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HEAD & NECK

Radioguided occult lesion localization in patients with recurrent thyroid cancer

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Abstract

Purpose Well planned re-surgery is critical for recurrent/persistent thyroid cancer (TC). We aimed to investigate the clinical outcome of radioguided-occult lesion localization (ROLL) guided surgery in patients with recurrent/persistent TC.

Methods This study includes 29 patients [F/M: 22/7, median age 43 ± 12 years (18–58)] with a diagnosis of TC (22 papillary, 2 follicular and 5 medullary). Before surgery, all patients underwent ultrasonography (USG) guided mapping and intra-lesional radioactivity injection. Surgery was performed based on the excision of radioactivity injected lesions by a gamma probe and non-injected tumor foci via USG-neck map. Researchers determined surgical success by post-operative tumor markers and neck-USG.

Results Among 29 patients, 60 metastatic lesions were identified by USG [median size 10 ± 6.3 mm (range 5–30)]. Neck-USG performed after surgery provided no evidence of disease (NED) in %97 (28/29) of TC patients. In the follow-up, stimulated thyroglobulin (Tg) levels were less than 1 ng/ml in 79%(19/24) of DTC patients and suppressed Tg < 0.2 ng/ml was noted in 92% (22/24).In patients with DTC with an incomplete structural response, we dramatically changed the American Thyroid Association (ATA) response category and achieved an excellent response in 92% (22/24) of patients. Among patients with MTC, 5/5 patients had normal USG and calcitonin levels were reduced by 60–80% in 4/5 and > 80% in1/5 patients.

Conclusions In this study we have shown that, ROLL-guided surgery yielded NED rate of %97 (28/29) and increased excellent response rates according to ATA guidelines. Further studies with larger patient groups and longer follow-up should be performed to confirm the efficacy of this surgery.

Keywords Radioguided occult lesion localization · Thyroid cancer · Surgery · Ultrasonography

Introduction

Thyroid cancer is the most common endocrine malignancy and constitutes 1–1.5% of all cancers with an increasing incidence. Most thyroid cancers (90–95%) are well-differentiated and effectively treated by surgery with or without radioiodine (RAI) [1, 2]. Well planned and successful surgery plays a critical role in optimal therapy and reduces re-operation rates for the recurrent/persistent disease. However, there is a lack of patient exposure to high-volume surgeons and experienced ultrasonographers, thus leading to inadequate surgeries. Despite effective treatment, up to 30% of these patients recur within 10 years of primary surgery [3, 4]. The recommended therapy of these incomplete surgeries and recurrences is re-operation, and successful surgery significantly affects patient survival [5, 6]. Although a high-volume surgeon could make 72% of patients structurally disease-free after re-operation, approximately 40% of patients suffered from additional relapse [7]. Recurrent surgery is hampered by altered anatomy and fibrosis due to previous surgeries. Post-surgical changes may also increase operation time and morbidity [8–11]. A major problem in recurrent surgery is the failure to resect occult lesions that can be hardly identifiable with a naked eye or hidden by overlying structures. Improved surgical technique or preoperative localization had been found to decrease these failures and increased the success of recurrent surgery in 15–20% of the patients with less morbidity [7]. Among these localization techniques, several authors proposed insertion

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of hook-wire, but the risk of complications, such as hook rupture, vessel injury, and patient discomfort, limit the utility of this technique [12]. Radiotracers, such as I-131 and Tc-99m sestamibi, were also used for intraoperative gamma probe-guided surgery; however, most of the recurrent thyroid cancer exhibited low or no radiotracer uptake [13]. Recently, radio-guided occult lesion localization (ROLL) technique that, aids in the detection of recurrent lesions with a gamma probe after ultrasound-guided intra-lesional radiotracer injection, was introduced by several authors [14]. In this study, we aimed to investigate the clinical outcome of this ROLL technique in a group of patients with recurrent/persistent thyroid cancer after primary surgery.

Subjects and methods

Study design

We retrospectively reviewed electronic medical records of 29 patients undergoing ROLL-guided re-operative surgery for recurrent thyroid cancer at a tertiary medical center in Ankara, Turkey from 2011 to 2016.

Setting /study population

This study includes 29 consecutive patients [F/M: 22/7 median age 43 ± 12 years (18–58)] with a diagnosis of thyroid cancer [22 papillary (PTC), two follicular cancer (FTC) and five medullary thyroid cancer (MTC)].

All patients were referred to our hospital (Hacettepe University) with recurrent or persistent thyroid cancer after the initial surgery. In total, there were 76% of patients (22/29) with and 24% of patients (7/29) without neck dissection who had biopsy-confirmed recurrent (55%) or persistent thyroid cancer (45%) with elevated tumor markers [thyroglobulin (Tg) or calcitonin]. None of the patients had distant metastases. Approximately, 67% (16/24) of the patients with differentiated thyroid cancer experienced recurrence despite high dose RAI. There were 5/29 patients with MTC with metastatic lesions in ultrasonography (USG) and elevated post-operative calcitonin levels. Detailed clinical characteristics of the study patients were presented in Tables 1 and 2.

Institutional Ethical Committee at the University-Hospital Hacettepe approved this study (Approval number: GO 15/561-05).

