

**Differentiated Thyroid Carcinoma (DTC). Stimulation of endogenous TSH with multiple doses of TRH and its treatment with <sup>131</sup> I. A three year experience.**

**“Dr. Hugo Claire” award to the best Clinical Research Paper presented at the Alasbimn Congress in Santa Cruz, Bolivia, December 2007.**

**Jara Yorg, J.A<sup>1</sup>  
Jara, M.,  
Jara Ruiz, J.M..**

CEDIN “Centro de Diagnóstico y Tratamiento Nuclear” Asunción, Paraguay.

<sup>1</sup>Professor of Nuclear Medicine and Endocrinology,  
Cathedral of Medical Pathology,  
National University of Asuncion and  
Director of the Nuclear Diagnostic and Treatment Center  
Endocrinological Center of Diagnostic by Imaging (CEDIN) Asuncion,  
Paraguay, South America

**Correspondence**

**Jorge Antonio Jara Yorg M.D.**  
e-mail: [jorgeantoniojara@yahoo.com](mailto:jorgeantoniojara@yahoo.com)

**Reference:**

Jara Yorg, Jorge Antonio, Jara, Mark Anthony Jara Ruiz, Jessica María Jara Ruiz – Differentiated Thyroid Carcinoma (CDT). Stimulation of endogenous TSH with multiple doses of TRH and its treatment with <sup>131</sup> I. A three year experience.  
<http://www.alasbimnjournal.cl/>

## Summary

The search of an alternative method to the rh-TSH to stimulate endogenous rising of TSH previous to thyroid ablation with  $^{131}\text{I}$  in patients with CDT operated. The purpose of the work began in 2001 in Paraguay using multiple dose of TRH IV (200 $\mu\text{U}$  of TRH Threlea® Argentina) to stimulate the own TSH of patients previous to  $^{131}\text{I}$  ablation. It is known that the injection of a unique dose of 200 $\mu\text{U}$  of TRH IV achieves the increasing of the endogenous TSH in patients with differentiated thyroid carcinoma up to 30 - 35 mU/L at the end of the first hour, however, there is not statistical data of the effects of multiple injections of TRH applied IV or IM in operated patients of DTC previous to the ablation with  $^{131}\text{I}$ .

Since 2001-2007, two hundred patients operated for DTC were studied by this method, 120 were papillary cancer and 80 follicular cancer. One hundred eighty did not have distance metastasis and 20 presented metastasis in thorax, pelvis and dorsal spine. Total thyroidectomy was carried out in 120 and total lobectomy with itsmectomy plus hemilobectomy of the other lobe in 80. All were treated with ablative dose of 100 mCi (3.700 mBq) of  $^{131}\text{I}$ , except those with metastasis which receive 150 mCi (5.500 mBq) with the previous stimulation with TRH IV with two daily dose for three days with previous suspension of L-tiroxine for 25 days and replaced by triyodotiroxine 25 mcg/d for 15 days with suspension 10 days before the stimulation with TRH and treatment with  $^{131}\text{I}$ . Two patients with metastasis received another extra dose of 150 mCi (5.550 MBq) 6 months later. One presented uptake in thyroid bed one year after the ablation received a new ablative dose of 100 mCi (3.700 mBq) of  $^{131}\text{I}$ . All the patients were interned and isolated by 48 hours.

Twenty feminine patients had later pregnancies in 1-3 years after their ablative dose with healthy products.

