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Factors associated with distant metastasis in pediatric thyroid cancer: evaluation of the SEER database

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Abstract

Objectives: Controversies regarding factors associated with distant metastasis in pediatric thyroid cancer remain among the scientific community. The aim of this study was to investigate factors influencing distant metastasis in pediatric thyroid cancer.

Methods: We reviewed 1376 patients (aged 2 to 18 years) with thyroid cancer treated between 2003 and 2014. Data collected and analyzed included sex, race, age at diagnosis, year of diagnosis, pathological type, number of tumor foci, tumor extension, T-stage, N-stage, surgical procedure and radiation. Univariate and multivariate analyses were conducted to evaluate factors influencing distant metastasis of pediatric thyroid cancer.

Results: In the univariate analysis, factors influencing distant metastasis of thyroid cancer were age at diagnosis ($P < 0.001$), N-stage ($P < 0.001$), number of tumor foci ($P = 0.003$), tumor extension ($P < 0.001$) and T-stage (T1 vs T2 ($P = 0.803$), T3 ($P < 0.001$) and T4 ($P < 0.001$)). In multivariate analysis, factors influencing distant metastasis of thyroid cancer were age at diagnosis ($P = 0.001$), N-stage ($P < 0.001$) and T-stage (T1 vs T3 ($P = 0.036$) and T4 ($P < 0.001$)). Sex, race, year of diagnosis, pathological type, number of tumor foci, tumor extension, surgical procedure and radiation had no significant influence on distant metastasis (all $P > 0.05$). Furthermore, according to chi-squared test, younger pediatric thyroid cancer patients with higher T- and N-stages are more likely to have distant metastasis.

Conclusion: Age at diagnosis, T-stage and N-stage influence distant metastasis of thyroid cancer patients aged 2 to 18 years; accordingly, more radical treatments may need to be used for patients with those risk elements.

Key Words

- ▶ endocrine malignant tumor
- ▶ thyroid cancer
- ▶ children
- ▶ distant metastasis

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Introduction

Thyroid carcinoma is the most common malignant tumor in the endocrine system (1) and mainly consists of papillary thyroid carcinoma, follicular thyroid carcinoma, undifferentiated thyroid carcinoma and medullary

thyroid carcinoma. Among pediatric patients, papillary thyroid carcinoma and follicular thyroid cancer account for more than 90% (2) of all childhood cases. However, medullary thyroid cancer, poorly differentiated tumors

and undifferentiated (anaplastic) thyroid carcinomas are rare in young patients (3).

According to the Surveillance, Epidemiology and End Results (SEER) program, cases of thyroid cancer in individuals aged 2 to 18 years represent 1.44% of all diagnosed thyroid malignancies. Hence, there are more published studies concerning thyroid cancer in adults than in children. However, recommendations for adults may not be appropriate for children, for whom thyroid cancer characteristics slightly differ from those in adults. Compared with adult patients, the incidence and mortality rate of pediatric thyroid cancer is low; moreover, pediatric differentiated thyroid cancer has a higher rate of distant metastasis (4). Thus, there seems to be a significant need for relevant studies in children and adolescents with thyroid tumors based on large, population-level data (5).

Thyroid nodules can be discovered by patients themselves or by a physician during a routine physical examination; they may also be observed incidentally during imaging for organs such as brain and lung. Furthermore, distant metastasis can be found in pediatric thyroid patients even during the early course of the disease. Specifically, according to previous studies, the extent of cervical disease at the time of diagnosis correlates with risk for distant metastasis, which may require additional treatment, and is also considered during postoperative staging, which allows for stratification of patients who may or may not benefit from further therapy (6). Thus, more comprehensive information regarding distant metastasis of childhood thyroid nodules may help to develop recommendations to improve rates of early diagnosis. Therefore, we investigated factors influencing distant metastasis in pediatric patients with thyroid cancer to inform the management of pediatric patients with suspected and known distant metastases.

