Published in final edited form as:

Ann Surg Oncol. 2013 May ; 20(5): 1451–1455. doi:10.1245/s10434-012-2757-9.

Hereditary Medullary Thyroid Cancer: Age-Appropriate Thyroidectomy Improves Disease-Free Survival

Kevin Shepet, BS, Amal Alhefdhi, MD, Ngan Lai, BA, Haggi Mazeh, MD, Rebecca Sippel, MD, FACS, and Herbert Chen, MD, FACS

Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison, WI

Abstract

Background—Twenty-five percent of Medullary Thyroid Cancer (MTC) cases are hereditary. The ideal age for prophylactic thyroidectomy is based upon the specific RET mutation involved. The aim of this study is to determine if such age-appropriate prophylactic thyroidectomy results in improved disease-free survival.

Methods—Twenty-eight patients underwent thyroidectomy for hereditary MTC at our institution. Age-appropriate thyroidectomy was defined according to the North American Neuroendocrine Tumor Society (NANETS) guidelines. Patients having age-appropriate surgery (Group 1, n=9) were compared to those having thyroidectomy past the recommended age (Group 2, n=19).

Results—The mean age was 13 ± 2 years and 61% were female. Patients in Group 1 were younger than Group 2 (4 ± 1 vs. 17 ± 2 years, $p < 0.01$). There were no significant differences in gender or RET mutation types between these two groups. Group 1 patients were cured with no disease recurrence as compared to Group 2 patients who had a 42% recurrence rate ($p = 0.05$). Sub-analysis of Group 2 identified that patients who underwent surgery without evidence of disease did so at a shorter period following the guidelines as compared to those who underwent therapeutic surgery (2 ± 2 vs. 16 ± 2 years, $p = 0.01$) and had longer disease-free survival (100% vs. 27%, $p = 0.005$).

Conclusion—Patients with hereditary MTC should undergo age-appropriate thyroidectomy based on RET mutational status to avoid recurrence. Patients who are past the recommended age should have surgery as early as possible in order to improve disease-free survival.

INTRODUCTION

Medullary Thyroid Cancer (MTC) is a neuroendocrine malignancy of the thyroid C cells (parafollicular cells). MTC has a varied presentation from tumors that remain stable for many years to highly malignant tumors [1]. Currently MTC accounts for 3% of all thyroid cancers, but is responsible for 14% of all thyroid cancer related deaths [2,3]. MTC may occur sporadically or may be inherited. Sporadic MTC accounts for 75% of all cases [4,5].

Hereditary MTC is caused by a single germline mutation in the rearranged during transfection (RET) protooncogene. In 1991, the RET gene was found to be located on chromosome 10q11.2 where it encodes a transmembrane tyrosine receptor [6]. In 1993, it was first discovered that mutations in RET were associated with MEN and MTC [7]. While

Address for Correspondence Herbert Chen, MD, FACS Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, K3/705 Clinical Science Center, 600 Highland Avenue, Madison, WI 53792, USA Tel: +1 608-263-1387 Fax: +1 608-252-0912 chen@surgery.wisc.edu.

Disclosure: No disclosure.

sporadic MTC usually presents as a unifocal clonal population of tumor cells, hereditary MTC is typically multifocal and bilateral. Also, hereditary MTC has an earlier age of onset and usually a more aggressive course [8].

Hereditary MTC may occur in association with other neuroendocrinopathies in the setting of multiple endocrine neoplasia type 2 (MEN 2A or 2B) or alone as Familial MTC (FMTC) [9]. In the setting of hereditary MTC, disease prognosis is dependent on the specific RET mutation involved [1,10]. The North American Neuroendocrine Tumor Society (NANETS) has classified RET mutations into 3 risk levels, based on the age-associated risk of development of MTC. For all forms of hereditary MTC, prophylactic total thyroidectomy is recommended [2].

Although the practice of prophylactic thyroidectomy begun in the 1990's, the risk of disease recurrence is still not well defined [2]. While previous studies have reported positive outcomes for those undergoing prophylactic surgery at a young age, the prognosis of those having surgery past the recommended age is not well characterized [11]. Furthermore, the relationship between the amount of time waited past guidelines and the risk of developing disease is also indeterminate.

The aim of the present study was to determine if age-appropriate thyroidectomy improves disease free-survival compared to having surgery past the recommended age. Furthermore, the time past the guidelines of the thyroidectomy performed was correlated to disease status at surgery and disease recurrence following surgery.

