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ORIGINAL ARTICLE

Intraoperative gamma probe guidance with ^{99m}Tc-pertechnetate in the completion thyroidectomy

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Abstract
Aim Intraoperative gamma probe (GP) guidance with ^{99m}Tc-pertechnetate in the completion total thyroidectomy after a first thyroidectomy was investigated in this prospective study.
Methods The study group comprises of fourteen consecutive patients (14 females, age mean 50.2 ± 12.0 years, age range 29–73 years). All patients underwent a second thyroidectomy due to inadequate (5/14 patients) and complementary (9/14 patients) interventions. Serum-free three iodothyronine, free thyroxin and thyroid stimulating hormone measurements, a neck ultrasonography (USG) and thyroid scintigraphy (TS) were performed in the preoperative and postoperative period. After a 185 MBq (5 mCi) injection of ^{99m}Tc-pertechnetate, background (BG), left thyroid lobe (LTL), right thyroid lobe (RTL) and pyramidal tyroid lobe (PTL) regions were counted in time before and after resection of thyroid remnants by intraoperative GP. All resection materials were evaluated by histopathologic examination.
Results Preoperative TSH was less than 30 mIU/mL (mean 21 ± 7) in all patients. Functioning thyroid remnants were shown in 13/14 patients on the preoperative TS and USG, which were diagnosed by USG in one but by TS in other one. We calculated that percentage median (minimum–maximum) values were 220.90% (56.00–411.11%) in LTL, 80.43% (11.54–471.05%) in RTL and 66.60% (−3.33 to 158.33%) in PTL for counts before resection, on the other hand, 15.96% (−20.55 to 47.62%) in LTL, 17.59% (−15.07 to 38.46%) in RTL and 17.59% (−1.96 to 57.14%) in PTL regions for counts after resection. There were statistically significant differences between these values belonging to before and after resection for LTL ($p = 0.001$), RTL ($p = 0.001$) and PTL ($p = 0.008$). Bilateral small foci in a patient and unilateral focus in other patient were observed in postoperative TS. Unilateral focus was detected on the RTL by GP, but not bilateral foci. Postoperative TSH levels increased to 30 mIU/mL (mean 69 ± 26) at least. There was a statistically significant difference between preoperative and postoperative TSH values ($p < 0.001$). Histopathologic confirmation revealed that all removed materials were the thyroid tissues.
Conclusions Gamma probe guidance with ^{99m}Tc-pertechnetate seemed to be a good option and easy available method in patients undergoing the completion total thyroidectomy.

Keywords Completion thyroidectomy · Gamma probe · ^{99m}Tc-pertechnetate · Differentiated thyroid cancer · Recurrent goiter

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Introduction

Radio-guided surgery concept has become popular on detection of the sentinel lymph node in patients with cancer, such as breast cancer, melanoma, etc. [1]. Today, new clinical applications about other malignancies have also been presented. The studies about radio-guided thyroid

surgery technique with gamma probe (GP) are still limited numbers in the literature. Mainly topic was confined to identification of metastatic lymph nodes in patients with recurrent differentiated thyroid cancer (DTC) by mainly using ^{131}I, ^{123}I [2–5]. In this present study, we focused on using intraoperative GP guidance with ^{99m}Tc-pertechnetate in patients undergoing completion total thyroidectomy after a first thyroidectomy.

Subtotal and total thyroidectomies have been used to treat the patients with DTC and goiter. A total or near total thyroidectomy is the most preferable intervention with an acceptable morbidity in patients DTC. As it eliminates possible occult contra-lateral disease and improves effect of ^{131}I treatment to destroy thyroid remnants and/or metastases from DTC. Some surgeons have selected subtotal thyroid surgeries due to decision of adequate operation. However, subtotal thyroidectomy may require a subsequent completion total thyroidectomy due to incidental detection of thyroid carcinoma by histopathologic examination or inadequate first intervention [6, 7]. Second thyroidectomy may be trouble because of following difficulties, especially if the time interval between first and second surgery is longer than expected. Minimal tissue volume, disintegrated anatomy, fibrotic and scatriciel tissues resulted from previously thyroidectomy can cause poor recognizing and resection of the remnants. Intraoperative GP guidance can play complementary and facilitative role in such conditions.

