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Ultrasonography Should Not Guide the Timing of Thyroidectomy in Pediatric Patients Diagnosed with Multiple Endocrine Neoplasia Syndrome 2A through Genetic Screening

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Abstract

Background—American Thyroid Association (ATA) guidelines suggest that thyroidectomy can be delayed in some children with multiple endocrine neoplasia syndrome 2A (MEN2A) if serum calcitonin (Ct) and neck ultrasonography (US) are normal. We hypothesized that normal US would not exclude a final pathology diagnosis of medullary thyroid cancer (MTC).

Methods—We retrospectively queried a MEN2A database for patients aged <18 years, diagnosed through genetic screening, who underwent preoperative US and thyroidectomy at our institution, comparing preoperative US and Ct results with pathologic findings.

Results—35 eligible patients underwent surgery at median age of 6.3 (range 3.0–13.8) years. Mean MTC size was 2.9 (range 0.5–6.0) mm. The sensitivity of a US lesion ≥ 5 mm in predicting MTC was 13 % [95 % confidence interval (CI) 2 %, 40 %], and the specificity was 95 % [95 % CI 75 %, 100 %]. Elevated Ct predicted MTC in 13/15 patients (sensitivity 87 % [95 % CI 60 %, 98 %], specificity 35 % [95 % CI 15 %, 59 %]). The area under the receiver operating characteristic curve (AUC) for using US lesion of any size to predict MTC was 0.50 [95 % CI 0.33, 0.66], suggesting that US size has poor ability to discriminate MTC from non-MTC cases. The AUC for Ct level at 0.65 [95 % CI 0.46, 0.85] was better than that of US but not age [AUC 0.62, 95 % CI 0.42, 0.82].

Conclusions—In asymptomatic children with MEN2A diagnosed by genetic screening, preoperative thyroid US was not sensitive in identifying MTC of any size and, when determining the age for surgery, should not be used to predict microscopic MTC.

Medullary thyroid carcinoma (MTC), a neuroendocrine tumor that arises from the calcitonin-secreting parafollicular C cells, represents <5 % of thyroid cancers.¹ In a quarter of cases, MTC is due to germline point mutations in the rearranged during transfection (*RET*) proto-oncogene on chromosome 10. The *RET* mutation, inherited in an autosomal dominant pattern, is associated with the hereditary syndromes of multiple endocrine neoplasia syndrome 2A (MEN2A; characterized by MTC, pheochromocytoma, and hyperparathyroidism) and MEN2B (characterized by MTC, pheochromocytoma, and ganglioneuromas). While degree of expressivity varies, MTC is highly penetrant in the MEN2A population and represents the leading cause of MEN2A-related morbidity and death. Since the relationship between MEN2A and mutations in the *RET* proto-oncogene was first described in 1993, the practice of performing “prophylactic” thyroidectomy in asymptomatic children who test positive for a germline *RET* mutation has become common;^{2,3} the goal of this early surgical treatment is to cure or prevent MTC.⁴

To help guide the timing of thyroidectomy in children with screening-detected MEN2A, the American Thyroid Association (ATA) recently divided MEN2A codon mutations into three risk categories based on the natural history of MTC development in patients with such mutations.^{5,6} These guidelines recommend that children with risk level C mutations (codon 634) undergo thyroidectomy before 5 years of age; in contrast, children with risk level A or B mutations may delay thyroidectomy if there is no evidence of lymph node (LN) metastases, all thyroid nodules are <5 mm on ultrasonography (US), and the basal calcitonin level (Ct) is <40 pg/ml.⁵ These US and Ct criteria have also been applied in determining the timing of thyroidectomy before age 5 years in risk level C patients. These clinical parameters seek to allow further personalization of the timing of thyroidectomy within a mutation risk group.

Ct level was recently shown to be an independent predictor of the presence of MTC in this population, and it has been suggested that this tumor marker may be used to guide treatment decisions.^{7,8} However, the sensitivity of neck US in predicting MTC in asymptomatic patients with screening-detected MEN2A has not been determined. We hypothesized that a normal neck US study would not exclude an MTC diagnosis on final pathology. Further, we projected that the US nodule size criterion suggested in the ATA guidelines (<5 mm) would not be helpful in predicting MTC.