TSH was measured during the stimulation with TRH in all patients. Whole body scan was done with a gamma camera Spect LFOV (Mediso) with of high sensibility collimator carried out at 5 days of the administration of  $^{131}\text{I}$ . Substitutive hormonotherapy with L-Tiroxine was done to all the patients at 24 hours after the administration of  $^{131}\text{I}$ . All the patients without metastasis achieved the total ablation at 6 months except one that was depicted previously with  $^{131}\text{I}$  with a single administration of TRH and that the total ablation was achieved later on. The lymph nodes metastatic lesions remitted with a single dose of 100 mCi (3.700 mBq). A patient that presented metastases at distance improved extraordinarily, with disappearance of their lesions in dorsal spine after the re-treatment at 6 months. The total ablation of the diffuse and focal metastatic lesions in lung also were possible in one year. Metastasis in skull and in neck disappeared after two dose of 150 mCi (5.500 mBq). Increased uptake of the thyroid remnant and their metastasis has been very evident with the stimulation of the TRH. The appearance of symptoms of hypothyroidism is very light at 7 days, except in old patients that tolerate the suspension of its hormonotherapy worse.

Our results suggest that multiple dose of TRH could be a new tool to be used in the stimulation of the endogenous TSH in patients with (DTC) previously operated that they should be treated with radioiodine.

### **Key Words:**

Differentiated Thyroid Carcinoma, Papillary Thyroid Ca, Follicular Thyroid Ca, TRH, rh-TSH, <sup>131</sup>I ablation, Na levothyroxine.

### **Antecedents**

The differentiated thyroid cancer (Papillary and Follicular) has an incidence in diverse parts of the world that varies from 0.5-10 cases for 100.000 inhabitants and it is one of cancers more curable [1], however, some patients have high recurrency risk or death depending on the stage. The survival to the 10 years of the papillary carcinoma is 93%, the follicular 85%, Hürtle cells 76%, medullary 75% and of the anaplastic 14%[2].

The papillary carcinoma is multifocal and bilateral many times, reason why the proposed treatment is the surgery (total thyroidectomy) or the total lobectomy of the affected side with hemilobectomy of the contra lateral side and the ablation of the remainder tissue with radioactive <sup>131</sup>I [3].

In the patient's evaluation with this pathology, several elements exist to keep in mind among which can be mentioned the size of the thyroid nodule, the presence or not of metastasis, the election of the type of thyroid surgery to be carried out, the ablation of the thyroid remnant tissue with <sup>131</sup>I with or without stimulation of the TSH, the addition of supplementary thyroid hormone and the follow up with the purpose of evaluating the total destruction of the thyroid remnant and metastasis if they were present, all that which is related to the survival and to the quality of life that will have. The tumor recurrence is around 30% and the mortality of the stage 2 and 3 is around the 10%[4].

In the patient's evaluation with this pathology, several elements exist to keep in mind among which can be mentioned the size of the thyroid nodule, the presence or not of metastasis, the election of the type of thyroid surgery to be carried out, the ablation of the thyroid remainder tissue with <sup>131</sup>I with or without stimulation of the TSH, the addition of supplementary thyroid hormone and the follow up with the purpose of evaluating the total destruction of the thyroid remnant and metastasis if they were present, all that which is related to the survival and to the quality of life that will have. The recurrence of the tumor is around 30% and the mortality of the stage 2 and 3 is around the 10%[4].

Nuclear Medicine plays a very important paper in the diagnosis and treatment of the benign or malignant thyroid affections. The differentiated thyroid carcinoma (DTC) can be treated using the  $^{131}\text{I}$ , which is highly effective not only for the ablation of the remnant tissue but to avoid the propagation from these neoplastic cells to other tissues [5]. In the presence of metastasis, the destruction of these cells is very positive using the radiation when cells capturing the  $^{131}\text{I}$  [6, 7, 8].

The total ablation requires a dose of 300 Gy in thyroid remnant tissue; reason why the dosymetry can be necessary to specifies or estimate the dose of  $^{131}\text{I}$  that should be given [5, 6, 7, 8, 9, 10, 11, 12]. The dosage of the serum tyroglobulin and the whole body scan with appropriate dose of  $^{131}\text{I}$  carried out in routine form they complete a very important paper in the evaluation of these patients and in its later pursuit that which precise a previous suspension of the supplementary hormonotherapy with L-tiroxine or of the use of the stimulation by rh-TSH (TSH recombinant - Thyrogen Genzyme, Cambridge, Mass) that elevates the serum level of the TSH in order to achieve a good uptake of the  $^{131}\text{I}$  for the thyroid remnant, of the local recurrences' and/or the metastasis at distance, reason why the treatment should be made in the moment of the maximum elevation of the serum TSH.

