



ORIGINAL ARTICLE

Use of radioguided surgery technique for the treatment of thyroid cancer recurrence: clinical, surgical and anatomopathological aspects

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Abstract

Introduction: Surgery is the treatment of choice in locoregional thyroid neoplasia recurrence. The intense tissue healing process observed after surgery changes the neck anatomy, makes reoperation difficult, and interferes with surgical success. The use of the Radioguided Occult Lesion Localization (ROLL) technique has become a viable option to localize thyroid tumors. **Objective:** To analyze the use of the ROLL technique for the treatment of thyroid cancer recurrence with respect to its clinical, surgical and anatomopathological aspects. **Methods:** A descriptive cross-sectional study that analyzed 56 medical records and anatomopathological examinations of patients of both sexes who had thyroid neoplasms, underwent previous surgeries on this topography, and were submitted to the ROLL technique for recurrence removal from March 2011 to March 2019. **Results:** Most patients were women aged 46.05 years, on average. Papillary thyroid neoplasm was the most prevalent histological finding. In 100% of the cases, application of the ROLL technique identified and removed the lesions marked with suspicion for malignancy. **Conclusion:** Radioguided surgery has proved to be a very effective and safe tool to assist with lesion localization for the treatment of thyroid cancer recurrence. This technique has brought no additional side effects to patients, required minimal radiation and made surgery less invasive, reducing postoperative complication rates.

Keywords: thyroid; cancer; recurrence; radioguided surgery; ROLL.

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Introduction

Thyroid cancer is the most common endocrine and head and neck malignancy¹. Surgery is the treatment of choice for this type of neoplasia, with indication of total or partial thyroidectomy according to the patient's risk factors. In high risk cases, there may be therapeutic complementation using radioactive iodine

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Study carried out at Núcleo Integrado de Cirurgia de Cabeça e Pescoço (NICAP), Centro Diagnóstico Otorrinolaringológico (CDO), IMP Laboratório Médico, Florianópolis, SC, Brasil.



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(RAI). When metastatic spread to cervical lymph nodes occurs, treatment should be associated with selective neck dissection².

After surgery, patient follow-up should be performed aiming mainly at early detection of disease recurrence or persistence. In general, this is done through clinical examination, imaging tests, and measurement of serum thyroglobulin (TG) levels³⁻⁶.

Surgery is the treatment of choice in cases of locoregional recurrence⁷; however, it can be particularly challenging when lesions occur in the same site of the primary surgery⁸. The intense tissue healing process that occurs after surgery distorts the neck anatomy, makes reoperation very difficult, and interferes with surgical success because of the difficulty in localizing and removing the recurrent lesions. In addition, these factors increase the risk of postoperative complications, especially in relation to damage caused to the inferior laryngeal nerve and parathyroid glands⁹.

In this context, radioguided surgery using the ROLL technique is a very useful tool to perform less invasive surgeries in recurrent thyroid neoplasms¹. This technique was developed to be used in non-palpable lesions in breast cancer, but it has recently been gaining space in surgeries on the thyroid topography¹⁰. It has been used in patients with previous operations in the neck compartments in order to better localize the lesions and reduce complication rates associated with extensive field re-explorations⁹. It consists in marking the lesion using an ultrasound (US)-guided injection of radiopharmaceutical technetium-99m micro-aggregated albumin (^{99m}Tc-MAA). After that, in the operating room, a hand-held gamma probe is used to identify and accurately remove the marked areas¹¹.

In this context, this study aimed to analyze the use of ROLL for the treatment of recurrent thyroid cancer with respect to its clinical, surgical and anatomopathological aspects, since the use of this technique on the thyroid topography brings several advantages for both surgeons and patients, and there are still few studies addressing its use for pathologies unrelated to breast cancer. In addition, the effectiveness of ROLL in the treatment of recurrences is described, that is, whether it was able to correctly localize and remove the target lesion previously identified with suspicion for malignancy.

