Published in final edited form as:

J Surg Res. 2020 October ; 254: 154–164. doi:10.1016/j.jss.2020.04.013.

Treatment Variation in Older Adults with Differentiated Thyroid Cancer

Whitney Sutton, MD¹, Joseph K. Canner, MHS¹, Dorry L. Segev, MD, PhD¹, Martha A. Zeiger, MD², Aarti Mathur, MD¹

¹Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

²Department of Surgical Oncology, National Cancer Institute, National Institute of Health, Bethesda, MD, USA.

Abstract

Background: The growth of the aging population coupled with the increasing incidence of thyroid cancer warrants a better understanding of thyroid cancer in older adults. We aimed to investigate the variation of treatment patterns and determine if extent of surgery is associated with disease-specific mortality in older adults with differentiated thyroid cancer (DTC).

Methods: We performed a population-based study using the Surveillance, Epidemiology, and End Results (SEER-18) program to examine patients diagnosed with DTC between 2004–2015. Patients were stratified by age: younger adults(18–54 years old), middle adults(55–64), older adults(65–79), and super-elderly(≥ 80). Disease-specific mortality was estimated using Kaplan-Meier curves and compared using log-rank test. Multivariable Cox regression was utilized to assess associations between clinico-pathological characteristics and treatment patterns on disease-specific mortality.

Results: Of 117,098 patients with DTC, 72,368 were younger adults, 23,726 middle adults, 18,119 older adults, and 2,885 were super-elderly. In patients with DTC, compared to younger adults, fewer middle, older, and super-elderly adults underwent any surgery (99.0%, 98.4%, 97.4%, 89.1%, respectively, $p < 0.001$) or received radioactive iodine (RAI) (48.7%, 42.5%, 39.7%,

Corresponding Author: Aarti Mathur MD: Department of Surgery, Johns Hopkins University School of Medicine. 600 North Wolfe Street, Balock 606, Baltimore, MD, 21287. amathu10@jhmi.edu, +1 (410) 614-1197.

Whitney Sutton, MD: Department of Surgery, Johns Hopkins University School of Medicine. 600 North Wolfe Street, Balock 606, Baltimore, MD, 21287. +1(913)302-1683

Joseph K. Canner, MHS: Department of Surgery, Johns Hopkins University School of Medicine. 600 North Wolfe Street, Balock 606, Baltimore, MD, 21287.

Dorry L. Segev, MD, PhD: Department of Surgery, Johns Hopkins University School of Medicine. 601 N. Caroline St., Baltimore, MD 21287.

Martha A. Zeiger, MD: Center for Cancer Research, National Cancer Institute, Building 10, Room 4-3752, Bethesda, MD 20892

Author Contributions:

Dr. Aarti Mathur designed and directed the project with the input of Dr. Martha Zeiger and Dr. Dorry Segev. Joseph Canner carried out the statistical analyses in conjunction with Dr. Mathur. Dr. Whitney Sutton wrote the manuscript and designed the figures. All authors discussed the results and edited the manuscript.

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Disclosures:

No financial disclosures to report.

30.7%, respectively, $p<0.001$). Furthermore, middle, older, and super-elderly adults had higher risk of mortality from DTC (HR:4.0,95%CI:3.2–4.8, $p<0.001$, HR:7.6,95%CI:6.3–9.1, $p<0.001$, and HR:17.2,95%CI:13.8–21.3, $p<0.001$, respectively). On multivariable Cox regression while adjusting for clinico-pathologic confounders, management was a significant prognostic factor (No surgery HR:3.8,95%CI:3.1–4.6, $p<0.001$; RAI HR:0.7,95%CI:0.6–0.8, $p<0.001$).

Conclusions: In patients with DTC, fewer older adults (> 65 years) underwent surgery or treatment with RAI, and this was associated with a worse disease-specific survival. Surgical decision-making in the older population is complex, and future prospective studies are needed to assess this age-related treatment variation.

Keywords

Thyroid Cancer; Aging; Thyroidectomy; Disease-Specific Mortality

Introduction:

The US census bureau estimates a 58% increase in the population aged > 65 and an 85% increase in the population age > 85 by the year 2035(1). The incidence of thyroid cancer in the US is on the rise, attributable mostly to an increase in papillary thyroid cancer (PTC)(2–4). With the growth of the aging population, the incidence of thyroid cancer is expected to continue to increase(5).

