/LT3 combination therapy showed no benefit on measures of fatigue, anxiety, depression, body pain and quality of life. However, a higher preference for the combination was shown by a meta-analysis[16], especially when patients received supraphysiologic LT3 doses.

Dr Cooper also mentioned the role of genetics, the polymorphisms of Thr92Ala and thyroid hormone transporters which may be infrequent findings but could explain much of this conundrum. However, for the moment, these polymorphisms cannot be explored in clinical practice, and perhaps future innovations such as sustained-release T3 sulfate or the development of new long-acting formulations may help resolve this issue. An article by Jonklaas J, et al, 2021[17] reviewing a recent ATA, British Thyroid Association and European Thyroid Association joint conference on combination therapy was recommended for an insight on this topic, including consensus statements to guide the development of future clinical trials of LT4/LT3 combination therapy. The results of such purposefully designed trials are expected to be of benefit to patients and of value to inform future thyroid hormone replacement clinical practice guidelines treatment recommendations.

Dr Lars Moeller (Germany), who spoke on **How do thyroid hormones act and why could it be important to know it?** started by reminding us that what we measure as TH function tests does not exactly reflect what occurs inside the cells that are controlled by TH action. TH action depends on its transport through the cell membrane, its metabolism through deiodination and α and β thyroid receptors (TR).

Dr Moller's presentation focused on his work on the action of TH on receptors and its 4 ways of signaling: types 1 and 2: canonical or genomic; and types 3 and 4: noncanonical or nongenomic, occurring rapidly and independently of gene induction and protein synthesis.[18]
To distinguish between these actions, knock-out mice for each model of signaling have been developed, which has revealed that canonical TRβ action stimulates hepatocyte proliferation which may confer benefits in patients with liver failure, reducing hepatocyte loss. Several genes are induced

by T3 in the liver and they can be key to hepatic triglyceride concentration in patients with type 2 diabetes and steatosis. The administration of low dose T3 for 16 weeks led to a 2% reduction in intrahepatic fat content. Some thyromimetic analogs such as MGL-3196 depend on hepatocyte-specific transport and are a TRβ agonist that can effectively reduce liver fat content.
However, in the liver, the noncanonical TRβ action is also relevant, demonstrated in experiments with TRβ GS mice (noncanonical model). After TH treatment of these mice, the triglyceride concentration in the serum and liver is the same as in wild-type mice. The noncanonical effect is also confirmed by T3 administration that causes a rapid decrease in glucose. Bone development is another canonically regulated TRα action.

TH is key for heart function (by increasing contractility through well-known mechanisms on TRα) and there is evidence that TH action is beneficial in heart failure. However, in the TRα GS model, where the action is noncanonical, mice treated with TH develop cardiac hypertrophy. This mechanism could be considered beneficial or detrimental in certain situations of compensatory hypertrophy. Moreover, in the vascular system in the TRα GS model, noncanonical TRα signaling mediates rapid relaxation.

As regards tumor progression and weight - T4 promotes tumor growth, which is abolished by TETRAC binding to the avβ3 effecting a typical type 4 noncanonical T4 effect. In summary, liver failure, heart failure and tumor growth are all areas where TH will continue to be actively evaluated in future research.

Dr Arturo Hernandez (USA) addressed the topic of the **Transgenerational epigenetic effects of thyroid hormones** by explaining that there are several conditions in humans without a heritable explanation. Genome-wide analysis (GWA) studies have been performed to address this, and to look for intergenerational epigenetics. Some candidate genes explain certain clinical cases, yet there is still missing heritability, so, can intergenerational epigenetics be the explanation?
Diet, nutritional status, disease, stress, chemicals, and social interactions are all environmental influences, but so also may be exposure to supraphysiological levels of thyroid hormones. To study the effects of these environmental factors, researchers developed different mouse models in the 1960s, such as the Neo T4 model, a mouse with a normal genotype but an abnormal phenotype. Mice were exposed when pregnant to T4 and experienced neonatal thyrotoxicosis. The animals developed central hypothyroidism, growth retardation, defective pituitary responses to TRH and small testes. The newer DIO3 deficiency model is a comparable model, exposing the fetus to high TH levels resulting in a similar or worse phenotype than produced with the Neo T4 Model. All the research presented by Dr Hernandez leads to the conclusion that if an ancestor is exposed to high levels of TH it produces germline epigenetic modifications that are transmitted to the offspring and subsequent generations who might have neurological and endocrinological alterations.[19]

