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Does Levothyroxine Administration Impact Parathyroid Localization?

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Abstract

Background—Proper localization is crucial in performing minimally invasive parathyroidectomy for primary hyperparathyroidism (PHPT). Ultrasonography (US) and Tc-99m sestamibi (MIBI) scintigraphy are common methods used for localization. As the appearance and activity of the thyroid gland may impact parathyroid localization, the purpose of this study was to determine how exogenous use of the thyroid hormone, levothyroxine (LT), affects parathyroid localization.

Methods—Adult patients with non-familial PHPT who underwent initial parathyroidectomy from 2000 to 2014 were retrospectively identified. Levothyroxine (+LT) and non-levothyroxine (-LT) patients were matched 1:3 based on age, gender, goiter status, and preoperative parathyroid hormone levels. Subgroup analysis was performed on patients previously treated with radioactive iodine and patients undergoing single adenoma resection.

Results—Of the 1,737 patients that met inclusion criteria, 286 were on LT at the time of their parathyroid localization scan. Use of LT not did impact the percentage of correct MIBI localization scans when compared to −LT patients (p=0.83). Interestingly, use of LT significantly hindered localization by US in comparison to the −LT group (48.4 vs 62.2%, p<0.01). When examining only patients where a single upper gland was removed, the +LT group was less likely to have a correct US compared to the −LT group (50 vs. 72.8%, p<0.01). However, there was no difference in US accuracy for patients who only had a single lower gland removed (p=0.51).

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Conclusions—Exogenous levothyroxine is associated with impaired parathyroid localization with US but not MIBI. Surgeons should be aware of localization efficiency for this subset of patients in the era of personalized medicine and cost effectiveness.

Keywords

Keywords: primary hyperparathyroidism; preoperative localization; levothyroxine; ultrasound; sestamibi scintigraphy

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by over-secreting parathyroid glands which affects approximately 1% of the population. Surgery is the only curative treatment for PHPT with success rates of 95% in the hands of an experienced endocrine surgeon (1-3). While the traditional surgical approach was a bilateral neck exploration with subsequent identification of all four parathyroid glands, imaging techniques and intraoperative parathyroid hormone (PTH) monitoring have now allowed surgeons to offer a unilateral, minimally invasive parathyroidectomy. The key to a minimally invasive approach is proper localization of the parathyroid glands prior to surgery (4-6).

Two common methods of localization include ultrasonography (US) of the anterior neck and Tc-99m sestamibi (MIBI) scintigraphy. MIBI is a lipophilic monovalent cation that has an increased uptake in epithelial cells rich in mitochondria, such as parathyroid adenomas. However, MIBI retention is not specific to the parathyroids and uptake is observed in mitochondrial rich thyroid tissue, especially in the case of hypermetabolic thyroid nodules (7). Therefore the metabolic activity of the thyroid and its uptake of MIBI affect parathyroid localization. Furthermore, thyroid gland size and echotexture affects US localization of the parathyroids (8).

Conditions which alter thyroid appearance and activity, such as hypothyroidism, may impact parathyroid localization. The most common cause of hypothyroidism is the autoimmune disease, Hashimoto's thyroiditis, which destroys thyroid follicles and gives the thyroid a nodular, stippled appearance on US. Hypothyroid patients require exogenous use of the thyroid hormone, levothyroxine (LT), to maintain a euthyroid state. However, LT inhibits the patient's natural thyroid activity. Therefore, we hypothesized that compared to patients not taking LT, PHPT patients who are on LT may have improved MIBI localization due to diminished thyroid uptake but impaired US localization from an abnormal thyroid echotexture. As the impact of hypothyroidism and thyroid hormone on MIBI and US localization has not been well-studied, the purpose of this research was to determine LT's effect on parathyroid localization.

