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Trends and Predictors of Chemotherapy Use among Thyroid Cancer Patients in the National Cancer Database (2004–2013)

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Key Words
Differentiated thyroid cancers · Medullary thyroid cancer · Multikinase inhibitor

Abstract
Background/Aim: Beginning in 2011, the Food and Drug Administration (FDA) approved the use of multikinase inhibitors (MKIs) for medullary thyroid cancers (MTCs), and in 2013 MKIs were approved for metastatic differentiated thyroid cancers (DTCs). However, little is known about the use of chemotherapy in thyroid cancer patients. Thus, the goal of our study was to describe patterns of chemotherapy use, including MKIs, among DTC and MTC patients in the National Cancer Database (NCDB). ***Methods:*** Chemotherapy use, along with other treatment types (surgery and radiation), was assessed between 2004 and 2013. The primary predictor was the year of diagnosis (2004–2010 and 2011–2013), based on the FDA's approval of chemotherapy for MTC (2011). Baseline use of MKIs in DTCs in 2013 was also examined. Multivariable logistic regression was used to estimate odds ratios (OR) and 95% CI of receipt of chemotherapy. ***Results:*** Overall, 199,654 patients were included in our analytic sample with 194,667 nonmetastatic DTCs, 1,633 metastatic DTCs, and 3,354 MTCs. Among MTCs, chemotherapy use significantly increased from 3.1% in 2004–2010 to 5.0% in 2011–2013 ($p = 0.018$) in unadjusted and adjusted (OR = 1.54, 95% CI: 1.00, 2.36) analyses. In metastatic DTCs, 4.9% of patients received chemotherapy in 2013, which was not significantly higher than in previous years ($p = 0.755$). ***Conclusions:*** Overall, chemotherapy use among MTCs increased marginally following the FDA's approval of MKIs in 2011, although their use remains very low. MKIs were infrequently used in metastatic DTCs in 2013. Future studies examining patterns of chemotherapy in thyroid cancer patients are warranted.

Introduction

Each year, 64,300 men and women are diagnosed with thyroid cancer [1]. Approximately 90% of thyroid cancers are differentiated tumors comprised of papillary and follicular tumors that are commonly diagnosed at an early stage and have high cause-specific survival rates that, on average, exceed 95% [2]. Yet, there is subset of differentiated thyroid cancers (DTCs) that do not respond to traditional therapies and have worse outcomes. Furthermore, medullary thyroid cancers (MTCs) have poorer

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survival outcomes as well where 10-year disease-specific survival rates drop from 95% for patients with localized disease to 76 and 40% in patients with regional and distant stage disease, respectively [3].

Until recently, there were no effective curative treatments for advanced or metastatic MTCs as patients with these tumors do not respond to radioactive iodine [4] and there is conflicting evidence regarding the benefit of external beam radiation [5]. However, beginning in 2011, the Food and Drug Administration (FDA) approved the use of several multikinase inhibitors (MKIs) based on recent clinical trials showing their ability to limit disease progression [6–11]. It is not known, however, whether the assimilation of chemotherapy use in thyroid cancer patients in clinical practice has increased in recent years and whether it varies by patient demographics and facility characteristics. Thus, the primary goal of our study was to describe patterns of chemotherapy use, including MKIs, among MTC patients in relation to the FDA's 2011 approval of these drugs using the National Cancer Database (NCDB) between 2004 and 2013. The secondary goal of the study was to examine baseline chemotherapy use in metastatic DTCs in light of the FDA's more recent approval (November 2013) of MKIs for metastatic DTCs [10].

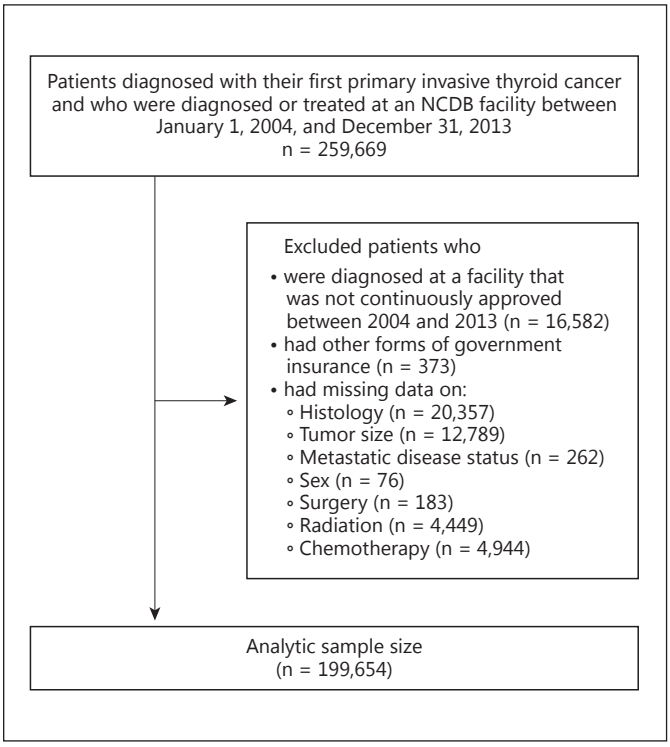

Fig. 1. Study population and exclusion criteria.

