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Original Article

Epidemiology, risk factor and prognostic factor of young differentiated thyroid carcinoma with distant metastasis: a retrospective cohort study

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Abstract: This study aimed to characterize the epidemiology, risk factors, and survival outcomes of differentiated thyroid carcinoma (DTC) patients aged <55 years with distant metastasis (DM). The Surveillance, Epidemiology, and End Results (SEER) database was researched retrospectively for young DTC patients. Multivariate Logistic and Cox regression analyses were used to identify DM predictors and survival determinants. The overall survival (OS) and cancer-specific survival (CSS) were evaluated and compared by Kaplan-Meier analysis and Log-Rank test, respectively. The risk and prognostic nomogram were constructed and validated using ROC curves, calibration plots, and decision curve analysis. A total of 68,373 young DTC patients were identified. The DM prevalence was 0.65% (95% CI: 0.59-0.72%), predominantly involving the lungs (35.8%). Independent risk factors for DM included male sex (OR=1.84), follicular histology (OR=2.43), advanced T4 (OR=22.3) and N1 stages (OR=4.91). The 5-year and 10-year OS rates for young DTC patients with DM were 83.6% and 73.3%, while the 5-year and 10-year CSS rates were 85.0% and 79.9%, respectively. Multivariate Cox analysis identified several independent prognostic factors for both OS and CSS including age, the presence of lung, bone, liver, and brain metastases, as well as the use of surgery and chemotherapy. Established prognostic nomograms demonstrated robust performance (C-index =0.87 for OS; C-index =0.85 for CSS), with time-dependent area under the curves (AUCs) exceeding 0.80 at 5, and 10 years. In conclusion, this study presents the first population-level analysis of young DTC patients with distant metastases and establishes SEER-derived predictive models for assessing risk and survival among these patients.

Keywords: Differentiated thyroid carcinoma, distant metastases, SEER database, epidemiology, nomogram, risk-stratification

Introduction

Differentiated thyroid carcinoma (DTC), which mainly includes papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), accounts for over 90% of all thyroid cancer cases and generally exhibits favorable prognosis, with a 10-year survival rate exceeding 90% [1, 2]. However, there is significant heterogeneity in the clinicopathological characteristics and demographic profiles of DTC patients, with age serving as a crucial determinant of tumor behavior and clinical outcomes [3-5]. DTC patients aged <55 years exhibit distinct biological characteristics. Emerging evidence indicates that patients <55 years had less differently expressed genes and less altered pathways associated with aggressiveness of thyroid cancer when compared with older groups [6]. Notably, the 8th edition of the AJCC-TNM staging system identifies 55 years as a critical age threshold for risk stratification, reflecting distinct biological behaviors, metastatic patterns, and survival in younger patients (those under 55 years) compared to older patients [7, 8]. Epidemiological studies further emphasize the rising incidence of thyroid cancer among young populations, highlighting the necessity for age-specific investigations [9].

Distant metastasis (DM), although it occurs in less than 10% of DTC cases, remains a signifi-

cant indicator of poor prognosis, reducing the 10-year disease-specific survival (DSS) rate to approximately 50% [10, 11]. Established risk factors for DM include a primary tumor size greater than 4 cm, follicular histology, lymph node metastasis, and vascular invasion [12, 13]. Recent evidences suggested that advanced age is an independent predictor of both susceptibility to distant metastases and adverse survival outcomes [11, 14]. While young patients demonstrate superior overall survival, emerging data indicate that the occurrence of distant metastases in this subgroup may carry substantial risks of disease progression, warranting further attention.

Current knowledge gaps persist regarding the epidemiology of distant metastases and its prognostic determinants, in young DTC populations. Traditional clinical studies are limited in their ability to capture rare distant metastasis events within this cohort due to low incidence rates and the need for extended follow-up when conducting survival analysis. Moreover, previous investigations have predominantly focused on all-age cohorts or elderly patients [10, 11, 15, 16], potentially overlooking the unique clinical features of younger individuals - such as dynamic hormonal environments and increased treatment tolerance - that may influence metastatic propensity and survival patterns. The Surveillance, Epidemiology, and End Results (SEER) database, with its extensive sample size and longitudinal design, provides unprecedented opportunities to address these challenges by facilitating robust analyses of rare events.

The objectives of this study using the SEER program were to: 1) describe the epidemiological feature of distant metastases in DTC patients aged under 55 years; 2) identify clinicopathological and demographic factors associated with the risk of distant metastases; 3) characterize survival outcomes for young DTC patients with distant metastases, and 4) develop predictive models for risk stratification and prognosis.

Methods and materials

Participants

The database (Incidence - SEER Research Plus Data, 17 registries, Nov 2023 Sub, 2000-2021) was analyzed to identify young DTC patients diagnosed between 2010 and 2021 using histology ICD-O-3 codes (PTC: 8050, 8052, 8130, 8260, 8340, 8341, 8342, 8343, 8344 and FTC: 8330, 8331, 8332, 8335, 8346) and their corresponding locations (Site recode ICD-O-3/World Health Organization [WHO] 2008: thyroid). The inclusion criteria for young DTC patients were as follows: 1) age at diagnosis of less than 55 years; 2) complete documentation of AJCC T/N staging; 3) adequate information on survival time and survival status. The exclusion criteria included: 1) medullary thyroid carcinoma (MTC), anaplastic thyroid carcinoma (ATC), and other rare histological subtypes; 2) DTC not being the primary malignancy; 3) patients with incomplete documentation of metastasis; and 4) patients with missing data on age, AJCC-TNM staging, survival or follow-up.

Variables

Demographic and clinicopathological characteristics, as well as treatment modalities for each patient, were extracted using the SEER*Stat 8.4.5 software. Previous AJCC staging systems (7th editions) set 45 years as a prognostic cutoff, prompting the inclusion of 45-54 year subgroup. Subsequent decadal intervals were selected to standardize age-based comparisons. For younger populations, pediatric population exhibit differences in pathophysiology, clinical presentation, and long-term outcomes. Younger patients were divided into <18 years (pediatric) and 18-24 years cohorts. Therefore, age at diagnosis were categorized as <18 years, 18-24 years, 25-34 years, 35-44 years, 45-54 years. Other variables included sex (female, male), race/ethnicity (white, black, other), and marital status (married, single, other). Clinicopathological characteristics encompassed histological subtype (PTC, FTC), AJCC 7th edition TNM stage (T1/T2/T3/T4, N0/N1). Treatment modalities included surgery, radiation, and chemotherapy. Distant metastasis (DM) was defined as metastatic lesions identified at time of initial diagnosis based on the standardized clinical or pathological evidence. For young DTC patients with distant metastases, the status of lung, bone, liver, and brain metastases should also be documented. Survival outcomes included overall survival (OS) and cancer-specific survival (CSS). OS was measured from diagnosis to all-cause death or the last follow-up, while CSS was defined as the

time from diagnosis to death caused by DTC or the last follow-up.