2) LOCAL SPEAKERS

A) THYROID AND PREGNANCY

Dr Marcos Abalovich (Argentina) stressed that ovarian reserve and thyroid autoimmunity are related as he began his presentation on **Infertility and thyroid**. TSH levels are higher in infertile euthyroid women than in women with negative thyroid antibodies. He described how the TRH/TSH test to detect mild hypothyroidism was useful in his clinical practice and quoted the paper discussing assisted reproduction techniques (ART) by Poppe K, 2018,[20] where it was shown that intracytoplasmic sperm injection (ICSI) could have potential benefit in TPO positive euthyroid infertile women. Dr Abalovich

concluded that the prevalence of subclinical hypothyroidism (Sch) is high among infertile women and that thyroid autoimmunity, even in euthyroid women, has been linked to an increased risk of miscarriage. Patients with positive antithyroid antibodies who become pregnant with ART have a higher risk of miscarriage, although this has been reduced with the use of ICSI.
Should an infertile euthyroid woman with positive antithyroid antibodies be treated with LT4? Two prospective and randomized studies[21,22] have both suggested not, however, this topic needs further investigation.

Dr Lorena Mosso (Chile) covered the **Impact on pregnancy outcomes,** recalling that in 2016 the Consortium on Thyroid and Pregnancy was created,[23] which included data on TSH levels of Chilean women together with details of pregnancy loss, low birth weight infants, and preterm births. Dr Mosso also presented data from the papers by Rao M, et al, 2019[24] and the RCT by Nazarpour S, et al, 2017[25] showing that the benefit of treatment with LT4 during pregnancy in reducing the risk of preterm birth depends on TSH levels and anti-thyroperoxidase antibody (TPO Ab) positivity.

Dr Gisah Amaral de Carvalho (Brazil) presented on **Development of fetal thyroid,** covering the association of Sch with preterm birth. Preterm birth is the most common cause of adverse neuropsychological development in children, however, the CATS1[26] trial did not find an IQ score difference between children from mothers with Sch who were treated with LT4 and children from mothers with Sch who were not treated during the first 12 gestational weeks. The CATSII trial explored the IQ of the children from CATS1 at the age of 9.5 years[27] and found that overtreated patients had a higher proportion of children with attention deficit hyperactivity disorder symptoms and behavioral difficulties with no positive effect on IQ.

The Generation R study of 646 children by Korevaar T, et al, 2016[28] found that both low and high maternal free thyroxine concentrations during pregnancy were associated with lower child IQ at 6 years and lower grey matter and cortex volume at 8 years (assessed by brain magnetic resonance imaging).
The association between high maternal free thyroxine and low child IQ suggests that levothyroxine therapy during pregnancy, which is often initiated in women with Sch during pregnancy, might carry the potential risk of adverse child neurodevelopmental outcomes when treatment aims to achieve high-normal thyroid function test results.
Another conclusion from the CATSII trial[29] was that LT4 supplementation of women with suboptimal gestational thyroid function did not affect long-term offspring anthropometric, bone and cardiometabolic measurements. However, the absence of treatment was associated with a sustained long-term increase in BMI and fat mass in these women.

B) THYROID CANCER

STRATEGIES FOR THE MANAGEMENT OF LOW-RISK DTC AND THE LATIN AMERICA EXPERIENCE

Dr Anabella Smulever (Argentina) discussed outcomes and the incidence of adverse events following AS versus immediate surgery in patients with low-risk PTC.[30] In her study, 41 patients opted for AS and an increase of more than 3 mm in tumor size was observed in 14.6% of these patients, and 4.8% were diagnosed with lymph-node metastases after a median of 37.5 months (range, 12–65) follow-up. Dr Smulever concluded that postoperative complications could be avoided if AS was performed as the initial approach in patients with low-risk PTCs. But the challenging question

remains - who is the ideal candidate for AS? High medical costs and possible permanent adverse effects of thyroidectomy should be considered even with high volume surgeons, so if AS is feasible, that may be of some benefit to the patient.

Dr Jorgelina Guerra (Argentina) spoke in depth on **Lobectomy**. She described data on 61,775 PTC patients from the National Cancer Database from 2014[31] where 54,926 underwent total thyroidectomy and 6849 lobectomies. After multivariable adjustment, OS was similar with both procedures for tumors sized 1.0–4.0 cm.
According to Dr Michael Tuttle,[32] certain features are important in deciding when a patient is a good candidate for lobectomy:

- The selection for preoperative candidates for lobectomy should take into consideration tumor/imaging, patient and medical team characteristics:
  It would be divided into:
  - Ideal: <1 cm intrathyroidal. Normal US cN0
  - Appropriate: 1–4 cm tumors. Minor ETE. cN0 or <5 N1 micrometastasis. Minor vascular invasion. Benign appearing changes on US (thyroiditis, benign nodules). Desire to keep normal thyroid function.
  - Inappropriate: extensive vascular invasion. Larger aggressive variants. cN1. Gross ETE. Distant metastases
- Postoperative candidates are defined according to their histological confirmation: The Inappropriate category would include those with extensive vascular invasion.

