Association between age and disease specific mortality in medullary thyroid cancer☆

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Abstract

Background: The aim of this study was to evaluate the association between age and disease specific mortality (DSM) among adults diagnosed with medullary thyroid cancer (MTC).

Method: Surveillance, Epidemiology, and End Results (SEER-18) was used to analyze adult MTC patients stratified by age (18–64, 65–79, 80 years). Associations between patient demographics, tumor size, nodal status, metastatic disease, and extent of surgery on DSM was assessed with multivariable Cox regression.

Results: Among 1457 patients with MTC, 1008 (69.2%) were younger adults, 371 (25.5%) older adults, and 78 (5.4%) were super-elderly. A significantly higher proportion of older adults and super-elderly had less than the recommended operation for MTC. On multivariable analysis, older

adults and super-elderly were 2.9 and 6.7 times more likely to have an increased DSM (HR:2.91, 95% CI: 1.83–4.63; p < 0.001 and HR: 6.70, 95%CI: 3.69–12.20; p < 0.001). Extent of surgery or lymphadenectomy did not affect DSM.

Conclusions: Increased age is an independent predictor of DSM in patients with MTC.

Keywords

Medullary thyroid cancer; Disease-specific mortality; Aging; Elderly; Older adults; Survival

Introduction

An estimated 52,070 new cases of thyroid cancer were diagnosed in the United States in 2019, with an estimated 2170 cancer related deaths.[1] Although medullary thyroid cancer (MTC) only accounts for approximately 5% of these new diagnoses, its incidence is rising.[2] It represents approximately 13% of all thyroid cancer related deaths with an estimated 10-year survival of 65%–71% overall and 40%–44% with distant metastasis.[2,3] The standard minimum surgical management of MTC without evidence of nodal involvement includes a total thyroidectomy with a bilateral prophylactic central neck dissection.[4] However, variation in practice patterns exists regarding extent of surgery and lymphadenectomy for MTC despite the presence of guidelines.[5] Factors associated with this variation, including patient age, are unclear. Interestingly, over time, disease specific mortality (DSM) among all MTC patients has improved, although it is unknown if this is also seen across all patient age groups.[2]

The combination of a rise in the proportion of older patients (age 65 years) in the US, an increase incidence of thyroid cancer, and advances in surgical techniques will lead to more thyroidectomies being performed in older adults.[6–9] Additionally, older patients tend to present at advanced stages and with more aggressive histology.[10,11] Therefore, the improvement in prognosis must be balanced against risk of surgery in an older patient with comorbidities. While the relationship between increasing age and prognosis among patients with differentiated thyroid cancer (DTC) is well established and incorporated into the American Joint Committee on Cancer (AJCC) staging system,[12,13] the impact of age on MTC is less clear. Therefore, the aim of this study was to evaluate the association between age and DSM among adults diagnosed with MTC.

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 with MTC, according to the International Classification of Diseases (ICD) for Oncology-3 codes

8345 and 8510, with tumor size 1.0 cm were included. 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. Consequently, 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 three groups consistent with prior studies evaluating age associations with well differentiated thyroid cancer[15–17]: 18–64 (younger 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. Thyroid procedure was classified as none, lobectomy, or total thyroidectomy. 'Lymph nodes removed' categories were predefined through the SEER database.

Statistical analysis

The association among the three categories of age with gender, race, tumor size, grade, nodal status, and type of surgical intervention 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 DSM. The proportional hazards assumption was checked using survival function plots. Multivariable Cox regression was utilized to assess associations between patient demographics, tumor size, nodal status, presence of metastatic disease, and extent of surgery on DSM. All analyses were performed using Stata 14.0/MP for Linux (College Station, Texas).

Results

Characteristics and treatment patterns of entire cohort

Our study cohort consisted of 1457 patients with MTC (Table 1). The majority of patients were female (59.8%). The majority of patients were of non-Spanish-Hispanic-Latino (SHL) (85.3%) ethnicity and white race (85.2%), followed by black (7.7%), and other (7.1%). The majority of patients were from the Pacific coast (46.8%), East coast (40.4%), Northern plains (8.2%), Southwest (4.4%), and Alaska (0.2%).

