Is radioguided occult lesion localization (ROLL) an effective and reliable method in thyroid cancer and parathyroid redo surgery?

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Is radioguided occult lesion localization (ROLL) an effective and reliable method in thyroid cancer and parathyroid redo surgery?

OBJECTIVE: *The aim of this study is to share the efficacy of the radionuclide occult lesion localization (ROLL) technique in secondary neck exploration in patients who had undergone neck exploration due to thyroid or parathyroid pathology and to share our clinical experience.*
MATERIAL AND METHOD: *Data of 25 patients who underwent secondary neck exploration for recurrent thyroid cancer and parathyroid adenoma between January 2016 and December 2018 at the General Surgery Clinic of Balcalı Hospital, Çukurova University Faculty of Medicine were collected retrospectively. On the operation day, 0.5 mCi Tc-99m macroaggregate albumin was injected into the lesion under ultrasound guidance (USG). Nerve monitoring was used in all patients.*
RESULTS: *Twenty-five patients (21 females, 4 males) were included in the study. The mean age of the patients was 54.5 (24-79) years. Five patients were operated for parathyroid adenoma, 6 patients for papillary cancer after subtotal thyroidectomy, 13 patients for papillary cancer recurrence, 2 patients for medullary cancer recurrence, 2 patients for papillary cancer cervical lymph node metastasis and 1 patient for anaplastic cancer recurrence.Mean operative time was 100.6 min (60-160 min). Two patients had transient hypocalcemia and no other complications were seen. Parathyroid hormone (PTH) levels in patients with hyperparathyroidism, Thyroglobulin (Tg) levels in patients with recurrent papillary cancer, were significantly lower than preoperative levels ($p<0.05$).*
CONCLUSION: *We believe that ROLL technique reduces the complication rate by decreasing dissection time and width. We recommend using it for thyroid cancer and parathyroid redo surgery.*

KEY WORDS: Parathyroid redo surgery, Radioguided surgery, Thyroid cancer

Introduction

Thyroid cancer is the most common endocrine malignancy and its incidence is increasing [1]. It is the ninth most common cancer with an incidence of 10.2 per 100,000. It is seen 3 times more commonly in women 90-95% are well differentiated. Radioactive iodine (RAI) treatment of thyroid cancer combined with surgery is an effective treatment method [2]. Recurrence rate varies between 10-45% depending on prognostic risk factors [3]. Primary hyperparathyroidism (PHPT) is a disease characterized by hypercalcemia, hypophosphatemia and excessive bone resorption as a result of excessive parathormone release [4]. Most cases are sporadic and approximately 5% are familial. In 80-85% of cases there is a are single parathyroid adenomas, in 4-5% there are double adenomas, in 10-15% there are multiple gland hyperplasia and in less than 1% there are parathyroid cancers [5].

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Parathyroidectomy can be performed with a success rate over 95% in experienced centers. However, 1-10% recurrence and 2-22% persistent disease are reported in the literature. Recurrent and persistent disease may require secondary surgical procedures. In secondary surgeries, the risk of complications may be higher and success rates may be lower [6-8].

Redo surgery of persistent/recurrent thyroid cancer and parathyroid diseases should be well planned. Redo surgery is more difficult due to changing anatomy and fibrosis. Another problem is the inability to resect lesions that cannot be detected with the naked eye or those which can be hidden by structures above it. Failure to remove occult lesions is another problem. The complication rate is higher. Successful redo surgery positively affects the patient's quality of life and operation duration [9].

In oncological surgery, "*Radionuclide Occult Lesion Localization*" (ROLL) is based on both preoperative interventional imaging planning and the intraoperative radiological guidance of clinically occult neoplastic lesions. ROLL was first used for the preoperative localization of occult lesions of the breast, but has recently been used to excise non-palpable lesions in patients undergoing reoperative thyroid surgery [10-12].

Recently, the efficacy of the ROLL technique, which helps to detect recurrent lesions with gamma probe after ultrasound-guided intra-lesion radiotracer injection, has been proven in many studies [9,12-14].

In this study, we aimed to share the efficacy of ROLL technique in secondary neck exploration in patients who had previously undergone surgery for thyroid cancer or parathyroid disease and our clinical experience.