Methods

We performed a retrospective review of a prospectively collected database of patients who underwent parathyroidectomy at the University of Wisconsin Hospital between 2000 to May 2014. Included in the study were adults patients with PHPT who underwent an initial parathyroid operation. Familial disease, secondary, tertiary or re-operative cases were excluded. Additionally we excluded patients who underwent a concurrent thyroid operation. Lastly, due to lithium's association with hyperparathyroidism, patients with prior lithium exposure were not included in the study. Patients were stratified into two groups, patients on levothyroxine (+LT) and patients not on levothyroxine (-LT). Because −LT patients far outnumbered +LT patients, +LT patients were matched 1:3 to −LT patients based on age, gender, presence of goiter, and baseline parathyroid hormone (PTH) levels.

Preoperative patient characteristics and clinical parameters were recorded. Additionally, parathyroid operation findings were contrasted. Finally, number and correctness of MIBI and US parathyroid localization studies were evaluated. US was performed by the operating endocrine surgeon. Additionally, interpretation of the MIBI scan preoperatively was confirmed by the surgeon. A MIBI scan was considered correct if the gland removed was on the same side as the gland identified by MIBI. A US was defined as correct if the gland removed was the same gland (laterality and upper vs. lower) identified on US. A negative MIBI or US was correct only if the patient was found to have hyperplasia (three or more enlarged glands).

At our institution, parathyroidectomies are performed using intraoperative PTH testing. A 50% decline in PTH from the peak PTH level measured at 5, 10 or 15 minutes post-excision is required. Additionally, gamma probe radiation counts are utilized which include background counts read at the thyroid isthmus and ex-vivo counts read outside the body. A % of background value, defined as ex-vivo/background count, is calculated with a ratio above 20% indicating an abnormal parathyroid has been removed (9).

Subgroup analysis was conducted on patients who had previous radioactive iodine (RAI) and on patients who had a single adenoma removed, including further analysis comparing upper and lower single adenoma patients. Subset analysis was also performed on +LT patients to determine the effect of a LT dose equal to or greater than 100 mcg. Gamma probe radiation counts were obtained for subset analysis.

The data were analyzed using SPSS statistical software (IBM Corp 2013, Armonk, NY). Continuous variables were compared using Student t-tests or Wilcoxon rank sum tests where appropriate. Categorical variables were compared using Chi-squared tests or Fischer's exact tests where appropriate. P value < 0.05 was considered significant.

Results

Patient Characteristics and Operative Findings

From January 2000 to May 2014, 1,737 patients underwent parathyroidectomy meeting inclusion criteria for this study. Of these patients, 286 were on LT (+LT) at the time of their localization study and were matched to 858 patients not on LT (-LT). Patients in the +LT and −LT group had no significant differences in terms of demographics, co-morbidities, and disease features (Table 1). −LT patients had more thyroid nodules than patients on LT (20.3% vs 14.0%, $p = 0.02$). No difference was found between the +LT and −LT patients in terms of operative findings (Table 2).

Localization Accuracy

A similar number of patients had a MIBI scan or US performed in each group (Table 3). The percentage of correct MIBI scans was not significantly different between the +LT and −LT patients (64.3% vs 65.0%, p = 0.82, Table 3). +LT patients had a significantly lower percentage of correct US studies compared to patients not on LT (48.4% vs 62.2%, p < 0.01, Table 3).

Radioactive Iodine Subgroup Analysis

Next, we performed subset analysis for patients on LT due to previous radioactive iodine therapy. 31 patients with previous RAI treatment on LT were matched to 93 −LT patients. Patient demographics, pre-operative clinical parameters, and parathyroid operation and characteristics were all comparable for these two groups of patients. Only 63.3% of the +LT patient MIBI scans and 69.2% of the −LT patient MIBI scans were correct (p = 0.55). +LT post-RAI patients had less US scans than patients not on LT (29.0% vs 49.5%, p = 0.05). Patients with previous RAI treatment also had a lower percent of correct US studies than −LT patients (22.2% vs 67.4%, p = 0.02).

Single Adenoma Subgroup Analysis

Out of the 286 +LT patients, 209 (73.1%) had a single adenoma resected. 107 patients had an upper adenoma and 102 patients had a lower adenoma. Of the 858 patients not on LT, 671 (78.2%) had a single adenoma removed with 320 of these with upper adenomas, 348 with lower adenomas, and 3 patients without the position of the removed gland recorded. Clinical parameters and pre-operative lab values were similar between the +LT single adenoma and −LT single adenoma patients. +LT single adenoma patients had a higher resected parathyroid gland weight than −LT single adenoma patients but this was not found to be significant (744.8 vs 627.8 mg, p = 0.12).

