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INTRAOPERATIVE NEURO-MONITORING VERSUS OPTICAL MAGNIFICATION IN THE PREVENTION OF RECURRENT LARYNGEAL NERVE INJURY IN THYROID SURGERY: A PROSPECTIVE RANDOMIZED STUDY

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INTRAOPERATIVE NEURO-MONITORING (IOMN) VERSUS OPTICAL MAGNIFICATION (OM) IN THE PREVENTION OF RECURRENT LARYNGEAL NERVE (RLN) INJURY IN THYROID SURGERY: A PROSPECTIVE RANDOMIZED STUDY

INTRODUCTION

Thyroid surgery is undoubtedly a very common procedure practiced worldwide. In Italy during 2019 over 32,000 operations of thyroidectomy were performed and the incidence of thyroid disorders that require total or partial thyroidectomy is increasing constantly [1]. Although thyroid surgery has been practiced with a standardized technique in the last decades, still has a certain percentage of both early and late postoperative complications. Among them, postoperative bleeding, which generally occurs within the first 24 hours after surgery, and more frequently in the first 12 hours, is often linked to postoperative hypertensive crises, especially in patients with chronic blood pressure disorders [2,3]. Both early and late hypoparathyroidism is more frequently due to the accidental avulsion of one or more parathyroid glands, especially during total thyroidectomy and more often in patients with hyperfunctioning thyroid disease or in operations for recurrence or cancer [4]. But the most fearful complication remains the recurrent laryngeal nerve (RLN) paralysis, transient or permanent, which if bilateral can cause the death of the patient and in any case, even when unilateral and temporary, affects significantly the quality of life [5].

In the early 19th century Lahey et al. pointed out the importance of an accurate identification and dissection of the inferior laryngeal nerve (ILN) during thyroidectomy in reducing the risk of injuries [6]. Towards the end of the 20th century, Wheeler et al. expressed the same opinion, stressing the need to identify the RLN during thyroid surgery in order to avoid injury [7].

For that reason, early identification and visualization of RLN during thyroidectomy is now considered the gold standard method to prevent injuries [8]. Nevertheless, as reported by the most experienced endocrine surgeons, the RLN cannot be visualized in

6.8% to 11.5% of thyroidectomies and this rate raise to 42% - 66% in those patients with recurrent disease [9,10].

Furthermore, the direct visual recognition of RLN injury permit to reveal only 10% to 14 % of nerve injuries [4,11,12] and, as stated by many authors, the anatomical integrity of RLN does not always related with a normal vocal cord function postoperatively [2,13-16]. A RLN that appears morphologically intact during surgery might be functionally damaged, and a nerve apparently compromised or with neoplastic infiltration can still preserve electrical signal if stimulated [17].

Thus, different technological innovations have been introduced in thyroid surgery over the last 50 years with the aim to guarantee major accuracy and decrease the risk of severe complications, such as permanent hypoparathyroidism and laryngeal nerve palsy. The last decades, the effort was mostly concentrated on developing intraoperative systems that could allow non only a more precise RLN identification and dissection, but also provide information on the integrity and functionality of the laryngeal nerves.

Magnification systems, such as surgical microscope and magnification loupes, combined with microsurgical technique are mostly applied in reconstructive surgery, in neurosurgery and many other surgical specialties. Undoubtedly, the imaging magnification enhances the surgeon’s ability to operate with higher precision due to a clearer vision of the anatomy. This is extremely advantageous, for both surgeons and patients, as permits to perform surgery in a bloodless operating field, reducing the incidence of complications and reducing the operating time [18] (Suffat et al. 2020).

A microsurgical approach in thyroid surgery by using optical magnification or surgical microscope is stated to increase the surgeon’s precision and noble anatomical structures such as vessels and nerves, could be identified with major accuracy during the operation [19].

On the other hand, in order to obtain information on the RLN function the intraoperative neuromonitoring (IONM) was used. The usefulness of the IONM in thyroid surgery consists in laryngeal nerve identification and mapping, facilitate dissection, detect any type of nerve injury and predict the postoperative and functional nerve status. Particularly, intraoperative monitoring is a valid functional system that permits an early recognition of the most common RLN injury mechanisms such as traction, thermal stress and compression [20].

Among the literature, we found a wide series of systematic reviews and meta-analyses of studies comparing IONM versus direct visual RLN identification alone [5,21,22-30]. Curiously, many of these studies came to opposite conclusions.

In consideration of these assumptions, we compared the technique of identification, preparation and dissection of the RLN in the course of total thyroidectomy with the aid of IONM against the use of optical magnification devices and microsurgery technique alone. The aim of our study is to compare optical magnification with neuromonitoring in terms of the incidence of RLN paralysis, but also with regard to other parameters commonly used to validate the new methods in thyroid surgery.

MATERIALS AND METHODS

In our prospective randomized longitudinal study, total thyroidectomy with open technique was performed in our Institution from October 2018 to February 2020 on a population of 100 consecutive patients that was divided into two groups of 50 patients.

The first group (OM - Optical Magnification) underwent thyroidectomy using only optical magnification as an aid in the RLN identification and dissection. The surgical devices were selected with specific technical characteristics such as weight, the magnification power and the focal distance, technical aspects that affect the surgical performance. For this reason, we have opted for binocular loupes with 2.5x-4.5x magnification and focal range of about 17 inches (43 cm), combined with head-mounted, battery-powered, led coaxial light to increase operative field brightness **(Figure 1)**.

In the second group (IONM – Intraoperative Neuromonitoring), instead, only intraoperative neuromonitoring was used during total thyroidectomy as an aid to isolation and preparation of the RLN. For this purpose, we used a neuromonitoring device named NIM 3.0 by Medtronic (Florida, USA), applied only in intermittent modality and therefore without automatic periodic stimulation (APS) **(Figure 2)**. An endotracheal tube (Flex Medtronic) with surface electrodes incorporated was used to perform the acquisition of electromyographic signal (EMG) **(Figure 3)**. The diameter of endotracheal tubes used was 7 mm and 7.5-8 mm on female and male patients, respectively. Particular attention was paid to positioning correctly the endotracheal tube, about 20-22 cm from the incisors of the dental arch, in order to obtain precise localization of the electrodes between the vocal cords [31].

Conventionally, a loss of signal (LOS) was defined as a decrease in the RLN amplitude less than 100 MicroV or complete loss of amplitude after proper vagus stimulation on upper threshold limit (1-2 mA). Typically, the signal loss was distinct in two types: Type 1, in which a defined level of RLN injury was detected corresponding to a segmental nerve lesion; Type 2, in which a total LOS was detected regarding both RLN and vagus nerve [16].

After a probable LOS was perceived, we immediately controlled the laryngeal contraction and the response of contralateral vagus nerve to stimulation [16,32,33]. All the patients with RLN with LOS were divided into 4 categories taking into consideration the two types of LOS and the intraoperative status of recovery: Category I patients found with type 1 LOS and intraoperative recovery; Category II patients had type 1 LOS without intraoperative recovery; Category III had type 2 LOS with intraoperative recovery; and Category IV patients found with type 2 LOS without intraoperative recovery [34].

The two groups (OM and IONM) were homogeneous in distribution of age, sex and type of thyroid disease and all patients had normal preoperative vocal cord motility as verified by indirect laryngoscopy and / or preoperative fibrolaringoscopy.

Written informed consent was obtained by each patient for both the operation with magnification loupes and IONM and for the data analysis; the clinical protocol for this study was approved by the local Independent Ethical Committee of our Institution.

Thyroid surgery was performed by the same experienced surgeons of the team.

Exclusion criteria for our study were: previous thyroid surgery, lobectomy, previous neck irradiation, concomitant parathyroidectomy, lymph node dissection for malignancy, minimally invasive procedures such as MIVAT, TOETVA and so on.

The parameters evaluated for each patient were: sex, age, admission diagnosis, thyroid Doppler ultrasonography report, the presence or absence of hyperfunction, laboratory evidence of thyroiditis (high anti-TG Ab levels), the presence of antibodies (anti-TG, anti-TPO, anti -TSH receptor) , preoperative cytology (FNA), the duration of the operation in minutes, the demonstration of RLN unilateral or bilateral postoperative injury, the presence of other complications such as hemorrhage and temporary or permanent hypocalcemia, the cortisone therapy performed intraoperatively and during the hospitalization, the eventually presence of avulsed parathyroid glands on the specimen, the results of the histological examination.

