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ORIGINAL SCIENTIFIC REPORT

National Trends in the Surgical Treatment of Non-advanced Medullary Thyroid Cancer (MTC): An Evaluation of Adherence with the 2009 American Thyroid Association Guidelines

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Abstract

Background Medullary thyroid cancer (MTC) represents the third most common type of thyroid cancer, and the prognosis depends on the stage of the disease at diagnosis and completeness of tumor resection. In 2009, the American Thyroid Association (ATA) published guidelines with evidence-based recommendations for the treatment of MTC. This study aimed to determine national adherence rates of the treatment according to the ATA guidelines specific for MTC.

Methods Patients diagnosed with MTC from 2004 to 2013 were identified from the National Cancer Database. Guideline adherence rates for the treatment of MTC before and after the publication of ATA guidelines were analyzed and compared to determine patient and clinical variables that affected treatment.

Results A total of 3693 patients diagnosed with MTC were identified. We found 60.3 % of the patients had localized MTC and 39.7 % had regional metastases. Older age, female sex and having Medicaid or being uninsured were directly correlated with more advanced disease upon diagnosis ($p < 0.001$). Overall, a greater proportion of patients received care in accordance with the recommendations following the ATA guidelines' publication in 2009: 61.4 % of patients treated between 2004 and 2008 versus 66.8 % of patients treated between 2009 and 2013 received care in accordance with the recommendations ($p < 0.01$). Factors such as older age, African American race, localized disease at diagnosis, lower estimated median zip code household income and being treated in a community versus an academic hospital were associated with a lower likelihood of receiving care in accordance with the guidelines.

Conclusion Adherence rates to the ATA recommendations for the treatment of MTC increased modestly following the publication of guidelines in 2009 with the largest increase seen in community hospitals. Being older, African American, diagnosed with localized disease and treated in a community hospital rather than in an academic institution was correlated with a lower likelihood of receiving treatment in accordance with the guidelines. Efforts should be made to continuously increase the adherence rates to the MTC ATA guidelines and to decrease socioeconomic disparities that continue to exist in the treatment of MTC.

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Introduction

Thyroid cancer is the twelfth most common cancer in the USA with the estimated incidence of 62,980 cases and 1890 deaths in 2014 [1]. There are four distinct subtypes of thyroid cancers: papillary, follicular, medullary and anaplastic. Medullary thyroid cancer (MTC) represents the third most common type of thyroid cancer and is associated with a worse prognosis when compared to the well-differentiated types of thyroid cancers, the papillary and follicular subtypes [2]. The incidence rate of MTC is thought to be 0.11 per 100,000 person-years and represents 3–5 % of all thyroid neoplasms [3, 4]. MTC is associated with over 13 % of all thyroid cancer related deaths [5]. The prognosis of patients diagnosed with MTC depends on the stage of the disease at diagnosis, as completeness of tumor resection without presence of regional or distal spread of the disease is a main factor in determining the survival outcome [6]. However, the tendency of MTC to have early metastatic spread at presentation and variation in its clinical course can often make the management of this disease both complex and challenging [5, 7].

The American Thyroid Association (ATA) is a non-profit international organization that serves as an educational resource for the public by promoting the prevention, diagnosis and treatment of thyroid disorders and thyroid cancer. The ATA created and published a specific set of clinical guidelines with evidence-based recommendations for the treatment of MTC in 2009 [8]. The goals of these guidelines are to assist physicians and surgeons in the clinical care of MTC patients and also to standardize the quality of care, thereby potentially improving survival outcomes [4]. Recent observational studies have shown that receiving treatment in accordance with the ATA guidelines was associated with an improvement in survival outcomes [4, 9]. Goffredo et al. [9] conducted an analysis using the surveillance, epidemiology and end results (SEER) program to determine the compliance rate with the 2006 ATA guidelines for the management of differentiated thyroid cancers. The authors concluded that there was a statistically significant improvement in disease-specific survival outcomes in the patients who received treatment according to the ATA guidelines. Similar results were reported by Panigrahi et al. [4]. The authors found a statistically significant decrease in survival in the patients who received care that was discordant with the 2009 ATA guidelines for MTC when analyzing trends based on SEER data from 1998 to 2006. However, the latter study by Panigrahi et al. [4] benchmarked the national practice patterns in the treatment of MTC between 1973 and 2006 against the MTC ATA guidelines that were published in 2009. This led us to design the current study to describe the impact of the publication of the 2009 MTC ATA guidelines on the national practice and to determine whether there have been any changes in the socioeconomic disparities in the treatment of MTC that were previously described by Panigrahi et al. [4].

