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Reevaluating the Prognostic Significance of Age in Differentiated Thyroid Cancer

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Abstract

Objective. To determine the impact of age on disease-specific survival in differentiated thyroid cancer.

Study Design. Retrospective analysis of a large population database.

Setting. Surveillance, Epidemiology, and End Results (SEER) database/multiple settings.

Subjects and Methods. The SEER database was examined to identify patients diagnosed with either papillary or follicular carcinoma of the thyroid between the years 1988 and 2003. Information obtained included patient age, sex, tumor type, size, extension, and nodal or distant metastases. Kaplan-Meier survival analyses were used to estimate disease-specific survival based on patient age range, and the log-rank test was used to assess for statistical differences between survival curves. A multivariate analysis was performed including the variables listed above to determine disease-specific hazard ratios of death for various age cutoffs.

Results. A total of 42,209 patients were identified. Patients 45 years and older had significantly worse survival than younger patients ($P < .0001$). A significant decrease in disease-specific survival was first seen in patients aged 35 years and older, and survival continued to steadily decrease with each additional decade of age ($P < .001$). Patients aged 35 years and older were 14 times more likely to die from differentiated thyroid cancer than patients younger than 35 years.

Conclusion. Increasing age is associated with poorer survival in differentiated thyroid cancer. This relationship represents a continuum with an initial decrease in survival starting at age 35 years that continues to decline with further advancing age.

Keywords

differentiated thyroid cancer, age, survival, SEER database

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Well-differentiated thyroid cancer (DTC) represents greater than 90% of all thyroid malignancies and has the best prognosis, with 10-year survival rates greater than 90%.[1] Both papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) are considered DTC, although they represent distinct clinical entities.[2] While it is common for advanced age to be associated with poorer survival in many types of cancer, DTC is the only human cancer to include age as a part of the staging criteria. Age first appeared in the second edition of the *AJCC Cancer Staging Manual* published in 1983, with patients grouped according to age less than 45 years or 45 years and older.[3] Interestingly, none of the cited sources in this manual actually evaluated an age cutoff of 45 years. Halan's study of 344 patients with all subtypes of thyroid cancer followed for 10 years specifically examined the age groups of 0 to 40, 41 to 60, and greater than 60 years and demonstrated a steady decline in survival with increasing age.[4] The Lahey clinic data of 792 patients with DTC presented by Cady and colleagues[5] suggested an increased risk of mortality for PTC greater than 50 years and greater than 40 years of age for FTC.

Now, 5 editions and 26 years later, the current thyroid cancer staging guidelines continue to use an age cutoff of 45 years.[6] Patients in the younger age group are considered stage I for any extent of disease short of distant metastasis and stage II when metastases are present. No patient younger than 45 years can have stage III or IV disease. Conversely, a patient 45 years and older has stage III disease if the tumor is larger than 4 cm, has minimal extrathyroidal extension, or has nodal disease in the central neck compartment. Frank extrathyroidal extension, nodal disease in the lateral neck, or

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distant metastases are classified as stage IV for patients in the older age group.[6]

Studies have confirmed the survival advantage of patients younger than 45 years compared with the older age group.[7,8] However, other authors have suggested alternate age cutoffs ranging from 40 to 60 years.[4,9-11] All of these studies have examined DTC as a group or PTC alone, but none have explored the prognostic role of age in FTC specifically. While patient age clearly affects prognosis in DTC, the ideal age cutoff has not been fully defined. The staging system divides patients into 2 dichotomous groups by age, but it is more likely that the mortality risk with advancing age is better depicted as a continuum. Nevertheless, the true relationship between age and prognosis has not been fully elucidated, and reports in the literature are variable. The aim of this study is to determine the impact of patient age on disease-specific survival in both PTC and FTC.