The follow-up period was 6 months after surgery and included a clinical and laboratory assessment of the patients performing an indirect laryngoscopy and / or fibrolaringoscopy and the dosage of total serum calcium, ionized calcium, phosphorus, magnesium, PTHi, calcitonin, albumin and total protein serum levels.

We did not record any cases of intraoperative or postoperative mortality in our series.

Statistical analysis was performed using SAS software, version 6.1. Continuous variables were expressed as median and Interquartile Range (IQR), while categorical variables as proportions and percentages. Student's t test was used to compare continuous variables with normal distribution. The chi-square test and Fisher's exact test were used to evaluate differences between categorical variables through the logistic regression model and backwards analysis, hence verify the accuracy of the outcomes and estimate the Odds Ratio (OR). The level of significance was set at $p < 0.05$.

Surgical technique

All the patients included in the study underwent total extracapsular thyroidectomy in open technique. A Kocher skin incision of about 5-6 cm was performed. Once the superior and inferior subplatysmal flap was prepared, the strap muscles were divided longitudinally in the midline and the thyroid lobe was exposed and medially dislocated, after the middle thyroid vein was divided. We proceeded with the dissection of the superior vascular pole, by separated ligation and division of the two branches of the superior thyroid artery, identifying and preserving the upper parathyroid and the motor branch of the superior laryngeal nerve. The ipsilateral RLN was identified with digital technique and optical magnification in the first group of patients (OM Group), traced along its entire cervical course, up to the entrance in the larynx **(Figure 4-5)**. In the second group of patients (IONM Group), the RLN was identifying applying the IONM. The distal branches of the inferior thyroid artery were divided, identifying and preserving the inferior parathyroid gland with its vascular peduncle. The same procedure was performed for the contralateral lobe, completing the thyroidectomy by removing the pyramidal lobe. Hemostasis was performed using bipolar electrocautery and surgical ligatures. The cervicotomy was closed after placement of two suction drains of 10-12 Fr.

RESULTS

OM Group

In the **OM group** of 50 patients, 9 patients were males (18%) and 41 females (82%) with a median age of 53.5 years and range between 22 and 77 years old.

Regarding the diagnosis of admission, in 2 cases it was a papillary carcinoma and in 48 cases a plurinodular goiter which in 21 cases also presented with cervico-mediastinal involvement.

Hyperfunctioning thyroid disease was present in 7 patients.

Preoperative fine needle aspiration (FNA) cytology was not performed in 19 of the 50 patients (38%). The following preoperative diagnoses were found in 31 patients with cytology: 0 TIR5, 2 TIR4, 11 TIR3B, 3 TIR3A, 14 TIR2 and 2 TIR1C (note that in a female patient the cytological examination reported double diagnosis of TIR3B and TIR4 on different nodules).

The final histological examination documented the presence of a total of 20 carcinomas (40%), all of them reported as papillary histotype (11 follicular variant, 8 classic type and 1 diffuse sclerosing variant), 9 follicular adenomas (18%) and 1 differentiated follicular tumor with uncertain potential for malignancy (FT-UPM) (2%). Surprisingly, we discovered that 37.5% occult carcinomas were documented (18 out of 48 patients with non-neoplastic diagnosis at the admission). As reported in the **Table 1** and **Table 5**, 7 out of the 11 TIR3B (63.63%) were positive for malignancy while 6 of the 14 TIR2 (42.85%) were positive for carcinoma. Finally, 1 of the 2 TIR1C (50%) tested positive for cancer.

Also, we noted that 4 out of 19 (21%) malignant neoplasms have been documented in patients who had not performed the cytological examination on FNA preoperatively.

Thyroiditis was found in 14 patients (28%), 7 of which were clinically documented by ultrasound (1 Hashimoto's thyroiditis; 4 chronic lymphocytic and 2 chronic nonspecific). A preoperative antibody movement accompanied only 5 of 7 clinical thyroiditis (1 Hashimoto and 4 chronic lymphocytic). In the other 7 cases, the status of thyroiditis emerged from the final histological examination, without any preoperative clinical evidence (1 chronic autoimmune; 4 chronic nonspecific and 2 chronic lymphocytic).

The duration of the total thyroidectomy surgery (calculated from skin incision to extubation) was a median of 80 minutes with a range from 50 to 150 minutes (IQR 70-90).

A cortisone therapy with 8 mg of intravenous dexamethasone was administered intraoperatively in all patients according to the anesthetic protocol of our Institute. In 1 patient a therapy with iv betamethasone 4 mg x 2 / day was instituted postoperatively for the entire duration of hospitalization.

Postoperative hypocalcemia (total Ca <8mg / dl) was recorded in 17 patients (34%) but only in 5 cases this laboratory finding was accompanied by related symptoms.

In 5 patients (10%), transient postoperative dysphonia was found which regressed during the hospital stay and in any case within the first week after surgery.

No cases of unilateral or bilateral RLN paralysis were recorded in the OM group.

The median hospital stay of the OM group was 2 days with a range between 2 and 4 days (IQR 2-2).

At the definitive histological examination 2 patients had a parathyroid gland found on the surgical specimen, but only 1 of these had had a symptomatic hypocalcemia in the postoperative period.

The clinical follow-up at 6 months, reported all patients with a preserved vocal cord motility and no case of permanent hypocalcemia or hypoparathyroidism were detected.

All the data regarding the results of the OM group are summarized in **Table 1**.

IONM group

In the **IONM group** of 50 patients, 8 patients were men (16%) and 42 were women (84%). The median age was 55 years with a range between 21 and 87 years old.

Regarding to the diagnosis of admission, in 3 cases it was a papillary carcinoma and in 47 a plurinodular goiter which in 25 cases also had a cervico-mediastinal involvement.

A hyperfunctioning clash was present in 6 patients.

The preoperative cytological examination was absent in 28 out of 50 patients (56%). In the remaining 22 patients were reported: 3 TIR5, 8 TIR3B, 3 TIR3A and 8 TIR2

The definitive histological examination revealed a total of 15 carcinomas (30%) (10 papillary and 5 follicular, 3 of which with subtype of Hurtle cell) with a percentage of occult carcinomas detected of 25.53% (12 out of 47 patients). Remarkably, 5 of the 8 TIR3B (62.5%) were positive for carcinoma. Furthermore, 7 out of 28 (25%) neoplasms were discovered in patients who had not performed preoperative FNAB.

In 14 patients a status of thyroiditis was associated (28%), highlighted by the preoperative ultrasound report (3 Hashimoto, 3 chronic nonspecific and 8 chronic lymphocytic), but only in 6 patients there was a preoperative antibody movement (in 3 Hashimoto and 3 chronic lymphocytic).

The duration of the operation (calculated from skin incision to extubation) was a median of 100 minutes with a range between 60 and 210 minutes (IQR 90-119).

In all patients a cortisone therapy with 8 mg of intravenous dexamethasone was administered intraoperatively as per the anesthetic protocol of our Department. In 8 patients (16%), treatment with iv Betamethasone 4 mg x 2 / day plus Beclomethasone 100 mg x 3 / day by aerosol was instituted postoperatively for the duration of the hospitalization.

Postoperative hypocalcemia (total Ca <8mg / dl) was recorded in 6 patients (12%), but only in 1 case was this laboratory finding accompanied by related symptoms.

In 6 patients (12%) there was a transient post-operative dysphonia which regressed during the hospital stay. In 2 patients, diagnosed with papillary carcinoma, a bilateral RLN paralysis occurred during surgery and verified at the extubation which forced the anesthesiologist to reintubate the patients and admitted them to intensive care for 3 days. In these two patients, the RLN paralysis still allowed to have sufficient respiratory space for which it was not necessary to practice a tracheostomy. A patient also developed a tracheal fistula 7 days after surgery with air loss in the subcutaneous. This complication was treated with a compression bandage and resolved within three weeks spontaneously. Consequently, the hospitalization lasted 14 days in the first case and 22 days in the second case. At the direct fibrolaringoscopic examination performed 3 months after surgery, both patients had regained full motility of both vocal cords.