Methods

Study Population and Patient Selection

Data from the NCDB, a hospital-based cancer registry jointly sponsored by American Cancer Society and the American College of Surgeons, were used in this study. The NCDB includes approximately 76% of all malignant thyroid cancers in the United States from over 1,400 facilities accredited by the American College of Surgeons' Commission on Cancer (CoC) that collect and submit data to the NCDB [12]. The NCDB contains standardized data elements on patient sociodemographic, insurance status, tumor characteristics, and first course of treatment and facility factors [13]. The Morehouse University Institutional Review Board reviewed American Cancer Society studies using the NCDB and determined this study exempt from institutional review board review.

Adults ≥18 years and older who were diagnosed with their first primary medullary or metastatic well-differentiated thyroid tumors between January 1, 2004, and December 31, 2013, and who received all or part of their first course of treatment at a CoC-accredited facility were selected from the NCDB (n = 259,669). 2013 data were the most recent available. This population was further restricted by excluding patients with missing data on histology, tumor size, chemotherapy, surgery, radiation, and facility characteristic variables, as outlined in figure 1. We excluded insured patients with other government forms of insurance (e.g. Indian Bureau of Affairs) from analyses because of small numbers (n = 373). In order to more accurately examine temporal changes in chemotherapy use, patients treated at noncontinuously approved CoC-accredited facilities were also excluded from the study (n = 16,582) as the number of CoC-accredited facilities contributing data to the NCDB increased over time. The final analytic cohort contained 199,654 patients.

Histologic type was based on the World Health Organization's International Classification of Diseases for Oncology version 3 (ICD-O3), and the following ICD-O3 codes were used to define differentiated tumors (8290, 8330:8332, 8335, 8050, 8260, 8340–8341, 8343–8344, 8350) and medullary tumors (8345, 8346, 8510) [14].

Outcome Measures

The primary outcome of this study was overall receipt of chemotherapy use, which was considered as a binary variable (yes/no). All MKIs are coded as chemotherapy based on the Surveillance Epidemiology End Results*Rx coding guidelines, which are also followed by the NCDB. The NCDB does not collect data on the type or dosage of chemotherapy, so we were unable to determine differences between non-MKI and MKI chemotherapy agents [13].

Predictor Variables

Several patient, area, and facility level characteristics were included in our analyses. The primary predictor was the year of diagnosis, which was grouped into categories based on the recent (2011) FDA approval of chemotherapy for MTC (2004–2010 vs.

2011–2013). For DTCs, changes in chemotherapy between 2004 and 2012 versus 2013 were assessed based on the FDA's 2013 approval for this group of patients. We also examined changes in chemotherapy use among metastatic DTCs in 2004–2010 versus 2011–2013 to see if potential patterns mirrored those of MTCs. Patient race/ethnicity was categorized as white, black, and other. Insurance types at the time of diagnosis were grouped into the following categories: uninsured/Medicaid and Medicare/private, and missing/other. Tumor size was also considered and grouped as: <2 cm, 2–3.9 cm, and ≥4 cm. Surgery was grouped into two main categories (no surgery, subtotal thyroidectomy, or total thyroidectomy) and receipt of radiation was considered as a binary variable (yes/no).

Facility-level characteristics included facility type and were classified based on accreditation program of the CoC: community cancer, comprehensive community cancer, and teaching or research centers. Community centers treat at least 300 cancer patients a year and have a full range of services for cancer care, but patients need a referral for portions of their treatment. Comprehensive community cancer centers offer the same range of services as the community hospitals but treat at least 650 annual cancer patients and conduct weekly cancer conferences. Teaching/research facilities have residency programs and ongoing cancer research, and this group also includes National Cancer Institute (NCI)-designated centers.

Statistical Analyses

Statistical analyses were performed with SAS software (version 9.3; SAS Institute Inc., Cary, N.C., USA). Differences in patient demographic and clinical factors by histologic type were examined using χ^2 tests and corresponding p values. These test statistics were also employed to analyze the relationship between chemotherapy and the aforementioned patient and physician characteristics stratified by histologic type. We also examined the receipt of other treatments, including surgery and radiation, in the most recent time period (2011–2013) using descriptive statistics. Marginal logistic regression models, accounting for clustering of patients within facility types, were used to estimate odds ratios (OR) and corresponding 95% CI of receipt of chemotherapy over time. Multivariate models were also used to examine the association between chemotherapy and patient and facility factors in the most recent diagnosis years (2011–2013). Additional multivariable models with an interaction between time (2004–2010 vs. 2011–2013) and patient as well as facility characteristics were conducted to determine if certain patients or facilities adopted chemotherapy sooner. We also examined chemotherapy use by patient and facility characteristics in 2013 for metastatic DTCs; however, model estimates were unstable due to the small number of cases diagnosed in this year (n = 225).