Total thyroidectomy (89.3%) was the most common procedure followed by thyroid lobectomy (6.2%), and non-operative management (4.5%) (Table 2). Majority of the patients in the cohort (n = 1457) underwent lymphadenectomy with removal of 4 lymph nodes (61.7%) or removal of 1–3 nodes (10.9%). However 24.5% did not have any lymph nodes

removed with the index thyroidectomy. The majority of our cohort (n = 1457) had T1 and T2 (65.8%), N0 (55.9%), and M0 (92.1%) disease. Most patients had solitary focus of MTC (72.9%). There were 229 (15.7%) patient deaths over the study period, of which, 109 (47.5%) were attributable to MTC.

Characteristics and treatment patterns stratified by age

Of the 1457 patients with MTC, 69.2%, 25.5%, and 5.4% were younger adults (18–64 years), older adults (65–79 years), and super-elderly (80 years), respectively (Table 1). Demographic characteristics in each age group were reflective of the entire cohort, however, the proportions of non-SHL among the three age groups varied significantly (83.3% *vs* 89.2% *vs* 92.3%, in younger adults, older adults, super elderly respectively, p = 0.005). There were no other significant differences in cohort demographics when stratified by age.

A significant difference among the three age groups was observed in regards to surgical management including extent of thyroidectomy and extent of lymphadenectomy (Table 2). Younger patients underwent total thyroidectomy more frequently than the super-elderly (90.7% *vs* 78.2%, p = 0.006). Thyroid lobectomy was more prevalent in the super-elderly group than in younger adults (10.3% *vs* 5.5%, p = 0.006). Additionally, a greater proportion of the super-elderly underwent non-operative management compared to older and younger adults (11.5% *vs* 4.9% *vs* 3.9%, respectively; p = 0.006). Lymphadenectomy with removal of 4 lymph nodes was more frequent among those <65 years old compared to those 65–79 years old and 80 years old (65.4% *vs* 55.8% *vs* 42.3%, p = 0.000). Among the super-elderly and older adults, a significantly lower proportion underwent lymphadenectomy compared to the younger cohort (53.8% and 65.8% *vs* 76.6%, p = 0.000).

In regards to tumor size, there was a significant difference in the distribution of T staging among the three age groups (Fig. 1). T1 disease was the most common presentation in older adults compared to the super-elderly and younger adult groups (T1: 39.1% *vs* 32.1% and 31.4%), whereas higher proportion of T2 disease was observed among younger adults compared to older adults and super-elderly (T2: 35.1% *vs* 25.6% and 32.5%, p = 0.043). T3 disease presentation was more common in the super-elderly group (T3: 28.2% *vs* 26.4% older adults and 25.2% younger adults, p = 0.043) and T4 was more common in older adults (T4: 8.9% *vs* 7.7% super elderly and 8.3% younger adults, p = 0.043). Interestingly, no significant difference among age groups was observed in presence of nodal or distant metastases. Unifocal disease was more common in super elderly patients than the younger and older adult groups (84.6% *vs* 69.4% and 79.8%, respectively).

Of the 229 deaths that occurred over the study period, 44.1%, 41.0%, and 14.8% occurred in younger adults, older adults, and the super-elderly (p = 0.000). Overall survival at 5 years was 90.3%, 76.8%, and 57.8% for younger adults, older adults, and super-elderly, respectively (p = 0.000). Overall survival at 10-years was 89.9%, 74.7%, and 56.4% for younger adults, older adults, and super-elderly, respectively (p = 0.000). Of the 109 deaths attributable to MTC, 6.0%, 8.9%, and 20.5% occurred in younger, older, and super-elderly groups, respectively (p = 0.000). Disease-specific survival at 10-years was 90.5%, 81.8%, and 61.6% among younger, older, and super-elderly groups, respectively (p = 0.000).

