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Original Article

Impact of Age on the Prognosis of Papillary Thyroid Carcinoma

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Abstract

Background: Papillary thyroid carcinoma (PTC) is a common subtype of thyroid carcinoma with a rising incidence rate. The purpose of this study was to provide a better understanding of age and PTC using the Surveillance, Epidemiology, and End Results (SEER) Program.

Methods: The study derived patients' information from the SEER Program (2010–2015). Chi-square or Fisher exact tests, and Kaplan–Meier method were used to analyze survival. Prognostic factors associated with survival were analyzed by Cox multivariate regression.

Results: A total of 1738 records were included from SEER, with 1079 PTC in the age group <55 years, and 659 PTC in the age group ≥55 years. The 5-year survival rate was 94% and the overall survival (OS) curve in different age groups indicated that patients younger than 55yr have a longer survival time ($P<0.05$). In multivariate Cox regression, age, M stage and surgery treatment were independent risk factors ($P<0.05$). Regarding PTC-specific survival, age and surgery treatment were the two main independent prognostic factors in multivariate regression. However, AJCC and M stage were not in the disease specific survival.

Conclusion: Age is a prognostic factor in OS and PCT specific survival. AJCC I stage and surgery treatment are also significant in predicting prognosis.

Keywords: Papillary thyroid cancer, Prognosis, SEER Program

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Introduction

Thyroid carcinoma is the most prevalent endocrinal malignancy with an increasing rate in the past few decades.[1,2] Some population-based researches indicate that papillary thyroid carcinoma (PTC) is the fundamental type of thyroid carcinoma. It accounts for 74% to 80% of all histological types of thyroid carcinoma.[2-5] Moreover, cervical lymph node metastasis and early invasion are quite common in PTCs.[6] Although with current treatment and technical progress patients can enjoy a relative longer overall survival (OS), the recurrence occurs in 5%–20% of all patients, even those who undergo total thyroidectomy.[7,8] Up to now, PTC still remains a disease with unsatisfactory outcome and limited treatment options.

It is known that patients' age at diagnosis is associated with prognosis.[9] Recently, the 8th edition of the American Joint Committee on Cancer (AJCC) staging system has raised the age threshold from 45 to 55 years for staging well-differentiated thyroid cancer.[10] However, more evidence is required about the relationship between the new age cutoff and PTC to be provided for doctors and educate patients.

The Surveillance, Epidemiology, and End Results (SEER) Program is a well-known database in the United States, which nearly covers 28% of the US population.[11] The SEER Program collects clinical information of US population and provides assistance in studying the incidence and mortality as concerns multiple cancers.[12] Therefore, the purpose of this study was to estimate the impact of age on prognosis for PTC by collecting data from the past five years from the SEER Program.

Materials and Methods

Data Collection

The data were obtained from the publicly available SEER program regarding the period 2010–2015 as detailed information about radiation therapy and chemotherapy was not included before 2010. Since the program is free to the world, this study does not pertain to any studies with human participants performed by any of the authors.

SEER*Stat software version 8.3.5 was utilized to gather useful data from the SEER. The inclusion criteria were patients diagnosed with PTC identified either by biopsy or surgical pathology and using histopathology codes of the

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International Classification of Disease for Oncology, third edition (ICD-O-3) codes 8260/3. Hence, other diagnostic methods such as radiography, autopsy, death records and clinical diagnoses were excluded. Moreover, the exclusion criteria also contained unknown sex, uncertain tumor according to the American Joint Committee on Cancer (AJCC) Staging System, 7th edition,[13] the presence of secondary malignancies and patients who were lost to follow-up. Finally, 1738 records were included. The following demographic variables were collected from the SEER database: age at diagnosis (<55 and ≥55 years),[14,15] sex (male and female), and race (white, black, other and unknown). The cancer-related variables were tumor size (less than 1 cm, 1.1 to 2 cm, 2.1 to 4 cm, and larger than 4 cm),[16] grade (I, II, III, IV and unknown), treatment of PTC (surgery, radiation therapy and chemotherapy) and tumor stage (T, N, and M stage, which was defined using the 7th edition of the AJCC Staging System). The vital status was defined as *Alive* or *Dead* and survival months were calculated for each patient in the SEER dataset.

