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Original Article

The prognosis of NX stage differentiated thyroid cancer based on propensity score matching and SEER data

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Abstract: Few studies have evaluated the prognosis or treatment of patients with differentiated thyroid cancer (DTC) according to their NX status. This study investigated this issue to provide a new perspective regarding the treatment guidelines for these patients. Data from 92,447 patients with DTC were obtained from the Surveillance, Epidemiology, and End Results (SEER) database (2004-2013). Survival outcomes were evaluated using Kaplan-Meier analyses with the log-rank test and Cox proportional hazards regression analysis. The rates of cancer-specific mortality and all-cause mortality (per 1,000 person-years) were significantly higher for patients with NX disease, compared to patients with N0 or N1 disease. Multivariate Cox regression modeling revealed that NX stage was an independent risk factor for cancer-specific mortality compared to N1 stage, but not to N0 stage. Similar results were observed for all-cause mortality. After adjustment using propensity score matching, the cancer-specific and all-cause mortality rates were lower for NX stage compared to N0 stage, whereas no significant difference was observed when comparing the NX stage and N1 stage groups. The unexpectedly poor prognosis of patients with NX stage DTC provides new information that may be relevant for treating these patients.

Keywords: Differentiated thyroid cancer, NX stage, prognosis, SEER

Introduction

Differentiated thyroid cancer (DTC) is becoming increasingly prevalent [1, 2], and the diagnosis and management of DTC is a growing problem for clinicians, researchers, and health policy makers. DTC mainly consists of papillary thyroid cancer or follicular thyroid cancer, and the regional lymph nodes include the central compartment, lateral cervical, and upper mediastinal lymph nodes. Nodal status is an important prognostic factor in many scoring systems, including the TNM system, and can be used to predict the risk of mortality among patients with DTC [1, 3-5]. The current TNM system from the American Joint Committee on Cancer (AJCC) is considered the gold standard for predicting cancer mortality, and the NX stage is assigned to patients whose regional lymph nodes cannot be assessed.

The Surveillance, Epidemiology, and End Results (SEER) program provides cancer data from the National Cancer Institute. However, few studies have focused on the prognosis or treatment of patients with NX stage DTC. Therefore, the present study investigated the prognosis of patients according to their N stage (NX vs. N1 and N0) using SEER data from 2004-2013 and propensity score matching.

Materials and methods

Data collection

The SEER program is an American population-based cancer registry that was launched in 1973 to promote disease control and prevention. The SEER data are obtained from multiple geographic regions, and include information regarding the incidence, prevalence, primary tumor characteristics, and mortality for various cancers. The present study evaluated data from patients with DTC in the SEER database (2004-2013), based on the C73.9 code from the International Classification of Diseases for

Table 1. Characteristics for Patients with different N stage

Covariate	Level	N stage				
		NX (n = 834)	N0 (n = 73256)	*p* value	N1 (n = 18387)	*p* value
Age		45.37 ± 19.86	50.33 ± 14.85	< 0.001	45.55 ± 16.33	0.001
Sex	Female (%)	628 (75.3)	58199 (79.4)	0.003	12476 (67.9)	< 0.001
	Male (%)	206 (24.7)	10566 (20.6)		5911 (32.1)	
Race	White (%)	587 (75.4)	59742 (82.5)	< 0.001	15209 (83.7)	< 0.001
	Black (%)	78 (10.0)	5396 (7.5)		570 (3.1)	
	Other (%)	114 (14.6)	7226 (10.0)		2400 (13.2)	
Histology type	PTC (%)	708 (84.9)	67950 (92.8)	< 0.001	18184 (98.9)	< 0.001
	Other (%)	126 (15.1)	5306 (7.2)		203 (1.1)	
T-stage	T1 (%)	164 (35.0)	48296 (66.6)	< 0.001	6618 (37.0)	< 0.001
	T2 (%)	83 (17.7)	12370 (17.1)		2865 (16.0)	
	T3 (%)	77 (16.5)	10479 (14.5)		6529 (36.5)	
	T4 (%)	144 (30.8)	1353 (1.9)		1869 (10.5)	
M-stage	M0 (%)	656 (78.7)	72697 (99.2)	< 0.001	17737 (96.5)	< 0.001
	M1 (%)	178 (21.3)	559 (0.8)		650 (3.5)	
Multifocality	No (%)	316 (64.5)	46165 (64.1)	0.849	7857 (44.2)	< 0.001
	Yes (%)	174 (35.5)	25883 (35.9)		9924 (55.8)	
Extension	No (%)	328 (65.7)	66029 (90.5)	< 0.001	10783 (60.2)	0.012
	Yes (%)	171 (34.3)	6965 (9.5)		7141 (39.8)	
Radiation	None or refused	534 (67.1)	41037 (57.2)	< 0.001	4409 (24.7)	< 0.001
	Radiation beam or radiation implants (%)	55 (6.9)	1063 (1.5)		599 (3.3)	
	Radiosotopes or radiation beam and isotopes/implants (%)	207 (26.0)	29646 (41.3)		12858 (72.0)	
Surgery	Lobectomy (%)	106 (22.4)	12790 (17.9)	0.021	420 (2.3)	< 0.001
	Subtotal or near-total thyroidectomy (%)	24 (5.1)	3028 (4.2)		340 (1.9)	
	Total thyroidectomy (%)	344 (72.5)	55665 (77.9)		17125 (95.8)	
Survival months		38.41 ± 35.66	49.92 ± 33.82	< 0.001	44.68 ± 32.16	< 0.001