STEPS would define the parameters suggested above pre-operatively, intra-operatively and post-operatively to decide on the surgical extent.

Dr Guerra also presented her data from the Hospital Universitario Austral from 66 carefully selected patients for lobectomy versus 383 patients who underwent TT. All patients had no evidence of disease (NED) after 2 years of follow-up.

Dr Daniel Rappoport (Chile) defended **Total thyroidectomy,** presenting studies that showed that lobectomy had a higher recurrence rate and less OS after 5 years than TT, including the classic paper by Bilimoria KY, et al. 2007.[33] Dr Rappoport showed the results of a meta-analysis where OS was improved with TT in tumors measuring 2–4 cm,[34] and discussed the need for LT4 treatment as a consequence of lobectomy.[35] Much of the decision between elective lobectomy or TT depends on the surgeon´s experience,[36] and according to Dr Tuttle, this requires a shared decision with patients, and the decision regarding procedure is probably better defined after surgery.
In Chile, a country of 18,950,000 inhabitants, of whom 80% rely on the public health service - of all thyroid surgeries, 50% are lobectomies. As patients can be on waiting lists for a long time, and the time to completion of surgery is also long, many patients favor one procedure (as in TT). For these patients, one procedure reduces their wait time, and, according to Dr Rappoport, there is also better RFS and OS in the long run with TT.

In another symposium, Dr Ana Hoff (Brazil) discussed **Selective use of kinase inhibitors.** She confirmed that RAI is first-line therapy, but some RAI refractory thyroid cancers need further options – either AS or targeted therapies. The targeted therapies now available include multikinase inhibitors (sorafenib, lenvatinib, cabozantinib) or specific inhibitors, for example larotrectinib for NTRK (prevalence of 5% in adults and up to 25% in pediatrics) or other specific inhibitors for RET or BRAF.

Current questions remain: When should tumor molecular profiling be done? Is it feasible? Available? Is the presence of the DRIVER mutation always found? Which to use: Foundation One or others? In primary tumor or metastases or liquid biopsy (blood cfDNA)?
Other unanswered questions include: Which is the best sequence of therapy? (ideally, the most efficacious with fewest side-effects). Which drug should be started? (some contraindications to anti-angiogenic drugs include chronic heart failure, recent myocardial infarction, hemoptysis, anticoagulation, uncontrolled hypertension, large unhealed wounds). Approved drugs in Brazil are sorafenib, lenvantinib, and larotrectinib.

3) HIGHLIGHTED ORAL COMMUNICATIONS (CLINICAL)

From Argentina: the **Long-term follow-up of low-risk thyroid cancer patients** - a prospective multicenter study comparing ablation with 30 mCi ^{131}I versus non-ablation. This study looked at patients with low risk of recurrence who were assigned to RAI (n=87) or NONRAI (n=87) with a median 60-month follow-up. No difference in the final response at follow-up was observed with 80% in NED status. In conclusion, low-risk DTC had similar excellent response regardless of RAI. This study was a collaborative effort by the Argentine Thyroid Department.

From Argentina: **Is Hürthle cell carcinoma a differentiated thyroid cancer with aggressive behavior?** Hürthle cell carcinoma (HCC) makes up 3–5% of all thyroid cancers, with invasive HCC known to behave aggressively. In the high ATA recurrence risk classification, HCC has a higher structural incomplete response rate than DTC. In this study, 28 patients had a diagnosis of HCC (28/1355; 2%) and at least 12 months of follow-up. The risk of recurrence was low in 54% of patients, intermediate in 21%, and high in 25%. The median follow-up was 53.5 months (range: 13–240). Nine patients had distant metastasis, and age was found to be a predictor of survival. Estimated 5-year disease-specific survival in patients with HCC was 78% versus 97% in the DTC group; disease-specific survival after the discovery of metastasis was 49 versus 120 months respectively; global mortality was 14%. The conclusion of this study was that HCC was a more aggressive cancer than DTC, but only in patients with a high risk of recurrence. Although patients with HCC have lower disease-specific survival in comparison with DTC patients, those with a low or intermediate risk of recurrence do not seem to have a poorer rate of structural incomplete response.

From Argentina: The **Argentinian multicenter study of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP**) showed the outcome and molecular profile of patients with this tumor. Data on all patients with NIFTP were gathered from 2006 to 2016 from 11 referral centers in Argentina. Of 2677 patients with PTC, 456 patients had follicular variants, 51 had probable NIFTP, but only 30 were finally included in this study. Of these, 19 tumours were genetically profiled with 6 genes studied. The median patient age was 53 years, 83% were female, and median tumour size was 14.5 mm. Cytologically, Bethesda IV accounted for 33% of these tumours, and Bethesda VI 33%. All patients received TT: 51% received 100 mCi as RAI median dose. No patients had structural incomplete response, nor additional therapies. Molecular analysis found 2 NRAS, 2 HRAS, and a BRAF 1. Finally, the prevalence of NIFTP in this series was the lowest reported worldwide, with a different molecular profile to those reported previously.