The aims of this retrospective observational study were twofold. The main objective was to determine whether 2009 ATA guidelines for MTC led patients receiving guideline concordant care. We first determined the national practice patterns for the treatment of MTC prior to the publication of ATA guidelines from 2004 to 2008. We then analyzed the national pattern of treatment from 2009 to 2013 and compared adherence rates to the ATA guidelines by period. The secondary objectives of the study were to determine whether there were disparities present in the presentation and in the treatment of MTC based on specific clinical and patient variables.

Methods

The National Cancer Data Base (NCDB) is a nationwide oncology outcomes database, a joint program that was founded by the Commission on Cancer of the American College of Surgeons and the American Cancer Society in 1988 [10, 11]. The NCDB is sourced from hospital tumor registries that collect data on newly diagnosed cancer cases from more than 1500 Commission on Cancer-accredited facilities across the USA. The database contains approximately 70 % of all incident cancer diagnoses occurring each year in the USA and captures nearly 88 % of all newly diagnosed thyroid malignancy cases annually [10, 11]. The information that can be extracted from the NCDB includes patients' demographic characteristics, clinical and pathological staging of the primary tumor, presence of local metastases, distant metastases or both, and types of treatment and survival. Additionally, the NCDB also includes data regarding health insurance at time of diagnosis and socioeconomic status (SES) as measured by education and household income quartiles of the patients' zip codes [11].

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We identified patients diagnosed with MTC between 2004 and 2013 from the NCDB 2013 Participant User File using the International Classification of Diseases for Oncology, 3rd Edition (ICD-0–3) histology reference coding for MTC (8510, 8513 and 8345). The cases with secondary malignancies were eliminated from the sample.

Clinical features of the MTC tumors obtained from the database included type of surgery for the primary site (total and subtotal thyroidectomy, lobectomy, isthmectomy or no surgery), extrathyroidal extension, presence of metastasis at diagnosis, evidence of neck dissection and types of radiation treatment [i.e., external beam radiation therapy (EBRT) or radioactive iodine (RAI) treatment]. A patient was considered to have received neck dissection if there was evidence of a regional lymph node surgery with at least one lymph node examined by a pathologist. For our analysis, the cohort was divided into localized, regional and advanced disease. Disease was considered localized if the tumor was intrathyroidal without any evidence of regional or distant metastases. We defined regional disease as a tumor with evidence of extrathyroidal extension or cervical metastases. Disease was classified as advanced if the tumor had evidence of invasion into trachea, esophagus, larynx, mediastinum, prevertebral fascia or great vessels or presence of distant metastases.

Recommendations 61–63 from the 2009 ATA guidelines for MTC were analyzed in aggregate to determine the adherence rate for the treatment of localized and regional MTCs. According to these recommendations, total thyroidectomy with central (level VI) and possible lateral (levels II, III, IV, V) neck dissections should be performed for patients with MTC in the absence of distant metastases. Recent studies have demonstrated that the median lymph node counts for central neck dissection are typically low with wide ranges (1–16 lymph nodes), and patients with $\geq$6 central compartment lymph nodes removed have similar outcomes compared to patients with <6 lymph nodes removed [12, 13]. Based on these studies, we classified patients who had lymph node surgery and $\geq$1 lymph node removed as having received a neck dissection. Patients were deemed to have received care discordant with the recommendations if they did not receive total thyroidectomy and if there was no evidence that neck dissection was performed.

Recommendations 64–66 were analyzed as a group to determine the adherence rate to the guidelines for advanced diseases. According to these recommendations, surgery may be less aggressive or even deferred in the presence of advanced disease with or without distant metastases for palliative purposes. Given the variability in managing advanced stage disease, we elected not to include these patients in our analysis.

Recommendation 85 indicates that postoperative RAI should not be administered to patients with MTC in the absence of concomitant differentiated thyroid cancer. MTC cases without any concomitant secondary malignancy diagnoses were selected for this cohort. Therefore, patients who received surgery followed by RAI treatment were considered to have received care discordant with the guidelines' recommendation unless they were found to have a mixed histology of MTC and papillary/follicular carcinoma.

Data on patient race/ethnicity, rural or urban residence, SES (zip code quartiles of education and income) and health insurance classified as Medicaid or uninsured versus other insurance were extracted for further analysis. Hospitals were categorized as academic versus community, and race and ethnicity were categorized as non-Hispanic Whites, non-Hispanic Blacks, Hispanic and others/or unknown.

Estimated zip code median household income was derived from year 2000 US Census data and included the lowest quartile (<$30,000), the second and third quartiles (<$30,000–$34,999 and $35,000–$45,999, respectively) and the highest quartile (>$46,000).

Zip code education level was measured by the proportion who did not graduate from high school. The lowest quartile was defined 29 % or higher prevalence who did not graduate from high school, the second and third and highest quartiles were defined as 20–28.9, 14–19.9 and <14 % non-high school graduates, respectively.

