Title

Disease-Specific Survival Trends for Patients Presenting with Differentiated Thyroid Cancer and Distant Metastases in the United States, 1992-2018.

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Title: Disease-specific survival trends for patients presenting with differentiated thyroid cancer and distant metastases in the United States, 1992-2018

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ABSTRACT

Objective: Differentiated thyroid cancer (DTC) is associated with an excellent prognosis, but patients with distant metastatic DTC have a 10-year disease-specific survival (DSS) of just 50%. The incidence of distant metastatic DTC has steadily increased in the U.S. since the 1980s. The aim of this study was to examine trends in survival and treatment for patients with distant metastatic DTC.

Methods: In this population-based, retrospective cohort study, patients with distant metastatic DTC were identified from the Surveillance, Epidemiology, and End Results-13 (SEER-13) cancer registry program. Multivariable logistic and Cox regression analyses were used to examine factors associated with DSS and management. Annual percent changes (APC) in treatment patterns were calculated using log-linear regression.

Results: During 1992-2018, 1,991 patients (69.7% white, 58.0% female, 47.5% aged ≥ 65 years) were diagnosed with distant metastatic DTC. Papillary thyroid cancer was the most common histologic type (74.5%). While the 10-year DSS for overall DTC increased over time (95.4% for patients diagnosed in 1992-1998, 96.6% in 1999-2008, and 97.3% in 2009-2018; $p<0.01$), 10-year DSS for DTC with distant metastases did not change (50.2%, 47.3%, and 52.4%, respectively; $p=0.48$). 10-year DSS rates were reduced for patients aged ≥ 65 years (28.1%), patients undergoing non-surgical treatment with external beam radiation therapy and/or systemic therapy (6.0%), and patients undergoing no/unknown treatment (32.8%). On multivariable analysis, oncocytic carcinoma, age 65-79 and ≥ 80 years, male sex, node-positive disease, larger tumor size, non-surgical treatment, and no/unknown treatment were associated with increased risk of thyroid cancer death. Between 1992-2018,

the rate of non-surgical treatment increased, on average, 1.3% per year (1992-1998 22.9% vs. 2009-2018 25.6%; p=0.03), and the rate of patients receiving no/unknown treatment increased 1.9% per year (1992-1998 11.3% vs. 2009-2018 15.6%; p=0.01). Patients aged 65-79 and ≥ 80 years were more likely than younger patients to receive non-surgical management or no/unknown treatment.

Conclusion: Patients diagnosed with distant metastatic DTC have experienced no improvement in DSS over the last three decades. An increasing proportion of patients diagnosed with distant metastatic DTC are receiving non-surgical treatment or no/unknown treatment over time; the proportion was highest among the oldest patients.

INTRODUCTION

Differentiated thyroid cancer (DTC), including papillary (PTC), follicular (FTC) and oncocytic carcinoma, is generally associated with an excellent prognosis. However, patients with distant metastatic DTC historically have had substantially lower 10-year disease-specific survival (DSS) compared to patients with non-metastatic DTC (44% vs. 98%, respectively).[1] Since the 1980s, there has been a steady increase in the incidence of distant metastatic DTC in the United States.[2]

The American Thyroid Association (ATA) guidelines regarding the appropriate management of distant metastatic DTC describe a hierarchy of treatment strategies beginning with surgical excision of locoregional disease followed by radioactive iodine (RAI), external beam radiation therapy (EBRT), and consideration of systemic therapy with conventional chemotherapy or kinase inhibitors for RAI-resistant tumors.[3] These recommendations reflect the body of evidence documenting superior outcomes among patients treated with surgery and RAI, and the more recent emergence of promising novel kinase inhibitor therapies such as sorafenib in 2013 and lenvatinib in 2015.[4-7] An initial trial of sorafenib demonstrated a considerable increase in progression free survival, from under six months in the control group to 10.8 months among patients treated with sorafenib.[6] Prior to the emergence of these targeted therapies, previous iterations of the ATA guidelines had noted doxorubicin as the main option for systemic therapy despite its having limited efficacy.[8]

Despite these advances in targeted therapies for RAI-resistant tumors, the incidence-based mortality for advanced stage DTC has increased over the last two decades.[2] Notably, incidence-based-mortality is a population-level measure that provides a breakdown of mortality by variables associated with cancer occurrence.[9] There is a lack of evidence

regarding contemporary trends in disease specific survival (DSS) from distant metastatic DTC that could reflect the recent evolution in available treatments.