Table 1 Clinical characteristics of study patients (*n*: 29)

Variable	*N*	%
Median age (range), years	43 ± 12 (18–58)	
Gender F/M	22/ 7	76/24
Thyroid cancer type PTC/MTC/FTC	22/5/2	76/17/7
Previous surgery before ROLL-guided surgery		
TT	7	24
TT + LND	8	28
TT + BLND	3	10
TT + CND + LND	7	24
TT + BLND + CND	4	14
Post-operative RAITx (*n*:24)		
RAITx+	16	66.7
RAITx−	8	33.3
Previous RAI dose (*n*:16)		
3.7 GBq	3	19
5.5 GBq	8	50
2 × 5.5 GBq	2	13
2 × 6.47 GBq	1	6
5.5 + 7.4 GBq	1	6
2 + 3.7 + 3.7 GBq	1	6

PTC Papillary thyroid cancer, *FTC* Follicular thyroid cancer, *MTC* Medullary thyroid cancer, CND Central neck dissection, defined as removal of the prelaryngeal, pretracheal, and both the right and left paratracheal nodal basins. Simple node removal as a part of TT was not accepted as CND (15), *LND* Lateral neck dissection, as defined by American Thyroid Association consensus review (16), *BLND* Bilateral lateral neck dissection, *TT* Total thyroidectomy, *RAITx* Radioiodine therapy

Roll-guided surgery

Preoperative preparation and injections

Before surgery, all patients underwent USG-guided mapping by an experienced nuclear medicine physician who was aware of the patients' previous therapy and imaging data. Researchers used USG-guided drawings of the detected malignant and suspicious lesions (both radioactivity injected and non-injected neighboring malignant lesions) as a map in the operation room (Fig. 1). Two hours before surgery, 11 MBq Tc-99m-labeled macroaggregates (MAA) in 0.1 ml was injected intra-lesionally under USG guidance. The accuracy of the intra-lesional injection was confirmed with spot planar gamma camera (*n*:29) and SPECT-CT images (*n*:4) via hybrid SPECT-CT gamma camera (GE Hawkeye USA) (Fig. 2).

Operative technique

Surgery was performed based on the excision of radioactivity injected lesions by a gamma probe (Crystal gamma probe, Crystal Photonics, Germany) and non-injected tumor foci based on guidance from USG-neck map that depicted the location of injected and non-injected lesions (Fig. 3). In patients with multiple residual lesions near each other, one or two of the dominant lesions in the same location were injected with radioactivity to avoid unnecessary injections.

Table 2 Patient characteristics before surgery

Time interval between initial surgery-ROLL-guided surgery	7 ± 14 (1–43) months
*TSH stimulated Tg levels before ROLL-guided surgery (*n*:24 pts with PTC/FTC)	median: 16 ± 54 (1–156) ng/ml
Tg: < 10 ng/ml	6 (25%)
Tg: 10–100 ng/ml	16 (67%)
Tg > 100 ng/ml	2 (8%)
Calcitonin levels of 5 patients with MTC before ROLL-guided surgery	78 ± 55 (35–295) pg/ml

*TSH levels > 30 μIU/ml were accepted for TSH stimulation, no patients had elevated anti-Tg levels that may interfere with Tg levels

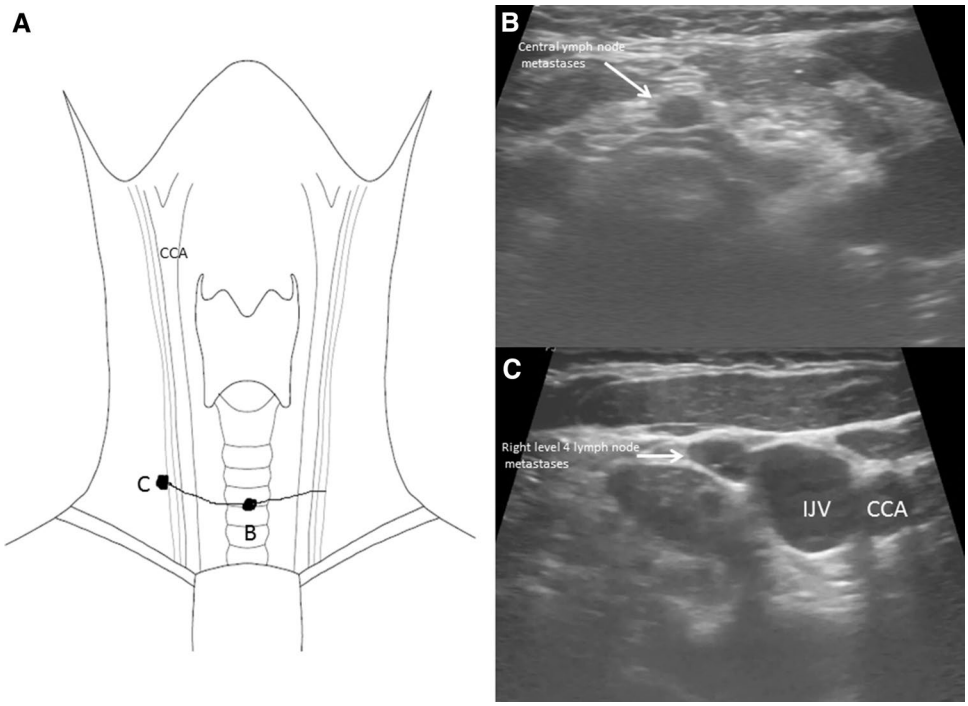

Fig. 1 (**a**) Preoperative schematic mapping of recurrent metastatic (**b**) central and (**c**) right lateral level 4 lymph nodes (arrows) found at USG. CCA: Common carotid Artery and IJV: Internal jugular vein

Also in patients without previous neck dissections, metastatic lesions located in the area of standard dissection was only mapped by USG. Radioactivity injection of lesions in systemic dissection is performed according to the surgeon's demand to ensure complete resection of lesions that may be missed in standard dissection, like lesions located in dissection margin, or behind major vessels. The ultrasonographer was also present in the operation room to guide the surgeon using the USG map and gamma probe.