Results

Overall, 199,654 patients were included in our analytic sample with 194,667 nonmetastatic DTCs, 1,633 metastatic DTCs, and 3,354 MTCs. The average age was 48.8 years in nonmetastatic DTC, 60.2 years in metastatic DTC, and 54.0 years in MTC patients (table 1). The majority of patients were female and white, regardless of the histology. Approximately 41.3% of MTCs had positive regional lymph nodes and 5.5% had metastatic disease. A greater proportion of metastatic DTCs and MTCs were treated at teaching/research facilities compared to nonmetastatic DTCs.

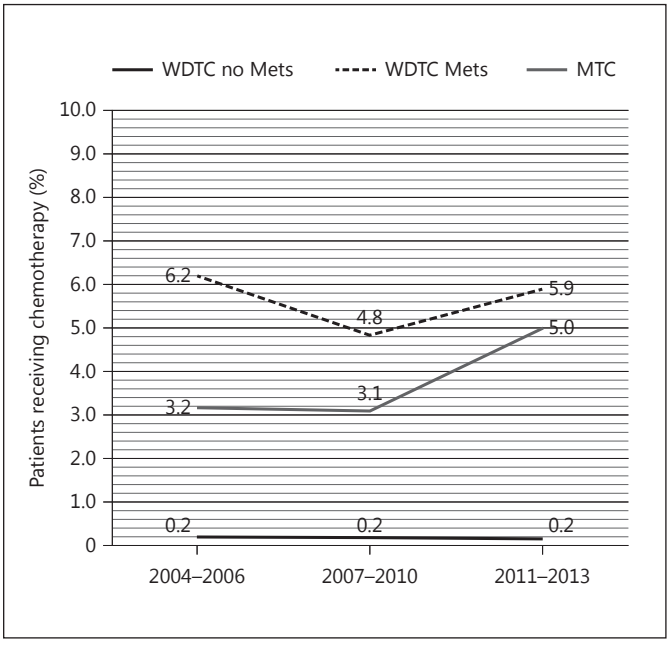

Fig. 2. Proportion of patients receiving chemotherapy over time by type of thyroid cancer, NCDB 2004–2013. WDTC = Well-differentiated thyroid cancer; Mets = metastatic. p values comparing chemotherapy use in 2011–2013 with 2004–2010: DTC no Mets p = 0.389, DTC Mets p = 0.595, MTC p = 0.018.

Among MTCs, 5.0% of patients received chemotherapy in 2011–2013, which was significantly higher than 3.1–3.2% in 2004–2010 (p = 0.018; fig. 2). After adjusting for patient sociodemographic and clinical factors as well as facility type, the odds of receipt of chemotherapy in 2011–2013 were higher than in 2004–2010 (OR = 1.54, 95% CI: 1.00, 2.36). Among metastatic MTCs, the prevalence of chemotherapy use increased nonsignificantly between 2004–2010 and 2011–2013, from 29.7 to 41.1% (p = 0.112). In 2011–2013, the large majority of nonmetastatic MTCs were treated surgically and approximately 37% of metastatic MTC patients received surgery (with or without radiation; fig. 3). For metastatic DTCs, 6.15% of patients received chemotherapy in 2011–2013, which was not significantly higher than 4.8–6.4% in 2004–2010 in unadjusted (p = 0.595) or adjusted analyses (OR = 1.19, 95% CI: 0.78, 1.81). Among the 225 metastatic DTCs

Table 1. Patient and facility factors by type of thyroid cancer, NCDB (2004–2013)