Statistical analysis

Categorical data were described in terms of frequency and percentage, and differences were examined using the Chi-square test. A multivariate logistic regression model was employed to identify risk factors for the occurrence of distant metastases, with results expressed as adjusted odds ratios (OR) and 95% confidence intervals (CI). Survival outcomes were assessed and compared using Kaplan-Meier curves and log-rank tests, while multivariable Cox proportional hazards models were adjusted for various variables. Independent risk factors and prognostic factors were incorporated into the construction of risk and prognostic nomograms. Model discrimination was assessed through receiver operating characteristic (ROC) curves and concordance indices (C-index), while calibration accuracy was used to verify the correlation between predicted and observed probabilities. Decision curve analysis (DCA) evaluated clinical utility by quantifying net benefits across threshold probabilities. All statistical tests were two-sided, with a significance level of $P<0.05$, and were performed using R version 4.2.1.

Results

The prevalence of distant metastases among young DTC patients

A total of 68,373 young cases of DTC were identified from the SEER database between 2010 and 2021, according to the inclusion criteria. Among these patients, 447 DTC cases presented with distant metastases at the time of initial diagnosis. The prevalence of distant metastases among young DTC patients was 0.65% (95% CI: 0.59%-0.72%). Of the 447 cases, 160 developed lung metastases, 60 patients had bone metastases, 13 had brain metastases, 7 had liver metastases.

Clinicopathological features of young DTC patients with distant metastases

As described in **Table 1**, the demographic and clinicopathological characteristics, as well as treatment modalities, of young DTC patients with and without distant metastases were compared. Patients with distant metastases exhibited distinct age and gender disparities, including a higher proportion of middle-aged individuals (ages 45-54: 39.8% vs. 34.5%) individuals, and a male predominance (40.5% vs. 19.8%; all $P<0.01$). Unmarried status was also more prevalent in the metastatic group (38.5% vs. 29.7%; $P<0.01$). Metastatic patients had higher-risk disease features, including a greater prevalence of follicular thyroid carcinoma (FTC: 7.2% vs. 4.2%), advanced tumor staging (T3/T4: 68.0% vs. 20.4%), and lymph node involvement (N1: 78.5% vs. 30.0%; $P<0.01$). Regarding treatment patterns, metastatic cases had slightly lower resection rates (95.5% vs. 98.7%) but significantly higher rates of radiation therapy (71.1% vs. 42.8%) and chemotherapy (6.5% vs. 0.2%; $P<0.01$), indicating a more aggressive multimodal management approach for advanced disease.

Risk factors for developing distant metastases among young DTC patients

Multivariable logistic regression analysis identified age, sex, histological subtype, T stage, and N stage as independent predictors of distant metastasis among young DTC patients (**Figure 1**). Male individuals exhibited a significantly higher risk of distant metastasis compared to females (OR=1.84, 95% CI: 1.51-2.24). Patients with FTC demonstrated a greater propensity for metastasis than those with PTC (OR=2.43, 95% CI: 1.62-3.52). Advanced T and N stages were strongly correlated with the risk of distant metastasis, with T4 stage showing the most pronounced association (OR=22.3, 95% CI: 16.5-30.3). These results underscore the critical roles of tumor biology (histological subtype, T/N progression) and demographic factors (age, sex) in the development of distant metastasis.

Risk nomogram for predicting distant metastases

All these independent risk factors were incorporated into the establishment of a risk-nomogram for predicting distant metastases. As shown in **Figure 2**, the T stage had the greatest contribution to this model, followed by the N stage and age. The nomogram demonstrated excellent discrimination, with an area under the ROC curve (AUC) of 0.85 (95% CI: 0.83-0.87), indicating strong predictive accuracy (**Figure**

Table 1. The demographic and clinicopathological characteristics of young DTC patients with and without distant metastases

Characteristics	Young DTC patients without distant metastases (N=67,926)	Young DTC patients with distant metastases (N=447)	*P* value
Age			
<18y	1390 (2.0%)	37 (8.3%)	<0.01
18-24y	4818 (7.1%)	38 (8.5%)	
25-34y	15922 (23.4%)	78 (17.4%)	
35-44y	22350 (32.9%)	116 (26.0%)	
45-54y	23446 (34.5%)	178 (39.8%)	
Gender			
Female	54481 (80.2%)	266 (59.5%)	<0.01
Male	13445 (19.8%)	181 (40.5%)	
Race			
White	53226 (78.4%)	355 (79.4%)	0.65
Black	4130 (6.1%)	29 (6.5%)	
Other	9324 (13.7%)	58 (13.0%)	
Unknown	1246 (1.8%)	5 (1.1%)	
Marital status			
Married	39044 (57.5%)	228 (51.0%)	<0.01
Single	20159 (29.7%)	172 (38.5%)	
Other	5031 (7.4%)	32 (7.2%)	
Unknown	3692 (5.4%)	15 (3.4%)	
Pathological type			
PTC	65054 (95.8%)	415 (92.8%)	<0.01
FTC	2872 (4.2%)	32 (7.2%)	
AJCC-T			
T1	40454 (59.6%)	80 (17.9%)	<0.01
T2	13653 (20.1%)	63 (14.1%)	
T3	12623 (18.6%)	173 (38.7%)	
T4	1196 (1.8%)	131 (29.3%)	
AJCC-N			
N0	47536 (70.0%)	96 (21.5%)	<0.01
N1	20390 (30.0%)	351 (78.5%)	
Surgery			
No	865 (1.3%)	20 (4.5%)	<0.01
Yes	67061 (98.7%)	427 (95.5%)	
Radiation			
None/Unknown	38833 (57.2%)	129 (28.9%)	<0.01
Yes	29093 (42.8%)	318 (71.1%)	
Chemotherapy[§]			
None/Unknown	67822 (99.8%)	418 (93.5%)	<0.01
Yes	104 (0.2%)	29 (6.5%)	

[§]Chemotherapy refers to Systemic Chemotherapy (non-RAI).

3A). Calibration plots revealed a close agreement between predicted and observed probabilities (**Figure 3B**). DCA further confirmed the clinical utility of the model, demonstrating a