METHODS

A review of a prospective database was performed on all patients undergoing thyroidectomy or neck dissection from 1994-2010 using the University of Wisconsin Thyroid Surgery Database. All patients with a pre- or post-operative diagnosis of MTC as well as those tested positive for RET mutations were identified in the database. Those who tested positive for RET mutations or those with three or more family members diagnosed with MTC were classified as hereditary MTC patients. The remaining patients were classified as sporadic MTC patients and were excluded.

The 28 hereditary MTC patients were subdivided into two groups: Group 1: those having age-appropriate thyroidectomy and Group 2: those having surgery past the recommended age. Age-appropriate surgery was defined by the NANETS guidelines, which recommend surgery before age 10 for level 1 mutations, before age 5 for level 2 mutations, and before age 6 months for level 3 mutations. These are identical to the ATA guidelines, which existed during the period of study. Data for these two groups were then collected including demographics, mutation level, pre and post-operative diagnosis, disease recurrence status, and time of last follow-up.

A sub-analysis of Group 2 was then performed. This group was divided into Group 2a: those patients having no radiographic or clinical evidence of MTC at surgery (prophylactic thyroidectomy) (ATA) and Group 2b: those were having a diagnosis of MTC at surgery (therapeutic thyroidectomy). These two subgroups were compared based on disease recurrence and how long past the NANETS recommended age each group waited to have their thyroidectomy (Figure 1).

To identify differences between Group 1 and Group 2 and between Group 2a and 2b, univariate statistical analysis was performed using the Fisher's exact test and t-test. Also, a survival analysis between Group 1 and 2 and between Group 2a and 2b was performed using Kaplan Meier analysis. All statistical calculations were completed using statistical software

SPSS version 17 (SPSS Inc, Chicago IL). A p-value of 0.05 was considered to represent statistical significance for all comparisons.

RESULTS

Forty-one patients underwent prophylactic or therapeutic total thyroidectomy for MTC from 1994-2010 at the University of Wisconsin. Twenty-eight cases were classified as hereditary MTC, while 13 cases were sporadic MTC. Of the hereditary MTC cases, 9 (32%) patients had age-appropriate surgery (Group 1), while 19 (68%) patients had surgery past the recommended age (Group 2).

Of the 28 hereditary MTC patients, 61% were female and the mean patient age at the time of surgery was 13 ± 2 years. 24 patients were diagnosed with MEN type 2A, 1 patient with MEN type 2B, and 3 with familial MTC. Serum calcitonin level was not detectable in any of the patients who underwent a prophylactic surgery, but the mean level was 380.3 ± 144 pg/ml in patients who underwent therapeutic surgery.

Patients in Group 1 and Group 2 had an average follow-up time of 5.1 ± 1.8 and 11.2 ± 1.9 years following thyroidectomy. At the most recent follow-up all 9 patients in Group 1 had no evidence of MTC. However, 8 (42%) patients in Group 2 had recurrent MTC, which required one or more additional surgical interventions. Kaplan-Meier survival analysis indicated that those in Group 1 had an improved disease-free survival compared to those in Group 2 ($p=0.05$) (Figure 1).

Of the 19 patients in Group 2 that had their surgery past the recommended age, 8 (42%) patients (Group 2a) still underwent a prophylactic thyroidectomy. The remaining 11 (58%) patients (Group 2b) had therapeutic thyroidectomy due to a diagnosis of MTC at the time of surgery. One patient from Group 2b had left neck lymph nodes metastasis at initial presentation. Patients in Group 2a were significantly younger than those in Group 2b (12 ± 3 vs. 21 ± 2 years, $p=0.04$). Those in Group 2a underwent thyroidectomy a median time of 2 ± 2 years past the NANETS recommended age, while those in Group 2b were 16 ± 2 years past the guidelines ($p=0.01$). All Group 2a patients had no recurrence of MTC, however 8 of 11 patients in Group 2b (73%) had recurrent disease requiring reoperation ($p=0.005$) (Figure 2).

DISCUSSION

In our patient population it is evident that age-appropriate thyroidectomy, based on RET mutation status, prolongs disease-free survival in the setting of hereditary MTC. In the 9 patients who underwent age-appropriate thyroidectomy, 100% remained disease-free at their latest follow-up. An awareness of a family history of MTC allowed for early genetic screening to identify these RET carriers and prompt surgical intervention. This finding underscores the continued importance of early genetic screening when a family history of MTC or MEN syndrome exists.