Methods

This study was approved by the Research Ethics Committee of the University of South Santa Catarina (UNISUL) under protocol CAAE: 02305018.7.0000.5369.

This descriptive cross-sectional study was carried out at the Integrated Head and Neck Surgery Center (NICAP), Otorhinolaryngological Diagnosis Center (CDO), and IMP Medical Laboratory, which are reference treatment and diagnosis centers located in the municipality of Florianópolis, state of Santa Catarina, Brazil.

The study sample was composed of 56 patients who were diagnosed with thyroid neoplasms, underwent previous surgeries on this topography - thyroidectomy with cervical dissection of the central compartment (level VI), and were submitted to the ROLL technique for recurrence removal.

Tumor recurrence was identified through US examinations, measurement of serum thyroglobulin (TG) levels, and fine-needle aspiration puncture (FNAP). In these patients, the ROLL technique was used in order to ensure removal of the affected lymph nodes. Patients of both sexes aged ≥ 18 years with thyroid cancer recurrence in the central compartment (level VI) who were operated on using the ROLL technique from March 2011 to March 2019 were included in the study.

Data were collected from the patients' medical records and their respective anatomopathological reports of the removed surgical specimens. All patients underwent the procedures with the same surgical and nuclear medicine team and the anatomopathological examinations were performed in the same clinic aiming to provide greater degree of reliability and standardize the assessment of cases.

The following demographic and clinical variables were analyzed: sex, age, histological type of primary tumor, radioactive iodine (RAI) therapy, measurement of serum TG level at the time of recurrence, cervical US examination, FNAP, and signs or not of neoplasia (recurrence) preoperatively. As for surgical information, the following variables were investigated: number of previous surgeries on the thyroid topography, total number of lymph nodes removed, number of affected lymph nodes removed, anatomopathological study results, tumor recurrence or not after surgery, and surgical efficacy.

Surgical efficacy was assessed by confirming that the target lesion, previously identified with suspicion for malignancy, could be localized and excised using the ROLL technique.

The data were organized and analyzed using Windows Excel® and Statistical Package for the Social Sciences (SPSS) 18.0 (Chicago: SPSS Inc; 2009) software. The qualitative data were presented as simple and relative frequencies and the quantitative data as mean and standard deviation (SD).

Results

Analysis of the 56 patients submitted to the ROLL technique for the treatment of recurrent thyroid cancer showed that all lesions with suspicion for malignancy marked using US-guided injection of radiopharmaceutical technetium-99m micro-aggregated albumin ($^{99m}\text{Tc-MAA}$) were identified and removed.

As for the demographic characteristics, the study sample comprised individuals aged 19-83 years, and 69.9% of them were women aged 46.05 ± 14.88 years (Table 1).

Regarding the clinical characteristics, papillary thyroid neoplasm was the primary tumor in 98.2% of the cases. Before recurrence, 44 of the patients (78.6%) underwent RAI therapy. Neoplasia recurrence was evidenced by increased TG level in 30 of the 37 cases where this information was available. All patients underwent preoperative cervical US and FNAP to identify recurrence, and malignancy was confirmed by anatomopathological study of the lymph node tissue in 53 of the 56 cases (Table 1).

Table 1. Demographic and clinical characteristics of patients undergoing the Radioguided Occult Lesion Localization (ROLL) technique for the treatment of recurrent thyroid cancer - Florianópolis/SC - Brazil, 2011 to 2019.

Variables (n= 56)	n	(%)
Sex		
Female	39	69.6
Male	17	30.4
Age		
46.05 ±14.88 (19-83) years	56	100
Histological type of primary tumor		
Papillary	55	98.2
Medullary	1	1.8
RAI therapy		
Yes	44	78.6
No	12	21.4
Measurement of serum TG level at the time of recurrence (n=37)		
Positive (>0)	30	81.1
Negative (=0)	7	18.9
Cervical US examination to identify recurrence		
Yes	56	100
No	-	-
Preoperative FNAP		
Yes	56	100
No	-	-
Indication of neoplasia (recurrence) in preoperative FNAP		
Yes	53	94.6
No	3	5.4

Captions: US = ultrasound; FNAP = fine-needle aspiration puncture; RAI = radioactive.