The average length of hospitalization in the IONM group, obviously influenced by the two patients with bilateral RLN injury, was a median of 4 days with a range between 3 and 22 days (IQR 4-5).

At the definitive histological examination 5 patients presented a parathyroid gland found on the surgical specimen, but only 2 of these had had signs of postoperative hypocalcemia, one symptomatic and the other not.

At the clinical follow-up at 6 months after surgery, all patients had preserved chordal motility and no cases of hypocalcemia or hypoparathyroidism were detected.

All data regarding the results of the IONM group are summarized in **Table 2**.

The statistical analysis of the data was performed by comparing the results obtained in the two groups through specific methodology **(Table 3)**.

The descriptive analysis demonstrated the homogeneity of the two groups by sex, age and diagnosis of admission. No statistically significant differences in the presence of hyperfunction or thyroiditis was found. Although occult carcinomas in the two groups are not statistically different, the finding of occult carcinomas in relation to the histological report and cytological examination for each group are relevant (90% and 80% of incidence rate in OM and IONM group respectively) and the presence of overall histological carcinomas in the OM group becomes statistically significant ($p<0,05$), **(Table 4, Table 5)**.

Furthermore, the comparison between the two groups demonstrated statistically relevant data regarding the duration of the operation, transient hypocalcemia and the length of hospitalization ($p<0.05$) **(Table 3)**, **(Figure 6)**.

In multivariate analysis of the categorical variables the methodology of regression logistic model documented a high level of accuracy only for transient postoperative hypocalcemia (74-80%) and transient dysphonia (89%) as represented by the ROC curves. **(Figure 7)**.

As reported on **Table 5**, both univariate e multivariate analysis reported a statistically significant difference regarding transient hypoparathyroidism in the two groups with the OM group having a 4-fold higher risk developing transient hypocalcemia than the IONM group (OR 3.78, Adj OR 4.11, $p=0.01$). Regarding the transient postoperative dysphonia, despite the univariate analysis did not reported significant differences in the 2 groups of the study, the multivariate analysis adjusted by group and gender documented for this outcome a statistically relevant difference with the males having a 5-fold higher risk developing transient dysphonia than the females (Adj OR 5.19, 95% IC 0.99-27.18, $p=0.05$), as shown on **Table 6**.

DISCUSSION

Nowadays, thyroid surgery is considered a specialistic procedure that must be carried out in high-volume dedicated centers and by surgeons with specific experience to minimize the risk of complications. Consequently, these centers, worldwide, have adopted new surgical techniques and innovative devices that have been developed with the purpose to prevent such complications, but still need to be validated and standardized. However, even in experienced surgical centers, the risk of permanent RLN paralysis is estimated to be quite high (30%), especially in case of reoperations [33,35], while the same risk is very low (<1%) for multinodular non-toxic goiters thyroidectomies [33,36].

Undoubtedly, RLN injuries are the most fearful complications in thyroid surgery. The unilateral, permanent o transient, RLN paralysis can heavily affect the quality of life of the patients, while bilateral injury, can be a life-threatening complication in the immediate postoperative period, leading to asphyxiation [32,37,38]. In addition, such complications can be frustrating for the surgeons due to legal controversies.

As stated by Jeannon et al. in a systematic review of 27 articles (25,000 patients undergoing thyroid surgery), the incidence of temporary and permanent RLN palsy was 9.8% and 2.3% respectively [39]. Similarly, for Hayward et al. the temporary RLN paralysis occurs after thyroidectomy with an incidence rate from 2% to 13% while the incidence of permanent vocal cord palsy (VCP) rates from 0.4% to 5.2% [40].

Surprisingly, data reported from two wide national databases (the Scandinavian Quality Register and the British Association of Endocrine and Thyroid Surgeons audit) advocate a twofold increase of the rates of RLN paralysis, when patients routinely undergo postoperative laryngoscopy [4,11]. Therefore, the incidence reported in the various series is often underestimated. Among the English literature, when after thyroid surgery a bilateral vocal cord palsy is reported, it is found to be permanent in 45% of patients [11,40-47]. It is estimated that the risk of tracheotomy in case of bilateral VCP is 30% mean, with an additional of 21% needing other type of acute airway surgical management. Hence, global 50% of the patients with bilateral vocal fold palsy demand acute airway management [48].

The contribution of Jatzko et al. with a multicenter study regarding 12,211 patients undergoing thyroidectomy was fundamental in dissolving any controversies regarding the necessity to identify the ILR; they demonstrated that in the group without IRN identification, the incidence of temporary and permanent RLN paralysis is 7.9% and 5.2%, respectively, that is much higher than the group with nerve identification, in which the incidence rates respectively 2.7% and 1.2% [31,49].

According to Dionigi et al [50], the most common injury mechanisms of RLN during thyroidectomy in order of frequency, were traction, thermal stress, compression, clamping, ligature entrapment, suction and transection. The incidence of RLN injuries associated with permanent postoperative vocal cord palsy (in parenthesis) were, respectively: for traction 98% (1.4%), thermal stress 72% (28%), compression injury 100% (0%), clamping injury 50% (50%), ligature entrapment 100% (0%), suction 100% (0%), and transection 100% (100%). Therefore, thermal stress, clamping, and transection are the most significant injuries in terms of risk for permanent vocal fold paralysis [11,50].

As we underlined previously, the most frequent mechanism of recurrent laryngeal nerve paralysis is the traction that occurs mainly during the dissection of Berry's suspensory ligament **(Figure 5)**. Several reports in the literature support this thesis. Schneider et al. in their series of 115 RLN with LOS during IONM documented that traction was responsible for the 83% of nerve injuries and in the 60% of them the neuropraxic segment was localized to the Berry’s ligament [51]. Similarly, Chiang et al. reported a rate of 75% of RLN injuries as a result of traction during dissection of the ligament of Berry [11,52]. Both authors documented how an extreme anterior medial traction on the thyroid lobe could induce recurrent nerve injury by transmitting the stretch to the nerve through the Berry’s ligament [52,53,54]. In the opinion of Steurer, during total thyroidectomy for diffuse toxic goiter the greatest difficulties arise in the dissection of the thyroid parenchyma in the area of Berry's ligament [55]. Serpel and Chiang argue that this surgical step frequently causes RLN injury and incomplete resection of the thyroid gland [56,57]. Moreover, Schneider emphasizes the importance to identify anatomical variants of RLN with a high risk of injury, such as an extralaryngeal subdivision of the nerve in an anterior motor branch and a posterior sensitive branch. The risk of neuropraxic traction injury during dissection of Berry's ligament is higher for a tubular anterior motor branch, with an inferior caliber that extends more medially [11,53]. Finally, Schneider et al. in their study (2018), concluded that a rate of 80% of all RLN injuries associated with vocal cord palsy is due to stretching [11].

Optical magnification systems certainly have an important role in preventing many of the causes of RLN damage (thermal; compression; ligation; suction; transection) [19,44,58].

In the dawn of 1900, Faley was the first author to emphasize the importance not only of the systematic identification and preparation of the RLN but also to introduce the concept of the use of optical magnification means by any surgeon who practices thyroidectomy in order to avoid recurrent nerve injuries [6,59]. Later in 1975, Attie et al. reported the first microsurgical approach in thyroid surgery [60], followed by the study of Cavallaro et al in 1998, suggested the using of optical magnification loupes to facilitate surgical dissection and to prevent damage to both RLN and parathyroid glands [61]. Since then, the experiences of some expertized centers in microsurgical approach of thyroidectomy have been presented in the literature. According to them, either surgical microscope or magnification loupe with microsurgical technique are recommended in thyroid surgery due to a lower incidence of complications [3,19,61-66]. In agreement with this concept, Testini et al. suggested that the use of 2.5x loupe magnification was extremely useful for the RLN identification, especially in high-risk thyroidectomies, allowing a significant reduction in operation time. In addition, this method permits diagnosis of vascular variations which can be easily differentiated from the inferior laryngeal nerve [58]. Thus, optical magnification loupes (2.5x- 4.5x) can be considered a helpful support in thyroid surgery, as they make the RLN preparation more precise and safer by increasing the definition of the operating field and growing the surgeon's visual acuity in recognizing the anatomical structures [18,62] **(Figure 4-5)**.