Disease-specific survival analysis

On univariable analysis, DSM was associated with advancing age, 'other' race, male gender, T3 and T4 disease, lymph node and distant metastases, and non-operative management (Table 3, Fig. 2). Older age was associated with a higher DSM when adjusted for surgical intervention and for each T stage (Figs. 3 and 4).

On multivariable analysis (Table 4), older age (65–79 years HR = 2.908, 95%CI: 1.828–4.626, p = 0.000; 80 years HR = 6.709, 95%CI: 3.688–12.203, p = 0.000), African American race (HR = 2.182, 95%CI: 1.129–4.219, p = 0.020), T3 and T4 disease (T3 HR = 2.044, 95%CI: 1.047–3.992; p = 0.000 and T4 HR = 3.676, 95% CI: 1.798–7.516; p = 0.000), lymph node metastases (N1a HR = 3.138, 95%CI: 1.556–6.332, p = 0.001; N1b HR = 3.570, 95%CI: 1.914–6.659, p = 0.000), distant metastasis (HR = 19.716, 95%CI: 13.449–28.903, p = 0.000), and non-operative management (HR = 2.603, 95%CI: 1.131–5.995, p = 0.024) were all independently associated with worse DSM. Therefore, even after controlling for disease stage and management of MTC, older age was an independent prognostic factor for worse DSM. Gender, extent of lymph node dissection, extent of thyroidectomy, and Hispanic ethnicity were not significantly associated with DSM (Table 4).

Discussion

In summary, our study represents one of the largest population-based studies over a 10-year period demonstrating an association between increased age (65 years) and increased DSM regardless of disease stage or surgical management of MTC. Among our cohort of 1457 patients, 109 (7.48%) patients died due to MTC. DSM was 2.9 and 6.7 times higher among patients 65–79 years and 80 years, respectively. Moreover, African American race was associated with increased DSM. Other factors such as non-operative management, T3 and T4 staging, and lymph node and distant metastasis were also associated with increased DSM.

Our results are in agreement with previously published studies showing an association between age and DSM among MTC patients.[18–21] However, previously published nomograms for MTC that predict DSM did not take into account extent of surgical management.[18,19] A 2015 retrospective single institution study by Ho et al. designed a predictive nomogram for MTC DSM using age, gender, postoperative calcitonin, perivascular invasion, pathologic T status, pathologic N status, and M status.[18] After M status, age had the highest hazard ratio (1.71) for DSM. Moreover, Qu et al. proposed an age cutoff of 45 and 69 years to further classify MTC patients into three risk groups to be used with sex, race, and conventional AJCC TNM status to identify highrisk patients.[19] Patient age 50–69 years and 70 years were significantly associated with increased DSM (HR: 2.853 and 5.804, respectively; p = 0.001). In contrast to our results, a 2006 retrospective single institutional study by De Groot et al. reported extrathyroidal extension and stage at diagnosis were the only independent predictors of MTC survival.[22] However, a small patient cohort of 120 limited the study.

The alternate implication of our findings is that prognosis in older adults and super-elderly is worse because they present with more aggressive disease or that a significantly larger

proportion of younger patients present with familial disease. Numerous studies have found more favorable outcomes among familial MTC patients when compared to those with sporadic MTC.[23–25] Since sporadic MTC has a worse prognosis compared with hereditary MTCs, we would expect that those that are younger in age with MTC would be associated with a lower mortality due to the association familial MTCs. This is thought to be partly due to increased screening and, thus, earlier diagnosis among familial cases of MTC. Among our cohort, the T stage distribution varied with age group with older adults presenting more frequently with T1 and T4 disease. Younger adults had the highest proportion of T2 disease. Older and super-elderly groups presented more frequently with T3 disease. Despite presenting with more advanced stages (T3–4), older age was independently associated with increased DSM within each T stage.