Material and Method

Patients who underwent redo surgery for recurrent thyroid cancer and parathyroid adenoma between January 2016 and December 2018 at the General Surgery Clinic of Balcalı Hospital, Çukurova University Faculty of Medicine were included in the study. A common database was created by examining patient files and hospital information system records. Patient data were evaluated retrospectively. Follow-up data was supported by phone calls.

Age, sex, cause of first operation, indications for redo surgery, surgical procedure performed in redo surgery, duration of operation, postoperative complications, postoperative pathology results, preoperative and postoperative calcium (Ca) and parathormone (PTH) values in patients undergoing redo parathyroid surgery, preoperative and postoperative thyroglobulin (Tg) values in patients undergoing redo thyroid surgery and preoperative and postoperative calcitonin levels in patients with medullary cancer were evaluated.

1-2 hours before the operation, 0.5 mCi Tc-99m MAA was injected into the lesion under USG guidance. The mark of the lesion on the skin was marked with a pen in accordance with the surgical position. After incision, high radioactivity areas were identified with 11-mm collimated gamma probe (Neoprobe 2000, Ethicon Endo-Surgery Breast-Care, Cincinnati, OH). All areas with a highcount rate were recorded for 10 seconds. Exploration was made with the help of the regions with high counts and the mark on the skin. Ex-vivo gamma counting was performed to confirm resection of the lesion after surgery. The area with the highest gamma count was sent separately for postoperative histopathological examination as Tc-99m MAA-labeled surgical specimen. At the surgical site after excision, the residual radioactivity value was measured. The decrease of radioactivity below 10% in areas with a high count, and the surgeon concluding that they excised the lesion were accepted as criteria to end the operation.

Miami criterion was used for rapid parathyroid evaluation [15]. If less than 50% of the highest preoperative PTH value was obtained at 10 minutes after excision, the operation was terminated.

Frozen section examination was used in all patients to confirm parathyroid tissue. Success in redo parathyroid surgery was defined as normocalcemia (Ca ≤ 10.3 mg/dl) for 6 months or more.

Local recurrence was detected in case of increased serum Tg level by neck USG, RAI scan, magnetic resonance imaging, positron emission tomography or combination of imaging techniques. Suspicious lymph nodes were identified by neck ultrasound. Preoperative USG guided fine needle aspiration cytology confirmed the diagnosis. The surgical procedure was determined according to the underlying etiology. Nerve monitoring was used in all patients.

The patients were informed about the surgical procedure and written consent was obtained.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA). Categorical measurements were summarized as numbers and percentages, and continuous measurements were summarized as mean and standard deviation (minimum-maximum where necessary). Pearson Correlation Coefficient and related p value were obtained to examine the interaction of numerical measurements. Statistical significance was taken as 0.05 in all tests.

Results

25 patients with a mean age of 54.5 ± 15.3 years were included in the study. 84% of the patients were female. Two patients underwent parathyroid adenoma surgery and three patients underwent total thyroidectomy

for parathyroid adenoma. Among the patients who underwent redo thyroid surgery, 36% (n: 9) patients were the most common total thyroidectomy group due to papillary carcinoma. Demographic characteristics and initial operations of the patients are shown in Table I. Our indication for redo parathyroid surgery was persistent and recurrent hyperparathyroidism. Adenoma excision was performed in all patients. Because of recurrence of papillary thyroid cancer in 9 (36%) patients, central lymph node dissection (CLND) was performed in one patient, unilateral regional excisionin four patients and bilateral regional excision in four patients. Six (24%) patients who underwent surgery due to benign thyroid nodule and were diagnosed with papillary thyroid cancer after surgery with residual tissue, underwent completion thyroidectomy. The mean operation time was 100.6 ± 27 min. Postoperative transient hypocalcemia developed in 2 patients. Recurrent laryngeal nerve injury was not seen in any patient. Surgical indications and surgical methods are shown in Table II.

PTH and Ca levels were lower after redo parathyroid surgery, compared to preoperative values (p=0.000). Postoperative thyroglobulin levels were found to be significantly lower in patients who underwent completion surgery for PTC, recurrence excision, and metastatic cervical lymph node excision (p=0.047).Tg levels did not decrease significantly in 1 patient who had recurrent anaplastic cancer surgery (p>0.005). Calcitonin levels were nıt significantly lower when compared to preoperative levels in patients who underwent CLND due to central region lymph node recurrence of medullary cancer (p=0.305). Preoperative and postoperative laboratory values are shown in Table III.