The aim of this study was to examine trends in treatment and survival for patients with distant metastatic DTC.

METHODS

Data source

In this population-based, retrospective cohort study, patients with thyroid cancer diagnosed between 1992-2018 were identified from the Surveillance, Epidemiology, and End Results-13 (SEER-13) cancer registry program of the National Cancer Institute.[10] The SEER-13 datafile contains information from 13 high-quality, population-based cancer registries in 10 states and covers 14% of the U.S. population. Date of last available follow-up was December 31, 2018.

Tumor characteristics

DTC cases were identified using the *International Classification of Diseases for Oncology*, third edition, and classified according to histologic type[11]: PTC (histologic codes 8050, 8260, 8337, 8340-8344, 8350, 8450-8460), FTC (8330-8335), and oncocytic carcinoma (8290). According to a recent update of the WHO classification of thyroid neoplasms, histologies previously known as Hürthle cell cancer are termed oncocytic carcinoma.[12] Aggressive variants included the diffuse sclerosing variant (8350), tall cell variant (8344), and insular thyroid cancer (8337).[13,14]

The definition of distant metastatic disease was based on the presence or absence of distant organ or extra-cervical lymph node metastases. For cases diagnosed between 1992-

2003, the Extent of Disease-10 (EOD-10) codes for distant organ metastases and metastases in distant lymph nodes were used.[15] The American Joint Committee on Cancer (AJCC) derived TNM staging variables were used for cases diagnosed between 2004-2018.[16,17] These codes were combined to categorize all cases diagnosed between 1992-2018 by M-stage.

Nodal status was defined between 1992-2018 by similarly combining the EOD-10 nodes for patients diagnosed from 1992-2003 and the AJCC-derived N-stage variables from 2004-2018.[15-17]

Tumor size has been captured in SEER since 1983. Cases diagnosed between 1992-2018 were categorized by tumor size using three different schemata[3]: EOD-10 size codes for 1992-2003, Collaborative Staging codes for 2004-2015, and Tumor Size Summary codes for 2016-2018.

Study patients were divided into three different groups based on the year of diagnosis: patients diagnosed between 1992-1998, 1999-2008, and 2009-2018.

Demographic and clinical characteristics

Demographic characteristics and treatment information of interest are shown in **Table 1**. SEER captures treatment data by reviewing medical records. When multiple surgical procedures are coded, SEER reports the most invasive, extensive, or definitive initial treatment procedure.[18] Surgical procedure was determined using codes from the Site Specific Surgery (1992-1997) and RX Summ—Surgery Primary Site (1998-2018) SEER variables. Patients coded as having "lobectomy, isthmectomy and partial removal of contralateral lobe (near total thyroidectomy)," "subtotal or near total thyroidectomy," or "total thyroidectomy" were considered to have had total thyroidectomy (TTx). Patients coded as having "lobectomy with or without isthmusectomy" were considered to have undergone lobectomy. Patients who

underwent “no cancer-directed surgery of primary site” were coded as having no surgery. Patients receiving radiation therapy were captured using the radiation recode variable. Patients who had “internal (radioactive implants & radioisotopes)” radiation therapy were determined to have had RAI. The chemotherapy recode variable was used to identify patients receiving systemic therapy (chemo). Patients then were categorized into the corresponding treatment groups (**Table 1**). Patients who received “non-surgical treatment” included all patients who did not undergo cancer-directed surgery, including patients receiving no/unknown treatment, EBRT, systemic therapy, or any other treatment.

Statistical analysis

Demographic, clinical, and pathological characteristics of patients with distant metastatic DTC were compared between patients diagnosed between 1992-1998, 1999-2008, and 2009-2018 using analysis of variance (ANOVA) for continuous variables and $\chi 2$-tests for categorical variables. Kaplan-Meier analysis was used to estimate the probability of DSS of DTC overall and distant metastatic DTC beyond a certain time point (e.g., 10 years) and to display the estimated DSS function; unadjusted comparisons between two or more survival curves were made using the log-rank test. In patients with distant metastatic DTC, multivariable logistic and Cox regression models were used to evaluate the associations of specific demographic and clinical factors with non-surgical or no/unknown treatment and risk of thyroid cancer death, respectively. Covariates included time period of diagnosis, patient age, sex, race, marital status, number of malignant tumors per patient, treatment, lymph node dissection, DTC histology, tumor size, and N-stage. Patients with missing information on covariates were excluded from analysis. A two-sided alpha of 0.05 was used in all analyses to