From Brazil: **Is antithyroglobulin antibody associated with the prognosis of patients with differentiated thyroid carcinoma?** This retrospective cohort study included 45 patients with DTC and positive TgAb and found that serum antibody concentrations below 50.9 IU/mL after TT, as well as the time to achieve negativity in up to 13 months, seem to be associated with an excellent therapeutic response at the last assessment.

From Brazil: **The heterozygous advantage of the type II deiodinase Thr92Ala polymorphism**

on intrahospital mortality of COVID-19 was explored in this longitudinal, prospective cohort study, involving 220 consecutive COVID-19 patients in whom the DIO2 Thr92Ala polymorphism was evaluated relative to mortality. Heterozygous carriers were found to be at lower mortality risk from COVID-19 compared with those carrying homozygous alleles.

4) HIGHLIGHTED ORAL COMMUNICATIONS (BASIC AREA)

From Brazil: **Kisspeptin treatment improves fetal development and placental morphogenesis and function in hypothyroid rats.** This is the first study to assess the role of kisspeptin, a key reproductive neuropeptide, in fetal-placental dysfunction caused by maternal hypothyroidism. The results of this study in hypothyroid pregnant Wistar rats suggests that kisspeptin analogs may be helpful for gestational diseases, such as hypothyroidism, which are associated with fetal growth restriction.

From Brazil: **Manganese porphyrin-based treatment blocks placental stress caused by maternal hypothyroidism and improves placental morphogenesis and fetal development in a rat experimental model.** This study revealed that maternal hypothyroidism causes oxidative stress and endoplasmic reticulum stress at the maternal-fetal interface and indicate that manganese porphyrins are promising new redox-active therapeutics for protection against placental stress and improvement of fetal-placental development in maternal hypothyroidism.

From Argentina: **Impact of the mutational landscape of the sodium/iodide symporter in congenital hypothyroidism.** Iodide transport defect is an uncommon cause of dyshormonogenic congenital hypothyroidism due to homozygous or compound heterozygous pathogenic variants of the SLC5A5 gene. This gene encodes the sodium/iodide symporter (NIS), and the variants cause deficient iodide accumulation in thyroid follicular cells, impairing thyroid hormonogenesis. These authors aimed to uncover novel SLC5A5 gene variants involved in the pathogenesis of dyshormonogenic congenital hypothyroidism and developed a machine learning-based NIS-specific variant classifier to improve the prediction of pathogenicity of missense variants. They predicted the mutational landscape of NIS, revealing that most missense variants located in transmembrane segments are pathogenic. This study is the first NIS-specific variant classifier, which aims to improve the interpretation of missense NIS variants in clinical practice.

From Spain: **The aggressiveness promoted by LDL-cholesterol in the thyroid tumor cell can be mediated through BRAF v600E mutation.** Having previously described the relevance of low-density lipoproteins (LDL) in cell growth and aggressiveness in thyroid tumors, this research group investigated if the different mutational status of BRAF v600E in the tumor cells can modify the LDL-mediated signaling pathways, thereby affecting LDL uptake, tumoral growth and cell migration. They found that targeting cholesterol metabolism could be a new therapeutic strategy for thyroid tumors that present with the BRAF v600E mutation and poor prognosis.

From Brazil: **The influence of nectin1 gene variants in herpes virus infection in patients with thyroid nodules.** The authors have previously found that the herpes virus is associated with malignancies and may be implicated in the physiopathology of thyroid tumors. Nectin1 is a cell adhesion molecule and is the main herpes virus receptor in neurons and epithelial tissue. The aim of this study was to investigate the possible role of variants of this gene on the susceptibility to the herpes virus and the development of thyroid cancer. Study participants were screened for HSV-2 and 405 individuals from a control group and 405 thyroid nodules patients were genotyped for SNPs rs199962982, rs14125361 and rs7940667 of Nectin1. The serological titres of IgG HSV-2 were significantly lower

in the thyroid nodules which also presented with a polymorphic heterozygous AC genotype compared with the control group and/or those with latent infection. The two polymorphic homozygous CC rs7940667 thyroid nodules (1 benign and 1 malignant) were both HSV-2 negative. A larger series of cases may confirm a possible protective role of the Nectin1 variant against viral infection and its relationship to thyroid malignancy.