Usually after the thyroid surgery, the TSH begins to increase to the 2<sup>nd</sup> weeks reaching the maximum pick between the fourth and the eighth week. The time of elevation of the TSH varies from patient to patient due to the variable metabolism of the circulating T4 and the one stored, however, 6-8 weeks it is enough so that 90% of the patients reaches high levels of TSH [9]. This is the moment of maximum reception, reason why the ablation of the thyroid remainder tissue with  $^{131}\text{I}$  would be more successful if one chooses the method of suspension of the supplementary hormonotherapy for L-Tiroxine.

The ablation of the thyroid remnant is better when the TSH level is more than 30  $\mu\text{IU/ml}$ , having been demonstrated that an appropriate stimulation of the TSH is an essential requirement for the complete ablation [7].

As the T4 or sodium Levotiroxine it contains 66% of iodine, when administering a dose of substitution of 200 mcg from L-Tiroxine to a patient orally, this receives 112 micrograms of iodine, therefore it should be thought of reducing the levels of iodine in the patient's serum for a better reception of the glandular remnant and their ablation. When the recombinant TSH is used to stimulate the TSH, usually one month before the rh-TSH administration the T4 is replaced by triiodotironine (T3). If we administer 25 to 37 mcg of T3 to the patients, these will end up being more quickly hypothyroid and they will capture the  $^{131}\text{I}$  better that using the T4.

The resulting hypothyroidism when often suspending the substitution hormonotherapy with T4 is poorly tolerated by some patients, reason why the election method for the thyroid ablation would be the use of the rh-TSH, but due to its high cost (>1.000 dollars) it becomes inaccessible to the routine use in most of the patients in Latin America, Africa and in other parts of the world that don't have a system of health that can cover this cost.

The obtained results of the WBS with  $^{131}\text{I}$  in patients with thyroid carcinoma which use rh-TSH compared with those that suspended the administration of the thyroid hormone were similar [11, 12, 13]

Two methods of the patients' preparation for the thyroid ablation are available at the moment, one is the retirement of supplementary hormone (L-T4) during 4 weeks and the measure of the serum TSH whose level should be above 30uU/L before the administration of  $^{131}\text{I}$  [13].

The second method consists on the administration of the rhTSH (Thyrogen, Genzyme Transgenics Corporation, Cambridge, MA) with the injection I.M. of 0.9 rhTSH mg in 2 serial days and the treatment with radioiodine 24 hours later orally. This is able to avoid the hypothyroidism and their unpleasant effects in the patients that are unable to tolerate when suspending for many days the supplementary L-T4 and to those that a high TSH doesn't generate, however it is important to highlight that is is advised to the patients a diet with contained low content of iodine for a period of 3 weeks before the administration of the rh TSH and the  $^{131}\text{I}$  in countries with high yoduria [11, 12, 13]. The rh-TSH elevates the level of the serum TSH achieving a good uptake of the thyroid remnants and of the metastasis. In the event of contamination with iodine, the administration of the radioiodine should be postponed during 3 months.

The search of an alternative method to the rh-TSH to stimulate the increasing of the endogenous serum TSH previously to the treatment with  $^{131}\text{I}$  in patients with operated DTC was the purpose of this work that we begin in the year 2001 in the Paraguay, and the OIEA was supported in the beginning of this project using multiple dose of TRH to stimulate the own TSH of the patients under a research protocol using ampoules of 200 $\mu\text{U}$  of TRH (Threlea® Argentina) administered IV to the patients in multiple doses to subject them then to the treatment with  $^{131}\text{I}$ .