Older adults pose unique challenges to the management of thyroid cancer. Management decisions must weigh the risks of surgery, which are increased with patient co-morbidities, against the likelihood of cancer progression, morbidity, and mortality. On one hand, the majority of thyroid cancers are small, slow-growing, and low-risk, which suggests that a more conservative approach to treatment in older adults is reasonable(6, 7). Furthermore, some evidence suggests that the increase in thyroid cancer can be attributed to over-diagnosis due to improved and more frequent use of imaging, as mortality from thyroid cancer has remained essentially stable over time(8). On the other hand, increasing patient age has been associated with higher rates of recurrence, worse prognosis, aggressive disease characteristics, lymph node metastasis, and increased mortality, suggesting that perhaps a more aggressive approach should be utilized in older adults(9–12). A SEER analysis from 1988 to 2003 found that elderly patients were less likely to undergo total thyroidectomy, which was the treatment recommended by the guidelines from the American Thyroid Association at that time(11). However, the current guidelines recommend consideration of active surveillance or thyroid lobectomy for treatment of thyroid cancer in select cases. Therefore, we seek to assess whether an age-related variation in treatment still exists. The projected rise of thyroid cancer along with the growth of an aging population warrants a better understanding of the clinical and pathological features that are associated with worse prognosis in thyroid cancer in older adults to understand optimal management (13). In this population-based study, we investigate the variation of treatment patterns in older adults with differentiated thyroid cancer, as well as determine if the extent of surgery affects disease-specific mortality.

Materials and Methods:

Data source and study population

The National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER-18) database was queried for thyroid cancer cases (primary site: thyroid, ICD-O-3: C73-9) diagnosed from 2004 to 2015(14). SEER captures approximately 28% of the United States population in 18 geographic regions and broadly represents the US population. These geographic regions include Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah, Greater California, Greater Georgia, Kentucky, Louisiana (except cases July-December 2005), and New Jersey. Patients were excluded if their age was < 18 years, if thyroid cancer was diagnosed at autopsy only or present on death certificate, or if their histologic subtype or tumor stage (TNM) was missing or classified as unknown. Patients with medullary, anaplastic, poorly differentiated, or undifferentiated thyroid cancers were also excluded. This study was exempt from review by an institutional review board because it is a limited data set subject to the requirements of a data use agreement.

Data collection

Seer*Stat version 8.3.5 was used to abstract the data routinely collected by SEER, which included patient demographics, tumor characteristics, stage of disease, treatment, and outcomes including vital status, cause of death, and survival time. Demographic data included patient age at diagnosis, which was stratified into 4 groups: 18–54 (younger adults), 55–64 (middle adults), 65–79 (older adults), and ≥ 80 years (super-elderly); gender (male or female), race (white, black, or other), and Hispanic origin. Clinical and pathologic variables included tumor stage, nodal status, and presence of metastases using the 7th edition of the American Joint Committee on Cancer (AJCC) staging system. The middle adults age group (55–64 years old) was added to correspond to the 8th edition of the AJCC staging system. Primary thyroid cancers were classified into 7 histologic types: PTC with histology codes 8050, 8052, 8053, 8260, 8340, 8344, 8450, and 8452, micro PTC with 8341, follicular thyroid cancer (FTC) with 8330–8339, and Hürthle cell cancer (HCC) with 8290 and 8342. Patients who were diagnosed with PTC and had a tumor size <10 millimeters were reclassified as micro PTC, and patients who were coded as micro PTC and had a tumor size ≥ 10 millimeters were reclassified as PTC. Thyroid procedure was classified into four groups: no surgery, total thyroidectomy, thyroid lobectomy, and thyroidectomy not otherwise specified. Receipt of radioactive isotope was also noted and assumed to be treatment for thyroid cancer.

Statistical analysis

All statistical analyses were performed using STATA version 15 (StataCorp., TX, USA). The association among the four categories of age with gender, race, tumor size, grade, histologic subtype, nodal status, type of surgical intervention, and receipt of radioiodine treatment was assessed using Pearson Chi-square (χ^2) for categorical variables and t-test for continuous variables. Survival was calculated as time in months after the diagnosis until either death or the end of the study period. Kaplan-Meier curve and 2-sided log rank tests were used to evaluate disease-specific survival as a function of age. Two-sided significance level was set

as ($\alpha=0.05$). Univariable Cox regression assessed the association between co-variables and disease-specific mortality. The proportional hazards assumption was assessed by reviewing survival function plots. A multivariable Cox proportional hazards regression was then performed using variables significant in the univariable models to evaluate the risk for disease-specific mortality.