The NCDB classifies a patient's residential area to be metropolitan based on its population size and rural by the degree of urbanization and its adjacency to a metro area. The NCDB has nine subclassifications, but for the purpose of our study, we divided them into three categories as follows: metro with populations >250,000, urban with populations >2500, and rural with populations <2500.

Hospitals were categorized as academic, representing academic and/or research programs including the National Cancer Institute designated comprehensive cancer centers or community hospitals.

Statistical analysis

The statistical significance of differences in proportions of patients who did or did not receive care according to the guidelines was assessed using Chi-square tests. Multivariate logistic regression was used to identify patients and hospital characteristics associated with the likelihood of receiving care discordant to the ATA guidelines. STATA version 13 (College Station, TX, USA) software was used for all analyses.

Results

There were 3693 patients with a confirmed diagnosis of MTC from 2004 to 2013 (Table 1). More than half of the patients (55.5 %) were between the age of 41 and 65, and the mean age at presentation was 54 years. A majority of the patients were female (62.4 %) and Caucasian (78.8 %). 60.3 % of the patients had local MTC, and 39.7 % of patients had regional metastases.

Table 1 illustrates the demographic and socioeconomic characteristics of the cohort. A higher percentage of patients of age ≤40 presented with regional disease (42.5 %) when compared to the other age groups. A higher percentage of men were diagnosed with regional stage when compared to women in the cohort (50.9 vs 33.0 %, $p < 0.001$). A greater proportion of Hispanics (44.0 %) presented with regional disease compared to other racial/ethnic groups ($p < 0.05$), and similarly, a greater proportion of patients who were uninsured or who were insured with Medicaid presented with regional disease when compared to the patients with other forms of insurance (50.5 vs 38.7 %, $p < 0.001$). Patients were more likely to be treated at academic hospitals rather than in community institutions ($p < 0.001$). There were no statistically significant differences in the demographic or socioeconomic characteristics of the patients before or after the publication of the ATA guidelines in 2009.

Treatment adherence to the MTC ATA guidelines is presented in Table 2. A greater proportion of patients diagnosed with localized or regional disease received care in accordance with the guidelines following publication in 2009 (66.8 vs 61.4 %, $p = 0.001$). Figure 1 illustrates the guideline adherence rate by year from 2004 to 2013. After publication of the guidelines in 2009, there was an increasing trend in guideline adherence.

The guidelines recommend that RAI not be given to patients with a sole diagnosis of MTC (recommendation 85). Prior to the publication of the guidelines, 2.1 % of the patients inappropriately received RAI for the treatment of MTC. This number decreased to 1.5 % (Table 2) following the publication of the guidelines ($p < 0.001$).

According to univariate analysis (Table 3), age was inversely correlated with the likelihood of receiving care concordant with the guidelines ($p < 0.001$). Female patients were less likely to receive care concordant with the guidelines (61.2 vs 67.1 %, $p < 0.001$). African Americans were found to be least likely to receive concordant care compared to Caucasians (55.2 vs 63.9 %, $p = 0.009$). Patients were more likely to receive care in accordance with the guidelines when diagnosed and treated after 2009 (66.0 vs 60.3 %, $p < 0.001$). Patients were more likely to receive concordant care if they were diagnosed with regional disease compared to local disease alone (84.7 and 49.5 %, $p < 0.001$). The patient's estimated median zip code household income and education level appeared to be directly related to his or her likelihood of receiving concordant care ($p < 0.01$). A higher percentage of patients received treatment in accordance with the guidelines at academic institutions compared to community hospitals (68.7 vs 51.4 %, $p < 0.001$). The insurance status and degree of urbanization of the patient's residence did not appear to be statistically significant factors associated with care in accordance with the guidelines.

The multivariate logistic regression model is summarized in Table 3. Briefly, the likelihood of guideline adherence revealed that patient age >65 had a 57 % lower likelihood of receiving concordant care when compared to patients who were <40 [OR 0.43, 95 % CI (0.25–0.74)]. African American patients were 31 % less likely to receive concordant care [OR 0.69, 95 % CI (0.53–0.90)]. Patients diagnosed with regional disease were most likely to receive appropriate care when compared to the patients diagnosed with localized disease [OR 5.68, 95 % CI (4.77–6.77)]. Patients diagnosed and treated in academic institutions had an increased likelihood of receiving treatment according to the guidelines: academic hospital patients had higher odds of receiving concordant care [OR 1.97, 95 % CI (1.67–2.33)] as compared to community hospital patients. There was an increase in care in accordance with the guidelines following their publication in 2009 [OR 1.34, 95 % CI (1.15–1.56)]. Income status, education, insurance and the degree of urbanization of the patient's residence did not appear to be significant factors in determining the likelihood of receiving concordant care according to the multivariate analysis.