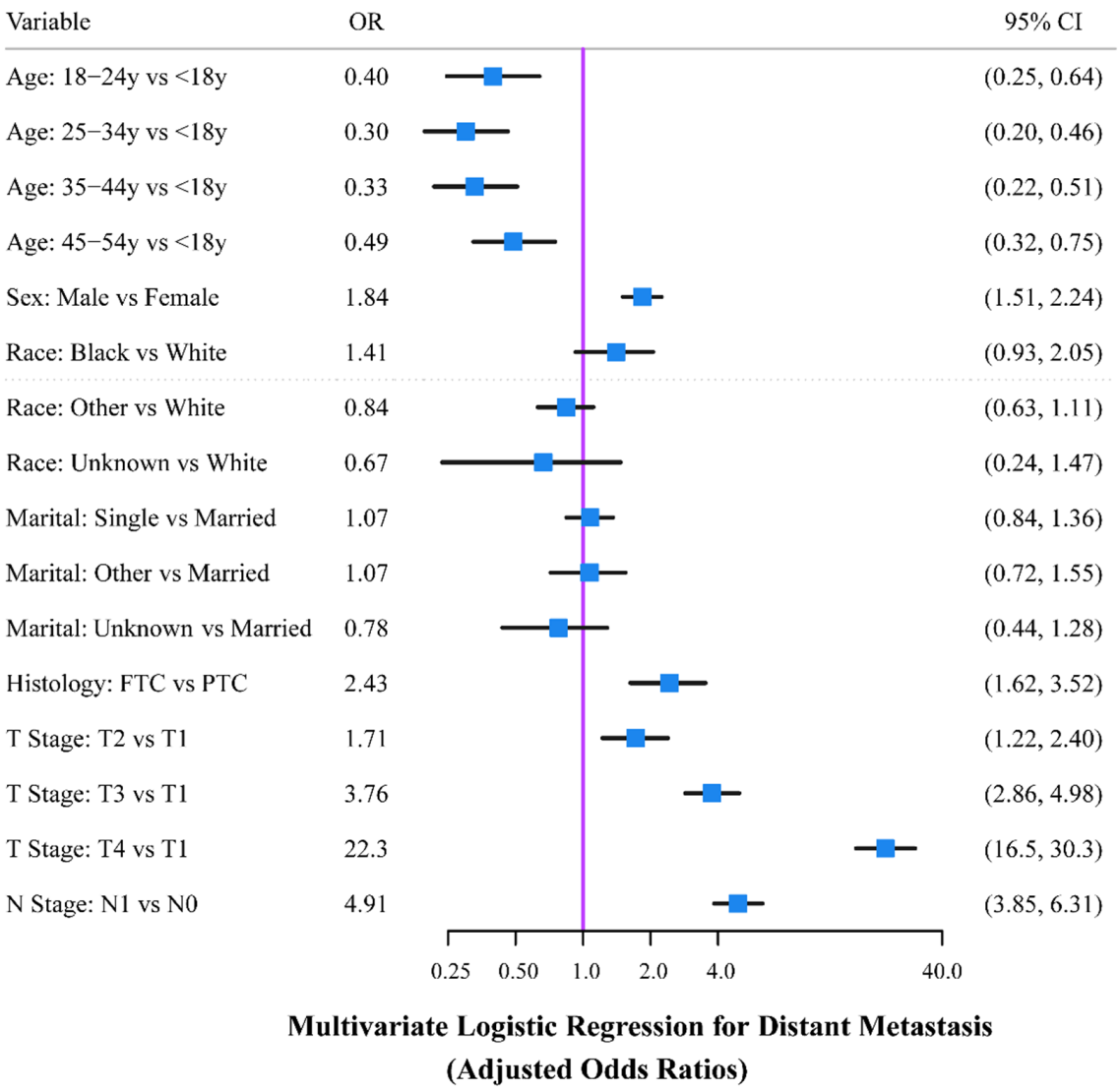

Figure 1. Multivariate logistic regression analysis of independent risk factors for distant metastases among patients with young differentiated thyroid carcinoma (DTC). PTC: papillary thyroid carcinoma, FTC: follicular thyroid carcinoma.

superior net benefit across threshold probabilities compared to alternative strategies (**Figure 3C**).

Survival analysis of young DTC patients with distant metastases

Survival analysis indicated that patients with distant metastases have significantly poorer survival outcome compared to those without distant metastases, regardless of OS and CSS (P<0.01 for all, **Figure 4**). The 5-year and 10-year OS rates for young DTC patients with distant metastases were 83.6% and 73.3%, respectively, while the 5-year and 10-year CSS rates were 85.0% and 79.9%, respectively.

Prognostic factors for OS and CSS

As shown in **Table 2**, multivariate Cox regression analysis identified several independent prognostic factors for both OS and CSS including age, the presence of lung, bone, liver, and brain metastases, as well as the use of surgery and chemotherapy. Patients aged 45 to 54 years were significantly associated with worse OS (HR=4.11, 95% CI: 2.32-7.30; P<0.01) and CSS (HR=3.85, 95% CI: 2.03-7.30; P<0.01) compared to younger patients (≤44 years). The presence of distant metastases in specific organs conferred markedly elevated risks of death: lung metastases (OS: HR=2.44, P<0.01; CSS: HR=3.50, P<0.01), bone metastases (OS:

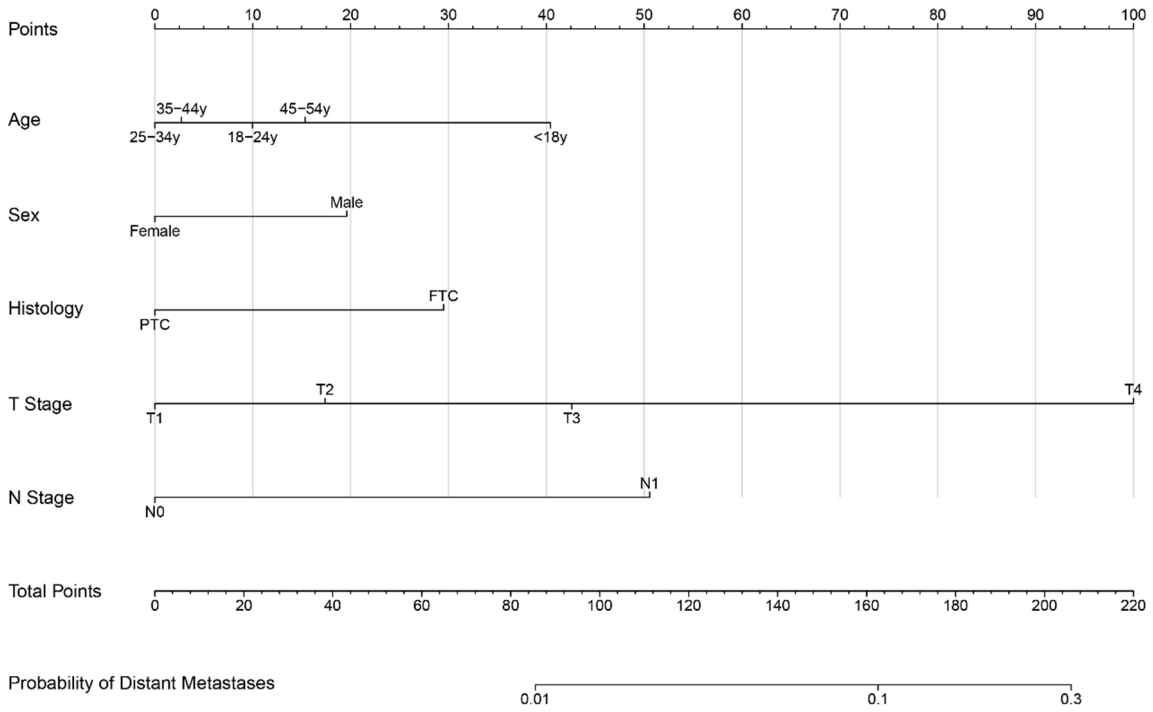

Figure 2. Establishment of risk-nomogram for predicting distant metastases among patients with young differentiated thyroid carcinoma (DTC).