Based on data regarding previous surgeries, localization and distribution of recurrent and persistent lesions, patients underwent either local excision, selective compartmental dissection or systemic dissection. Local excision included total removal of the USG-detected and radioactivity injected lesion. Selective compartmental dissection, included excision of radioactivity injected lesions in that compartment with USG-detected neighboring malignant, suspicious lesions and standard systemic dissection included excision of all lymph nodes, including USG-detected, radioactivity injected lesions in a predefined area [15, 16]. Surgery was completed when the all USG malignant or suspicious lesions were dissected, and gamma probe counts returned to background levels. Intraoperative gamma probe counts, radioactivity injection success and post-surgery complication rates were also noted.

Post-operative adjuvant therapy

Forty-six percent of patients with differentiated thyroid cancer (11/24) received adjuvant RAI therapy after ROLL-guided surgery according to the recommendations of the American Thyroid Association (ATA) guideline [17]. Eleven patients received RAI approximately 3 months after re-operative surgery. Seventy-three percent (8/11) of these patients had no prior RAI therapy and received 5.5 GBq RAI as adjuvant therapy. Two patients who had 3.7 GBq after TT received an additional 5.5 GBq RAI after ROLL-guided LND. One patient who received 5.5 GBq RAI at the different

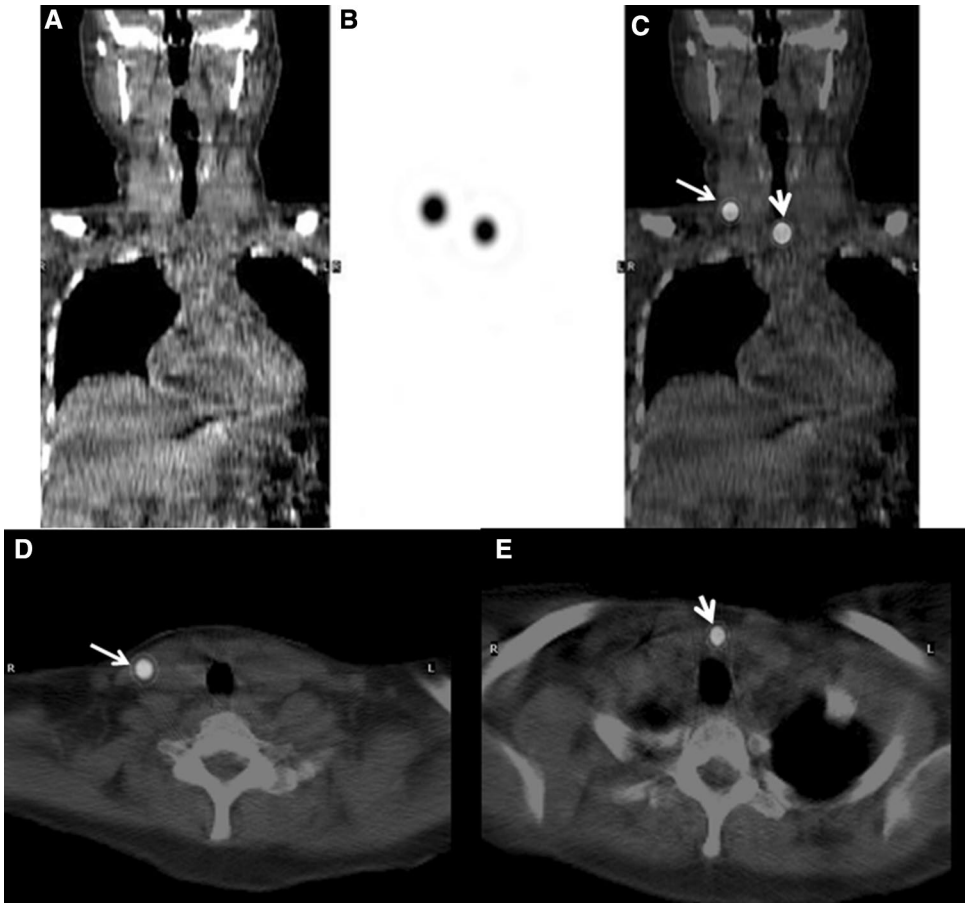

Fig. 2 SPECT-CT imaging of metastatic lymph nodes labeled with ROLL technique. (**a**) CT, (**b**) SPECT and (**c**–**e**) SPECT-CT fusion images show radiolabelled right level 4 metastatic lymph node (white arrow) and central metastatic lymph nodes (white arrowhead)

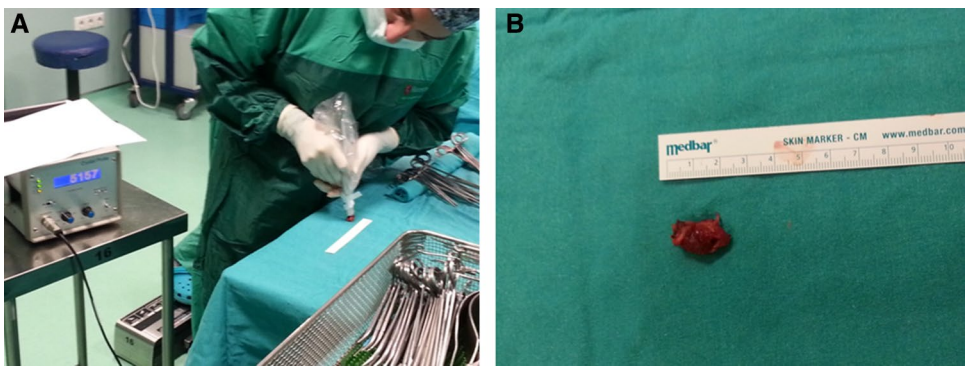

Fig. 3 **a** Ex-vivo gamma probe counting of millimetric lymph node metastases **b**

hospital received an additional 5.5 GBq RAI dose due to suspicion of inappropriate therapy preparation and patient demand. Patients with MTC did not receive radioiodine or any other adjuvant therapy.