5) THE YOUNG LATS INVESTIGATOR CANDIDATES (CLINICAL AREA), PRESENTED STUDIES

From Chile: **Hobnail variant papillary thyroid cancer (HVPTC) by itself is not associated with a worse prognosis than classic variant: a propensity score analysis.** This study included 431 patients, of whom 399 (92.5%) had C-PTC and 32 (7.5%) HVPTC. Mean age of patients was 39.3 ± 12.2 years, and 352 (81%) were female. Patients were followed for 3.9 (0.5–31.2) years. Incomplete response was associated with N1 and ATA's high risk of recurrence, but not with HVPTC (p=0.530) after adjusting for the study propensity score. The authors concluded that HVPTC had a more aggressive clinical presentation than C-PTC. N1 status and ATA high risk were associated with incomplete response, while HVPTC by itself did not, after adjusting for covariates.

From Argentina: **Active surveillance of small metastatic cervical lymph nodes and cancer.** While the resection of large cervical lymph nodes (LN) improves long-term prognosis, the clinical benefit of early intervention of small LNs is uncertain. To explore this issue, the authors assessed the frequency of growth and/or the need for surgery in a group of patients with LN metastases selected for active surveillance (AS), to determine predictive factors for their outcomes. Patients with cytologically confirmed metastatic LN (n=46) were followed for a median time of 28 months (range: 2–124). Ten patients (22%) had an increase in the size of the metastatic LN, 7 (70%) of which were surgically removed; none of these evolved with a structural incomplete response at follow-up. The remaining 3 patients continued with observation due to the small volume of disease (median size 10 mm). The 5-year progression-free survival rate was 58%. The only predictive factor for metastatic LN growth was the increase of Tg level ≥0.5 ng/mL (p=0.048). In conclusion, only 21% of the patients with small loco-regional recurrences under active surveillance showed growth of ≥3 mm, with no evidence of local complications or new metastatic sites. AS of small LNs could be a feasible alternative in properly selected patients and after discussion with the patient to decrease the incidence of postoperative complications.

From Argentina: **Classical and next-generation sequencing approaches applied to the molecular diagnosis of congenital hypothyroidism.** This meta-analysis demonstrated that only 5–10% of patients with thyroid dysgenesis and 45–88% of patients with thyroid dyshormonogenesis are diagnosed using single-gene sequencing. Applying an appropriate gene sequencing panel revealed variants in genes that would have been excluded *a priori* based on the phenotype of the patient.

From Brazil: **Preoperative early identification and exclusion of medullary thyroid carcinoma: Development and validation of a highly sensitive and specific microRNA-based molecular classifier test using fine-needle aspiration (FNA) smear slides.** This presentation showcased the development and validation of a molecular classifier able to diagnose or exclude MTC with high sensitivity, specificity, and predictive values. It could be a powerful and cheap tool in the early diagnosis of MTC by analyzing the expression of only two microRNAs by qPCR directly from the available FNA smear slides, without the need of a new FNA biopsy.

From Brazil: **Diet quality influences urinary iodine concentration in pregnant women from a coastal Brazilian state.** A cross-sectional study, with 199 women in the first trimester of gestation, not taking iodine-containing supplements, was conducted. It showed that the intake of fruits and grain was associated with lower urinary iodine in pregnant women.

From Brazil: **GLYCA levels as a marker of systemic inflammation in hypothyroid patients under inadequate levothyroxine replacement.** GlycA, a novel marker of systemic inflammation, is associated with cardiovascular disease independently from traditional risk factors, and is a marker of systemic inflammation in hypothyroid patients under inadequate levothyroxine replacement. This was a cross-sectional study including hypothyroid patients prescribed levothyroxine replacement from a large sample of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). A total of 345 participants were receiving levothyroxine and 61.7% had serum TSH in the normal range, 24.1% were undertreated and 14.2% were overtreated. Lower levels of GlycA were detected in those with serum TSH within target levels (405; interquartile range [IR] 86 mmol/L) compared with those under (423, IR: 86 mmol/L; p=0.02) or overtreated (432, IR: 75 mmol/L; p=0.04). In conclusion, patients under inadequate treatment for hypothyroidism, those both over- and undertreated, have higher levels of GlycA, which may be associated with greater cardiovascular risk.

6) THE YOUNG LATS INVESTIGATOR CANDIDATES (BASIC AREA), STUDIES PRESENTED

From Brazil: **Blockage of ezh2/prc2-mediated chromatin modification alters anaplastic thyroid cancer differentiation.** ATC is a lethal undifferentiated thyroid malignancy, with rapid growth, an invasive nature and few therapeutical options. Understanding the molecular evolution of ATC is a current challenge that may lead to the identification of new targets for treatment. To this extent, deregulation of the epigenetic regulator Polycomb Repressive Complex 2 (PRC2)/EZH2 contributes to ATC aggressiveness by altering the chromatin state. High levels of EZH2 lead to deposition of H3K27me3 in histones, heterochromatin formation and repression of target gene expression, such as tumor suppressors and differentiation genes. The effect of blockage of PRC2/EZH2 on ATC biology was investigated using strategies to inhibit ESchZH2 methyltransferase activity pharmacologically or permanently using CRISPR/Cas9-mediated gene editing. This demonstrated that EZH2/PRC2 is upregulated in ATC while thyroid differentiation genes and transcription factors are reduced, suggesting that epigenetics regulate ATC biology as EZH2 inhibition contributed to restoring thyroid cell differentiation and epithelial morphology to some extent.

