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Utility of Thyroglobulin Measurements Following Prophylactic Thyroidectomy in Patients with Hereditary Medullary Thyroid Cancer

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Abstract

Introduction—Prophylactic thyroidectomy can be curative for patients with hereditary medullary thyroid cancer (MTC) caused by RET proto-oncogene mutations. Calcitonin is a sensitive tumor marker used to follow patients. We suggest that thyroglobulin (Tg) levels should also be monitored postoperatively in these patients.

Methods—We reviewed patients with RET mutations who underwent prophylactic thyroidectomy between 1981 and 2011 at an academic endocrine surgery center. Patients were excluded if they had no postoperative Tg levels.

Results—Of the 22 patients who underwent prophylactic thyroidectomy, 14 were included in final analysis. The average age at thyroidectomy was 9.8 years (range 4 to 29). Tg levels were detectable 1.5 months to 31 years postoperatively in 11 patients (79%), all of whom were younger than 15 years-old at thyroidectomy. Median TSH was 2.5 mIU/L and 13.4 mIU/L in patients with undetectable and detectable Tg, respectively. Of those with detectable Tg, five had neck ultrasounds: Two showed no residual tissue in the thyroid bed, and three showed remnant thyroid tissue.

Conclusions—Tg levels can identify patients with remnant thyroid tissue after prophylactic thyroidectomy. Ultrasound can determine if thyroid tissue remains posterolaterally and is at risk of MTC recurrence. Maintaining normal TSH may prevent growth of remaining thyroid follicular cells.

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INTRODUCTION

Prophylactic total thyroidectomy can be curative treatment for patients at risk of developing medullary thyroid cancer (MTC) due to mutations in the RET proto-oncogene. MTC has an early and high penetrance in hereditary syndromes caused by RET mutations, including Multiple Endocrine Neoplasia (MEN) type 2A or type 2B and familial MTC (FMTC), and progresses to regional lymph node and then distant metastases if untreated[1]. MTC is derived from parafollicular C cells that migrate from the neural crest into the developing thyroid gland during fetal development and are responsible for the production of calcitonin. MEN2A, MEN2B, and FMTC patients who undergo prophylactic thyroidectomy are followed with serial calcitonin levels postoperatively to monitor for the recurrence or development of MTC. Calcitonin has been shown to be a sensitive and specific tumor marker for MTC[2].

Routine surveillance of patients with RET mutations who have undergone prophylactic thyroidectomy proceeds under the assumption that all thyroid tissue, and therefore C cells predisposed to malignant degeneration, has been surgically removed. However, there is evidence that remnant thyroid tissue is present in a sizeable subset of patients following total thyroidectomy for differentiated thyroid cancer (DTC), as documented by elevated postoperative Tg levels and positive diagnostic radioiodine uptake scans[3]. Thyroid surgeons often have to balance the risk of harm in the operating room with the prognosis of the underlying pathology, especially when it relates to preservation of the recurrent laryngeal nerve (RLN), which is responsible for vocal cord function. When surgeons encounter difficult dissection of apparently benign thyroid tissue adjacent to the RLN, they may choose to leave a small portion of the tubercle of Zuckerkandl in place to prevent injury to this nerve and subsequent vocal cord paralysis, which is associated with long-term morbidity especially in young patients. As a result, a small amount of thyroid tissue may remain posterolateraly in the tracheoesophageal (TE) groove after thyroidectomy. Patients with DTC who are at high risk for recurrence often undergo radioactive iodine (RAI) ablation to address the malignant potential of remnant thyroid follicular cells and improve postoperative surveillance[4]. However, the implications of this remnant thyroid tissue in patients with RET mutations who have undergone prophylactic thyroidectomies have not been well addressed.

Thyroglobulin (Tg) is a protein precursor of triiodthyronine and thyroxine that is produced exclusively by thyroid follicular cells, both benign and malignant. Detectable Tg levels following total thyroidectomy are indicative of remnant thyroid tissue or persistent/recurrent DTC. Tg levels are routinely obtained following total thyroidectomy for DTC, but are not generally recommended as an important surveillance test in patients with MEN2A, MEN2B, or FMTC following prophylactic thyroidectomy. Given the possibility of remnant thyroid tissue in these patients, as has been demonstrated in the general population of patients who have undergone total thyroidectomy, we propose that Tg levels may be a useful test following prophylactic thyroidectomy to help direct postoperative surveillance strategies and, potentially, further surgical or medical management.

