ORIGINAL RESEARCH

Young age increases the risk of lymph node positivity in papillary thyroid cancer patients: a SEER data-based study

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Introduction: Currently in papillary thyroid cancer (PTC), the correlation between lymph node positivity (LN+) and patient's age at diagnosis is still inconclusive. The aim of this study was to investigate whether younger PTC patients had higher LN+ rates.

Patients and methods: From the 1998–2013 Surveillance, Epidemiology, and End Results database, we analyzed PTC patients with at least 1 LN examined. The patients were divided into 5 groups by age separately for each T stage: ≤30; 31–40; 41–50; 51–60; >60 years.

Results: A total of 46,077 PTC patients were identified, including 8,386 (18.2%) patients aged ≤30 years, 10,971 (23.8%) patients aged 31–40 years, 11,646 (25.3%) patients aged 41–50 years, 8,596 (18.7%) patients aged 51–60 years, and 6,478 (14.1%) patients aged >60 years. In each T stage, LN+ rates were inversely associated with age at diagnosis, which was validated by multivariate logistic regression analysis ($p<0.001$). In addition, the subset of patients 30 or younger had the highest lymph node ratio compared with other subsets ($p<0.001$).

Conclusion: We identified that younger PTC patients have an increased predisposition for LN+ regardless of T stage. This finding could help surgeons to select the optimal treatment for younger PTC patients.

Keywords: papillary thyroid cancer, age at diagnosis, lymph node positivity, lymph node ratio, recurrence, Surveillance, Epidemiology, and End results

Introduction

Due to advanced diagnostic level and periodic health screening, thyroid cancer has become the cancer with one of the highest incidences in America.[1,2] Younger patients with papillary thyroid cancer (PTC) contribute a large proportion to this increasing trend.[3] Despite the rate of survival for PTC being favorable, with 98% survival rate for the next 5 years,[1] several studies demonstrated that the risk of recurrence ranges from 5% to 21% in PTC.[4,5]

Multiple risk factors were well known to be associated with recurrence and/or survival of PTC patients, including age at diagnosis, T stage, N stage, massive extrathyroid extension, BRAF mutation, and histological subtypes.[6–9] For example, several reports identified that the number of positive lymph node (PLN) appears to predict the rate of recurrence in PTC.[10,11] It is generally agreed that the LN+ status is also affected by the patient's individual clinicopathologic characteristics in malignancies.

Patients' LN+ status was affected by the patients' age at diagnosis, which was demonstrated in carcinoma of the rectum, breast, and in melanomas.[12–14] In 2016 in the analysis of 56,074 patients, Meyer et al[12] had pointed out that young age at diagnosis

was associated with increased LN+ rates in early-stage rectal cancer. Similarly, Chao et al[13] also showed that the incidence of sentinel LN+ declined with increasing age at diagnosis for melanoma. This pattern was also seen in the study of early-stage breast cancers by Anders et al.[14]

However, the correlation between LN+ and patient's age at diagnosis in PTC is still inconclusive. While several studies claimed that young age at diagnosis could be an independent predictor of LN+,[15–19] one study showed that older PTC patients were more likely to exhibit higher LN+ rates,[20] and another study did not find a correlation between age and LN+.[21] Therefore, based on a large population dataset, we aimed to investigate whether younger PTC patients were associated with higher LN+ rates.

Patients and methods
Patients

All the PTC patients who were diagnosed between 1988 and 2013 from the Surveillance, Epidemiology, and End Results (SEER) database were analyzed in current study. The SEER database is a national collaboration program set up by the National Cancer Institute of United States. It covers up to 26% of America's population, using 17 population-based cancer registries (totaling approximately 3 million cases).

Patients diagnosed with PTC were identified using histopathology codes of the International Classification of Diseases for Oncology, 3rd edition: 8050, 8260–8263, 8340–8344, 8450. Pathologically staged patients who underwent thyroidectomy with 1 or more LNs surgically examined and no evidence of distant metastasis were included. Patients who received radiotherapy prior to surgery or whose thyroid malignancy was not their first primary cancer were excluded.