Results:

Characteristics of the Patient Cohort

The cohort included 117,098 patients with differentiated thyroid cancer (DTC), 72,368 were younger adults (<55 years old), 23,726 were middle adults (55–64 years), 18,119 were older adults (65–79 years), and 2,885 were super elderly (≥80 years old) (Table 1). Thyroid cancer was more common in females (76.7%) and in white patients (81.5%). The majority of patients presented with T1 (60.0%) and unifocal (59.0%) tumors, 21.6% had nodal metastases, and only 1.1% presented with metastatic disease. The most common histological subtype was PTC (57.8%), followed by micro PTC (34.5%), FTC (5.2%), and HCC (2.5%). The Pacific Coast region accounted for 53,349 (45.6%) cases of thyroid cancer, the East region 45,792 (39.1%) cases, the Northern plains 10,353 (8.8%) cases, the Southwest 7,489 (6.4%) cases, and Alaska with 115 (0.1%) cases.

A 62.3% increase in the overall incidence of thyroid cancer between 2004 and 2015 was observed and attributed to a 63.8% increase in the incidence of PTC, as well as an 89.2% increase in the incidence of micro PTC. The incidence rates of HCC and FTC remained stable. Of the 6,385 deaths that occurred during the study period, 1,050 deaths were attributed to differentiated thyroid cancer. The five-year overall mortality and disease-specific mortality for the cohort was 4.9% and 0.9%, respectively. Over the study period, the disease-specific mortality rate increased for the entire patient cohort, and disease-specific mortality also varied by age cohort (Figure 1A & 1B).

Characteristics Stratified by Age Groups

Demographic trends in each age group were reflective of the entire cohort, however, frequency of histology varied (Table 1). Similar to the entire cohort, PTC was the most common type of cancer accounting for 61.2%, 52.3%, 51.4%, and 59.7% of the cancers in younger adults, middle adults, older adults, and the super-elderly respectively ($p<0.001$), followed by micro PTC, which accounted for 32.4%, 40.0%, 37.7%, and only 21.6% of the cancers in younger adults, middle adults, older adults, and the super-elderly, respectively ($p<0.001$). HCC and FTC were increasingly more prevalent with increasing age groups. FTC was most prevalent in the super-elderly accounting for 8.4% of DTC compared to 4.8%, 5.0%, and 6.7% in younger, middle, and older adults, respectively. HCC accounted for 7.1% of DTC in the super-elderly versus in 1.8%, 2.8%, and 4.5% in younger, middle, and older adults, respectively ($p<0.001$).

The majority of younger (59.6%), middle (63.6%), and older adults (59.0%) presented with T1 tumors, whereas fewer super-elderly (44.2%) presented at the same tumor stage ($p<0.001$). Conversely, of the thyroid cancers in the super-elderly, 10.7% were classified as

T4 disease, compared to 5.3% in older adults, 3.2% in middle adults, and 2.3% in younger adults ($p<0.001$). Multifocal disease was more prevalent in younger adults accounting for 40.2% of thyroid cancer compared to 40.0% in middle adults, 37.2% in older adults, and 30.1% of the super-elderly ($p<0.001$). Nodal metastases were more frequent in the younger adults (24.8%), followed by the super-elderly (18.8%), then the middle (16.7%) and older (15.5%) adults ($p<0.001$). However, distant metastasis occurred in 4.8% of the super-elderly, compared to 2.5% of older adults, 1.3% of middle adults, and only 0.6% of adults ($p<0.001$).

Of the 6,385 deaths that occurred over this study period, 1,369 (1.9%), 1,400 (5.9%), 2,485 (13.7%), and 1,131 (39.2%) occurred in the younger adults, middle adults, older adults, and the super-elderly, respectively ($p<0.001$). Overall survival was 98.1%, 94.1%, 86.3%, and 60.8%, for the younger, middle, older adults, and super-elderly ($p<0.001$). Of the 1,050 deaths attributed to thyroid cancer, 171 (0.2%), 237 (1.0%), 430 (2.4%), and 212 (7.4%) occurred in younger adults, middle adults, older adults, and super-elderly, respectively ($p<0.001$). Twelve-year disease-specific survival was 99.4%, 97.7%, 93.5%, and 83.9% in younger adults, middle adults, older adults and super-elderly, respectively ($p<0.001$).