Categories	Total (n = 199,654), n (%)	Nonmetastatic DTC (n = 194,667), n (%)	Metastatic DTC (n = 1,633), n (%)	MTC (n = 3,354), n (%)	p value
Sex					<0.0001
Male	45,169 (22.6)	43,106 (22.1)	719 (44)	1,344 (40.1)	
Female	154,485 (77.4)	151,561 (77.9)	914 (56)	2,010 (59.9)	
Age group					<0.0001
<50 years	104,612 (52.4)	102,898 (52.9)	416 (25.5)	1,298 (38.7)	
50–70 years	78,588 (39.4)	76,345 (39.2)	706 (43.2)	1,537 (45.8)	
>70 years	16,454 (8.2)	15,424 (7.9)	511 (31.3)	519 (15.5)	
Race					<0.0001
White	145,169 (72.7)	141,684 (72.8)	1,044 (63.9)	2,441 (72.8)	
Black	14,792 (7.4)	14,260 (7.3)	204 (12.5)	328 (9.8)	
Other	26,333 (13.2)	25,678 (13.2)	299 (18.3)	356 (10.6)	
Missing	13,360 (6.7)	13,045 (6.7)	86 (5.3)	229 (6.8)	
Insurance status					<0.0001
Uninsured/Medicaid	16,818 (8.4)	16,281 (8.4)	228 (14)	309 (9.2)	
Medicare/private	179,324 (89.8)	174,987 (89.9)	1,372 (84)	2,965 (88.4)	
Missing	3,512 (1.8)	3,399 (1.7)	33 (2)	80 (2.4)	
Charlson Comorbidity Score					<0.0001
0	168,136 (84.2)	164,182 (84.3)	1,203 (73.7)	2,751 (82)	
1	25,454 (12.7)	24,658 (12.7)	300 (18.4)	496 (14.8)	
≥2	6,064 (3)	5,827 (3)	130 (8)	107 (3.2)	
Facility type					<0.0001
Community cancer program	10,682 (5.4)	10,484 (5.4)	78 (4.8)	120 (3.6)	
Comprehensive cancer center	85,547 (42.8)	83,841 (43.1)	619 (37.9)	1,087 (32.4)	
Teaching/research/NCI	88,008 (44.1)	85,287 (43.8)	837 (51.3)	1,884 (56.2)	
Other	15,417 (7.7)	15,055 (7.7)	99 (6.1)	263 (7.8)	
Tumor size					<0.0001
≤2 cm	168,136 (84.2)	164,182 (84.3)	1,203 (73.7)	2,751 (82)	
2–3.9 cm	25,454 (12.7)	24,658 (12.7)	300 (18.4)	496 (14.8)	
≥4 cm	6,064 (3)	5,827 (3)	130 (8)	107 (3.2)	
Positive regional nodes					<0.0001
No	155,360 (77.8)	152,727 (78.5)	733 (44.9)	1,900 (56.6)	
Yes	40,510 (20.3)	38,352 (19.7)	772 (47.3)	1,386 (41.3)	
Missing	3,784 (1.9)	3,588 (1.8)	128 (7.8)	68 (2)	
Metastatic disease					<0.0001
No	197,837 (99.1)	–	–	3,170 (94.5)	
Yes	1,817 (0.9)	–	–	184 (5.5)	
Diagnosis period					<0.0001
2004–2006	48,160 (24.1)	46,960 (24.1)	291 (17.8)	909 (27.1)	
2007–2010	83,057 (41.6)	80,971 (41.6)	663 (40.6)	1,423 (42.4)	
2011–2013	68,437 (34.3)	66,736 (34.3)	679 (41.6)	1,022 (30.5)	
Surgery type					<0.0001
No surgery or local	1,672 (0.8)	1,361 (0.7)	202 (12.4)	109 (3.2)	
Thyroidectomy	169,680 (85)	165,347 (84.9)	1,345 (82.4)	2,988 (89.1)	
<Thyroidectomy	28,302 (14.2)	27,959 (14.4)	86 (5.3)	257 (7.7)	
Radiation					<0.0001
None	95,044 (47.6)	91,733 (47.1)	402 (24.6)	2,909 (86.7)	
Radioactive iodine	101,436 (50.8)	100,407 (51.6)	930 (57)	99 (3)	
External beam	1,446 (0.7)	833 (0.4)	276 (16.9)	337 (10)	
Other	1,728 (0.9)	1,694 (0.9)	25 (1.5)	[a]	
Chemotherapy use					<0.0001
No	199,082 (99.7)	194,309 (99.8)	1,543 (94.5)	3,230 (96.3)	
Yes	572 (0.3)	358 (0.2)	90 (5.5)	124 (3.7)	
Mean age (SD), years	49 (14.71)	48.8 (14.63)	60.2 (16.59)	54 (15.41)	

[a] Data suppressed due to small numbers (<11 patients).

