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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Improved Adherence to ATA Medullary Thyroid Cancer Treatment Guidelines

Jessica Liu McMullin, MD, MS, Jyotirmay Sharma, MD, Theresa Gillespie, PhD, Snehal G. Patel, MD, Collin J. Weber, MD, and Neil D. Saunders, MD

Department of Surgery, Emory University, Atlanta, GA

ABSTRACT

Background. The 2009 American Thyroid Association (ATA) guidelines for medullary thyroid cancer (MTC) were created to unify national practice patterns. Our aims were to (1) evaluate national adherence to ATA guidelines before and after 2009, (2) identify factors that are associated with concordance with guidelines, and (3) evaluate whether there is an association between survival and concordant treatment.

Patients and Methods. Patients with MTC were identified from the 2009 to 2015 National Cancer Database. Adherence to ATA recommendations regarding extent of surgery (R61–R66) was analyzed. Logistic regression was used to determine predictors of discordance and propensity score matching was used to compare concordant treatment rates between time periods. Kaplan–Meier survival analysis was used to determine association between survival and concordant treatment.

Results. There were 3421 patients with MTC, and of these 3087 had M0 disease and 334 had M1 disease. We found that 72% of M0 cases adhered to R61–66, and 68% of M0 cases without advanced local disease were adherent to R61–63. Following propensity score matching, the adherence rate was 67% before 2009 and 74% after. Patient factors associated with discordant treatment were female gender, older age, treatment at a nonacademic facility, and living within 50 miles of the treatment facility. Adherence to guidelines was associated with improved overall survival (OS) ($p < 0.01$).

Conclusions. Treatment of MTC was discordant from guidelines in 26% of cases from 2009 to 2015 compared with 33% prior to 2009 in a propensity matched analysis, and was most often in cases with localized, noninvasive disease. Improved adherence to guidelines may improve overall survival.

Medullary thyroid cancer (MTC) is a cancer from parafollicular cells, and it is one of the more aggressive thyroid cancers. While representing only 5% of thyroid cancers, 13.4% of deaths from thyroid cancer are attributed to MTC.[1,2] MTC is unfortunately associated with worse overall survival (OS) than differentiated thyroid cancers and requires more aggressive upfront surgical treatment as well. Surgery remains the mainstay of treatment, and radioactive iodine (RAI) has not been found to be effective in the treatment of MTC as parafollicular cells do not take up RAI.[3] More recently, molecular targeted agents have been approved for use in patients with MTC that has progressed or metastasized.[4]

In an effort to unify national practice patterns regarding MTC, guidelines were released in 2009 by the American Thyroid Association (ATA).[5] Surgery remains the cornerstone of treatment and is considered optimal MTC management, but guidelines only remain helpful if followed.[6] Adherence rates to the ATA guidelines up until 2013 have been described using both the National Cancer Database (NCDB)[7] and Surveillance, Epidemiology, and End Results (SEER) program.[8] However, a direct propensity matched comparison of pre- and post-guideline

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N. D. Saunders, MD
e-mail: neil.saunders@emory.edu

patients has not previously been performed. Additionally, the impact of adherence rates on survival has not been evaluated previously.

Our aims were to (1) utilize propensity score matched cohorts to evaluate national adherence to ATA guidelines and compare with adherence prior to 2009, (2) identify factors that are associated with discordance to guideline adherence, and (3) evaluate whether there is an association between survival and guideline-concordant treatment.

PATIENTS AND METHODS

Data Source and Study Population

The participant user file from the 2004 to 2015 National Cancer Database (NCDB) was used for this retrospective cohort study. The majority of the analysis was performed on patients from 2009 to 2015, focusing on the time period following the release of the 2009 ATA recommendations. Patients from 2004 to 2008 were used only for comparison of adherence rates to guideline recommendations. The NCDB is maintained jointly by the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society and was established in 1989.[9] More than 1 million cases per year are added from more than 1500 CoC-accredited cancer programs that participate, and reflect 70% of newly diagnosed cancer cases annually.[10] Data are abstracted using nationally standardized definitions by trained registrars with periodic auditing and edit checks and these data are then used to generate performance and benchmarking reports that are fed back to hospitals.[9–11]

NCDB records were queried for all MTC cases between 2004 and 2015 using the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) histology code 8510 for MTC. All patients with this histology code were included in the study population. For propensity score matching, only patients with all variables complete were included for possible matching. This study analyzed deidentified, preexisting data and thus was exempt from oversight by the Chesapeake Institutional Review Board.