Statistical analyses

Our analyses included demographic characteristics (race, sex, age at diagnosis), tumor characteristics (T stage, LN+ status), and type of surgery. According to the SEER extent of disease extension codes for cases from 1988 to 2003, and the American Joint Committee on Cancer–derived T stage for cases from 2004 to 2008, T stage was categorized as T1, T2, T3, and T4. In addition, T1 group of the PTC patients was classified into T1a and T1b, due to different histopathologic characteristics among them.[22,23] Age was divided as a categorical variable using 10-year intervals, except for the group of ages ≤30 and >60 years, because of the relatively smaller number of cases. The primary analysis of the study was LN+ status. It was illustrated by LN+ rates, number of PLN and lymph node ratio (LNR). The LNR was calculated as the ratio of number of PLN divided by the total number of lymph nodes examined. Trends in the mean number of PLN and LNR by age were evaluated using quantile regression models. Trends in LN+ rates with age were evaluated with Cochran Armitage trend tests.

All data were analyzed by the SPSS version 21.0 (IBM Corporation, Armonk, NY, USA) and the R software version 3.13 (http://www.r-project.org/). A p-value <0.05 was considered to be statistically significant, and all the tests were 2-sided.

Ethical approval

SEER data are deidentified before release and do not contain any personally identifying information. As the data is publicly available, no ethical approval is required.

Results
Clinicopathologic characteristics of patients

A total of 46,077 nonmetastatic PTC patients who received surgery between 1988 and 2013 were included in this study. The clinicopathologic characteristics of PTC were separated by age at diagnosis (Table 1). Overall, the mean age at diagnosis was 44.3±14.5 years. A total of 8,386 (18.2%) patients' age at diagnosis were 30 years or younger, 10,971 (23.8%) patients were diagnosed between the age of 31 and 40 years, 11,646 (25.3%) patients between the age of 41 and 50 years, 8,596 (18.7%) patients between the age of 51 and 60 years, and 6,478 (14.1%) patients' age at diagnosis was more than 60 years. More than 78.2% patients were female. The majority of the patients was white (83.9%). A total of 20,850 (45.3%) patients had at least 1 PLN. The greatest T-stage proportion was T1a (29.2%).

The LN+ rate was 24.8%, 40.8%, 47.5%, 65.9%, and 78.7% for T1a, T1b, T2, T3, and T4 stage patients, respectively. As shown in the Table 2, the mean number of PLN and LNR increased by T stage with each age at diagnosis. With the increasing age at diagnosis, the LN+ rate and mean number of PLN and LNR all decreased with each T stage (all $p<0.001$).

As shown in Figure 1, as the T stage increases the LN+ rates also increased. Additionally, there is a reverse association between age at diagnosis and LN+ rates with each T stage (all $p<0.001$).

Multivariable analysis of LN+

The association between age at diagnosis and LN+ was identified by logistic analysis. As shown in the Table 3, younger

