Heliyon 10 (2024) e24798

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Establishment and verification of the first prognostic nomograms in locally advanced thyroid cancer based on the analysis of clinical and follow-up information on 2396 patients

Yonghao Li [a], Huiqiang Zhang [a], Yifan Cao [b], Ningyu He [a], Weichao Li [a], Xuefei Gao [a], Tiantian Guo [a], Jing Liu [c,*]

[a] The First Clinical Medical College of Shanxi Medical University, Taiyuan, 030001, Shanxi, China
[b] The Fifth Clinical Medical College of Shanxi Medical University, Taiyuan, 030001, Shanxi, China
[c] Department of Thyroid Surgery, The First Hospital of Shanxi Medical University, Taiyuan, 030001, Shanxi, China

ARTICLE INFO

Keywords:
Extrathyroidal extension (ETE)
Cancer-specific survival (CSS)
Overall survival (OS)
Locally advanced thyroid cancer (LATC)
Prognosis nomograms
Risk stratificatio

ABSTRACT

Background and objectives: The purpose of this research was to develop and validate the first prognostic nomograms for 3-, 5-, and 10-year cancer-specific survival (CSS) and overall survival (OS) in patients diagnosed with locally advanced thyroid cancer (LATC) by evaluating independent predictors of prognosis in a population of LATC patients.

Methods: Demographics, clinicopathologic characteristics, treatment, and follow-up of 2396 LATC patients in the surveillance, epidemiology, and end results database from 2004 to 2015 were retrospectively analyzed and compared with patients with LATC according to staging. We randomized all LATC patients into training and validation groups in a 7:3 ratio. Cox regression analyses helped us to derive independent prognostic factors for LATC patients. According to these results, we established and validated the first prognostic nomograms and risk stratification.

Results: In our research, the clinical information of LATC patients was compared and significant differences were found in the relevant variables including CSS and OS ($P < 0.05$), with CSS of 82.0 % and 49.0 %, and OS of 70.6 % and 40.0 %, respectively. Cox regression analyses showed that age at diagnosis, tumor diameter, presence of DM, extrathyroidal extension sites, histological type, thyroidectomy scope, radiotherapy status, and chronological sequence of radiotherapy and surgery were observably correlated with CSS in LATC patients, and in addition to the above factors, gender, marital status, and chemotherapy status were also observably correlated with OS in LATC patients. The prognostic predictive power of the above factors is visualized by the Kaplan-Meier survival curve. The concordance index of nomograms for CSS and OS were 0.933, 0.925, and 0.926 (CSS), 0.918, 0.909, and 0.906 (OS), respectively, and the time-dependent receiver operating characteristic curve, area under curve, calibration curve and decision curve analysis curve indicate that the nomograms have good discriminatory ability, accuracy and clinical applicability in both the training and validation groups.

Conclusions: In these findings, we drawed a conclusion that there were significant differences in clinical information between patients with T4a and T4b LATC, and we established and validated the first prognostic nomograms and risk stratification of CSS and OS for LATC patients at 3, 5, and

* Corresponding author.
E-mail address: liujing5585@163.com (J. Liu).

https://doi.org/10.1016/j.heliyon.2024.e24798
Received 9 October 2023; Received in revised form 11 January 2024; Accepted 15 January 2024
Available online 30 January 2024

10 years, which will help clinicians to individualize their postoperative treatment and individualized follow-up.

1. Introduction

In the past several years, the incidence of thyroid cancer (TC) has increased rapidly worldwide [1], and although the majority of differentiated thyroid cancer (DTC) has a favorable prognosis, the 10-year disease-specific mortality rate for locally advanced thyroid cancer (LATC) can be as high as 38.3 % [2]. LATC is defined as TC with the invasion of surrounding vital organs or structures at the time of initial diagnosis or persistent or recurrent lesions, i.e., primary foci or metastatic lymph nodes invading the recurrent laryngeal nerves, trachea, esophagus, larynx, large blood vessels of the neck, upper mediastinum, or extensive cutaneous muscles with or without distant metastasis (DM). Previous studies have reported the incidence of LATC to be about 4 %–15 % with a poor prognosis, and studies have shown that LATC is one of the major causes of death and recurrence in TC [2–4]. LATC can involve various types of TCs, and its treatment and prognostic management remain the current focus and difficulty in the field of thyroid surgery because of the difficulty and limited effectiveness of its treatment, and because some tumors are inoperable or difficult to be completely resected by surgery.

The most widely used method for evaluating TC survival clinically is the American Joint Committee on Cancer (AJCC) TNM staging, which divides TC invasion of different surrounding organs into different T stages from the perspective of the primary focus, such as dividing TC invasion of the laryngeal recurrent nerve, trachea, esophagus, or subcutaneous soft tissues into the T4a stage, and invasion of the prevertebral fascia or encircling the carotid artery or superior mediastinal vessels is classified as T4b stage [5]. Stage T4a and T4b patients aged <55 years were stage I, with a 10-year cancer-specific survival (CSS) of 97 %–100 %, whereas stage T4a patients aged >55 years were stage III, and stage T4b patients were stage IVA, with a 10-year CSS of 70 %–80 % and 48.5 %–60 %, respectively [6]. It is worth noting that the TNM staging included only tumor diameter, presence or absence of extrathyroidal extension (ETE), lymph node metastasis (LNM) and DM, it did not include patient gender, marital status, specific ETE site, multifocal nature, specific histopathological type, detailed surgical scope, and other treatment details. However, the above clinicopathological features do not include population patient information and treatment information that may greatly affect patient prognosis, which is also believed in previous studies [7]. So the current existing evaluation system is still not able to accurately evaluate the specific prognosis of the patients with LATC, and there is a need to develop a more complete prognostic evaluation system for LATC.

Due to the low prevalence of LATC, there is no large-scale population-based study in academia on the prognostic survival of LATC patients, according to the search of Pubmed and Google Scholar databases, there is no clinical prognostic nomogram for LATC established and verified. The SEER database program can provide data on cancer-related incidence, staging, treatment and patient survival for clinical research. This research aimed to construct the first prognostic nomograms for LATC patients in the SEER database by comparing and analysing the demographics, clinicopathologic characteristics, treatment, and follow-up of 2396 LATC patients and deriving the relevant predictive factors affecting their prognostic situation, to validate and risk-stratify the prognostic nomograms of LATC patients.

2. Materials and methods

2.1. Patient population

The clinical information of the patients in this research was obtained from the SEER*STAT8.4.2 database, which retrospectively analyzed 124895 patients with pathologically confirmed thyroid malignancies between 2004 and 2015, and a total of 5765 patients staged

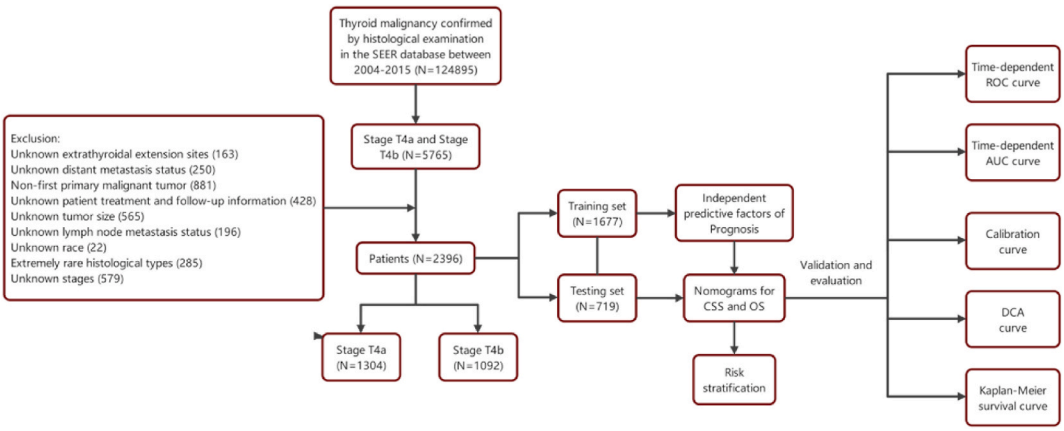


Fig. 1. The flowchart of the LATC patients screening for this research.

Table 1
Demographics, clinicopathologic characteristics, treatment, and follow-up of 2396 locally advanced thyroid cancer patients.