It is known that the injection of an unique dose of 200 $\mu\text{U}$  of TRH IV achieves the increasing of the endogenous TSH in patients with differentiated carcinoma of thyroid being able to elevate the TSH among 30 - 35 mUI/L at the end of the first hour by Ismailov and collaborators, however, they are not had statistical data of the effects of multiple injections of TRH applied IV or IM in the operated patients of thyroid for DTC previously to the ablation with  $^{131}\text{I}$ .

## **Objective**

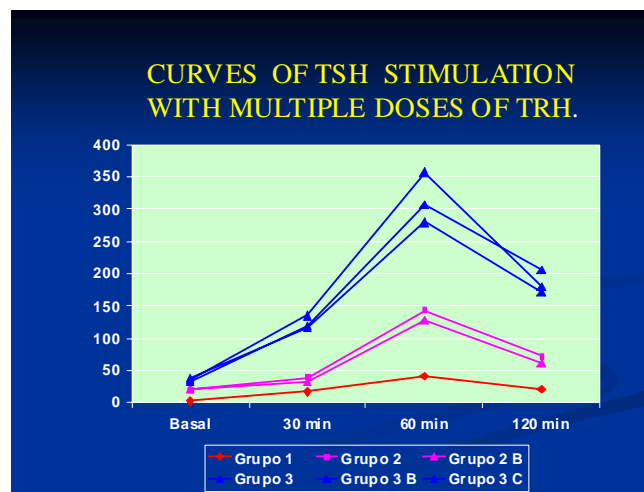
The ablation of the thyroid remnant and their metastasis in patients operated by DTC carried out with  $^{131}\text{I}$  with previous stimulation of the endogenous TSH for multiple dose of TRH IV.

## **Material and Method**

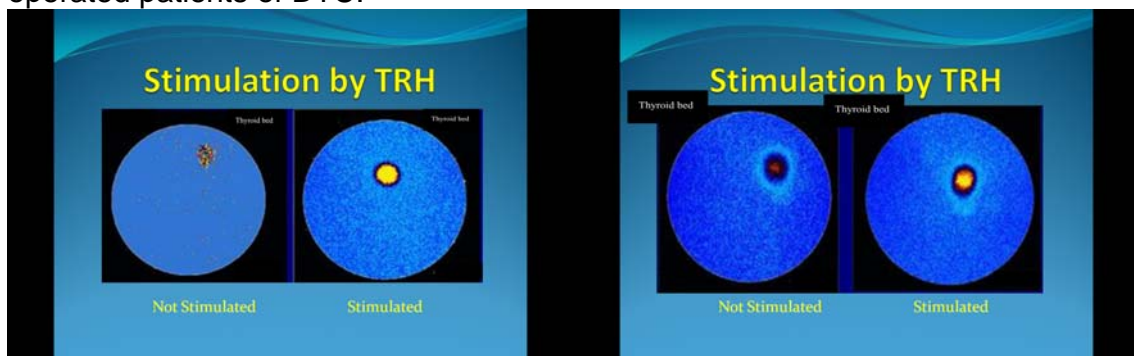
In 2001, we begin to compare three different methods of stimulation of the secretion of the endogenous TSH in 70 patients with CDT and a group control of 20 using multiple dose of TRH administered via IV in the candidates to the total ablation of the thyroid remnant and of their metastasis with  $^{131}\text{I}$ . That research

served as a base to the present work and it was presented in the congress of Alasbimn in Punta del Este, Uruguay in the year 2005.(Fig 1-2-3-4).

Levels of Serum TSH(mU/l)						
Subjets			Before TSH infusión	Duration of the TSH induction (minutes)		
				30	60	120
Control (# 15)		1 injection	1.8	4	12	8
Group 1 (#20)		1 injection	1.6	16.46	41.06	19.9
Group 2 (# 25)		2 injection	19.8	22.5 15.7	135.3 80.85	68.7 44.0
Group 3 (#25)		3 injection	37.6	59.25 43.7 39.5	222 168.7 103.6	102 91.3 71.3



**Figures 1–2:** Grades of induction of serum TSH after the infusion of multiples injections of 200µU of TRH previous to the administration of therapy with <sup>131</sup>I in operated patients of DTC.