Postoperative histopathological evaluation of all patients undergoing redo parathyroid surgery was reported as parathyroid adenoma. One of the patients who underwent redo surgery for PTC recurrence was diagnosed as lymph node metastasis and eight patients were diagnosed as PTC recurrence. Histopathological examination results of patients who underwent redo surgery are shown in Table IV.

Discussion

In recent years, thyroid and parathyroid surgery under

TABLE I - *Demographic characteristics and first operations*

Variable	N(%)
Sex	
Male	4(16)
Female	21(84)
Average Age, mean ± SD (min-max)	54.5±15.3 (24-79)
First operations	
Parathyroid adenoma	2(8)
Thyroidectomy due to benign thyroid nodule (final pathology benign)	3(12)
Subtotal thyroidectomy due to benign thyroid nodule (final pathology PTC)	6(24)
TT due to PTC	9(36)
Suspicious cervical lymph node excision (final pathology PTC)	2(8)
TT + CLND + BLCLND due to MC	2(8)
TT + LCLND due to anaplastic cancer	1(4)

SD= standart deviation, PTC= Papiller thyroid carcinom, TT= Total thyroidectomy, CLND= central lymph node dissection, BLCLND= Bilatrelal central lymph node dissection, LCLND= Lateral central lymph node dissection

TABLE II - *Operation indications and performed operations*

Variable Operation Indication	Performed operation	N(%)
Primary hyperparathyroidism	Adenoma excision (2 lower right, 3 lower left)	5(20)
PTC, residual tissue after subtotal thyroidectomy	Completion thyroidectomy (2 right, 1 left, 3 bilateral)	6(24)
PTC recurrence	1 right CLND, 4 unilateral, 4 bilateral regional excision	9(36)
Suspicious cervical LN excision	TT+CLND+LCLND	2(8)
Medullary cancer central region recurrence	Right CLND	2(8)
Anaplastic cancer recurrence	Right regional excision	1(4)
Mean operation duration - mean ± SD (min-max) min		100.6±27(60-160)
Postoperative complication		
Transient hypocalcemia		2(8)

SD =standart deviation, PTC= Papiller thyroid carcinom, TT= Total thyroidectomy, CLND= central lymph node dissection, BLCLND= Bilatrelal central lymph node dissection, LCLND= Lateral central lymph node dissection

TABLE III - *Preoperative and Postoperative Laboratory Results*

Operation indication	Preoperative	Postoperative	N(%)	P
Primary hyperparathyroidism	PTH:216.3(174-337)pg/mL Ca: 11.4(9.7-12.3) mg/dL	PTH: 11.2(1.7-18.9) pg/mL Ca:8.8(8.2- 10.3) mg/dL	(20) 5	p=0.000 p=0.003
PTC, residual tissue	Tg: 63.4(1.6-280) ng/mL	Tg: 0.35(0.04-1.19) ng/mL	6(24)	p=0.229
PTC recurrence	Tg: 67.3 (3.17-336) ng/mL	Tg: 1.8(0.04-6.29) ng/mL	9(36)	p=0.047
Suspected cervical LN dissection (final pathology PTC)	Tg: 73 ng/mL Tg:64 ng/mL	Tg: 0.04 ng/mL Tg: 1.2 ng/mL	2(8)	p=0.004
Medullary cancer Central region recurrence	Calcitonin: 414 pg/mL Calcitonin: 67 pg/mL	Calcitonin: 4 pg/mL Calcitonin: 2 pg/mL	2(8)	p=0.305
Anaplastic cancer recurrence	Tg: 307 ng/mL	Tg: 216 ng/mL	1(4)	p=1.000

Normal ranges for biochemical parameters; Ca:8.9-10.3 mg/dL, PTH 12-69 pg/mL, Tg: 1,15-35 ng/mL, calcitonin Male:<16 pg/ml, Female: <8 pg/ml

TABLE IV - *Pathology results*

Operation indication	Preoperative	N(%)
Primary hyperparathyroidism	Parathyroid adenoma	5(20)
PTC, residual tissue	3 persistent PTC, 3 Benign	6(24)
PTC recurrence	1 LN metastasis, 8 PTC recurrence	9(36)
Suspected cervical LN dissection	2 PTC metastasis	2(8)
Medullary cancerCentral region recurrence	2 LN metastasis	2(8)
Anaplastic cancer recurrence	1 anaplastic cancer recurrence	1(4)

the guidance of radioactive substances has become increasingly popular. Radioguided Surgery (RGS) is based on the accumulation of a certain proportion of radioactive material in the target tissue. Intraoperative hand-gamma probe detection of radiolabeled tumors facilitates surgery. Recurrent/persistent thyroid cancer and completion thyroidectomy for residual tissue are the most common indications for RGS in thyroid surgery [12,16]. In studies on reoperative parathyroid surgery, it has been reported that RGS is a valuable aid in persistent or recurrent hyperparathyroidism [14].