Variables

Variables captured included patient characteristics, demographics, comorbidities, and socioeconomic variables. Socioeconomic variables of interest included insurance type, income level, highest achieved level of education, and city type (metro, urban, or rural). The variables income level and highest achieved level of education are not directly reported, and instead are estimated by matching US census data to the zip code of the patient at the time of diagnosis. Cancer-specific variables captured include tumor–node–metastasis (TNM) status and extrathyroidal extension. Local disease was defined as $\leq$ T3 and $\leq$ N1b. Advanced disease was defined as T4 and M1. Treatment-specific variables include type of surgery performed, whether a neck dissection was performed, and other treatment use such as iodine (RAI) or external beam radiation therapy (EBRT).

Outcomes

The primary outcomes of interest were adherence to 2009 ATA recommendations pertaining to the appropriate allocation and extent of surgery (R61–66).[5] These recommendations included that patients without advanced local invasion or with limited local metastatic disease without disease in the lateral neck compartments should undergo total thyroidectomy and prophylactic level VI central lymph node dissection (CLND) (R61–62). The recommendations suggest that patients with limited local metastasis with lateral neck disease should undergo a central (level VI) and modified radical neck dissection with lateral neck dissection (levels IIA, III, IV, and V) (R63). In the setting of distant metastatic disease, less aggressive surgery may be used to prevent central neck morbidity (R64–66). Adherence to guidelines was defined as a binary term where all components of the recommendation were followed. Other treatment modalities were also evaluated. The use of cytotoxic chemotherapy is recommended against (R83). Additionally, the use of RAI is also not recommended (R85). OS was compared between patients treated according to ATA guidelines and those who were not.

Statistical Analysis

Descriptive statistics were used to describe concordant versus discordant adherence to ATA guidelines. Associations between patient characteristics and adherence to guideline recommendations were obtained using a hierarchical multivariable logistic regression model accounting for patient clustering at the hospital level utilizing forward selection to identify variables with $p < 0.05$ remaining in the model.

Propensity score matching was utilized to create equal populations to compare adherent treatment rates prior to and following the release of the 2009 ATA guidelines. A greedy match was used between the two groups, and covariates entered into the propensity model included T, N, and M stages individually resulting in an identically matched cohort of MTC patients prior to 2009 and after. Chi-squared analysis was used to compare adherence rates between the two matched groups. Kaplan–Meier survival

analysis was used to determine differences in overall survival between adherent versus discordant patients.

RESULTS

A total of 3421 patients with MTC from 2009 to 2015 from 843 hospitals met the inclusion criteria. The breakdown of patient disease severity can be seen in Fig. 1. Of these, 3087 had M0 disease and 334 had M1 disease. A total of 427 patients had advanced disease (T4 and M1), while among M0 cases, 608 had advanced locoregional disease ($\leq$ T3 and $\leq$ N1b).

Of those with nonadvanced disease (n = 2994), 2572 patients (86%) had a total thyroidectomy performed, while 2049 patients (68%) had lymph node dissection (Table 1). R61–63 recommends total thyroidectomy and lymph node dissection in M0 cases without advanced local disease. In our cohort 2049 patients (68%) adhered to R61–63. In those with advanced disease (n = 427), 217 patients (51%) underwent surgery (all patients who underwent a total thyroidectomy, subtotal thyroidectomy, or limited resection), with 232 patients (54%) undergoing lymph node dissection (Table 1). When evaluating adherence to R61–66, which includes patients with advanced disease, in our cohort 2476 patients (72%) adhered to R61–66. Regarding other treatment modalities, 201 patients (5.8%) underwent cytotoxic chemotherapy, and 79 patients (2.3%) underwent RAI, both of which are not recommended.