Methods

Data Source

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute is a coordinated system of population-based cancer registries that is widely used to study a large variety of malignancies. Strategically located across the United States, the SEER registries routinely collect data on patient demographics, primary tumor site, tumor morphology, stage at diagnosis, first course of treatment, and follow-up vital status. The SEER program performs continuous quality control activities to ensure the collection of high-quality data, and the 17 registries included in our analysis represent an estimated 26% of the US population from several geographic regions.[12]

Patient Selection

The SEER database was queried for patients diagnosed with papillary or follicular thyroid carcinoma based on International Classification of Diseases for Oncology (ICD-O-3) anatomy and histology codes, between the years 1988 and 2003. Data were obtained from all 17 US cancer registries participating in the SEER program using SEER*Stat version 7.0.4 (www.seerstat.gov/).

Patient demographics including age at diagnosis, sex, and tumor factors were reviewed. Patients younger than 18 years were excluded from this study. For most analyses, patients were classified according to age <45 years or ≥ 45 years, according to the current AJCC classification system.[6] A separate analysis was conducted to further investigate the effect of increasing age on prognosis; for this, patients were grouped according to age ranges 18 to 24 years, 25 to 34 years, and by decades progressively up to a group that included all patients 85 years and older. Tumor factors included tumor size, extent, presence of regional nodal metastases, and distant metastases. Tumor extent was classified according to the SEER Extent of Disease variable as intrathyroidal, limited to the thyroid capsule, limited extension beyond the thyroid capsule (to pericapsular soft/connective tissue, parathyroid, strap muscle[s], recurrent laryngeal nerve, or vagus nerve), or distant extension beyond the thyroid capsule (to the carotid artery, thyroid artery or vein, jugular vein, sternocleidomastoid muscle, esophagus, larynx including thyroid and cricoid cartilages, trachea, bone, skeletal muscle other than strap or sternocleidomastoid muscle, further contiguous spread, or when the tumor is fixed to adjacent tissues). Papillary and follicular carcinoma cases were analyzed separately to allow for comparison between the 2. The mean follow-up time was 104.6 months and 113.0 months for patients with papillary and follicular cancer, respectively. This study was exempted from institutional review board review at our institution.

Statistical Analysis

Kaplan-Meier survival analyses were used to estimate disease-specific survival for patients with papillary and follicular thyroid cancer. The log-rank test assessed statistical differences between survival curves. Comparisons of data were performed with the Student t test for continuous variables and χ^2 for categorical data. To explore the effect of various dichotomous age divisions on prognoses, hazard ratios with 95% confidence intervals were calculated using Cox proportional hazards models to estimate the risk of death from thyroid cancer at different age splits (ie, risk of death in patients ≥ 30 years versus those <30 years for each 5-year age interval up to age 85 years). Each model adjusted for the effect of sex, tumor size, extension, nodal metastasis, and distant metastasis on survival. Statistical significance was set at $P < .05$. Stata version 10.0 (StataCorp, College Station, Texas) statistical software was used for all statistical analysis.

Results

Overall, 42,209 adults with DTC were identified from the SEER database during this time frame. There were 38,412 (91%) patients diagnosed with PTC, and 3797 (9%) had FTC. Females made up 76% of this cohort, and 52% of patients were 45 years or older. Further classification of patients by age, tumor size, extent, nodal spread, and distant metastasis is demonstrated in **Table 1**. Relative to patients with PTC, those with FTC were older with larger tumors and more distant metastases ($P < .0001$). Patients with PTC, however, had higher rates of nodal spread and an increased incidence of limited intrathyroidal tumors ($P < .0001$). Analysis of disease-specific survival (DSS) among patients with PTC demonstrated significantly improved survival for patients younger than 45 years compared with those aged 45 years and older ($P < .0001$; **Figure 1A**). Similarly, for patients with FTC, those younger than 45 years had improved survival compared with the older cohort ($P < .0001$; **Figure 1B**).