Table 1 Characteristic of PTC patients stratified by age at diagnosis

Characteristic	Total		Age at diagnosis (year)				
			≤30	31–40	41–50	51–60	>60
	n.	%	n. (%)				
Total	46,077	100	8,386 (18.2)	10,971 (23.8)	11,646 (25.3)	8,596 (18.7)	6,478 (14.1)
Sex							
Female	30,613	78.2	7,018 (83.7)	8,878 (80.9)	9,067 (77.9)	6,412 (74.6)	4,638 (71.6)
Male	10,064	21.8	1,368 (16.3)	2,093 (19.1)	2,579 (22.1)	2,184 (25.4)	1,840 (28.4)
Race							
White	38,640	83.9	7,090 (84.5)	9,059 (82.6)	9,793 (84.1)	7,237 (84.2)	7,237 (84.2)
Black	1,552	3.4	248 (3.0)	341 (3.1)	428 (3.7)	313 (3.6)	313 (3.6)
API	5,079	11.0	852 (10.2)	1,344 (12.3)	1,232 (10.6)	925 (10.8)	925 (10.8)
AI	270	0.6	81 (1.0)	74 (0.7)	59 (0.5)	32 (0.4)	32 (0.4)
Unknown	536	1.2	115 (1.4)	153 (1.4)	132 (1.2)	81 (1.0)	132 (1.2)
T stage							
T1a	13,458	29.2	1,665 (19.9)	2,994 (27.3)	3,770 (32.4)	2,969 (34.5)	2,060 (31.8)
T1b	11,682	25.4	2,240 (26.7)	3,030 (27.6)	3,033 (26.4)	2,065 (24.0)	1,274 (19.7)
T2	8,261	17.9	2,092 (24.9)	2,187 (19.9)	1,857 (15.9)	1,254 (14.6)	871 (13.4)
T3	9,013	19.6	1,700 (20.3)	2,010 (18.3)	2,144 (18.4)	1,708 (19.9)	1,451 (22.4)
T4	3,663	7.9	689 (8.2)	750 (6.8)	802 (6.9)	600 (7.0)	822 (12.7)
LN status							
Negative	25,227	54.7	3,347 (39.9)	5,665 (51.6)	6,853 (58.8)	5,386 (62.7)	3,976 (61.4)
Positive	20,850	45.3	5,039 (60.1)	5,306 (48.4)	4,793 (41.2)	3,210 (37.3)	2,502 (38.6)
Total LNs examined (mean ± SD)	7.9±12.8		10.7±15.7	8.2±13.1	7.1±11.7	6.8±11.5	6.9±11.5
Surgery							
Lobectomy	4,430	9.6	647 (7.7)	986 (9.0)	1,158 (9.9)	914 (10.6)	725 (11.2)
Total thyroidectomy	38,103	82.7	6,784 (80.9)	8,598 (81.7)	9,716 (83.4)	7,278 (84.7)	5,467 (82.8)
Other surgery	3,544	7.7	955 (11.4)	1,027 (9.4)	772 (6.6)	404 (4.7)	386 (6.0)

Abbreviations: AI, American Indian or Alaska Native; API, Asian or Pacifc Islander; LN, lymph node; PTC, papillary thyroid cancer.

patients (age at diagnosis ≤30 years) had higher correlation with higher LN+ rates at each T stage. We used multivariate logistic regression model to evaluate whether the association between the patient's age at diagnosis and the LN+ rates was independent of other risk factors. Patient age at diagnosis, sex, race, and surgery types were included into the adjusted model. According to the multivariate analysis, the age at diagnosis still correlated with the LN+ rates (Table 3).

Discussion

In the current study, a total of 46,077 PTC patients from the SEER database were analyzed. We first identified that within each T stage, younger patients have an increased risk of LN+. The results were validated in multivariable analyses which including sex, race, and surgery types.

Thyroid cancer is unique among malignant tumors, because age is a vital prognostic factor in its staging systems.[24,25] Our study showed that younger age at diagnosis is significantly associated with higher LN+ rates. In 2016, Zhang et al[26] also made a similar finding by comparing 3 different age groups, but they ignored the influence of T stages.[26] While some studies had reported that more

advanced T stage is an important predictive factor for LN+, it is influenced (to some extent) by the presence of the total tumor load.[27,28] In our study, we were able to show the inverse association between age at diagnosis and LN+, regardless of patient's T stage.

Interestingly, we also found that younger patients are associated with a higher PLN and LNR when compared to older patients at the same T stage. Several studies highlighted that LNR could be an independent predictor for the recurrence for PTC.[29–31] In our analysis, the subset of patients aged 30 or younger had the highest LNR, compared with other subsets ($p<0.001$). This finding also supports the notion that locoregional LN recurrence rate is higher for younger patients.[32,33]

Recurrence of PTC carries not only a higher surgical complication, but also psychological repercussions for the patient. Therefore, this present study could be interpreted as an implication for a change in surgical management of younger PTC patients. For instance, the results showed that LN+ rate of younger patients in T1a group reached up to 37.3%; the rate of older patients in T1a group was 16.8% relatively, which was consistent with the findings of Zhang et al.[26] They came up with the opinion that the treatment

Table 2 The LN+ rate and mean number of PLN and LNR stratified by T stage and age

