

### In The Pursuit of The Perfect Thyroid Care

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Since the first thyroidectomy was described in 912 AD by Abu al-Qasim, considered Islam's greatest medieval surgeon, many things have changed in the field of thyroidology (fortunately for us).<sup>1</sup> Going through Leonardo Da Vinci's early drawing, showing it as an anatomical organ, *not of a human exactly*, and Thomas Wharton giving the name to the gland, as we spell it today, hinting the shape of an ancient Grecian shield, both described from the beginning of the XV century until the middle of the XVI century.<sup>2</sup> There have been a series of epic events that have allowed a level of improvement in the management of thyroid diseases, both benign and malignant. The speed with which these scientific advances have been documented increased markedly from the nineteenth century after the

discovery of the Iodine by Bernard Courtois and named as *Iode* by Gay-Lussac, right in the middle of the French Revolutionary Wars, a rhythm that has been maintained until the current date.<sup>3</sup> Taking a more recent journey into the history of the events that spawned the current focus of well-differentiated thyroid cancer (DTC), we can see that after the first publication of the guidelines for the management of thyroid nodules and DTC by the American Thyroid Association (ATA) in 1966, there have been multiple advances in the diagnosis and management of such pathologies, and some of them have revolutionized the way in which our head and neck surgeons and the multidisciplinary team, in general, are trained today, in order to offer patients not only the best results in terms

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of prognosis, but under the perspective of attention to fine detail taking care of previously considered aspects as futile as the presence or not of a scar on the neck, and even the early use of high resolution imaging as the PET-CT in the follow-up of survivors.

After the first description published by Tempka and collaborators in 1948 about the US-guided fine needle aspiration (US-FNA) as a diagnostic method, more than 50 years had to pass before there was another advance regarding the non-invasive evaluation of the thyroid nodule, which occurred after development of thyroid elastography in clinical application that was first reported by Rago et al in 2007, with several modifications after applying the different proposed scales and subsequently the appearance of shear wave elastography (SWE), described 7 years ago by Sebag, for the diagnosis of thyroid nodule and it does not convince many since it does not have reproducible cut-off values in the different studies that allow the standardization of its reading.<sup>4,5</sup>

To reach the present: making use of conventional ultrasound and elastography to improve the specificity and sensitivity in the detection of malignant lesions of the thyroid. Although in the particular case of nodules with "indeterminate" or "nondiagnostic" cytology, the voice that supports the use of SWE to discriminate between malignancy and benignity has been turned off. It is a point to highlight that in the last decade, thanks to the improvement in imaging techniques and interventional skills now we are suffering an important overdiagnosis with its corresponding overtreatment.<sup>6</sup>

Image-guided ablations are achieving a promising and quite novel application in the care of patients with thyroid benign and malignant tumors, even in patients with metastatic lymph nodes from papillary thyroid carcinoma.<sup>7</sup>

Two techniques are those that are mainly used for neck disease: radiofrequency ablation (RFA) and laser ablation(LA). Both are similarly feasible, safe and effective in treating benign thyroid nodules when performed by the same team<sup>8,9</sup>

It is important to mention that the use of a conventional technique for ultrasonographic tracking is

not feasible, being necessary the use of a contrast-enhanced ultrasound (CEUS), which is another particularly useful imaging modality in thermal ablations that provides a precise visualization of the vascularization of the lesion, due to the use of microsphere contrast agents called microbubbles that are revolutionizing traditional ultrasonography, improving the precision of diagnostic sonograms and expanding the clinical scope of a widely used imaging modality.<sup>10</sup> Efficacy and safety of percutaneous ultrasound guided radiofrequency ablation for treating cervical metastatic lymph nodes from papillary thyroid carcinoma.<sup>11</sup>