Additionally, we conducted an adjusted multivariable Cox survival analysis that demonstrated improved survival in patients that received guideline-adherent care compared to patients who did not [hazard ratio (95 % CI) 0.61 (0.57–0.79), $p < 0.001$].

Discussion

To our knowledge, this is the first observational study to analyze the national practice patterns and trends in the treatment of MTC following the publication of the 2009 MTC ATA guidelines. The newly revised 2015 MTC guidelines were recently published by the ATA in 2015. The changes in the recommendations are summarized and listed in Table 4. While the guidelines used in this study are no longer clinically relevant, the aim of this study was to emphasize and analyze the changes in the clinical practice pattern that occur with the publication of new guidelines. Overall, there has been an increase in treatment

Table 1 Demographic, socioeconomic and hospital characteristics of the medullary thyroid cancer patients ($N = 3693$) by stage at diagnosis The National Cancer Database. 2004–2013

	Column%		Row%
	Local	Regional	Total
Total	2226 (60.3 %)	1467 (39.7 %)	3693 (100 %)
Age**			
40 and under	439 (57.5 %)	324 (42.5 %)	763 (20.7 %)
41–65	1323 (60.1 %)	819 (39.9 %)	2051 (55.5 %)
66 and over	555 (63.1 %)	324 (36.9 %)	879 (23.8 %)
Sex**			
Male	682 (49.1 %)	708 (50.9 %)	1390 (37.6 %)
Female	1544 (67.0 %)	759 (33.0 %)	2303 (62.4 %)
Race and ethnicity*			
Caucasian	1752 (60.2 %)	1159 (39.8 %)	2911 (78.8 %)
African American	223 (66.6 %)	112 (33.4 %)	335 (9.1 %)
Hispanic	181 (56.0 %)	142 (44.0 %)	323 (8.7 %)
Other or unknown	70 (56.5 %)	54 (43.5 %)	124 (3.4 %)
Years diagnosed			
2004–2008	1012 (60.9 %)	650 (39.1 %)	1662 (45.0 %)
2009–2013	1214 (59.8 %)	817 (40.2 %)	2031 (55.0 %)
Income (zip code)			
Lowest quartile	243 (58.1 %)	175 (41.9 %)	418 (11.3 %)
Second quartile	350 (61.7 %)	217 (38.3 %)	567 (15.3 %)
Third quartile	558 (61.0 %)	357 (39.0 %)	915 (24.8 %)
Highest quartile	986 (59.8 %)	664 (40.2 %)	1650 (44.7 %)
Unknown	89 (62.2 %)	54 (37.8 %)	143 (3.9 %)
Insurance status**			
Medicaid/uninsured	152 (49.5 %)	155 (50.5 %)	307 (8.3 %)
Other forms of insurance	2074 (61.3 %)	1312 (38.7 %)	3386 (91.7 %)
Education (zip code)			
Lowest quartile	338 (60.4 %)	222 (39.6 %)	560 (15.1 %)
Second quartile	462 (59.8 %)	310 (40.2 %)	772 (20.9 %)
Third quartile	459 (60.5 %)	300 (39.5 %)	759 (20.6 %)
Highest quartile	878 (60.2 %)	581 (39.8 %)	1459 (39.5 %)
Unknown	89 (62.2 %)	54 (37.8 %)	143 (3.9 %)
Area of residence (zip code)			
Metro	1841 (60.3 %)	1210 (39.7 %)	3051 (82.6 %)
Urban	270 (58.3 %)	193 (41.7 %)	463 (12.5 %)
Rural	32 (65.3 %)	17 (34.7 %)	49 (1.4 %)
Unknown	83 (63.8 %)	47 (36.2 %)	130 (3.5 %)
Type of hospital**			
Community	818 (65.5 %)	430 (34.5 %)	1248 (33.8 %)
Academic	1019 (58.1 %)	735 (41.9 %)	1754 (47.5 %)
Unknown[a]	389 (56.3 %)	302 (43.7 %)	691 (18.7 %)

* $p < 0.05$; ** $p < 0.001$

[a] Patients <40 years old have unknown facility type information

of MTC concordant with the guidelines in the time period between 2009 and 2013 when compared to the national practice patterns prior to the publication of the guidelines (60.3–66.0 %, $p < 0.001$, Table 3).