Post-operative response evaluation

A post-operative decrease in Tg or calcitonin levels and neck-USG were used for the determination of surgical success. The absence of a residual metastatic or recurrent lesion in the neck was defined as no evidence of disease (NED) by USG. Therapy response results of patients with differentiated thyroid cancer were further evaluated according to ATA guidelines' response criteria [17]. According to these guidelines, therapy response was categorized as an excellent response, incomplete biochemical response, indeterminate response, and incomplete structural response. The primary goal of the therapy is an excellent response which was defined as negative imaging and either and suppressed Tg < 0.2 ng/mL or TSH-stimulated Tg < 1 ng/mL.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics, version 23.0 (SPSS Inc., Chicago, IL). The results are expressed as the mean/median values ± SD (range) where appropriate. Data were analyzed using the Chi-square and Mann–Whitney tests to analyze parametric and nonparametric data, respectively. A p value of < 0.05 was considered significant.

Results

Preoperative findings

Among 29 patients, USG identified 60 metastatic lesions [median size 10 ± 6.3 mm (range 5–30)]. Seventy-two percent (43/60) [median size 12 ± 6.6 mm (range 5–30)] of these were injected with radioactivity for detection via gamma probe. The remaining 28% (17/60) of the lesions were marked only on USG-guided map. The common locations of recurrent lesions were at ipsilateral level 6 in 33% (20/60) and ipsilateral level 4 in 25% (15/60). Table 3 shows detailed recurrent lesion characteristics of the study patients.

Table 3 Surgery and recurrent lesion characteristics of 29 patients

Previous surgery *n* (%)	Site of residual/recurrent disease per patient *n*: number of lesions in specific localization	Roll-guided surgery
TT: 7/29 (24)	Ipsilateral L6 (*n*:2) + ipsilateral L4 (*n*:1)	CND + RLND
	Ipsilateral L3 (*n*:2) + ipsilateral L6 (*n*:2)	CND + Left LND
	Ipsilateral L6 (*n*:1)	Selective compartmental dissection
	Ipsilateral L6 (*n*:1)	Selective compartmental dissection
	Ipsilateral thyroid bed (*n*:1) + ipsilateral L4 (*n*:1)	Local excision + RLND
	Ipsilateral thyroid bed (*n*:1)	Local excision
	Ipsilateral L6 (*n*:3) + ipsilateral L4 (*n*:2)	CND + RLND
TT + right LND: 5/29 (18)	Ipsilateral thyroid bed (*n*:1)	Local excision
	Ipsilateral level 2 (*n*:2)	Selective compartmental dissection
	Ipsilateral level:4 (*n*:2)	Selective compartmental dissection
	Ipsilateral level:6 (*n*:2)	Selective compartmental dissection
	Ipsilateral level 2 (*n*:2) + ipsilateral L6 (*n*:2)	Selective compartmental dissection + RLND
TT + left LND: 3/29 (10)	Ipsilateral thyroid bed (*n*:2)	Local excision
	Ipsilateral L3 (*n*:1)	Local excision
	Ipsilateral level:6 (*n*:1)	Selective compartmental dissection
TT + right LND + CND 4/29 (14)	Contralateral L3 (*n*:3) and L6 (*n*:1)	Left LND + CND
	Ipsilateral L4 (*n*:1) and ipsilateral and contralateral L6 (*n*:3)	Local excision + Selective compartmental dissection
	Ipsilateral L4 (*n*:1) and contralateral L6 (*n*:1)	Local excision + Selective compartmental dissection
	Contralateral L6 (*n*:1)	Selective compartmental dissection
TT + left LND + CND: 3/29 (10)	Ipsilateral L7 (*n*:1)	Local excision
	Ipsilateral L6 (*n*:1)	Local excision
	Ipsilateral L6 (*n*:1) + Ipsilateral L4 (*n*:2)	Selective compartmental dissection
TT + BLND: 3/29 (10)	Ipsilateral L4 (*n*:1), contralateral L2 (*n*:1)	Local excision
	Ipsilateral L6 (*n*:2), contralateral L6 (*n*:1)	Selective compartmental dissection
	Ipsilateral L4 (*n*:1)	Local excision
TT + BLND + CND: 4/29 (14)	Ipsilateral L2 (*n*:2), ipsilateral L6 (*n*:1)	Selective compartmental dissection + local excision
	Ipsilateral L4 (*n*:1)	Local excision
	Ipsilateral L4 (*n*:1)	Local excision
	Ipsilateral L4 (*n*:1)	Local excision

L Level, *CND* central neck dissection, LND lateral neck dissection, *BLND* bilateral lateral neck dissection, TT total thyroidectomy

*Ipsilateral defines the lesion in the same localization of the largest primary tumor

ROLL-guided re-operative surgery

ROLL-guided local excision was performed in 38% (11/29), selective compartmental dissection in 31% (9/29), systemic dissection in 14% (4/29), and in other combination of these techniques. Table 3 shows detailed surgery data.