METHODS

Approval from The University of Texas MD Anderson Cancer Center’s institutional review board was obtained for this retrospective study. We queried an internal database to identify patients operated on between March 2002 and August 2011 who met the following inclusion criteria: (1) <18 years old at surgery, (2) diagnosed with MEN2A based on genetic screening prompted by a positive test in a relative, (3) no preoperative physical examination evidence of thyroid cancer, (4) thyroidectomy performed at MD Anderson, and (5) at least one preoperative US study done at MD Anderson with digital images available for review (after 2001). The electronic medical records of included patients were reviewed, and preoperative Ct and US results were compared with pathologic findings.

US of the soft tissues of the neck had been performed in all patients with high-resolution scanners (Philips-ATL, Bothell, Washington; or Aloka, Tokyo, Japan) equipped with high-frequency (7–13-MHz) linear-array transducers with color and power Doppler capability. The neuroradiology technologists had performed US of the soft tissues of the neck according to a standardized protocol that included evaluation of the thyroid and LNs in the lateral and central neck compartments.

Preoperative US images from patients who met the inclusion criteria were reviewed in a blinded fashion by a senior neuroradiologist (B.S.E.) who specializes in head and neck US. Notations were made of the presence, size, laterality, and appearance of thyroid nodules. An abnormal US study of a thyroid nodule included the presence of hypervascularity and calcifications. Size was noted for descriptive purposes only and not as a criterion for malignancy. For the purpose of analyzing the ATA US size criterion in the present study, we categorized thyroid nodules as ≤ 5 or > 5 mm on US. The original preoperative US report was not considered in this analysis.

Over the time period studied, basal Ct levels had been measured at MD Anderson by three different assays: Nichols chemiluminescence (June 2000 to January 2003), Nichols manual radioimmunoassay (February 2003 to June 2006), and Siemens chemiluminescence immunometric methodology (July 2006 to present). Some patients had prereferral Ct measurements obtained by unknown modalities. Because of the variations in measurement methods, Ct levels were reported as “fold above normal” or dichotomized as “normal” or “elevated” based upon assay-specific reference ranges.

Thyroidectomy had been performed by one of three MD Anderson endocrine surgeons. The timing of thyroidectomy had been based on the timing of presentation for genetic testing and physician and parent preference. LN dissection had been performed at the discretion of the surgeon.

Associations between MTC and its potential predictors of disease were investigated using Fisher’s exact test for categorical variables and the Kruskal–Wallis test for ordinal variables. A logistic regression model was also run to examine the association between ATA risk level while controlling for patient age. The properties (sensitivity, specificity, positive predictive value, and negative predictive value) of using ATA risk level, Ct, and US lesion size to predict cancer were calculated with corresponding exact binomial 95 % confidence intervals (CIs). In addition, the area under the receiver operating characteristic curve (AUC) and corresponding 95 % Wald confidence limits were computed for three potential predictors of MTC: lesion size on thyroid US, Ct fold increase above normal, and patient age. All *p* values were two-tailed and considered significant at $\alpha < 0.05$. Analyses were conducted using SAS for Windows software (release 9.2, SAS Institute, Cary, NC).

RESULTS

The 35 patients included in this study were from 18 families, ranged in age at surgery from 3.0 to 13.8 (median 6.3) years old, and underwent surgery at MD Anderson between March 2002 and August 2011 (Table 1). Twenty-six patients (74 %) were ATA risk level C, eight (23 %) were risk level B, and one (3 %) was risk level A. The median age at *RET* testing was 5.6 years. A median of 3.8 months elapsed between positive genetic testing and thyroidectomy (range 0.1–63.0 months). Eight patients underwent total thyroidectomy more than 12 months after the initial positive *RET* test for the following reasons: initial *RET* testing during the first 2 years of life ($n = 4$), family issues ($n = 2$), and presence of a lower risk level (level B) mutation ($n = 2$).

None of the patients had palpable thyroid nodules or neck lymphadenopathy on physical examination. All patients underwent total thyroidectomy. Three patients also underwent compartment-oriented central LN dissection owing to a combination of factors: elevated Ct (three patients), age ≥ 10 years at surgery (two patients), and/or presence of suspicious thyroid nodules on preoperative US (two patients) (Table 1). Five patients had deliberate excision of one or more lymph nodes intraoperatively without a formal neck dissection.