Panigrahi et al. [4] compared the national practice patterns for the treatment of MTC from 1998 to 2006 against the ATA guidelines' recommendations published in 2009. Our study differs in that it was conducted over the

Table 2 Percentage of patients who received treatment in accordance with 2009 medullary thyroid cancer American Thyroid Association guidelines recommendations 61–66 and 85: 2004–2008 (prior to the publication of the guidelines) versus 2009–2013 (post-publication of the guidelines)

Characteristics	*N* (%)
Recommendations 61–63: medullary thyroid cancer without evidence of advanced local disease or distant metastases should undergo total thyroidectomy with central ± lateral neck dissection(s)*	
2004–2008	1020 (61.4 %)
2009–2013	1357 (66.8 %)
Recommendation 85: postoperative RAI should not be given to patients with MTC in the absence of concomitant differentiated thyroid cancer*	
2004–2008	1516 (97.9 %)
2009–2013	1864 (98.5 %)

* $p < 0.001$

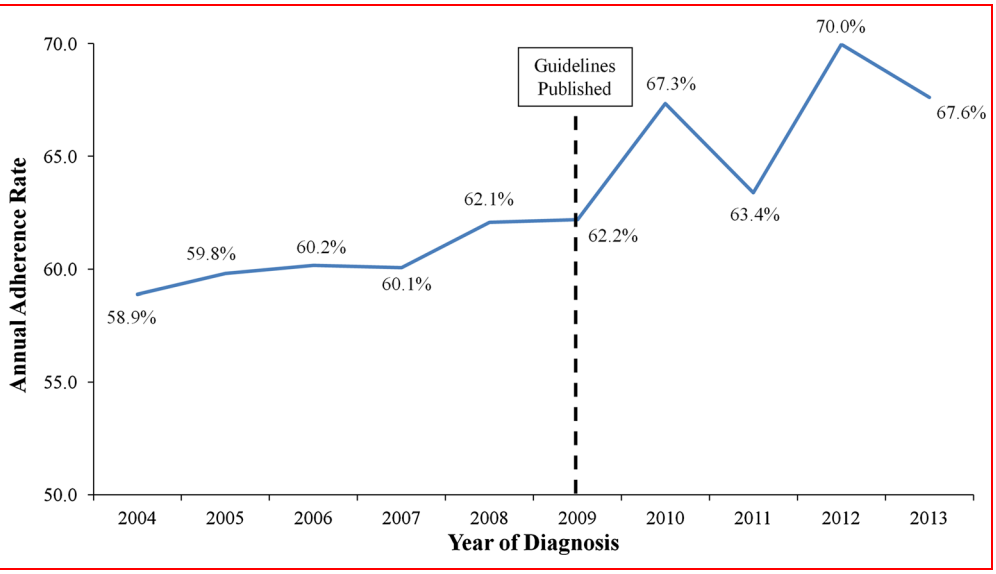

Fig. 1 Annual guideline adherence rate from 2004 to 2013

2004–2013 time period to assess change in practice patterns with surgery after publication of the 2009 guidelines. Panigrahi et al. were unable to assess the association between publication of the ATA guidelines and national practice patterns. Our study had the advantage of being able to compare the adherence rates to the guidelines before and after their publication to determine the relationship of guidelines' publication with national practice patterns.

The present study showed an increase in adherence rate to the MTC ATA guidelines following its publication in 2009. Although it was a modest increase, this improvement is significant given that it occurred over a short period (2009–2013). This increase in adherence rate also demonstrates the potential influence of ATA guidelines on the national thyroid management pattern. We hypothesize that the guideline adherence rate will have further improved since 2013, although this hypothesis needs to be confirmed with further studies. This finding may translate to a significant clinical improvement for patients as well, since Panigrahi et al. [4] showed that higher adherence to guidelines is associated with improved patient survival outcomes. Moreover, ATA guideline compliance has also been shown to reduce reoperation in MTC [14]. Additionally, in order to emphasize the importance of guideline adherence, we conducted an adjusted multivariable Cox survival analysis that demonstrated improved survival in patients that received guideline-adherent care compared to patients who did not.

Looking at adherence rates to the guidelines, a lesser likelihood of receiving care in accordance with the guidelines was observed among the elderly, patients diagnosed with localized disease, African American patients and those treated in a community hospital rather than in an academic institution.

Age has been consistently found to be an important prognostic factor associated with lower compliance with the guidelines in previously published observational studies on thyroid cancer [4, 9, 15, 16]. Wenaas et al. [15] and Famakinwa et al. [16] analyzed adherence rates to the 2006 ATA guidelines for well-differentiated thyroid cancer and

Table 3 Demographic, socioeconomic and hospital characteristics of the medullary thyroid cancer patients ($N = 3693$), univariate and multivariate analyses The National Cancer Database. 2004–2013