PTC: papillary thyroid cancer.

Table 2. Hazard Ratios of different surgery for the cancer specific deaths and all cause deaths of thyroid cancer

Surgery	Cancer-Specific Deaths, No.	%	Cancer-Specific Deaths per 1,000 Person-Years	95% CI	All Cause Deaths, No.	%	All Cause Deaths per 1,000 Person-Years	95% CI
N0	435	0.59	1.34	1.22-1.48	3003	4.10	9.49	9.15-9.84
N1	494	2.69	6.91	6.31-7.56	1171	6.37	16.62	15.68-17.62
NX	90	10.79	29.22	23.40-36.48	156	18.71	42.38	42.38-59.45

Oncology (thyroid, papillary, and/or follicular histology). Cases were included in the study if they had diagnosis codes for "papillary carcinoma", "papillary adenocarcinoma", "oxyphilic adenocarcinoma", "papillary carcinoma, oxyphilic cell", "follicular adenocarcinoma", or "papillary and follicular adenocarcinoma". The 92,477 eligible cases were subsequently classified according to their N stage, based on the 6th and 7th versions of the AJCC guidelines (Supplementary Tables 1 and 2). All patients had available information regarding age, sex, race, T and M stage, histological type, surgery (biopsy, lobectomy, subtotal or near-total thyroidectomy, and total thyroidectomy), and radiation treatment (none or refused, external beam radiation therapy, and radioactive I-131 ablation).

Statistical analyses

All patients had been followed until December 2013, and the survival curves (thyroid cancer-specific mortality and all-cause mortality) were compared using Kaplan-Meier analyses with the log-rank test. Propensity score matching was used to further adjust for potential baseline confounders. Cox proportional hazard

Table 3. Risk factors for survival: outcome of thyroid cancer specific mortality and all-cause mortality