Single adenoma patients had a similar number of MIBI and US scans performed (Table 4). +LT single adenoma patients had a comparable percentage of correct MIBI scans to −LT single adenoma patients (p =0.31, Table 4). However, +LT single adenoma patients had a lower percentage of correct US studies than −LT single adenoma patients (56.7% vs 71.8%, p <0.01, Table 4). In the patients with incorrect US studies, +LT single adenoma patients had resected adenoma gland weights that were not significantly different than −LT single adenoma patients (684.8 vs 482.7 mg, p = 0.12). Hence, US did not simply miss smaller glands in +LT patients.

We then did a subset analysis looking at whether there was difference in localization based on the gland position. Looking only at the +LT single adenoma patients with an upper gland adenoma, we found no difference in the percentage of correct MIBI scans compared to −LT upper adenoma patients (p = 0.48). +LT upper adenoma patients had a significantly lower percentage of correct US studies in contrast to −LT upper adenoma patients (50.0% vs 72.8%, p < 0.01, Figure 1). Next we looked at only the patients with a lower adenoma removed. Interestingly, in the patients with a lower adenoma removed there was a similar percentage of correct MIBI scans compared to −LT lower adenoma patients (p = 0.52) as well as a similar percentage of correct US studies (65.0% vs 70.5%, p = 0.51, Figure 1).

Dosage of LT

Since the dosage of LT may impact the amount of MIBI uptake, we also analyzed our results by dividing patients into high or low dose LT. Patients on a LT dose greater than or equal to 100 mcg (+LT high dose) were compared to patients on a LT dose less than 100 mcg (+LT low dose). There were 147 +LT high dose patients and 124 +LT low dose patients. 19 patients did not have doses listed in their charts and 15 patients who were on Armour Thyroid Tablets were excluded. The two groups had similar MIBI and US localization accuracy results ($p = 0.41$ and $p = 0.26$).

Gamma Probe Counts

Gamma probe radiation counts were similar for the overall +LT and −LT group ($p = 0.27$). +LT high dose patients had similar ex-vivo counts ($p = 0.99$) but lower background counts compared to +LT low dose patients (178.4 vs 223.2, $p < 0.001$).

Discussion

This study compared the accuracy of MIBI and US parathyroid localization techniques for PHPT patients taking exogenous thyroid hormone to those without supplementation. Correct localization is crucial for a successful unilateral minimally invasive procedure which has been shown to have lower costs, shorter hospital stays, fewer complications, and a quicker recovery time (1,11-14). Contrary to our original hypothesis, patients on LT did not have superior MIBI localization compared to those not on LT, regardless of the dose. However, patients on LT are less likely to correctly localize using US. The finding that only US localization of an upper single adenoma was hindered suggests that this relates to the thyroid's echotexture in patients on LT more so than a direct interference of the medication. A large majority of the patient population on LT in this study had Hashimoto's thyroiditis which likely interferes with localization of the posteriorly located upper parathyroid glands. The lower parathyroid glands are situated inferiorly and more superficial where there is possibly less diseased hypothyroid tissue present to hinder the US. Alternatively, patients with Hashimoto's thyroiditis may present with enlarged lymph nodes in the level VI compartment which may make US localization of the parathyroid glands more difficult although for our hypothroid patient population lymphadenopathy was not a common finding on preoperative physical exam.

One concern is the size of the parathyroid gland at clinical presentation influencing the US results. A couple factors could contribute to +LT patients having smaller and thus more difficult to find adenomas on US imaging. First, patients on LT may be more likely to have parathyroid function tests as they are monitored by endocrinologists who may detect parathyroid disease earlier than it may have been otherwise. Second, patients requiring treatment with LT often require higher than normal free T4 to maintain a euthyroid thyroid stimulating hormone (TSH) level. This higher than normal T4 may elevate calcium levels earlier in the disease and so patients on LT may be diagnosed when they have a smaller gland size. However, we found that +LT patients did not have significantly smaller weighing glands, which was used as a surrogate for gland size, than −LT patients. This suggests gland weight and/or size are not the only factors influencing US accuracy in these patients.