Materials and methods

SEER database and eligible study population

The data for the present study was derived from the SEER Program (SEER 18) of the National Cancer Institute; SEER, which is supported by the Surveillance Research Program (SRP) in NCI's Division of Cancer Control and Population Sciences (DCCPS), is an openly accessible database, and it currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34.6% of the US population. This study was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University. We examined

the data from 1376 cases of pediatric thyroid cancer patients aged 2 to 18 years treated between 2004 and 2013. Evaluated characteristics included demographic (age at diagnosis, sex, race), clinical (tumor size and extent, operation type, lymph node involvement, distant metastasis) and prognostic (cancer-specific cause of death and overall cause of death) data. Informed consent was obtained from each patient after fully explaining of the purpose and nature of all procedures used, and patient records were anonymized and de-identified prior to the analysis.

Data were categorized as follows: sex (male, female), race (white, black, other), age at diagnosis (≤ 15 , >15 years), year of diagnosis (2004–2008, 2009–2013), tumor size (≤ 10 , 10–20, >20 –40, >40 mm), T-stage (tumor size/extension evaluation: T1, T2, T3, T4), N-stage (regional lymph node metastasis status: N0, N1) and radiation (none or refused, radiation beam or radioactive implants, radioisotopes or radiation beam+isotopes/implants). In our study, we considered all subtypes of papillary and follicular cancer as papillary thyroid cancer and follicular thyroid cancer, respectively. To assure accuracy of the results, missing or unknown data were considered as missing values.

Statistical analysis

Descriptive statistics are presented as summarized data. Continuous variables and discrete variables are reported as proportions. Univariate analysis of factors such as age, sex and other clinicopathological parameters were performed using binary logistic regression. Multivariate analysis of factors such as age at diagnosis, N-stage and M-stage was carried out using binary logistic regression and the chi-squared test. We used the Kaplan–Meier method for the following variables: age at diagnosis, N-stage and T-stage. All statistical analyses were performed using SPSS software (version 22.0, Chicago, IL, USA). *P* values <0.05 were considered statistically significant.

Results

Patient characteristics are shown in Table 1. Mean age at diagnosis was 15.33 years, including 1126 (81.8%) girls and 250 (18.2%) boys. Papillary thyroid cancer incidence was higher than follicular thyroid cancer incidence (papillary to follicular, 10.4:1). Extension was present in 22.7%, and there were 13 cases of pulmonary metastasis. Based on M-stage, M0 and M1 were observed in 1324 (96.2%), 52 (3.8%) cases, respectively.

Table 1 Demographics and clinical characteristics of pediatric thyroid cancer patients.

Variable	n (%)
Gender	
Female	1126 (81.8)
Male	250 (18.2)
Race	
White	1145 (84.9)
Black	63 (4.7)
Other	140 (10.4)
Age at diagnosis	
≤15	565 (41.1)
>15	811 (58.9)
Year of diagnosis	
2004–2008	586 (42.6)
2009–2014	790 (57.4)
Tumor size (mm)	
≤10	233 (18.3)
10–20 (including 20)	358 (28.2)
20–40 (including 40)	463 (36.5)
>40	216 (17.0)
Number of tumor foci	
1	822 (61.6)
≥2	512 (38.4)
Extension	
No	1047 (77.3)
Yes	308 (22.7)
Pathological type	
Papillary	1253 (91.2)
Follicular	121 (8.8)
T-stage ^a	
T1	518 (39.1)
T2	351 (26.5)
T3	390 (29.5)
T4	65 (4.9)
N-stage ^a	
N0	728 (53.3)
N1	638 (46.7)
M-stage ^a	
M0	1324 (96.2)
M1	52 (3.8)
Pulmonary metastasis	
Yes	13 (0.9)
Other	1363 (99.1)
Surgical procedure	
Lobectomy	128 (9.5)
Subtotal or near-total thyroidectomy	46 (3.4)
Total thyroidectomy	1171 (87.1)
Radiation	
None or refused	458 (34.2)
Radiation beam/radioactive implants	11 (0.8)
Radioisotopes/radiation beam + isotopes/implants	871 (65.0)

^aT-stage: describes the size of the original (primary) tumor and whether it has invaded nearby tissue; N-stage: describes nearby (regional) lymph nodes that are involved; M-stage: describes distant metastasis (spread of cancer from one part of the body to another).