Variables	Overall (N = 2396)					
	Stage T4a (N = 1304)	Stage T4b (N = 1092)	*P value*	Training set (N = 1677)	Testing set (N = 719)	*P value*
Age (years)			<0.001			0.442
mean (±sd)	55.80 (±16.235)	62.00 (±15.926)		58.46 (±16.272)	59.01 (±16.648)	
M(IQR)	56 (44,68)	63 (52,74)		60 (47,71)	60 (47,72)	
Sex			0.192			0.094
Female	855 (65.6 %)	688 (63.0 %)		1062 (63.3 %)	481 (66.9 %)	
Male	449 (34.4 %)	404 (37.0 %)		615 (36.7 %)	238 (33.1 %)	
Marital status			0.111			0.728
Married	808 (62.0 %)	635 (58.2 %)		1011 (60.3 %)	432 (60.1 %)	
Unmarried	456 (35.0 %)	427 (39.1 %)		620 (37.0 %)	263 (36.6 %)	
Unknown	40 (3.1 %)	30 (2.7 %)		46 (2.7 %)	24 (3.3 %)	
Race			<0.001			0.651
White	1009 (77.4 %)	880 (80.6 %)		1330 (79.3 %)	559 (77.7 %)	
Black	52 (4.0 %)	73 (6.7 %)		84 (5.0 %)	41 (5.7 %)	
Other*	243 (18.6 %)	139 (12.7 %)		263 (15.7 %)	119 (16.6 %)	
Sites of ETE			<0.001			0.444
Strap muscles or surrounding tissue	0 (0.0 %)	66 (6.0 %)		50 (3.0 %)	16 (2.2 %)	
Parathyroid or nerves (vagus or recurrent laryngeal)	494 (37.9 %)	13 (1.2 %)		350 (20.9 %)	153 (21.3 %)	
Cricoid cartilage, esophagus, larynx or sternocleidomastoid muscle	320 (24.5 %)	31 (2.8 %)		237 (14.1 %)	114 (15.9 %)	
Thyroid cartilage	0 (0.0 %)	80 (7.3 %)		57 (3.4 %)	23 (3.2 %)	
Blood vessels	0 (0.0 %)	192 (17.6 %)		140 (8.3 %)	52 (7.2 %)	
Bone or Skeletal muscle (Except for strap or sternocleidomastoid muscle)	0 (0.0 %)	331 (30.3 %)		245 (14.6 %)	86 (12.0 %)	
Trachea	490 (37.6 %)	147 (13.5 %)		443 (26.4 %)	198 (27.5 %)	
Mediastinal tissues or Prevertebral fascia	0 (0.0 %)	232 (21.2 %)		155 (9.2 %)	77 (10.7 %)	
Tumor size(mm)			<0.001			0.975
mean (±sd)	34.53 (±22.923)	51.32 (±30.848)		42.14 (±28.171)	42.29 (±27.935)	
M(IQR)	29 (18,45)	48 (27,70)		35 (21,60)	35 (20,57.5)	
Mulifocality			<0.001			0.734
No	616 (46.8 %)	679 (62.0 %)		906 (54.0 %)	383 (53.5 %)	
Yes	699 (53.2 %)	416 (38.0 %)		771 (46.0 %)	336 (46.7 %)	
Histology			<0.001			0.845
PTC	1140 (87.4 %)	567 (51.9 %)		1199 (71.5 %)	508 (70.7 %)	
CCV-PTC	53 (4.1 %)	42 (3.8 %)		63 (3.8 %)	32 (4.5 %)	
FTC	25 (1.9 %)	56 (5.1 %)		53 (3.2 %)	28 (3.9 %)	
MTC	41 (3.1 %)	37 (3.4 %)		57 (3.4 %)	21 (2.9 %)	
ATC	12 (0.9 %)	348 (31.9 %)		251 (15.0 %)	109 (15.2 %)	
ITC	13 (1.0 %)	10 (0.9 %)		15 (0.9 %)	8 (1.1 %)	
OCA	20 (1.5 %)	32 (2.9 %)		39 (2.3 %)	13 (1.8 %)	
LNM			<0.001			0.935
No LNM	220 (16.9 %)	168 (15.4 %)		268 (16.0 %)	120 (16.7 %)	
CLNM	445 (34.1 %)	245 (22.4 %)		481 (28.7 %)	209 (29.1 %)	
LLNM	323 (24.8 %)	221 (20.2 %)		386 (23.0 %)	158 (22.0 %)	
No LND	316 (24.2 %)	458 (41.9 %)		542 (32.3 %)	232 (32.3 %)	
DM			<0.001			0.084
Absence	1175 (90.1 %)	778 (71.2 %)		1382 (82.4 %)	571 (79.4 %)	
Presence	129 (0.9 %)	314 (28.8 %)		295 (17.6 %)	148 (20.6 %)	
Thyroidectomy scope			<0.001			0.550
None	48 (3.7 %)	226 (20.7 %)		184 (11.0 %)	90 (12.5 %)	
Unilateral thyroidectomy and/or isthectomy	54 (4.1 %)	113 (10.3 %)		118 (7.0 %)	49 (6.8 %)	
Total or subtotal thyroidectomy	1202 (92.2 %)	753 (69.0 %)		1375 (82.0 %)	580 (80.7 %)	
Lymph node dissection			<0.001			0.100
No LND	316 (24.2 %)	458 (41.9 %)		542 (32.3 %)	232 (32.3 %)	
Yes,pLNs≤4	412 (31.6 %)	232 (21.2 %)		470 (28.0 %)	174 (24.2 %)	
Yes,pLNs≥5	576 (44.2 %)	402 (36.9 %)		665 (39.7 %)	313 (43.5 %)	
Radiation			<0.001			0.619
None/Unknown	290 (22.2 %)	340 (31.1 %)		440 (26.2 %)	190 (26.4 %)	
Radioisotopes	862 (66.1 %)	400 (36.6 %)		879 (52.4 %)	383 (53.3 %)	
Beam radiation	118 (9.0 %)	316 (28.9 %)		304 (18.1 %)	130 (18.1 %)	
Both	34 (2.6 %)	36 (3.3 %)		54 (3.2 %)	16 (2.2 %)	
Radiotherapy and surgery time sequence			<0.001			0.962
No radiation and/or surgery	310 (23.8 %)	451 (41.3 %)		529 (31.5 %)	232 (32.3 %)	
Radiation after surgery	986 (75.6 %)	626 (57.3 %)		1131 (67.4 %)	481 (66.9 %)	
Radiation prior to surgery	3 (0.2 %)	9 (0.8 %)		9 (0.5 %)	3 (0.4 %)	
Radiation before and after surgery	5 (0.4 %)	6 (0.5 %)		8 (0.5 %)	3 (0.4 %)	
Chemotherapy			<0.001			0.734

(*continued on next page*)

Table 1 (*continued*)

Variables	Overall (N = 2396)					
	Stage T4a (N = 1304)	Stage T4b (N = 1092)	*P value*	Training set (N = 1677)	Testing set (N = 719)	*P value*
No	1268 (97.2 %)	866 (79.3 %)		1496 (89.2 %)	638 (88.7 %)	
Yes	36 (2.8 %)	226 (20.7 %)		181 (10.8 %)	81 (11.3 %)	
Systemic therapy and surgery time sequence			<0.001			0.779
No systemic therapy and/or surgery	535 (41.0 %)	569 (52.1 %)		782 (46.6 %)	322 (44.8 %)	
Systemic therapy after surgery	743 (57.0 %)	506 (46.3 %)		864 (51.5 %)	385 (53.5 %)	
Systemic therapy prior to surgery	5 (0.4 %)	7 (0.6 %)		8 (0.5 %)	4 (0.6 %)	
Systemic therapy before and after surgery	21 (1.6 %)	10 (0.9 %)		23 (1.4 %)	8 (1.1 %)	
Months from diagnosis to treatment			0.169			0.598
< three months	1146 (87.9 %)	939 (86.0 %)		1464 (87.3 %)	622 (86.5 %)	
≥three months	158 (12.1 %)	153 (14.0 %)		213 (12.7 %)	97 (13.5 %)	
CSS	1069 (82.0 %)	535 (49.0 %)	<0.001	1138 (67.9 %)	466 (64.8 %)	0.146
OS	920 (70.6 %)	436 (40.0 %)	<0.001	962 (57.4 %)	394 (54.8 %)	0.245
Survival months			<0.001			0.703
mean (±sd)	90.89 (±55.49)	55.49 (±54.024)		75.09 (±52.059)	73.98 (±53.106)	
M(IQR)	93 (63,128)	40 (4102)		76 (22,120)	77 (16,119.5)	

Data notes: ETE extrathyroidal extension, PTC papillary thyroid cancer, CCV-PTC columnar cell variant of papillary thyroid cancer, FTC follicular thyroid cancer, MTC medullary thyroid cancer, ATC anaplastic thyroid cancer, OCA oncocytic cancer of thyroid, ITC insular thyroid cancer, LNM lymph node metastasis, CLNM central lymph node metastasis, LLNM lateral lymph node metastasis, LND lymph node dissection, DM distant metastasis, pLNs positive lymph nodes. CSS cancer-specific survival, OS overall survival.