Pathology

On final pathology, 15 patients (43 %) had MTC, 14 (40 %) had C-cell hyperplasia (CCH) only, and 6 (17 %) had normal thyroid tissue. Patients with MTC had a median age of 6.3 (range 3.7–13.8) years, and those without MTC had a median age of 6.4 (range 3.0–12.4) years ($p = 0.22$) (Table 2). The mean size of MTC on pathologic examination was 2.9 mm (range 0.5–6.0 mm). All patients with MTC had stage I disease.

US

To determine the accuracy of ATA US size recommendations in predicting MTC, we compared the incidence of MTC diagnosed on pathologic examination with the incidence of MTC identified on preoperative US. Two of 15 patients with MTC had a US lesion of ≤ 5 mm. The sensitivity of an abnormal US lesion ≤ 5 mm in predicting MTC was 13 % [95 % CI 2 %, 40 %], and the specificity was 95 % [95 % CI 75 %, 100 %] (Table 3). When we removed the size cutoff and considered all lesions with any abnormal US finding as predictive of MTC, US identified two additional patients with MTC; this increased US's sensitivity to 27 % [95 % CI 8 %, 55 %], but decreased its specificity to 70 % [95 % CI 46 %, 88 %]. The AUC for using US lesion size to predict MTC was 0.50 [95 % CI 0.33, 0.66], suggesting that US size has poor ability to discriminate between MTC and non-MTC cases. The AUC for using US lesion size to predict either CCH or MTC was 0.55 [95 % CI 0.32, 0.77].

When an abnormal US with thyroid nodule ≤ 5 mm was used to predict MTC, there were 19 (54 %) true negatives and 2 (6 %) true positives. US falsely predicted an MTC in 1 case (3 %) and could not image the pathologic lesion in 13 cases (37 %). The probability of having MTC (positive predictive value, PPV) was 67 % if US showed an abnormal lesion ≤ 5 mm. Among patients with negative US, 59 % did not have MTC (negative predictive value, NPV) (Table 3).

Among patients with MTC, when US imaged an abnormal lesion of any size ($n = 4$), the mean size of lesions on final pathology was 3.4 mm (range 2–6 mm); when US imaged no abnormal lesions of any size ($n = 11$), the mean size of lesions on final pathology was 2.7 mm (range 0.5–4 mm) ($p = 0.45$).

Ct

Among the 26 (74 %) patients with elevated preoperative basal Ct, Ct was 1.02- to 15.57-fold above normal values (median elevation 2.3-fold above normal). Ct was elevated in 87 % and 86 % of patients with MTC and CCH, respectively, but in only 17 % of patients with benign pathology findings ($p = 0.005$) (Table 2). Elevated basal Ct was able to predict MTC in 13 of 15 patients, for a sensitivity of 87 % [95 % CI 60 %, 98 %] and a specificity of 35 % [95 % CI 15 %, 59 %] (Table 3). The AUC for the Ct level (measured as fold increase above normal), at 0.65 [95 % CI 0.46, 0.85], was better than that of US but no better at discriminating MTC than was age [AUC 0.62, 95 % CI 0.42, 0.82] (Table 3). The AUC for using Ct level to predict either CCH or MTC was 0.91 [95 % CI 0.82, 1.00].

ATA Risk Level

Of the 15 patients diagnosed with MTC, 14 were risk level C (Table 4). The one patient with risk level B and MTC was 9.9 years old at operation; the median age of non-MTC risk level B cases was 7.8 (range 5.2–12.4) years. Twelve risk level C patients did not have MTC. Among risk level C patients, no statistically significant association was observed between age and MTC. Median age among those with MTC was 6.3 years ($n = 14$, range 3.7–13.8 years) versus 5.6 years among those without MTC ($n = 12$, range 3.0–10.6 years) ($p = 0.14$).

Two of the risk level C patients who had MTC were younger than 5 years (3.7 and 4.8 years old). There were no significant differences in Ct level or US findings between ATA risk level C patients who did or did not have MTC (Table 4).