A total of 6108 patients with MTC were identified in our dataset from 2004 to 2015. After propensity score matching, our total matched cohort with patients from 2004 to 2008 prior to 2009 ATA guidelines and 2009–2015 included 2890 patients, with 1445 in each group. The adherence rate prior to 2009 was 67% compared with 74% following 2009 ($p < 0.01$). The trend of rates of adherence in our overall cohort over time can be seen in Fig. 2.

Patient factors associated with discordant treatment were treatment at a nonacademic facility [odds ratio (OR) 1.8, 95% confidence interval (CI) 1.45–2.22], female gender (OR 1.73, CI 1.46–2.05), living within 50 miles of the treatment facility (OR 1.44, CI 1.08–1.94), and older age (OR 1.02, CI 1.01–1.03) (Table 2). Of note, 77.1% of those traveling > 50 miles were traveling to an academic center ($p < 0.01$) (Table 2). Adherence to guidelines correlates with improved OS ($p < 0.01$) (Fig. 3).

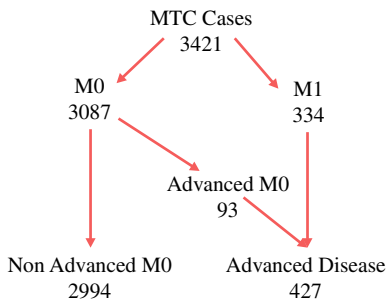

FIG. 1 Breakdown of patient population within cohort

DISCUSSION

The 2009 MTC ATA guidelines were developed in 2009 to unify national practice patterns. The national adherence to ATA guidelines has not been described recently using the NCDB and factors associated with discordance to guidelines, and its impact on survival remains poorly defined. In this study, we found an overall 72% adherence rate to R61–66 in the years following the 2009 ATA guidelines. Additionally, we utilized propensity score matched cohorts to evaluate factors associated with discordance and found that female gender, older age, treatment at a nonacademic facility, and living within 50 miles of the treatment facility was associated with discordant treatment, and that adherence to guidelines was associated with improved OS.

We sought to evaluate the national adherence rates to the ATA guidelines in propensity score matched groups, and overall found an increasing rate of adherence in patients from 2009 to 2015 compared with patients from 2004 to 2008. Adherence to ATA MTC guidelines has been evaluated previously using other large datasets such as SEER.[8] In a study by Panigrahi et al, SEER was used to evaluate concordance in patients undergoing MTC treatment from 1998 to 2006 prior to the release of the guidelines and found that only 59% of their 1344 patients received concordant treatment to the guideline recommendations.[8] That study evaluated the national practice patterns prior to the publication of the ATA guidelines, so they were unable to assess any changes associated with the release of the guidelines. They did find that there was significant variation in practice patterns within the USA and advocated for the benefit of standardized guidelines to optimize treatment such as the ATA MTC guidelines.[8] Chang et al. were able to evaluate guideline adherence in 2016 using the NCDB data from 2004 to 2013, allowing them to compare adherence rates before and after the release of the guidelines.[7] They had similar findings to ours in that they found a significant increase in adherence following the release of the guidelines in the short period up to 2013 following the release. They hypothesized that adherence was likely continuing to increase in the years following their study, and this result remains consistent with what we found.

Additionally, Chang et al. also evaluated factors associated with increased adherence to the ATA guidelines and found that elderly patients, patients with localized disease,

TABLE 1 Number of cases of each procedure performed and number of cases with lymph node resection in nonadvanced and advanced disease

	Procedure performed		Any lymph nodes resected	
	N	%	*n*	%
Nonadvanced disease (n= 2994)				
Total thyroidectomy	2572	86	2049	68
Subtotal thyroidectomy	64	2	39	1
Limited resection	215	7	94	3
No thyroid surgery	98	3	20	1
Unknown	45	2	19	1
Advanced disease (n = 427)				
Total thyroidectomy	185	43	176	41
Subtotal thyroidectomy	7	2	6	1
Limited resection	25	6	18	4
No thyroid surgery	202	47	32	8
Unknown	8	2	5	1