In patients with distant metastasis, the mean age at diagnosis was 16.37 years, including 40 (76.9%) girls and 12 (23.1%) boys. The papillary to follicular ratio was

Table 2 Demographics and clinical characteristics of pediatric thyroid cancer patients with distant metastasis.

Variable	n (%)
Gender	
Female	40 (76.9)
Male	12 (23.1)
Race	
White	42 (80.8)
Black	6 (11.5)
Other	4 (7.7)
Age at diagnosis	
≤15	38 (73.1)
>15	14 (26.9)
Year of diagnosis	
2004–2008	22 (42.3)
2009–2014	30 (57.7)
Tumor size (mm)	
≤10	1 (2.7)
10–20 (including 20)	7 (18.9)
20–40 (including 40)	10 (27.0)
>40	19 (51.4)
Number of tumor foci	
1	19 (40.4)
≥2	28 (59.6)
Extension	
No	15 (32.6)
Yes	31 (67.4)
Pathological type	
Papillary	50 (96.2)
Follicular	2 (3.8)
T-stage	
T1	5 (10.2)
T2	4 (8.2)
T3	23 (46.9)
T4	17 (34.7)
N-stage	
N0	1 (2.0)
N1	49 (98.0)
Pulmonary metastasis	
Yes	13 (25.0)
Other	39 (75.0)
Surgical procedure	
Lobectomy	1 (2.0)
Subtotal or near-total thyroidectomy	3 (6.0)
Total thyroidectomy	46 (92.0)
Postoperative radioiodine treatment (mCi)	
None or refused	8 (15.4)
Radiation beam/radioactive implants	1 (1.9)
Radioisotopes/radiation beam + isotopes/implants	43 (82.7)

25:1. Compared with the data from all pediatric thyroid cancer patients, characteristics were similar, excluding extrathyroidal invasion, which was present in 67.4% of patients (Table 2).

In the univariate analysis, age of diagnosis, number of tumor foci, tumor extension, N-stage and T-stage were significant prognostic factors. Multivariate analysis using binary logistic regression found that age at diagnosis, N-stage and M-stage were independent prognostic

Table 3 Odds ratios for distant metastasis: outcome of univariate logistics regression.

Covariate	Level	Distant metastasis	
		Odds ratio (95% CI)	P-value
Gender	Female	Ref	
	Male	1.37 (0.71–2.65)	0.351
Race	White	Ref	
	Black	2.76 (1.13–6.78)	0.026
	Other	0.77 (0.27–2.19)	0.627
Age at diagnosis		0.83 (0.77–0.89)	<0.001
Year of diagnosis	2004–2008	Ref	
	2009–2013	1.01 (0.58–1.77)	0.976
Pathological type	Papillary	Ref	
	Follicular	0.40 (0.10–1.68)	0.213
Number of tumor foci	1	Ref	
	≥2	2.45 (1.35–4.43)	0.003
Extension	No	Ref	
	Yes	7.70 (4.10–14.47)	<0.001
T-stage	T1	Ref	
	T2	1.18 (0.32–4.44)	0.803
	T3	6.43 (2.42–17.07)	<0.001
	T4	36.34 (12.84–102.82)	<0.001
N-stage	N0	Ref	Ref
	N1	60.48 (8.33–439.29)	<0.001
Surgical procedure	Lobectomy	Ref	
	Subtotal or near-total thyroidectomy	8.86 (0.90–87.45)	0.062
	Total thyroidectomy	5.19 (0.71–37.98)	0.105
Postoperative radioiodine treatment (mCi)	None or refused	Ref	
	Radiation beam or radioactive implants	5.63 (0.64–49.33)	0.119
	Radioisotopes or radiation beam + isotopes or implants	2.92 (1.36–6.27)	0.006