Although this study hypothesized that LT would improve MIBI localization, the data suggests that LT had no impact using this method of localization. The assumption was LT would inhibit the thyroid's natural metabolic activity thus allowing greater uptake in the parathyroid's for improved visualization. Upon further analysis of gamma probe radiation counts, patients on LT had a similar % of background gamma probe count compared to non-LT patients which questioned the assumption that patients on LT had decreased thyroid activity. If the thyroid is not significantly inhibited by LT, this may be why LT use does not affect MIBI uptake and subsequent parathyroid localization. On the contrary, dosage analysis revealed patients on a dose of LT 100 mcg or greater did have the expected lower background gamma probe counts and higher % of background. However, these patients had analogous MIBI localization results compared to patients on a lower dose of LT. Therefore, thyroid inhibition may not be sufficient enough to cause improved localization using MIBI as originally hypothesized. In fact, even patients with previous RAI treatment who had presumably little to no thyroid tissue and no thyroid function present did not have improved MIBI localization.

Although this is one of the first studies to focus on the impact of LT on parathyroid localization accuracy, numerous studies have investigated the impact of other factors that contribute to localization sensitivity. In a study on the factors affecting MIBI localization, Kannan et al. found that higher serum calcium and serum PTH levels were associated with a higher likelihood of a positive scan (5). For this reason, we used preoperative PTH values as one criteria to match +LT and −LT patients. Presence of a multinodular goiter was found to hinder US localization (15) and presence of thyroid nodules has been identified as a factor which limits US and MIBI sensitivity (16, 17). The presence of a goiter was accounted for in this study. However, the −LT group had more thyroid nodules than the +LT group even though one would expect the +LT group to have more nodules due to the fibrosis and nodularity associated with Hashimoto's thyroiditis (18, 19).

Finally, although few studies have documented adenoma location as a significant contributing factor to US localization, conventional wisdom tells us that anatomic differences in superior and inferior glands do affect US results. Upper glands are generally more posterior and closer to the transesophageal groove where air from the digestive tree may prevent US resolution. Lower glands are generally located more anteriorly and can be shielded by the clavical or sternum. Upper versus lower adenoma US localization in our single adenoma control population was not significantly different but these anatomic influences should not be forgotten. Parathyroid gland size and BMI are other factors found to influence imaging studies that were not directly accounted for in this study (20, 21).

Outside of these factors, localization accuracy is improved if an imaging study is read by an experienced surgeon as opposed to a nuclear medicine reading alone (22). Zia et al. found similar results with a higher likelihood of successful MIBI localization if the scan is read by the operating surgeon (23). This study presented here used the surgeon's interpretation of the localization results to determine accuracy.

Although LT supplementation did not affect MIBI localization in this study, possibly due to lack of significant thyroid inhibition, other researchers have found that thyroid suppression can improve MIBI localization in initially non-localizing imaging studies (24). Gomez-Ramirez et al. found similar thyroid suppression with thyroxine prior to imaging can positively impact MIBI sensitivity (25). However, transient high dose LT use is different from the long term LT use investigated in our study.

Controversy exists over which localization method is best and what the most cost effective imaging strategy is (26-33). The results of this study suggest MIBI is the best imaging modality for patients with hypothyroidism taking LT, especially if an upper adenoma is suspected. Furthermore, this study may be helpful for the surgeon to develop a successful surgical strategy in the era of personalized medicine and cost effectiveness.

This study is limited by its retrospective nature. Additionally, the patient population studied was a hetergenous group, but matching was utilized to account for differences. Furthermore, subgroup analysis based on etiology of the disease did not reveal any important differences. While our dataset did not contain exact measurements of the thyroid gland, presence of a goiter as indicated by the operating surgeon was used as an estimate of an enlarged thyroid. In addition to supplementation, this patient population likely has a heterogeneous spread of thyroid function which could be made homogenous by matching of the LT and TSH levels; however, we tried to differentiate between full replacement (at least 100 mcg) versus lower supplemental doses, and found no differences in localization.