METHODS

We performed a retrospective review of all patients who underwent prophylactic total thyroidectomy solely based on a known RET mutation at the University of California, San Francisco between 1981 and 2011. Patients were excluded from the study if they underwent a therapeutic thyroidectomy (i.e. had a known diagnosis of MTC preoperatively) or did not have available postoperative Tg levels. Patient demographic information, pathologic findings, and laboratory results, including preoperative and postoperative basal calcitonin levels as well as postoperative Tg and thyroid stimulating hormone (TSH) levels, were collected. The maximum postoperative Tg and TSH levels were used to calculate median values. Comparison between median TSH in patients with detectable and non-detectable Tg levels were made with the Wilcoxon rank-sum test with a significance level of 0.05. Findings from ultrasounds performed on patients with detectable Tg levels (>0.9 ug/L) were recorded.

RESULTS

A total of 22 patients underwent prophylactic thyroidectomy at the University of California, San Francisco during the study period. Of these patients, 14 had available postoperative Tg levels and were included in our analysis. A summary of patient characteristics, labs and ultrasound findings (if available) are presented in Table 1. Eight of the 14 patients (57%) were female and 6 out of 14 (43%) were male. RET mutations causing MEN 2A were present in twelve patients (86%), with codon 634 mutations being the most common. The other two patients had FMTC with codon 768 mutations. The average age at prophylactic thyroidectomy was 9.8 years, with a range of 4 to 29 years. Only one patient was over the age of 18 at the time of thyroidectomy. On pathologic review, benign thyroid tissue was found in 7 out of 14 (50%), C cell hyperplasia (CCH) alone in 2 out of 14 (14%), and MTC in 5 out of 14 (36%) specimens. Lymph node dissections were not performed in any patients, and none of the incidentally obtained lymph nodes were positive for MTC.

Detectable postoperative Tg levels were identified in 11 out of 14 patients (79%), all of whom were less than 15 years-old at the time of total thyroidectomy. These detectable Tg levels were observed as early as 1.5 months and as late as 31 years following thyroidectomy. The median detectable Tg level was 3.9 ug/L with a range of 1.3 to 17.8 ug/L. The median TSH level was 11 mIU/L for all patients together, and was 2.5 mIU/L in patients with undetectable Tg and 13.4 mIU/L in patients with detectable Tg (non-significant difference by Wilcoxon rank-sum test, $p = 0.10$). Postoperative Tg antibody levels and basal calcitonin levels remained undetectable throughout patient follow-up.

Of the 11 patients with detectable thyroglobulin levels, five had postoperative ultrasounds performed. Two ultrasounds showed no thyroid tissue in the thyroid bed. However, three of the ultrasounds performed identified patients with remnant thyroid tissue. One patient had thyroid tissue that was interpreted by the radiologist as likely representing a residual pyramidal lobe (2.6 cm), one patient had thyroid tissue reported in the central neck (1.2 cm) without further description of anatomic location, and one patient had residual thyroid tissue in the left posterolateral thyroid bed (1 cm). This latter patient elected to undergo

reoperation for removal of the residual thyroid tissue. The final pathologic specimen was confirmed as normal thyroid tissue and was negative for C cells or MTC based on calcitonin staining.

DISCUSSION

This study demonstrates that even in experienced hands elevated Tg levels and, therefore, remnant thyroid tissue is not uncommon following prophylactic thyroidectomy in patients with MEN 2A and FMTC. Given that two of the five patients who had detectable Tg levels and underwent imaging had no identifiable thyroid tissue on ultrasound, the remnant thyroid tissue may not always be readily identifiable. However, the overall elevated median TSH in the study patients suggests that inadequate thyroid hormone replacement and increased TSH stimulation may partially account for the large proportion of patients with detectable Tg levels.

We believe these results highlight the need for further investigation of remnant thyroid tissue following prophylactic thyroidectomy in patients with RET mutations and could have important implications on strategies for postoperative surveillance going forward. Most importantly, our study supports the use of Tg in addition to calcitonin as a component of postoperative laboratory surveillance in these patients. While calcitonin serves as a sensitive and specific tumor marker for MTC, it will only become elevated once CCH or MTC develop. Elevated postoperative Tg levels, however, would serve as an indicator that remnant thyroid tissue is present, prompting radiographic evaluation prior to the onset of pathologic changes. This information would be an additional tool with which to monitor this at-risk population, especially those patients with mutations that are associated with a high likelihood of recurrence.