Materials and methods

Patients

From February 2006 to April 2007, admitted to surgery department, fourteen consecutive patients (14 females, age range 29–73 years, age mean 50.2 ± 12.0 years) with DTC and recurrent goiter consist of this study group. In the first operation, 9 of 14 patients underwent a subtotal thyroidectomy for a thyroid benign disease. DTC was diagnosed incidentally in six of these nine patients at the time of histopathologic examination. After 5 of 14 patients had undergone a total or near total thyroidectomy in a peripheral hospital for DTC, they referred to our surgery department for revision thyroidectomy. A completion total thyroidectomy with intraoperative GP guidance was decided for removing the thyroid remnants because of less than total or near total thyroidectomy in 11 of 14 patients and recurrent goiter in 3 of 14 patients. The time ranges between first and second operations were 3–36 months (mean 7.0 ± 8.5 months).

Diagnosed and treatment-related characteristics of these 14 patients are summarized in Table 1.

Table 1 Characteristics of the patients

Characteristics	Number (*n*: 14)	%
Age (years)		
Mean ± SD	50.2 ± 12.0	–
Median (min.–max.)	50 (29–73)	–
Gender		
Female	14/14	100
Histopathology		
Papillary	8/14	58
Follicular	3/14	21
Multinodular goiter	3/14	21
Surgery		
First operation (subtotal/total thyroidectomy)	14/14	100
Completion total thyroidectomy	14/14	100
Time interval (month) (between first and second operations)		
Mean ± SD	7.0 ± 8.5	–
Median (min.–max.)	4 (3–36)	–
^{131}I therapy		
After the first operation	1/14	7
After the completion thyroidectomy	10/14	71

SD standard deviation

Preoperative examinations

All patients were evaluated routinely with some exams before the completion thyroid surgery. A ^{99m}Tc-pertechnetate-thyroid scintigraphy (TS) and a neck ultrasonography (USG) were done to show residual thyroid tissues and loco-regional lymph node involvements as well as free three iodothyronine (FT3), free thyroxin (FT4) and TSH concentrations were measured on the hypothyroid state (L-thyroxin off, 4 weeks) before the operation.

Gamma probe-guided surgery

A completion total thyroidectomy was performed with a guidance hand-held GP in all patients. Five minutes prior to the starting of surgical incision, 185 MBq (5 mCi) of ^{99m}Tc-pertechnetate was injected through a peripheral intravenous line. After neck was dissected, strap muscles activity was measured first by GP to define the background counts. Then, intraoperative GP counts were obtained to detect hot spots indicated that residual thyroid tissues in thyroid regions before and after resection. These regions were right thyroid lobe, left thyroid lobe and pyramidal lobe in accordance with the thyroid remnant localizations. As an intraoperative GP count rate was meaningfully higher than a background count rate, we marked this focus as a hot spot. The highest count rates were noted during the operation. All hot spots removed surgically. Finally, the GP counts were

repeated on the same regions after the resection to check whether detected remnants removed successfully or not.

Measuring unit (count rate) is count per second/second (cps/s). Each count was collected with 10-s intervals in rate-meter mode with linear scale. The counts on the submandibular and submental salivary glands were evaluated attentively. Probe direction was kept away from these areas to avoid from possible false-positive results.

Same commercial hand-held gamma probe (Europrobe, Eurorad, France) was used in all operations. Technical characteristics of this probe were as follows: linear-collimated probe equipped with a cadmium telluride detector, 11 mm external diameter of probe head, 20–170 keV energy range, >60% detecting efficiency and 140 keV photopeak energy for the ^{99m}Tc.

Postoperative examinations

FT3, FT4, TSH concentrations were measured again in all patient's sera on the postoperative third week. Postoperative and preoperative TSH values were compared with each other to check successful resection of the functioning thyroid remnants. All cases were evaluated with postoperative TS 4 week after the operation. Histopathologic examination was carried out on all resection materials to verify whether they were thyroid remnants or not.