define statistical significance. Statistical analyses were performed using Stata/BC version 16.1 (StataCorp LLC, College Station, TX). Moreover, a propensity score (PS) analysis to adjust for potential confounding variables, was performed.[19,20] Patients undergoing surgical and non-surgical treatment were matched using optimal full propensity score (PS) matching. PSMATCH in SAS version 9.4 was used to perform optimal full PS matching. The National Cancer Institute's Joinpoint Regression Analysis program (v. 4.9.1.0) was used to calculate annual percentage changes (APCs) in treatment patterns.[21] This study was granted an exemption by our Institutional Review Board due to use of de-identified data.

RESULTS

Demographic, clinical, and pathologic characteristics

A total of 1,991 patients with a diagnosis of distant metastatic DTC between 1992 and 2018 were identified in the SEER database (**Figure 1**). Of those, 69.7% were white and 58.0% female. The most common histologic type was PTC (74.5%), and 46.5% of patients had cervical lymph node metastases. The proportion of aggressive histologic variants with distant metastases was 3.7%. TTx followed by RAI was the most frequent treatment approach (46.2%).

The unadjusted variations in demographic, clinical, and pathologic variables over time are shown in **Table 1**. There was no significant difference in the rate of female patients, in marital status, and in the number of malignant tumors per patient. Lymph node dissection, tumor size, and N-stage categories all differed significantly overall by time period ($p<0.01$).

Survival analysis

Of all DTC patients, 3.1% (n=3,394) died from thyroid cancer, compared to 43.1% (n=858) with distant metastatic DTC. Median survival time for DTC overall was 92 months (Interquartile range: 41-162) compared to 41 months (IQR: 11-99) for distant metastatic DTC. While the 10-year DSS for DTC of all stages differed significantly over time (patients diagnosed in 1992-1998: 95.4%, 1999-2008: 96.6%, 2009-2008: 97.3%; p<0.01), 10-year DSS for distant metastatic DTC did not change (50.2%, 47.3%, and 52.4%, respectively; p=0.48) (**Figure 2**). The 10-year DSS rates were reduced among patients aged 65-79 years (32.7%) and ≥ 80 years (10.7%), in patients who underwent EBRT and/or systemic therapy only (6.0%), and in patients who underwent no/unknown treatment (32.8%). Patients who underwent TTx followed by RAI and those who underwent TTx alone had the highest 10-year DSS rates of 64.4% and 56.9%, respectively (**Figure 3**).

After multivariable adjustment, oncocytic carcinoma compared to PTC (HR 2.07, 95%CI 1.51-2.83), age 65-79 (HR 1.95, 95%CI 1.63-2.33), age ≥ 80 (HR 3.04, 95%CI 2.38-3.87), male sex (HR 1.44, 95%CI 1.24-1.71), cervical lymph node-positive disease (HR 1.42, 95%CI 1.15-1.74), tumor size greater than 4 cm compared to ≤ 1 cm (HR 2.33, 95%CI 1.65-3.28), no/unknown treatment compared to TTx (HR 2.26, 95%CI 1.65-3.09), and EBRT and/or systemic therapy compared to TTx (HR 3.33, 95%CI 2.42-4.59) were associated with an increased risk of thyroid cancer death (**Table 2**). TTx followed by RAI compared to TTx only (HR 0.67, 95%CI 0.52-0.87) and lymph node dissection compared to no lymph node dissection (HR 0.78, 95%CI 0.62-0.97) were associated with a lower risk of thyroid cancer death.

Treatment trends

The rate of non-surgical treatment increased, on average, 1.3% per year (22.9% between 1992-1998 vs. 25.6% in 2009-2018; p=0.03), and the rate of patients undergoing no/unknown treatment for distant metastatic DTC increased 1.9% per year (11.3% in 1992-1998 vs. 15.6% in 2009-2018; p=0.01) (**Figure 4**). The proportion of patients receiving systemic therapy increased 2.0% per year (1992-1998: 7.4%, 2009-2018: 8.7%; p=0.04). After multivariable adjustment, patients aged 65-79 and ≥ 80 years were more likely to undergo non-surgical treatment (OR 1.96, 95%CI 1.41-2.71; OR 3.90, 95%CI 2.59-5.85, respectively) and patients ≥ 80 years more likely to undergo no/unknown treatment (OR 3.68, 95%CI 2.48-5.46) (**Tables 3 and 4**).