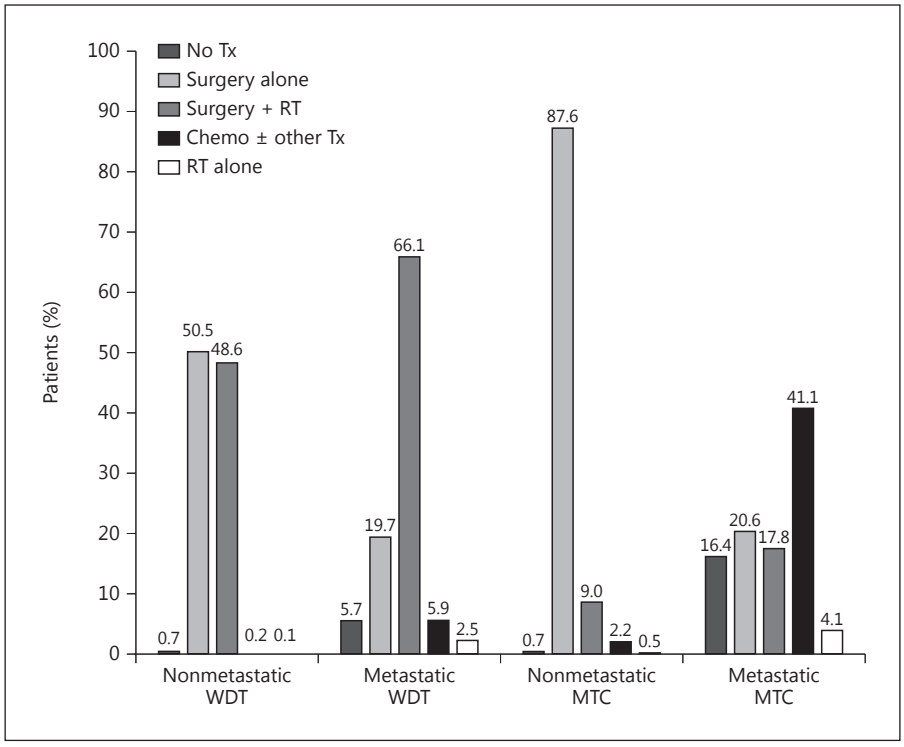

Fig. 3. Treatment patterns among well-differentiated and MTC patients in the most recent time period, NCDB 2011–2013.

diagnosed in 2013, 4.9% received chemotherapy, which was not significantly different than in 2004–2012 where 5.6% of patients (n = 1,408) received chemotherapy (p = 0.755). Surgery remains the most common form of treatment in metastatic DTCs. Overall, <1% of DTC patients without metastatic disease received chemotherapy, which was consistent throughout our study period.

Table 2 displays the proportion of patients receiving chemotherapy by patient and facility factors between 2011 and 2013. Among MTCs, over 40% of metastatic patients received chemotherapy compared to <2% of nonmetastatic patients (p < 0.001), and chemotherapy use was more common among patients with larger tumors and regional lymph node spread. Chemotherapy use was more common in males and in uninsured/Medicaid patients in MTCs, but did not vary by facility type. Among metastatic DTCs, chemotherapy use did not vary by patient demographics or facility type, but was more common in patients with larger tumors. Among nonmetastatic DTCs, <1% of patients received chemotherapy, regardless of patient or facility characteristics.

Table 3 presents adjusted models factors related to chemotherapy use by histologic type in the most recent time period (2011–2013). Among MTCs, several clinical factors, including presence of metastatic disease (OR = 22.61, 95% CI: 11.42, 44.76), regional lymph node spread, and larger tumor size category, were associated with increased odds of chemotherapy. The aforementioned differences in chemotherapy use among MTCs by gender and insurance were no longer significant in adjusted analyses. Among metastatic DTCs, the only prominent factor associated with chemotherapy use was tumor size. Results were similar in models restricted to patients diagnosed in 2013, though model estimates were unstable due to the small number of patients diagnosed within a single year (n = 225).

In sensitivity analyses to examine if certain facility types adopted chemotherapy sooner, the interactions between facility type and year of diagnosis (2004–2010 vs. 2011–2013) were not statistically significant in MTCs and DTCs (data not shown). Further, interaction terms for patient demographics and year of diagnosis were not statistically significant.

Discussion

To our knowledge, this study is the first to examine chemotherapy use among DTCs and MTCs in clinical practice. Overall, chemotherapy use among MTC pa-

Table 2. Proportion of thyroid cancer patients receiving chemotherapy by patient and facility factors, NCDB (2011–2013)