Radioiodine therapy

None of the patients with DTC received the radioiodine ablation after the first operation except one; this patient received 3.7 GBq (100 mCi) dose of ^{131}I. After the completion total thyroidectomy, ^{131}I therapy was planned for 10 DTC patients. L-Thyroxin was stopped 4 weeks before the therapy. Low-iodine diet was applied in all patients for 4–6 weeks. Each patient was given with a high fixed ablative dose of ^{131}I [range 2.78–4.63 GBq (75–125 mCi)]. TSH levels were higher at least 50 ng/ml before radioiodine therapy.

Follow-up of complications

The patient was followed according to clinical status, findings and biochemical test results. Permanent recurrent laryngeal nerve injury and hypocalcaemia has not developed in any patients during 3 weeks follow-up period after the surgery.

Statistical analysis

Shapiro Wilk test was performed to test the data appear to follow a normal distribution. Continuous and categorical data were described as the median (minimum–maximum) and percentage if data no appear to follow a normal distribution, but the mean ± standard deviation if data appear to follow a normal distribution. An exchange ratio calculation formula [(thyroid lobe region counts − background counts)/background counts × 100)] was used to standardize the GP counts obtained from thyroid lobe regions according to their background counts for measurements before and after the resection. Wilcoxon matched pairs test (non-parametric test) was used to calculate the difference between each set of pairs. Statistical analyses were carried out using the SPSS software package, version 11.5.0, SPSS Inc. (Chicago, IL, USA). The p values less than 0.05 were considered to be statistically significant changes.

Results

Thyroid remnants were verified with the preoperative TSH values, neck ultrasonography and TS in all patients. Preoperative TSH level was less than a 30 mIU/mL (mean 21 ± 7) on the hypothyroid state. None of patients had pathologic lymph node involvement, but 13/14 patients had residual thyroid tissues in the neck area on the preoperative neck USG. Functioning thyroid remnants were shown in 13/14 patients on the preoperative TS. The remainder thyroid tissues were diagnosed by the neck USG in one, but by the TS in other one.

When GP counts of the thyroid regions standardized to background counts were evaluated statistically, we found that percentage median (minimum–maximum) values were 220.90% (56.00–411.11%) in left thyroid lobe region, 80.43% (11.54–471.05%) in right thyroid lobe region and 66.60% (−3.33 to 158.33%) in pyramidal thyroid lobe region for the counts obtained before resection, on the other hand, 15.96% (−20.55 to 47.62%) in left thyroid lobe region, 17.59% (−15.07 to 38.46%) in right thyroid lobe region and 17.59% (−1.96 to 57.14%) in pyramidal thyroid lobe region for the counts obtained after resection. There were statistically significant differences between these values calculated in time before and after removal of the remnants for the left thyroid lobe region ($p = 0.001$), the right thyroid lobe region ($p = 0.001$) and pyramidal thyroid lobe region ($p = 0.008$) (Fig. 1, Table 2).

Residual thyroid tissues were not observed in postoperative TS in all patients except two; bilateral small two foci were seen in one of them and unilateral focus (on the right lobe localization) was seen in other patient. These bilateral foci could not be found by the GP counts. The unilateral focus was detected on the right lobe via GP, but surgeon shown that it was belonging to the recurrent laryngeal nerve invasion and it could not be removed surgically. Postoperative TSH level was higher than a 30 mIU/ml (mean 69 ± 26) in all patients. There was statistically

significant difference ($p < 0.001$) between preoperative and postoperative TSH values (Table 3). Histopathologic confirmation revealed that all removed materials were the thyroid tissues.