Sensitivity analysis

A sensitivity analysis grouping patients in 5-year intervals showed similar survival rates for DTC overall and distant metastatic DTC (**Supplemental figure 1**). To address potential selection bias, we conducted a subgroup analysis of patients with more extensive primary tumors, i.e., N1-stage and/or tumor size >4cm (**Supplemental figure 2**) that showed similar survival rates by treatment compared to the main cohort. Sample balance after propensity score matching is shown in **Supplemental table 1**, all covariates used in matching met sample balance criteria. Patients undergoing non-surgical treatment had significantly higher risk of death from thyroid cancer (log-rank test p<0.001; Cox model HR 4.36, 95% CI 3.32-5.73). Disease-specific survival analysis by treatment of the matched patient cohort (**Supplemental figure 3)** showed similar results compared to the main cohort. In addition, DSS rates of patients with more extensive vs. localized primary tumors are displayed in **Supplemental figure 4**. A trend analysis of the proportion of patients with DTC and distant

metastases and DTC-Mx stage among all new DTC diagnoses per year is presented in **Supplemental figure 5**.

DISCUSSION

The 10-year DSS for DTC overall increased between 1992-2018, likely because of earlier diagnoses at less advanced stages. In contrast, there was no significant change in the 10-year DSS for patients presenting with DTC and distant metastases. In parallel, there was an increase in the proportion of patients undergoing non-surgical treatment or receiving no/unknown treatment for distant metastatic DTC. Patients aged 65-79 and ≥ 80 years were more likely than younger patients to receive non-surgical treatment. Patient age, non-surgical treatment, and no/unknown treatment were associated with decreased survival.

The observed increase in the proportion of patients receiving non-surgical treatment likely contributes to the lack of improvement in the 10-year DSS. The current standard of care for DTC with distant metastases is resection of locoregional disease, if surgically accessible, followed by RAI.[3] Unlike many cancers in other organ systems, distant DTC metastases do not preclude resection of the primary tumor because DTC metastases may respond to RAI administration.[3] In a study of 49 patients with distant metastatic DTC at the time of diagnosis, only histology and iodine avidity were significantly associated with improved survival after adjustment for patient age.[22] In a study of 444 patients, 10-year overall survival was 56% among patients with ^{131}I uptake compared to 10% among those without uptake.[5] Among patients without ^{131}I uptake, distant metastasectomy can be considered in selected patients.[23,24] In the present study, total thyroidectomy with or without RAI ablation was associated with decreased risk of death and higher DSS rates. Together

with previously published literature, these results support a continued central role for the surgical management of distant metastatic DTC.

The reasons for the increase in patients receiving non-surgical treatment are unclear. It is possible that some of the tumors were not resectable because of extensive extrathyroidal extension into critical structures. In SEER, the variable that codes for extrathyroidal tumor extension (EOD-extension) is the same one that defines distant metastatic disease for cases diagnosed from 1992-2003; hence, it was not possible to determine extrathyroidal extension for all patients. However, larger tumors with nodal metastases are more likely to preclude surgical resection if they extensively involve certain critical structures like the aerodigestive tract or major arteries, and this can be used as a surrogate for resectability of the primary tumor. In the present study, tumor size >4 cm and nodal metastases were not associated with an increased likelihood of non-surgical treatment, suggesting that the observed trend of increased non-surgical treatment is unlikely to be limited to unresectable tumors.

Among patients with unresectable primary tumors or tumors that are not RAI-avid, EBRT and systemic therapy are potential treatment options.[3] According to this analysis, treatment with systemic therapy increased over time. Before 2013, systemic therapy for non-RAI avid distant metastatic DTC was limited to cytotoxic chemotherapy, with doxorubicin as the most commonly-used agent despite limited efficacy.[7,25-27] More recently, the tyrosine kinase inhibitors sorafenib and lenvatinib have been FDA-approved for the treatment of RAI-refractory DTC and have been shown to improve progression-free survival.[7,28,29] Given the short follow-up of patients diagnosed after FDA approval of sorafenib and lenvatinib, it is unlikely that potentially higher use had an impact on survival rates. Furthermore, in our study, it was not possible to draw conclusions about the efficacy of these treatments, especially considering the limitations of SEER, i.e., it was an observational study and not a