Covariate	Level	Thyroid Cancer specific mortality				All-cause mortality			
		Univariate Cox regression		Multivariate Cox regression		Univariate Cox regression		Multivariate Cox regression	
		Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value
Age		1.097 (1.092-1.102)	< 0.001	1.065 (1.059-1.071)	< 0.001	1.087 (1.084-1.089)	< 0.001	1.077 (1.074-1.08)	< 0.001
Sex	Female	Ref		Ref		Ref		Ref	
	Male	2.892 (2.565-3.260)	< 0.001	1.348 (1.154-1.574)	< 0.001	2.473 (2.33-2.625)	< 0.001	1.65 (1.538-1.77)	< 0.001
Race	White	Ref		Ref		Ref		Ref	
	Black	1.088 (0.856-1.384)	0.490	1.065 (0.762-1.488)	0.714	1.307 (1.174-1.454)	< 0.001	1.412 (1.245-1.601)	< 0.001
	Other	1.454 (1.226-1.726)	< 0.001	0.926 (0.739-1.161)	0.506	0.91 (0.821-1.007)	0.068	0.805 (0.712-0.91)	0.001
Histological types	PTC	Ref		Ref		Ref		Ref	
	Other	3.559 (3.059-4.140)	< 0.001	1.573 (1.254-1.972)	< 0.001	2.012 (1.839-2.202)	< 0.001	1.217 (1.08-1.372)	0.001
T stage	T1	Ref		Ref		Ref		Ref	
	T2	2.928 (2.162-3.966)	< 0.001	2.409 (1.707-3.398)	< 0.001	1.088 (0.99-1.195)	< 0.079	1.098 (0.988-1.222)	0.084
	T3	8.613 (6.769-10.958)	< 0.001	4.394 (3.086-6.256)	< 0.001	1.6 (1.476-1.733)	< 0.001	1.223 (1.066-1.402)	0.004
	T4	95.16 (76.242-118.771)	< 0.001	15.932 (10.642-23.85)	< 0.001	7.768 (7.172-8.413)	< 0.001	2.732 (1.276-3.279)	< 0.001
N stage	NX	Ref		Ref		Ref		Ref	
	N0	0.045 (0.035-0.056)	< 0.001	1.052 (0.581-1.903)	0.868	0.171 (0.146-0.201)	< 0.001	1.04 (0.724-1.495)	0.832
	N1	0.218 (0.174-0.272)	< 0.001	2.249 (1.246-4.061)	0.007	0.296 (0.251-0.35)	< 0.001	1.613 (1.122-2.319)	0.01
M-stage	M0	Ref		Ref		Ref		Ref	
	M1	50.738 (44.873-57.370)	< 0.001	6.373 (5.288-7.68)	< 0.001	14.198 (13.057-15.44)	< 0.001	3.65 (3.197-4.167)	< 0.001
Multifocality	No	Ref		Ref		Ref		Ref	
	Yes	0.913 (0.798-1.044)	0.185	0.797 (0.682-0.933)	0.005	0.901 (0.845-0.96)	0.001	0.967 (0.9-1.039)	0.361
Extension	No	Ref		Ref		Ref		Ref	
	Yes	14.482 (12.571-16.684)	< 0.001	1.419 (1.038-1.939)	0.028	2.766 (2.595-2.948)	< 0.001	1.089 (0.935-1.269)	0.274
Radiation	None or refused	Ref		Ref		Ref		Ref	
	Radiation Beam or Rdioactive implants	16.208 (13.841-18.979)	< 0.001	2.56 (2.017-3.247)	< 0.001	3.967 (3.557-4.424)	< 0.001	1.418 (1.216-1.652)	< 0.001
	Radioisotopes or Radiation beam + isotopes/implants	0.986 (0.859-1.133)	0.847	0.812 (0.675-0.978)	0.028	0.628 (0.589-0.669)	< 0.001	0.695 (0.643-0.751)	< 0.001
Surgery	Lobectomy	Ref		Ref		Ref		Ref	
	Subtotal or near-total thyroidectomy	2.062 (1.467-2.9)	< 0.001	1.037 (0.693-1.551)	0.861	1.06 (0.909-1.238)	0.457	1.012 (0.857-1.193)	0.892
	Total thyroidectomy	1.417 (1.134-1.77)	0.002	0.937 (0.719-1.22)	0.627	0.829 (0.762-0.903)	< 0.001	0.935 (0.851-1.029)	0.169

PTC: papillary thyroid cancer.