Treatment Patterns Stratified by Age

Younger adults underwent thyroid surgical intervention more frequently (99.0%) than middle adults (98.4%), older adults (97.4%) or the super-elderly (89.1%). Younger adults were also more likely to receive RAI than middle or older adults or super-elderly (48.7% vs. 42.5% vs. 39.7% vs. 30.7%, $p<0.001$). Of the entire cohort, 1,892 patients (1.6%) did not undergo surgery. This included only 735 (1.0%) of younger adults, 378 (1.6%) of middle adults, 463 (2.6%) of older adults, and 316 (11.0%) of super-elderly ($p<0.001$). For each T, N, and M stage of observed thyroid cancers, a higher proportion of the older adults and super-elderly cohorts did not undergo surgery (Figure 2). For patients with T1 cancers, 9.3% of the super-elderly adults did not undergo surgery as compared to 2.1% of older adults, 1.5% of middle adults, and only 1.0% of the younger adults ($p<0.001$). Similarly, of patients with T2 tumors, 13.8% of the super-elderly did not have surgery, compared to 1.3%, 1.5%, and 3.5% of the younger, middle, and older adults, respectively ($p<0.001$). For T3 tumors, 6.5% of the super-elderly did not undergo an operation, in comparison to 0.5%, 0.8%, and 1.4% of younger, middle, and older adults, respectively ($p<0.001$). Fewer patients with T4 cancers underwent surgery across all age groups, but the super-elderly still had a significantly higher proportion of patients who did not have surgery measuring 22.4%, whereas only 1.1% of younger adults, 4.4% of middle adults, and 7.6% of older adults did not undergo surgery for tumors of this size ($p<0.001$, Figure 2A).

For patients with nodal metastases (Figure 2B), 99.5% of younger adults, 98.3% of middle adults, 97.4% of older adults underwent surgery as compared to 84.7% of super-elderly patients ($p<0.001$). In patients with known distant metastases (Figure 2C), 93.7% of younger adults underwent an operation, compared to 88.7%, 86.0%, and 61.6% of middle adults, older adults, and super-elderly adults, respectively ($p<0.001$).

The most frequent reason cited for patients who did not undergo surgery was that it was “not recommended” (58.5%). Of the cohort as a whole, 0.6%, 0.9%, 1.5%, and 7.0% of younger adults, middle adults, older adults, and super-elderly patients were in the “surgery not

recommended” group, respectively ($p<0.001$). Conversely, the least common known reason that surgery was not performed was that it was “not recommended, secondary to patient comorbidities” (5.2%). This accounted for 0.02% of younger adults in the study vs. 0.06% middle adults vs. 0.22% older adults vs. 1.04% super-elderly ($p<0.001$). Surgery was recommended but not performed in 16.8% of the entire cohort.

Survival Analysis by Surgical Intervention Stratified by Age

A significant difference in survival among age groups was observed between patients who underwent surgery (total thyroidectomy or thyroid lobectomy) versus those who did not ($p<0.001$). Twelve-year disease specific survival in those who underwent total thyroidectomy was 99.4%, 97.7%, 93.7%, and 86.7% in younger adults, middle adults, older adults, and super-elderly respectively ($p<0.001$, Figure 3A). Disease-specific survival at 12 years in those who underwent thyroid lobectomy was 99.6%, 99.1%, 97.1%, and 93.8% in younger adults, middle adults, older adults, and super-elderly, respectively ($p<0.001$, Figure 3B). On the other hand, in those who did not undergo surgery, the disease-specific survival at 12 years was 93.0%, 69.0%, 49.4%, and 39.4% in younger adults, middle adults, older adults, and super-elderly respectively ($p<0.001$, Figure 3C).