297 randomized trial, so selection bias/confounding cannot be excluded. Also, SEER does not
298 capture information on type of systemic therapy. However, increasing availability and
299 experience with targeted treatments may change treatment strategies and lead to improved
300 survival. So, this could be reexamined again when longer follow-up has been accrued.
301 Although systemic therapy with conventional chemotherapy or targeted tyrosine
302 kinase inhibitors are potential options for patients with unresectable DTC, after multivariable
303 adjustment, the risk of thyroid cancer death was higher among patients who received non-
304 surgical treatment with EBRT and/or systemic therapy and those who received no/unknown
305 treatment. The reason for this could be selection bias. For example, it is possible that among
306 patients with unresectable disease, those with greater disease burden received EBRT and/or
307 systemic therapy, while those with less extensive disease elected to undergo an active
308 surveillance approach given the risk of adverse events. Since SEER does not capture
309 information on the molecular profile of the tumors, this powerful predictor of prognosis could
310 not be considered in multivariable adjustment.
311 Between 1992-2018, patients aged 65-79 years and ≥ 80 years were more likely to
312 receive non-surgical treatment. Patient age at diagnosis is an important prognostic factor for
313 DTC.[30,31] In a study of 3,664 patients with DTC, there was a 37-fold increase in the risk of
314 thyroid cancer death among patients >70 years compared to patients <40 years.[30] The
315 proportion of patients undergoing non-surgical treatment was highest among patients aged
316 ≥ 80 years which has been shown previously to be not limited to patients with distant
317 metastatic disease.[32] However, the compromised prognosis associated with diagnosis at an
318 older age should not prevent older patients from receiving potentially life-prolonging or life-
319 saving therapies for which they may be eligible. Because SEER has no information on

comorbidities, this could not be considered as a possible reason for the higher likelihood of non-surgical or no/unknown treatment at older age.

There are limitations to this study. SEER is a retrospective database, and coding errors are possible. Although SEER includes data regarding systemic therapy use, there is no data on what agent was used. For example, it is unknown whether patients received conventional chemotherapy or targeted therapy with a tyrosine kinase inhibitor. SEER does not include data on why a treatment modality was chosen; it is unknown whether patients who were not treated were offered therapy but declined it. SEER only reports data on radiation and systemic therapy given as first-course treatments, including systemic therapy in clinical trials.[33,34] Consequently, it is unknown whether patients may have received these treatments later in their disease course, such as after disease recurrence or progression. A recent publication comparing SEER with SEER-Medicare data for other cancer types found an overall sensitivity of 80% for SEER-radiotherapy data and 68% for SEER-chemotherapy data, with an overall positive predictive value of greater than 85% for all treatments.[35] Therefore, underestimation of radiotherapy, such as EBRT and RAI, and systemic therapy is expected, whereas overestimation is less likely. According to the SEER treatment data limitations, it is possible that some of the patients may have had radiation treatment or systemic therapy that was not captured in the SEER records, especially if the treatment was received outside a hospital setting; surgery information, in contrast, is expected to be largely complete.[34] As a result, it is unlikely that there is significant impact on our main conclusion, which is the lack of improvement in survival of distant metastatic DTC, likely due to an increase in non-surgical treatment. It was not possible to precisely determine all aspects of non-surgical treatment approaches because therapies such as radiofrequency, ethanol, or ablation techniques are not specifically coded in SEER. It is likely that, at least in part, tumor

size was not coded if patients did not undergo surgery. Cancer registries such as SEER use algorithms to process causes of death from death certificates to identify a single, disease-specific, underlying cause of death. To minimize misattribution, the algorithm introduced in 2010 by Howlader et al. was used for all cases diagnosed from 1992-2018.[36,37] Despite these limitations, SEER includes data from a large, diverse population across the United States and is an important resource to study epidemiologic trends.

CONCLUSION

While earlier diagnoses at less advanced stages may have led to an improvement in DSS for DTC overall over the past three decades, there has been no improvement in DSS for patients presenting with DTC and distant metastases. A growing proportion of patients are receiving non-surgical treatment or no/unknown treatment over time. Future studies are needed to understand the lack of improvement in DSS for distant metastatic DTC, including investigation of possible changes in tumor biology and factors affecting patient access to surgical and systemic treatments.

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FIGURES

Figure 1: Participant flow diagram

Figure 2: Disease-specific survival of (A) DTC overall, and (B) distant metastatic DTC between 1992-2018.

Figure 3: Disease-specific survival of distant metastatic DTC by treatment between 1992-2018.

Figure 4: Treatment trends of distant metastatic DTC between 1992-2018. Abbreviations: Annual percent change (APC).