Analysis of DSS among PTC patients by age range using the age categories described above demonstrated no difference in survival among patients aged 18 to 34 years. Patients 35 to 44 years old had a statistically significant decrease in DSS compared with the decade from 25 to 34

Table 1. Characteristics of 42,209 Patients with Differentiated Thyroid Cancer

	Papillary		Follicular		
	n = 38,412	%	n = 3797	%	*P* Value
Male	8956	23.3	1053	27.7	<.0001
Age, y					
Mean (range)	46.9 (18-100)		50.7 (18-100)		<.0001
18-24	2064	5.4	226	6.0	.13
25-34	6913	18.0	540	14.2	<.0001
35-44	9631	25.1	776	20.4	<.0001
45-54	8521	22.2	733	19.3	<.0001
55-64	5389	14.0	570	15.0	.10
65-74	3737	9.7	531	14.0	<.0001
75-84	1845	4.8	328	8.6	<.0001
85+	312	0.8	93	2.5	<.0001
Size, cm					
≤2.00	22,034	57.4	836	22.0	<.0001
2.01-4.00	8960	23.3	1397	36.8	<.0001
>4.00	2717	7.1	866	22.8	<.0001
Not recorded	4701	12.2	698	18.4	<.0001
Tumor extent					
Intrathyroidal	27,572	71.8	1875	49.4	<.0001
Extension limited to thyroid capsule	3064	8.0	1118	29.4	<.001
Limited extension beyond capsule[a]	4301	11.2	235	6.2	<.001
Distant extension beyond capsule[b]	1565	4.1	139	3.7	.22
Not recorded	1295	3.4	145	3.8	.15
Node positive	8679	22.6	110	2.9	<.001
Distant metastasis	615	1.6	285	7.5	<.001

[a]Extension to pericapsular soft/connective tissue, parathyroid, strap muscle(s), recurrent laryngeal nerve, or vagus nerve.
[b]Extension to the carotid artery, thyroid artery or vein, jugular vein, sternocleidomastoid muscle, esophagus, larynx (including thyroid and cricoid cartilages), trachea, skeletal muscle other than strap or sternocleidomastoid muscle, bone, mediastinal tissues, or further contiguous extension; or tumor described as "fixed to adjacent tissues."

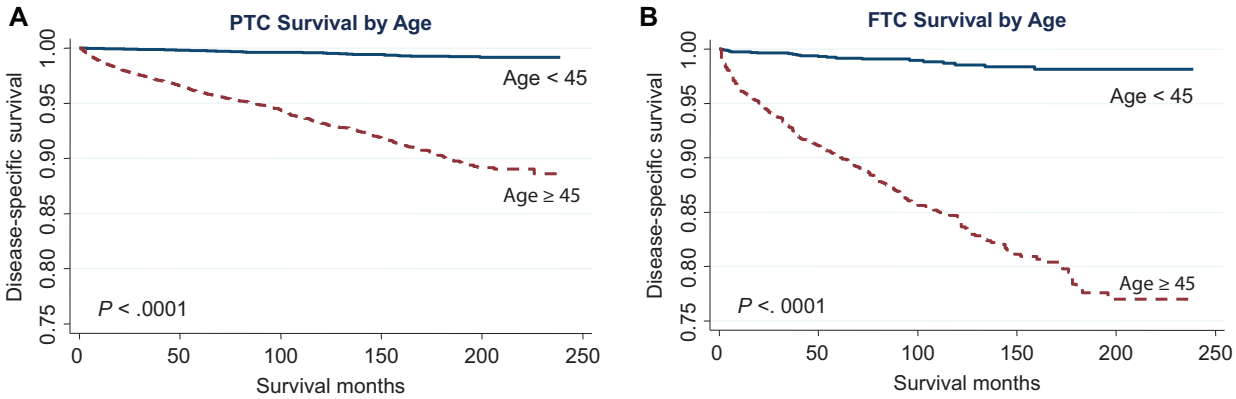

Figure 1. (A) Disease-specific survival of patients with papillary thyroid carcinoma based on 45-year age cutoff. (B) Disease-specific survival of patients with follicular thyroid carcinoma based on 45-year age cutoff.