Univariable and multivariable analysis for disease-specific survival by age groups

Univariable analysis for disease-specific survival demonstrated that middle adults, older adults, and super-elderly have a significantly higher risk of disease-specific mortality compared to younger adults (HR: 4.6, 11.5, and 41.1, respectively, $p<0.001$, Table 2). Univariable models also showed that male sex (HR: 2.8, 95% CI: 2.5–3.2, $p<0.001$), spread to lymph nodes (HR: 4.1, 95% CI: 3.6–4.6, $p<0.001$), and distant metastases (HR: 51.1, 95% CI: 44.8–58.3, $p<0.001$) were associated with an increased risk of disease-specific mortality. On the other hand, receiving radioisotope (HR: 0.79, 95% CI: 0.70–0.90, $p<0.001$), thyroid lobectomy (HR: 0.03, 95% CI: 0.02–0.04, $p<0.001$), total thyroidectomy (HR: 0.05, 95% CI: 0.04–0.06, $p<0.001$), or thyroidectomy, not otherwise specified (HR: 0.11, 95% CI: 0.06–0.18, $p<0.001$) significantly lowered the disease-specific mortality. As expected, micro-PTC had the least risk of disease-specific mortality, whereas differentiated HCC had the highest risk.

In the multivariable model, all of the significant explanatory variables from the univariate models were still found to be significantly associated with higher disease-specific mortality (middle adults HR: 4.0, 95% CI: 3.2–4.8, $p<0.001$; older adults HR: 7.6, 95% CI: 6.3–9.1, $p<0.001$; super-elderly HR: 17.2, 95% CI: 13.8–21.3, $p<0.001$; male sex HR: 1.3, 95% CI: 1.2–1.5, $p<0.001$; lymph node metastasis HR: 2.1, 95% CI: 1.8–2.4, $p<0.001$; distant metastasis HR: 7.4, 95% CI: 6.4–8.7, $p<0.001$). Undergoing surgery and radiation again reduced the disease-specific mortality (thyroid lobectomy HR: 0.2, CI: 0.2–0.3, $p<0.001$; total thyroidectomy HR: 0.3, CI 0.2–0.3, $p<0.001$; thyroidectomy, not otherwise specified HR: 0.2, 95% CI: 0.1–0.4, $p<0.001$; RAI HR: 0.7, CI: 0.6–0.8, $P<0.001$).

Discussion:

Our work is one of the largest population-based studies to investigate the clinical and pathological differences of thyroid cancer across strata of age and to incorporate the extent of surgery or lack thereof with disease-specific survival among those patients. While the majority of older adults presented with DTC, fewer adults ≥ 55 years old underwent any surgery or radiotherapy compared to younger adults, and these patients had a worse disease-specific survival. In this cohort, 11.0% of the super-elderly (age ≥ 80) did not undergo surgery, followed by 2.6% of older adults (age 65–79), 1.6% of middle adults (age 55–64), and 1.0% of younger adults (age <55). Furthermore, the most common reason listed for those not undergoing surgery was that it was “not recommended”, while the least common reason was that it was “not recommended due to comorbidities”. Age-related differences in surgical management were seen across tumors of all TNM stages. On multivariable Cox regression, adjusting for TNM classification and histopathology, older age, male sex, lymph node metastasis, and distant metastasis were significantly associated with lower disease-specific survival, whereas undergoing radiation or surgical treatment was associated with higher disease-specific survival. While surgical decision-making in older adults includes many clinical subtleties, our findings highlight the age-related treatment variation that continues to exist in the setting of evolving management guidelines for differentiated thyroid cancer.

Similar to the findings in our study, others have also described the association between decreased survival from well-differentiated thyroid cancer and male sex, increasing age, tumor stage, and distant metastasis (3, 9, 10, 15, 16). In our cohort of patients, disease-specific survival was similar in patients who underwent total thyroidectomy or lobectomy, but significantly worse for those who did not undergo surgery at all. Older adults were more frequently recommended for active surveillance across all TNM stages. While T4 tumors and distant metastases were more prevalent in older adults, and may perhaps account for some patients undergoing active surveillance, they still occurred with low frequency. Furthermore, younger adults were more likely to present with nodal metastases, which is similar to the findings from other studies (17–19), but only 1.6% underwent non-surgical management.