Supplemental figure 1: Disease-specific survival of (A) DTC overall, and (B) distant metastatic DTC between 1992-2018 (5-year intervals)

Supplemental figure 2: Subgroup analysis of disease-specific survival by treatment among patients with N1-stage and/or tumor size>4cm (n=1,151)

Supplemental figure 3: Disease-specific survival by treatment after propensity score matching (n=1,399)

Supplemental figure 4: Disease-specific survival by disease severity (n=1,484)

Supplemental figure 5: Proportion of patients presenting with (A) DTC and distant metastases (M1-stage), and (B) DTC Mx-stage among all new DTC diagnoses per year

TABLES

Table 1: Demographic and clinical characteristics of patients diagnosed with distant metastatic DTC between 1992-2018

	Time period of diagnosis			
	1992-1998 (n=380)	**1999-2008** (n=713)	**2009-2018** (n=898)	*P* value*
Patient Characteristics				
Female sex	227	410	518	0.75
Age, years				<0.01
<65	217	378	450	
65-79	135	241	316	
≥80 years	28 (7.4%)	94 (13.2%)	132	
Race				0.01
White	293	483	613	
Black	31 (8.2%)	71 (10.0%)	85 (9.5%)	
Other/Unknown	56 (14.7%)	159	200	
Marital Status				0.70
Married	206	384	468	
Not married	174	329	430	
Number of malignant tumors/patient				0.43
1	296	544	670	
≥2	84 (22.1%)	169	228	
Median annually household income				<0.01
< $50,000	19 (5.0%)	29 (4.1%)	78 (8.7%)	
$50,000 - $74,999	204	384	521	
≥ $75,000	157	300	299	
Area of residency (urban vs. rural)				<0.01
Metropolitan	333	663	833	
Nonmetropolitan	31 (8.2%)	47 (6.6%)	63 (7.0%)	
Unknown	16 (4.2%)	3 (0.4%)	2 (0.2%)	
Clinical Characteristics				
Treatment				<0.01
No/Unknown treatment	43 (13.7%)	83 (12.8%)	140	
TTx only	43 (13.7%)	99 (15.3%)	116	
TTx + RAI	141	314	376	
TTx + RAI +/- EBRT +/- chemo	31 (9.8%)	40 (6.2%)	30 (3.6%)	
TTx +/- EBRT +/- chemo	29 (9.2%)	66 (10.2%)	98 (11.7%)	
EBRT and/or chemo	28 (8.9%)	44 (6.8%)	76 (9.1%)	
Lymph node dissection (LND)				<0.01
No LND	209	351	363	
LND performed	123	316	472	
Unknown	48 (12.6%)	46 (6.5%)	63 (7.0%)	
Number of lymph nodes examined				<0.01
None	209	351	363	
1-2	44 (11.6%)	120	104	

3	12 (3.2%)	22 (3.1%)	28 (3.1%)	
4-7	16 (4.2%)	38 (5.3%)	58 (6.5%)	
≥ 8	51 (13.4%)	136	282	
Unknown	48 (12.6%)	46 (6.5%)	63 (7.0%)	
Pathologic Characteristics				
Differentiated thyroid cancer histology				<0.01
Papillary thyroid cancer	264	515	704	
Follicular thyroid cancer	100	166	159	
Oncocytic carcinoma	16 (4.2%)	32 (4.5%)	35 (3.9%)	
Aggressive variants (tall cell variant, diffuse sclerosing variant, insular thyroid cancer)	1 (0.3%)	27 (3.8%)	46 (5.1%)	<0.01
Tumor Size				<0.01
≤ 1cm	24 (6.3%)	90 (12.6%)	85 (9.5%)	
1.1 - 2cm	40 (10.5%)	90 (12.6%)	114	
2.1 - 4cm	69 (18.2%)	166	241	
> 4cm	79 (20.8%)	187	313	
Unknown	168	180	145	
N-stage				<0.01
N0	61 (19.7%)	205	351	
N1	113	311	446	
Nx	135	155	96 (10.8%)	
Number of positive lymph nodes				<0.01
0	22 (5.8%)	82 (11.5%)	133	
1-3	63 (16.6%)	113	113	
4-5	12 (3.2%)	27 (3.8%)	44 (4.9%)	
>5	37 (9.7%)	102	194	
Unknown/no LND	246	389	414	