Statistical Analysis

Chi-square test and Fisher exact test were used to investigate categorical variables. Test of proportional hazard hypothesis in Cox model was adopted before processing Cox regression analyses. The Kaplan-Meier analysis was performed to evaluate the association between age and OS; also, the 5-year survival rate was calculated with this method. Then, all characteristics were put into single factor Cox regression analysis to select suitable ones to enter the multivariate analysis. The characteristics with P value < 0.05 were considered significant and entered into multivariable Cox analysis to reduce the impact of interactions between multiple factors. Afterwards, Cox proportional hazards regression were utilized to assess the relationship between age groups and probability of survival in patients. The hazard ratio (HR) and 95% confidence interval (95% CI) were used to show the risks. HR > 1.0 showed an increased risk of death. P value < 0.05 was considered statistically significant. Finally, in the same age group, to observe the risk of death in respective AJCC stage, Kaplan-Meier analysis was used again. All of the statistical analyses were performed using SPSS Statistics 22.0 (IBM, NY, United States).

Results

Patients' Characteristics

A total of 1738 patients were involved in this study. The age cutoff point was set at 55 years based on the 8th AJCC staging system. Among these patients, 1079 were under 55 years of age and 659 patients were 55 years of age or older. The demographics and cancer-related characteristics of the two age groups are compared in Table 1. As Table 1 depicts, female patients were more frequent compared to males (P < 0.05). Also, the size of tumor in both younger

Table 1. Characteristics of Patients with Papillary Thyroid Cancer in Different Age Groups

Variables	Age <55 y n = 1079(%)	Age ≥55 y n = 659(%)	*P* Value
Sex			<0.001
Male	205 (49.9)	206 (50.1)	
Female	874 (65.9)	453 (34.1)	
Race			0.253
White	859 (61.8)	532 (38.2)	
Black	70 (57.9)	51 (42.1)	
Other + Unknown	150 (66.4)	76 (33.6)	
Grade			0.304
I	189 (63.6)	108 (36.4)	
II	51 (59.3)	35 (40.7)	
III	7 (38.9)	11 (61.1)	
IV	1 (50.0)	1 (50.0)	
Unknown	831 (62.2)	504 (37.8)	
Tumor size (cm)			0.017
≤1.0	395 (60.7)	256 (39.3)	
1.1-2.0	320 (64.3)	178 (35.7)	
2.1-4.0	233 (66.8)	116 (33.2)	
≥4	75 (58.1)	54 (41.9)	
Unknown	56 (50.5)	55 (49.5)	
AJCC stage group			<0.001
I	867 (73.4)	314 (26.6)	
II	38 (38.4)	61 (61.6)	
III	85 (39.0)	133 (61.0)	
IV	33 (28.0)	85 (72.0)	
Unknown	56 (45.0)	66 (54.1)	
T stage			<0.001
T0	1 (100.0)	0 (0.0)	
T1	641 (63.5)	369 (36.5)	
T2	179 (70.5)	75 (29.5)	
T3	169 (56.9)	128 (43.1)	
T4	21 (35.6)	38 (64.4)	
Unknown	68 (58.1)	49 (41.9)	
N stage			<0.001
N1	713 (59.0)	495 (41.0)	
N2	295 (70.9)	121 (29.1)	
N3	71 (62.3)	43 (37.7)	
M stage			0.005
M1	1071 (62.5)	643 (37.5)	
M2	8 (33.3)	16 (66.7)	
Surgery			<0.001
Yes	1012 (63.6)	578 (36.4)	
No	60 (46.9)	68 (53.1)	
Unknown	7 (35.0)	13 (65.0)	
Radiation therapy			0.003
Yes	392 (67.0)	193 (33.0)	
None + Unknown	687 (59.6)	466 (40.4)	
Chemotherapy			0.437
Yes	3 (42.9)	4 (57.1)	
No + Unknown	1076 (62.2)	655 (37.8)	

Note: Chi-square and Fisher exact test were used.

and older age groups was usually smaller than 1.0 cm ($P < 0.05$). When compared for the AJCC stage, T stage, N stage and M stage, the results revealed that in both age groups, most of the patients were diagnosed in an early stage ($P < 0.05$). Regarding treatment, surgery and radiation therapy were more prevalent in the younger age group ($P < 0.05$). However, we did not find any association between race, disease grade, and chemotherapy and the age groups ($P > 0.05$).