The relatively high frequency of detectable Tg levels, and therefore remnant thyroid tissue, in the study patients suggests that it may be reasonable to perform at least one interval neck ultrasound following prophylactic thyroidectomy. Ultrasound is important both to determine if there is identifiable remnant thyroid tissue and, if present, to determine where the tissue is located. Autopsy studies have shown that parafollicular C cells are concentrated near the junction of the middle and upper thirds of the lateral thyroid lobes and rarely are located in the isthmus[5]. This suggests that remnant pyramidal lobe or pre-tracheal thyroid tissue is unlikely to be at risk of developing MTC, whereas remnant thyroid tissue in the posterolateral thyroid bed adjacent to the TE groove is more worrisome. This is supported by a recent review of clinico-pathologic data from 150 patients with MTC and 192 patients with solitary thyroid isthmus nodules that showed: (1) carcinoma was located in the lateral lobes for all MTC patients; (2) none of the 17 patients found to have malignant isthmus nodules had MTC; and (3) immunohistochemical staining of 50 specimens from each group with no C cells in the isthmi of either set of specimens[6]. Based on this information, it may be prudent to follow patients with residual thyroid tissue in the central neck more conservatively with serial ultrasounds in addition to calcitonin levels, whereas reoperation may be indicated in patients with posterolateral remnants adjacent to the TE groove, weighing the risks of developing MTC with potential injury to the RLNs and parathyroid glands in addition to anesthetic risk. However, further investigation is required before such

recommendations can be made. Regardless of the location of the remnant thyroid tissue, our data emphasizes that these patients will require close long-term follow-up.

Thyroid hormone suppression therapy is a mainstay of treatment in DTC, but is not generally recommended in patients with MTC because C cells are not stimulated by TSH. Thyroid hormone is therefore administered at dosages to achieve a euthyroid state following prophylactic thyroidectomy. There is evidence that TSH levels fluctuate significantly in younger patients, potentially due to physiologic changes and growth in addition to medication compliance[7]. Our data support this. The overall high median postoperative TSH and the trend toward a higher median TSH in patients with detectable Tg levels suggests that remnant thyroid follicular cells in these patients respond to TSH stimulation with cell proliferation and greater Tg secretion, potentially resulting in larger foci of remnant thyroid tissue. Given that significant hypothyroidism has adverse effects on pediatric growth and intellectual development, surgeons and endocrinologists should reinforce the importance of hormone replacement to patients and, if applicable, their parents and caretakers.

RAI is regularly used in patients with DTC who have extra-thyroidal tumor extension, nodal or distant metastases, vascular invasion or multifocal disease[4]. However, unlike follicular cells, parafollicular C cells do not concentrate iodine. Historically RAI was considered postoperatively in patients with MTC for the theoretical “bystander effect,” which hypothesized that radioactive iodine taken up by thyroid follicular cells would prove toxic to adjacent C cells via β-ray emission. There have been some case reports and small series reporting decreased calcitonin levels in patients with known MTC treated with RAI, in addition to decreased CCH following RAI in animal studies[8-11]; however, other series have not shown an improvement in outcomes, and a survival benefit has never been demonstrated[12-15]. One recent small study of patients with documented MTC showed a decrease in postoperatively elevated basal and stimulated calcitonin levels after RAI administration in three out of seven treated patients, all of whom had no evidence of lymph node or distant metastases[10]. This led the authors to conclude that RAI may play an adjuvant role in patients with residual CCH or micro-MTC that is confined to the thyroid bed (based on the 2mm range of β-ray emission)[10]. In addition, a larger multiinstitutional study of RAI in patients with MTC from the Netherlands included a small subset of patients who underwent prophylactic thyroidectomies (n = 56), and found that none of the nine patients who received RAI developed biochemical or radiologic evidence of MTC, compared to 40% of those who underwent surgery alone. However, the univariate hazard ratio for disease-free survival in these patients was not statistically significant[15]. While it seems clear RAI should not play a role in the treatment of MTC, our findings and those described above suggest further investigation of its role as adjuvant preventative therapy following prophylactic thyroidectomy, weighing the long-term risks of adverse effects including leukemia[16].