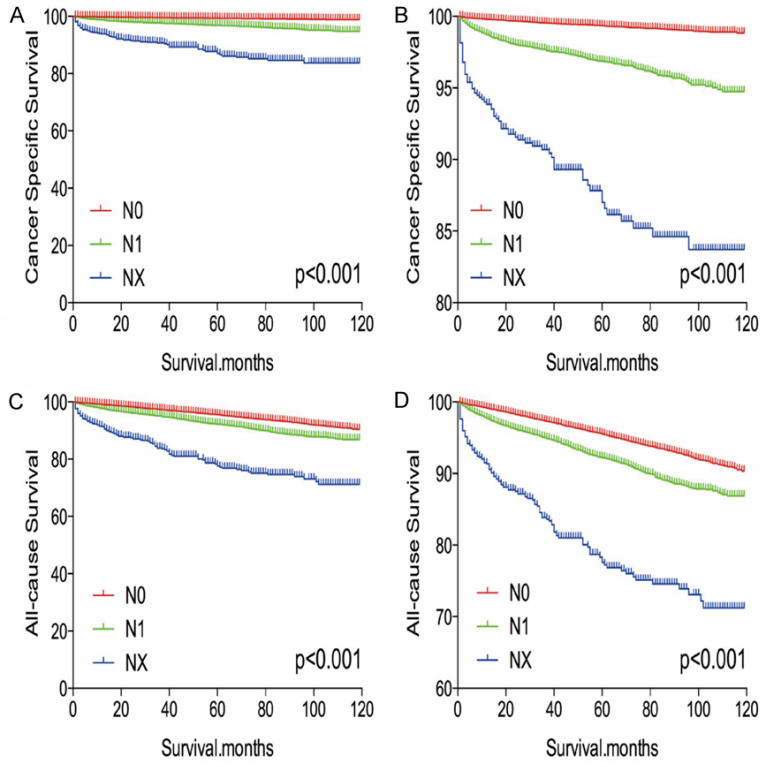

Figure 1. Kaplan Meier curves among patients stratified by N stage for cancer-specific mortality (A, B) and all cause mortality (C, D).

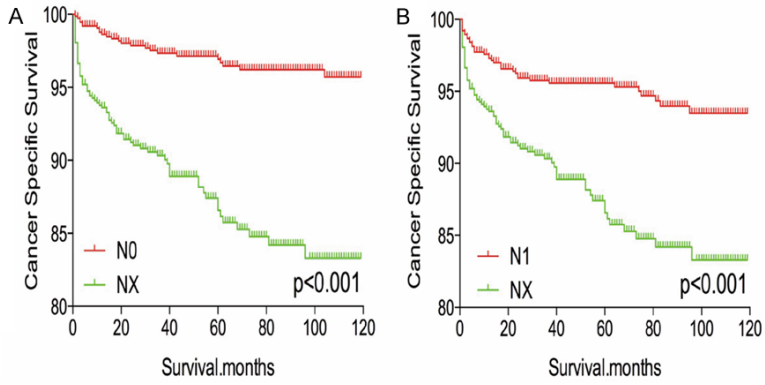

Figure 2. Kaplan Meier curves of cancer-specific mortality for matched stage pairs. Age, sex and race matching between NX and N0 (A), NX and N1 (B) respectively.

regression analyses were performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of the N stages with cancer-specific and all-cause mortality. All tests were two-sided, and differences were considered statistically significant at a *p*-value of < 0.05. All analyses were performed using IBM SPSS software (version 19.0; IBM Corp.), Stata/SE software (version 12, Stata Corp.), and GraphPad Prism (version 6, GraphPad Software Inc.).

Results

Patient characteristics and outcomes

The N stages for the 92,477 eligible patients were N0 for 73,256 patients, N1 for 18,387 patients, and NX for 834 patients. The patients' demographic and clinical characteristics according to N stage are shown in **Table 1**. Patients with NX disease had a significantly shorter follow-up, compared to patients with N1 or N0 disease.

The rates of cancer-specific mortality per 1,000 person-years for N0 disease, N1 disease, and NX disease were 1.34 (95% CI: 1.22-1.48), 6.91 (95% CI: 6.31-7.56), and 29.22 (95% CI: 23.40-36.48), respectively (**Table 2**). The rates of all-cause mortality per 1,000 person-years for N0 disease, N1 disease, and NX disease were 9.49 (95% CI: 9.15-9.84), 16.62 (95% CI: 15.68-17.62), and 42.38 (95% CI: 42.38-59.45), respectively (**Table 2**).

Risk factors for thyroid cancer-specific and all-cause mortalities

Univariate Cox regression analyses revealed that age, male sex, race, TNM stage, follicular subtype, extension, radiation treatment, and surgery were significant risk factors for cancer-specific mortality. In the multivariate Cox regression model, the risk of cancer-specific mortality was higher for N0 compared to NX stage (HR: 1.052, 95% CI: 0.581-1.903, P = 0.868). Furthermore, the risk of cancer-specific mortality for N1 was

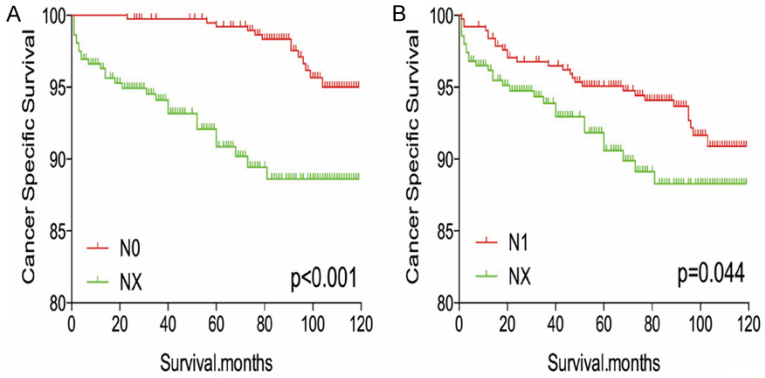

Figure 3. Kaplan Meier curves of cancer-specific mortality for matched stage pairs. Age, sex, race, T/M stage, histology type, multifocality, extension matched between NX and N0 (A), NX and N1 (B) respectively.