	Univariate Adherence rates *N* (%)	Multivariate Local and regional OR (95 % CI)
Age*		
40 and under	548 (71.8 %)	Ref.
41–65	1320 (64.4 %)	0.63 (0.37–1.09)
66 and over	475 (54.0 %)	0.43‡ (0.25–0.74)
Sex**		
Male	933 (67.1 %)	Ref.
Female	1410 (61.2 %)	1.04 (0.89–1.23)
Race and ethnicity*		
Caucasian	1861 (63.9 %)	Ref.
African American	185 (55.2 %)	0.69+ (0.53–0.90)
Hispanic	209 (64.7 %)	0.90 (0.68–1.21)
Other or unknown	88 (71.0 %)	1.27 (0.82–1.98)
Years diagnosed**		
2004–2008	1002 (60.3 %)	Ref.
2009–2013	1341 (66.0 %)	1.34‡ (1.15–1.56)
Extent of disease**		
Local	1101 (49.5 %)	Ref.
Regional	1242 (84.7 %)	5.68‡ (4.77–6.77)
Income (zip code)**		
Lowest quartile	252 (60.3 %)	Ref.
Second quartile	330 (58.2 %)	0.98 (0.72–1.32)
Third quartile	876 (63.0 %)	1.18 (0.86–1.60)
Highest quartile	1104 (66.9 %)	1.31 (0.94–1.84)
Insurance status**		
Medicaid/uninsured	221 (72.0 %)	Ref.
Other forms of insurance	2122 (62.7 %)	1.31 (0.97–1.77)
Education (zip code)*		
Lowest quartile	334 (59.6 %)	Ref.
Second quartile	487 (63.1 %)	1.14 (0.87–1.50)
Third quartile	471 (62.1 %)	1.07 (0.80–1.44)
Highest quartile	970 (66.5 %)	1.14 (0.84–1.55)
Area of residence (zip code)		
Metro	1949 (63.9 %)	Ref.
Urban	290 (62.6 %)	1.10 (0.86–1.41)
Rural	27 (55.1 %)	0.99 (0.51–1.91)
Unknown	77 (59.2 %)	0.97 (0.57–1.65)
Type of hospital**		
Community	641 (51.4 %)	Ref.
Academic	1205 (68.7 %)	1.97‡ (1.67–2.33)
Unknown[a]	497 (71.9 %)	1.29 (0.73–2.30)

For univariate analysis: * $p < 0.05$; ** $p < 0.001$

For multivariate analysis: + $p < 0.05$; ‡ $p < 0.001$

[a] Patients <40 years old have unknown hospital type information

Table 4 Summary of major changes in diagnosis and treatment of sporadic medullary thyroid cancer from 2009 to 2015 guideline publication Adapted from the ATA 2009 and 2015 MTC Guidelines (refs.)

	2009 Guidelines	2015 Guidelines
Diagnosis	52: This guideline defers the recommended approach to thyroid nodules, including FNA and serum calcitonin (Ctn) testing, to the ATA guideline that addresses thyroid nodules (5). However, if obtained, a basal or stimulated serum Ct level >100 pg/mL should be interpreted as suspicious for MTC and further evaluation and treatment should ensue (Fig. 1). Grade A recommendation	19: Thyroid nodules that are 1 cm or greater in size should be evaluated by FNA depending on the ultrasound characteristics. FNA findings that are inconclusive or suggestive of MTC should have calcitonin measured in the FNA washout fluid and IHC staining of the FNA sample to detect the presence of markers such as Ctn, chromogranin, and CEA and the absence of thyroglobulin. Grade B recommendation
Treatment	61: Patients with known or highly suspected MTC with no evidence of advanced local invasion by the primary tumor, no evidence cervical lymph node metastases on physical examination and cervical US, and no evidence of distant metastases should undergo total thyroidectomy and prophylactic central compartment (level VI) neck dissection. Grade B recommendation	24: Patients with MTC and no evidence of neck lymph node metastases by US examination and no evidence of distant metastases should have a total thyroidectomy and dissection of the lymph nodes in the central compartment (level VI). Grade B recommendation
	62: MTC patients with suspected limited local metastatic disease to regional lymph nodes in the central compartment (with a normal US examination of the lateral neck compartments) in the setting of no distant (extracervical) metastases, or limited distant metastases should typically undergo a total thyroidectomy and level VI compartmental dissection. A minority of the Task Force favored prophylactic lateral neck dissection when lymph node metastases were present in the adjacent peritracheal central compartment. Grade B recommendation	25: In patients with MTC and no evidence of neck metastases on US, and no distant metastases, dissection of lymph nodes in the lateral compartments (levels II–V) may be considered based on serum Ctn levels. The Task Force did not achieve consensus on this recommendation. Grade I recommendation
	63: MTC patients with suspected limited local metastatic disease to regional lymph nodes in the central and lateral neck compartments (with US-visible lymph node metastases in the lateral neck compartments) in the setting of no distant metastases, or limited distant metastases should typically undergo a total thyroidectomy, central (level VI), and lateral neck (levels IIA, III, IV, V) dissection. Grade B recommendation	26: Patients with MTC confined to the neck and cervical lymph nodes should have a total thyroidectomy, dissection of the central lymph node compartment (level VI) and dissection of the involved lateral neck compartments (levels II–V). When preoperative imaging is positive in the ipsilateral lateral neck compartment but negative in the contralateral neck compartment, contralateral neck dissection should be considered if the basal serum calcitonin level is >200 pg/mL. Grade C recommendation
	64: In the presence of distant metastatic disease, less aggressive neck surgery may be appropriate to preserve speech, swallowing, and parathyroid function while maintaining locoregional disease control to prevent central neck morbidity. Grade C recommendation	27: In the presence of extensive regional or metastatic disease less aggressive surgery in the central and lateral neck may be appropriate to preserve speech, swallowing, parathyroid function, and shoulder mobility. External beam radiotherapy (EBRT), systemic medical therapy, and other nonsurgical therapies should be considered to achieve local tumor control. Grade C recommendation
	65: In the presence of advanced local or distant disease, less aggressive neck surgery may be appropriate to maintain local disease control while preserving speech, swallowing, and parathyroid function. Grade C recommendation	
	66: In patients with extensive distant metastases a palliative neck operation may still be needed when there is pain, or evidence of tracheal compromise and the need to maintain a safe airway. Otherwise, in the setting of moderate to high-volume extracervical disease, neck disease may be observed and surgery deferred (Task Force opinion was not unanimous). Grade C recommendation	