We also observed a significant difference in extent of surgical management among the three age groups. Younger patients underwent more total thyroidectomy and lymphadenectomy than the super-elderly. This may be related to greater proportion of diagnostic lobectomies performed for patients with an indeterminate pre-operative biopsy (Bethesda III/IV) and on final pathology were discovered to have MTC. Therefore, the appropriate operation would not have been performed at the index operation as the MTC diagnosis was not available. This variation in surgical management did not affect DSM. However, we were unable to prove this association using the SEER data due to the lack of pre-operative biopsy results. It is also possible older patients may have been offered less than the recommended treatment due to age or co-morbidities, however, this dataset does not provide that level of granularity.

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 on relevant risk factors including family history of thyroid cancer, history of radiation exposure, and mutational or RET status. It also lacks information regarding receipt of chemotherapy post-operatively, follow up methods, development of recurrence, socioeconomic status, or recognized biochemical variables such as CEA or calcitonin levels. Elevated post-operative calcitonin levels have been associated with increased DSM after adjusting for age.[18,25] However, a study by De Groot et al. found no association between persistent biochemical MTC and disease-specific survival.[22] Calcitonin doubling time of less than one year was associated with a worse recurrence free survival independent of age. Our analysis was unable to adjust for calcitonin levels or doubling time. The description of the extent and type of lymph node dissection among patients with MTC was also not clearly delineated in this database. This information was inferred from nodal staging and reported number of lymph nodes removed, which was categorized into specific ranges in the SEER database. Furthermore, the database does not have information regarding patient comorbidities in order to determine frailty or comorbidity scores and whether MTC is familial or sporadic. However, most familial cases would be expected to present prior to age 65. We limited our analysis to a modern cohort of patients diagnosed between 2004 and 2015 because the presentation and treatment of MTC have changed over time and survival has improved.

Despite these limitations, the results presented in this paper illustrate that regardless of disease stage or surgical management of MTC, DSM is increased among older patients. Due

to MTC's low incidence and lack of prospective studies, there is a paucity of convincing evidence to demonstrate a significant correlation between prognostic indicators and DSM. Moreover, our results also show an increased DSM among African American patients. Additional prospective studies are needed to validate these findings and identify risk factors such as frailty, comorbidity scores, and calcitonin levels and doubling time to evaluate the association with DSM. This will allow clinicians to improve oncologic patient counselling among this patient population. Identifying this highrisk patient population can potentially help with determining the need for increased frequency of follow-up and imaging.

Conclusion

Increased age (65 years) is an independent predictor of increased DSM regardless of disease stage or surgical management of MTC. Additional prospective studies are needed to understand the true association between age and DSM among adults with MTC.

Funding source

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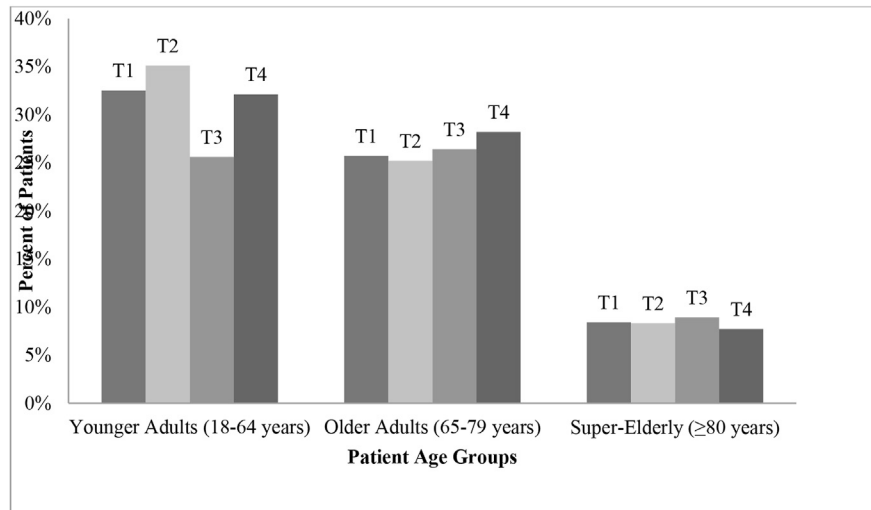
Fig. 1.
Distribution of tumor stage among each patient age group.