[*] Includes: American Indian, Native Alaskan and Asian, Pacific Islander.

as T4a and T4b were included in the research according to the seventh edition of the AJCC TNM staging system. The exclusion criteria were as follows: (1) patients with unknown race, tumor diameter, ETE sites, DM status, number of lesions, and LNM detail area and number; (2) non-first-time primary tumors; and (3) patients with unknown information about their treatment and follow-up; (4) extremely rare histological types. Since the SEER database does not publish identifiable information from patients, this research did not require special approval from the Ethics Committee of the First Hospital of Shanxi Medical University. All of our authors have signed the author Statement form for this research. A total of 2396 LATC patients were enrolled in this research and were divided into training and testing groups according to a ratio of 7:3 randomly. Fig. 1 shows the flowchart of the LATC patients screening for this research.

2.2. Data selection

The endpoint events in this research were CSS and overall survival (OS), the CSS was described as the time from the date of surgery to date of death due to LATC or date of final follow-up, and OS was described as the time from the date of surgery to date of final follow-up. A total of 17 predictor variables were included in this research to identify independent predictors of CSS and OS in patients with LATC. Demographic variables included gender, race, age at diagnosis, and marital status. Based on the histological coding of TCs in the SEER database, the histological types of LATCs in this research could be classified as: papillary thyroid cancer (PTC) (ICD-*O*-3: 8050/8260/8340/8341/8342/8343), columnar cell variant of papillary thyroid cancer (CCV-PTC) (ICD-*O*-3: 8344), follicular thyroid cancer (FTC) (ICD-*O*-3: 8330/8331/8332/8335), medullary thyroid cancer (MTC) (ICD-*O*-3: 8345/8510), anaplastic thyroid cancer (ATC) (ICD-*O*-3: 8020/8321/8330/8331/8332/8352/8370/8371/8374), oncocytic cancer of thyroid (OCA) (ICD-*O*-3: 8290) and insular thyroid cancer (ITC) (ICD-*O*-3: 8337). Clinicopathological characteristics included histological type, tumor diameter, sites of ETE, LNM area and number, number of tumor foci and presence of DM. Treatment-related variables included thyroidectomy scope, the extent of lymph node dissection (LND), radiotherapy and chemotherapy, chronological order of radiotherapy and systemic therapy about the surgery and the time from the first treatment to diagnosis, respectively. It is important to note that if a patient has ETE at multiple sites, the SEER database usually selects the site that is more severe or more indicative of staging. All methods involved in this research were analyzed in strict accordance with the relevant guidelines of the SEER database.

2.3. Statistical analysis

All statistical analyses in this research were applied using R software (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria) (http://www.r-project.org/(version 26; IBM Corp., Armonk, NY). We divided all LATC patients according to their stage (T4a and T4b) and subsequently compared the relevant variables by $\chi 2$ test, two independent samples T-test, and non-parametric rank-sum test, in addition we divided all patients into training and testing groups according to a ratio of 7:3 randomly, and subsequently compared the relevant variables between the two groups. Further analysis was facilitated by the use of X-tile software to determine optimal thresholds for age and tumor diameter in the LATC patient population. Independent predictors were evaluated using univariate Cox regression analysis, which allowed us to screen out variables that might be relevant to patient survival from a wide range of variables that could be part of the model construction. We use the P values in univariate analysis. Variables with P-values <0.1 were included in multivariate Cox regression analysis. Multivariate analysis can evaluate the relationship between different variables and the survival of patients, and then select the most closely related variables to construct a final prognostic nomogram, with

P-values <0.05 considered statistically significant and identified as the final independent predictors of CSS and OS in LATC patients. The hazard ratio (HR) and 95 % confidence intervals (95 % CI) were counted. Subsequently, the nomograms were plotted using R software, and the C index (consistency index), time-dependent subject operating characteristic curve (ROC) curves and time-dependent area under the time-dependent curve (AUC) curves were used to assess the predictive performance of prognostic nomograms. We assessed the precision and clinical value of the nomograms by drawing calibration curves and decision curve analysis (DCA) curves. In addition, we validated and evaluated the model through a testing group using the methods described above. The Kaplan-Meier survival curves reflect the effect of predictors on CSS and OS in LATC patients. The risk score thresholds in the nomograms were derived by calculating the Jordon's index and the group of LATC patients was classified into two subtypes, low and high risk, in addition, we plotted risk factor maps to visualize the prognosis of the LATC patients in this research.

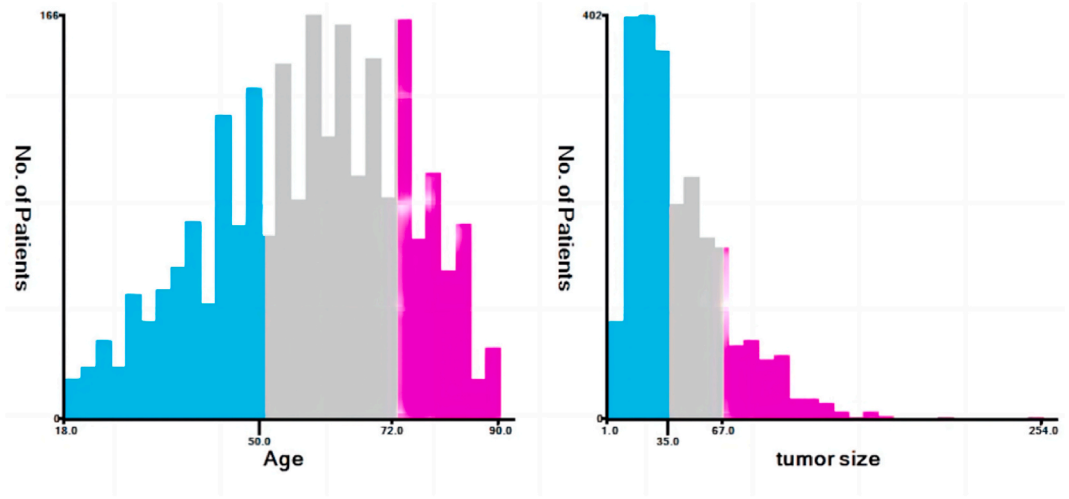
3. Results

3.1. Demographics, clinicopathologic characteristics, treatment, and follow-up of 2396 LATC patients

A total of 2396 LATC patients were included in this retrospective research, including 1304 patients with stage T4a and 1092 patients with stage T4b. We compared demographic, clinicopathological characteristics, treatment, and follow-up information between the two. As shown in Table 1, there were significant differences ($P < 0.05$) in all 17 variables except gender, marital status and time from first treatment to diagnosis. The most common sites of ETE in patients with stage T4a LATC were the parathyroid glands and nerves (37.9 %), whereas it was the mediastinal tissues or anterior vertebral fascia in patients with stage T4b (21.2 %), and there was a large difference between the two in terms of tumor diameter, with their mean diameters of 34.53 mm (±22.923) and 51.32 mm (±30.848), respectively. Meanwhile, the incidence of DM was much higher in the T4b stage LATC patient group than in the T4a stage patient group (28.8 % vs 0.9 %), but the percentage of total or subtotal thyroidectomy and the percentage of LND were lower in the T4b stage patient group than in the T4a stage patient group (69.0 % vs 92.2 % and 58.1 % vs 75.8 %), and the percentage of chemotherapy was performed at a higher rate than the T4a stage patient group (20.7 % vs 2.8 %). Meanwhile, there were also large differences in survival status, with CSS of 82.0 % and 49.0 %, OS of 70.6 % and 40.0 %, and median survival time of 93 months and 40 months for T4a and T4b patients, respectively, in this research. All patients were divided into the training group (1677 patients) and the testing group (719 patients) randomly, and there was no significant difference in the relevant factors between the two ($P > 0.05$).