In ROLL-guided surgeries, a high lesion/background count rate can be achieved by direct radioactive material injection into the lesion, unlike systematically administered radiopharmaceuticals. Furthermore, some lesions may not show the natural uptake of the systematically applied radiotractor and reduce the effectiveness of this surgical method.

Similar to the literature, female sex was higher in our study. This can be explained by the fact that endocrine tumors are more common in women. Our mean age was higher than those reported in the literature. In similar studies in the literature, which are predominantly related to thyroid surgery, the mean age of patients who underwent thyroid surgery is reported to be between 40-45 years, and those who underwent parathyroid surgery are reported in the range of 55-60 [9,12,-14].

The most common causes of persistent and recurrent hyperparathyroidism are ectopic localization and multiple gland disease. Although these reasons are important in the development of persistent disease, surgical experience in the first operation is another important factor affecting this possibility 4. Another point in failure is previous surgery for thyroid, carotid, vertebral and tracheal diseases. The risk of complications is higher and the success rate is seen to be lower in secondary surgical procedures [6-8].

Pitt et al. reported the success rate of ROLL technique as 96% in parathyroid surgery after previous neck surgery. No recurrent laryngeal nerve injury occurred in their series [14]. In our study, our success rate was found to be 100% similar to the literature. There was no postoperative complication. There are studies reporting that the success rates in surgeries performed due to recurrent or persistent hyperparathyroidism are as low as 80% [14,17,18]. Therefore, ROLL is clearly superior to parathyroid surgery after parathyroid redo surgery and previous neck surgery. In addition, preoperative localization studies in combination with imaging methods in reoperative parathyroidectomies seem to be advantageous for

guiding dissection.This discourse can be accepted as true even if they have undergone non-parathyroid surgery in the neck region and will undergo parathyroid surgery for the first time. The use of gamma probes in an area with intense scarring, fibrotic and anatomical changes may provide minimal dissection advantage by facilitating intraoperative localization [14].

Recurrence is most commonly seen in ipsilateral central and lateral cervical lymph node compartments and thyroidectomy site in differentiated thyroid cancer (DTC) [19,20]. If high Tg values are detected, the use of high frequency neck USG has a high success rate in detecting DTC loco-regional metastases before they become palpable [21,22]. Detection of small malignant lesions between fibrotic tissues in a surgical area is a challenge. Injection of radioactive material and intraoperative gamma probe use does not only help localize the lesion but also facilitates dissection. With this method, a compartment-oriented approach can be achieved without damaging vital structures [12,23].

In 2013, Borso et al. reported the use of the ROLL technique with a success rate of 95% in selected patients with local recurrence of DTC. Histopathological examination confirmed the presence of metastatic/recurrent disease with radiolabeled lesions. There were no significant complications such as recurrent laryngeal nerve injury or hypoparathyroidism. These results confirmed the clinical importance of ROLL in difficult surgeries, especially for cervical recurrence of DTC with previous cervical dissection [24].

There are only a limited number of studies on ROLL guided surgery. Ilgan, et al. reported a 100% no evidence of disease rate in 8 patients who underwent surgery for central lymphatic compartment recurrence. Except for those with distant metastasis, Tg values decreased below 2ng/mL [25]. Giles et al. compared ROLL (n = 11) and intraoperative USG (IOUSG) (n = 9) techniques. They reported 100% and 89% surgical success rates in the ROLL and IOUSG groups, respectively[9]. Tuncel, et al. found that stimulated Tg levels were lower than 1 ng/ml in 79% patients and that suppressed Tg levels were below 0.2ng/ml in 92% of patients with relapsed DTC who underwent ROLL-guided surgery. In the same study, neck USG examinations performed in patients operated for recurrent medullary thyroid cancer at the postoperative 20th month follow-up were normal and calcitonin levels decreased by 60-80% in 4 patients and >80% in 1 patient [13]. Gulcelik et al. reported 10% success in 20 patients with metastatic DTC using the ROLL technique [26].