In conclusion, this study found that exogenous levothyroxine is associated with impaired US localization but has no effect on MIBI localization. This effect may be due to the thyroid's echotexture in these hypothyroid patients which limits the ability of US to detect posteriorly located upper glands. Therefore MIBI localization may be superior for hypothyroid patients, especially in the case of upper adenomas. Surgeons may use this data in order to minimize unnecessary and less effective tests for this subset of patients taking levothyroxine.

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	% correct MIBI all patients
+LT	64.3
-LT	65

	% correct US all patients
+LT	48.4
-LT	62.2

	% correct US for SA patients
+LT	50
-LT	72.8
+LT	65
-LT	70.5

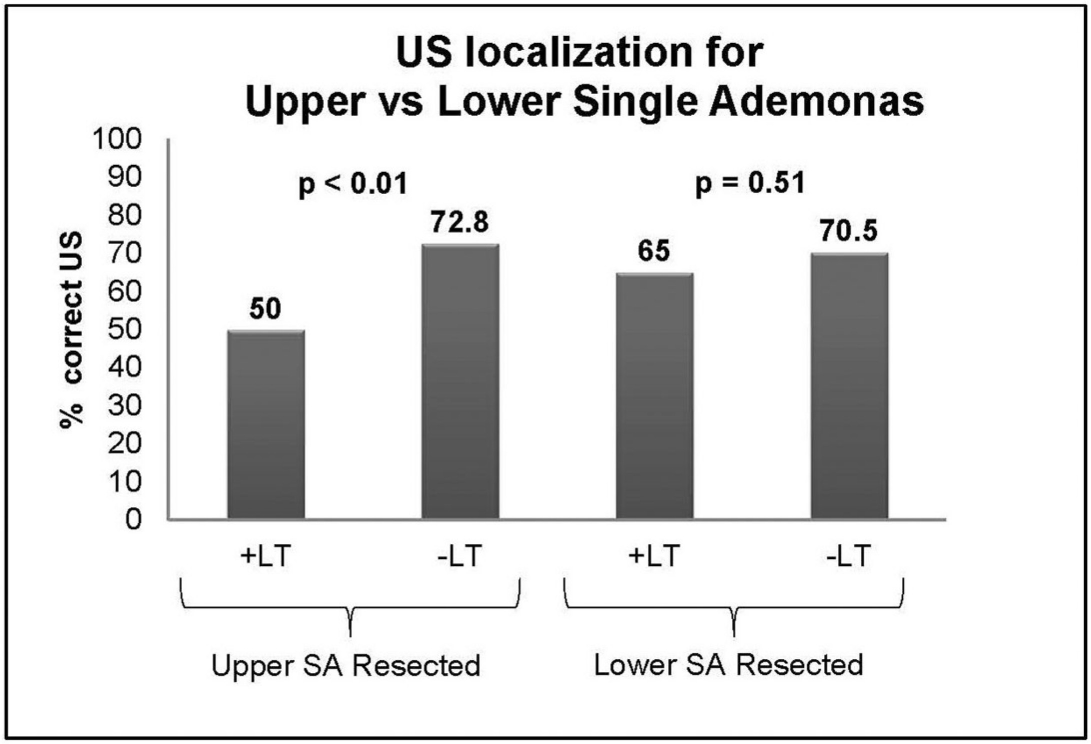

Figure 1. Impact of Levothyroxine on Ultrasound Localization for Patients Undergoing Single Adenoma Resection

Bar graphs show the percentage of correct ultrasound (US) localization studies for patients on levothyroxine (+LT) and patients not on levothyroxine (-LT). SA = single adenoma.