Age (year)	T1a				T1b				T2	
	n.	LN+ NO (%)	PLN	LNR (%)	n.	LN+ NO (%)	PLN	LNR (%)	n.	LN+ NO (%)
≤30	1,664	620 (37.3)	1.5	18.5	2,237	1,189 (53.2)	2.7	31.0	2,091	1,275 (61.0)
31–40	2,988	847 (28.3)	1.0	14.4	3,030	1,345 (44.0)	1.8	25.4	2,187	1,079 (49.3)
41–50	3,765	903 (24.0)	0.7	12.1	3,070	1,144 (37.3)	1.4	21.1	1,856	790 (42.6)
51–60	2,967	609 (20.5)	0.5	9.9	2,065	690 (33.4)	1.1	17.4	1,254	456 (36.4)
>60	2,059	346 (16.8)	0.4	8.8	1,273	395 (31.0)	1.0	16.8	871	320 (36.7)
p*		<0.001	<0.001	<0.001		<0.001	<0.001	<0.001		<0.001

Notes: *The LN+ rates within each T stage were compared by Cochran Armitage trend tests model. The PLN and LNR within each T stage were compared by quantile regression model.
Abbreviations: LN+, lymph node positivity; LNR, lymph node ratio; PLN, positive lymph node.
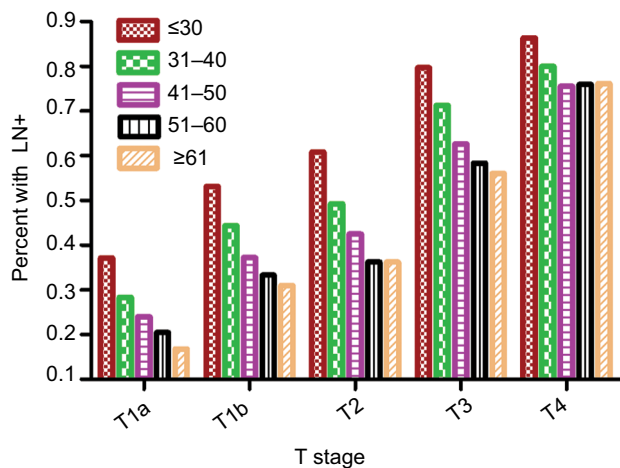
Figure 1 LN+ and age at diagnosis by T stage.
Abbreviation: LN+, lymph node positivity.

strategy of younger PTC patients could be more aggressive, with the consideration of long life span and recurrent risk.[26] Ito et al[34] also pointed out that younger PTC patients (<40 years of age) have a higher progression risk during observation without immediate surgery, compared with older patients. Although the presence or absence of cervical LN+ does not affect mortality in younger PTC patients, locoregional LN recurrence would inevitably result in reoperation. Indeed, the rate of injuring the recurrent nerve, parathyroid glands, or their circulation during reoperation is much higher than initial surgery.[35,36] With the increased risk associated with reoperations, the quality of life of these patients may be affected to some extent. Therefore, we should pay more attention to the patient's age. The very young age may not be the indicator to narrow surgical scope. On the contrary, adequate primary surgery and prophylactic/therapeutic LN dissection should be routinely performed for younger PTC patients, due to high LN+ rates.

The reasons why the probability of LN+ is higher in the younger group compared to the older patients had been demonstrated in other cancers. In 2012, Chang et al[37] reported that early-onset (≤40 years of age) colorectal adenocarcinoma patients were much more vulnerable to positive circumferential margins, due to signet ring cell differentiation, venous invasion, and perineural invasion. A study of melanoma suggested that the mitotic rate plays an important role in younger patients.[38] With respect to PTC, Moses et al[39] found multiple genetic alterations in younger patients. For instance, RET/PTC1 rearrangements, 1 key somatic genetic alteration in PTC development, were more common in childhood PTC.[40] These findings may lend more support to the hypothesis that thyroid follicular cells in the young are more susceptible to promoting DNA damage than in the old.[39,41] As a result, young PTC patients could be more likely to develop nonthyroid second primary cancers after treatment with radioisotope therapy.[42] Moreover, there is also data showing that the incidence of capsule infiltration and vascular invasion is higher among younger patients.[18,43–45] These aggressive histological features are thought to be associated with high rates of LN+.[45]

This study has several potential limitations. First, the SEER database collected information on large numbers of patients from 17 population-based cancer registries. Some clinicopathologic information may be miscoded or missed during registration process. For instance, patients' *BRAF* gene mutations were not provided in the current dataset. Second, SEER database did not capture the preoperative data, such as neck ultrasonography and computed tomography. Therefore, we could not analyze the discrepancy between prophylactic LN dissection and therapeutic LN dissection, radical neck dissection, and modified radical neck dissection.