ATA risk level C increased the odds of having MTC [OR 9.33, 95 % CI 1.02, 85.70]. The association between ATA risk level (C versus A or B) and MTC remained when simultaneously accounting for age in the model. The sensitivity of ATA risk level in correctly categorizing patients who did and did not have MTC was good [93 %; 95 % CI 68 %, 100 %], but the specificity was poor [40 %; 95 % CI 19 %, 64 %].

US and Ct Combined

Finally, we examined US and Ct as combined predictors of MTC in this patient population. Nine patients had both negative Ct and negative US. Four of those patients had a histologic abnormality on final pathologic examination; two patients had MTC, and two additional patients had CCH. Using abnormal Ct and abnormal US together to predict MTC yielded a sensitivity of 13 % [95 % CI 2, 40 %], specificity of 95 % [95 % CI 75, 100 %], PPV of 67 % [95 % CI 9, 99 %], and NPV of 59 % [95 % CI 41, 76 %]. There were no patients who had normal Ct with an US lesion $\geq$ 5 mm. Thus, using normal Ct and normal US to predict the absence of MTC has the same operating characteristics as using normal Ct alone.

Of the four patients who had normal neck US findings and Ct levels but had CCH or MTC on final pathology, all were ATA risk level C. The two patients with MTC were 5.7 and 6.3 years old at the time of surgery, and both had 2-mm lesions on final pathology (Fig. 1). The two patients with CCH were 5.6 and 7.1 years old at the time of surgery.

Follow-Up

Follow-up data were available for all but four patients. Median follow-up time was 0.7 months (range 0.0–78.6 months), with follow-up greater than 12 months available for seven patients; none had persistent or recurrent MTC based on an undetectable Ct level.

DISCUSSION

With the availability of *RET* genetic testing, initial recommendations about the timing of surgery were based on the specific *RET* mutation present and the earliest age at which clinically relevant MTC had been reported for that particular mutation.⁹ At the 7th International Workshop on MEN in 1999, a consensus statement was created that was the first to classify *RET* mutations associated with MEN2A into two risk levels. In 2009, the ATA further stratified mutations associated with MEN2A into three risk levels; a unique higher risk category was assigned to patients with a codon 634 mutation.⁵ These revised guidelines also introduced the idea of expectant monitoring, rather than a definitive age for surgery, in the lower risk categories based on analysis of a combination of factors including Ct levels, US findings, and family history. The concept of personalization of timing of early thyroidectomy beyond mutation type is appealing given the varied phenotypic expression within mutation types, and even within kindred. In addition, given the risks of surgery and the medicalization of children who are committed to a lifetime of thyroid hormone replacement, personalizing the timing of surgery can allow for decision-making appropriate for variable family circumstances and preferences.

While medical and surgical endocrinologists do not universally agree on whether thyroidectomy needs to be performed in MEN2A patients before or after the development of small, intrathyroidal MTC, all can agree that thyroidectomy prior to LN metastasis is imperative. Once MTC has spread beyond the thyroid gland, the disease is usually incurable

and is in fact the most common cause of death in patients with MEN2.^{4,10–14} Therefore, detection of MTCs prior to their becoming clinically relevant is essential. The focus of the current study was to determine whether US is a reliable modality for predicting these small MTCs in this asymptomatic population.

The ATA guidelines suggest that thyroid nodules <5 mm on US may be expectantly monitored in the appropriate clinical scenario. In our study we found that an abnormal US lesion ≥ 5 mm in this patient population had no ability to discriminate between MTC and non-MTC cases (AUC = 0.50). Only 59 % of patients with a negative US (no abnormal lesion ≥ 5 mm) did not have MTC. In no instance when Ct was normal did an abnormal US detect a cancer. The nodule size cutoff value of 5 mm used for the ATA guidelines was based on work by Machens et al., who found that LN metastases did not occur with primary tumors below this size.¹⁵ However, Machens et al. studied adult patients (mean age at MTC diagnosis was 45 years) with primarily sporadic disease (>60 %). Further, the 5-mm size cutoff in that study was based on a pathologic MTC measurement. This is potentially problematic as US shows a magnification of nodule size when compared with final pathology.¹⁶ This magnification effect is due to the distance between the transducer and the nodule on US examination. We noted a similar difference in estimation comparing US and pathologic nodule size in MEN2A children.