Fig. 2.
Kaplan Meier curve for disease-specific survival among three age categories.

Fig. 3.

Kaplan Meier disease-specific survival among three age categories (a) after total thyroidectomy (b) after lobectomy (c) after non-operative management.
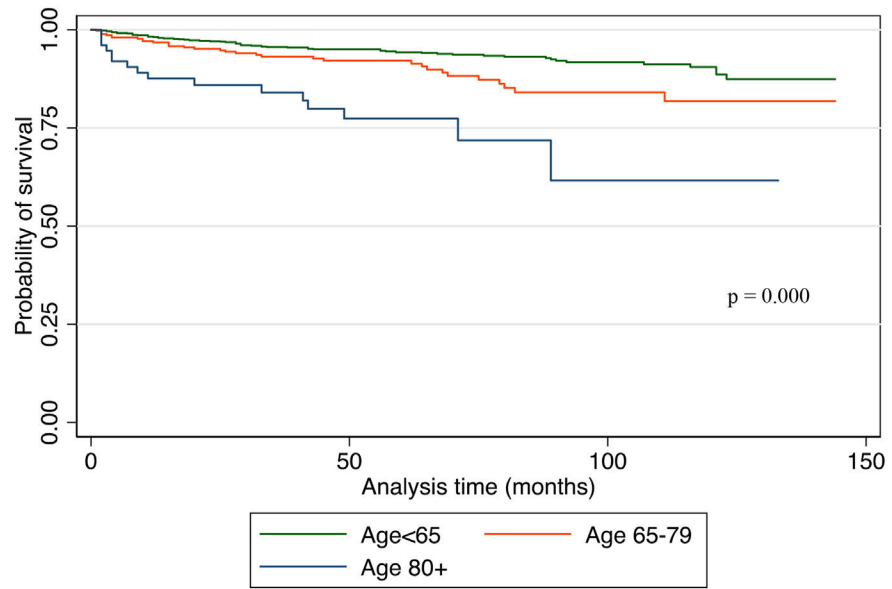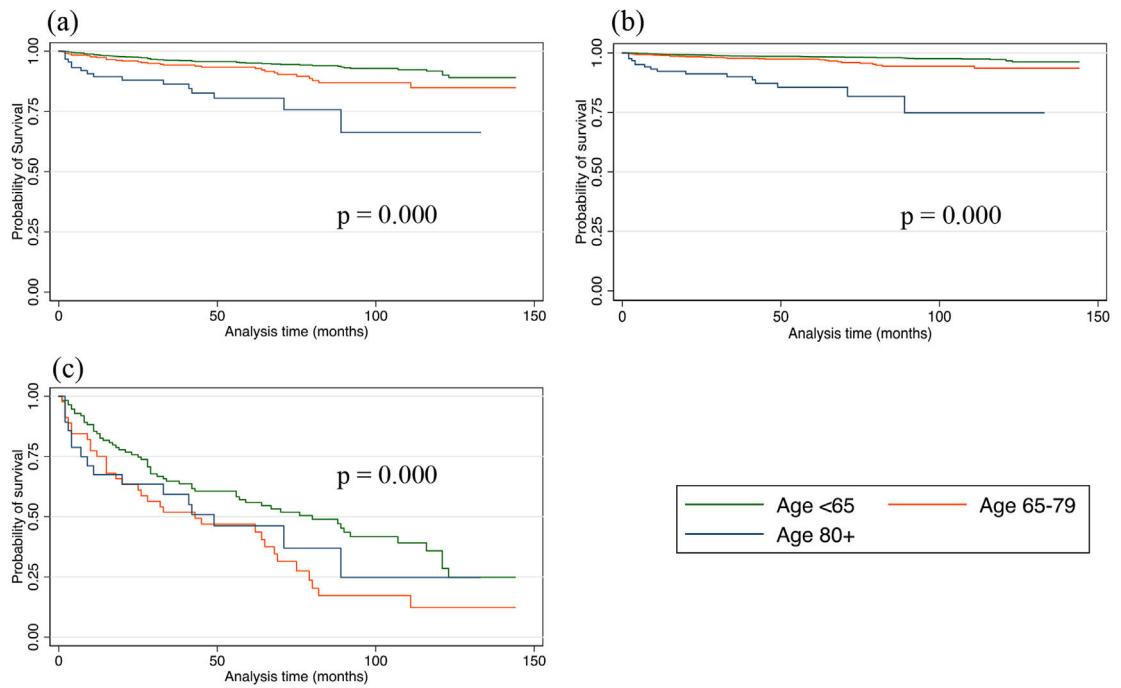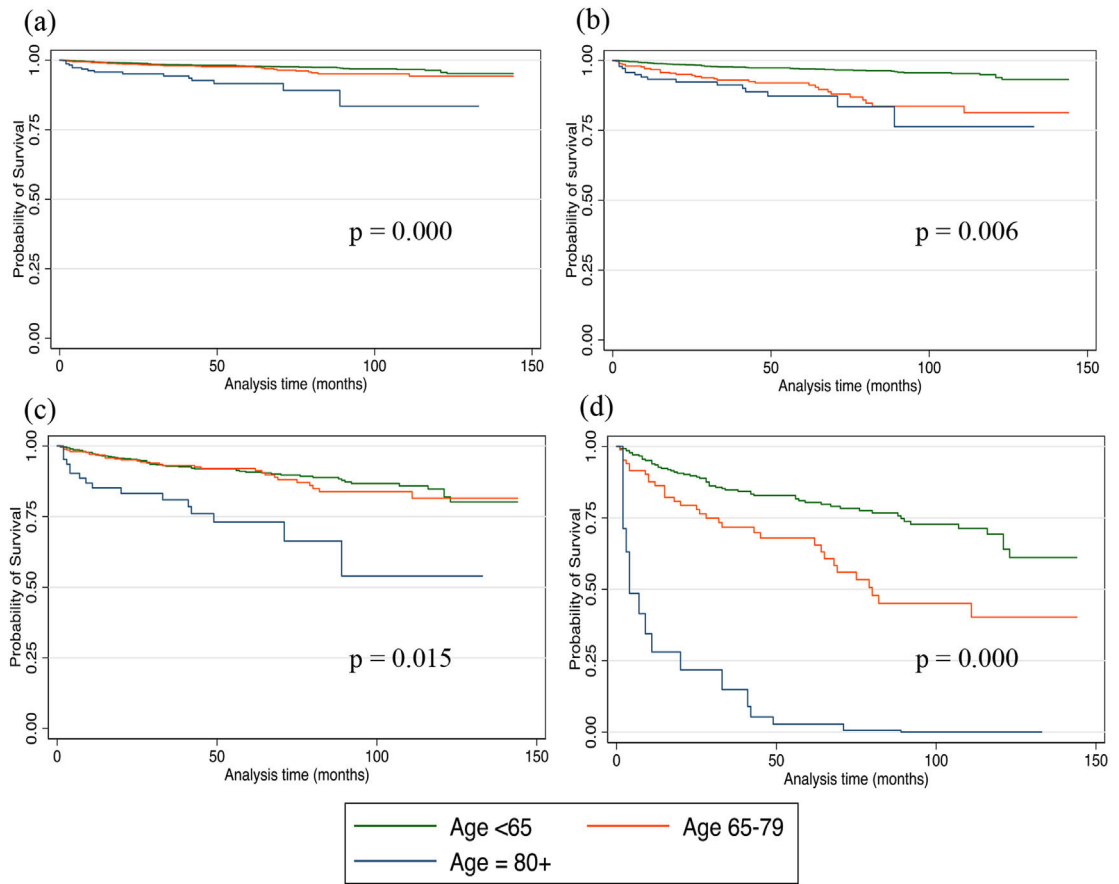
Fig. 4.
Kaplan Meier disease-specific survival among three age categories who presented with stage (a) T1 (b) T2 (c) T3 and (d) T4 disease.