Radioactivity injection was effective in 41/43 lesions, and gamma probe counts returned to background levels after excision (in vivo median lesion counts: 2250 ± 3300: (750–11,200) counts/s vs. in vivo background counts: 35 ± 45 (5–100) counts/s). ROLL technique confirmed accurate excision of 41/43 recurrent/persistent lesions, however, failed in 2/43 lesions. In one patient, radioactivity was located in strap muscles due to flush back from hard calcified metastases, in the other patient with a lesion size of 6 mm, half of the radioactivity leaked to the neighboring soft tissue. However, all of these two lesions were effectively resected using USG-guided mapping.

ROLL gamma probe-guided surgery aided in the identification of lesions that were missed by the surgeon regardless of the use of a USG-guided map. These lesions were; in 3/9 patients local recurrence in the thyroid bed [8 ± 1.6 (6–10) mm], in 3/9 patients 4 small lymph nodes [6 ± 1.4 (5–10) mm] in the central neck region, in 2/9 patients, metastatic lymph nodes, with longest diameters measuring 10 and 8 mm in the posterolateral of the jugular vein, and in 1/9 patient a metastatic lymph node at level 7 that was 15 mm in size. Although useful for guidance to the region of interest, USG-guided maps cannot always determine the target in a fibrotic area with several overlaying soft tissue (benign lymph nodes and fat tissue.).

Post-operative complications

We had seen post-operative complications in 4/29 patients. In 2/4 patients, we had observed leakage of chylous fluid due to the involvement of lymphatic channels in the metastatic lymph node & ductal channels and repaired intraoperatively. In one of these two patients, chylous leakage continued for a few days after surgery, but total healing was achieved with medical treatment.

In 2/4 of these patients, we had seen unilateral vocal cord paralysis (one permanent and one transient). All these patients underwent re-operation due to extensive central compartment metastatic lymph node involvement.

Post-operative histopathology results

Before ROLL-guided surgery all patients, had a biopsy (fine needle biopsy) proof of metastatic involvement in the radiolabeled/USG-guided mapped metastatic lymph nodes. These findings were also confirmed post-surgery pathology specimens. In patients in whom re-operative surgery was performed in a selective compartmental or standard dissection manner, additional metastatic lymph nodes not seen by USG, but detected by pathology was seen in 8% (1/13) of selective compartmental dissection and 20% (2/10) of standard dissections.

The clinical outcome of re-operative surgery and follow-up

We have evaluated the clinical outcome of re-operative surgery by USG and tumor markers. USG that was performed 3 ± 2 (1–6) months (median) after surgery was normal in 96.5% (28/29) of the patients. In one patient with 3 previous surgeries (TT, completion TT and LLND) and a total RAI dose of 12.4 GBq, recurrence at the left lateral tracheoesophageal grove could only be partially dissected. Histopathological findings revealed PTC which infiltrated the surrounding strap muscles. Although gamma probe counts did not return to the background level, surgery was completed because the surgeon could not identify any recurrent lesion despite adequate dissection. Magnetic resonance imaging and FDG PET-CT was normal in the follow-up. USG revealed a minimally visible 6-mm residual lesion (Pre-ROLL-guided surgery size: 12 mm), which remained stable over 3 years.

Post-operative TSH-stimulated Tg at a median of 6 ± 2 (3–7) months before additional RAI therapy was reduced by greater than 90% in 16/24 and greater than 50% in 23/24 differentiated (PTC or FTC) thyroid cancer patients (Table 4). None of the parameters, such as preoperative Tg, re-operative surgery type, lesion size, localization of recurrent lesions, age and gender, could predict this > 90% decrease in Tg (Table 5).

Forty-six percent of patients with differentiated thyroid cancer (11/24) received adjuvant RAI therapy. Post-RAI scans revealed uptake only in the residual thyroid remnant, except in one patient who had high uptake in the retropharyngeal lymph node. This patient experienced complete remission after an additional 5.5 GBq of RAI. Three of these 11 patients who previously received RAI in an external hospital had post-RAI scans with no abnormal uptake.

In the follow-up [median 25 ± 9,6 (10–62) months], no changes in the USG findings were noted. Stimulated Tg levels of patients with differentiated thyroid cancer further reduced after RAI therapy (Table 4) and sTg levels were less than 1 ng/ml in 79% (19/24) of patients, and suppressed Tg < 0.2 ng/ml was noted in 92% (22/24) of patients. In our group of differentiated thyroid cancer patients with incomplete structural response according to ATA guideline, we dramatically changed the response category and achieved an excellent response in 92% (22/24) of patients. Eight percent (2/24) of patients experienced an incomplete biochemical response, and 4% (1/24) of patients maintained incomplete

Table 4 ROLL-guided surgery results of 24/29 differentiated thyroid cancer (PTC or FTC) patients

Variable	*N*	%
Post-op USG		
Negative	23	96
Positive	1*	4
Preoperative sTg	Median:19 ± 48 (1–196)	
Post-operative sTg	Median:1.1 ± 8.2 (0.2–33)	
Post-op Δ% sTg change at 6 ± 2 (3–7) months		
>90	16	67
>85–90	4	17
>50–85	3	12
0–50	1	4
Δ% sTg change after additional RAI at 12 ± 2 (11–15) months		
>90	20	84
>85–90	2	8
>50–85	1	4
0–50	1	4
Follow-up [median: 25 ± 9,6 (10–62) months]		
sTg < 1 ng/ml	19	79
sTg ≥ 1 < 10 ng/ml	3	13
sTg ≥ 10 < 20 ng/ml	2	8
Suppressed Tg < 0,2 ng/ml	22	92
Suppressed Tg > 1 < 2 ng/ml	2	8

sTg stimulated Tg

*Patient received 3 previous surgery and RAI dose of total 12.4 GBq. The recurrence at the left lateral tracheoesophageal grove could only be partial dissected. Her MRI and FDG PET-CT were normal in the follow-up with only 6 mm residual diseases (pre-Roll-guided surgery 12 mm) at USG which is stable over 3 years

structural response although the decrease in the size of the recurrent lesion was observed (Table 4).