Discussion

Although the differentiated thyroid carcinomas are the most frequent malignant endocrine tumors, they generally have good prognosis with related to biologic behavior of the tumor and good management of the patients. Today, incidental thyroid micro-metastases (occult disease) are more frequently diagnosed because of advanced diagnostic strategies and its widespread usage. Total and near total thyroidectomy with radioiodine ablation are recommended as initial treatment strategy if the primary tumor is 1 cm or more in diameter or extra-thyroidal extension or distant metastases are present. After this aggressive initial approach, higher rates of cure and lower rates of loco-regional recurrence and mortality are achieved in majority of patients. A subtotal thyroidectomy (unilateral lobectomy and isthmectomy) can be selected by an experienced thyroid surgeon to minimize the postoperative risks such as permanent hypoparathyroidism and recurrent laryngeal nerve injury, when the tumor is occult (1 cm or less in diameter) and confined to one lobe [8, 9].

Usually, the extent of gland resection in thyroid surgery is less than complete if preoperative conventional techniques do not allow making a decision regarding whether a nodule is a benign or not. Therefore, when a nodule is found the malignant at histopathologic exam after first operation, effective completion total thyroidectomy can warrant making subsequent efficient radioiodine therapy as well as an exact evaluation and monitoring of the patients in follow-up period. Good resection of the functioning thyroid remnants is an important requirement. As it eliminates possible occult contra-lateral disease and facilitates ^{131}I treatment for the remainder or metastatic thyroid tissues.

A revision thyroidectomy should be considered in selected patients with inadequate surgery. Some investigators recommend that surgeons should not deter doing a completion thyroidectomy due to fear of increased morbidity after the procedure, especially in a specialist thyroid surgery center. However, the detection and exact removal of these tissues during the revision might be ineffective and/or stressful due to disintegrated anatomy, presence of fibrotic and scatriciel tissues, minimal tissue volume and complication risks.

The usage of radio-guided surgery concept is becoming widespread after great successful on the sentinel lymph node detection in patients with breast cancer and

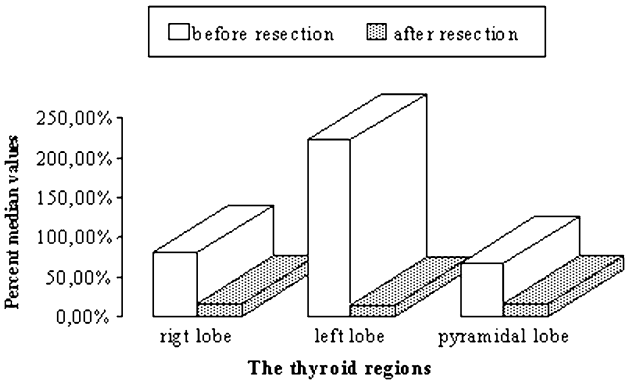

Fig. 1 The comparison of the percent median values calculated for right lobe, left lobe and pyramidal lobe of the thyroid gland in time before and after resection of the thyroid remnants

Table 3 Preoperative and postoperative TSH values (mIU/ml)

Values	Preoperative TSH level	Postoperative TSH level
Mean ± SD	21 ± 7	69 ± 26
p	<0.001	

SD standard deviation

Table 2 The percentage median (min.–max.) values of the right thyroid, left thyroid and pyramidal tyroid lobe's GP counts standardized to background counts and statistical difference (*p* value) between these values in time before and after excision of lesions

Values	Regions					
	BG_b–LTL_b	BG_a–LTL_a	BG_b–RTL_b	BG_a–RTL_a	BG_b–PTL_b	BG_a–PTL_a
Median (%)	220.90	15.96	80.43	17.59	66.60	17.59
Minimum (%)	56.00	−20.55	11.54	−15.07	−3.33	−1.96
Maximum (%)	411.11	47.62	471.05	38.46	158.33	57.14
p	0.001		0.001		0.008	

BG_b background before resection, *BGa* background after resection, LTL_b left thyroid lobe before resection, *LTLa* left thyroid lobe after resection, RTL_b right thyroid lobe before resection, RTL_a right thyroid lobe after resection, PTL_b pyramidal thyroid lobe before resection, PTL_a pyramidal thyroid lobe after resection

melanoma. Intraoperative GP-guided thyroid surgery is one of the new investigated clinical applications [1].