Three cases presented negative results in the FNAP: one showed signs of reactive lymphoid hyperplasia with anatomopathological confirmation of tumor recurrence postoperatively; one presented suspicion of parathyroid, but the possibility of follicular injury was questioned, and follow up histology of the surgical specimen indicated thyroid tissue with hyperplastic nodules without neoplasia; one showed possibility of thyroid remnants or follicular lesion, and the first was confirmed postoperatively.

Assessment of the surgical characteristics showed that 76.8% of the patients had undergone only one previous surgery on the thyroid topography, namely, total thyroidectomy with cervical dissection of the central compartment (level VI). Regarding the number of lymph nodes removed during surgery

using the ROLL technique, 46.4% of the cases presented excision of more than three lymph nodes, and half of the patients had only one affected lymph node and half presented more than one. Anatomopathological study of the surgical specimen showed malignancy, that is, disease recurrence, in 96.4% of the cases. Only seven patients had a recurrence after being submitted to the ROLL technique, and 87.5% presented no recurrence at the time when this study was concluded (Table 2).

Table 2. Surgical and anatomopathological characteristics of patients undergoing the Radioguided Occult Lesion Localization (ROLL) technique for the treatment of thyroid cancer recurrence - Florianópolis/SC - Brazil, 2011 to 2019.

Variables (n= 56)	n	(%)
Number of previous surgeries on thyroid topography		
1	43	76.8
2	11	19.6
≥3	2	3.6
Total number of lymph nodes removed during surgery		
1	14	25.0
2	10	17.9
3	6	10.7
>3	26	46.4
Number of affected lymph nodes removed		
1	28	50.0
2	15	26.8
3	6	10.7
>3	7	12.5
Pathology of the surgical specimen		
Malignant disease (recurrence)	54	96.4
Benign disease	2	3.6
Recurrence after ROLL		
Yes	7	12.5
No	49	87.5

Discussion

This study sought to evaluate the demographic, clinical, surgical and anatomopathological characteristics associated with the use of the ROLL technique for the treatment of recurrent thyroid cancer.

There was prevalence of female patients aged 46 years, on average. These results were similar to those reported by both the Brazilian National Institute of Cancer (INCA)¹² and the Global Cancer Observatory (GCO)¹³ on the epidemiology

of thyroid neoplasms. They also corroborated the findings of other studies that evaluated thyroid tumor recurrences in Italy¹⁴⁻¹⁵, Turkey^{9,16-19}, and Brazil²⁰⁻²¹.

In the present survey, papillary thyroid neoplasm was the most prevalent primary tumor, observed in 55 of the 56 cases studied. In fact, this is the most prevalent tumor histological type¹² and, despite its good prognosis, with a 10-year survival rate >90%²², locoregional tumor recurrence occurs in more than 30% of patients^{1,16,17}. This is mainly because there is primary lymph node metastasis in 80% of cases, thus contributing to the appearance of recurrences²³.

In addition, according to the American Thyroid Association (ATA), this type of tumor recurrence is most likely a persistent manifestation of the disease that survived the initial treatment and which is generally incurable with RAI therapy, and thus should be treated surgically in a new approach^{2,15}.

In the cases studied, most individuals underwent RAI therapy after the first treatment. RAI ablation is considered a safe and effective method to eliminate remaining thyroid tissue, especially in the case of microscopic disease². However, this does not guarantee that tumor recurrences will not occur, since, as previously mentioned, most cases of recurrent disease are caused by cells unresponsive to iodine^{2,15,24}.