Categories	Nonmetastatic DTC (n = 66,736)		Metastatic DTC (n = 679)		MTC (n = 1,022)	
	n (%)	p value	n (%)	p value	n (%)	p value
Gender						
Male	47 (0.3)	<0.01	23 (8.2)	0.035	27 (6.7)	0.04
Female	68 (0.1)		17 (4.3)		24 (3.9)	
Age						
<70 years	89 (0.1)	<0.01	32 (6.8)	0.14	20 (5.1)	0.92
≥70 years	26 (0.4)		[c]		22 (4.7)	
Race/ethnicity						
White	23 (0.1)	0.15	26 (5.8)	0.88	37 (4.8)	0.56
Non-white[a]	92 (0.2)		14 (6.1)		14 (5.7)	
Insurance						
Uninsured/Medicaid	13 (0.2)	0.44	[c]	0.75	12 (9.7)	0.027
Medicare/private	99 (0.2)		34 (6)		39 (4.4)	
Missing	[c]		[c]		[c]	
Charlson Comorbidity Score						
0	89 (0.2)	0.16	34 (6.6)	0.16	42 (5.1)	0.84
≥1	26 (0.2)		[c]		[c]	
Facility type						
Community cancer program	[c]	0.93	[c]	0.11	[c]	0.89
Comprehensive cancer center	45 (0.2)		10 (3.9)		14 (4.6)	
Teaching/research/NCI	56 (0.2)		28 (8)		32 (5.3)	
Other	[c]		[c]		[c]	
Tumor size						
<4 cm	74 (0.1)	<0.01	11 (2.8)	<0.01	26 (2.9)	<0.01
≥4 cm	41 (0.6)		29 (10.4)		28 (13.7)	
Metastatic disease						
No	115 (0.2)		40 (5.9)		21 (2.2)	<0.01
Yes	–		–		30 (41.1)	
Regional nodes						
No	57 (0.1)	<0.01	[c]	0.01	[c]	<0.01
Yes	56 (0.4)		30 (9.1)		45 (10.1)	
Missing	[c]		[c]		[c]	
Surgery						
No surgery or local	9 (1.8)	<0.01	15 (21.1)	<0.01	17 (38.6)	<0.01
Thyroidectomy[b]	106 (0.2)		25 (4.2)		34 (3.6)	
Radiation treatment						
None	36 (0.1)	<0.01	[c]	0.77	29 (3.2)	<0.01
Received radiation treatment	79 (0.2)		30 (6.0)		22 (17.2)	

[a] Includes 'missing'. [b] Includes subtotal and total thyroidectomy. [c] Data suppressed due to small numbers (<11 patients).

Table 3. Adjusted OR and 95% CI for receipt of chemotherapy among thyroid cancer patients by histologic type, NCDB 2011, 2013

	Nonmetastatic DTC (n = 66,736)		Metastatic DTC (n = 679)		MTC (n = 1,022)	
	OR	95% CI	OR	95% CI	OR	95% CI
Gender						
Female	1.00		1.00		1.00	
Male	1.62	1.1, 2.38	1.62	0.85, 3.09	1.05	0.52, 2.13
Facility characteristics						
Teaching/research and NCI-designated programs	1.00		1.00		1.00	
Community cancer program	0.83	0.29, 2.4	0.36	0.05, 2.79	1.1	0.16, 7.3
Comprehensive cancer center program	0.88	0.54, 1.44	0.54	0.25, 1.16	1.03	0.44, 2.41
Other	0.95	0.52, 1.76	0.36	0.05, 2.8	0.8	0.25, 2.5
Race/ethnicity[a]						
White	1.00		1.00		1.00	
Non-white	0.97	0.91, 1.04	1.03	0.94, 1.13	1.08	0.97, 1.21
Metastatic disease						
No	–		–		1.00	
Yes	–		–		22.61	11.42, 44.76
Regional lymph node involvement						
No	1.00		1.00		1.00	
Yes	1.18	1.11, 1.27	1.05	0.93, 1.18	1.19	0.99, 1.43
Tumor size category	2.28	1.82, 2.86	2.25	1.29, 3.92	1.80	1.10, 2.93
Diagnosis age	1.04	1.02, 1.05	1.01	0.99, 1.02	1.00	0.98, 1.01
Charlson Comorbidity Score	1.00	0.71, 1.41	0.56	0.29, 1.07	1.00	0.54, 1.86

[a] Missing race included in the non-white category.

tients remains low although it increased marginally following the FDA's approval of MKIs in 2011. Approximately 3% of all MTC patients received chemotherapy in 2004–2010 compared to 5% in 2011–2013. Several tumor characteristics were associated with chemotherapy use among MTCs, most notably the presence of metastatic disease, though facility characteristics and patient demographics were not. Chemotherapy use among patients with metastatic DTC was rare and did not increase over the study period.

Among MTCs, chemotherapy use was more common among patients with metastatic disease; however, less than half of all recent metastatic patients were treated with chemotherapy. Studies of targeted chemotherapeutic agent use in other cancers have shown varying patterns of uptake [15–17]. Among elderly patients with stage IV colorectal cancer, there was a rapid uptake of bevacizumab (Avastin), a monoclonal antibody, following the FDA's approval of this drug in 2004 [16]. Following the FDA's approval of rituximab, a targeted therapy for non-Hodgkin's lymphoma, use remained low (<5%) among diffuse large B-cell non-Hodgkin lymphoma patients within the first 3 years, but rapidly increased 4–5 years after the FDA's approval [15]. Additionally, sorafenib utilization was low among elderly hepatocellular carcinoma patients in the 2-year period following its FDA approval [17]. The cost of such targeted therapies remains a concern [18] and may influence its adoption in clinical practice [19]. For example, a monthly cycle of sorafenib, one MKI approved for the treatment of thyroid cancer, is approximately USD 10,555 [18], which may be prohibitively expensive for some patients. The limited effectiveness of MKIs in treating thyroid cancers may also contribute to their slow uptake in clinical practice [6–9]. For example, in one phase III randomized clinical trial among MTC patients, progression-free survival among patients randomized to cabozantinib was 11.2 months compared to 4 months in the placebo group [8].