Among patients with MTC, at 20-month follow-up, 5/5 patients had normal USG and calcitonin levels were reduced by 60–80% in 4/5 and > 80% in 1/5 patients.

Discussion

The main focus of therapy in well-differentiated thyroid cancer is disease-free survival [18]. Although most of the differentiated thyroid cancers are successfully cured with surgery and RAI, up to 30% of patients recur [3, 4]. The main goal of re-operative surgery for the recurrent/persistent disease is to prevent local disease progression, [19]. After successful surgery, post-operative imaging findings and Tg levels predict disease-free and overall survival. Several response criteria were used for response evaluation after re-operative surgery. Among these no evidence of structural disease (NED), as defined by neck-USG, was commonly used. In our patient group, re-operative surgery yielded NED in the neck in % 97 (28/29) of patients with thyroid cancer. Although disease characteristics, previous therapies and follow-up periods of patients, differed among studies, our NED (%) rate was superior when compared with Hughes et al., who reported a rate of 72% without intraoperative guidance [20]. Similar lower NED rates were reported by Hariri et al., who reported a 51% NED rate by methylene blue guidance [21] and Rubello et al., who reported a rate of 81% using I-131 for intraoperative guidance for recurrence surgery [22]. In ROLL-guided surgery, contrary to systematically administered radiopharmaceuticals, a high lesion/background count ratio could be obtained by direct injection of radioactivity into the lesion. Additionally, some lesions do not exhibit inherent uptake of the systematically administered radiotracer and decrease the efficacy of this surgical method. Limited studies have reported on ROLL-guided surgery; Ilgan et al. obtained a 100% NED rate in a small number of patients (*n*:8) with central recurrences. Except for two patients with distant metastases, a Tg level of < 2 ng/mL on L-T4 suppression was achieved for all patients [14]. Giles et al. compared ROLL ($n = 11$) and intraoperative USG (IOUSG) ($n = 9$). The operative success rates in the ROLL and IOUSG groups were 100% and 89%, respectively. The authors used no metastatic lesion on post-operative imaging and a decrease in post-operative Tg level < 50% of preoperative Tg level as a therapeutic response [23]. In another study by Bellotti et al., ROLL-guided surgery was helpful

Table 5 Variables that predict < 90% Tg decrease after ROLL-guided surgery

Variable	< 90% Tg decrease (*n*:8)	> 90 Tg decrease (*n*:16)	*P* value
Age (years)	37 ± 15	38 ± 10.5	0.79
Gender			
F	6 (75%)	12 (75)	0.21
M	2 (25%)	4 (25)	
PreTg (ng/ml)	33.9 ± 27.6	38.5 ± 55.9	0.36
*Total lesion size (mm)	27.4 ± 14	27.7 ± 2	0.85
Lesion number	2.3 ± 1	2.12 ± 1	0.68
Lesion number			
Single lesion	3 (37.5%)	6 (37.5%)	0.85
Multiple lesions	5 (62.5%)	10 (62.5%)	
Lesion localization			
Single site	4 (50%)	10 (62.5%)	0.71
Multiple sites	4 (50%)	6 (37.5%)	
Previous surgery			
TT	4 (50%)	5 (31%)	0.43
TT + CND	1 (12.5)	1 (6.5%)	
>TT + LND	3 (37.5)	10 (62.5%)	
Recurrent surgery type			
Local excision	2 (25)	6 (37, 5%)	0.83
Selective compartmental dissection	3 (37.5)	6 (37, 5%)	
Standard systemic dissection	3 (37.5)	4 (25%)	

TT total thyroidectomy, *CND* central lymph node dissection, *LND* lateral neck lymph node dissection

*Obtained with the addition of largest size of malignant lesions

in resection of recurrent disease, and none of the patients (*n*: 22) in the study experienced recurrent nodal disease. However, the authors did not define surgery success using USG or Tg levels [24]. Although USG is an effective method for recurrence detection, Tg is the main follow-up tool for differentiated cancer. However, the determination of biochemical recurrence or persistent disease by Tg is a matter of debate in the literature. Many of the studies do not report TSH levels in conjunction with Tg or define several arbitrary different thresholds, which decreases the reliability and comparability. For example, using a Tg level cut-off < 2 ng/ml, McCoy et al. reported a 50% biochemical remission rate [25], whereas Lee et al. reported a rate of 64% [26]. Gulcelik MA reported post-operative Tg < 0.2 ng/ml rate of 70% (14/20), however, did not mention corresponding TSH levels [27]. In patients with differentiated cancer, our results revealed an improved biochemical remission rate 79% using the criterion of stimulated Tg < 1 ng/ml and 92% using the criterion of suppressed Tg < 0.2 ng/ml. In our group of differentiated thyroid cancer patients with incomplete structural response according to ATA guidelines [17], we dramatically changed the response category and achieved an excellent response in 92% (22/24) of patients. When this achieved, 1–4% of these patients experience recurrence, and < 1% experience disease-specific death [17]. Eight percent (2/24) of the patients experienced an incomplete biochemical response, and 4% (1/24) of patients maintained incomplete structural response although the decrease in the size of the recurrent lesion was observed. The patient with an incomplete structural response had a partially resected 6-mm residual lesion at the central neck area, which is only detectable by high-resolution USG. This patient was subsequently followed with active surveillance as suggested by Tuttle et al. [28], and her stimulated Tg levels and lesion size were stable for 3 years. Only recently Garbaccio et al. reported response rates of ROLL-guided surgery according to ATA guidelines in a group of patients with 15 recurrent differentiated thyroid cancer. At a median post-surgery follow-up of 16 months, authors classified eight patients as; complete response ($n = 4$), incomplete biochemical response ($n = 3$), indeterminate response ($n = 1$) with no evidence of structural disease and the remaining seven patients were classified as an incomplete structural response [29]. Although patient characteristics differ their results were inferior to our achieved excellent complete response rate in 92% (22/24) of patients.