However, these results are not in total compliance with the study of Pata et al., in which the use of magnification loupes (2.5x) had no effect on the rate of RLN injuries [67].

Furthermore, Davidson et al. compared the surgical microscope with magnification loupes and concluded that there were no significant differences between the two systems regarding the incidence of complications during thyroid surgery [62].

It is worth noting that only few studies were identified through the review of the literature regarding the use of microsurgical technique and optical magnification as a support to traditional thyroid surgery. Interestingly, though, the results show that such surgical approach is useful non only for the RLN identification and dissection along its cervical course, but also for safeguard the integrity of parathyroid glands, for ensure an accurate hemostasis and for performing a total extracapsular thyroid excision, improving the outcomes [19,60,62].

To our experience, the magnification loupes are more comfortable than the surgical operating microscope and allow a surgeon greater freedom in moving the head and the body during the operation. The surgeons in our series used loupes magnification not only during the dissection of the RLN but for the entire period of thyroidectomy (from the skin incision to the skin closure).

Even if optical magnification can positively affect most of the causes of recurrent nerve injury, with regard to the effects on traction related injuries, neuromonitoring can be more effective and probably only if applied in continuous modality.

Since 1965, when Shedd and Durham first introduced the IONM in thyroid surgery [68], significant technological improvements have been made, particularly the last decades [69]. Lamade in 1996 performed the first RLN intraoperative neuromonitoring with an endotracheal tube connected to a non-invasive surface electrode [70]. The same author developed also a vagus probe for continuous neuromonitoring of the RLN [20,71].

It is widely accepted that the incidence of RLN palsy is related to the thyroid disorder treated, the surgical technique and the level of experience of the surgeon. On the report of Sanabria et al. [28] and Barczyński et al. [72,73], the application of IONM is subordinate to the equipment availability and the age, training and experience of the surgeons.

Moreover, it has been shown that the direct visual identification of RLN is facilitated by the preliminary use of electrical mapping of the nerve [69] and as a study reported, in nearly 35% of cases the electrical RLN recognition anticipated direct visual nerve identification [74]. Furthermore, the velocity of RLN isolation is improved using IONM compared to visual identification alone [11,75].

Dralle et al. (2004) in their series noted that as most of the injured RLNs appear morphologically intact, the use of IONM can correctly prognosticate postoperative nerve function, which is quite difficult to obtain by direct visual identification [76]. Similarly, Deniwar et al. (2015) claimed the importance of IONM identifying anatomical variations and atypical courses of the laryngeal nerve, which are linked with high risk of nerve damage if not properly recognized [76]. Regarding the nonrecurrent laryngeal nerves (non-RLNs), challenging to isolate, the IONM application on the vagus nerve can improve their early and precise identification during thyroidectomy [11,77]. Another study in patients found intraoperatively to have right sided non-RLNs, reported a tenfold increase risk of permanent nerve injury during thyroidectomy [78] and the use of IONM, in the case of non-RLNs, is related with much lower incidence of nerve injuries [77,79].

The International Neural Monitoring Study Group (INMSG) guideline (2018) recognizes that IONM not only improve the functional outcome on thyroid surgery, but also contributes to early identification of those laryngeal nerves not always functionally intact, even if they maintain visually their anatomical integrity [11]. However, an injury occurred on a morphologically intact RLN regularly results in a temporary reversible palsy rather than a permanent vocal fold paralysis [52,53,54]. IONM not only facilitates the RLN to be identify easily, but also allows us to understand the mechanisms of injury and permits to predict intraoperatively the nerve function in the postoperative period [31,69,80-82].

Statistically, across the world the use of IONM is widespread. For instance, in German more than 90% of thyroidectomies are performed using IONM; in the United States it is used in up to 40% of operations, while in France the rate is nearly 15% of thyroid procedures [16,20,83,84]. In Italy, from 2007 to 2013 the number of thyroidectomies performed with IONM steadily increased from 253 to 5100 respectively, reflecting the rapid popularization of this method [31,85].

According to some authors, only continuous neuromonitoring during the dissection of RLN can prevent the nerve from traction injuries [34,86-88]. However, it was shown that the continuous IONM probe registered a decline just right during the mobilization and dissection of the thyroid gland. Therefore, we agree with those authors that did not use routinely the IONM in continuous modality [34]. The application of intermittent IONM in thyroid surgery is not exempt of risk, as the RLN traction injuries yet occurred in 7% of the cases. Interestingly, all the injured nerves recovered their function; in a rate of 70% recovered intraoperatively within 20 minutes since the release of traction and the other 30% of the injured RLN regain function postoperatively into 12 weeks after surgery [34].

Among the literature there is evidence for the useful of the IONM in thyroid surgery. A milestone data study published recently by the Scandinavian Endocrine Surgical Quality Registry, undoubtedly reports lower incidence of permanent RLN paralysis with the use of IONM [89]. Furthermore, the rates of RLN palsy decreased with the use of neuromonitoring in specific subgroups like high-risk thyroidectomies, surgery for malignancy and operations performed by less experienced endocrine surgeons [5,11,90-92]. Pardal-Refoyo et al. (2016) in a meta-analysis of 40 studies with 30922 patients undergoing total thyroidectomy, reported that the incidence of bilateral RLN paralysis was quite lower in the group with IONM (average 2.43% versus 5.18%) [10,93]. Another large study of 4000 German patients with multinodular goiter supported that the use of IONM decrease significantly either the temporary or permanent vocal fold palsy ratio from 2.1% to 1.4% and from 0.8% to 0.4%, respectively [91]. Similarly, a significant reduction in the incidence of temporary and permanent vocal cord palsy with the use of IONM, is reported by a meta-analysis of 34 controlled trials (3 randomized and 31 nonrandomized) with more than 59000 recurrent nerves-at-risk [23]. As stated by Schneider et al. (2015), continuous IONM applicated by experienced surgeons manage to reduce the rate of permanent vocal cord palsy to 0% (1.314 RLN at risk), versus a favorable comparison to 0.4% ratio in case of intermittent IONM (965 RLN at risk; P=0.019) [21,48]. In support of this opinion is the study of Le Zhou et al. (2018), which reports an inferior RLN morbidity with IONM; 2.7% in the continuous IONM subgroup against the 3.6% in the intermittent subgroup and 5.4% in the control group (P=0.058) [94] and the use of IONM by less experienced surgeons is associated with similar results with the experienced ones [95].

Despite different well-designed high-volume studies accepted the reduction of RLN injuries with IONM, opinions are not always concordant. For example, there was evidence suggesting that IONM reduces the incidence of both temporary and permanent RLN trauma [21,23,30], or only temporary RLN injury [5,22,], or only permanent RLN injury [29]. On the contrary, in other studies reported no significant reduction of permanent RLN damage [25], or both temporary and permanent RLN injuries [26-28].

Surprisingly, most studies did not demonstrate a relevant difference in the rates of RLN injuries between IONM and visual identification alone [77,83,96]. Contrarily, a limited number of studies reported significant advantages in using IONM during high-risk thyroid surgery, such as re-intervention, malignancy, toxic or retrosternal goiter [5]. In addition, the French Society of Oto-rhino-laryngology and Head and Neck surgery, as well as the American Academy of Otolaryngology Head and Neck Surgery recommend using the IONM in all difficult cases of thyroidectomy [97,98].

Zheng and Higgins in their meta-analysis reported no significant difference in permanent vocal cord palsy rates with the use of IONM [28,99]. The Scandinavian Quality registry for Thyroid, Parathyroid and Adrenal Surgery in their multiparametric analysis observed that IONM was associated only with a permanent vocal cord paralysis low rate (OR 0.43, 0.19-0.93) [100]. Barczyński et al. with a randomized clinical trial established an important decline of transient RLN paralysis ratio only during high-risk thyroidectomies, such as central lymph node dissection for malignancy, cervicomediastinal goiter, Grave's disease or thyroiditis [14,101]. Finally, as claimed by Pisanu et al. (2016) with another meta-analysis, there is no significant reduction on the overall rates of transient, or permanent, RLN injuries using IONM [27].