Table 4 continued

2009 Guidelines	2015 Guidelines
72: Patients treated with hemithyroidectomy who demonstrate unifocal intrathyroidal sporadic MTC confined to the thyroid who have no CCH, negative surgical margin and no suspicion for persistent disease on neck US may be considered for additional surgery or follow-up without additional surgery if the basal serum Ct is below the upper normal of the reference range more than 2 months after surgery Those with a basal serum Ct above the normal reference range should undergo additional testing and therapy (to often include completion thyroidectomy and central lymph node dissection). Grade B recommendation	28: Following unilateral thyroidectomy for presumed sporadic MTC completion thyroidectomy is recommended in patients with a RET germline mutation, an elevated postoperative serum Ctn level, or imaging studies indicating residual MTC. The presence of an enlarged lymph node in association with a normal serum Ctn level is not an indication for repeat surgery. Grade B recommendation
	29: In patients having an inadequate lymph node dissection at the initial thyroidectomy a repeat operation, including compartment oriented lymph node dissection, should be considered if the preoperative basal serum CTN level is <1000 pg/mL and five or fewer metastatic lymph nodes were removed at the initial surgery. Grade C recommendation
93: Postoperative EBRT to the neck and mediastinum may be indicated in patients who undergo a gross incomplete resection (R2 resection). Prior to initiating EBRT, physicians should ensure that optimal surgery has been performed as reoperation (other than major ablative procedures) is much more difficult, and may not be safely or technically possible, after EBRT. Grade B recommendation	52: Postoperative adjuvant EBRT to the neck and mediastinum should be considered in patients at high risk for local recurrence (microscopic or macroscopic residual MTC, extrathyroidal extension or extensive lymph node metastases), and those at risk of airway obstruction. The potential benefits must be weighed against the acute and chronic toxicity associated with the therapy. Grade C recommendation
83: The routine use of cytotoxic chemotherapy should be discouraged in patients with MTC. It may be considered for selected patients with rapidly progressive disease not amenable to clinical trials or other palliative therapies discussed below under management of persistent or recurrent metastatic MTC. Grade E recommendation	65: In patients with significant tumor burden and symptomatic or progressive metastatic disease according to RECIST treatment with TKIs targeting both RET and VEGFR tyrosine kinases should be considered as systemic therapy. The TKIs vandetanib or cabozantinib can be used as single agent first-line systemic therapy in patients with advanced progressive MTC. Grade A recommendation

identified age ≥65 to be significantly associated with lower accordance rates with the guidelines. Similarly, Panigrahi et al. [4] assessed national practice patterns in the treatment of MTC and their accordance with the 2009 ATA guidelines and noted that increasing age was associated with lower adherence rates, with age ≥65 being the most significant prognostic factor.

In the present study, 62.4 % of the patients were female, and this proportion was statistically significant. This proportion of women is similar to that in the observational study published on MTC using the SEER database by Panigrahi et al. [4], who noted that 58 % of patients diagnosed with MTC and registered in the SEER database between 1973 and 2006 were women. However, the correlation between gender and disease stage at diagnosis was not analyzed. Our results revealed that men presented with more regionally advanced disease compared to women. This finding is consistent with previous studies that examined the disease stage at diagnosis for all thyroid cancers and reported that men were more likely to present with advanced disease and subsequently had a greater mortality from thyroid cancer than women [17, 18].