Eleven (46%) patients received RAI approximately 3 months after re-operative surgery. Seventy-three percent (8/11) of these patients had no prior RAI therapy. Post-RAI scans only revealed uptake in the residual thyroid remnant except in one patient who had high uptake in the retropharyngeal lymph node. This patient experienced complete remission after an additional 5.5 GBq of RAI. Radioiodine-avid lymph node metastases were only noted in one patient, and post-RAI scans revealed only faint uptake in patients without previous RAI treatment. Thus, changes in the Tg levels were mainly due to effective dissection rather than a therapeutic effect of RAI, which is also rapidly observed before additional RAI. The further decrease in Tg levels after RAI is mainly due to the ablation of remnant thyroid tissue except in one patient. Although our patient number is relatively small, none of the parameters, including preoperative Tg, re-operative surgery type, lesion size, localization of recurrent lesions, age, and gender, could predict a > 90% reduction in stimulated Tg. Patient-specific surgery, surgeon skills, heterogeneity of patient characteristics and disease virulence variances may have led to these results.

USG-guided map was useful to guide the area of interest; however, it was difficult to identify small malignant lesions among fibrotic soft tissue in a previously dissected area. Radioactivity injection and intraoperative gamma probe counting not only guide the surgeon, but also confirm accurate dissection. In 9 patients, although the surgeon excised suspicious lesions, persistent counts from the radioactivity injected malignant lesions provided accurate dissection. These dissected

malignant tissues may be overseen in the absence of radioactivity injection and resection of non-malignant tissues may be considered sufficient by the surgeon.

Patients with MTC

Our study also included patients with MTC. These patients had 100% NED rate in the neck, and their calcitonin levels reduced by 60–80% in 4/5 and > 80% in 1/5. The response rate of patients with MTC seems different than well-differentiated cancer. Although NED could be achieved in locally metastatic MTC, the biochemical remission rate was poor. In a meta-analysis, Rowland et al. reported overall normalization of calcitonin after reoperation for MTC in 16.2% of patients regardless of the procedure performed [30]. Our study is one of the first studies to show the outcome of ROLL-guided surgery for MTC. In patients with MTC, the primary goal of re-operative surgery should be NED in neck and surgeons should not expect a high rate of biochemical remission even with ROLL-guided surgery.

Post-operative complications

Although ROLL-guided surgery is effective, the procedure is not without complications, especially in the re-operative central neck area. Post-operative complications were noted in 4/25 patients who underwent re-operation for extensive central compartment metastatic lymph node involvement. Similar rates of vocal cord paralysis (4.1–6.6%) have been reported in recurrent thyroid cancer surgery, including the central neck compartment [31, 32].

Limitations of this study

We acknowledge the heterogeneity of patient characteristics, a small number of patients and a limited follow-up period [median 20 ± 9,6 (10–62) months] as limitations of our study and plan to report larger series.

Our study proved that ROLL-guided surgery and USG mapping are effective methods for managing recurrences as assessed by USG and stimulated Tg. However, as can be observed from our different surgery protocols we would like to emphasize that systemic dissection is the preferred surgery type and ROLL technique is a helpful adjunct to recurrent surgery and is not meant to encourage node plucking behavior.

Conclusion

In this study we have shown that, ROLL-guided surgery with USG-guided mapping is an effective method in the management of recurrent thyroid cancer. This method yielded a NED rate of %97 (31/32 patients) in the neck area and increased excellent response rates according to ATA guidelines. Further studies with larger patient groups and longer follow-up should be performed to confirm our results.

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Compliance with ethical standards

Conflict of ınterest Authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Institutional Ethical Committee at the University-Hospital Hacettepe approved this study (Approval number: GO 15/561-05).

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. American Thyroid Association Guidelines Taskforce on Thyroid N, Differentiated Thyroid C, Cooper DS, Doherty GM, Haugen BR, Kloos RT et al (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 19(11):1167–1214
2. Mazzaferri EL, Kloos RT (2001) Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 86(4):1447–1463
3. Landis SH, Murray T, Bolden S, Wingo PA (1998) Cancer statistics, 1998. CA Cancer J Clin 48(1):6–29
4. Mazzaferri EL, Jhiang SM (1994) Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 97(5):418–428
5. Shen WT, Ogawa L, Ruan D, Suh I, Kebebew E, Duh QY et al (2010) Central neck lymph node dissection for papillary thyroid cancer: comparison of complication and recurrence rates in 295 initial dissections and reoperations. Arch Surg 145(3):272–275
6. Pai SI, Tufano RP (2010) Reoperation for recurrent/persistent well-differentiated thyroid cancer. Otolaryngol Clin North Am 43(2):353–363
7. Onkendi EO, McKenzie TJ, Richards ML, Farley DR, Thompson GB, Kasperbauer JL et al (2014) Reoperative experience with papillary thyroid cancer. World J Surg 38(3):645–652
8. Shaha AR, Jaffe BM (1998) Parathyroid preservation during thyroid surgery. Am J Otolaryngol 19(2):113–117
9. Levin KE, Clark AH, Duh QY, Demeure M, Siperstein AE, Clark OH (1992) Reoperative thyroid surgery. Surgery 111(6):604–609
10. Goretzki PE, Simon D, Frilling A, Witte J, Reiners C, Grussendorf M et al (1993) Surgical reintervention for differentiated thyroid cancer. Br J Surg 80(8):1009–1012
11. Tisell LE, Hansson G, Jansson S, Salander H (1986) Reoperation in the treatment of asymptomatic metastasizing medullary thyroid carcinoma. Surgery 99(1):60–66
12. Triponez F, Poder L, Zarnegar R, Goldstein R, Roayaie K, Feldstein V et al (2006) Hook needle-guided excision of recurrent differentiated thyroid cancer in previously operated neck