Furthermore, there are conflicting opinions regarding the cost-benefit ratio of using the IONM. The full equipment cost for the IONM may amount from $5,000 to $40,000 while the cost for the disposables fluctuate from $72 to $500 for single use. Hence, the application of IONM can amount up to 7% of the hospital expenses charged for thyroid surgery [21,102]. However, the use of IONM has been proven cost-effective when the rate of RLN paralysis is reduced by up to 50.4%, comparing with the direct visual nerve identification alone [103].

The application of IONM is also associated with the possibility to change surgical planning intraoperatively. Thus, the concept of stage thyroidectomy was introduced. In case of a LOS during the dissection of the first lobe performing a total thyroidectomy, likely the recurrent laryngeal nerve injury will result in a postoperative paralysis of the ipsilateral vocal cord, so the contralateral lobectomy could be postponed avoiding the occurrence of bilateral RLN paralysis with dramatic consequences for the patient. Once the RLN functionality is restored, the thyroidectomy will be completed and as stated by Riddell in 1970, the surgeon should never perform a total thyroidectomy unless the integrity of the RLN during the first lobe resection has been proven [8,32]. In the last decades, the stage thyroidectomy for benign disease when a LOS on the first lobe dissection occurs, have been recommended by numerous authors [104-107]. Recently, Salari et al. suggested the IONM staged approach as a validate surgical strategy to decrease the incidence of complications in patients undergoing surgery for advanced thyroid cancer [108]. According to the International Neuromonitoring Study Group Guidelines (2018), it is fundamental when IONM is applied to inform properly the patients regarding the probability of two-stage thyroidectomy in the event a LOS occur on the first surgical side [17,69]. Goretzki et al. documented that the rate of postoperative bilateral vocal cord palsy was 0% when a staged thyroid surgery was performed prior to IONM with LOS, versus a 17% rate in patients that surgery proceeded to a total thyroidectomy despite of intraoperative monitoring of signal loss [10,104,109]. Further studies reported that a two-stage surgery after initial LOS is associated with a zero rate of bilateral vocal fold palsy [51,110,111].

In the opinion of Schneider et al. [112] (2018), it may be reasonable to wait at least 20 minutes after LOS for possible recovery of the neurological signal amplitude and before attempting the excision of the contralateral lobe [13,112]. The same authors suggest that when LOS happens during first thyroid lobe dissection in elective total thyroidectomy for benign disease, surgeons may consider three alternatives for the correct intraoperative management [51,112]. Primarily, if the signal loss is permanent in the first lobe dissection, the surgeon should consider postponing the total thyroidectomy at a later time, as more than 95% of patients with segmental signal loss of type 1 and 70% of those with type 2 global loss have been documented with early ipsilateral vocal cord paralysis in the postoperative period.

Secondly, in case of incomplete signal recovery after LOS (lower than 50% of the signal amplitude), a two-stage thyroidectomy must be considered, as the 95% of patients with type 1 signal loss and 48% of those with type 2 signal loss have an early vocal cord palsy. Finally, a complete recovery of the signal after LOS (greater than 50% of its amplitude) indicates a normal function of the vocal cord, therefore, it is reasonable to consider proceeding with the total exeresis of the thyroid gland in the same surgical session.

It is now widely accepted that neuromonitoring an intact signal at the end of thyroidectomy is associated with a positive result regarding the functionality of the vocal cords. The negative predictive value of this procedure is very high: 97% to 99% [44,77], which means that if 100 patients have an intact IONM signal at the end of the operation, 97 of these patients will have normal vocal cord function. To the contrary, if occurs a LOS at the end of surgery, the positive predictive value of the procedure is low (33% to 37%) and results challenging to predict the incidence of vocal cord paralysis [113]. This indicates that if there is a LOS in 100 patients, 33 to 37 of them will have vocal cord paralysis.

Regarding to the statistical analysis of the results of our study, the descriptive statistics demonstrated the homogeneity of the two groups by sex, age and diagnosis of admission. No statistically significant differences in the presence of hyperfunction or thyroiditis was shown. On the other hand, the data on the presence of occult carcinomas in the two groups **(Table 4)** are relevant (37.5% occult cancers with 90% incidence rate in the OM Group and 25.53% occult cancers with 80% incidence rate in the IONM Group), which makes us reflect on the indication, reported by many guidelines, of simple surveillance for some cytological categories. To support this, **Table 5** reports the distribution of carcinomas verified in the histological analysis and related with the cytological classes established through preoperative FNA.

The duration of the operation seems to be significantly shorter in the OM Group (median 80 vs 100 minutes, $p<0.05$) **(Figure 6)**, but this does not surprise us since it is known how the various measurements and recordings made during the intervention in the IONM Group might be quite dispendious. However, the average difference between the two groups was 20-25 minutes and thus not too high.

In the IONM group, the most relevant data is the presence of 2 bilateral RLN paralysis that their management involved the reintubation of both patients and their transfer to intensive care unit therapy, until the subsequent extubation. This resulted in the lengthening of hospitalization staying to 14 and 22 days respectively.

This clearly made the difference in the length of hospital staying, statistically significant in favor of the OM Group (median 2 vs 4 days, $p<0.05$) **(Figure 6)**. However, extrapolating the data regarding the other 48 patients of the IONM Group, the variable of hospital stay is distributed similarly with the OM group.

In any case the two transients bilateral RLN paralysis in the IONM Group (4%) versus none in the OM Group (0%) are not statistically significant ($p>0.05$).

Furthermore, there is a 4-fold higher risk in the OM group than in the IONM group of developing postoperative hypocalcemia. The risk in men compared to women of developing transient dysphonia is 5 times higher **(Table 6, Table 7)**.

In both cases of RLN paralysis, at the end of each thyroid lobe dissection, the RLN function was tested with the IONM and was found preserved. Only after completing the hemostasis by electrocoagulation, we recorded a bilateral LOS of type 2. Therefore, we must assume that the RLN injuries were likely caused by the transfer of thermal energy during the electrocoagulation maneuvers, which took place not in close proximity to the recurrent nerves but on the thyroid cartilage shield or medially on the trachea axis. The thermal damage must have affected, bilaterally, the intralaryngeal branches of the recurrent nerve through the wall of the thyroid cartilage. As reported by the literature, moderate to severe thermal injuries of the RLNs involve an increase rate of permanent vocal cord palsy that needs longer time to recovery [34,114,115]. This could explain the longer hospital staying of the 2 patients in our series. On the other hand, technical problems during application of IONM occur more frequent in the first 50 thyroidectomies [31,116] and numerically is corresponding to our group of patients.

Duclos et al. [54,117] reported wide variations in the learning curve among surgeons using IONM. As claimed by Dionigi et al. the rate of positive outcome of IONM rised over 90% after 50 applications and the operative time decrease significantly after 100 thyroidectomies [116]. Similarly, Snyder et al. registered a decline of the RLN injury ratio after a year and a half of consecutive IONM application, including > 50 total thyroidectomies with bilateral central lymph node dissection [75].

In the other 48 patients of IONM group we recorded 3 cases of LOS type 2 during the dissection of the second lobe, which however did not result in a postoperative RLN deficit, an event reported also in the literature. Indeed, a LOS registered intraoperatively with intermittent IONM is not associated with vocal cord palsy in up to 33% of the cases [118-120]. We therefore believe that these cases were due to a malpositioning of the surface of the electrodes, which probably occurred during the dissection phase of the operation.

Finally, no significant statistical difference was found regarding definitive hypoparathyroidism and the data are in line with those of our previous experiences. The results of the follow-up at six months after surgery were completely unified in the two groups.

A special mention merits the importance of perioperative cortisone therapy. In our department we routinely use the administration of dexamethasone 8 mg i.v. during thyroidectomy. Beyond the two patients with bilateral vocal cord palsy in which the cortisone therapy was continued for several days, also in the 6 cases with moderate postoperative dysphonia we continued the cortisone therapy with betamethasone 4 mg x2 i.v./day plus Beclomethasone 100 mg x3 / day by aerosol, obtaining the regression of the dysphonia by the dismission of the hospital occurred on the third day after surgery. The effects of dexamethasone are manifested on the steroid receptors through an upregulation on the expression of anti-inflammatory mediators which, thus, prevents the initiation of the inflammatory cascade [51]. As stated recently by the authors of the POLT study (2016) [16,51], the intraoperative use of corticosteroids did not reduce the rate of postoperative vocal cord paralysis after LOS. However, the administration of steroids reduced the recovery time in those cases with temporary vocal cord palsy [121].