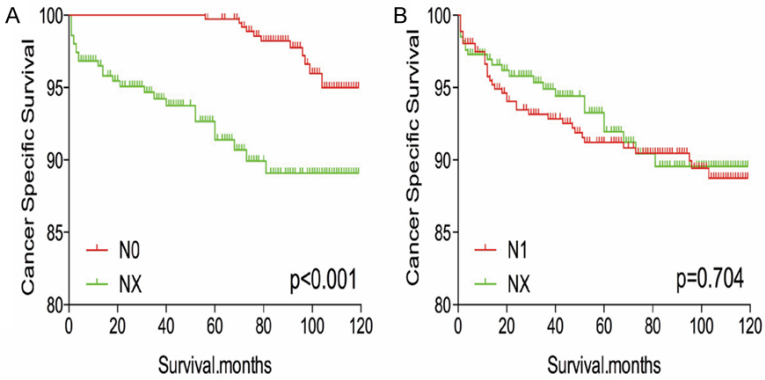

Figure 4. Kaplan Meier curves of cancer-specific mortality for matched stage pairs. Age, sex, race, T/M stage, histology type, multifocality, extension and radiation treatment matched between NX and N0 (A), NX and N1 (B) respectively.

significantly higher than NX stage (HR: 2.249, 95% CI: 1.246-4.061, P = 0.007) (**Table 3**).

Univariate Cox regression analyses revealed that age, male sex, race, TNM stage, multifocality, follicular subtype, extension, radiation treatment, and surgery were significant risk factors for all-cause mortality. In the multivariate Cox regression model, the risk of all-cause mortality was higher for N0 compared to NX stage (HR: 1.04, 95% CI: 0.724-1.495, P = 0.832). Furthermore, the risk of all-cause mortality was significantly higher for N1 compared to NX stage (HR: 1.613, 95% CI: 1.122-2.319, P = 0.01) (**Table 3**).

Propensity score matching

The Kaplan-Meier analysis and log-rank test revealed that patients with NX disease had higher rates of cancer-specific and all-cause mortality, compared to patients with N0 or N1 disease (**Figure 1A-D**). Propensity score matching was performed to minimize any bias regarding age, sex, race, N/M stage, histological subtype, and surgical or radiation treatment. After propensity score matching for age, sex, and race, NX stage was associated with lower DTC-specific mortality, compared to N0 or N1 stage (both P < 0.001, **Figure 2A**, **2B**). Furthermore, after propensity score matching for age, sex, race, T/M stage, histological type, multifocality, and extension, NX stage was associated with lower cancer-specific mortality, compared N0 or N1 stage (P < 0.001 and P = 0.044, respectively; **Figure 3A**, **3B**). After matching for all potential confounders, the cancer-specific mortalities were similar for NX and N1 stage (P = 0.704, **Figure 4B**), although the cancer-specific mortality was lower for NX compared to N0 stage (P < 0.001, **Figure 4A**).

After matching for age, sex, and race, NX stage was associated with a worse prognosis, compared to N0 or N1 stage (both P < 0.001, **Figure 5A**, **5B**). Similar results were obtained after matching for age, sex, race, T/M stage, histological type, multifocality, and extension (**Figure 6A**, **6B**). After matching for all potential confounders, NX and N1 stage were associated with similar all-cause mortality (P = 0.328, **Figure 7B**), although DX disease was associated with lower all-cause mortality, compared to N0 stage (P < 0.001, **Figure 7A**).