While not specifically addressing the ATA guidelines, two previous studies in the MEN2A population also suggested that US is not a sensitive predictor of small (<1 cm) intrathyroidal MTC. Rodriguez Gonzalez et al. found that, among 22 MEN2A patients with a codon 634 mutation and normal basal and stimulated Ct, only 3 (20 %) of 15 patients with MTC had nodules detected on preoperative US. The median pathologic tumor size in that series was 2 mm (range 1–7 mm).¹⁷ In a Brazilian evaluation of 41 MEN2A patients ≥ 25 years old who underwent thyroidectomy (92 % with a codon 634 mutation), Punaes et al. found that, among the 20 patients with MTC and a normal physical examination, US did not reveal thyroid abnormalities in 60 %.¹²

When we considered an abnormal lesion of any size on US, not just those ≥ 5 mm, the predictive ability of US did not improve greatly. On US, MTC nodules are hypoechoic, predominantly solid nodules, with intranodular calcifications.^{18,19} The US features of MTC overlap with those of papillary thyroid cancer and other malignancies.²⁰ However, studies of the US features of MTC included mostly adults with sporadic disease and larger lesions; no such studies have been conducted in children or in the MEN2A population specifically. Because the US features of benign and malignant thyroid nodules overlap, unless a nodule is purely cystic or contains crystalline colloid, a benign nodule cannot be distinguished from a malignant nodule. Further, one thyroid malignancy cannot be distinguished from another based on US characteristics alone. Therefore, by US criteria, 30 % of MTC nodules in prior studies were misdiagnosed as benign or indeterminate.^{19,20}

Although we found that US cannot distinguish between MTC and non-MTC cases in children with asymptomatic MEN2A, we believe that US still has a critical role in the pre-thyroidectomy workup. While routine LN dissection is not recommended in asymptomatic MEN2A patients, identifying pathologic lymphadenopathy or a thyroid nodule preoperatively can guide the appropriate compartment-oriented LN dissection.⁵ All patients should undergo routine preoperative US examination of the thyroid and central and lateral neck compartments.

In this study of asymptomatic MEN2A patients, all were <14 years old at the time of surgery, and the majority were operated on within a year of initial *RET* testing; fewer than half the patients (15, 43 %) had MTC on final pathology. Our study showed that US is not

an accurate predictor of MTC in this setting. A negative US should not be used in isolation or combined with other factors (e.g., Ct or ATA risk level) to reassure physicians or families regarding the absence of disease. However, we potentially overtreated 20 patients who did not have MTC. These patients represent a cohort who potentially could have been expectantly managed. A limitation of this study is our lack of long-term follow-up to determine whether any of our patients with MTC on final pathology ultimately developed clinical disease outside the thyroid. Our data suggest that Ct may better predict the presence of MTC and therefore may be able to guide management. This finding has been corroborated by the recent studies by Elisei et al. and Rohmer et al.^{7,8} On the basis of our results, we believe that US findings should not be used to predict the presence or absence of MTC in children with screening-detected MEN2A; however, US of the neck should continue to be performed preoperatively to help guide the extent of surgery.

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FIG. 1. Presence of medullary thyroid carcinoma (MTC) and C-cell hyperplasia (CCH) on final pathology by basal calcitonin (Ct) and ultrasonography (US) findings. +, positive; -, negative

TABLE 1

Characteristics of 35 germline *RET* mutation-positive patients under age 18 years diagnosed through genetic screening, and operated upon from 2002 to 2011

Characteristic	No. of patients (%)
Female:male ratio	1.7:1
ATA risk level codon mutation	
A, 804	1 (3 %)
B	8 (23 %)
609	2 (6 %)
618	4 (11 %)
620	2 (6 %)
C, 634	26 (74 %)
Elevated basal preoperative Ct level	26 (74 %)
Age at surgery, median (range)	6.3 (3.0–13.8) years
Total thyroidectomy	
With central neck dissection	3 (9 %)
Without compartmental LN dissection	32 (91 %)
Histology	
Normal	6 (17 %)
CCH	14 (40 %)
MTC	15 (43 %)
Age at <i>RET</i> testing, median	5.6 years
Time elapsed between positive <i>RET</i> test and thyroidectomy, median (range)	3.9 (0.1–63.9) months