In our study, ROLL was most commonly used for the relapse of DTC, similar to the studies in the literature [9,11,12,13,23]. Two patients had recurrence of medullary cancer and one patient had recurrence of anaplastic carcinoma. The removal of the lesions was demonstrated with histopathology and laboratory values. Stimulated Tg levels did not decrease to <2 ng/mL in 3 patients.One of these patients had local recurrence and one had lung metastasis. The other patient underwent local recurrence excision due to recurrence of metastatic anaplastic cancer. Calcitonin levels decreased to normal limits in patients operated for medullary thyroid cancer recurrence.

Although complication rates are lower in ROLL-guided operations, complications may occur at a high rate, especially in re-operative central neck surgery. Tuncel, et al. found the complication rate to be 13% in patients operated for thyroid cancer recurrence. The most common complications were chylous fistula and unilateral vocal cord paralysis [13]. Surgical treatment of central and lateral neck recurrences is difficult due to impaired and complicated anatomy and intense fibrosis.In redo surgeries, 1-12% RLN injury, 1-3% permanent hypoparathyroidism, 0.8-1% Horner's syndrome, 0.7-1% spinal accessory nerve injury and 0.2% chylous fistula due to ductus thoracicus injury is reported [27]. All patients underwent intraoperative nerve monitoring. Nerve injury did not develop in any patient. Postoperative transient hypocalcemia developed in 2 patients. It was treated with intravenous and oral calcium replacement. There was no persistent hypocalcemia and chylous fistula.

In conclusion, ROLL technique is very effective in defining the localization of thyroid and parathyroid gland-related lesions using peroperative radioisotope in patients who had previously undergone surgery for thyroid or parathyroid diseases. It makes compartment-based dissections in thyroid cancer recurrences possible. Recurrent hyperparathyroidism also helps in localization. It can reduce complication rates in redo surgeries.The most important limitations of our study were the fact that we only included patients who ROLL was used on and its retrospective nature. However, the number of patients was as large as those reported in the literature. We believe that our study provides comprehensive data on the reliability and effectiveness of the ROLL technique and will contribute to valuable reference data. We think that more studies are needed to evaluate the effect of ROLL technique on thyroid and parathyroid redo surgeries.

Riassunto

Lo scopo di questo studio è condividere la nostra esperienza clinica circa l'efficacia della tecnica di localizzazione delle lesioni occulte con da radioisotopi (ROLL) nell'esplorazione chirurgica reiterata del collo in pazienti già esplorati chirurgicamente per patologia tiroidea o paratiroidea.

Sono stati raccolti retrospettivamente i dati di 25 pazienti sottoposti a esplorazione reiterata del collo per carcinoma tiroideo recidivo e adenoma paratiroideo tra gennaio 2016 e dicembre 2018 presso la Clinica di Chirurgia Generale dell'Ospedale Balcalı, Facoltà di Medicina dell'Università Çukurova.

Il giorno dell'operazione sono stati iniettati nella lesione

sotto guida ecografica (USG) 0,5 mCi Tc-99m di albumina macroaggregata. In tutti i pazienti è stato eseguito il monitoraggio dei nervi laringei.
I venticinque pazienti (21 femmine, 4 maschi) inclusi nello studio erano di età media di 54,5 (24-79) anni. Cinque pazienti sono stati operati per adenoma paratiroideo, 6 pazienti per carcinoma papillare dopo tiroidectomia subtotale, 13 pazienti per recidiva del carcinoma papillare, 2 pazienti per recidiva del carcinoma midollare, 2 pazienti per metastasi del linfonodo cervicale del carcinoma papillare e 1 paziente per recidiva del carcinoma anaplastico. Durata dell'intervento 100,6 minuti (60-160 minuti). Due pazienti presentavano ipocalcemia transitoria e non sono state osservate altre complicanze. Significativamente inferiori rispetto ai livelli preoperatori i livelli di ormone paratiroideo (PTH) nei pazienti con iperparatiroidismo e i livelli di tireoglobulina (Tg) nei pazienti con carcinoma papillare recidivo (p <0,05). In conclusione riteniamo che la tecnica ROLL riduca il tasso di complicanze diminuendo il tempo e la estensione della dissezione chirurgica, e si consiglia di utilizzarlo per il cancro alla tiroide e la chirurgia paratiroidea.

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