Discussion

In the previous and current editions of the AJCC guidelines (6th and 7th versions), NX stage is assigned to patients whose regional lymph nodes cannot be assessed [1]. Many studies have evaluated the risk factors and outcomes

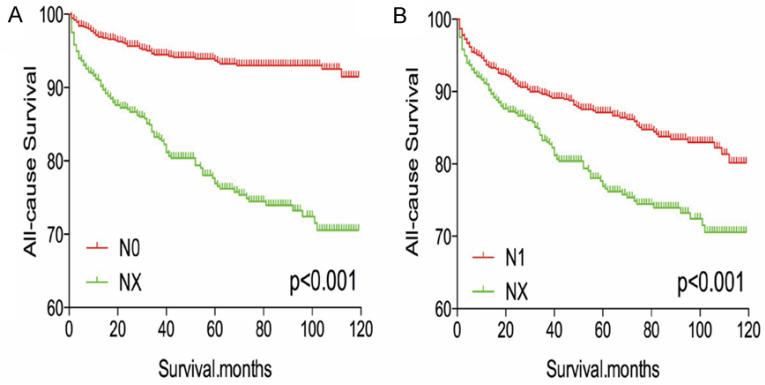

Figure 5. Kaplan Meier curves of all cause mortality for matched stage pairs. Age, sex and race matching between NX and N0 (A), NX and N1 (B) respectively.

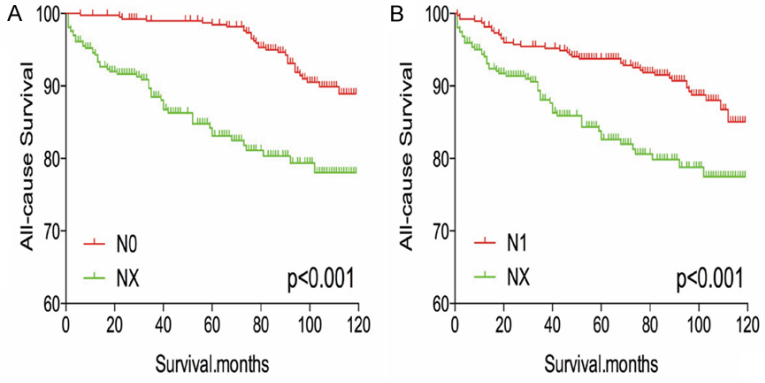

Figure 6. Kaplan Meier curves of all cause mortality for matched stage pairs. Age, sex, race, T/M stage, histology type, multifocality, extension matching between NX and N0 (A), NX and N1 (B) respectively.

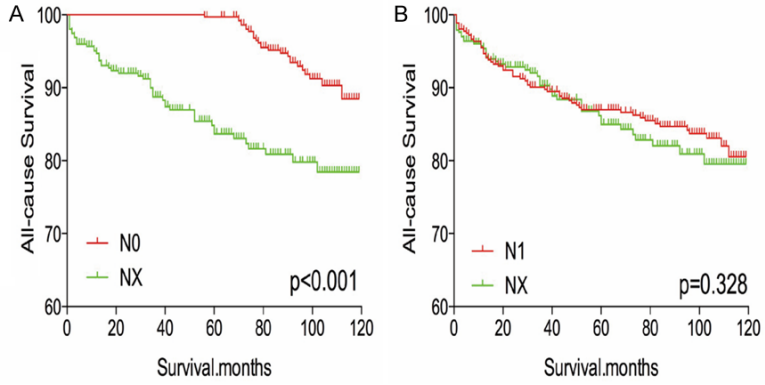

Figure 7. Kaplan Meier curves of all cause mortality for matched stage pairs. Age, sex, race, T/M stage, histology type, multifocality, extension and radiation treatment matching between NX and N0 (A), NX and N1 (B) respectively.

of N0-N1 stage DTC [6-10], although no studies have thoroughly investigated NX stage DTC. Therefore, we evaluated the characteristics and prognosis of patients with NX stage DTC in the SEER database (2004-2013), and found that NX disease was associated with an unexpectedly poor prognosis after adjusting for influential risk factors.

The regional nodes around the thyroid gland can be divided according to their location into levels I-VII [11, 12]. However, it is difficult to identify lymph node metastasis from DTC, even after prophylactic lymph node dissection, because of tissue coverage around the retropharyngeal, cervical, or superior mediastinal lymph nodes [1]. Nevertheless, there is little evidence to support a lymph node evaluation if dissection is not performed in DTC cases.