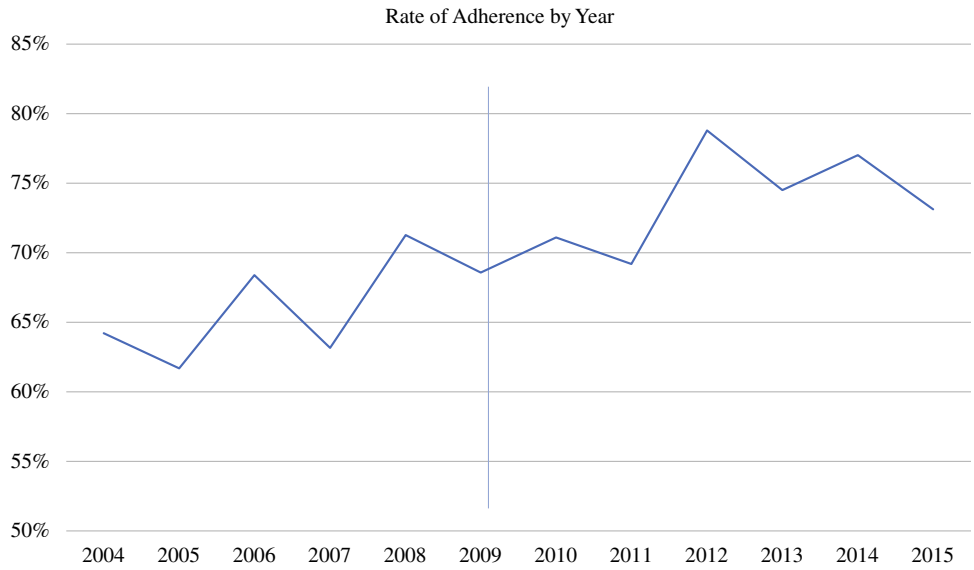

FIG. 2 Rates of adherence by year

African American patients, and those treated in a community hospital were less likely to receive care in concordance with the guidelines.[7] We similarly found that older age and treatment at a nonacademic facility were associated with guideline-discordant treatment. However, unlike Chang et al. we did not find a statistically significant difference in receipt of guideline-adherent care among African American patients. We also found that female gender and patients living within 50 miles of a treatment facility were also associated with guideline-discordant treatment; however, the majority of patients who were traveling > 50 miles to the facility were traveling to an academic center, which may be a confounding factor in this analysis.

While we sought to examine adherence specifically to the ATA guidelines, it is important to note that these guidelines are similar to the recommendations through the National Comprehensive Cancer Network (NCCN) and the adherence rates are not impacted by which guidelines were followed.[12] The NCCN guidelines for MTC recommend total thyroidectomy with bilateral central neck dissection, much like R61–62 within the ATA guidelines, and they also recommended therapeutic ipsilateral or bilateral modified neck dissection including levels II–V for clinically or radiologically identifiable disease.[12] Additionally, in 2015, the ATA released updated guidelines for the management of MTC.[13] The updated ATA recommendations that pertained to the appropriate allocation and extent of surgery included R24–26. The recommendations regarding extent of surgery still align with the recommendations from 2009 and do not impact the adherence rates from our study. These updated recommendations included that patients with MTC and no evidence of neck lymph node metastasis should undergo a total