Various tumor-seeking radiopharmaceuticals were tried for radio-guided thyroid surgery. Iodine radiopharmaceuticals were frequently preferred for follicle cell-derived papillary and follicular thyroid carcinomas. Iodine accumulates in thyroid cells by the specific localization mechanism. ^{131}I and ^{125}I have inappropriate long half-life (approximately 8 and 60 days, respectively) for optimization of target/background ratio and necessity of flexible operating room scheduling. ^{131}I emits high-energy gamma photon (364 keV) and non-diagnostic beta radiation. ^{123}I is more feasible than other iodine radiopharmaceuticals with 159 keV gamma photon energy and moderate half-life (13 h) for gamma probe detection. The technetium radiopharmaceuticals are the most important agents for nuclear medicine studies. The ^{99m}Tc-pertechnetate is used for routine thyroid scintigraphy in many centers and it trapped by non-specific localization mechanism in thyroid cell [6]. The ^{99m}Tc has favorable features to thyroid imaging with 140 keV gamma photon emission and 6 h half-life. It is easy accessible with low cost price and flexible scheduling by the generator system worldwide. As ^{99m}Tc-pertechnetate is compared with ^{123}I-iodine to mark the thyroid tissues, both of them are suitable in same degree for gamma probe detection with low radiation exposure dose in the operating room, but ^{99m}Tc-pertechnetate is more cost-effective and easy available whenever is needed.

A re-operative thyroidectomy may be associated with a high incidence of complication such as the recurrent laryngeal nerve injury in several problematic conditions (2, 4 and 7). GP-guided surgery technique can be helpful to overcome following difficulties during the revision thyroidectomy. Importance of small thyroid remnants into or around some disintegrated structures can be decided quantitatively by the intraoperative GP. Gamma probe counts can differ accurately the functioning thyroid tissues from fibrotic and scatriciel tissues [4–8]. Therefore, safe dissection can be succeeded in many times when unnecessary resection around the recurrent laryngeal nerve is avoided. In our study, intraoperative GP guidance determined successfully the functioning thyroid remnants in 13 out of 14 cases. When standardized percent median values before resection were compared with after resection, we found that there were statistically significant difference between the values before and after the resection in left, right and pyramidal thyroid lobe regions ($p = 0.001$, 0.001 and $p = 0.008$, respectively). In addition, there was statistically significant difference between preoperative and postoperative TSH values ($p < 0.001$) and the excision materials were confirmed as the thyroid tissues by the histopathologic exam. These findings approved to that resection were successful. GP failed to detect functioning thyroid remnants in only one patient who were bilateral small two foci were seen on the postoperative TS. GP detected intraoperative the unilateral focus localized right thyroid lobe was shown on the postoperative TS, but it could not be removed by surgeon because of its recurrent laryngeal nerve invasion. Nevertheless, GP achieved to detect the remnants in 13 of 14 cases. Vocal cord palsy has not developed in any patients during 3 weeks follow-up period after the surgery. In other words, safe thyroid surgery could be accomplished with aid of gamma probe guidance nearby recurrent laryngeal nerve.

Although, radio-guided thyroid surgery was performed successfully and any complication did not occur in our study group, but it did not include a series of patients without gamma probe guidance and real complication ratio could not clearly evaluated in small group of the patients. Cumulative information in the literature is still not enough. The experience to date is focused on metastatic lymph node detection in recurrent DTC [1–5]. We found only one study in the review of the literature interested in removal thyroid remnants, including a small group of patients [10]. They reported that intraoperative gamma probe application might be to the patient's benefit in revision thyroidectomy rather than conventional approach. We think that the further succession and practicability of this guided technique presented on the completion total thyroidectomy should be tried in other studies with larger series.

Conclusion

As a result, the findings based on gamma probe counts, thyroid stimulating hormone level, thyroid scintigraphy and histopathologic examination showed that the gamma probe-guided completion total thyroidectomy with ^{99m}Tc-pertechnetate seemed to be a good option and easy available method to detect and remove the functional thyroid remnants in patients with DTC and recurrent goiter.

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