HR=2.59, P<0.01; CSS: HR=2.46, P=0.01), liver metastases (OS: HR=4.03, P=0.02; CSS: HR=5.42, P=0.01), and particularly brain metastases (OS: HR=5.57, P<0.01; CSS: HR=8.20, P<0.01). The use of surgery was strongly protective for both OS (HR=0.24, P<0.01) and CSS (HR=0.30, P=0.01), whereas chemotherapy was associated with increased risk of mortality (OS: HR=2.16, P=0.03; CSS: HR=2.69, P=0.01). Advanced T4 staging significantly impacted CSS (HR=4.45, P=0.04) but did not significantly affect OS (P=0.12). These findings underscore the critical roles of metastatic organ involvement, age, and therapeutic interventions in determining prognosis.

Establishment of OS-/CSS-nomogram

The nomograms for OS and CSS exhibited excellent predictive performance (**Figures 5A**, **6A**). The C-index for the OS-nomogram was 0.87 (95% CI: 0.78-0.95), while the CSS-nomogram achieved a C-index of 0.85 (95% CI: 0.78-0.93). Time-dependent ROC analysis further validated the discriminative ability of the models, with AUC values of 0.86 and 0.93 for 5-year and 10-year OS predictions, respectively (**Figure 5B**). Similarly, the CSS nomogram showed robust discrimination, with AUC values of 0.84 and 0.91 for 5-year and 10-year CSS predictions, respectively (**Figure 6B**). DCA demonstrated significant clinical utility, with both nomograms providing superior net benefits across a wide range of threshold probabilities compared to alternative strategies (**Figures 5C**, **6C**). Calibration plots demonstrated strong agreement between predicted and observed survival probabilities, indicating high accuracy of the nomograms (**Figures 5D**, **6D**). These results underscore the reliability and clinical applicability of the nomograms for individualized survival prediction in patients with distant metastases.

Discussion

This population-based study investigated the clinical epidemiology and prognostic determinants of distant metastasis in young patients with DTC, utilizing the SEER database to address critical knowledge gaps in this understudied cohort. Our findings reveal a distant metastasis prevalence of 0.65% among young DTC patients, with the lungs being the predominant metastatic site (35.8%), followed by bone (13.4%) and brain/liver metastases

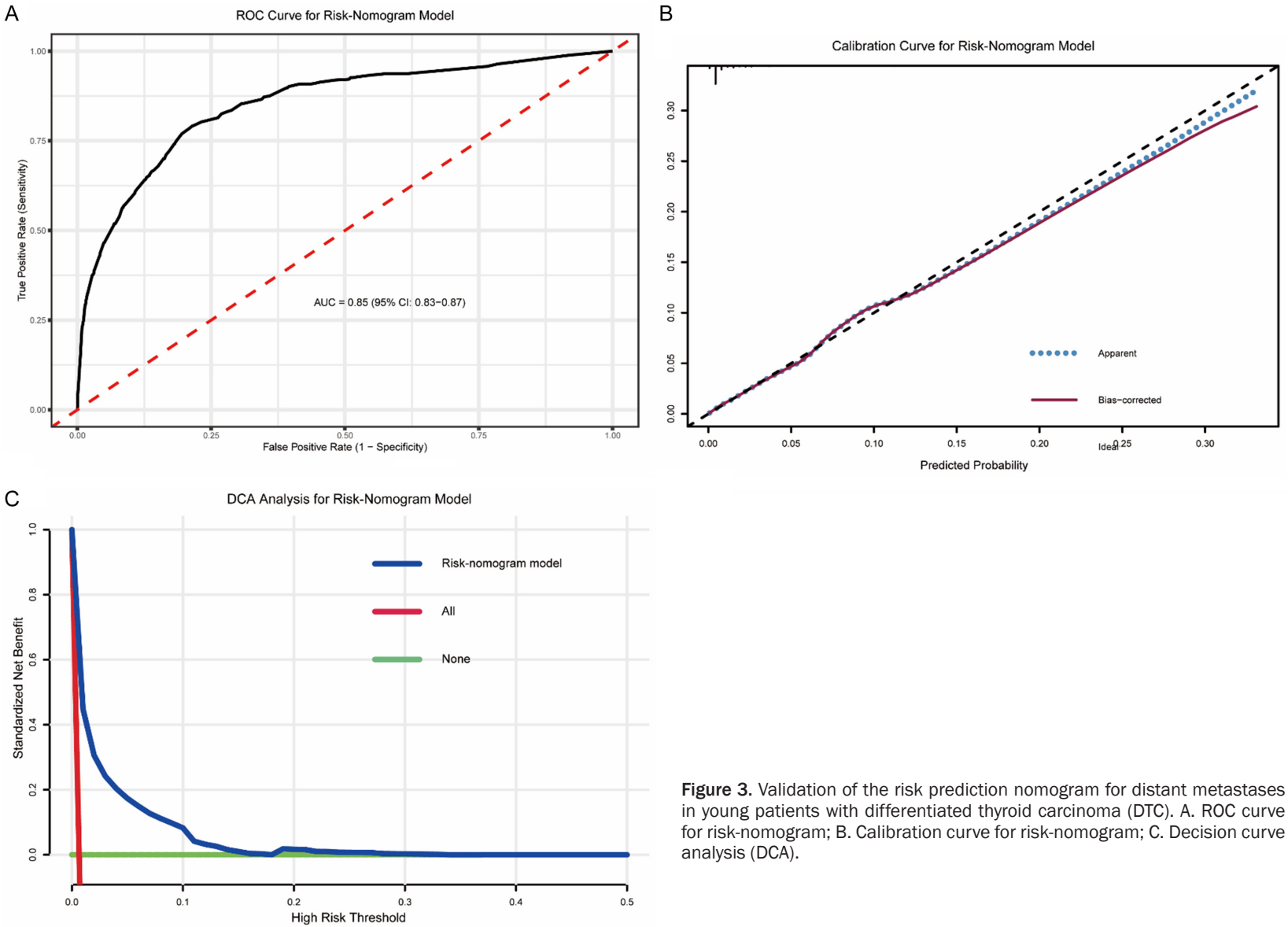

Figure 3. Validation of the risk prediction nomogram for distant metastases in young patients with differentiated thyroid carcinoma (DTC). A. ROC curve for risk-nomogram; B. Calibration curve for risk-nomogram; C. Decision curve analysis (DCA).