Previous studies note earlier adoption of innovative cancer treatments and procedures in specialized cancer

centers and vary based on physician-related factors, including the practice of their peers [20–22]. We did not observe a significant difference in the use or early adoption of chemotherapy by facility type. This could be due to the relatively high proportion of MTCs (>50%) who were treated at teaching/research or NCI facilities, likely a result of these high-risk patients being referred to and treated at specialized facilities [23]. Further, we did not observe differences in receipt of chemotherapy by patient sociodemographic factors among MTCs and metastatic DTCs, while studies of innovative treatments among other cancers have [15]. Overall, chemotherapy use in our study was relatively uncommon. Previous studies note that disparities tend emerge after innovations become more common in clinical practice [15]. Further, a recent study of MTCs note similar rates of thyroidectomy among blacks and whites, but lower odds of lymph node dissection following surgery among blacks compared to whites, after accounting for clinical factors [24]. Similarly, studies of DTCs note comparable use of thyroidectomy and cause-specific survival rates in blacks and whites after controlling for clinical factors [2, 25, 26].

Several clinical factors were associated with chemotherapy use among MTCs and metastatic DTCs. Among MTCs, the presence of larger, metastatic tumors as well as having positive lymph nodes were associated with receipt of chemotherapy, as expected. Our results are consistent with patients included in clinical trials for MKIs who had locally advanced or metastatic disease [7, 9]. Further, among metastatic DTCs, larger tumor size was positively associated with receipt of chemotherapy, though results in the most recent time period for which MKIs were approved (2013) are limited due to the small number of cases within a single diagnosis year.

There were several limitations of this study. First, we lacked detail on the type of chemotherapy administered. Based on NCDB coding rules, MKIs are coded as chemotherapeutic agents, and while the likelihood that well-differentiated and medullary thyroid cancer patients were treated with traditional chemotherapeutic agents is low, we were not able to differentiate the chemotherapy type or dose. Further, we were not able to capture all the clinical features that may influence a physician's decision to recommend MKIs and determine who may most benefit from chemotherapy [27], including specific MTC tumor markers or detailed clinical information regarding resistance to radiation among patients with DTC. Further, the NCDB only captures patients treated at CoC-accredited facilities, and these patients may not be representative of all patients; however, case characteristics between the current study and a previous study utilizing a population-based registry (Surveillance Epidemiology and End Results) are similar [24]. The precision of our multivariable models estimates are also wide as a result of our modest sample size; however, due to the rarity of MTC and metastatic DTCs, our study contains a relatively large number of cases. Additionally, our study only captured the 2-year period following the FDA's approval of MKIs for thyroid cancer, which may provide a baseline measurement of chemotherapy use in these patients, but different patterns could develop in the future.

To our knowledge, this study is the first to examine chemotherapy use among MTCs and DTCs in clinical practice. Overall, chemotherapy use among MTC patients marginally increased following the FDA's approval of MKIs in 2011, though its utilization in these patients remains low. Several tumor characteristics, most notably the presence of metastatic disease, were associated with chemotherapy use among MTCs, but facility characteristics and patient demographics were not. Continuous monitoring of chemotherapy in thyroid cancer patients is warranted to assess the effect of the FDA's approval of these drugs.

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Disclosure Statement

The authors report no conflicts of interest.

References

1 Siegel RL, Miller KD, Jemal A: Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
2 Krook KA, Fedewa SA, Chen AY: Prognostic indicators in well-differentiated thyroid carcinoma when controlling for stage and treatment. Laryngoscope 2015;125:1021–1027.
3 Roman S, Lin R, Sosa JA: Prognosis of medullary thyroid carcinoma: demographic, clinical, and pathologic predictors of survival in 1,252 cases. Cancer 2006;107:2134–2142.
4 American Thyroid Association Guidelines Task Force, Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, Moley JF, Pacini F, Ringel MD, Schlumberger M, Wells SA Jr: Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565–612.