factors for distant metastasis. Among these factors, age at diagnosis of ≤15 years (odds ratio (OR) 0.29; 95% confidence interval (CI) 0.14–0.61) and N1 stage (OR 36.98; 95% CI 4.07–336.25) were risk factors for increased incidence of distant metastasis. Higher T-stage also increased the risk of distant metastasis (T2, OR 0.81, 95% CI 0.19–3.49; T3, OR 4.06, 95% CI 1.10–15.02; T4, OR 23.51, 95% CI 4.85–113.96). However, sex, race, year of diagnosis, pathological type, number of tumor foci, tumor extension, surgical procedure and radiation were not independent predictors of distant metastasis (Tables 3 and 4).

Meanwhile, 1.73% of patients aged >15 years had distant metastasis, whereas 6.73% of patients aged ≤15 years had distant metastasis. This provides evidence of a higher risk of metastasis in younger pediatric thyroid cancer patients. Furthermore, higher N-stage and T-stage were associated with a higher probability of distant metastasis (Tables 5, 6 and 7). There were 49 patients with distant metastasis who exhibited lymph node metastasis, whereas there was only one patient without lymph node metastasis.

However, there were only seven cases of all-cause mortality and three cases of cancer-specific mortality.

These numbers were too low to evaluate the hazard ratios (Supplementary Tables 1, 2, 3 and 4, see section on [supplementary data](#) given at the end of this article). However, cancer-specific mortality for T-stage was statistically significant in a Kaplan–Meier survival curve ($P=0.024$), whereas all-cause mortality was not significant. Moreover, a log-rank test also demonstrated no statistically significant difference between the overall survival or cancer-specific survival curves based on age at diagnosis and N-stage (Figs 1, 2 and 3).

Discussion

The risk for thyroid cancer is much higher in the pediatric population compared with that in adults (7), and nodules self-discovered by families represent 41% of diagnosed cases. Of these, 64% had lymph node metastasis, and 7% had pulmonary metastasis (8), indicating that distant metastasis at first prognosis comprises a large percentage of differentiated pediatric thyroid cancer. Even though the prognosis of most children with thyroid cancer is favorable (9), early detection improves outcome (10) and may help decrease the obligate risks of aggressive

Table 4 Odds ratio for distant metastasis: outcome of multivariate logistic regression.

Covariate	Level	Distant metastasis	
		Odds ratio (95% CI)	P-value
Gender	Female	Ref	
	Male	0.82 (0.35–1.89)	0.635
Race	White	Ref	
	Black	2.22 (0.51–9.68)	0.288
	Other	0.67 (0.18–2.47)	0.552
Age at diagnosis		0.29 (0.14–0.61)	0.001
Year of diagnosis	2004–2008	Ref	
	2009–2013	1.37 (0.67–2.80)	0.384
Pathological type	Papillary	Ref	
	Follicular	1.22 (0.09–16.49)	0.883
Number of tumor foci	1	Ref	
	≥2	1.50 (0.73–3.09)	0.271
Extension	No	Ref	
	Yes	0.52 (0.17–1.57)	0.246
T-stage	T1	Ref	
	T2	0.81 (0.19–3.49)	0.776
	T3	4.06 (1.10–15.02)	0.036
	T4	23.51 (4.85–113.96)	<0.001
N-stage	N0	Ref	
	N1	36.98 (4.07–336.25)	0.001
Surgical procedure	Lobectomy	Ref	
	Subtotal or near-total thyroidectomy	0.46 (0.02–9.13)	0.609
	Total thyroidectomy	0.41 (0.04–4.83)	0.481
Radiation	None or refused	Ref	
	Radiation beam or radioactive implants	3.50 (0.21–57.24)	0.379
	Radioisotopes or radiation beam + isotopes or implants	1.27 (0.46–3.54)	0.643

treatments required to treat advanced disease. Thus, improved understanding of distant metastasis will help improve surgical treatment and prognosis.