Even though our study excluded aggressive thyroid cancers, the alternate implication might be that older adults and super-elderly had less surgical intervention due to tumor-related factors and therefore had increased disease-specific mortality due to the disease biology. While this may be for older adults and super-elderly patients who presented with T4 (5.3% and 10.7% of older adults and super-elderly, respectively) or M1 disease (2.5% and 4.8% of older adults and super-elderly, respectively), many patients with T1 and T2 disease were also not recommended to have surgery (Figure 2). Furthermore, with improvements in diagnostic methods for thyroid cancer, there is an increased proportion of cancers being diagnosed at earlier T stages contributing to lead-time bias, but the disease-specific survival continues to be significantly lower for the older and super-elderly cohorts(21). It is important to note that some patients in the older and super-elderly cohorts had a more limited life expectancy, with a one-year disease-specific survival of 93.5% and 82.8% for adults aged 65–79 and ≥ 80 years old, respectively, and 3-year disease-specific survival of 85.3% and 71.7%, suggesting

that some of these patients would less likely benefit from surgical intervention. However, the decreasing trend of the disease-specific survival curve to 12 years also highlights that some older adults did not benefit from active surveillance.

To minimize the overtreatment of thyroid cancer, the 2015 ATA clinical practice guidelines recommend more conservative treatment methods including thyroid lobectomy and active surveillance in select cases, leaving room for clinical interpretation(22). There is growing evidence supporting active surveillance for PTC measuring <1.5cm, and some studies have shown that older adults have a lower likelihood of tumor growth when presenting with these small tumors(23). However, a study by Ho, et al. found that the disease-specific mortality significantly worsens when active surveillance is pursued for DTC ≥ 2cm and/or when the patient is ≥ 72 years old(24). Their study was restricted to patients without nodal or distant metastases, whereas our cohort of patients included those with nodal or distant metastases. The continuous expansion of conflicting data coupled with the evolving clinical guidelines may be another contributing factor to the observed treatment variation.

In a recent study among Medicare beneficiaries, a 6.2-fold difference in surgical management of thyroid cancer was seen across U.S. regions. The variation did not appear to be related to geographical healthcare availability, socioeconomic status, or volume of surgeons, which suggests a wide discrepancy in local preferences and practice patterns for this disease(25).

Surgical decision-making in older adults is complex, multi-factorial, and not well understood. It requires aggregating and weighing multiple patient-related factors, including the risk of co-morbidities and disease-specific factors to provide the best recommendation. Multiple single institutions studies cite the safety and efficacy of thyroidectomy in older adults and even ability for same-day discharge (26, 27). However, population-based studies cite increased overall complications, length of stay, and readmission rates. The knowledge of possible worse outcomes and typical indolent nature of DTC may perhaps deter some to operate, which may subsequently contribute to worse survival and compound the disease biology. Risk indices dedicated to older adults have yet to be applied to older patients with thyroid cancer to help determine the optimal approach to treatment while simultaneously weighing patient perspectives, co-morbidities, and functional status. Future studies to understand surgical decision-making in older adults may shed light on this variation. Incorporation of a geriatric risk assessment tool and management guidelines specific to the treatment of older adults with differentiated thyroid cancer may facilitate more consistent clinical decision-making in this population.

There are several limitations in this study in addition to those inherent in retrospective database studies including coding errors, missing values, confounding by indication, and selection bias into the database. The SEER database lacks information regarding the clinical subtleties that are essential in management decisions, especially in caring for older adults, including patient desires, severity of comorbidities, patient-reported symptoms and quality of life, and functional status. It also does not have information on relevant risk factors including family history of thyroid cancer, history of radiation exposure, and mutational status. This cohort precedes the revision in pathology of NIFT-P and thus some cancers in

this database may be misclassified. It also lacks information regarding follow up methods, development of recurrence, dose of radioactive iodine, or socioeconomic status. Furthermore, understanding the effect of surgeon-volume or evaluation at a tertiary referral center on the decision to not recommend surgery could not be performed.

Conclusions:

Older adults 65 years old most commonly present with DTC, but with higher frequency of larger tumor size (>T1), distant metastasis, and aggressive histology, as compared to younger adults. Despite the benefits of surgery in decreasing mortality and recurrence, older adults are more likely to pursue active surveillance, and also have worse disease-specific survival. With the current trends of increasing incidence in thyroid cancer, growth of the aging population and the projected increase in life expectancy, understanding the clinical, treatment, and pathologic characteristics of thyroid cancer that can affect prognosis is critical. Future studies are needed to understand the variation in treatment patterns for older adults with thyroid cancer and also to evaluate risk indices and clinical practice guidelines dedicated to older adults to distinguish which patients may benefit from surgical intervention.