*ANOVA for continuous variables; chi-squared tests for categorical variables

Abbreviations: **TTx:** Total/subtotal thyroidectomy, **RAI:** Radioactive iodine treatment, **EBRT:** External beam radiation treatment, **chemo:** Systemic therapy, **+/-:** with or without, **LND:** Lymph node dissection

Table 2: Multivariable-adjusted Cox proportional hazard regression of death from thyroid cancer among patients diagnosed with distant metastatic DTC between 1992-2018

Variable	aHR (95% CI)	*P* value
Age		
65-79 years	1.95 (1.63-2.33)	<0.01
≥80 years	3.04 (2.38-3.87)	<0.01
Male sex	1.44 (1.24-1.71)	<0.01
Race		
Black	0.90 (0.67-1.20)	0.47
Other/Unknown	0.86 (0.70-1.05)	0.15
Not married	1.06 (0.90-1.24)	0.50
≥2 malignant tumors/patient	0.90 (0.75-1.08)	0.25
Median annually household income		
$50,000 - $74,999	0.28 (0.65-1.31)	0.65
≥ $75,000	0.93 (0.64-1.35)	0.71
Nonmetropolitan area of residency	1.08 (0.79-1.47)	0.64
Treatment		
No/Unknown treatment	2.26 (1.65-3.09)	<0.01
TTx + RAI	0.67 (0.52-0.87)	<0.01
TTx + RAI +/- EBRT +/- chemo	1.42 (1.00-2.03)	0.05
TTx +/- EBRT +/- chemo	1.95 (1.46-2.61)	<0.01
EBRT and/or chemo	3.33 (2.42-4.59)	<0.01
Lymph node dissection performed	0.78 (0.62-0.97)	0.03
Differentiated thyroid cancer histology		
Follicular thyroid cancer	1.09 (0.90-1.33)	0.39
Oncocytic carcinoma	2.07 (1.51-2.83)	<0.01
Tumor Size		
1.1 - 2cm	1.32 (0.88-1.98)	0.18
2.1 - 4cm	1.59 (1.11-2.26)	0.01
> 4cm	2.33 (1.65-3.28)	<0.01
Unknown	1.78 (1.24-2.55)	<0.01
N1-stage	1.42 (1.15-1.74)	<0.01

*Multivariable Cox regression adjusted for: time period of diagnosis, patient age, sex, race, marital status, number of malignant tumors per patient, median annually household income, area of residency, treatment, lymph node dissection, DTC histology, tumor size, N-stage

**Reference categories: diagnosis 1992-1998, patient age<65 years, female sex, white race, married marital status, one malignant tumor per patient, <$50,000 median annually household income, metropolitan area of residency, total thyroidectomy, no lymph node dissection, papillary thyroid cancer, tumor size ≤1cm, N0

Abbreviations: **aHR:** adjusted hazard ratio, **TTx:** Total/subtotal thyroidectomy, **RAI:** Radioactive iodine treatment, **EBRT:** External beam radiation treatment, **chemo:** Systemic therapy, **+/-:** with or without

Table 3: Multivariable-adjusted odds (aOR) of non-surgical treatment for distant metastatic DTC between 1992-2018

Variable	aOR (95% CI)	*P* value
Age		
65-79 years	1.96 (1.41-2.71)	<0.01
≥80 years	3.90 (2.59-5.85)	<0.01
Male sex	0.95 (0.70-1.29)	0.73
Race		
Black	0.79 (0.48-1.28)	0.33
Other/Unknown	1.16 (0.79-1.68)	0.45
Not married	1.45 (1.07-1.96)	0.02
≥2 malignant tumors/patient	1.06 (0.76-1.49)	0.72
Median annually household income		
$50,000 - $74,999	0.71 (0.38-1.33)	0.28
≥ $75,000	0.67 (0.34-1.30)	0.23
Nonmetropolitan area of residency	0.76 (0.40-1.45)	0.41
Differentiated thyroid cancer histology		
Follicular thyroid cancer	1.15 (0.81-1.63)	0.45
Oncocytic carcinoma	1.17 (0.60-2.27)	0.65
Tumor Size		
1.1 - 2cm	0.69 (0.35-1.35)	0.28
2.1 - 4cm	0.41 (0.22-0.73)	<0.01
> 4cm	0.81 (0.47-1.39)	0.45
Unknown	4.04 (2.37-6.90)	<0.01
N1-stage	0.87 (0.61-1.25)	0.47
Radiation therapy		
EBRT	0.59 (0.42-0.84)	<0.01
RAI	0.06 (0.04-0.09)	<0.01
Combination (EBRT + RAI)	0.09 (0.04-0.20)	<0.01
Systemic therapy	2.05 (1.28-3.29)	<0.01