As RET mutational testing and direct-DNA sequencing techniques have become more widely used, an increasing number of studies have been published documenting good overall outcomes in MEN2A, MEN2B, and FMTC patients following prophylactic thyroidectomy. However, no studies to our knowledge have directly addressed the detection of remnant thyroid tissue[17]. Published series with more than two years of follow-up have shown favorable cure rates ranging from 88 to 100%, especially when thyroidectomy is performed

at a young age based on a patient's specific RET mutation phenotype[7,18,19]. However, most studies report a subset of patients with persistent disease or who develop MTC on follow up. Frank-Raue et al.[7] reported long-term outcomes from 46 patients with hereditary RET mutations who underwent prophylactic thyroidectomy. This included one patient who was operated on at age 16 and found to have only CCH on pathologic exam with undetectable calcitonin immediately postoperatively, but who subsequently developed an elevated calcitonin level consistent with recurrent CCH versus MTC[7]. It is not possible to determine if this patient or any others with a hereditary RET mutation have ever developed MTC as a result of C cells left in remnant thyroid tissue, but the theoretical possibility of malignant degeneration and the frequency of elevated Tg levels warrants close follow-up.

Our findings serve as a preliminary investigation of the utility of Tg measurement following prophylactic thyroidectomy in patients with RET mutations. Our analysis and conclusions are limited by the small number of eligible patients due to the rarity of MEN2A, MEN2B, and FMTC. In addition, we are lacking complete data on serial Tg levels and, more significantly, ultrasound findings in these patients because neither have previously been recommended as routine surveillance, and, as a tertiary referral center, many patients who undergo thyroidectomy are subsequently managed at community institutions. As a result, we are unable to fully assess how this added information would affect the management or outcomes of these patients. Regardless, our findings indicate that further investigation of this topic is needed and should be performed to guide future management following prophylactic thyroidectomy, likely in the form of a multi-institutional study with long-term follow-up and a large sample size.

CONCLUSIONS

Tg should be recommended as routine laboratory follow-up in patients who have had prophylactic thyroidectomies for RET proto-oncogene mutations and perhaps for all patients undergoing a total thyroidectomy for MTC. Even in experienced hands, prophylactic thyroidectomy may leave residual thyroid tissue, as indicated by a detectable Tg level. The significance of this depends on location, due to the embryologic predominance of parafollicular C cells in the posterolateral thyroid. Ultrasound can be used to determine if thyroid tissue remains in the posterolateral thyroid bed and is at high risk of MTC recurrence. Maintaining a normal TSH may help to prevent growth of any TSH-responsive thyroid cells that remain after thyroidectomy.

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References

1. Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001; 86:5658–71. [PubMed: 11739416]
2. Pellegriti G, Leboulleux S, Baudin E, Bellon N, Scollo C, Travagli JP, et al. Long-term outcome of medullary thyroid carcinoma in patients with normal postoperative medical imaging. Br J Cancer. 2003; 88:1537–42. [PubMed: 12771918]