Acknowledgments:

We have no further acknowledgments to report.

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Highlights:

- Fewer older adults (≥ 65 years) underwent surgery or RAI compared to younger adults
- Disease-specific survival was significantly worse in those who did not have surgery
- The most common reason for not undergoing surgery was it was “not recommended”
- Future prospective studies are needed to better understand this treatment variation

Figure 1A. Annual disease-specific mortality of the entire cohort.

Figure 1B. Annual disease-specific mortality stratified by age group

Figure 1. Annual disease-specific mortality of (A) the entire cohort and (B) stratified by each age group.

2A.

2B. **2C.** **Figure 2.**

Comparison of surgical vs. non-operative management of thyroid cancer for each age group based upon (A) T stage, (B) N stage, and (C) M stage on presentation.

Figure 3.

Kaplan-Meier disease-specific survival curves stratified by age groups comparing patients who have undergone (A) total thyroidectomy, (B) thyroid lobectomy, or (C) no surgical intervention.

Table 1.

Clinical, pathological, and treatment characteristics of patients with differentiated thyroid cancer stratified by age.

	Younger Adults Age 18–54 n = 72,368 No. (%)	Middle Adults Age 55–64 n = 23,726 No. (%)	Older Adults Age 65–79 n = 18,119 No. (%)	Super-elderly Age 80 n = 2,885 No. (%)	<i>P</i> value
Female Sex	58,293 (80.6)	17,168 (72.4)	12,416 (68.5)	1,937 (67.1)	<0.001
Race					<0.001
White	58,507 (80.9)	19,420 (81.9)	15,085 (83.3)	2,455 (85.1)	
Black	4,673 (6.5)	1,773 (7.5)	1,173 (6.5)	164 (5.7)	
Other	9,188 (12.7)	2,533 (10.7)	1,861 (10.3)	266 (9.2)	
Hispanic origin	12,386 (17.1)	2,685 (11.3)	1,814 (10.0)	251 (8.7)	<0.001
Region					<0.001
Alaska	73 (0.1)	17 (0.1)	20 (0.1)	5 (0.2)	
East	27,934 (38.6)	9,538 (40.2)	7,215 (39.8)	1,105 (38.3)	
Northern Plains	6,235 (8.6)	2,104 (8.9)	1,717 (9.5)	297 (10.3)	
Pacific Coast	33,255 (46.0)	10,601 (44.7)	8,163 (45.1)	1,330 (46.1)	
Southwest	4,871 (6.7)	1,466 (6.2)	1,004 (5.5)	148 (5.1)	
Histology					<0.001
MicroPTC	23,330 (32.2)	9,501 (40.0)	6,823 (37.7)	717 (24.9)	
PTC	44,285 (61.2)	12,397 (52.3)	9,266 (51.1)	1,723 (59.7)	
FTC	3,482 (4.8)	1,176 (5.0)	1,222 (6.7)	241 (8.4)	
HCC	1,271 (1.8)	652 (2.8)	808 (4.5)	204 (7.1)	
Focality					<0.001
Solitary	42,218 (58.3)	14,009 (59.0)	11,001 (60.7)	1,904 (66.0)	
Multifocal	29,124 (40.2)	9,384 (39.6)	6,756 (37.3)	885 (30.7)	
No evidence of primary	277 (0.4)	90 (0.4)	110 (0.6)	26 (0.9)	
Unknown	749 (1.0)	243 (1.0)	252 (1.4)	70 (2.4)	
T Stage (AJCC 7th Edition)					
T0	99 (0.1)	48 (0.2)	62 (0.3)	21 (0.7)	
T1	43,146 (59.6)	15,083 (63.6)	10,691 (59.0)	1,275 (44.2)	
T2	13,605 (18.8)	3,347 (14.1)	2,649 (14.6)	471 (16.3)	
T3	13,884 (19.2)	4,492 (18.9)	3,764 (20.8)	810 (28.1)	
T4	1,634 (2.3)	756 (3.2)	953 (5.3)	308 (10.7)	
N Stage					<0.001
N0	54,419 (75.2)	19,773 (83.3)	15,313 (84.5)	2,344 (81.3)	
N1	17,949 (24.8)	3,953 (16.7)	2,806 (15.5)	541 (18.8)	
M Stage					<0.001
M0	71,961 (99.4)	23,426 (98.7)	17,668 (97.5)	2,747 (95.4)	
M1	407 (0.6)	300 (1.3)	451 (2.5)	138 (4.8)	