From Brazil: **Chronic T3 treatment reduces the expression of gluconeogenesis-related genes in alloxan-induced diabetic rats. A promising therapeutic possibility for diabetes mellitus?** Treatment of alloxan-induced diabetes mellitus rats with triiodothyronine (T3) reduces blood glucose by mechanisms that involve the reduced expression of inflammatory cytokines[37] and hepatic glucose production. This study aimed to identify the molecular targets involved in hepatic glucose production that are differentially expressed in the liver of control (C), diabetic (D), and diabetic rats treated with T3 (DT3). According to the authors, this is the first work to show a negative correlation between T3 treatment and the proteins involved in gluconeogenesis in rats with diabetes mellitus, which is in line with previous results from this research group, suggesting that T3 may have therapeutic potential in the treatment of patients with diabetes mellitus who may also have hypothyroidism.

From Brazil: **Physiological triiodothyronine dose modulates genes associated with coronavirus disease (COVID-19) in human subcutaneous adipocytes cell culture.** This study aimed

to identify genes expressed in human subcutaneous adipocytes that are affected by T3, focusing on genes deregulated by SARS-CoV-2. T3 treatment significantly decreased the expression of TLR3, KDM5B, FURIN and ADAM1,0 (all associated with increased virus replication), SOCS3 (involved in lipid metabolism) and IFNAR2 (related to inflammation) indicating potential beneficial T3 effects on lipid metabolism, the immune system and the viral load of tissue infected by SARS-CoV-2.

From Brazil: **Role of type 3 deiodinase in the progression of non-alcoholic liver disease: oxidative stress, respiratory changes and macrophage activation.** New data were presented on the role of type 3 deiodinase (D3) inactivation in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). D3 is the enzyme responsible for T3 inactivation of immune cells of diseased liver and muscle. However, the interrelationship between these mechanisms is under debate in NAFLD. The authors evaluated D3 induction, redox homeostasis, mitochondrial respiration, and their effects in the liver of an animal model of NAFLD. Excess liver fat, lipid peroxidation and the induction of D3 decreases the amount of T3 available for mitochondrial uncoupling and shifts the Krebs cycle. Excitingly, D3 protein was observed on the plasma membrane of recruited macrophages. Taken together, these results can shed light on novel roles of thyroid hormone metabolism in NAFLD.

From Brazil: **Maternal exposure to DEHP during pregnancy disrupts the hypothalamus-pituitary-thyroid (HPT) axis function of the offspring rats.** A widely used plasticizer, di(2-ethylhexyl) phthalate (DEHP) was evaluated during pregnancy and was found to disrupt the function of the HPT axis of offspring newborn and adult rats. This study also suggests that intrauterine DEHP exposure increases the offspring's susceptibility to developing thyroid dysfunction during adulthood, especially female offspring rats.

From Brazil: **Intra-uterine exposure to triclosan (TCS) disrupts the hypothalamus-pituitary-thyroid axis function and thyroid gene expression in adult male offspring rats.** Intra-uterine exposure to TCS decreased the expression of genes involved in the biosynthesis of TH, such as TPO, TG, TSHR, Mct8 and Foxe1 in male offspring rats during adulthood, indicating disruption to the gene expression and function of the thyroid gland by this agent. Moreover, epigenetic mechanisms commonly involved in the repression of gene transcription seem to be involved in the programming of the thyroid gene expression repression in these animals. TCS exposure during a critical period of development increased the susceptibility of the male offspring animals to develop hypothyroidism during adult life.

7) LATS AWARDS

The Senior LATS Awards 2021 were presented to the Brazilian scientists Dr Carmen Cabanelas Pazoz de Moura for **Contributions to the thyroid field: Regulation of the hypothalamic-pituitary-thyroid axis and thyroid hormone action** and to Dr Maria Tereza Nunes for **A journey into the basic thyroidology.**
The 2 Young Investigator Awards were presented to Fernando Jerkovich (Argentina) for **Active surveillance of small metastatic lymph nodes in thyroid cancer** and to Rafael Aguiar Marschner (Brazil) for **Role of type 3 deiodinase in the progression of non-alcoholic liver disease: oxidative stress, respiratory changes and macrophage activation.**

CONCLUSIONS

The XVIII LATS Congress was the perfect place for updates on all things thyroid, and moving to a virtual arena enabled people all over the world to join in and to discuss the results and express their opinions. Exciting new data from researchers in Latin America were presented and will no doubt form the core of future published papers.
In the meantime, you are warmly welcomed to save the date for the next LATS Congress which will take place from April 20–23, 2023 in Curitiba, Brazil.