Unfortunately many patients harboring RET mutations present for thyroidectomy past the recommended age. In these cases the disease-free survival time following surgery is highly variable [11, 12, and 13]. In the 19 patients who had surgery past the guideline age, 42% had noted recurrent MTC following thyroidectomy. This represents a significant decrease in disease-free survival as compared to patients having age-appropriate surgery. The reasons why RET carriers are often unidentified until after they present with disease remains unclear. It is possible that this is the result of a patient's lack of awareness of any family history of MTC. Also, some insurance companies do not routinely pay for RET mutation testing. This is an expensive test that many patients may be unable to afford. This factor may

contribute to a lack of comprehensive family screening for MTC in some cases. Lastly, it is possible that patients who are seen by endocrinologist or had been operated by endocrine trained surgeons are more likely to be identified as a potential RET carrier and undergo screening. However, many patients are from rural areas that do not have local expertise in the disease and are not screened or referred.

While having age-appropriate surgery is ideal, the chance for surgical cure of MTC remains high if the patient presents only shortly after the guideline age [11]. Of the 19 patients having surgery past the recommended age, the 8 patients who still had a prophylactic surgery had no disease recurrence following surgery. However, 11 had therapeutic surgery, with a high rate (73%) of disease recurrence following surgery. The largest identifiable difference between these two groups was the time length that had passed between the guideline age and the actual age for surgery. This finding emphasizes that if a patient is to present beyond the guideline age, they should still be advised to undergo thyroidectomy immediately. If surgery can be performed only a few years past the guideline time, the patient may possibly still have prophylactic surgery without evidence of MTC and this will result in significantly improved disease-free survival. However, the longer the patient waits beyond the guideline age, the greater their risk of developing disease before surgery and having disease recurrence following surgery.

The findings of our study are consistent with previous studies. Skinner *et al* found that MEN-2A patients having surgery before age eight had lower rates of persistent or recurrent disease than older patients [11]. Also in their series, 33 of 50 patients had developed MTC by the time of surgery, 6 of which developed recurrent disease following surgery. All 6 of these patients had surgery several years beyond the recommended age. Indeed, O'Riordain *et al* also found a strong correlation between age at surgery and rate of disease recurrence following surgery [12]. In a nation-wide study in the Netherlands, Schreinemakers *et al* reported a 34% disease-recurrence rate among those having surgery past the recommended age vs. 0% recurrence in those undergoing age-appropriate surgery [13]. The findings of these studies strongly concur with the findings of our study as it appears that the most important prognostic factor for disease-free survival in hereditary MTC is age at surgery. This association is believed to be due to the observation that disease advancement from C-cell hyperplasia to MTC is age-related [15,16]. As patients progress in age there is a greater risk of MTC development with local or distant metastases, making surgical cure highly improbable [15].

The ATA guidelines state that infants with MEN 2B should undergo prophylactic total thyroidectomy as soon as possible, ideally within the first year of life at an experienced tertiary care setting. It is also recommended that children with codon 634 mutations undergo prophylactic total thyroidectomy before they are 5 years old at an experienced tertiary care center. In addition, prophylactic total thyroidectomy may be delayed beyond age 5 for RET carriers in the setting of a normal annual basal stimulated serum calcitonin, normal annual neck US, less aggressive MTC family history, and family preference. Surgery is indicated if all of these features are not present. For higher risk mutations, treatment should be considered before age 5 years in an experienced tertiary care setting, regardless of other factors [14].

The main limitation of our study is the length of follow-up. The patients in Group 1 were followed for a significantly shorter period of time than the patients in Group 2, (5 vs. 11 years). Therefore, in order to ensure that those undergoing prophylactic surgery remain disease free in the future, a longer-term study is needed. Also, although 28 patients were included, a larger patient population may be needed to further validate the observed trends and to increase the power of the study. Lastly, this is a retrospective study that is prone to

selection bias due to inclusion of patients that had surgery. A prospective study is unlikely to be performed due to the rarity of the disease.

CONCLUSION

Prophylactic thyroidectomy for patients with hereditary MTC is a key for disease management. Following the NANETS age-appropriate thyroidectomy guidelines based on RET mutational status is recommended. Patients who have surgery after the recommended age should have surgery as early as possible, before disease development, in order to improve disease-free survival.