In 30 of the 37 cases in which the TG level was available in the medical records, it was the increase in the value of this marker that indicated the presence of thyroid neoplasia recurrence. A similar study carried out by Tuncel *et al.* in Turkey in 2019 showed increased TG levels in all patients¹⁸. Postoperative follow-up with measurement of TG levels is extremely sensitive and specific to identify the presence of tumor recurrence, because its values should not be detected in individuals who do not have thyroid tissue²⁵. In the patients of the present study who presented TG levels equal to zero, diagnostic suspicion was verified by cervical US examination. The combination of these two methods with FNAP is extremely accurate in detecting disease recurrence¹⁴.

In the present study, all patients had suspicion for tumor recurrence assessed through cervical US examination, measurement of serum TG levels, and performance of FNAP. According to the ATA, US examination is one of the methods of choice for postoperative follow-up², because it not only determines the presence, number and size of new lesions, but also documents their characteristics and risk of malignancy¹⁰. In all studies evaluated that showed thyroid tumor recurrence, the presence of cervical US examination was extremely important in the diagnosis and mapping of lesions^{9-10,14-20,26}.

Ultrasound-guided FNAP was performed in all cases investigated in this study, with positive results observed in 94.6% of patients. FNAP presents high sensitivity (65-98%) and specificity (72-100%) rates; however, although low, false positive (0-7%) and false negative (1-11%) rates have also been found²⁷. In addition, with advances in US devices, the examination is able to detect lesions <4 mm, which are non-palpable and difficult to localize²⁰. Thus, there is a great chance that little tumor tissue be removed during material collection, with little cellularity for analysis, which is also a possible explanation for one of the three cases described in the results that the FNAP did not indicate the presence of malignant material.

Regarding the number of previous surgeries on the thyroid topography, 43 patients were submitted to only one surgery and 13 underwent two or more surgeries. Among the similar studies evaluated, that conducted by Giles *et al.* was the only one that specified the number of previous surgeries: of the 11 patients analyzed, nine had undergone only one surgical procedure and two performed two surgeries¹⁹. The other articles analyzed only described the fact that patients had already been operated on and comment on reoperation difficulties^{9,15-18,26}.

Due mainly to the intense healing process when dealing with previously explored tissues, in addition to the distorted local anatomy, the chance of complications at reoperation increases significantly^{9,20}. Studies have shown that the risk of injury to the inferior laryngeal nerve in these cases increases from 0-4% at the first surgery to up to 25% at reoperation; in relation to hypoparathyroidism, it increases from 0-6% to 8.3%, respectively²¹.

In most cases, three lymph nodes were removed during surgery using the ROLL technique, and in half of the cases there was at least one affected lymph node among these. Similar studies have shown a larger number of lymph nodes removed in relation to those affected^{9,15-18,26}.

In the anatomopathological study of the surgical specimen, 54 patients had a confirmation of disease malignancy, that is, tumor recurrence. In two cases, there were doubts regarding the FNAP diagnosis, and benignity was evidenced. This fact is probably related to the few, but existing, limitations of the cervical US and FNAP examinations in the management of non-palpable malignant thyroid lesions¹⁵.

After surgery using the ROLL technique, only 12.5% of the patients presented new tumor recurrences. The criteria for defining these new tumor recurrences were the same used for the initial recurrence of the study: increased TG levels, cervical US examination, and FNAP. Borsò *et al.*¹⁴ conducted a study with 32 patients and found a recurrence rate after ROLL reoperation of 37.5%. Tuncel and Süslü¹⁸, in a study conducted with 29 patients, obtained a recurrence rate of 3.5%, and İlgan¹⁶, with eight patients, and Bellotti *et al.*²⁶, with 22 patients, did not observe any recurrence after using the ROLL technique. The following risk factors have been associated with tumor recurrence: aged ≥ 45 years, female, absence of RAI therapy, and elevated TG levels^{23,24}.