PLN	LNR (%)	T3				T4			
		n.	LN+ NO (%)	PLN	LNR (%)	n.	LN+ NO (%)	PLN	LNR (%)
3.3	39.0	1,697	1,355 (79.7)	7.5	47.1	689	595 (86.4)	6.8	57.8
2.3	30.0	2,010	1,433 (71.3)	5.1	41.1	748	600 (80.0)	5.1	51.4
1.7	24.5	2,143	1,344 (62.7)	3.6	35.8	801	606 (75.6)	3.9	46.6
1.3	21.3	1,704	997 (58.4)	3.1	31.0	597	456 (76.0)	4.1	43.5
1.4	20.5	1,450	814 (56.1)	2.8	29.7	821	626 (76.2)	3.7	44.6
<0.001	<0.001		<0.001	<0.001	<0.001		<0.001	<0.001	<0.001

Table 3 The association of age and LN+ by logistical analysis

T stage	Age (year)	Unadjusted			Adjusted		
		OR	95% CI	p-value	OR	95% CI	p-value
T1a	≤30	Ref		<0.001	Ref		<0.001
	31–40	0.67	0.59–0.77		0.67	0.58–0.76	
	41–50	0.53	0.47–0.60		0.51	0.45–0.58	
	51–60	0.44	0.38–0.50		0.42	0.36–0.48	
	>60	0.41	0.39–0.45		0.31	0.26–0.36	
T1b	≤30	Ref		<0.001	Ref		<0.001
	31–40	0.72	0.63–0.78		0.68	0.61–0.76	
	41–50	0.52	0.47–0.58		0.51	0.45–0.57	
	51–60	0.44	0.39–0.5		0.42	0.37–0.47	
	>60	0.40	0.34–0.46		0.36	0.31–0.42	
T2	≤30	Ref		<0.001	Ref		<0.001
	31–40	0.62	0.55–0.70		0.59	0.52–0.67	
	41–50	0.47	0.42–0.54		0.45	0.39–0.51	
	51–60	0.37	0.32–0.42		0.33	0.28–0.38	
	>60	0.37	0.32–0.44		0.34	0.28–0.40	
T3	≤30	Ref		<0.001	Ref		<0.001
	31–40	0.63	0.54–0.74		0.60	0.52–0.71	
	41–50	0.43	0.37–0.5		0.40	0.34–0.46	
	51–60	0.36	0.31–0.42		0.32	0.28–0.38	
	>60	0.33	0.28–0.38		0.30	0.25–0.35	
T4	≤30	Ref		<0.001	Ref		<0.001
	31–40	0.63	0.48–0.84		0.61	0.46–0.81	
	41–50	0.49	0.37–0.64		0.46	0.35–0.6	
	51–60	0.50	0.38–0.67		0.45	0.34–0.6	
	>60	0.50	0.39–0.66		0.45	0.34–0.59	

Abbreviations: CI, confidence interval; LN+, lymph node positivity; OR, odds ratio; Ref, reference.

Conclusion

In conclusion, our study demonstrated that younger PTC patients have an increased predisposition for LN+, across every T stage. Younger PTC patients could need more standardized treatment compared to older PTC patients with the same TNM stage. This finding could be useful for surgeons when selecting the optimal treatment for young PTC patients.

Author contributions

Shengying Wang conceived and designed the study. Jing Wang and Shengying Wang developed the methodology. Collection and assembly of data was done by Jing Wang and Jianjun Liu. Data analysis and interpretation was by Jing Wang, Jianjun Liu. All authors were involved with the writing, review, and/or revision of the manuscript. Admin-

Disclosure

The authors report no conflicts of interest in this work.

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