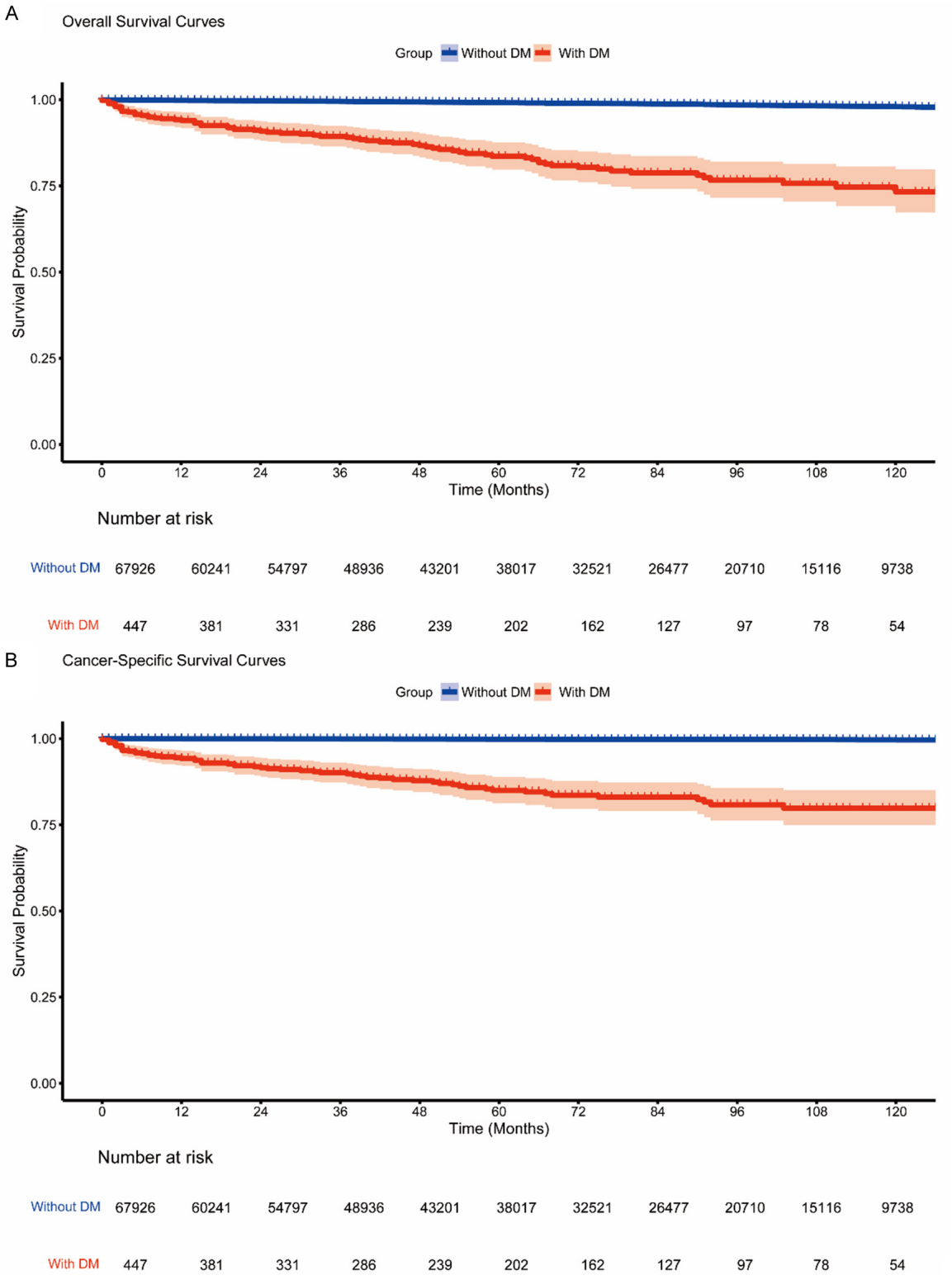

Figure 4. The Kaplan-Meier curve (A: Overall survival, OS; B: Cancer-specific survival, CSS) for young differentiated thyroid carcinoma (DTC) patients with and without distant metastases.

(2.9%/1.6%). These observations align with prior SEER analyses that reported similar patterns in metastatic DTC, where lung involvement predominates due to hematogenous dis-

Table 2. Multivariate Cox regression analysis for OS and CSS among young DTC patients with distant metastases

Characteristics	OS		CSS	
	95% CI	*P* value	95% CI	*P* value
Age				
≤44y	Reference		Reference	
45-54y	4.11 (2.32-7.30)	<0.01	3.85 (2.03-7.30)	<0.01
Gender				
Female	Reference		Reference	
Male	1.40 (0.85-2.30)	0.18	1.44 (0.83-2.49)	0.20
Race				
White	Reference		Reference	
Black	0.66 (0.21-2.09)	0.48	0.48 (0.11-2.13)	0.34
Other	1.51 (0.77-2.96)	0.23	1.44 (0.67-3.11)	0.35
Marital status				
Married	Reference		Reference	
Single	1.64 (0.94-2.88)	0.08	1.40 (0.76-2.59)	0.28
Other	1.94 (0.87-4.30)	0.10	1.83 (0.75-4.45)	0.18
Pathological type				
PTC	Reference		Reference	
FTC	1.53 (0.63-3.72)	0.35	1.27 (0.45-3.61)	0.65
AJCC-T				
T1	Reference		Reference	
T2	0.46 (0.12-1.75)	0.25	0.97 (0.17-5.63)	0.98
T3	1.08 (0.43-2.68)	0.88	2.11 (0.54-8.26)	0.28
T4	2.12 (0.83-5.43)	0.12	4.45 (1.10-18.07)	0.04
AJCC-N				
N0	Reference		Reference	
N1	1.25 (0.62-2.49)	0.53	1.32 (0.58-3.02)	0.51
Lung metastases				
No	Reference		Reference	
Yes	2.44 (1.38-4.34)	<0.01	3.50 (1.79-6.82)	<0.01
Bone metastases				
No	Reference		Reference	
Yes	2.59 (1.44-4.64)	<0.01	2.46 (1.27-4.75)	0.01
Liver metastases				
No	Reference		Reference	
Yes	4.03 (1.25-13.0)	0.02	5.42 (1.63-18.04)	0.01
Brain metastases				
No	Reference		Reference	
Yes	5.57 (2.21-14.0)	<0.01	8.20 (3.20-21.00)	<0.01
Surgery				
No	Reference		Reference	
Yes	0.24 (0.10-0.55)	<0.01	0.30 (0.12-0.75)	<0.01
Radiation				
None/Unknown	Reference		Reference	
Yes	0.98 (0.56-1.75)	0.96	1.25 (0.64-2.42)	0.51
Chemotherapy[§]				
None/Unknown	Reference		Reference	
Yes	2.16 (1.06-4.39)	0.03	2.69 (1.31-5.53)	0.01

[§]Chemotherapy refers to Systemic Chemotherapy (non-RAI).