Table 1

Patient demographics by age group.

	All Patients	Younger Adults (<65 years)	Older Adults (65–79 years)	
Age	1457	1008 (69.2%)	371 (25.5%)	78 (5.4%)
Gender				
Female	871 (59.8%)	611 (60.6%)	210 (56.6%)	50 (64.1%)	0.293
Race					0.270
White	1241 (85.2%)	847 (84.0%)	322 (86.8%)	72 (92.3%)	
Black	112 (7.7%)	85 (8.4%)	24 (6.5%)	3 (3.9%)	
Other	104 (7.1%)	76 (7.5%)	25 (6.7%)	3 (3.9%)	
Ethnicity					
Non-Hispanic	1243 (85.3%)	840 (83.3%)	331 (89.2%)	72 (92.3%)	**0.005**
Diagnosis Period					0.246
2004 – 2006	293 (20.1%)	211 (20.9%)	67 (18.1%)	15 (19.2%)	
2007 – 2009	356 (24.4%)	260 (25.8%)	77 (20.8%)	19 (24.4%)	
2010 – 2012	408 (28.0%)	271 (26.9%)	112 (30.2%)	25 (32.1%)	
2013 – 2015	200 (27.5%)	266 (26.4%)	115 (31.0%)	19 (24.4%)	
Region					0.603
Alaska	3 (0.2%)	3 (0.3%)	0 (0.0%)	0 (0.0%)	
East	588 (40.4%)	157 (42.3%)	157 (42.3%)	28 (35.9%)	
Northern Plains	120 (8.2%)	37 (10.0%)	37 (10.0%)	7 (9.0%)	
Pacific Coast	682 (46.8%)	161 (43.4%)	161 (43.4%)	41 (52.6%)	
Southwest	64 (4.4%)	16 (4.3%)	16 (4.3%)	2 (2.6%)	

Table 2–

Surgical intervention, tumor staging, and disease specific mortality stratified by age group.

	All Patients	Younger Adults (<65 years)	Older Adults (65–79 years)	Super-Elderly (80 years)	P-value
Staging					
Tumor Size					
T1	486 (33.3%)	316 (31.4%)	145 (39.1%)	25 (32.1%)	0.043
T2	474 (32.5%)	354 (35.1%)	95 (25.6%)	25 (32.1%)	
T3	374 (25.7%)	254 (25.2%)	98 (26.4%)	22 (28.2%)	
T4	123 (8.4%)	84 (8.3%)	33 (8.9%)	6 (7.7%)	
Nodal Status					
N0	815 (55.9%)	541 (53.7%)	228 (61.5%)	46 (59.0%)	0.066
N1a	268 (18.4%)	136 (13.5%)	50 (13.5%)	11 (14.1%)	
N1b	374 (25.7%)	331 (32.8%)	93 (25.1%)	21 (26.9%)	
Metastasis					
M0	1342 (92.1%)	924 (91.7%)	348 (93.8%)	70 (89.7%)	0.312
M1	115 (7.9%)	84 (8.3%)	23 (6.2%)	8 (10.3%)	
Focality					
Solitary	1062 (72.9%)	700 (69.4%)	296 (79.8%)	66 (84.6%)	**0.000**
Multifocal	368 (25.3%)	289 (28.7%)	67 (18.1%)	12 (15.4%)	
No Primary	3 (0.2%)	0 (0.0%)	3 (0.8%)	0 (0.0%)	
Unknown	24 (1.7%)	19 (1.9%)	5 (1.4%)	0 (0.0%)	
Surgical Intervention					
None	66 (4.5%)	39 (3.9%)	18 (4.9%)	9 (11.5%)	**0.006**
Lobectomy	90 (6.2%)	55 (5.5%)	27 (7.3%)	8 (10.3%)	
Total Thyroidectomy	1301 (89.3%)	914 (90.7%)	326 (87.8%)	61 (78.2%)	
Lymph Nodes Removed					
None	357 (24.5%)	207 (20.5%)	116 (31.3%)	34 (43.6%)	**0.000**
1 – 3	159 (10.9%)	113 (11.2%)	37 (10.0%)	9 (11.5%)	
4	899 (61.7%)	659 (65.4%)	207 (55.8%)	33 (42.3%)	
Other	42 (2.9%)	29 (2.9%)	11 (3.0%)	2 (2.6%)	
Disease Specific Mortality	109 (7.5%)	60 (6.0%)	33 (8.9%)	16 (20.5%)	**0.000**