In the present study, there was a statistically significant positive relationship of distant metastasis with T-stage and N-stage among thyroid cancer patients aged 2–18 years. Moreover, there was a higher risk of metastasis in patients aged less than 15 years.

Distant metastasis is considered in the clinical diagnosis and medical treatment of other cancers such as cervical (11) and oropharyngeal (12). Therefore, distant metastasis might also help to establish guidelines for determining the use of thyroid surgery, specific treatments and follow-up of children with thyroid neoplasia. Furthermore, the present data suggest that age at diagnosis, T-stage and N-stage should be considered in conjunction with distant metastasis.

Age is generally considered as an important determinant of clinical outcome for differentiated thyroid cancer (13). Recent studies have evaluated the relationship between age at diagnosis and the prognosis of patients with differentiated thyroid cancer and suggest that patients aged <20 or >70 years have a poor prognosis, independent of cancer stage (14). In addition, studies are inconclusive regarding the relationship between age at diagnosis and cancer-specific death (15). The present study confirms that younger patients (≤15 years) with thyroid cancer have a higher risk of distant metastasis than patients aged 16–18 years; further research is needed to corroborate and expound on this.

A previous study shows that for extrathyroidal growth to occur, the thyroid tumor must have reached a certain size, unless it arises from the periphery of the thyroid gland (16); this is consistent with the current results showing

Table 5 Association between age at diagnosis and distant metastasis in pediatric thyroid cancer patients.

Characteristic	M–	M+	P
Age at diagnosis			
Age ≤15	527	38	<0.001
Age >15	797	14	

Table 6 Association between N-stage and distant metastasis in pediatric thyroid cancer patients.

Characteristic	M–	M+	P
N-stage			
N0	721	1	<0.001
N1	589	49	

Table 7 Association between T-stage and distant metastasis in pediatric thyroid cancer patients.

	T-stage			
	T1	T2	T3	T4
Distant metastasis				
No. of patients (%)	5/518 (0.97)	4/351 (1.14)	23/390 (5.90)	17/65 (26.15)
OR (95% CI)	Ref	0.81 (0.19–3.49)	4.06 (1.10–15.02)	23.51 (4.85–113.96)
P-value		0.776	0.036	<0.001

distant metastasis is more likely with higher T-stage. Moreover, previous studies point out that smaller thyroid cancers, which have not yet developed locoregional or distant metastases, are more often surgically curable (17). Furthermore, tumor size is also an important prognostic factor of lymph node metastasis (18). Accordingly, the present results may help to provide guidance regarding the appropriateness of surgery.

Compared with adults, younger patients are more likely to exhibit cervical lymph node metastasis (19), and previous studies suggest that carcinoma cells from the upper region are more likely to be transported to the lateral lymph nodes by lymphatic flow along the superior thyroid artery (20). Furthermore, metastasis to the Delphian node or to the lymph nodes in general is considered to indicate a risk factor for poor clinical outcome (21, 22, 23).