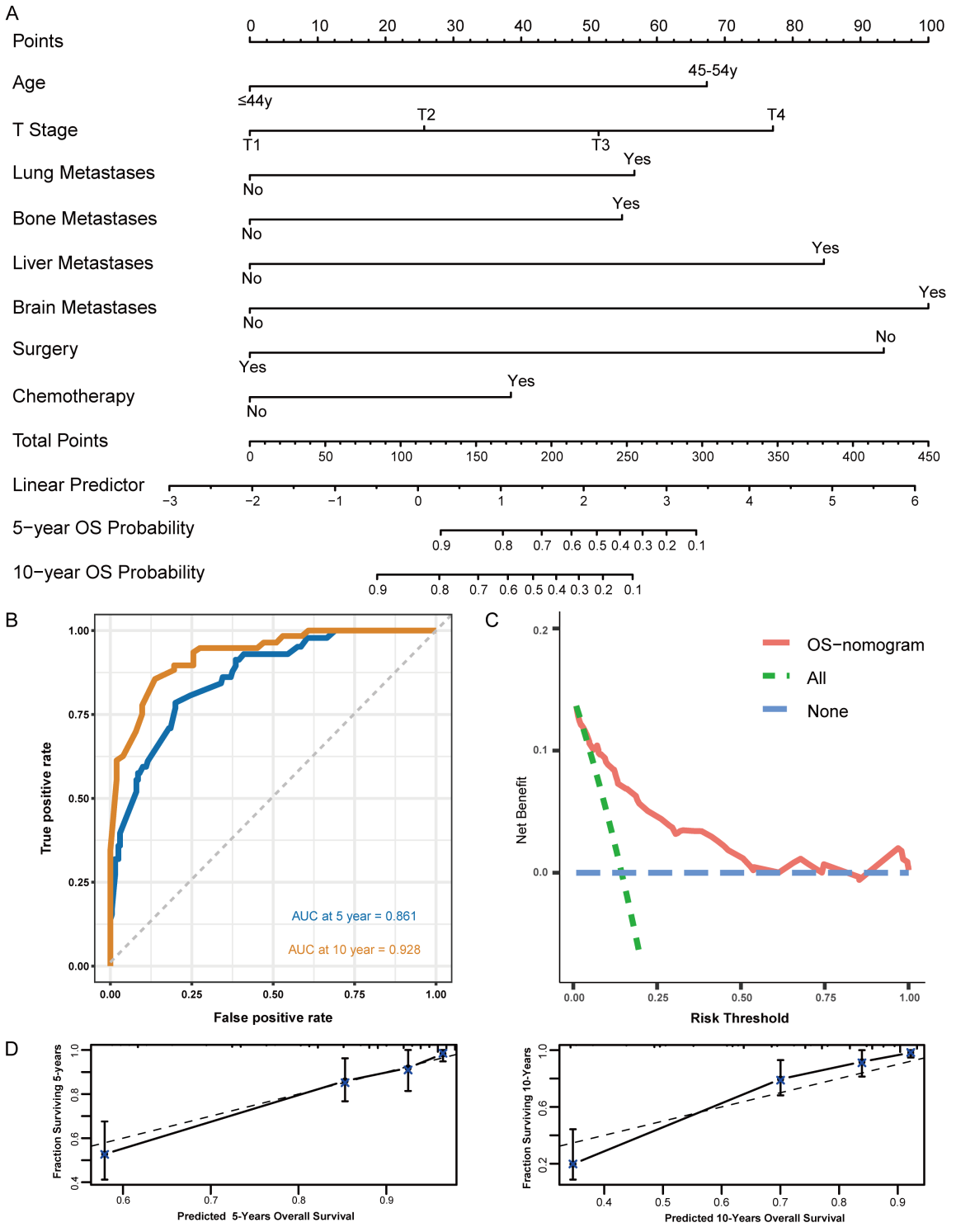

Figure 5. Establishment and validation of OS-nomogram for predicting OS among young patients with differentiated thyroid carcinoma (DTC) (A). ROC curve for OS-nomogram (B); Decision curve analysis (DCA) for OS-nomogram (C); Calibration curve for OS-nomogram (D).

semination mechanisms [11, 15, 16]. Notably, the lower incidence of liver metastases compared to older cohorts may reflect age-related differences in tumor microenvironment or

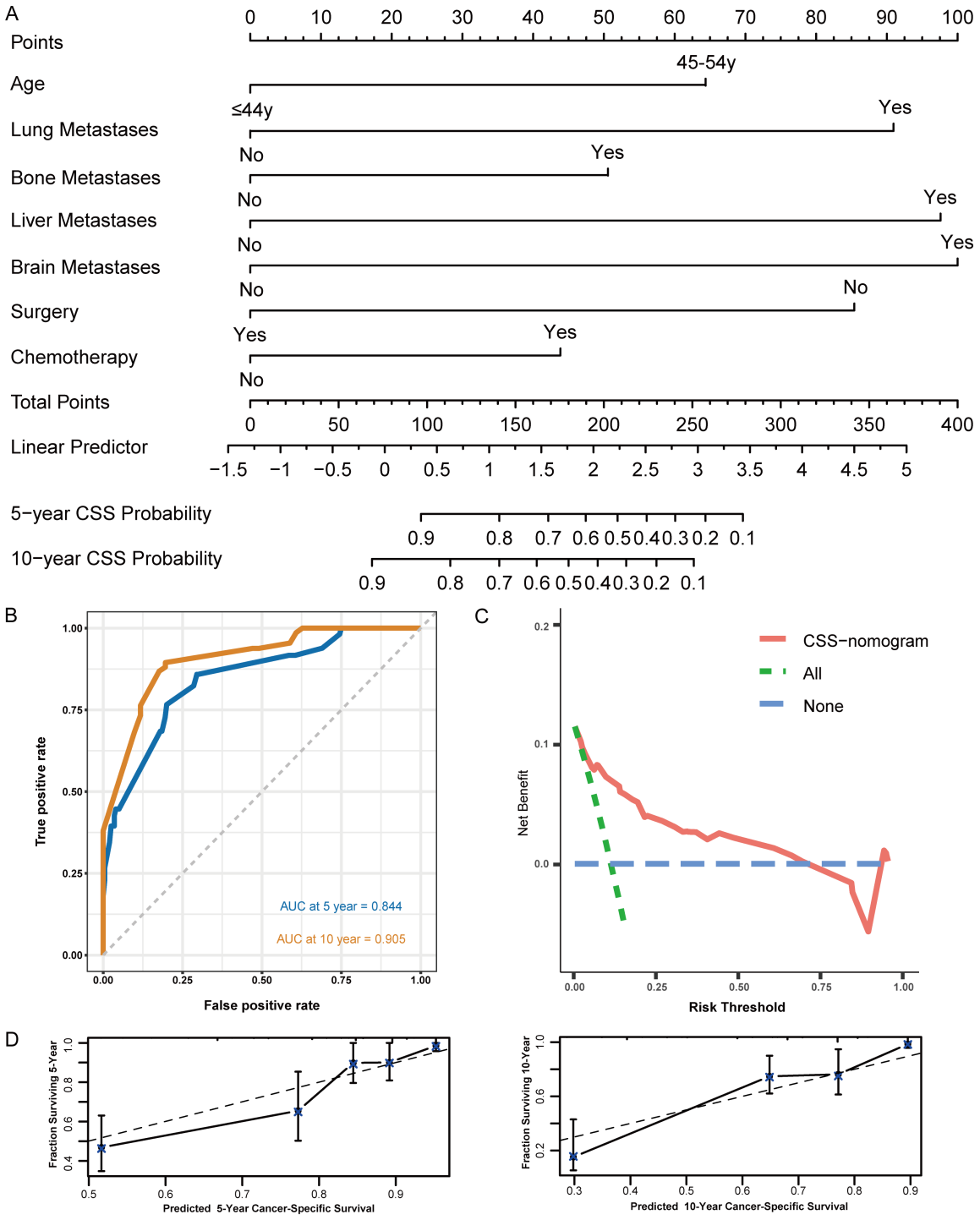

Figure 6. Establishment and validation of CSS-nomogram for predicting CSS among young patients with differentiated thyroid carcinoma (DTC) (A). ROC curve for CSS-nomogram (B); Decision curve analysis (DCA) for CSS-nomogram (C); Calibration curve for CSS-nomogram (D).

immune surveillance [17, 18]. However, our finding indicate that pediatric DTC patients (aged less than 18 year) have the highest potential risk for developing distant metastases. This is consistent with previous reports suggesting the relatively malignant biological behavior and treatment challenges associated with this specific pediatric DTC [19].