years ($P < .001$). Each increasing decade in age continued to demonstrate a significant decrease in DSS ($P < 0.0001$; **Figure 2A**). An identical pattern was seen in patients with FTC (**Figure 2B**), with an initial decrease in survival starting at age 35 years ($P = .0028$) and a continued drop in DSS for each advancing decade ($P < .001$). Raw mortality data and mean follow-up times are listed in **Table 2** for each of the age groups individually and based on the age division of 45 years. The disease-specific mortality for patients with FTC was significantly higher overall (9.27%

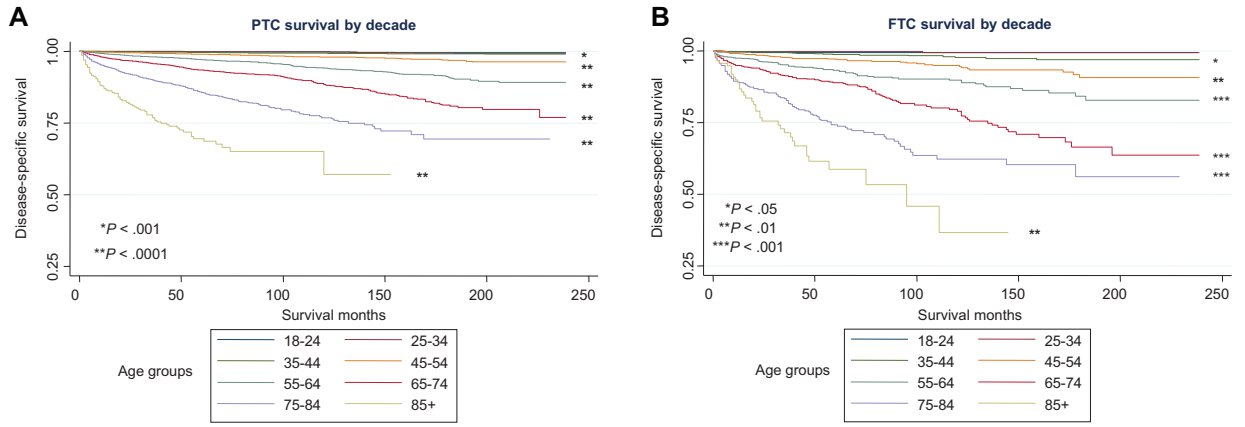

Figure 2. (A) Disease-specific survival of patients with papillary thyroid carcinoma based on age ranges. (B) Disease-specific survival of patients with follicular thyroid carcinoma based on age ranges.

Table 2. Mortality by Age Range for Papillary Thyroid Cancer and Follicular Thyroid Cancer

	Papillary Thyroid Cancer			Follicular Thyroid Cancer			
Age, y	Patients, n	Mean Follow-up, mo	Disease-Specific Mortality, %	Patients, n	Mean Follow-up, mo	Disease-Specific Mortality, %	*P* Value
18-24	2064	116.6	0.44	226	114.9	0.88	.35
25-34	6913	112.9	0.30	540	118.5	0.19	.63
35-44	9631	107.0	0.63	776	118.1	2.19	<.0001
45-54	8521	100.6	1.78	733	111.0	5.05	<.0001
55-64	5389	97.7	4.99	570	112.4	10.35	<.0001
65-74	3737	96.8	9.53	531	101.7	19.59	<.0001
75-84	1845	82.1	17.02	328	93.1	29.27	<.0001
85+	312	63.7	28.85	93	70.6	38.71	.071
Total	38,412	104.6	3.31	3,797	113.0	9.27	<.0001
18-44	18,608	110.3	0.49	1,542	117.8	1.30	<.0001
45+	19,804	98.0	5.96	2,255	108.2	14.72	<.0001

vs 3.31% for FTC and PTC, respectively, $P < .0001$) and in each age group (1.30% vs 0.49% in the younger age group and 14.72% vs 5.96% in the older age group for FTC and PTC, respectively, $P < .0001$ for all).

Examining the variables of age, sex, tumor size, tumor extension, nodal metastases, and distant metastases, a multivariate analysis was performed to determine the disease-specific mortality hazard ratio for various dichotomous age cutoffs from 30 to 85 years (**Figure 3**). The hazard ratios trended downward for both PTC and FTC with advancing age as an increasing number of older patients became counted in the younger age group. The hazard ratios tended to be higher for PTC than FTC. Age remained an independent predictor of disease-specific mortality when controlled for the variables indicated above (data not shown).