5 Martinez SR, Beal SH, Chen A, Chen SL, Schneider PD: Adjuvant external beam radiation for medullary thyroid carcinoma. J Surg Oncol 2010;102:175–178.
6 Bible KC, Suman VJ, Molina JR, Smallridge RC, Maples WJ, Menefee ME, Rubin J, Sideras K, Morris JC 3rd, McIver B, Burton JK, Webster KP, Bieber C, Traynor AM, Flynn PJ, Goh BC, Tang H, Ivy SP, Erlichman C; Endocrine Malignancies Disease Oriented Group, Mayo Clinic Cancer Center; Mayo Phase 2 Consortium: Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study. Lancet Oncol 2010;11:962–972.
7 Kloos RT, Ringel MD, Knopp MV, Hall NC, King M, Stevens R, Liang J, Wakely PE Jr, Vasko VV, Saji M, Rittenberry J, Wei L, Arbogast D, Collamore M, Wright JJ, Grever M, Shah MH: Phase II trial of sorafenib in metastatic thyroid cancer. J Clin Oncol 2009;27:1675–1684.
8 Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH, Licitra L, Jarzab B, Medvedev V, Kreissl MC, Niederle B, Cohen EE, Wirth LJ, Ali H, Hessel C, Yaron Y, Ball D, Nelkin B, Sherman SI: Cabozantinib in progressive medullary thyroid cancer. J Clin Oncol 2013;31:3639–3646.
9 Wells SA Jr, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, Baudin E, Elisei R, Jarzab B, Vasselli JR, Read J, Langmuir P, Ryan AJ, Schlumberger MJ: Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol 2012;30:134–141.
10 Food and Drug Administration: Sorafenib (NEXAVAR). http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm376547.htm.
11 Food and Drug Administration: FDA approves new treatment for rare form of thyroid cancer. 2011. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm250168.htm.
12 Lerro CC, Robbins AS, Phillips JL, Stewart AK: Comparison of cases captured in the National Cancer Data Base with those in population-based central cancer registries. Ann Surg Oncol 2013;20:1759–1765.
13 Bilimoria KY, Stewart AK, Winchester DP, Ko CY: The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol 2008;15:683–690.
14 World Health Organization: International Classification of Diseases for Oncology Version 3. Geneva, World Health Organization, 2000.
15 Flowers CR, Fedewa SA, Chen AY, Nastoupil LJ, Lipscomb J, Brawley OW, Ward EM: Disparities in the early adoption of chemoimmunotherapy for diffuse large B-cell lymphoma in the United States. Cancer Epidemiol Biomarkers Prev 2012;21:1520–1530.
16 Vargas GM, Sheffield KM, Parmar AD, Han Y, Gajjar A, Brown KM, Riall TS: Trends in treatment and survival in older patients presenting with stage IV colorectal cancer. J Gastrointest Surg 2014;18:369–377.
17 Ulahannan SV, Duffy AG, McNeel TS, Kish JK, Dickie LA, Rahma OE, McGlynn KA, Greten TF, Altekruse SF: Earlier presentation and application of curative treatments in hepatocellular carcinoma. Hepatology 2014;60:1637–1644.
18 Kantarjian HM, Fojo T, Mathisen M, Zwelling LA: Cancer drugs in the United States: justum pretium – the just price. J Clin Oncol 2013;31:3600–3604.
19 Meropol NJ, Schulman KA: Cost of cancer care: issues and implications. J Clin Oncol 2007;25:180–186.
20 Gansler T, Fedewa SA, Lin CC, Jemal A, Ward EM: Variations in cancer centers' use of cytology for the diagnosis of small cell lung carcinoma in the National Cancer Data Base. Cancer Cytopathol 2016;124:44–52.
21 Miller DC, Saigal CS, Banerjee M, Hanley J, Litwin MS; Urologic Diseases in America Project: Diffusion of surgical innovation among patients with kidney cancer. Cancer 2008;112:1708–1717.
22 Pollack CE, Soulos PR, Gross CP: Physician's peer exposure and the adoption of a new cancer treatment modality. Cancer 2015;121:2799–2807.
23 Haymart MR, Banerjee M, Yang D, Stewart AK, Griggs JJ, Sisson JC, Koenig RJ: Referral patterns for patients with high-risk thyroid cancer. Endocr Pract 2013;19:638–643.
24 Roche A, Fedewa SA, Chen AY: Disparities in the treatment and survival in medullary thyroid cancer. JAMA Otolaryngol Head Neck 2016;142:763–771.
25 Mitchell I, Livingston EH, Chang AY, Holt S, Snyder WH 3rd, Lingvay I, Nwariaku FE: Trends in thyroid cancer demographics and surgical therapy in the United States. Surgery 2007;142:823–828; discussion 828.e1.
26 Hollenbeak CS, Wang L, Schneider P, Goldenberg D: Outcomes of thyroid cancer in African Americans. Ethn Dis 2011;21:210–215.
27 Haugen BR, Sherman SI: Evolving approaches to patients with advanced differentiated thyroid cancer. Endocr Rev 2013;34:439–455.