The identification of age, male sex, follicular histology, and advanced T/N stages as independent risk factors for distant metastases underscores the interplay between demographic, pathological, and molecular drivers in metastatic progression. The significant risk elevation associated with T3/T4 tumors (OR=22.3) demonstrated the existing evidence that extrathyroidal extension facilitates vascular invasion and systemic spread through VEGF-mediated angiogenesis [20, 21]. Similarly, the male predominance in DM cases (40.5% vs. 19.8%) aligns with recent studies highlighting sex-specific disparities in the aggressiveness of DTC, potentially mediated by androgen receptor signaling pathways [22-24]. The increased risk of distant metastasis in FTC compared to PTC subtypes (OR=2.43) may be attributed to FTC's propensity for angioinvasion and RAS mutations, which drive distant dissemination [25, 26]. This finding necessitates stricter follow-up for FTC patients, including baseline bone scans and chest CT. Our findings extend prior SEER-based machine learning models by quantifying the hierarchical contributions of these variables through a nomogram, achieving superior discriminative performance [10, 11, 16].

The survival analysis reveals significant difference between metastatic and non-metastatic cohorts, with 10-year CSS rates plummeting from over 90% to 79.9% in patients with distant metastasis. This finding aligns with previous data indicating that distant metastasis is the strongest predictor of mortality in thyroid cancer. Notably, brain metastases conferred the highest mortality risk, likely due to the penetration of systemic therapies across the blood-brain barrier and the surgical inaccessibility of these lesions [27]. Furthermore, it should be noted that the limited number of patients with liver or brain metastases contributes to these wide confidence intervals, which may to some extent affect the precision of the results. The protective effect of surgery underscores the importance of controlling the primary tumor, even in metastatic settings. This highlights the necessity of adhering to guidelines that recommended total thyroidectomy for T3/T4 tumors, even in younger patients, to reduce the potential for metastases. In contrast, chemotherapy was associated with increased mortality, which may reflect its selective use in end-stage disease or complications related to treatment, a phenomenon previously documented in SEER-based competing risk models [15]. In addition, chemotherapy is often used for rapidly progressive, radioactive iodine (RAI)-refractory disease, which inherently shows a highly aggressive disease feature and poor prognosis. The observed negative association between chemotherapy and survival may be attributed to selection bias, as patients receiving chemotherapy typically have inherently poorer prognoses. Therefore, the efficacy of chemotherapy requires further evaluation through prospective studies to assess its role specifically in the RAI-refractory population.

The prognostic nomograms demonstrated exceptional accuracy in individualized prognostic stratification. These tools address a critical clinical need, as the current AJCC staging inadequately captures the heterogeneity of young DTC patients, particularly regarding metastatic organ burden. The calibration accuracy of the nomogram and the clinical utility derived from DCA reflect advancements in SEER-driven predictive models. By integrating site-specific metastatic risks, our models facilitate tailored surveillance protocols; for instance, prioritizing central nerve system imaging for high-risk subgroups identified by predictors of brain metastasis. This strategy allows for intensified monitoring in patients with aggressive histology [27].

Despite its strengths, this study has several limitations inherent to SEER-based analysis. First, the most significant confounder in our analysis is the lack of detailed treatment data, particularly radioactive iodine (RAI). SEER does not capture RAI dosage, administration, or response. RAI is the cornerstone of treatment for DTC patients, and its omission represents a major unmeasured variable. Second, SEER does not record critical molecular markers (e.g., BRAF/RAS mutations, NTRK fusions). These factors are increasingly central to risk stratification in DTC and are potent predictors of both metastatic pattern and treatment response. The lack of these information limits the biological insight of our findings and reflects these clinical nomograms lack modern genomic data. Third, for patients with advanced, RAI-refractory disease, the use of tyrosine kinase inhibitors (e.g., lenvatinib, sorafenib) is a key determinant of survival. SEER provides no information on

these therapies. Therefore, this limits the generalizability of the survival predictive model in the contemporary cohorts treated with modern systemic therapy strategies. Forth, the study utilized the AJCC 7th edition criteria due to SEER's delayed adoption of the 8th edition [28], particularly concerning the reclassification of T3 with microscopic extrathyroidal extension, which may affect the accuracy of the nomograms. Last, the analysis was restricted to cases were identified between 2010 and 2021, as SSER standardized documentation of distant metastases began in 2010, thereby precluding an analysis of epidemiological trends prior to 2010. In addition, while internal validation strategies (C-index, ROC analysis, calibration curve) support model robustness, external validation in independent cohorts is warranted but currently hindered by the rarity of distant metastasis in young DTC patients. Therefore, future research should validate these nomograms prospectively and investigate the molecular mechanisms underlying the observed disparities.

Conclusion

This study presented the first comprehensive characterization of the epidemiology and prognosis of distant metastases in young DTC patients. It established validated nomograms for risk stratification and survival prediction. This research enhances our understanding of this rare metastatic pattern; however, further studies are warranted to validate these findings.

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Disclosure of conflict of interest

None.

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References

[1] Houten PV, Netea-Maier RT and Smit JW. Differentiated thyroid carcinoma: an update. Best Pract Res Clin Endocrinol Metab 2023; 37: 101687.

[2] Boucai L, Zafereo M and Cabanillas ME. Thyroid cancer: a review. JAMA 2024; 331: 425-435.

[3] Sugino K, Nagahama M, Kitagawa W, Ohkuwa K, Matsuzu K, Suzuki A, Tomoda C, Hames KY, Akaishi J, Masaki C, Yoshioka K and Ito K. Cut-off age between pediatric and adult thyroid differentiated cancer: is 18 years old appropriate? Thyroid 2022; 32: 145-152.

[4] Kazaure HS, Roman SA and Sosa JA. The impact of age on thyroid cancer staging. Curr Opin Endocrinol Diabetes Obes 2018; 25: 330-334.

[5] Genpeng L, Yuting S, Xinyi W, Tao W, Rixiang G, Zhihui L, Jingqiang Z and Jianyong L. Assessment of age as different variable types for determining survival in differentiated thyroid cancer. Endocrine 2022; 78: 104-113.