3.2. Development and validation of the first clinical prognostic nomograms for LATC patients

The cut-off values for continuous variables in LATC patients were reached by X-tile software analysis, with optimal cut-off values for age at diagnosis of 50 and 72 years, and optimal cut-off values for tumor diameter of 35 mm and 67 mm, as detailed in Fig. 2. Cox regression analyses according to this classification criteria concluded independent predictors of CSS and OS in LATC patients (Tables 2 and 3), and age at diagnosis, tumor diameter, sites of the ETE, histological type, the presence or absence of DM, the extent of thyroidectomy scope, radiotherapy, and the sequential chronological order of radiotherapy and surgery were observably associated with CSS in LATC patients ($P < 0.05$), and in addition to the above factors, gender, marital status and chemotherapy were also observably associated with OS in patients with LATC ($P < 0.05$). Based on these findings, we developed the first prognostic nomograms for CSS and OS in the group of LATC patients (Fig. 3a/b).



(a) (b)

Fig. 2. The appropriate cut-off values for age(**a**) and tumor size(**b**) were identified by X-tile software.

Table 2
Univariate and multivariate Cox regression analyses were used to analyze the CSS.

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	P value	HR (95 % CI)	P value
Age (years)		<0.001		
≤50	1		1	
51–71	6.320 (4.457–8.961)		4.247 (2.979–6.057)	<0.001
≥72	15.482 (10.892–22.007)		8.390 (5.816–12.104)	<0.001
Sex		<0.001		
Female	1			
Male	1.476 (1.245–1.749)			
Marital status		0.011		
Married	1			
Unmarried	1.258 (1.058–1.496)			
Unknown	0.682 (0.363–1.280)			
Race		0.046		
White	1			
Black	1.368 (0.960–1.949)			
Other*	0.820 (0.641–1.049)			
Sites of ETE		<0.001		
Strap muscles or surrounding tissue	1		1	
Parathyroid or nerves (vagus or recurrent laryngeal)	0.069 (0.044–0.107)		0.420 (0.261–0.677)	<0.001
Cricoid cartilage, esophagus, larynx or sternocleidomastoid muscle	0.172 (0.115–0.258)		0.556 (0.365–0.848)	0.006
Thyroid cartilage	0.231 (0.132–0.404)		0.517 (0.293–0.912)	0.023
Blood vessels	0.364 (0.243–0.545)		0.735 (0.483–1.120)	0.152
Bone or Skeletal muscle (Except for strap or sternocleidomastoid muscle)	0.193 (0.130–0.288)		0.733 (0.483–1.112)	0.144
Trachea	0.276 (0.194–0.392)		0.778 (0.537–1.126)	0.183
Mediastinal tissues or Prevertebral fascia	0.652 (0.449–0.947)		0.690 (0.469–1.013)	0.058
Tumor size(mm)		<0.001		
≤35	1		1	
36–66	3.552 (2.870–4.396)		1.863 (1.483–2.341)	<0.001
≥67	6.554 (5.242–8.193)		2.088 (1.613–2.703)	<0.001
Mulifocality		<0.001		
No	1			
Yes	0.566 (0.474–0.676)			
Histology		<0.001		
PTC	1		1	
CC-PTC	3.150 (2.149–4.618)		1.801 (1.211–2.677)	0.004
FTC	2.730 (1.743–4.275)		0.850 (0.528–1.368)	0.503
MTC	3.788 (2.612–5.495)		1.941 (1.306–2.885)	0.001
ATC	17.329 (14.142–21.235)		4.024 (3.082–5.254)	<0.001
ITC	4.476 (2.373–8.443)		1.274 (0.664–2.443)	0.466
OCA	3.149 (1.970–5.036)		1.368 (0.829–2.258)	0.221
LNM		<0.001		
No LNM	1			
CLNM	0.335 (0.267–0.421)			
LLNM	0.437 (0.349–0.547)			
No LND	0.369 (0.281–0.484)			
DM		<0.001		
Absence	1		1	
Presence	5.880 (4.934–7.007)		3.276 (2.680–4.005)	<0.001
Thyroidectomy scope		<0.001		
None	1		1	
Unilateral thyroidectomy and/or isthectomy	0.344 (0.258–0.459)		0.543 (0.376–0.783)	0.001
Total or subtotal thyroidectomy	0.083 (0.068–0.102)		0.421 (0.306–0.579)	<0.001
Lymph node dissection		<0.001		
No LND	1			
Yes,pLNs≤4	0.361 (0.289–0.451)			
Yes,pLNs≥5	0.389 (0.320–0.473)			
Radiation		<0.001		
None/Unknown	1		1	
Radioisotopes	0.207 (0.164–0.262)		0.276 (0.181–0.422)	<0.001
Beam radiation	2.117 (1.736–2.580)		0.582 (0.421–0.803)	0.001
Both	0.879 (0.579–1.334)		0.683 (0.401–1.161)	0.159
Radiotherapy and surgery time sequence		<0.001		
No radiation and/or surgery	1		1	
Radiation after surgery	0.329 (0.277–0.390)		1.648 (1.115–2.434)	0.012
Radiation prior to surgery	0.751 (0.280–2.017)		0.736 (0.259–2.090)	0.565
Radiation before and after surgery	1.409 (0.627–3.165)		1.839 (0.720–4.697)	0.203
Chemotherapy		<0.001		
No	1			

(*continued on next page*)

Table 2 (*continued*)

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	P value	HR (95 % CI)	P value
Yes	4.972 (4.085–6.052)			
Systemic therapy and surgery time sequence		<0.001		
No systemic therapy and/or surgery	1			
Systemic therapy after surgery	0.616 (0.519–0.731)			
Systemic therapy prior to surgery	1.401 (0.522–3.757)			
Systemic therapy before and after surgery	0.474 (0.196–1.148)			
Months from diagnosis to treatment		<0.001		
< three months	1			
≥ three months	1.610 (1.282–2.021)			

The C-index of the prognostic nomograms for CSS and OS in the group of LATC patients were 0.933, 0.925 and 0.926 (CSS), 0.918, 0.909 and 0.906 (OS) at 3, 5 and 10 years, respectively (Fig. 4), and the time-dependent AUC curves (Fig. 5) can show the trend of changes in the C-index of each factor and model, thus reflecting the great discriminative ability of the above models, and it can be seen that the nomograms have better predictive ability compared with the individual elements. In addition, we plotted 3-, 5- and 10-year calibration curves (Fig. 6) and DCA curves (Fig. 7, Fig. 8) of the nomograms of CSS and OS for the model, which can be concluded that the nomograms perform excellently in terms of predictive accuracy and clinical applicability. The Kaplan-Meier survival curves also showed the strong predictive performance of each factor (Fig. 9). In addition, the model performed equally well in the testing set, with C-indexes of 0.957, 0.950, and 0.936 (CSS), 0.945, 0.928, and 0.922 (OS) for the prognostic models of CSS and OS at 3, 5, and 10 years, respectively (Supplementary Figure 1), and the calibration curves and DCA curves once again demonstrated the nomograms' high predictive and clinical applicability (Supplementary Figure 2, Figs. 3 and 4).

3.3. Risk stratification of patients with LATC based on CSS and OS prognostic nomograms

We predicted the survival status of the LATC patient group by summing the predicted scores corresponding to the different variables in the prognostic plot and calculating the total score. As shown in Table 4, we categorized the LATC patient group into low-risk and high-risk groups by calculating the critical value of the risk score. The actual survival rates of the LATC patients in the training set obtained by the CSS prognostic nomogram with the total score and according to this classification criterion were 92.8 % and 43.2 % for the low-risk group and the high-risk group ($P < 0.001$), and the actual survival rates of the two groups obtained by the OS prognostic nomogram with the total score according to this classification criterion were 71.2 % and 6.9 % ($P < 0.001$). The actual survival rates for the group of LATC patients in the testing set according to the above division criteria were 90.9 % vs 38.0 % (CSS) ($P < 0.001$) and 74.9 % vs 6.2 % (OS) ($P < 0.001$), respectively. Risk factor maps demonstrated significant differences in population share, survival time, and prognostic status between high- and low-risk groups of LATC patients (Fig. 10).