**Figures 3-4 :** Pre y post Stimulation with TRH.

Since that time until 2007 two hundred patients operated (Table 1) of DTC was studied by this method, 120 corresponds to papillary cancer and 80 follicular cancer.

**Table 1.** Characteristics of 200 patients with DTC.

<b>Characteristics</b>	<b>N° (%)</b>
Femenine sex	160 (80%)
Masculine sex	40 (20%)
<b>Type of cancer:</b>	
Papillary	120
Follicular	80
<b>Type of surgery:</b>	
Total Thyroidectomy	120
Lobectomy + Itsmectomy+ Hemilobectomy	80
<b>Type of Treatment:</b>	
Surgery + <sup>131</sup> I	200
<b>Sites of concentration of <sup>131</sup>I</b>	
No uptake	12
Glandular bed	168
Glandular bed and other cervical place	13
Intrathoracic	2
Pulmonary difusse	1
Pulmonary focalized	1
Skeleton	1
Scull	2
<b>Doses of <sup>131</sup>I</b>	
100 mCi ( 3.700 mBq)	180
150 mCi ( 5.500 mBq)	20
<b>Re-treatment with <sup>131</sup>I</b>	
100 mCi (3700 mBq)	1
150 mCi (5.500 mBq)	2

One hundred eighty didn't present metastasis at distance and 20 presented metastasis in thorax, pelvis and dorsal spine.

Total Thyroidectomy was carried out in 120 and total lobectomy and itsmectomy more hemilobectomy of the side against lateral in 80. All were treated with in ablative dose (100 MCI. (3.700 mBq) of <sup>131</sup>I previous stimulation with TRH IV in two daily dose for 2 days with previous suspension of L-tiroxine for 25 days before the treatment replacing it for triyodotironine 25 mcg/day for 15 days after that it was

also suspended 10 days before the stimulation with TRH and the giving the dose of treatment with  $^{131}\text{I}$

Twenty of them with metastasis at distance received 150 mCi of  $^{131}\text{I}$  (5.550 mBq) and two received another extra dose of 150 mCi (5.550 MBq) 6 months later.

One patient presented an area remnant of uptake in thyroid bed to the year of the ablation and it was again treated with an ablative dose of 100 mCi. (3,700 mBq). All the patients were interned and isolated by 48 hours.

Twenty patients of feminine sex had later pregnancies in 1-3 years after their ablative dose with healthy products. In all the patients were measured the TSH during the stimulation by TRH and the tiroglobulina. The WBS done with a gammacamera Spect LFOV (Mediso) with a high sensibility collimator was carried out 5 days later of the administration of  $^{131}\text{I}$ . Substitutive hormonotherapy with L-Tiroxine and Triyodotirone was administered to all the patients orally 24 hours after the administration of  $^{131}\text{I}$ .

## Results

All the patients that didn't present metastasis achieved the total ablation from the remnant to the 6 months during their control carried out except one that was treated with  $^{131}\text{I}$  with a single administration of TRH and that the total ablation was achieved later on.

The patients that presented metastasis at distance improved extraordinarily, one of them with disappearance of their metastatic lesions in dorsal spine (Figures 5-6) after the re-treatment at 6 months. The total ablation of the diffuse lung lesions and focal metastases also was possible at one year (Image 4-5).





**Figure 4-5.** Pre y post treatment of lung metastases with  $^{131}\text{I}$  with previous stimulation of TRH



**Figure 6-7.** Pre y post ablation of thyroid remnant with TRH stimulation.

Metastases in skull and in the neck disappeared after two doses of 150 mCi. Linfonodes metastatic lesions remitted with a single dose of 100 mCi.