[6] Kim K, Kim JH, Park IS, Rho YS, Kwon GH and Lee DJ. The updated AJCC/TNM staging system for papillary thyroid cancer (8th edition): from the perspective of genomic analysis. World J Surg 2018; 42: 3624-3631.

[7] Maggiore R, Perticone F, Mari G, Pasquali R, Bosi E, Scavini M, Lanzi R and Rosati R. Impact of the 8(th) edition of the AJCC-TNM staging system on estimated cancer-specific survival in patients aged 45-54 years at diagnosis with differentiated thyroid carcinoma: a single center report. Int J Endocrinol 2021; 2021: 8820364.

[8] Morosán Allo YJ, Bosio L, Morejón A, Parisi C, Faingold MC, Ilera V, Gauna A and Brenta G. Comparison of the prognostic value of AJCC cancer staging system 7th and 8th editions for differentiated thyroid cancer. BMC Endocr Disord 2022; 22: 146.

[9] Qian ZJ, Jin MC, Meister KD and Megwalu UC. Pediatric thyroid cancer incidence and mortality trends in the United States, 1973-2013. JAMA Otolaryngol Head Neck Surg 2019; 145: 617-623.

[10] Wilhelm A, Conroy PC, Calthorpe L, Shui AM, Kitahara CM, Roman SA and Sosa JA. Disease-specific survival trends for patients presenting with differentiated thyroid cancer and distant metastases in the United States, 1992-2018. Thyroid 2023; 33: 63-73.

[11] Chen DW, Carr G, Worden FP, Veenstra CM, Haymart MR and Banerjee M. Survival prognostication in patients with differentiated thyroid cancer and distant metastases: a SEER population-based study. Thyroid 2024; 34: 837-845.

[12] Liu Z, Chen S, Huang Y, Hu D, Zeng W, Wang M, Zhou W, Chen D, Feng H, Wei W, Zhang C, Zhou L and Guo L. Synergic effects of histology sub-

type, tumor size, and lymph node metastasis on distant metastasis in differentiated thyroid cancer. Ann Transl Med 2019; 7: 533.
[13] Vuong HG, Duong UNP, Pham TQ, Tran HM, Oishi N, Mochizuki K, Nakazawa T, Hassell L, Katoh R and Kondo T. Clinicopathological risk factors for distant metastasis in differentiated thyroid carcinoma: a meta-analysis. World J Surg 2018; 42: 1005-1017.
[14] Ma Q, Chen Z, Fang Y, Wei X, Wang N, Zhou X, Li S and Ying C. Development and validation of survival nomograms for patients with differentiated thyroid cancer with distant metastases: a SEER Program-based study. J Endocrinol Invest 2024; 47: 115-129.
[15] Jin S, Yang X, Zhong Q, Liu X, Zheng T, Zhu L and Yang J. A predictive model for the 10-year overall survival status of patients with distant metastases from differentiated thyroid cancer using XGBoost algorithm-a population-based analysis. Front Genet 2022; 13: 896805.
[16] Wang W, Shen C and Yang Z. Nomogram individually predicts the risk for distant metastasis and prognosis value in female differentiated thyroid cancer patients: a SEER-based study. Front Oncol 2022; 12: 800639.
[17] Li Z, Jia LI, Zhou HR, Zhang LU, Zhang M, Lv J, Deng ZY and Liu C. Development and validation of potential molecular subtypes and signatures of thyroid carcinoma based on aging-related gene analysis. Cancer Genomics Proteomics 2024; 21: 102-117.
[18] Thompson GR, Yu F, Han S, Tushoski-Aleman G, McKean JA, Hughes SJ and Shirali AS. Age-associated alterations in cytokine and extracellular matrix remodeling in the papillary thyroid cancer tumor microenvironment. Ann Surg Oncol 2026; 33: 1739-1747.
[19] Kim SM, Kim SY, Park CS, Chang HS and Park KC. Impact of age-related genetic differences on the therapeutic outcome of papillary thyroid cancer. Cancers (Basel) 2020; 12: 448.
[20] Wang H, Zhao S, Yao J, Yu X and Xu D. Factors influencing extrathyroidal extension of papillary thyroid cancer and evaluation of ultrasonography for its diagnosis: a retrospective analysis. Sci Rep 2023; 13: 18344.
[21] Abuduwaili M, Su A, Xing Z, Xia B, Wu Z, Fei Y, Zhu J and Chen Z. Clinical significance of extrathyroidal extension to major vessels in papillary thyroid carcinoma. J Endocrinol Invest 2023; 46: 1155-1167.
[22] Morand GB, Tessler I, Krasner J, Pusztaszeri MP, Yamin T, Gecel NA, Avior G and Payne RJ. Investigation of genetic sex-specific molecular profile in well-differentiated thyroid cancer: Is there a difference between females and males? Clin Otolaryngol 2023; 48: 748-755.
[23] Kwon H, Schafer JM, Song NJ, Kaneko S, Li A, Xiao T, Ma A, Allen C, Das K, Zhou L, Riesenberg B, Chang Y, Weltge P, Velegraki M, Oh DY, Fong L, Ma Q, Sundi D, Chung D, Li X and Li Z. Androgen conspires with the CD8(+) T cell exhaustion program and contributes to sex bias in cancer. Sci Immunol 2022; 7: eabq2630.
[24] Yang C, Jin J, Yang Y, Sun H, Wu L, Shen M, Hong X, Li W, Lu L, Cao D, Wang X, Sun J, Ye Y, Su B and Deng L. Androgen receptor-mediated CD8(+) T cell stemness programs drive sex differences in antitumor immunity. Immunity 2022; 55: 1268-1283, e1269.
[25] Riccio I, Laforteza A, Landau MB, Hussein MH, Linhuber J, Staav J, Issa PP, Toraih EA and Kandil E. Decoding RAS mutations in thyroid cancer: a meta-analysis unveils specific links to distant metastasis and increased mortality. Am J Otolaryngol 2025; 46: 104570.
[26] Hernandez-Prera JC and Wenig BM. RAS-mutant follicular thyroid tumors: a continuous challenge for pathologists. Endocrine Pathology 2024; 35: 167-184.
[27] Prinzi A, van Velsen EFS, Belfiore A, Frasca F and Malandrino P. Brain metastases in differentiated thyroid cancer: clinical presentation, diagnosis, and management. Thyroid 2024; 34: 1194-1204.
[28] Lamartina L, Grani G, Arvat E, Nervo A, Zatelli MC, Rossi R, Puxeddu E, Morelli S, Torlontano M, Massa M, Bellantone R, Pontecorvi A, Montesano T, Pagano L, Daniele L, Fugazzola L, Ceresini G, Bruno R, Rossetto R, Tumino S, Centanni M, Meringolo D, Castagna MG, Salvatore D, Nicolucci A, Lucisano G, Filetti S and Durante C. 8th edition of the AJCC/TNM staging system of thyroid cancer: what to expect (ITCO#2). Endocr Relat Cancer 2018; 25: L7-L11.