compartments: a safe technique for small, nonpalpable recurrent disease. J Clin Endocrinol Metab 91(12):4943–4947
13. Rubello D, Salvatori M, Pelizzo MR, Rampin L, Fanti S, Gregianin M et al (2006) Radio-guided surgery of differentiated thyroid cancer using (131)I or 99mTc-Sestamibi. Nucl Med Commun 27(1):1–4
14. Ilgan S, Ozturk E, Yildiz R, Emer O, Ayan A, Gorgulu S et al (2010) Combination of preoperative ultrasonographic mapping and radioguided occult lesion localization in patients with locally recurrent/persistent papillary thyroid carcinoma: a practical method for central compartment reoperations. Clin Nucl Med 35(11):847–852
15. American Thyroid Association Surgery Working G, American Association of Endocrine S, American Academy of O-H, Neck S, American H, Neck S et al (2009) Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. Thyroid 19(11):1153–1158
16. Stack BC Jr, Ferris RL, Goldenberg D, Haymart M, Shaha A, Sheth S et al (2012) American thyroid association consensus review and statement regarding the anatomy, terminology, and rationale for lateral neck dissection in differentiated thyroid cancer. Thyroid 22(5):501–508
17. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE et al (2016) American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 26(1):1–133
18. McCoy KL, Yim JH, Tublin ME, Burmeister LA, Ogilvie JB, Carty SE (2007) Same-day ultrasound guidance in reoperation for locally recurrent papillary thyroid cancer. Surgery 142(6):965–972
19. Grant CS (2015) Recurrence of papillary thyroid cancer after optimized surgery. Gland Surg 4(1):52–62
20. Tufano RP, Clayman G, Heller KS, Inabnet WB, Kebebew E, Shaha A et al (2015) Management of recurrent/persistent nodal disease in patients with differentiated thyroid cancer: a critical review of the risks and benefits of surgical intervention versus active surveillance. Thyroid 25(1):15–27
21. Hughes DT, Laird AM, Miller BS, Gauger PG, Doherty GM (2012) Reoperative lymph node dissection for recurrent papillary thyroid cancer and effect on serum thyroglobulin. Ann Surg Oncol 19(9):2951–2957
22. Harari A, Sippel RS, Goldstein R, Aziz S, Shen W, Gosnell J et al (2012) Successful localization of recurrent thyroid cancer in reoperative neck surgery using ultrasound-guided methylene blue dye injection. J Am Coll Surg 215(4):555–561
23. Rubello D, Salvatori M, Ardito G, Mariani G, Al-Nahhas A, Gross MD et al (2007) Iodine-131 radio-guided surgery in differentiated thyroid cancer: outcome on 31 patients and review of the literature. Biomed Pharmacother 61(8):477–481
24. Giles YS, Sarici IS, Tunca F, Sormaz IC, Salmaslioglu A, Adalet I et al (2014) The rate of operative success achieved with radioguided occult lesion localization and intraoperative ultrasonography in patients with recurrent papillary thyroid cancer. Surgery 156(5):1116–1126
25. Bellotti C, Castagnola G, Tierno SM, Centanini F, Sparagna A, Vetrone I et al (2013) Radioguided surgery with combined use of gamma probe and hand-held gamma camera for treatment of papillary thyroid cancer locoregional recurrences: a preliminary study. Eur Rev Med Pharmacol Sci 17(24):3362–3366
26. Lee L, Steward DL (2008) Sonographically-directed neck dissection for recurrent thyroid carcinoma. Laryngoscope 118(6):991–994
27. Gulcelik MA, Karaman N, Dogan L, Sahiner I, Akgul GG, Kahraman YS et al (2017) Radioguided occult lesion localization for locally recurrent thyroid carcinoma. Eur Arch Otorhinolaryngol 274(7):2915–2919
28. Rondeau G, Fish S, Hann LE, Fagin JA, Tuttle RM (2011) Ultrasonographically detected small thyroid bed nodules identified after total thyroidectomy for differentiated thyroid cancer seldom show clinically significant structural progression. Thyroid 21(8):845–853
29. Garbaccio V, Menga M, Mensa G, Passera R, Galati A, Codegone A et al (2017) Impact of radioguided occult lesion localization (ROLL) in the management of cervical recurrences from differentiated thyroid cancer. Q J Nucl Med Mol Imaging. https://doi.org/10.23736/S1824-4785.17.03027-8
30. Rowland KJ, Jin LX, Moley JF (2015) Biochemical cure after reoperations for medullary thyroid carcinoma: a meta-analysis. Ann Surg Oncol 22(1):96–102
31. Lee HS, Roh JL, Gong G, Cho KJ, Choi SH, Nam SY et al (2015) Risk factors for re-recurrence after first reoperative surgery for locoregional recurrent/persistent papillary thyroid carcinoma. World J Surg 39(8):1943–1950
32. Cayonu M, Acar A, Eryilmaz A, Oguz O (2014) Surgical approach and outcomes for revision surgery of the central neck compartment. J Craniofac Surg 25(5):1797–1800