Discussion

The current staging system for follicular and papillary thyroid cancer underscores the importance of patient age in the prognosis of these cancers but creates 2 dichotomous patient groups based on a somewhat arbitrary age cutoff of 45 years. With the current system, age carries more prognostic weight than does distant metastases. For example, a 44-year-old patient with a large, locally invasive tumor and distant metastasis is classified as stage II and theoretically has a better prognosis than a 46-year-old stage III patient with a 2-cm tumor that extends just beyond the thyroid capsule into the strap muscles without regional or distant metastases. Our results provide additional confirmation of the survival advantage for young patients with a significantly disparate survival using the existing cutoff of 45 years (**Figure 1**). This age cutoff also determines a clinically significant

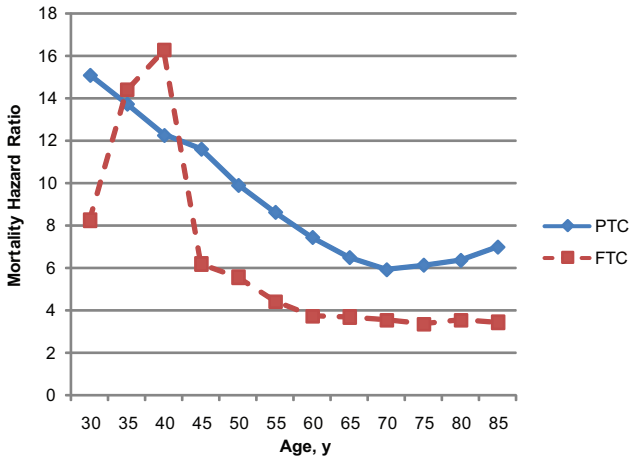

Figure 3. Disease-specific mortality hazard ratios for papillary thyroid carcinoma and follicular thyroid carcinoma.

change in survival with a disease-specific mortality rate of 0.49% and 1.30% in the younger age group compared with 5.96% and 14.72% in the group aged 45 years and older (PTC and FTC, respectively; **Table 2**).

Among this cohort of patients, the age at which survival begins to decline is 35 years for both PTC and FTC. This is at least 5 years younger than previously recognized. Patients aged 35 years and older are roughly 14 times more likely to die of DTC compared with patients younger than 35 years based on multivariate hazard ratios (**Figure 3**). The clinical significance of this finding is less pronounced; however, patients aged 35 to 44 years still have a good overall prognosis, with a disease-specific mortality of 0.63% for PTC and 2.19% for FTC over a mean follow-up of 8 years. Despite the good survival, this age split represents a large relative increase in disease-specific mortality between age groups, with mortality increasing by a factor of 2.1 (0.30% to 0.63%) and 11.5 (0.19% to 2.19%) for PTC and FTC, respectively (**Table 2**).

Our results also depict the continued decline in disease-specific survival with each advancing decade over age 35 years. Rather than a dichotomous division into 2 age groups, survival in DTC represents a continuum with advancing age conferring an independent risk factor for mortality. The clinical implication of this finding is realized when counseling patients in various age ranges older than 45 years, as patients in the 65- to 74-year age range have a 3- to 5-fold increase in disease-specific mortality compared with patients aged 45 to 54 years. The mortality rate for the 65- to 74-year-old patients in this study approaches 10% and 20% for PTC and FTC, respectively, with rates climbing even higher for older patients, far from the excellent prognosis generally associated with a diagnosis of DTC (**Table 2**). Here, the importance of measuring disease-specific survival is highlighted. Since the overall mortality in DTC is low, patients tend to live a long time and die of other causes as they age. In addition, advancing age itself carries risks of increased medical comorbidities and death. By measuring disease-specific survival, our analyses of survival and mortality were limited only to those patients who died of DTC as recorded in the SEER database. These findings are similar to a report by Hay,[13] who demonstrated a decreasing survival with advancing age in a study of 1500 consecutive patients with PTC. The 20-year cancer-specific mortality in his series was 0.8% for patients younger than 50 years, 7% for those aged 50 to 59 years, 20% for those aged 60 to 69 years, and 47% for those older than 70 years.[13] Similarly, Mazzaferri and Jiang[14] demonstrated a 1.8% disease-specific mortality rate in patients younger than 40 years, 12% mortality for patients aged 40 to 50 years, and 21% for patients older than 50 years in a group of more than 1300 patients with DTC.