ATA American Thyroid Association, Ct calcitonin, CCH C-cell hyperplasia, MTC medullary thyroid cancer, LN lymph node

TABLE 2

Age, ATA risk level, basal Ct levels, and US results by final pathologic findings

Characteristic	Pathologic finding			<i>P</i> Value
	MTC (<i>n</i> = 15)	CCH (<i>n</i> = 14)	Benign (<i>n</i> = 6)	
Median (range) age at operation (years)	6.3 (3.7–13.8)	6.4 (4.1–12.4)	6.7 (3.0–9.0)	0.41
ATA risk level	C = 14, B = 1	C = 10, B = 4	C = 2, B = 3, A = 1	0.02
Ct elevated	13 (87 %)	12 (86 %)	1 (17 %)	0.005
Ct 2-fold above normal	8 (53 %)	5 (36 %)	1 (17 %)	0.32
Ct > 40 pg/ml	1 (7 %)	0 %	1 (17 %)	0.31
Abnormal US lesion ≤ 5 mm	2 (13 %)	1 (7 %)	0 %	1.00
Abnormal US lesion of any size	4 (27 %)	5 (36 %)	1 (17 %)	0.79

ATA American Thyroid Association, *Ct* calcitonin, *US* ultrasonography, *MTC* medullary thyroid carcinoma, *CCH* C-cell hyperplasia Data are number of patients (%) unless otherwise specified

TABLE 3Accuracy of abnormal US (lesion ≥ 5 mm) and basal Ct in predicting medullary thyroid cancer

Measure	Value by test	
	Abnormal US ^a	Ct ^a
Sensitivity	13 % [95 % CI 2 %, 40 %]	87 % [95 % CI 60 %, 98 %]
Specificity	95 % [95 % CI 75 %, 100 %]	35 % [95 % CI 15 %, 59 %]
PPV	67 % [95 % CI 9 %, 99 %]	50 % [95 % CI 30 %, 70 %]
NPV	59 % [95 % CI 41 %, 76 %]	78 % [95 % CI 40 %, 97 %]
AUC	0.50 [95 % CI 0.33, 0.66]	0.65 [95 % CI 0.46, 0.85]

US ultrasonography, Ct calcitonin, CI confidence interval, PPV positive predictive value, NPV negative predictive value, AUC area under the receiver operating characteristic curve

^aFor sensitivity, specificity, PPV, and NPV, abnormal US was defined as any US lesion ≥ 5 mm, and Ct was categorized as abnormal versus normal according to laboratory reference values. For AUC calculations, we used abnormal US lesion of any size and fold increase above normal for Ct

TABLE 4

Characteristics by ATA risk level

Characteristic	Level A (n = 1)	Level B (n = 8)	Level C (n = 26)	P-Value
Age at surgery (years), median (range)	8.8	8.4 (5.2–12.4)	6.0 (3.0–13.8)	0.66 ^a
Final pathology				
MTC	0	1 (12.5 %)	14 (53.8 %)	0.021
CCH	0	4 (50.0 %)	10 (38.5 %)	
Benign	1 (100 %)	3 (37.5 %)	2 (7.7 %)	
Ct elevated	0	5 (62.5 %)	21 (80.8 %)	0.15
Ct 2-fold above normal	0	1 (12.5 %)	13 (50.0 %)	0.11
Ct > 40 pg/ml	0	0	2 (7.7 %)	1.00
Abnormal US lesion 5 mm	0	1 (12.5 %)	2 (7.7 %)	1.00
Abnormal US lesion of any size	0	4 (50.0 %)	6 (23.1 %)	0.32

P-Values are from Fisher's exact test unless otherwise noted

^aKruskal–Wallis test ATA American Thyroid Association, MTC medullary thyroid carcinoma, CCH C-cell hyperplasia, Ct calcitonin, US ultrasonography

Data are number of patients (%) unless otherwise indicated