Table 3

Factors associated with disease-specific mortality on univariable analysis.

	Hazard Ratio	95% CI		*P*-value
Age				
<65	Ref			
65–79	1.787	1.166	2.740	**0.008**
80+	4.801	2.754	8.372	**0.000**
Race				
White	Ref			
Black	1.225	0.656	2.286	0.525
Other	0.131	0.182	0.936	**0.043**
Gender				
Female	Ref			
Male	2.279	1.552	3.345	**0.000**
Ethnicity				
Non-Hispanic	Ref			
Hispanic	0.800	0.439	1.459	0.467
Multifocal				
No	Ref			
Yes	1.220	0.915	1.628	0.175
Diagnosis Period				
2004 – 2006	Ref			
2007 – 2009	0.796	0.478	1.325	0.381
2010 – 2012	1.058	0.620	1.803	0.836
2013 – 2015	1.033	0.516	2.071	0.927
Tumor Size				
T1	Ref			
T2	1.787	0.900	3.547	0.097
T3	4.053	2.159	7.610	**0.000**
T4	12.336	6.525	23.323	**0.000**
Nodal Status				
N0	Ref			
N1a	3.636	1.980	6.676	**0.000**
N1b	6.157	3.827	9.905	**0.000**
Metastasis				
M0	Ref			
M1	19.716	13.449	28.903	**0.000**
Surgical Intervention				
Total Thyroidectomy	Ref			
Lobectomy	0.482	0.152	1.526	0.215
No surgery	11.092	6.947	17.711	**0.000**
Lymph Nodes Removed				

	Hazard Ratio	95% CI		*P*-value
None	Ref			
1–3	1.356	0.727	2.528	0.338
4 +	0.985	0.623	1.559	0.950
Other	1.327	0.463	3.804	0.598

Table 4

Factors associated with disease-specific mortality on multivariable analysis.

	Hazard Ratio	95% CI		*P*-value
Age				
<65	Ref			
65–79	2.908	1.828	4.626	**0.000**
80+	6.709	3.688	12.203	**0.000**
Race				
White	Ref			
Black	2.182	1.129	4.219	**0.020**
Other	0.133	0.018	0.962	**0.046**
Gender				
Female	Ref			
Male	1.028	0.677	1.562	0.896
Ethnicity				
Non-Hispanic	Ref			
Hispanic	0.957	0.514	1.786	0.892
Tumor Size				
T1	Ref			
T2	1.758	0.860	3.593	0.122
T3	2.044	1.047	3.992	**0.036**
T4	3.676	1.798	7.516	**0.000**
Nodal Stage				
N0	Ref			
N1a	3.138	1.556	6.332	**0.001**
N1b	3.570	1.914	6.659	**0.000**
Metastasis				
M0	Ref			
M1	9.324	5.703	15.247	**0.000**
Surgical Intervention				
Total Thyroidectomy	Ref			
Lobectomy	0.724	0.219	2.399	0.598
No surgery	2.603	1.131	5.995	**0.024**
Lymph Nodes Removed				
None	Ref			
1–3	1.396	0.595	3.273	0.443
4 +	0.864	0.380	1.966	0.727
Other	0.335	0.105	1.069	0.065