REFERENCES

1. Zhang M, et al. Ultrasound-guided radiofrequency ablation versus surgery for low-risk papillary thyroid microcarcinoma: Results of over 5 years' follow-up. Thyroid. 2020 Mar;30(3):408-417. doi: 10.1089/thy.2019.0147.
2. Cho SJ, et al. Long-term follow-up results of ultrasound-guided radiofrequency ablation for low-risk papillary thyroid microcarcinoma: More than 5-year follow-up for 84 tumors. Thyroid. 2020 Dec;30(12):1745-1751. doi: 10.1089/thy.2020.0106.
3. Sosa JA, et al. Increases in thyroid nodule fine-needle aspirations, operations, and diagnoses of thyroid cancer in the United States. Surgery. 2013 Dec;154(6):1420-6; discussion 1426-7. doi: 10.1016/j.surg.2013.07.006.
4. Grani G, et al. Real-world performance of the American Thyroid Association risk estimates in predicting 1-year differentiated thyroid cancer outcomes: A prospective multicenter study of 2000 patients. Thyroid. 2021 Feb;31(2):264-271. doi: 10.1089/thy.2020.0272.
5. Tahara M, et al. Impact of lung metastases on overall survival in the phase 3 SELECT study of lenvatinib in patients with radioiodine-refractory differentiated thyroid cancer. Eur J Cancer. 2021 Apr;147:51-57. doi: 10.1016/j.ejca.2020.12.032.
6. Nascimento C, et al. Ultrasensitive serum thyroglobulin measurement is useful for the follow-up of patients treated with total thyroidectomy without radioactive iodine ablation. Eur J Endocrinol. 2013 Oct 4;169(5):689-93. doi: 10.1530/EJE-13-0386.
7. Durante C, et al; PTC Study Group. Long-term surveillance of papillary thyroid cancer patients who do not undergo postoperative radioiodine remnant ablation: is there a role for serum thyroglobulin measurement? J Clin Endocrinol Metab. 2012 Aug;97(8):2748-53. doi: 10.1210/jc.2012-1123.
8. Mourão GF, et al. Low postoperative nonstimulated thyroglobulin as a criterion to spare radioiodine ablation. Endocr Relat Cancer. 2016 Jan;23(1):47-52. doi: 10.1530/ERC-15-0458.
9. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014 Oct 23;159(3):676-90. doi: 10.1016/j.cell.2014.09.050.
10. Landa I, et al. Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. J Clin Invest. 2016 Mar 1;126(3):1052-66. doi: 10.1172/JCI85271.
11. Subbiah V, et al. Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): a multi-cohort, open-label, registrational, phase 1/2 study. Lancet Diabetes Endocrinol. 2021 Aug;9(8):491-501. doi: 10.1016/S2213-8587(21)00120-0. Erratum in: Lancet Diabetes Endocrinol. 2021 Oct;9(10):e4. PMID: 34118198.
12. Wirth LJ, et al. Efficacy of selpercatinib in *RET*-altered thyroid cancers. N Engl J Med. 2020 Aug 27;383(9):825-835. doi: 10.1056/NEJMoa2005651.
13. Pozdeyev N, et al. Genetic analysis of 779 advanced differentiated and anaplastic thyroid cancers. Clin Cancer Res. 2018 Jul 1;24(13):3059-3068. doi: 10.1158/1078-0432.CCR-18-0373.
14. Liang H, et al. Diagnostic value of 16 cellular tumor markers for metastatic thyroid cancer: an immunohistochemical study. Anticancer Res. 2011 Oct;31(10):3433-40.
15. Peterson SJ, et al. Is a normal TSH synonymous with "euthyroidism" in kevothyroxine monotherapy? J Clin Endocrinol Metab. 2016 Dec;101(12):4964-4973. doi: 10.1210/jc.2016-2660. Erratum in: J Clin Endocrinol Metab. 2017 Apr 1;102(4):1406.
16. Akirov A, et al. A systematic review and meta-analysis of patient preferences for combination thyroid hormone treatment for hypothyroidism. Front Endocrinol (Lausanne). 2019 Jul 24;10:477. doi: 10.3389/fendo.2019.00477.
17. Jonklaas J, et al. Evidence-based use of levothyroxine/liothyronine combinations in treating hypothyroidism: A consensus document. Eur Thyroid J. 2021 Mar;10(1):10-38. doi: 10.1159/000512970.
18. Flamant F, et al. Thyroid hormone signaling pathways: Time for a more precise nomenclature. Endocrinology. 2017 Jul 1;158(7):2052-2057. doi: 10.1210/en.2017-00250.
19. Hernandez A. Spermatogonial Dio3 as a potential germ line sensor for thyroid hormone-driven epigenetic inheritance. Biol Reprod. 2021 Sep 14;105(3):613-615. doi: 10.1093/biolre/ioab089.
20. Poppe K, et al. Thyroid autoimmunity and intracytoplasmic sperm injection outcome: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2018 Mar 12. doi: 10.1210/jc.2017-02633.
21. Dhillon-Smith RK, et al. Levothyroxine in women with thyroid peroxidase antibodies before conception. N Engl J Med. 2019 Apr 4;380(14):1316-1325. doi: 10.1056/NEJMoa1812537.
22. Wang H, et al. Effect of levothyroxine on miscarriage among women with normal thyroid function and thyroid autoimmunity undergoing in vitro fertilization and embryo transfer: A randomized clinical trial. JAMA. 2017 Dec 12;318(22):2190-2198. doi: 10.1001/jama.2017.18249.
23. Consortium on Thyroid and Pregnancy—Study Group on Preterm Birth, Korevaar TIM, et al. Association of thyroid function test abnormalities and thyroid autoimmunity with preterm birth: A systematic review and meta-analysis. JAMA. 2019 Aug 20;322(7):632-641. doi: 10.1001/jama.2019.10931. Erratum in: JAMA. 2019 Nov