As mentioned previously, many of the earlier studies evaluating age have examined DTC as a group or PTC alone. Few studies have examined FTC separately because of more limited patient numbers in most series, but the results from these studies have supported a similar age cutoff associated with decreased survival.[15-17] In our cohort of 3797 patients with FTC, we observed a similar survival pattern compared with the patients with PTC, with a few distinctions. Aside from the patient and tumor differences depicted in **Table 1**, patients with FTC had an overall higher mortality rate (9.27 vs 3.31%, $P < .0001$; **Table 2**). Both subtypes demonstrated a decrease in disease-specific mortality hazard ratio with increasing age cutoff, which is intuitive as a larger number of older patients are included in the younger age group as the age cutoff increases (**Figure 3**). The hazard ratios tended to be smaller for the FTC patients, however, suggesting that age may be a stronger prognostic indicator for patients with PTC. This is similar to the report by Lang and colleagues,[9] who found age to be a significant factor in cause-specific survival on multivariate analysis for PTC and FTC, but the relationship was much stronger for PTC.

There are several apparent limitations to this study. First, analyses are limited to the data collected by the SEER registries. Our cohort includes patients diagnosed under several different editions of the AJCC staging criteria, and the SEER database did not record TNM staging for patients until 2004; thus, we were unable to stratify patients by cancer stage. In addition, it is worthy of note that the SEER database does not contain data regarding tumor recurrence; hence, we were unable to discern recurrence patterns or determine the effect of increasing age on disease-free survival. Our average follow-up time of just less than 9 years is somewhat shorter than other series, which have reported up to 20-year follow-up data.

Despite these limitations, there are also inherent strengths provided by this database. Most importantly, population-based registry data allow for the identification of an exceptionally large cohort to study survival in DTC, given its usually indolent course and uniquely low mortality rate compared with most other malignancies. The significant amount of data necessary to detect differences in survival among patients with DTC is difficult to acquire in institutional studies; however, this database captured 38,412 patients with PTC, compared with 3797 patients with FTC,

and allowed us to detect significant differences among prognostic variables, even among subgroups. Furthermore, population-based data lack the referral and reporting biases that may be inherent in institutional studies and reflect the care of DTC across a spectrum of community hospitals, county hospitals, academic medical centers, and health maintenance organizations; thus, results may be more generalizeable.[18]

Among this cohort of patients, age was significantly associated with worsening DSS for both PTC and FTC. Young patients did uniformly well in both groups, but survival began to decline at greater than 35 years and continued steadily declining with further advances in age. The relationship between age and survival seems stronger for PTC than for FTC. The current staging system for DTC appropriately captures the risk associated with increasing age, and these data should not suggest a decrease in the age cutoff to 35 years, because the mortality rate in the group of patients between 35 and 44 years is still quite low, at under 1% for PTC and just more than 2% for FTC (**Table 2**). However, when counseling patients on their individualized risk of mortality from DTC, these results identify 2 important factors for clinicians to bear in mind: survival disadvantage may be seen beginning as early as age 35 years despite the favorable AJCC staging of patients younger than 45 years, and this decline in survival continues with advancing age for all patients older than 45 years.

Author Contributions

Samuel L. Oyer, conception and design, acquisition of data and analysis, interpretation of data, article drafting and revision, final approval; **Valerie A. Smith**, conception and design, acquisition of data, analysis, article drafting, revision, and final approval; **Eric J. Lentsch**, conception and design, interpretation of data, article revision and final approval.

Disclosures

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