	Younger Adults Age 18–54 n = 72,368 No. (%)	Middle Adults Age 55–64 n = 23,726 No. (%)	Older Adults Age 65–79 n = 18,119 No. (%)	Super-elderly Age 80 n = 2,885 No. (%)	<i>P</i> value
Year of diagnosis					<0.001
2004–2006	13,706 (18.9)	3,764 (15.9)	2,897 (16.0)	537 (18.6)	
2007–2009	17,425 (24.1)	5,492 (23.2)	4,052 (22.4)	712 (24.7)	
2010–2012	19,981 (27.6)	6,686 (28.2)	5,099 (28.1)	805 (27.9)	
2013–2015	21,256 (29.3)	7,784 (32.8)	6,071 (33.5)	831 (28.8)	
Surgical Intervention					<0.001
No surgery	735 (1.0)	378 (1.6)	463 (2.6)	316 (11.0)	
Thyroid Lobectomy	9,408 (13.0)	3,575 (15.1)	3,074 (17.0)	542 (18.8)	
Total Thyroidectomy	61,771 (85.4)	19,638 (82.8)	14,437 (79.7)	2,003 (69.4)	
Thyroidectomy, NOS	454 (0.6)	135 (0.6)	145 (0.8)	24 (0.8)	
Received RAI	35,254 (48.7)	10,092 (42.5)	7,195 (39.7)	886 (30.7)	<0.001

P values reflect chi2 test across columns

MicroPTC = micropapillary thyroid cancer

PTC = Papillary thyroid cancer

FTC = Follicular thyroid cancer

HCC = Hürthle cell thyroid cancer

RAI = radioactive iodine

Table 2.

Univariate and multivariable survival analysis for demographic, clinical and pathologic features, and surgical treatment of thyroid cancer

	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age group						
Younger adults (18–54)	Ref	Ref				
Middle adults (55–64)	4.6	3.7–5.6	<0.001	4.0	3.2–4.8	<0.001
Older adults (65–79)	11.5	9.6–13.7	<0.001	7.6	6.3–9.1	<0.001
Super-elderly (≥ 80)	41.1	33.6–50.4	<0.001	17.2	13.8–21.3	<0.001
Sex						
Female	Ref			Ref		
Male	2.8	2.5–3.2	<0.001	1.3	1.2–1.5	<0.001
Race						
White	Ref	Ref				
Black	1.2	0.9–1.5	0.154	1.2	0.9–1.5	0.17
Other	1.3	1.1–1.6	0.002	1.1	0.9–1.3	0.32
Hispanic Origin	1.2	1.0–1.4	0.089			
Histopathology subtype						
PTC	Ref			Ref		
Micro PTC	0.2	0.2–0.3	<0.001	0.7	0.6–0.9	0.02
Follicular	1.9	1.6–2.3	<0.001	1.5	1.2–1.8	<0.001
Hürthle	2.6	2.1–3.3	<0.001	1.8	1.5–2.3	<0.001
T Stage						
T1	Ref			Ref		
T2	2.6	2.0–3.3	<0.001	1.9	1.5–2.3	<0.001
T3	8.0	6.6–9.7	<0.001	4.5	3.6–5.6	<0.001
T4	54.4	45.0–65.8	<0.001	11.5	9.1–14.6	<0.001
LN metastasis						
N0	Ref			Ref		
N1	4.1	3.6–4.6	<0.001	2.1	1.8–2.4	<0.001
Distant metastasis						
M0	Ref	Ref				
M1	51.1	44.8–58.3	<0.001	7.4	6.4–8.7	<0.001
Surgery						
No surgery	Ref			Ref		
Lobectomy	0.03	0.02–0.04	<0.001	0.2	0.2–0.3	<0.001
Total thyroidectomy	0.05	0.04–0.06	<0.001	0.3	0.2–0.3	<0.001
Thyroidectomy, not otherwise specified	0.11	0.06–0.18	<0.001	0.2	0.1–0.4	<0.001

	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Radiation						
No radiation	Ref			Ref		
Radiation	0.8	0.7–0.9	<0.001	0.7	0.6–0.8	<0.001

HR: Hazard Ratio

CI: Confidence Interval

Ref: Reference group

P value across age groups