In our opinion, the only biases in our study are related to the use of IONM in intermittent modality alone and to the limited cohort of patients enrolled in a single center. Although the number of operations necessary for the learning curve of the neuromonitoring method has been reached, a new study using the continuous modality could certainly provide us further information. Also, associating IONM with the use of magnification loupes and microsurgery technique we expect to find better outcomes.

CONCLUSIONS

That optical magnification and the use of the IONM alone reduce the percentage of recurrent postoperative paralysis seems now to be certain. The IONM allows intraoperative assessment of the integrity and functionality of the recurrent nerve and has been shown to increase the recognition and prevention of recurrent injuries. To our knowledge, currently this is the first study in the literature that directly compares the use of IONM with optical magnification alone in the prevention of RLN injuries.

In comparison with the dissection of the inferior laryngeal nerve with the aid of optical enlargement, the neuromonitoring technique is not advantageous to the point that it is considered a substitute for the accurate visualization and identification of the recurrent nerve, but it can add greater confidence to the surgeon, especially if less experienced. In the two methods, the risk of recurrent complications remains comparable in the face of slightly higher costs and the need for specific equipment. However, there are still no reports in the literature in which the two methods are applied simultaneously. We therefore feel to adhere to Wu's recommendation. "... Meticulous anatomical dissection can be achieved by using loupes for magnification and IONM for mapping the RLN in patients with complicated anatomical characteristics and for evaluating nerve function during dissection ..." [54]. From our experience it emerges that both methods can be considered a standard in the future, at least in highly specialized endocrine-surgical centers.

The simultaneous application of optical magnification and IONM with microsurgery technique currently provides the highest level of safety in recurrent laryngeal nerve dissection, reducing the surgical causes of RLN paralysis to a percentage close to zero. The higher cost of the surgical procedure due to the use of these devices would be amply repaid by the drop in morbidity and the lack of use of the resulting therapies and clinical-instrumental checks.

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TABLES AND FIGURES

Table. 1 – Results in the Optical Magnification Group.

Demographic and perioperative characteristics of the 50 patients enrolled in the OM Group.

Gender	41 female 9 male
Age (years)	Median 53.5 Range 22-77
Admission diagnosis	2 pt papillary ca (TIR4) 27 pt multinodular goiter 21 pt multinodular cervicomediastinal goiter
Hyperthyroidism	7 pt
FNA with cytological examination * in 1 pt cytology with diagnosis of TIR3B and TIR4	Absent 19 pt (4 positive for ca to histology - 21%) TIR5 0 pt (0 positive for ca to histology - 0%) TIR4. 2 pt (2 positive for ca to histology– 100%) TIR3B 11 pt (7 positive for ca to histology - 63,63%) TIR3A 3 pt (0 positive for ca to histology– 0%) TIR2 14 pt (6 positive for ca to histology – 42,85%) TIR1C 2 pt (1 positive for ca to histology – 50%)
Histology	20 pt carcinoma (40%); 20 papillary ca with histotype: - 11 follicular variant - 8 classic variant - 1 sclerosing variant 9 pt follicular adenoma (18%); 1 FT-UMP (2 %) (Follicular Tumor of Uncertain Malignant Potential)
Occult thyroid cancer	18 in 48 pt (37,5%)
Thyroiditis • at the admission • at the histology	7 pt 1 Hashimoto with antibodies detected 4 chronic lymphocytic with antibodies detected 2 chronic nonspecific without antibodies detected 7 pt 1 chronic autoimmune 4 chronic nonspecific 2 chronic lymphocytic
Duration of the operation (min)	Median 80 Range 50-150
Cortisone Therapy • Intraoperative • Postoperative	50 pt Betamethasone 4 mg i.v. 1 pt Betamethasone 4 mg x2/day i.v.
Hypoparathyroidism	

• Transient - asymptomatic - symptomatic • Permanent	17 pt 12 pt 5 pt 0 pt
RLN paralysis • monolateral • bilateral	 None None
Dysphonia (transient)	5 pt Regression during hospital stay and within the first week
Length of hospitalization (days)	Median 2 Range 2-4
Parathyroid gland on the specimen	2 pt 1 pt with symptomatic hypocalcemia 1 pt with asymptomatic hypocalcemia
Follow-up at 6 months	None permanent RLN disfunction None permanent Hypoparathyroidism

Table. 2 – Results in the Intraoperative Neuromonitoring Group.

Demographic and perioperative information of the 50 patients enrolled in the IONM Group.

Gender	42 Female 8 Male
Age (years)	Median 55 Range 21-87
Admission diagnosis	3 pt papillary ca 22 pt multinodular goiter 25 pt multinodular cervicomediastinal goiter
Hyperthyroidism	6 pt
FNA with cytological examination	Absent 28 pt (7 positive for ca to histology - 25%) TIR5 3 pt (3 positive for ca to histology - 100%) TIR3B 8 pt (5 positive for ca to histology- 62,5%) TIR3A 3 pt TIR2 8 pt
Histology	15 pt carcinoma (30%); 10 papillary ca 5 follicular ca; - 3 Hurtle cell ca - classic variant
Occult thyroid cancer	12 in 47 pt (25,53%)
Thyroiditis	14 pt; 3 Hashimoto with antibodies detected 8 chronic lymphocytic with antibodies detected 3 chronic nonspecific without antibodies detected
Duration of the operation (min)	Median 100

	Range 60-210
Cortisone Therapy	
• Intraoperative	50 pt Desamethasone 8 mg i.v.
• Postoperative	8 pt Betamethasone 4 mg x2 /day i.v. + Beclomethasone 100 mg x3 /day by inhalation
Hypoparathyroidism	
• Transient	6 pt
- asymptomatic	5 pt
- symptomatic	1pt
• Permanent	0 pt
RLN paralysis	
• monolateral	None
• bilateral	2 pt (Complete recovery 3 months after surgery)
Dysphonia (transient)	6 pt Regression during hospital stay and within the first week
Length of hospitalization (days)	Median 4 Range 3-22
Parathyroid gland on the specimen	5 pt 1 pt with symptomatic hypocalcemia 4 pt with asymptomatic hypocalcemia
Follow-up at 6 months	None permanent RLN disfunction None permanent Hypoparathyroidism

Table. 3 - General characteristics and results in the 2 groups.

General characteristics	**OM Group (n=50)**	**IONM Group (n=50)**	**Total (n=100)**	**P**
Gender (F, %F)	41 (82%)	42 (84%)	83 (100%)	ns
Age (median, IQR)	53.5 (42-62)	55 (43-65)	55 (43-65)	ns
Admission diagnosis (n, %)				ns
• Multinodular goiter	27 (54%)	22 (44%)	49 (49%)	
• Multinodular CM goiter	21 (42%)	25 (50%)	46 (46%)	
• Papillary carcinoma	2 (4%)	3 (6%)	5 (5%)	
Hyperthyroidism (n, %)	7 (14%)	6 (12%)	13 (13%)	ns
FNA with cytological examination				ns
• Absent	19 (38%)	28 (56%)	47 (47%)	
• TIR5	0 (0%)	3 (6%)	3 (3%)	
• TIR4	1 (0.5%)	0 (0%)	1 (1%)	
• TIR3B/TIR4 *	1 (0.5%)	0 (0%)	1 (1%)	
• TIR3B	10 (20%)	8 (16%)	18 (18%)	
• TIR3A	3 (6%)	3 (6%)	6 (6%)	
• TIR2	14 (28%)	8 (16%)	22 (22%)	
• TIR1C	2 (4%)	0 (0%)	2 (2%)	
Histology				**<0.05**
• Papillary carcinoma	20 (40%)	10 (20%)	30 (30%)	
• Follicular carcinoma	0 (0%)	5 (10%)	5 (5%)	