An association between SES and thyroid cancer stage at presentation has been recently reported [17, 19]. This association was identified in studies looking at outcomes of only well-differentiated thyroid cancers. Zevallos et al. [19] found that low SES patients were more likely to present with an advanced stage of well-differentiated tumors after adjusting for demographic and tumor-related factors. Our study failed to find any association between the patient's estimated median zip code household income, or education level and the stage of MTC at presentation. We did find a significant association between having Medicaid or being uninsured and a higher likelihood of presenting with regionally advanced disease. These findings are not surprising as low SES has been strongly correlated with poor access to health care which often results in later presentation of disease [20].

Interestingly, we identified increased adherence to guidelines in Medicaid and uninsured patients on univariate analysis. This finding is likely a result of the increased number of Medicaid and uninsured patients presenting with regionally advanced disease, necessitating lymph node dissection as part of definitive treatment.

We also found that African Americans were 31 % less likely to receive concordant care in MTC. Racial disparities in guideline adherence have been described in differentiated thyroid carcinoma [19]. Evidence from SEER studies have shown African Americans have increased mortality in thyroid cancer; therefore, guideline adherence

may serve to improve outcomes in this patient population [21]. In addition, access to care must be addressed as it has been previously reported that African Americans may not have same access to high-volume institutions as white patients, which may affect the type of treatment that African Americans receive [22, 23].

A higher estimated median zip code household income was associated with a higher likelihood of receiving care in accordance with the guidelines, supporting current findings in the literature [15]. Wenaas et al. [15] conducted a retrospective cohort analysis in the SEER database and determined that higher income patients had an increased likelihood of receiving ATA-compliant care for the treatment of advanced papillary thyroid cancer. This phenomenon is likely due to the fact that the patients with high SES have the means and the ability to search and access institutions that have been associated with higher concordance to the guidelines.

We did find that being treated in community hospitals was associated with a lower adherence rate to the ATA guidelines although this adherence rate increased after the publication of the 2009 guidelines. This change illustrates the importance of disseminating guidelines and current best practices to all institutions. Our data also note the overall reduced rate of guideline adherence consistent with previous studies showing that teaching hospitals tend to offer higher quality of care when compared to nonteaching hospitals [24]. On multivariate analysis, the lower adherence rates to the guidelines in community hospitals in this study were independent of SES factors. Therefore, outreach programs promoting evidence-based practices to the community hospitals may be warranted as a quality improvement initiative.

This study had several limitations that are inherent to using large national database, such as the possibility of the ecologic fallacy associated with the use of country-level estimated zip code socioeconomic determinants as well as errors in coding and sampling. Previous studies have demonstrated that regional measures of SES such as area-based estimated median household income are decent indicators of SES at the individual level [16, 25–27]. In addition, the NCDB does not collect information regarding patient preferences for treatment or postoperative complications which may have influenced the treatment modalities used. There are also limitations in treatment data analysis given that there is no consensus of what constitutes as lymphadenectomy on national databases. Medullary thyroid-specific calcitonin levels and carcinoembryonic antigen (CEA) levels are also not available in the NCDB, making it difficult to address recurrence and adequacy of surgery. Furthermore, the NCDB offers both the American Joint Committee on Cancer (AJCC) Staging and Collaborative Stage Data Collection systems, and it is up to the researcher's discretion to choose either one of the systems to analyze the disease stages. Therefore, depending on the staging system used, there may be a slight difference in the prevalence of disease stages.

Another consideration to guideline-adherent treatment is that education regarding consensus guidelines can come from multiple sources not reviewed in this manuscript. Providers can obtain updated information on care through multiple sources such as publications, expert opinions, CME courses or conferences that are consistent with guidelines-associated care. In this case, they could have provided care in accordance to the guideline recommendations without being aware of the publication of guidelines.

One final limitation in need of consideration was the possibility that a patient with localized disease was understaged. 518 (23.3 %) patients with localized disease were coded as Nx and did not have lymph node surgery. Patients who did not have a neck dissection nor had any evidence of extrathyroidal extension were considered localized as there was no indication to define them otherwise. This potentially could have lead to understaging in the localized group. However, these patients did not receive guideline-adherent care due to the lack of a neck dissection which may help explain why patients with localized disease had lower rates of guideline adherence compared to regional disease on both univariate and multivariate analyses.

Conclusion

To our knowledge, this is the first observational study to demonstrate improved adherence to ATA guidelines for the treatment of MTC following its publications in 2009. Efforts should be made to identify and educate institutions and regions to increase the adherence rates to the MTC ATA guidelines as new guidelines are published. This process should, in effect, act to decrease socioeconomic disparities that continue to exist in the treatment of MTC.

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Compliance with ethical standards

Conflict of interest None.

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