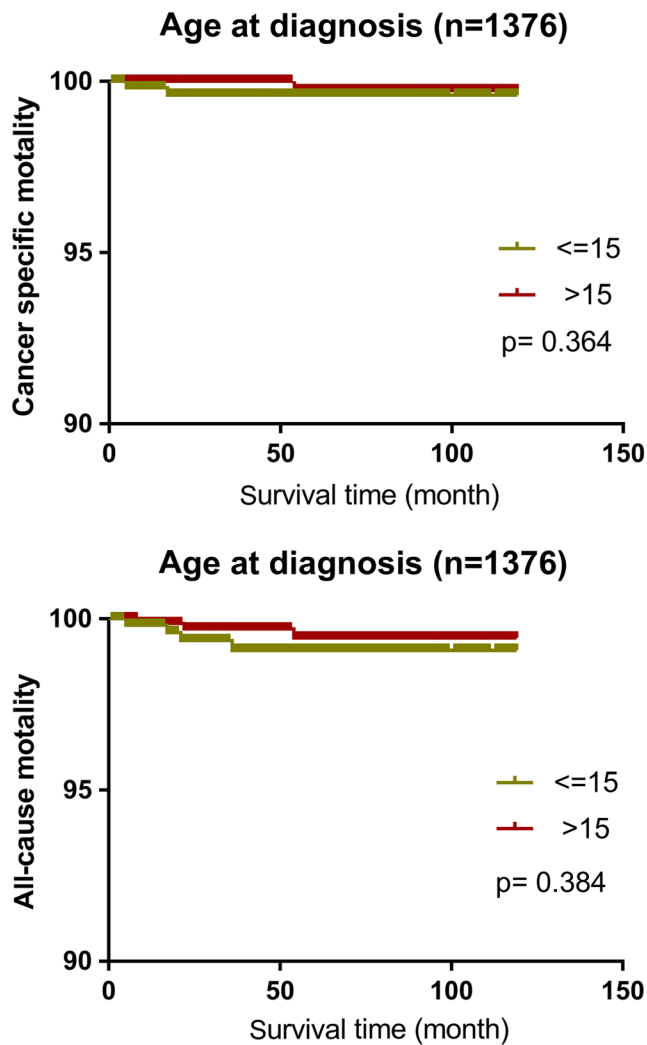


Figure 1 Kaplan-Meier curve based on age at diagnosis.

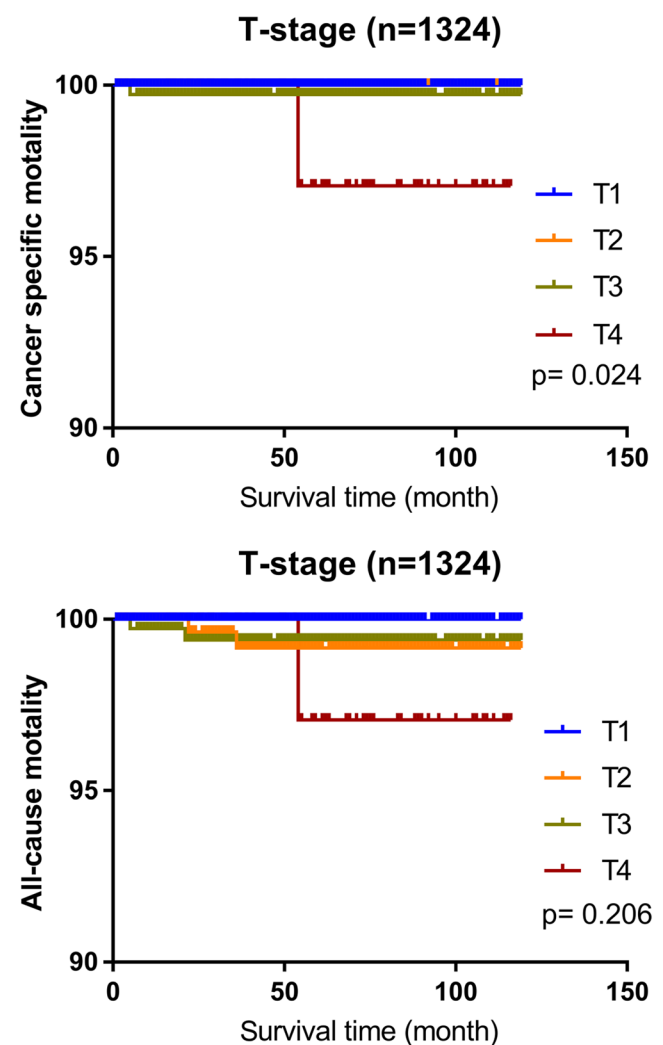


Figure 2 Kaplan-Meier curve based on T-stage.