• Follicular adenoma	9 (18%)	0 (0%)	9 (9%)	
• FT-UPM	1 (2%)	0 (0%)	1 (1%)	
• Iperplasia	20 (40%)	35 (70%)	55 (55%)	
Occult thyroid cancer (n, %)	18 in 48 (37.5%)	12 in 47 (25.5%)	30 in 95 (31.6%)	ns
Thyroiditis (n, %)				ns
• Absent	36 (72%)	36 (72%)	72 (72%)	
• Chronic lymphocytic	6 (12%)	8 (16%)	13 (13%)	
• Chronic nonspecific	6 (12%)	3 (6%)	8 (8%)	
• Chronic autoimmune	2 (4%)	3 (6%)	7 (7%)	
Duration of the operation in minutes (median, IQR)	80 (70-90)	100 (90-119)	90 (75-102)	**<0.05**
Lenght of hospitalization in days (median, IQR)	2 (2-2)	4 (4-5)	3 (2-4)	**<0.05**
Cortisone therapy (n, %)				**<0.05**
• Intraoperative	50 (100%)	50 (100%)	100 (100%)	
• Postoperative	1 (2%)	8 (16%)	9 (9%)	
Hypoparathyroidism (n, %)				**<0.05**
• Absent	33 (66%)	44 (88%)	77 (77%)	
• Transient	17 (34%)	6 (12%)	23 (23%)	
• Permanent	0 (0%)	0 (0%)	0 (0%)	
Dysphonia (transient) (n, %)				ns
• Absent	45 (90%)	44 (88%)	89 (89%)	
• Present	5 (10%)	6 (12%)	11 (11%)	
RLN paralysis (n, %)				ns
• Absent	50 (100%)	48 (96%)	98 (98%)	
• Monolateral	0 (0%)	0 (0%)	0 (0%)	
• Bilateral	0 (0%)	2 (2%)	2 (2%)	

Abbreviations: IQR interquartile range, CM cervicomediastinal, F female, FT-UPM Follicular Tumor of Uncertain Malignant Potential, p value, ns non statistically differences.

* 1 F patient with simultaneous cytological diagnosis of TIR3B and TIR4 on different nodule.

Table 4. Histological overall carcinomas, occult carcinomas and incidence rate of occult carcinomas in the 2 groups.

	Patients n	Overall histological carcinomas n (%)	Occult carcinomas n (%)	Incidence of Occult carcinomas (%)
OM Group	50	20 (40%)	18 (37,5%)	90
IONM Group	50	15 (30%)	12 (25,5%)	80
Total	100	35 (35%)	30 (30%)	85,7

Table 5. Distribution of FNA cytological and histological results in the 2 groups.

	Patients with FNA n (%)	Cytology - Patients n		Histology Carcinoma - (%)	
OM Group	31 (62%)	TIR1C	2	1	50%
		TIR2	14	6	42,85%
		TIR3A	3	0	0%
		TIR3B	11	7	63,63%
		TIR4	2	2	100%
		TIR5	0	0	0%
IONM Group	22 (44%)	TIR1C	0	0	0%
		TIR2	8	0	0%
		TIR3A	3	0	0%
		TIR3B	8	5	62,50%
		TIR4	0	0	0%
		TIR5	3	3	100%

Table 6 - Results of logistic backward analysis for transient hypocalcemia.

TRANSIENT HYPOCALCEMIA / GROUP	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	OR	**IC (95%)**	**p**	**Adj OR**	**IC (95%)**	**p**
IONM	1			1		
OM	**3.78**	**1.34 – 10.62**	**0.02**	**4.11**	**1.42 – 11.93**	**0.01**

Abbreviations: OR odds ratio, IC confidence interval, p value, Adj OR adjusted odds ratio

Table 7 - Results of logistic backward analysis for transient dysphonia.

TRANSIENT DYSPHONIA / GENDER	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	OR	**IC (95%)**	**p**	**Adj OR**	**IC (95%)**	**p**
F	1			1		
M	2.53	0.68 – 9.44	0.28	**5.19**	**0.99– 27.18**	**0.05**

Abbreviations: OR odds ratio, IC confidence interval, p value, Adj OR adjusted odds ratio

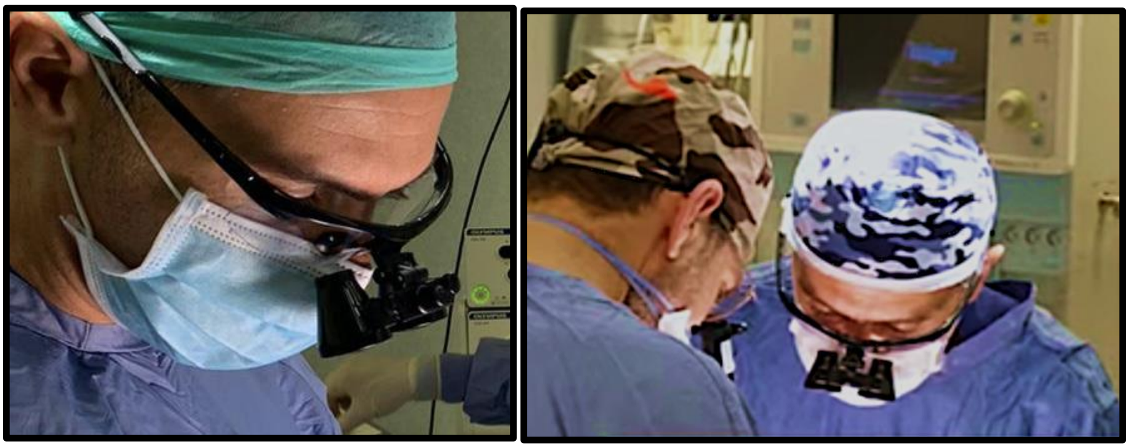


Figure 1. Magnification binocular loupes 2.5x-4.5x.

Advertencia: Monitorización de EMG desactivada

Figure 2. Medtronic NIM 3.0 monitor

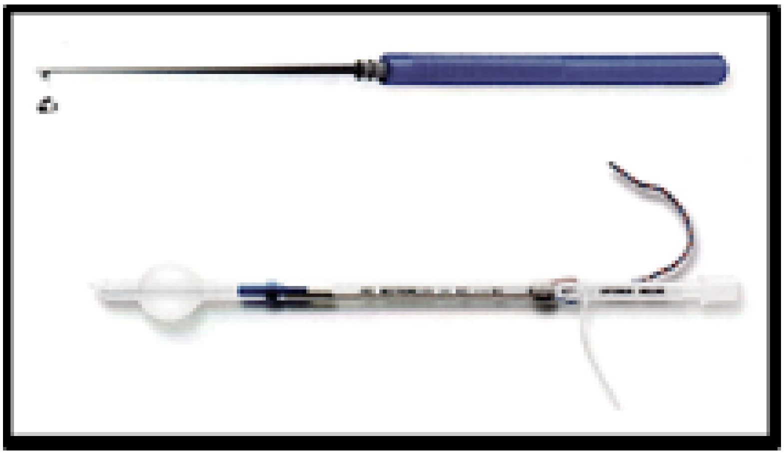


Figure 3. Endotracheal tube.

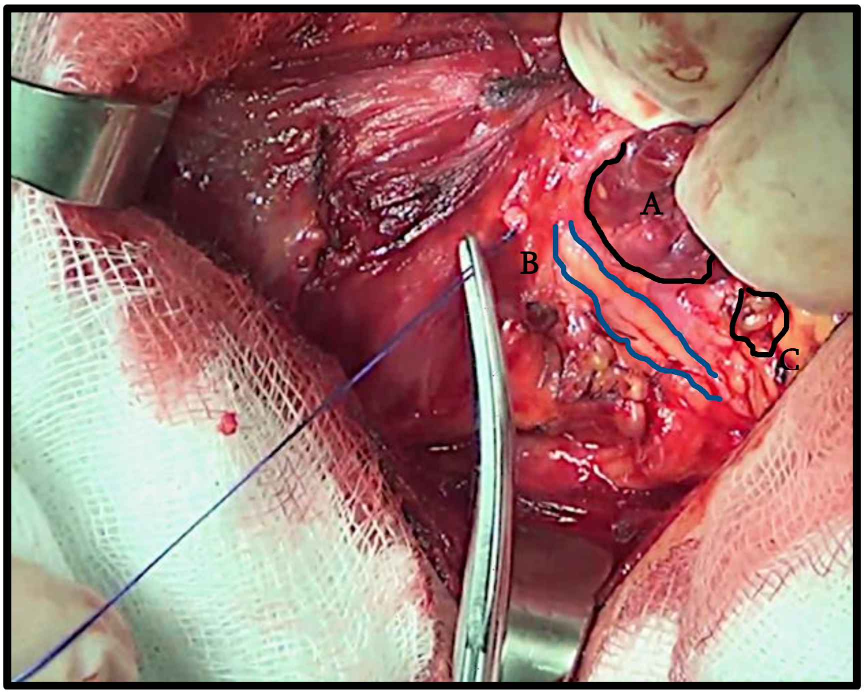


Figure 4. RLN dissection with Optical Magnification 2.5x.
A Thyroid gland **B** Right-sided RLN identificated and dissected among ligatures. **C** Inferior parathyroid gland.