TABLE 2 Factors associated with discordance to the 2009 ATA guidelines for MTC

Predictor	Adherent (%)	Discordant (%)	OR	95% CI	*p* value
Gender					**< 0.01**
Male	78.5	21.5	REF	REF	
Female	68.0	32.0	1.73	1.46–2.05	
Race					0.34
White	72.9	27.1	REF	REF	
Black	67.7	32.3	1.23	0.93–1.63	
Other	73.0	27.0	1.09	0.70–1.69	
Hispanic	73.3	26.7	0.95	0.71–1.29	0.76
Insurance					0.73
Private	75.9	24.1	REF	REF	
Uninsured	76.7	23.3	0.99	0.59–1.66	
Government	67.7	32.3	1.09	0.88–1.36	
Income					0.90
$46,000+	74.7	25.3	REF	REF	
$35,000–45,999	72.6	27.5	0.98	0.76–1.27	
$30,000–34,999	69.5	30.5	1.03	0.76–1.40	
< $30,000	70.5	29.5	0.91	0.63–1.31	
Education (by zip code)					0.45
1 (most educated)	74.5	25.5	REF	REF	
2	72.4	27.7	1.10	0.86–1.40	
3	71.6	28.4	1.17	0.86–1.58	
4 (least educated)	70.2	29.8	1.34	0.94–1.90	
City type					0.12
Metro	72.7	27.3	REF	REF	
Urban	70.3	29.7	1.32	0.99–1.74	
Rural	64.3	35.7	1.48	0.67–3.24	
Charlson–Deyo score					0.30
0	73.6	26.4	REF	REF	
1	68.7	31.3	1.14	0.91–1.42	
2	60.6	39.4	1.39	0.88–2.18	
3	61.3	38.7	1.47	0.68–3.19	
Facility type					**< 0.01**
Academic	78.1	21.9	REF	REF	
Nonacademic	64.4	35.6	1.8	1.45–2.22	
*Age**	55.2	59.3	1.02	1.01–1.03	**< 0.01**
Distance travelled					**0.02**
≥ 50 miles	78.5	21.5	REF	REF	
< 50 miles	71.2	28.8	1.44	1.08–1.94	

Statistically significant with $p < 0.05$ are given in bold

*Mean ± SD

thyroidectomy with dissection of the lymph nodes in the central compartment (R24), that lateral compartment lymph node dissection may be considered on the basis of serum calcitonin levels (R25), and that patients with positive preoperative imaging in the ipsilateral lateral neck compartment could still consider contralateral neck dissection if the serum calcitonin level is greater than 200 pg/mL.[13]

The clinical benefits of guideline adherence have also been evaluated previously using differentiated thyroid cancer (DTC) rather than MTC. The ATA released guidelines in 2006 on the management of DTC,[14] and Goffredo et al. utilized SEER to determine the clinical impact of the 2006 ATA guidelines on the management of DTC.[15] They found increased concordance with guidelines when comparing patients with DTC from 2004 to 2006