Acknowledgments

University of Wisconsin Department of Surgery NIH T32 Training Grant (5 T32 DC 9401-2)

REFERENCES

1. Chen H, Sippel RS, O'Dorisio MS, et al. The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. *Pancreas*. 2010; 39(6):775–83. [PubMed: 20664475]
2. Sippel RS, Kunnimalaiyaan M, Chen H. Current management of medullary thyroid cancer. *Oncologist*. 2008; 13(5):539–47. [PubMed: 18515739]
3. Greenblatt DY, Chen H. Palliation of advanced thyroid malignancies. *Surg Oncol*. 2007; 16(4):237–47. [PubMed: 17855077]
4. Chen H, Roberts JR, Ball DW, et al. Effective long-term palliation of symptomatic, incurable metastatic medullary thyroid cancer by operative resection. *Ann Surg*. 1998; 227(6):887–95. [PubMed: 9637552]
5. Moley JF, Lairmore TC, Phay JE. Hereditary endocrinopathies. *Curr Prob Surg*. 1999; 36(9):653–762.
6. Hansford JR, Mulligan LM. Multiple endocrine neoplasia type 2 and RET: from neoplasia to neurogenesis. *J Med Genet*. 2000; 37(11):817–27. [PubMed: 11073534]
7. Donis-Keller H, Dou S, Chi D, et al. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. *Human Mol Genet*. 1993; 2(7):851–6. [PubMed: 8103403]
8. Pinchot SN, Sippel RS, Chen H. Multi-targeted approach in the treatment of thyroid cancer. *Ther Clin Risk Manag*. 2008; 4(5):935–47. [PubMed: 19209276]
9. Eng C, Clayton D, Schuffenecker I, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET mutation consortium analysis. *JAMA*. 1996; 276(19):1575–9. [PubMed: 8918855]
10. Kouvaraki MA, Shapiro SE, Perrier ND, et al. RET proto-oncogene: a review and update of genotype-phenotype correlations in hereditary medullary thyroid cancer and associated endocrine tumors. *Thyroid*. 2005; 15(6):531–44. [PubMed: 16029119]
11. Skinner MA, Moley JA, Dilley WG, et al. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. *N Eng J Med*. 2005; 353(11):1105–13.
12. O'Riordain DS, O'Brien T, Weaver AL, et al. Medullary thyroid carcinoma in multiple endocrine neoplasia types 2A and 2B. *Surgery*. 1994; 116(6):1017–23. [PubMed: 7985081]
13. Schreinemakers JMJ, Vriens MR, Valk GD, et al. Factors predicting outcome of total thyroidectomy in young patients with multiple endocrine neoplasia type 2: a nationwide long-term follow-up study. *World J Surg*. 2010; 34(4):852–60. [PubMed: 20063095]
14. Kloos R, Eng C, Evans D, et al. Medullary Thyroid Cancer: Management Guidelines of the American Thyroid Association. *Thyroid*. 2009; 19(6):565–612. [PubMed: 19469690]
15. Machens A, Niccoli-Sire P, Hoegel J, et al. Early malignant progression of hereditary medullary thyroid cancer. *N Eng J Med*. 2003; 349(16):1517–25.

16. Wolfe HJ, Melvin KE, Cervi-Skinner SJ, et al. C-cell hyperplasia preceding medullary thyroid carcinoma. *N Eng J Med*. 1973; 289(9):437–41.

SYNOPSIS

In this study we demonstrated that patients with hereditary Medullary Thyroid Cancer (MTC) that underwent age-appropriate thyroidectomy had no disease recurrences as compared to the 42% recurrence rate in the patients having surgery past the recommended age. We conclude that patients with hereditary MTC should undergo age-appropriate thyroidectomy and patients having surgery beyond the recommend age should have surgery as early as possible.

Figure 1.
Study design

Figure 2.
Disease free survival rate between group 1 and 2

Figure 3.
Disease free survival rate between group 2a and group 2b

Table 1

Patient Demographics

	Group 1: Age-appropriate thyroidectomy	Group 2: Thyroidectomy past recommended age	p
n	9	19	-
Age (yrs)	4 ± 1	17 ± 2	0.0003
% Female	55%	63%	1
Follow-up time (yrs)	5.1 ± 1.8	11.2 ± 1.9	0.06

Table 2

Patient Disease Characteristics

	Group 1: Age-appropriate thyroidectomy	Group 2: Thyroidectomy past recommended age	p
n	9	19	-
<i>Diagnosis</i>			
MEN type 2A	8	16	1.00
MEN type 2B	0	1	1.00
FMTC	1	2	1.00
<i>Mutation Risk Level</i>			
Level 1	1	6	0.37
Level 2	8	12	0.21
Level 3	0	1	1