The uptake in thyroid remnant and their metastases has been very notorious with the stimulation of the TRH. The levels of TSH achieved under stimulation have been very high when these patients were treated with three serial days even reaching 300 uUI/l of TRH, reason why we consider that with two days of stimulation and suspending the T3 for 7 - 10 days the maximum effect wanted is achieved for the ablation.

The appearance of symptoms of hypothyroidism at 7 days was very light, except in those patients very old that worse tolerate the suspension of its hormonotherapy.

The quick medication at 24 hours after the therapeutic dose produces an effect of improvement and tolerance to the patients during its treatment.

## Discussion

We know that the response to the  $^{131}\text{I}$  is remarkable in metastases of the soft tissues being very difficult the total ablation in bones, however in our casuistry we have achieved in almost all the patients except one that was in stage 4 who comes for aid and that one has not been included in the present work.

In spite of the success of the innovative treatment that we have created and introduced, we believe that this effective methodology should be considered in the achievement of the quick improvement as an alternative for the treatment of the patients with DTC.

However, new researches will be necessary to improve the technique of its application to setting-up in the oncological therapy from the thyroid malignant pathology at low cost.

The total cost of the treatment stimulating the TSH with multiple doses of TRH reaches approximately 40 dollars.

## Conclusion

The therapy of DTC with TRH stimulation is an innovation in the therapeutic arsenal of the well differentiated thyroid carcinoma. Our results suggest that TRH could be used to stimulate the endogenous TSH of the patients previously operated of Well Differentiated Thyroid Carcinoma which should be treated with radioiodine with low cost reaching the whole population with this disease.

## Bibliography

1. Parkin DM, Muir CS, Whelan SL, Gao YT, Ferlay J, Powell J. Cancer incidence in five continents Vol 6. Lyon, France: International Agency for Research on Cancer, 1992. (IARC scientific publications n° 120).
2. SA et al. Relative survival in 10 years. *Hundahl Cancer* 1998; 83:2638-48).
3. Schlumberger, M.J. Papillary and Follicular Thyroid carcinoma *N Eng J Med*, Volume 338, Number 5, January 29, 1998.
4. Recurrency of tumor and death by Cáncer. Mazzaferri y Jhaing. *Thyroid Today* Volume XVIII, 3, 1995.
5. Maxon HR, Thomas SR, Hertzberg VS, et al. Relation between effective radiation dose and outcome of radioiodine therapy for thyroid cancer. *N Engl J Med* 1983;309:937-41.
6. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab* 1990; 71:414-24.
7. Simpson WJ, Panzarella T, Carruthers JS, Gospodarowicz MK, Sutcliffe

- SB. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. In J Radiat Oncol Biol Phys 1988; 14:1063-75.
8. Tubiana M, Schlumberger M, Rougier P, et al. Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. Cancer 1985;55:794-804.
  9. Maxon HR III, Englaro, Thomas SR, et al. Radioiodine-131 therapy for well differentiated thyroid cancer- a quantitative radiation dosimetric approach: outcome and validation in 85 patients. J. Nucl. Med 1992; 33:1132-6.
  10. S. V. Hiltz, D. Hellman, J. Anderson, J. Woolfenden, J. Van Antwerp, and D. Patton Serial TSH Determination after T3 Withdrawal or Thyroidectomy in the Therapy of Thyroid Carcinoma J. Nucl. Med. 1979;20:928-932.
  11. Ladenson PW, Braverman LE, Mazzaferri EL, et al. Comparison of administration of recombinant human thyrotropin with withdrawal of thyroid hormone for radioactive iodine scanning in patients with thyroid carcinoma. N. Eng J Med 1997;337:888-96.
  12. Samuel AM, Rajashekharrao B Radioiodine Therapy of Differentiated Thyroid Cancer W. J. Nucl. Medic, Vol 5, Number 3, July 2006.
  13. Task Force Sociedad Latinoamericana de Tiroides- Nov. 2007.