In general, the use of radioguided surgery has proved to be a very useful, highly effective and accurate tool in localizing marked lesions, since the lesion with suspicion for malignancy, which had been marked using ^{99m}Tc-MAA injection, was found and excised in 100% of the cases. Similar studies carried out in Italy^{14,15} and Turkey^{9,10,16,17,19} obtained the same rate of surgical success using the same analysis standards. The study by Tuncel *et al.* was the only one that described failure in localizing the marked lesions - only two cases out of 43, and these occurred because of deposition of large amounts of ^{99m}Tc-MAA in adjacent tissues; nonetheless, both lesions were resected using the patient's preoperative US mapping¹⁸.

Regarding the advantages of using the ROLL technique evidenced in the studies that have addressed it, the low amount of radiation to which the surgical

team and the patient are exposed has been widely mentioned^{1,9,14-16,19}. Another important point to be highlighted is the equipment used, which very often is already available in hospitals because of its widespread use in other tumor types, especially in breast cancer, thus not generating additional costs to the services¹⁴. Furthermore, it is a technique that can be simply executed, does not require specific training for surgeons^{1,19}, and does not bring additional side effects or other complications described for the use of ^{99m}Tc-MAA and ROLL in the literature^{9,10,16,26}.

In addition, when Ilgan *et al.* questioned surgeons whether the technique allowed tumor lesions to be found more safely and effectively, all responded that it was a very useful tool because it provided more safety to the surgeon during tissue dissection, offering better topographic information of the region during surgery¹⁶.

Other techniques have been described and used by several surgeons to assist with the same intraoperative situation; however, there are a number of disadvantages described regarding their use, which would be another point in favor of using the ROLL technique. With respect to preoperative US-guided needling, the difficulties encountered are related to the maintenance of the metallic thread in place during surgery and to the limited use in relation to the proximity of large vessels due to the risk of injury^{16,17}. As for injection of methylene blue dye, the following disadvantages have been described: potential for an allergic reaction to the product, local toxicity including tissue necrosis, and dye leakage to adjacent tissues, staining surrounding healthy regions that do not need to be marked^{9,16,17,21}. Finally, Tuncel and Süslü¹⁸ compared the no evidence of disease (NED) after the use of ROLL and other techniques, and concluded that this rate is considerably higher with the use of radioguided surgery.

In general, it could be observed that the characteristics of the patients in the present study were convergent with what is expected in the literature, as well as the results obtained when compared with those of similar studies. The use of the ROLL technique has shown excellent results in terms of safety and efficacy, and it is a new possibility that should be considered for the treatment of non-palpable tumor recurrences of thyroid cancer.

Limitations to this research refer to the fact that is a cross-sectional, retrospective study, and thus there is certain loss in the analysis of some variables. As an example, the absence of recurrence after use of the ROLL technique could be mentioned, since the data collection was performed in a single moment and these patients could not be followed for a longer time. Furthermore, because this is a retrospective study, it was not possible to compare, for instance, the surgical time with and without the use of ROLL - a variable that would enrich the analysis. Therefore, it is suggested that new studies on the subject be conducted prospectively in order to better assess some of the items mentioned.

Nevertheless, the present study was conducted with the largest number of cases in the literature and was the first to evaluate the use of the ROLL technique in thyroid tumor recurrence in Brazil. Furthermore, similar studies have also shown the same results, corroborating the promising character of

using ROLL for these cases. It is expected that a larger number of publications on the subject will enable a more widespread use of this technique due to its excellent results and the aforementioned advantages.

Conclusion

All patients followed the recommendations of the ATA for postoperative follow-up of thyroid neoplasms and that the ROLL technique assisted with the localization of the lymph nodes marked with suspicion for malignancy in 100% of the cases. Therefore, radioguided surgery has proved to be a very effective and safe tool to assist with lesion localization for the treatment of thyroid cancer recurrence. In addition, this technique has brought no additional side effects to patients, required minimal radiation and made surgery less invasive, reducing postoperative complication rates.

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