Continuing along the same line, surgical advances have continued, after Virchow performed thyroidectomies on animals in 1860, the path opened, and great masters of surgery gave meaning to thyroidectomy, starting with Billroth, followed by Kocher who in 1909 was awarded with a Nobel Prize for his work in the physiology, pathology, and surgery of the thyroid gland, he had no fear in making improvements to the technique and described even the deleterious effects on the human body of total thyroidectomy. Halsted and Mayo were not left behind, the latter being considered the "Father of the American Thyroid Surgery" he was the first to register death rates of 1%. However many more have achieved glory through the constant improvement of the technique, and it is such a noble gland, that even today, we have advanced from minimally invasive open thyroid surgery and video-assisted thyroidectomy (MIVAT), to the purely endoscopic approaches, which surely our predecessors would have been unable to imagine for the benign pathology and less for the treatment of cancer, through incisions hidden from sight such as in the retroauricular region and the armpit.<sup>12</sup> In the search for increasingly sophisticated techniques, one of the most promising derives from Natural Orifice Transluminal Endoscopic Surgery (NOTES); Richmond et al. describe in 2011 the transoral technique (TOETVA), acquiring fame soon not only because a vestibular approach is performed with an index of complications similar to the open procedure, but because of the evident absence of scar and above all, the possibility of accessing both sides of the neck, decreasing the possibility of leaving residual tissue as in

other accesses.<sup>13</sup>

With respect to the postoperative follow-up in patients undergoing surgery for DTC, the advances have resulted from the discovery of iodine, as well as the incorporation in 1917 by M. Seymour of X-rays as a treatment method for Graves' disease; to the introduction of the concept of radioactive tracers in 1924 by Hevesy, work that won him a Nobel Prize years later; and the implementation in 1936 by Saul Hertz of the radioactive iodine for the study of the thyroid. The whole-body scan (WBS) with radioiodine (<sup>131</sup>I) appears later as the most effective method to detect a thyroid tumor, to stage it and to address treatment as well as evaluating distant metastatic disease.<sup>14</sup>

Evolution of single photon emission tomography/computed tomography (SPECT/CT) has drastically revolutionized and overcome the limitations faced by <sup>131</sup>I –WBS. Many researchers have already proved the incremental value of SPECT/CT over the planar scintigraphy in the management of thyroid cancer.<sup>15</sup> And culminating with the combination of PET / CT from 1990 and until today, as a method to detect early recurrence. It has become a high-value instrument even though most DTCs tend to have slow growth and Fluoro-deoxy glucose (<sup>18</sup>F-FDG) may be negative in postoperative follow-up, due to the considerable number of patients who are may be suffering from a metastatic or residual disease. It will not be sensitive to the radioiodine, especially in those with an elevation of thyroglobulin and negative <sup>131</sup>I-WBS, (TENIS syndrome) assuming a true diagnostic challenge since the location of the tissue that begins to undergo dedifferentiation is undetectable and therefore it receives less radioiodine uptake, while the metabolism of the glucose tends to increase. Being of invaluable transcendence for the surgeon in those cases.<sup>16</sup>

Here comes another challenge, post-surgery, and post radioiodine treatment, in situation like TENIS syndrome, the role of redifferentiation agents like Thalidomide, rosiglitazone (an antidiabetic which has already been withdrawn by US FDA), Valproate, retinoic acid brought a new hope of light in the darkness. Pretreatment with these agents helped in some patients in the redifferentiation and reexpression of sodium iodide symporter (NIS) which is a key molecule for the

RAI therapy. A better understanding of the molecular pathology and different mutagenic variation was the need of the hour. And green signals to Tyrosine Kinase Inhibitors (TKI) like sorafenib and selumetinib by US FDA for use in advanced DTC was another landmark achievement in the management of RAI-refractory progressive DTC patients. These therapies improved progression-free survival.<sup>17</sup>

Better understanding the BRAF<sup>V600E</sup> and targeting MAP Kinase signaling by CKI has improved our patient care in iodine-refractory thyroid cancer patients. PSMA (prostate specific membrane antigen) expression has already been established in PTC which rays new hopes for targeted peptide receptor radionuclide therapy (PRRT) with <sup>90</sup>Y <sup>177</sup>Lu.<sup>18</sup>

Recurrence in thyroid cancer becomes a challenge for the surgeon as well as the nuclear physician also. Percutaneous Laser Ablation has been proven to be an important non invasive method of treatment of metastatic lymph nodes in papillary thyroid carcinoma.<sup>19</sup> The choice of local ablative thermal treatment for such recurrent metastatic lymph nodes (RFA, MWA, LA, HIFU) depends on local expertise.<sup>20</sup>

With thyroid cancer as the most rapidly increasing cancer at least in the US, advances in its diagnosis and treatment do not stop in this brief comment, but the future arises in front of us. It is our duty as men and women of science, to update ourselves as much as possible in order to improve our clinical performance, consolidating the multidisciplinary team of which surely we are part of.

Improving our understanding of pathology at the molecular level, focusing on specific pathways, will definitely lead us to a better patient management.

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