Inadequate and excessive treatments are becoming important concerns in the management of thyroid carcinoma [13-15], and a balance between these two extremes is needed. Thus, an appropriate surgical approach would decrease the cancer-specific mortality and recurrence rates while avoiding unnecessary surgical complications [16]. In the present study, only 72.5% of patients in the NX stage group underwent total thyroidectomy, which was less than the rate for the N1 stage group (95.8%). Therefore, the higher cancer-specific mortality rate for NX disease may be related to insufficient use of thyroidectomy. Furthermore, 21.3% of the patients in the NX stage group experienced distant metastasis, and this rate was much higher than the rates for N1 (0.8%) and N0 stage group (3.5%). Thus, the high cancer-specific mortality rate in the NX

stage group may be explained by the high distance metastasis rate, which is an important predictor of recurrence and cancer-specific mortality in DTC cases [1, 17]. Moreover, postoperative radioiodine ablation can eradicate normal thyroid remnants and destroy neoplastic foci, although it also reduces or eliminates serum thyroglobulin, to decrease the risks of mortality and recurrence [18-20]. In the present study, 67.1% of the patients in the NX stage group did not undergo radiation, which may also explain the association with a relatively low cancer-specific survival. Therefore, compared to the other two stages, NX stage DTC was associated with insufficient surgery, a high rate of distant metastasis, and infrequent postoperative radioiodine ablation, which may indicate that aggressive treatment is needed for patients with NX stage DTC.

The present study has several limitations. First, the SEER database does not include information regarding DTC recurrence, which may have introduced overestimation bias in the analysis of cancer-specific and all-cause mortality. Second, patients with NX stage DTC had relatively short follow-ups, which may have affected the prognostic analysis. Third, the present study did not consider important risk factors, such as family history, vascular invasion, histological findings, and genetic status (e.g., *BRAF* and *TERT* promoter mutations).

In conclusion, patients with NX stage DTC experienced significantly poorer survival, compared to patients with N0 stage DTC. However, after propensity score matching for relevant confounding factors, similar prognoses were observed in the NX stage and N1 stage groups. These findings are not consistent with current expectations regarding DTC progression, and provide new information regarding the radical treatment of patients with NX stage DTC.

Disclosure of conflict of interest

None.

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Supplemental Table 1. AJCC Cancer Staging Manual, 6th Edition: Protocol for Differentiated Thyroid Carcinoma

AJCC Staging Protocol for DTC, 6th Edition			
Primary tumor (T)			
Note: All categories may be subdivided: (a) solitary tumor, (b) multifocal (the largest determines the classification).			
TX Primary tumor cannot be assessed			
T0 No evidence of primary tumor			
T1 Tumor 2 cm or less in greatest dimension limited to the thyroid			
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension limited to the thyroid			
T3 Tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to the sternothyriod muscle or perithyroid soft tissues)			
T4a Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve			
T4b Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels			
Regional nodes (N)			
Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.			
NX Regional lymph nodes cannot be assessed			
N0 No regional node metastasis			
N1 Regional node involvement			
N1a Nodal metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)			
N1b Metastasis to unilateral, bilateral, or contralateral cervical or cervical or superior mediastinal lymph nodes			
Distant metastasis (M)			
MX Distant metastasis cannot be assessed			
M0 No distant metastasis			
M1 Distant metastasis			
AJCC Staging grouping			
For patients < 45 years			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
For patients ≥ 45 years			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVa	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
Stage IVb	T4b	Any N	M0
Stage IVc	Any T	Any N	M1

Supplemental Table 2. AJCC Cancer Staging Manual, 7th Edition: Protocol for Differentiated Thyroid Carcinoma

AJCC Staging Protocol for DTC, 7th Edition			
Primary tumor (T)			
TX Primary tumor cannot be assessed			
T0 No evidence of primary tumor			
T1 ≤ 2 cm, limited to the thyroid			
T1a ≤ 1 cm			
T1b > 1 cm and ≤ 2 cm			
T2 > 2 cm and ≤ 4 cm, limited to the thyroid			
T3 > 4 cm, limited to the thyroid or any tumor with minimal extra-thyroid extension (e.g., to the sternothyriod muscle or perithyroid soft tissues)			
T4a Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve			
T4b Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels			
Regional nodes (N)			
NX Regional lymph nodes cannot be assessed			
N0 No regional node metastasis			
N1 Regional node involvement			
N1a Nodal metastasis to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)			
N1b Nodal metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or cervical or superior mediastinal lymph nodes (Level VII)			
Distant metastasis (M)			
M0 No distant metastasis			
M1 Distant metastasis			
AJCC Staging grouping			
For patients < 45 years			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
For patients ≥ 45 years			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1-3	N1a	M0
Stage IVa	T4a	N0-1a	M0
	T1-4a	N1b	M0
Stage IVb	T4b	Any N	M0
Stage IVc	Any T	Any N	M1