4. Discussion

The 5-year survival rate of LATC ranges from 29 % to 96 %, and the recurrence rate ranges from 23 % to 61.5 %, which is one of the major causes of death and recurrence in TC [2,3,8], and the prevalence rate of LATC in all types of TC in this study was 4.6 %, which is comparable to previous studies [4]. Our study compared LATC according to different stages and found that patients with stage T4a differed significantly from those with stage T4b in 17 variables including CSS, OS, and DM status, which suggests that for patients with LATC, different sites of ETE occurrence may be a key factor affecting their treatment and prognosis. By analyzing a group of LATC patients and focusing on their risk of local recurrence, DM, and OS, Marco et al. [9] concluded that the most common site of ETE of LATC is the recurrent laryngeal nerve, and that LATC exhibits a more aggressive biological process and should be managed more decisively. By analyzing the detailed clinicopathological features and treatment follow-up information of 2396 LATC patients in the SEER database, our study covered the clinical information during the treatment of LATC patients to the maximum extent, so as to establish and verify a high-accuracy clinical prognosis prediction model, which was not available in previous studies.

In this research, we subdivided the portion of LATC patients who developed ETE into parathyroid or nerves (vagus or recurrent laryngeal nerves), cricoid cartilage, esophagus, larynx or sternocleidomastoid muscle, thyroid cartilage, bone or skeletal muscle (except for strap or sternocleidomastoid muscle), trachea, blood vessels, mediastinal tissues or prevertebral fascia and strap muscles or surrounding tissue. We concluded that the specific site of ETE was an independent prognostic predictor of CSS and OS in the LATC patients, and that LATC patients tended to have a poorer prognosis when the sites of ETE were located in the strap muscles, vasculature, trachea, and mediastinal tissues, or the prevertebral fascia. By matching the occurrence of ETE in different parts of PTC patients in the SEER database, Xu et al. [10]concluded that ETE in soft tissues or other organs was a high-risk factor for PTC, and PTC patients with belt muscle ETE were older (≥55 years old) and had larger tumor size (>2 cm) is very important for prognosis impairment, especially CSS. This is very consistent with the view of our study. Kim et al. [11] concluded that the incidence of tracheal invasion in DTC patients was 3.39 %, and the incidence of ETE in the trachea was 26.8 %. Shin et al. [12] classified the trachea into 4 grades according to the degree of tracheal involvement (grade I invades the tracheal epithelium, grade II invades the tracheal cartilage to varying degrees, grade III invades deep into the lamina propria of the tracheal mucosa, and grade IV invades the lumen of the trachea) and concluded that if the tumor does not invade the lumen of the trachea it has a little prognostic impact on patients with LATC, whereas when it does

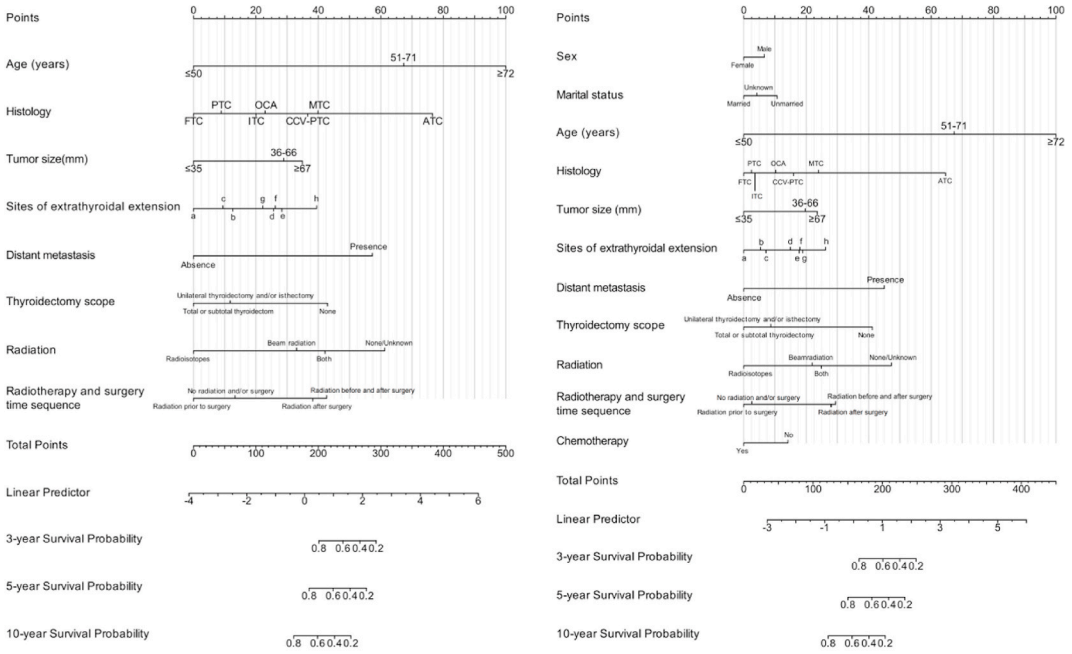
Table 3
Univariate and multivariate Cox regression analyses were used to analyze the OS.

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Age (years)		<0.001		
≤50	1		1	
51–71	6.320 (4.457–8.961)		4.247 (2.979–6.057)	<0.001
≥72	15.482 (10.892–22.007)		8.390 (5.816–12.104)	<0.001
Sex		<0.001		
Female	1			
Male	1.476 (1.245–1.749)			
Marital status		0.011		
Married	1			
Unmarried	1.258 (1.058–1.496)			
Unknown	0.682 (0.363–1.280)			
Race		0.046		
White	1			
Black	1.368 (0.960–1.949)			
Other*	0.820 (0.641–1.049)			
Sites of ETE		<0.001		
Strap muscles or surrounding tissue	1		1	
Parathyroid or nerves (vagus or recurrent laryngeal)	0.069 (0.044–0.107)		0.420 (0.261–0.677)	<0.001
Cricoid cartilage, esophagus, larynx or sternocleidomastoid muscle	0.172 (0.115–0.258)		0.556 (0.365–0.848)	0.006
Thyroid cartilage	0.231 (0.132–0.404)		0.517 (0.293–0.912)	0.023
Blood vessels	0.364 (0.243–0.545)		0.735 (0.483–1.120)	0.152
Bone or Skeletal muscle (Except for strap or sternocleidomastoid muscle)	0.193 (0.130–0.288)		0.733 (0.483–1.112)	0.144
Trachea	0.276 (0.194–0.392)		0.778 (0.537–1.126)	0.183
Mediastinal tissues or Prevertebral fascia	0.652 (0.449–0.947)		0.690 (0.469–1.013)	0.058
Tumor size(mm)		<0.001		
≤35	1		1	
36–66	3.552 (2.870–4.396)		1.863 (1.483–2.341)	<0.001
≥67	6.554 (5.242–8.193)		2.088 (1.613–2.703)	<0.001
Mulifocality		<0.001		
No	1			
Yes	0.566 (0.474–0.676)			
Histology		<0.001		
PTC	1		1	
CC-PTC	3.150 (2.149–4.618)		1.801 (1.211–2.677)	0.004
FTC	2.730 (1.743–4.275)		0.850 (0.528–1.368)	0.503
MTC	3.788 (2.612–5.495)		1.941 (1.306–2.885)	0.001
ATC	17.329 (14.142–21.235)		4.024 (3.082–5.254)	<0.001
ITC	4.476 (2.373–8.443)		1.274 (0.664–2.443)	0.466
OCA	3.149 (1.970–5.036)		1.368 (0.829–2.258)	0.221
LNM		<0.001		
No LNM	1			
CLNM	0.335 (0.267–0.421)			
LLNM	0.437 (0.349–0.547)			
No LND	0.369 (0.281–0.484)			
DM		<0.001		
Absence	1		1	
Presence	5.880 (4.934–7.007)		3.276 (2.680–4.005)	<0.001
Thyroidectomy scope		<0.001		
None	1		1	
Unilateral thyroidectomy and/or isthectomy	0.344 (0.258–0.459)		0.543 (0.376–0.783)	0.001
Total or subtotal thyroidectomy	0.083 (0.068–0.102)		0.421 (0.306–0.579)	<0.001
Lymph node dissection		<0.001		
No LND	1			
Yes,pLNs≤4	0.361 (0.289–0.451)			
Yes,pLNs≥5	0.389 (0.320–0.473)			
Radiation		<0.001		
None/Unknown	1		1	
Radioisotopes	0.207 (0.164–0.262)		0.276 (0.181–0.422)	<0.001
Beam radiation	2.117 (1.736–2.580)		0.582 (0.421–0.803)	0.001
Both	0.879 (0.579–1.334)		0.683 (0.401–1.161)	0.159
Radiotherapy and surgery time sequence		<0.001		
No radiation and/or surgery	1		1	
Radiation after surgery	0.329 (0.277–0.390)		1.648 (1.115–2.434)	0.012
Radiation prior to surgery	0.751 (0.280–2.017)		0.736 (0.259–2.090)	0.565
Radiation before and after surgery	1.409 (0.627–3.165)		1.839 (0.720–4.697)	0.203
Chemotherapy		<0.001		
No	1			