Survival Outcomes

Figure 1 shows the OS curve in different age groups, indicating that patients younger than 55 years had a longer survival time ($P < 0.05$). Table 2 indicates the results of single factor Cox regression analyses. As the Table depicts, except for race and radiation therapy ($P > 0.05$), the other factors had an association with OS. Table 3 shows the multivariate analyses of OS and PTC-specific survival which included the significant factors obtained from Table 2. In multivariate Cox regression, age, M stage and surgery treatment were independent risk factors ($P < 0.05$). AJCC II stage patients had similar OS (HR 1.19, 0.47-3.01, $P = 0.720$). Moreover, as presented in Table 3 indicating the PTC-specific survival, age and surgery treatment were the two main independent prognostic factors in multivariate regression which was in accordance with OS model. However, AJCC and M stage were not in this disease-specific survival.

In order to investigate the association between AJCC stage and different age groups further, we performed another OS analysis. Figure 2A shows that in AJCC stage I, patients in the age <55 years group enjoyed a longer survival span compared to those in the age ≥55 years group ($P < 0.05$). However, in AJCC stage II, III and IV, age did not show any significant difference (Figure 2B-2D).

Finally, the 5-year survival rate of patients was 94%, the median follow-up time was 36 months, and the 25% to 75% inter-quartile range of patients' follow-up time was 16-54 months.

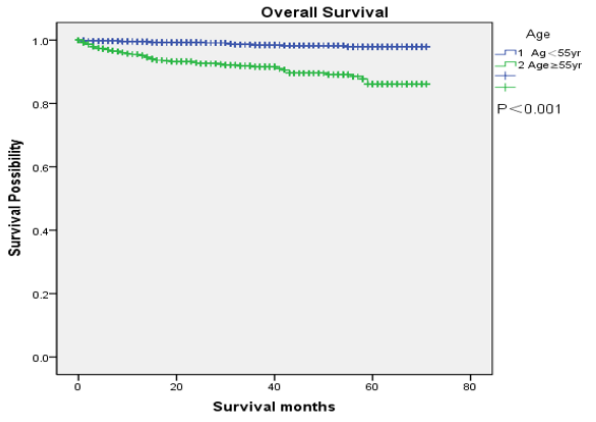

Figure 1. Overall Survival (OS) Curve in Different Age Groups.

Discussion

We performed OS and PTC specific survival (PTC-SS) analysis using SEER, a large national cancer database. We found that 1) age older than 55 years significantly affected both OS and PTC-SS; 2) in the subset of AJCC stage I, patients <55 years had a better prognosis; and 3) among all patients, surgery was also a prognostic factor not only for PTC-SS but also OS.

In the thyroid tumor field, the effect of age on the prognosis of thyroid cancer has been debated for a long time.[17] Londero et al demonstrated that 45 years can be an age cutoff in PTC patients, with patients older than 45 years more likely to die than younger patients.[18] Their results were corroborated by other researchers.[19,20]