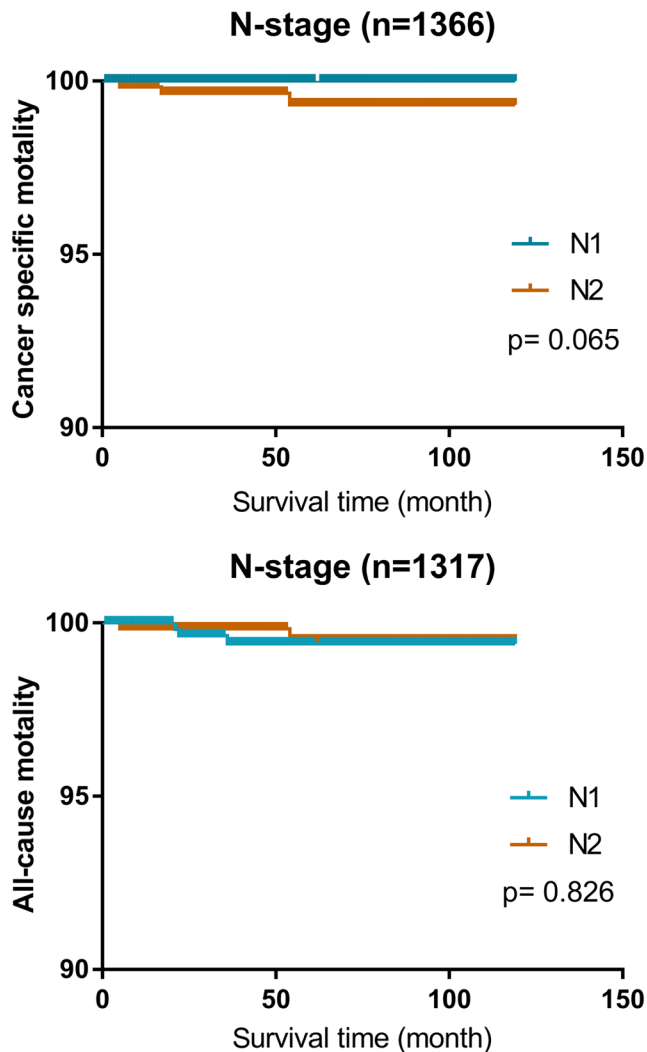


Figure 3
Kaplan-Meier curve based on N-stage.

However, there are limitations of the present study. Although a Kaplan-Meier analysis yielded significant results regarding T-stage and cancer-specific mortality, N-stage and age at diagnosis were not significant; it is possible that we were unable to detect a difference due to insufficient data. Additionally, there was no significance for any factor with all-cause mortality. Moreover, cancer-specific mortality is typically not analyzed because prognosis of most children with thyroid cancer is favorable or the findings are limited because most series regarding differentiated thyroid cancer in children average only a 9-year follow-up. Another limitation is that we only analyzed factors influencing distant metastasis, thus we are unable to determine the specific region of transfer or the subsequent influences. In addition, potential confounding factors such as family history,

vascular invasion and other factors related to selection bias were not in our analysis. Finally, inherent to the use of retrospective SEER data, the cases analyzed had heterogeneous management approaches over a relatively long-time period.

Hitherto, guidelines for diagnosis and treatment of children with thyroid cancer have not differed from those of adults. The objective of the current study was to determine factors that influence distant metastasis of pediatric thyroid cancer patients; these findings may help to provide data to support more specific guidelines for diagnosis and treatment of pediatric thyroid cancer patients and ultimately to improve prognosis.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-18-0441>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

All authors contributed to the design of the study and writing of the manuscript. W W, C Z, L Z, W Z, M W and H F F undertook the research, Y H H, S C C and W Z performed the analyses, Z M L and D H wrote the main manuscript text and prepared figures. All authors reviewed the manuscript.

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