(*continued on next page*)

Table 3 (*continued*)

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Yes	4.972 (4.085–6.052)			
Systemic therapy and surgery time sequence		<0.001		
No systemic therapy and/or surgery	1			
Systemic therapy after surgery	0.616 (0.519–0.731)			
Systemic therapy prior to surgery	1.401 (0.522–3.757)			
Systemic therapy before and after surgery	0.474 (0.196–1.148)			
Months from diagnosis to treatment		<0.001		
< three months	1			
≥ three months	1.610 (1.282–2.021)			



(**a**) (**b**)

Fig. 3. Prognostic nomograms to predict 3-, 5-year and 10-year CSS (**a**) and OS (**b**) for the locally advanced thyroid cancer patients. Notes: a: Parathyroid or nerves (Vagus or recurrent laryngeal nerves), b: Cricoid cartilage, esophagus, larynx or sternocleidomastoid muscle, c: Thyroid cartilage, d: Bone or Skeletal muscle (Except for strap or sternocleidomastoid muscle), e: Trachea, f: Blood vessels, g: Mediastinal tissues or Pre-vertebral fascia, h: Strap muscles or surrounding tissue.

invade the lumen of the trachea it significantly shortens survival, with a 5-year overall mortality of up to 40 %–71 % in patients with grade IV [12,13]. Similarly, the risk of recurrence of LATC correlates with the depth of tracheal invasion, with LATC invasion into the lumen of the trachea significantly increasing the risk of recurrence [8,14]. Cervical and mediastinal vascular invasion is less common and is mostly seen in FTC [15], but the present study yielded an incidence of cervical and mediastinal vascular invasion of 8.0 % in patients with LATC. The current study concluded that LATC invasion of the vein has less impact on survival if it is radically resected [16,17]. When LATC invades the common carotid artery periphery for epithelial debridement, the arterial wall may have microscopic tumor remnants, which can affect survival [18]. Studies have shown that the incidence of recurrent laryngeal nerve invasion in LATC is high [9], reaching 69.2 %, and the incidence of parathyroid and nerve invasion in T4a patients in this study is 37.9 %. Notably, tumor invasion of the parathyroid glands and nerves had the least effect on CSS and OS in LATC patients in this study, which is similar to the findings of previous studies [8], but Lee et al. [19] suggested that the invasion of the recurrent laryngeal nerve increases the risk of recurrence. In conclusion, due to the relative rarity of LATC in the clinic, there is still a lack of large-scale studies in the current academic community, and the relevant conclusions still need to be further justified.

Different histopathological types of TC tend to exhibit different biological properties and prognostic characteristics [20], and our study also verified this conclusion in the LATC patient population, but unlike previous studies, in this study, we further subdivided the TC according to the histological types into PTC, FTC, CCV-PTC, OCA, ITC, MTC and ATC, which were visualized by nomograms to accurately

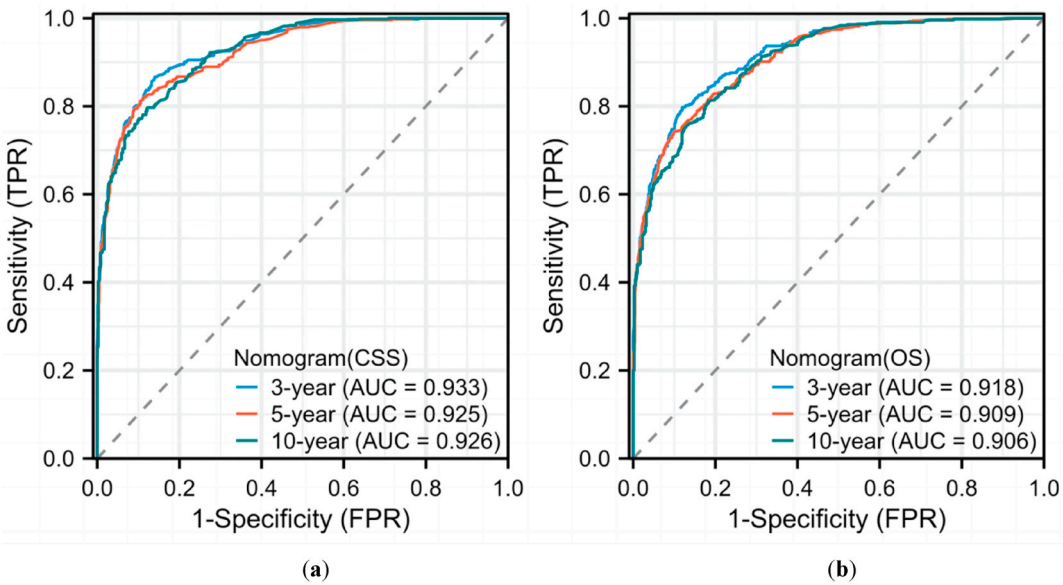


Fig. 4. The time-dependent ROC curve in the training set CSS nomogram(**a**) and OS nomogram(**b**).

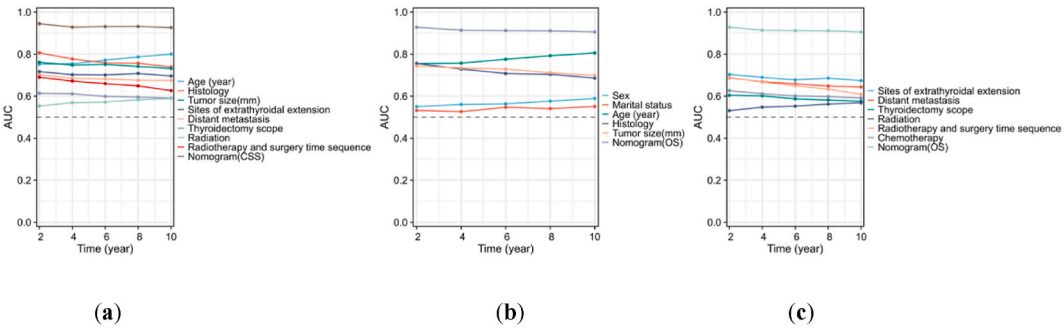


Fig. 5. Each independent predictive factor with the developed nomogram in the one time-dependent AUC curve The time-dependent ROC curve in the training set CSS nomogram(**a**) and OS nomogram(**b**)(**c**).

assess the prognosis of LATC patients with different histological types.Wang et al. [21] concluded that tumor diameter was an independent prognostic factor for OS and CSS in patients with locally advanced DTC. In the present study, tumor diameter was also a prognostic factor for the LATC patients, and it was also shown that the number of tumor lesions was not the ultimate prognostic predictor, which may suggest that tumor diameter may be useful for the prognostic stratification of LATC patients. The most frequent sites of DM in TC are the lungs, bones, brain, and liver [22], and in the present study, the LATC patients with DM had a lower CSS and OS compared with those without DM, with a risk ratio of 3.276 (95 %) and a risk ratio of 3.276 (95 %), respectively. 3.276 (95 % CI 2.680–4.005, $P < 0.001$) and 4.723 (95 % CI 4.031–5.534, $P < 0.001$), respectively, which is the same as the results of previous studies [22–24].