5;322(17):1718. Lancet Diabetes Endocrinol 2021 June 8 6 501-510 .
24. Rao M, et al. Effect of levothyroxine supplementation on pregnancy loss and preterm birth in women with subclinical hypothyroidism and thyroid autoimmunity: a systematic review and meta-analysis. Hum Reprod Update. 2019 May 1;25(3):344-361. doi: 10.1093/humupd/dmz003.
25. Nazarpour S, et al. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. Eur J Endocrinol. 2017 Feb;176(2):253-265. doi: 10.1530/EJE-16-0548.
26. Lazarus JH, et al. Antenatal thyroid screening and childhood cognitive function. N Engl J Med. 2012 Feb 9;366(6):493-501. doi: 10.1056/NEJMoa1106104. Erratum in: N Engl J Med. 2012 Apr 26;366(17):1650.
27. Hales C, et al. Controlled Antenatal Thyroid Screening II: Effect of treating maternal suboptimal thyroid function on child behavior. J Clin Endocrinol Metab. 2020 Mar 1;105(3):dgz098. doi: 10.1210/clinem/dgz098.
28. Korevaar TI, et al. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. Lancet Diabetes Endocrinol. 2016 Jan;4(1):35-43. doi: 10.1016/S2213-8587(15)00327-7.
29. Muller I, et al. CATS II Long-term anthropometric and metabolic effects of maternal sub-optimal thyroid function in offspring and mothers. J Clin Endocrinol Metab. 2020 Jul 1;105(7):dgaa129. doi: 10.1210/clinem/dgaa129.
30. Smulever A, Pitoia F. High rate incidence of post-surgical adverse events in patients with low-risk papillary thyroid cancer who did not accept active surveillance. Endocrine. 2020 Sep;69(3):587-595. doi: 10.1007/s12020-020-02310-8.
31. Adam MA, et al. Extent of surgery for papillary thyroid cancer is not associated with survival: an analysis of 61,775 patients. Ann Surg. 2014 Oct;260(4):601-5; discussion 605-7. doi: 10.1097/SLA.0000000000000925.
32. Tuttle RM, et al. A clinical framework to facilitate selection of patients with differentiated thyroid cancer for active surveillance or less aggressive initial surgical management. Expert Rev Endocrinol Metab. 2018 Mar;13(2):77-85. doi: 10.1080/17446651.2018.1449641.
33. Bilimoria KY, et al. Extent of surgery affects survival for papillary thyroid cancer. Ann Surg. 2007 Sep;246(3):375-81; discussion 381-4. doi: 10.1097/SLA.0b013e31814697d9.
34. Zhang C, et al. Total thyroidectomy versus lobectomy for papillary thyroid cancer: A systematic review and meta-analysis. Medicine (Baltimore). 2020 Feb;99(6):e19073. doi: 10.1097/MD.0000000000019073.
35. Wilson M, et al. Postoperative thyroid hormone supplementation rates following thyroid lobectomy. Am J Surg. 2020 Nov;220(5):1169-1173. doi: 10.1016/j.amjsurg.2020.06.052.
36. Sosa JA, et al. The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. Ann Surg. 1998 Sep;228(3):320-30. doi: 10.1097/00000658-199809000-00005.
37. Panveloski-Costa AC, et al. Thyroid hormone reduces inflammatory cytokines improving glycaemia control in alloxan-induced diabetic wistar rats. Acta Physiol (Oxf). 2016 Jun;217(2):130-40. doi: 10.1111/apha.12647.

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