Table 2. Single Factor Cox Regression Analyses

Variables	Hazard Ratio (95% CI)	*P* Value
Age (y)		<0.001
<55	1.00 (reference)	
≥55	6.80 (3.79–12.20)	
Sex		<0.001
Male	1.00 (reference)	
Female	0.35 (0.22–0.56)	
Race		0.117
White	1.00 (reference)	
Black	1.61(0.77–3.37)	
Other + Unknown	0.46 (0.17–1.26)	
Grade		0.028
I	1.00 (reference)	
II	0.89 (0.25–3.17)	
III	6.68 (2.13–20.98)	
IV	30.53 (3.89–239.71)	
Unknown	1.01(0.53–1.94)	
Tumor size (cm)		<0.001
≤1.0	1.00 (reference)	
1.1-2.0	1.36 (0.69–2.68)	
2.1-4.0	1.23 (0.56–2.72)	
≥4	4.86 (2.37–9.95)	
Unknown	5.44 (2.65–11.15)	
AJCC stage group		<0.001
I	1.00 (reference)	
II	3.32 (1.35–8.15)	
III	2.79 (1.39–5.60)	
IV	10.70 (5.92–19.35)	
Unknown	4.17 (1.93–9.02)	
Surgery		<0.001
Yes	1.00 (reference)	
No	13.86 (8.67–22.15)	
Unknown	3.40 (0.47–24.84)	
Radiation therapy		0.484
Yes	1.00 (reference)	
None + Unknown	1.41(0.84–2.36)	
Chemotherapy		<0.001
Yes	1.00 (reference)	
None + Unknown	0.06 (0.02–0.20)	

Table 3. Multivariate Analyses of Overall Survival

Variables	Overall Survival		Disease - Specific Survival	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Age (y)				
<55	1.00 (reference)	—	1.00 (reference)	—
≥55	5.24(2.90–9.46)	0.001	11.36 (2.59–49.90)	0.001
AJCC				
I	1.00 (reference)	—	1.0 (reference)	—
II	1.19(0.47–3.01)	0.720	—	—
III	2.08(1.01–4.28)	0.048	—	—
IV	2.36(1.11–5.04)	0.026	—	—
M stage				
M1	1.00 (reference)	—	1.00 (reference)	—
M2	2.84 (1.22–6.64)	0.016	—	—
Surgery				
Yes	1.00 (reference)	—	1.00 (reference)	—
No	11.70 (6.74–20.30)	<0.001	3.73 (1.19–11.63)	0.024

Some studies also reported the age of 50 or 60 years to be a prognostic factor.[21-23] In the recent study and staging system of AJCC, PTC patients younger than 55 years have better survival. Yasuhiro Ito et al interpreted this phenomenon that since the number of patients who died of PTC was small, because PTC had an indolent character.[24] Unlike these results, Orosco et al that reported based on their study on 85 740 patients, there was no one year between 25-55 years to choose to produce a high HR for survival.[25] In our study, we took the age of 55 years as the cutoff and found age above 55 years to have a tight association with OS and PTC-specific survival. Similarly, according to a Japanese research, the survival time of disease progression decreased gradually as from 60.3% in patients aged 20 years compared to 3.5% in those aged 70 years.[26] Moreover, in the subset survival analysis of AJCC stage in the two age groups, the results showed that AJCC stage I affected OS. Older patients had higher mortality than younger ones. In the other AJCC tumor stages, we did not find significant difference between the two groups. Some previous studies have stated that old age is a strong predictor of carcinoma death for M1 patients and those with the appearance of distant recurrence.[27,28] Another study suggested that the majority of patients with ≤1.0 cm thyroid tumors were of older populations.[29] But in a study by Ding et al, they believed that although the older patients had poorer prognosis, PTC patients of young age were more susceptible to recurrence.[30] From this point of view, the PTC patients need more frequent follow-up regardless of how old they are. The multivariate analyses of OS showed that only M stage and AJCC stage affected patients' survival time, while T and N stage of the tumor were not significant. Other studies have demonstrated that in older age (≥55 years), M0 stage is a stronger predictor of tumor-related death in multivariate analysis.[31,32] So, we estimated the major component of AJCC was the M stage which played a role in this process. Further research is needed in this regard.