3. Clark OH, Hoelting T. Management of patients with differentiated thyroid cancer who have positive serum thyroglobulin levels and negative radioiodine scans. Thyroid. 1994; 4:501–5. [PubMed: 7711516]
4. Cooper DS, Doherty GM, Haugen BR, Hauger BR, Kloos RT, Lee SL, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009; 19:1167–214. [PubMed: 19860577]
5. Gibson WG, Peng TC, Croker BP. Age-associated C-cell hyperplasia in the human thyroid. Am J Pathol. 1982; 106:388–93. [PubMed: 6175219]
6. Papi G, Rossi G, Corsello SM, Corrado S, Fadda G, Di Donato C, et al. Nodular disease and parafollicular C-cell distribution: results from a prospective and retrospective clinico-pathological study on the thyroid isthmus. Eur J Endocrinol. 2010; 162:137–43. [PubMed: 19793761]
7. Frank-Raue K, Buhr H, Dralle H, Klar E, Senninger N, Weber T, et al. Long-term outcome in 46 gene carriers of hereditary medullary thyroid carcinoma after prophylactic thyroidectomy: impact of individual RET genotype. Eur J Endocrinol. 2006; 155:229–36. [PubMed: 16868135]
8. Deftos LJ, Stein MF. Radioiodine as an adjunct to the surgical treatment of medullary thyroid carcinoma. J Clin Endocrinol Metab. 1980; 50:967–8. [PubMed: 7372781]
9. Hellman DE, Kartchner M, Van Antwerp JD, Salmon SE, Patton DD, O'Mara R. Radioiodine in the treatment of medullary carcinoma of the thyroid. J Clin Endocrinol Metab. 1979; 48:451–5. [PubMed: 429497]
10. Faik Erdogan M, Gursoy A, Erdogan G, Kamel N. Radioactive iodine treatment in medullary thyroid carcinoma. Nucl Med Commun. 2006; 27:359–62. [PubMed: 16531922]
11. Shah KH, Oslapas R, Calandra DB, Prinz RA, Ernst K, Hofmann C, et al. Effects of radiation on parafollicular C cells of the thyroid gland. Surgery. 1983; 94:989–94. [PubMed: 6648815]
12. Davis PW. A review of 17 cases of medullary carcinoma of the thyroid gland. Proc R Soc Med. 1967; 60:743–4. [PubMed: 6035396]
13. Saad MF, Ordonez NG, Rashid RK, Guido JJ, Hill CS, Hickey RC, et al. Medullary Carcinoma of the Thyroid - a Study of the Clinical-Features and Prognostic Factors in 161 Patients. Medicine. 1984; 63:319–42. [PubMed: 6503683]
14. Nieuwenhuijzen Kruseman AC, Bussemaker JK, Frölich M. Radioiodine in the treatment of hereditary medullary carcinoma of the thyroid. J Clin Endocrinol Metab. 1984; 59:491–4. [PubMed: 6746863]
15. Meijer JA, Bakker LE, Valk GD, de Herder WW, de Wilt JH, Netea-Maier RT, et al. Radioactive iodine in the treatment of medullary thyroid carcinoma: a controlled multicenter study. Eur J Endocrinol. 2013; 168:779–86. [PubMed: 23462866]
16. Sawka AM, Thabane L, Parlea L, Ibrahim-Zada I, Tsang RW, Brierley JD, et al. Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. Thyroid. 2009; 19:451–7. [PubMed: 19281429]
17. Dralle H, Gimm O, Simon D, Frank-Raue K, Görtz G, Niederle B, et al. Prophylactic thyroidectomy in 75 children and adolescents with hereditary medullary thyroid carcinoma: German and Austrian experience. World J Surg. 1998; 22:744–50. discussion 50-1. [PubMed: 9606292]
18. Schellhaas E, König C, Frank-Raue K, Buhr HJ, Hotz HG. Long-term outcome of "prophylactic therapy" for familial medullary thyroid cancer. Surgery. 2009; 146:906–12. [PubMed: 19744457]
19. Rodríguez GJ, Balsalobre MD, Pomares F, Torregrosa NM, Ríos A, Carbonell P, et al. Prophylactic thyroidectomy in MEN 2A syndrome: experience in a single center. J Am Coll Surg. 2002; 195:159–66. [PubMed: 12168961]

Table 1

Patients with RET proto-oncogene mutations who underwent prophylactic total thyroidectomy at the University of California, San Francisco from 1981 to 2011.

Patient	Sex	Hereditary Syndrome	Mutation Codon	Age at Thyroidectomy (years)	Pathology	Maximum Postoperative Tg (ug/L)	Maximum Postoperative TSH (mIU/L)	Ultrasound Findings
1	M	MEN 2A*	609	5	Benign	7.4	28.8	No remnant thyroid tissue
2	F	MEN 2A	609	7	Benign	< 0.9	10.5	N/A
3	F	MEN 2A	634	11	CCH§, MTC†	2.7	9.03	N/A
4	M	MEN 2A	634	7	Benign	17.8	22.2	1 cm remnant thyroid tissue in left thyroid bed
5	M	MEN 2A	618	5	Benign	5.2	100	2.6 cm remnant thyroid tissue, consistent with pyramidal lobe
6	M	MEN 2A	634	12	CCH, MTC	4.8	13.44	N/A
7	F	MEN 2A	634	6	Benign	3.9	6.42	N/A
8	M	MEN 2A	634	8	CCH	2.8	20.75	N/A
9	F	FMTC¶	768	6	CCH	8.5	29.1	No remnant thyroid tissue
10	M	FMTC	768	9	Benign	1.3	4.6	N/A
11	F	MEN 2A	804	29	MTC	< 0.9	1.7	N/A
12	F	MEN 2A	634	16	MTC	< 0.9	2.5	N/A
13	F	MEN 2A	634	14	MTC	1.5	11.5	N/A
14	F	MEN 2A	634	2	Benign	2.2	0.99	1.2 cm remnant thyroid tissue in central neck

*Multiple Endocrine Neoplasia type 2A.

§C cell hyperplasia.

†Medullary thyroid cancer.

¶Familial medullary thyroid cancer.