Age is an important indicator for determining the prognostic status of TC, and the eighth edition of the AJCC DTC staging system increased the age cut-off point from 45 to 55 years of age, although there is still controversy in the academic community about the determination of the age cut-off point for evaluating the condition of patients with TC [25], the present research concludes that age is an critical indicator for the assessment of CSS and OS in LATC patients. It is noteworthy that our study concluded that patients with single, widowed and separated status had worse prognosis and marital status as one of the predictive factors affecting OS in LATC patients, while Li et al. [26] also concluded that marital status in patients with TC was significantly associated with both CSS and OS. Previous studies have also concluded that good marital status has a positive effect on the prognosis of a variety of malignant tumors [27], and since TC, as an endocrine system disease, emotional changes and psychological well-being may be closely related to its prognosis, we believe that providing effective psychological counseling and social support to unmarried, widowed and separated patients may have a positive effect on the patients' prognosis. Similarly, we only found that males had a worse prognosis than females in the predictive analyses of OS in the LATC patients, which is very similar to the findings of Li et al. [28] However, Zhou et al. [29] found that the prognosis of male patients with DTC did not differ from that of females after matching by propensity score. It can be seen that the effect of gender on TC prognosis is still controversial, and future studies can be segmented by combining other patient information such as patient age.

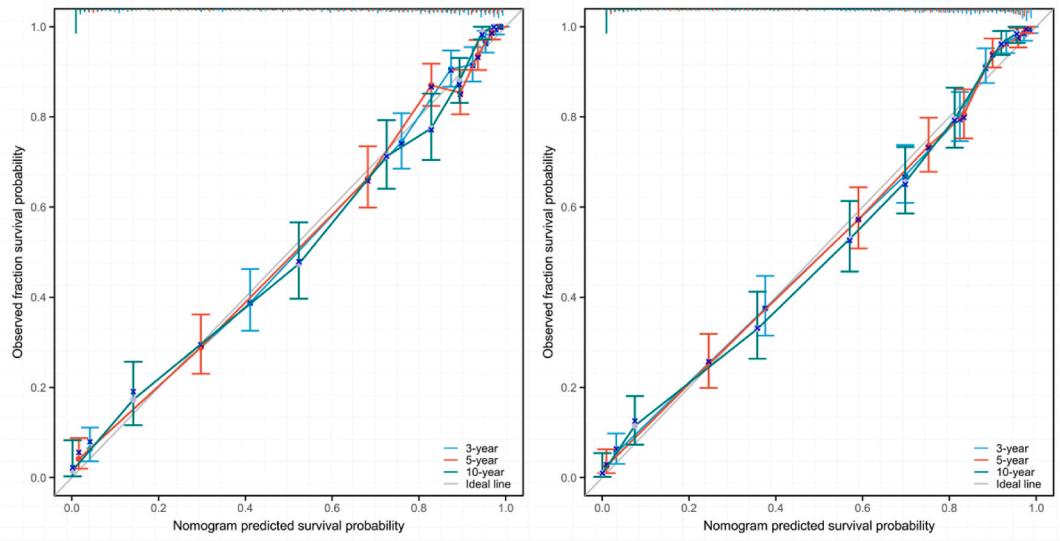


Fig. 6. 3-year, 5-year and 10-year CSS nomogram(**a**) and OS nomogram(**b**) calibration curves in the training set.

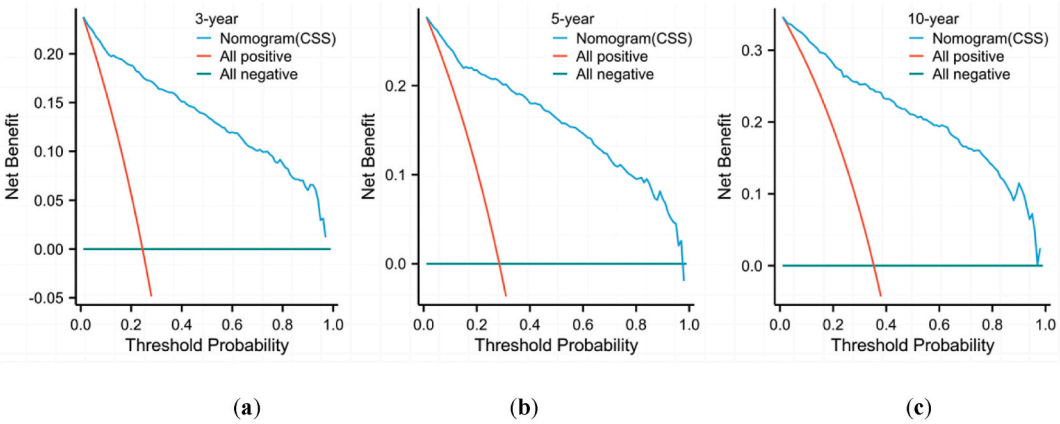


Fig. 7. 3-year(**a**),5-year(**b**) and 10-year(**c**) CSS nomogram DCA curves in the training set.

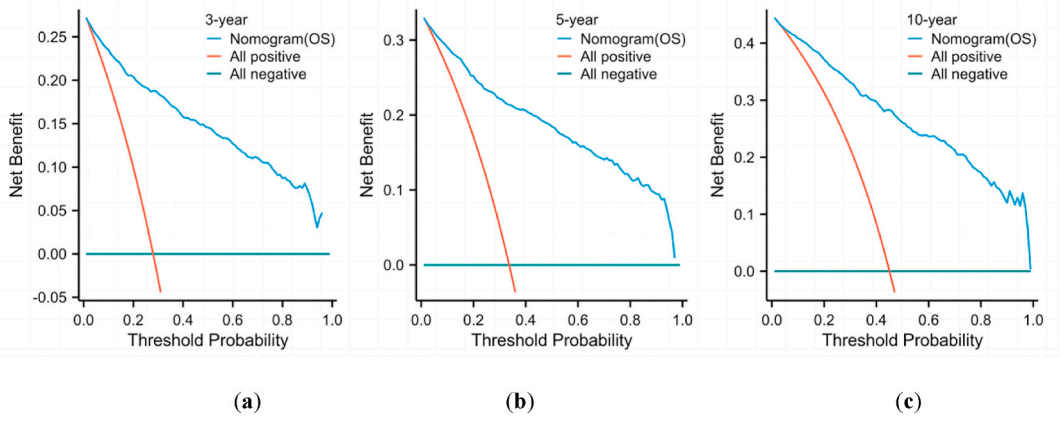


Fig. 8. 3-year(**a**),5-year(**b**) and 10-year(**c**) OS nomogram DCA curves in the training set.