Table 1

Patient Characteristics and Disease Features

Variable	Patients on levothyroxine (n = 286)	Patients not on levothyroxine (n = 858)	P-Value
Age (years)	64.2 ± 0.4	63.9 ± 0.7	0.71
Gender			0.95
Female	261 (91.3%)	782 (91.1%)	---
BMI (kg/m^2)	31.4 ± 0.3	30.6 ± 0.5 (n = 854)	0.10
Co-Morbidities			0.99
CAD	28 (9.8%)	85 (9.9%)	---
DM	35 (12.2%)	101 (11.8%)	---
Baseline Lab Values			---
PTH (pg/mL)	113.2 ± 3.8	111.7 ± 2.1	0.90
Ca (mg/dL)	10.80 ± 0.04	10.85 ± 0.02	0.12
Phos (mg/dL)	2.97 ± 0.04 (n = 200)	3.11 ± 0.09 (n = 547)	0.76
D-25-OH (ng/dL)	32.56 ± 0.97 (n = 208)	31.96 ± 0.57 (n = 621)	0.54
Creat (mg/dL)	1.33 ± 0.32 (n = 249)	0.97 ± 0.02 (n = 757)	0.37
Alk Phos (U/L)	93.72 ± 3.28 (n= 179)	95.46 ± 1.53 (n = 509)	0.28
Urine Ca (mg/24 hrs)	272.2 ± 12.4 (n= 123)	297.6 ± 7.6 (n = 371)	0.13
Bone Density Score	-2.02 ± 0.10 (n=134)	-2.11 ± 0.07 (n = 480)	0.73
Goiter	18 (6.3%)	55 (6.4%)	0.96
Presence of Kidney Stones	38 (13.3%)	107 (12.5%)	0.72

Data are represented as the number with the percentage in parentheses for categorical data and the mean ± the standard error of the mean for continuous variables.

BMI = body mass index, CAD = coronary artery disease, DM = diabetes mellitus

PTH = parathyroid hormone, Ca = blood calcium, Phos = phosphate, D-25-OH = Vitamin D, Creat = creatinine, Alk Phos = alkaline phosphatase, Urine Ca = urine calcium

Table 2

Comparison of Operative Findings

Variable	Patients on levothyroxine (n = 286)	Patients not on levothyroxine (n = 858)	P-Value
Parathyroid Operation			0.11
Unilateral	176 (61.5%)	573 (66.8%)	---
Bilateral	110 (38.5%)	285 (33.2%)	---
Etiology			0.15
SA	209 (73.1%)	669 (78.0%)	---
DA	35 (12.2%)	74 (8.6%)	---
H	42 (14.7%)	115 (13.4%)	---
Gland Removed			0.13
Upper	113 (39.5%)	340 (39.7%)	---
Lower	107 (37.4%)	362 (42.3%)	---
Multiple	66 (23.1%)	154 (18.0%)	---
Cure	281 (98.3%)	835 (97.3%)	0.38

Data are represented as the number with the percentage in parentheses

SA = single adenoma, DA = double adenomas, H = hyperplasia (three or more adenomas)

Upper = right upper and/or left upper parathyroid gland

Lower = right lower and/or left lower parathyroid gland

Table 3
Impact of Levothyroxine on MIBI and US localization

Variable	Patients on levothyroxine (n = 286)	Patients not on levothyroxine (n = 858)	P-Value
MIBI localization			
# of MIBI scans	277 (96.9%)	825 (96.2%)	0.59
# of correct MIBI scans	178 (64.3%)	537 (65.0%)	0.82
US localization			
# of US	122 (42.7%)	392 (45.7%)	0.37
# of correct US	59 (48.4%)	244 (62.2%)	<0.01

Data are represented as the number with the percentage in parentheses

MIBI = Tc-99m sestamibi scintigraphy, US = ultrasonography

Table 4
Impact of Levothyroxine on MIBI on and US localization of Single Adenomas

Variable	SA patients on levothyroxine (n = 209)	SA patients not on levothyroxine (n = 671)	P-Value
MIBI localization			
# of MIBI scans	202 (96.7%)	647 (96.4%)	0.88
# of correct MIBI scans	163 (80.7%)	500 (77.3%)	0.31
US localization			
# of US	90 (43.1%)	297 (44.3%)	0.76
# of correct US	51 (56.7%)	214 (71.8%)	<0.01

Data are represented as the number with the percentage in parentheses for categorical data.

MIBI = Tc-99m sestamibi scintigraphy, US = ultrasonography, SA = single adenoma