In addition, previous studies reported that initial surgical treatment with total thyroidectomy may be more appropriate for patients in the age group <55 years.[33] Our study also found that patients in all age groups who

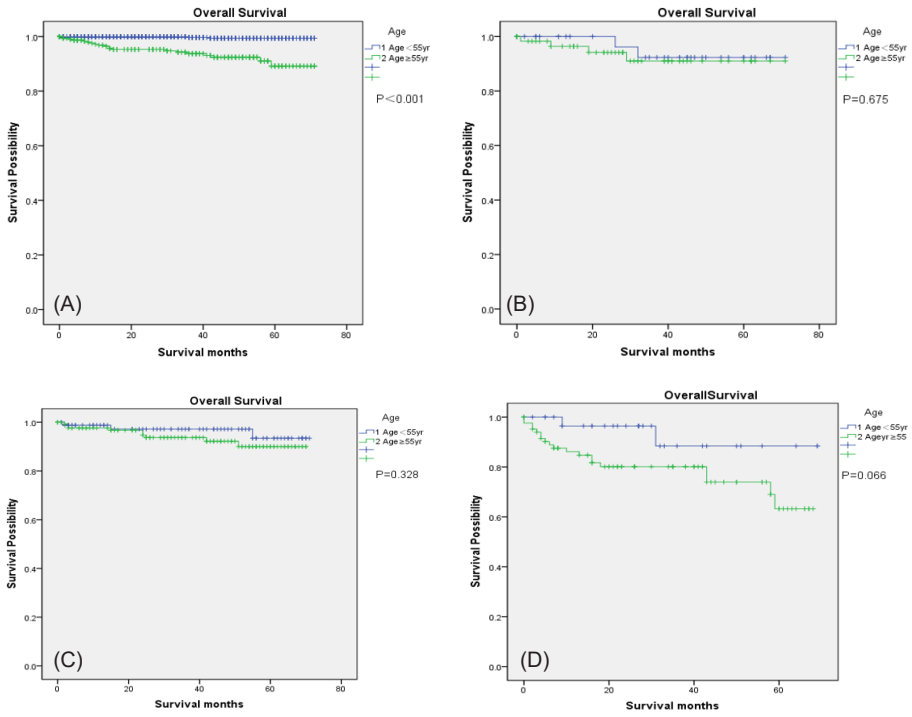

Figure 2. Overall survival (OS) Curve in Different Age Groups Based on (A) AJCC I, (B) AJCC II, (C) AJCC III and (D) AJCC IV.

received surgical treatment had a better prognosis based on OS and disease-specific survival analysis. Nevertheless, a report from Ho et al reported that in the younger age group, whether they underwent operation or not, the disease-specific mortality was approximately equal. Older non-surgical patients may be exposed to a higher risk of death.[34] Some discrepancies between our different age groups in terms of surgery influenced patients' survival and the differences with earlier studies may be due to differences in study design and the population included. Combination of various research results confirms that the diverse outcomes are due to different patients' individual disease situation. Hence, whether and when to intervene should be carefully weighed by doctors.[35] In summary, more precise research and analysis is needed to compare surgery outcomes in different age groups.

There are some limitations in this study. The data were obtained from the SEER program, which depends on institutions, and the problems of some selection bias and shortage of information cannot be avoided. After analysis, we found that the 95% confidence intervals or some HR estimates were huge from a statistical perspective.[36] In the multiple analysis, we first evaluated single characteristics and selected significant ones to enter into the OS and disease-specific survival analysis, but due to some unknown variables or missing information, the results may need to be assessed in the specific situation, limiting generalizability for all cases. Also, we divided the patients based on their age into only two groups according to the new guideline; perhaps more precise age groups are needed to be studied in our next research.

In conclusions, the study demonstrates that age is a prognostic factor in OS and PCT-specific survival: PTC patients older than 55 years have unsatisfactory survival compared to younger patients. AJCC stage I is also significant in predicting prognosis. Also, surgery treatment may affect patients' prognosis.

Authors' Contribution

NX conceived and designed the research. YS performed the research. WD analyzed the data. YS and WD completed the manuscript. YL revised the manuscript.

Conflict of Interest Disclosures

All authors declare that they have no conflict of interest.

Ethical Statement

The data were allocated from the SEER database. The study does not involve ethical problems.

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