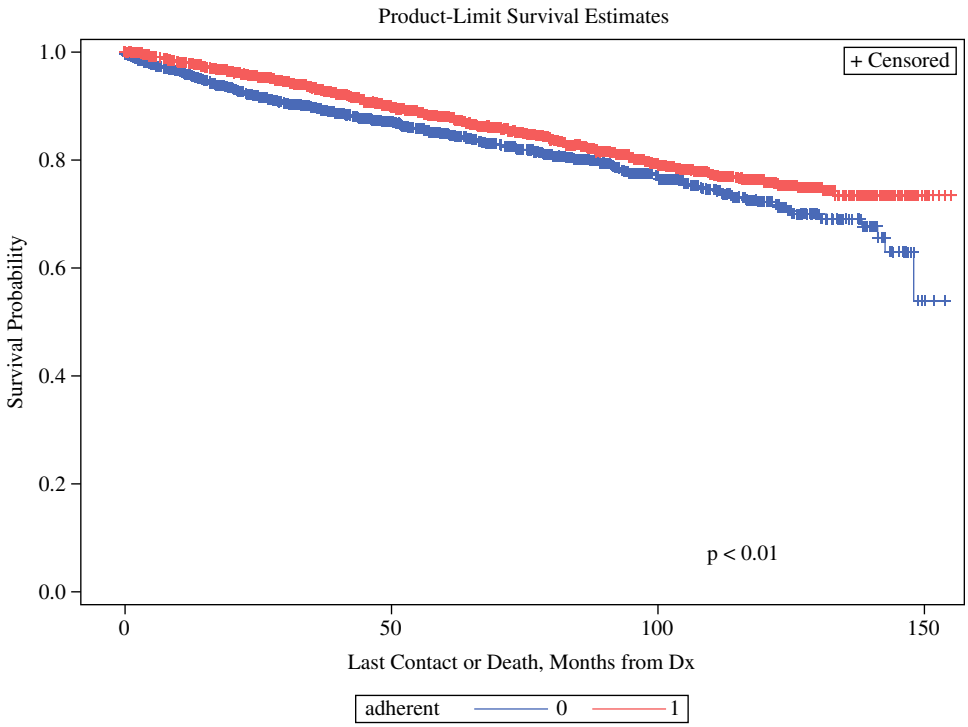

FIG. 3 Kaplan–Meier survival curves by adherent or nonadherent with guidelines

versus 2007 to 2009 and found that this increased concordance was associated with improved patient outcomes, including an improvement in overall and disease-specific survival for DTC after the ATA 2006 guidelines were released.[15] With MTC, Verbeek et al. found that adherence to ATA guidelines led to more biochemical cures and fewer cancer-related reoperations in a retrospective dual-institution study.[16] In our Kaplan–Meier survival analysis, we also noted that improved OS was associated with increased adherence to guidelines (Fig. 3). Our paper is novel in that it specifically uses propensity score matching to compare survival in identical TNM-staged groups.

Limitations to this study include those with using any large observational dataset, such as granularity of the data abstracted and the potential for error in its abstraction and coding. Disease-specific survival as well as extent of lymphadenectomy is unavailable in NCDB. Additionally, no data related to disease recurrence or treatment received beyond the initial 12 months post-diagnosis are included. Laboratory values such as calcitonin, biochemical responses to treatment, or biomarkers of recurrence are not included in the NCDB unless a laboratory test was used for initial diagnosis. For systemic therapy, the NCDB documents whether chemotherapy, hormonal therapy, or immunotherapy was given, as single or multiple agents, but specific names of drugs, doses, or dates of systemic therapy are not listed. This includes the use of molecular targeted agents that were approved for use in advanced disease and the impact these novel agents may be having on survival. The NCDB does not indicate whether a particular case is considered inherited or sporadic and does not include information related to prophylactic surgery. Furthermore, the NCDB dataset is unable to account for patient preference regarding preference of treatment or extent of surgery. Certain patient socioeconomic data, such as education and income levels, are based on zip codes and census data, so are not patient specific. Additionally, the NCDB is not a population-based dataset, so the number of participating centers in NCDB may change over time. Thus, we are able to identify trends, such as with adherence to guidelines, across the very large number of participating centers, but not volume of patients overall. These limitations can introduce fallacy into our analysis.

Other limitations of the NCDB are also pertinent to this study of guideline-adherent care. The NCDB includes both clinical and pathological staging (if the patient underwent surgery). While specific clinical data that contribute to that staging, e.g., radiographic evaluation, are not included in the NCDB, the actual staging assigned that reflects invasive disease and regional and distant metastasis is well documented. The accuracy of this staging in the NCDB is considered very accurate since only cancer programs that are accredited by the American College of Surgeons' Commission on Cancer are able to submit data to the NCDB. However, this remains a limitation to the study that is worth noting, as any inaccurate clinical data impact which surgical recommendation to follow.

Protocolization and standardization of therapy is one of the fundamental concepts to improving clinical care and surgical outcomes on a national level, and we have found that the dissemination of standardized guidelines has led to increased concordance with MTC guidelines and has led to improvement in patient outcomes and survival. However, 26% of cases from 2009 to 2015 still remain discordant from the 2009 ATA guidelines, and while this is an improvement from previous data showing up to 33% of patients not receiving recommended therapy, there continues to be room for improvement. Additionally, we identified certain patient populations, specifically female patients, elderly patients, those treated at a nonacademic facility, and those living within 50 miles of a treatment facility, that are associated with increased discordance to the guidelines. To reduce disparities in these specific populations, one approach would involve increased efforts in educating institutions on these guidelines. Additionally, just as care is moving toward focusing on specialized designated cancer centers for the management of complex abdominal cancers such as pancreatic adenocarcinoma, treatment of MTC in specialized centers may also improve adherence to guideline recommendations. The ATA released revised guidelines in 2015, and concordance of treatment with these revised guidelines should be assessed in the future.

Treatment of MTC was discordant with 2009 ATA guidelines in 26% of cases from 2009 to 2015 compared with 33% prior to 2009 in a propensity matched analysis, and was most often observed in cases with localized, noninvasive disease. We should continue to strive to increase adherence to guidelines, which may lead to improved patient outcomes and OS in patients with MTC.

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