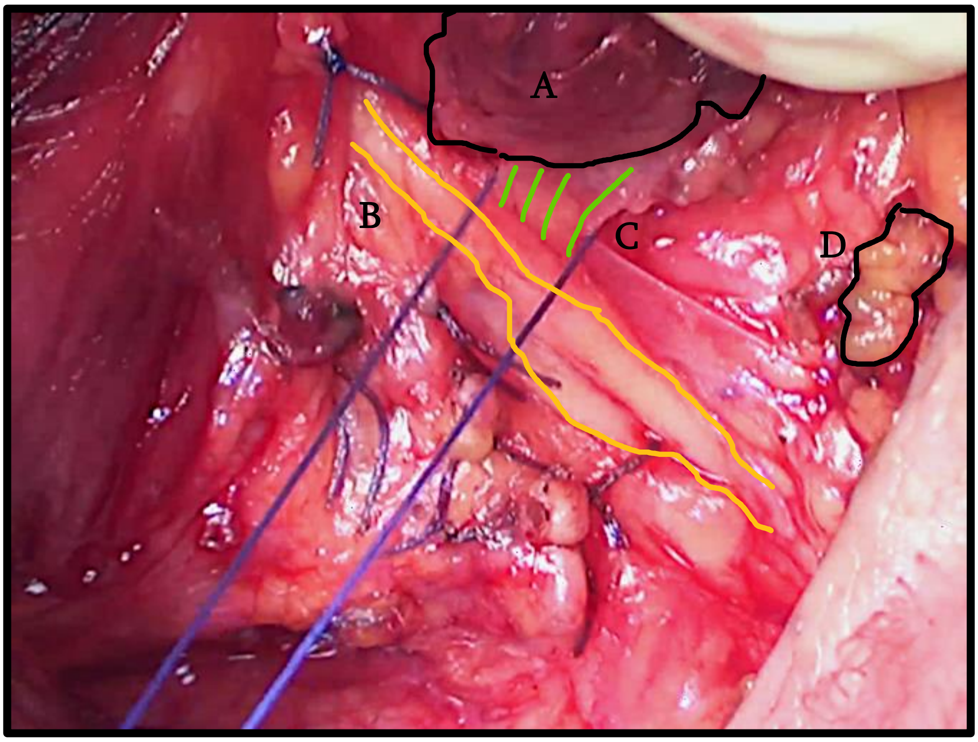


Figure 5. RLN dissection with Optical Magnification loupes 4.5x
A Thyroid gland **B** Right-sided RLN identificated and dissected among ligatures.
C Berry's ligament. Excessive traction during ligation may cause RLN injury.
D Inferior parathyroid gland.

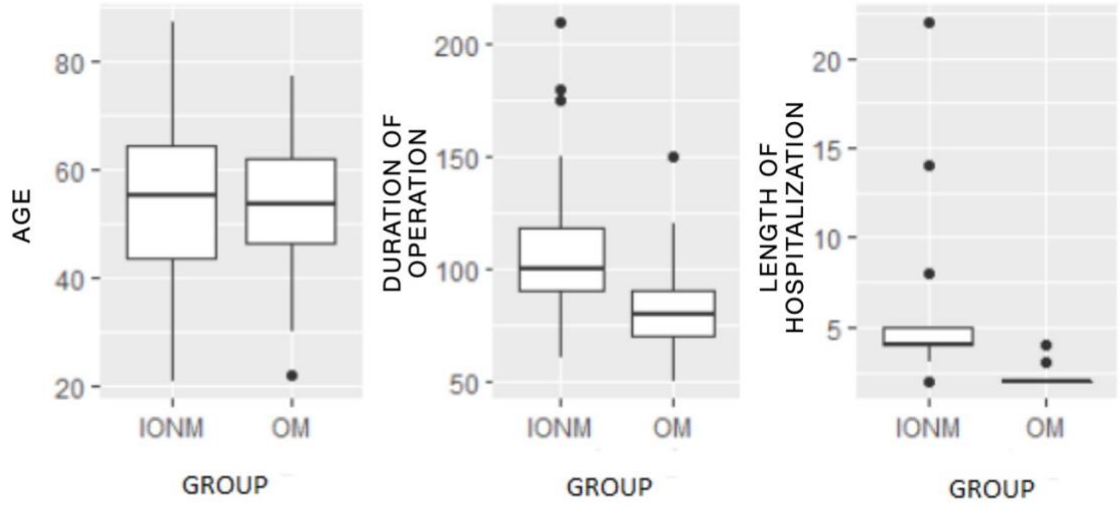
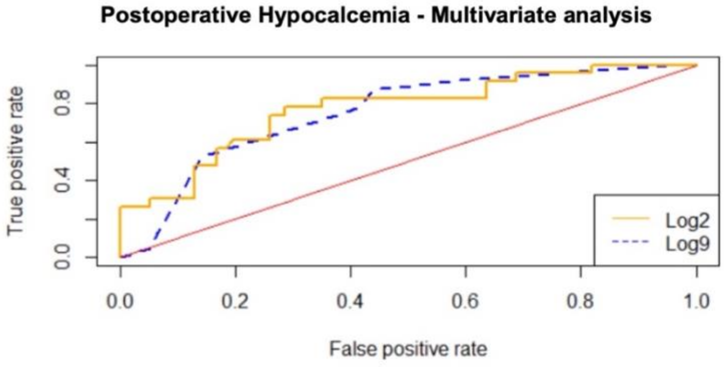
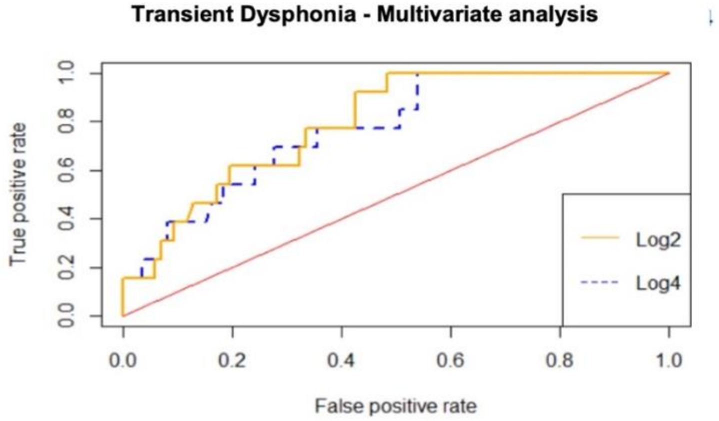


Figure 6. Box and Whisker plots of continuous variables; age, duration of the operation and length of hospitalization. No statistically difference for the median age in the 2 groups, while for the other variables there is an evident difference.



MODEL	ACCURACY	AUC
	TP+TN / N	AREA UNDER THE CURVE
Log 2	0,8	0,77
Log 9	0,74	0,75



MODEL	ACCURACY	AUC
	TP+TN / N	AREA UNDER THE CURVE
Log 2	0,89	0,793
Log 4	0,89	0,771

Figure 7. ROC curves and accuracy in multivariate analysis of the outcome transient postoperative hypocalcemia and transient dysphonia; The most appropriate logistic models through backward analysis were extrapolated and compared with those models including more or less variables but with similar statistical significance. For both outcomes the Log2 model reported higher accuracy and was chosen for the analysis.