*Multivariable logistic regression adjusted for: time period of diagnosis, patient age, sex, race, marital status, number of malignant tumors per patient, median annually household income, area of residency, DTC histology, tumor size, N-stage, radiation therapy, systemic therapy

**Reference categories: diagnosis 1992-1998, patient age<65 years, female sex, white race, married marital status, one malignant tumor/patient, <$50,000 median annually household income, metropolitan area of residency, papillary thyroid cancer, tumor size ≤1cm, N0, no radiation, no systemic therapy

Abbreviations: **aOR:** adjusted odds ratio, **RAI:** Radioactive iodine treatment, **EBRT:** External beam radiation treatment

Table 4: Multivariable-adjusted odds (aOR) of no/unknown treatment for distant metastatic DTC between 1992-2018

Variable	aOR (95% CI)	*P* value
Age		
65-79 years	1.26 (0.88-1.78)	0.20
≥80 years	3.68 (2.48-5.46)	<0.01
Male sex	0.91 (0.66-1.25)	0.56
Race		
Black	0.92 (0.55-1.52)	0.74
Other/Unknown	1.13 (0.76-1.68)	0.54
Not married	1.47 (1.08-2.00)	0.01
≥2 malignant tumors/patient	1.33 (0.95-1.85)	0.10
Median annually household income		
$50,000 - $74,999	0.66 (0.36-1.22)	0.19
≥ $75,000	0.62 (0.32-1.20)	0.16
Nonmetropolitan area of residency	0.70 (0.37-1.35)	0.29
Differentiated thyroid cancer histology		
Follicular thyroid cancer	0.93 (0.65-1.34)	0.70
Oncocytic carcinoma	1.19 (0.58-2.44)	0.64
Tumor Size		
1.1 - 2cm	0.85 (0.42-1.72)	0.65
2.1 - 4cm	0.44 (0.23-0.87)	0.02
> 4cm	0.89 (0.49-1.62)	0.71
Unknown	3.73 (2.11-6.60)	<0.01
N1-stage	0.78 (0.53-1.14)	0.18

*Multivariable logistic regression adjusted for: time period of diagnosis, patient age, sex, race, marital status, number of malignant tumors per patient, median annually household income, area of residency, DTC histology, tumor size, N-stage,
**Reference categories: diagnosis 1992-1998, patient age<65 years, female sex, white race, married marital status, one malignant tumor per patient, <$50,000 median annually household income, metropolitan area of residency, papillary thyroid cancer, tumor size ≤1cm, N0

Supplemental table 1: Sample balance after propensity score matching

Variable	No Surgery (n=231)	Any Surgery (n=1,168)	Standardized mean difference*	Variance Ratio*
Age			-0.006	0.997
<65 years	71 (30.7%)	682 (58.4%)		
65-79 years	86 (37.2%)	386 (33.0%)		
≥80 years	74 (32.0%)	100 (8.6%)		
Sex			0.08376	1.049
Female	142 (61.5%)	657 (56.3%)		
Male	89 (38.5%)	511 (43.8%)		
Race			-0.063	0.857
White	155 (67.1%)	809 (69.3%)		
Black	22 (9.5%)	103 (8.8%)		
Other/Unknown	54 (23.4%)	256 (21.9%)		
Marital status			-0.024	1.007
Married	100 (43.3%)	645 (55.2%)		
Not married	131 (56.7%)	523 (44.8%)		
Median annually household income			0.087	0.986
< $50.000	20 (8.7%)	75 (6.4%)		
$50,000 - $74,999	130 (56.3%)	654 (56.0%)		
≥ $75,000	81 (35.1%)	439 (37.6%)		
Area of residency			0.012	1.041
Metropolitan area	215 (93.1%)	1091 (93.4%)		
Nonmetropolitan area	16 (6.9%)	77 (6.6%)		
Locally advanced disease			0.063	0.936
N0-stage and tumor size ≤4cm	59 (25.5%)	331 (28.3%)		
N1-stage and/or tumor size>4cm	172 (74.5%)	837 (71.7%)		

* The absolute values of the weighted matched standardized mean differences are less than the recommended upper limit of 0.1, and all weighted matched variance ratios are between 0.5 and 2