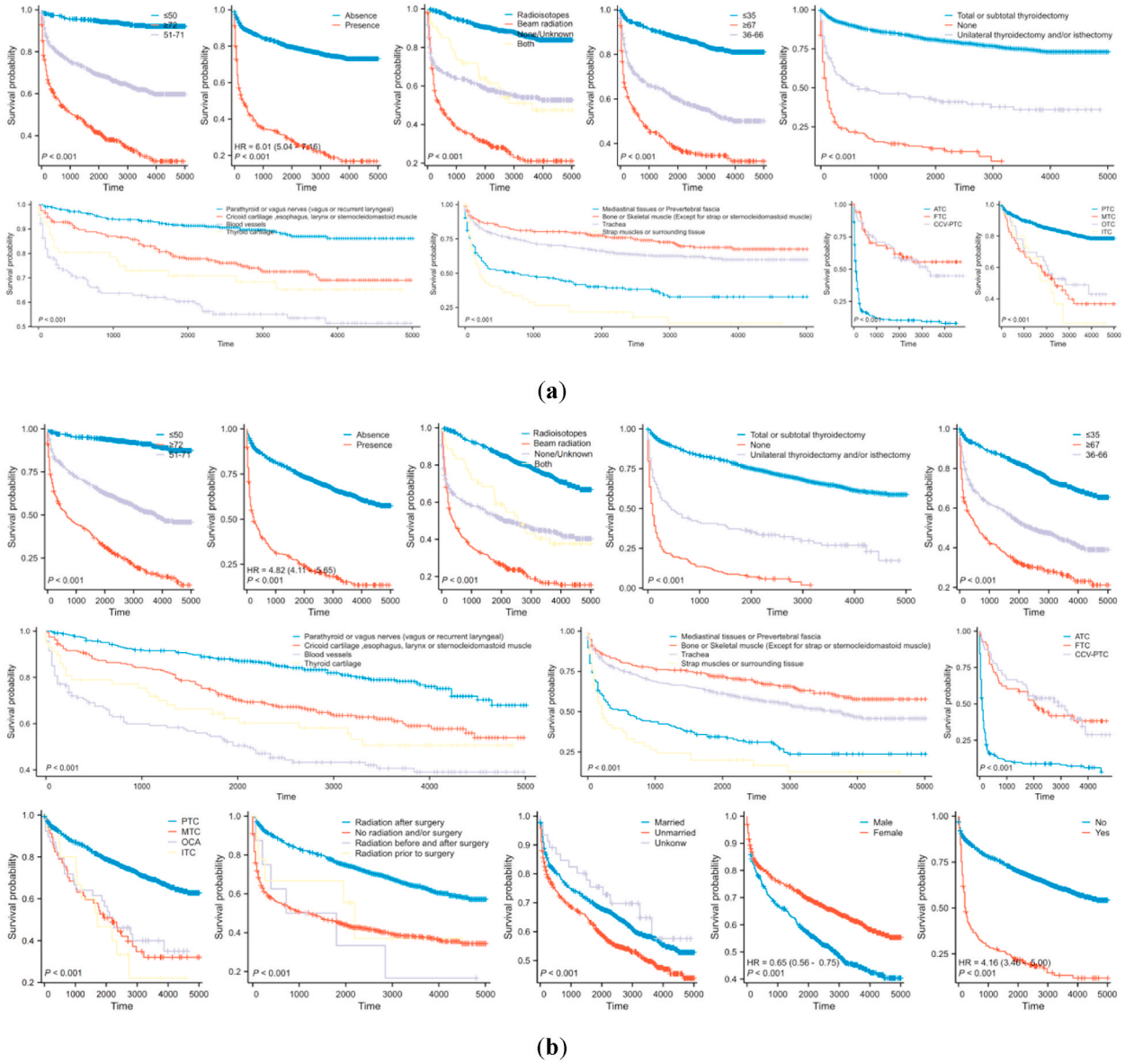


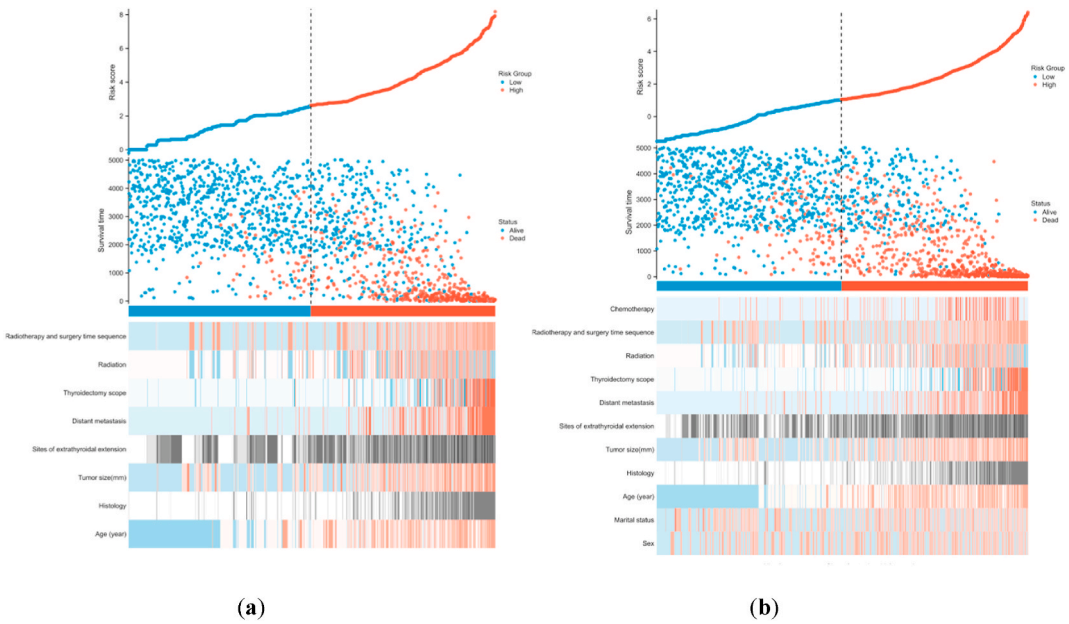
Fig. 9. Kaplan-Meier survival curves with respect to CSS (**a**) and OS (**b**) were plotted for each significant independent predictor in the training set. Note: Time (days).

Our study concluded that radical surgical treatment is an important influence on the prognosis of LATC, and long-term clinical practice and the results of a large number of case summaries have also proved that the choice of the first standardized surgical approach determines the final outcome of TC, and is the most important factor determining the prognosis and efficacy of treatment. However, studies have shown that despite initial standardized treatment, recurrence or DM still occurs in about 15 % of TC patients [30]. LATC can significantly invade the surrounding vital structures and has a poorer prognosis, and its surgical scope is extensive and involves the resection and reconstruction of vital organs, with greater surgical trauma and surgical risk and a higher complication rate, so discussions on the appropriate extent of surgical resection for LATC remain controversial [31]. Therefore, providing optimal choices of surgical strategies for LATC patients to further increase the resection rate, reduce surgical risks, decrease the incidence of post-operative complications and mortality, and safeguard the quality of life while prolonging survival as much as possible are the current hotspots of controversy and the direction of endeavor. However, it is worth noting that the current editions of academic guidelines [3, 32–34] for the surgical treatment of LATC emphasise the weighing of the surgical benefit-risk ratio, i.e., the need for the surgeon to weigh radical versus palliative tumor-reducing treatments. However, there is still a lack of convincing evidence in terms of comparing the assessment of the efficacy benefits of different treatment options. In conclusion, although previous studies have suggested that the benefits of R0 or R1 resection for LATC are greater, the quality of life of the patient after surgery also requires careful preoperative

Table 4
Risk stratification distribution of patients locally advanced thyroid cancer patients.

			LR	HR	Total	P value
Training set	CSS	Scoring range	<167.75	≥167.75		<0.001
		Dead (attributable to LATC)	60 (7.2 %)	479 (56.8 %)	107	
		Alive or dead of other cause	773 (92.8 %)	365 (43.2 %)	1138	
		Total	833	844		
	OS	Scoring range	<198.5	≥198.5		<0.001
		Dead	379 (28.8 %)	336 (93.1 %)	715	
		Alive	973 (71.2 %)	25 (6.9 %)	998	
		Total	1316	361		
Testing set	CSS	Dead (attributable to LATC)	33 (9.1 %)	220 (62.0 %)	253	<0.001
		Alive or dead of other cause	331 (90.9 %)	135 (38.0 %)	466	
		Total	364	355		
	OS	Dead	128 (25.1 %)	197 (93.8 %)	325	<0.001
		Alive	381 (74.9 %)	13 (6.2 %)	394	
		Total	509	210		

Data notes: LR low-risk, HR high-risk.



(**a**) (**b**)

Fig. 10. Risk factor map of the prognostic nomograms for CSS (**a**) and OS (**b**). Note: Survival time (days).

assessment by the clinician and active involvement of the patient in the decision-making process.

We included in our study the radiotherapy and chemotherapy status of patients initially diagnosed with LATC, and the chronological order of radiotherapy and systemic therapy versus surgery, which is rarely seen in previous studies, and all of the above factors were strongly associated with the prognosis of patients with LATC in univariate regression analyses, and ultimately, the only factors that were included in the prognostic nomograms were the status of chemotherapy, the status of radiotherapy, and its chronological order versus surgery. The fact that chemotherapy was only associated with OS in LATC patients and that patients without chemotherapy had a poorer prognosis may be due to the fact that most of these patients had poor prognostic outcomes such as DM and poor differentiation, but it is sufficient to demonstrate that treatment modalities other than surgery have a significant impact on the prognosis of LATC patients. As LATC involves all TC types, some patients are inoperable or have difficulty in complete surgical resection of the lesion, which is the current difficulty in the treatment of LATC. With the development of TC treatment, previous studies have concluded that neoadjuvant treatment of LATC can lead to tumor regression in some patients, giving the chance of complete surgical resection thereby improving patient prognosis [35–37]. However, due to the highly specialized nature of the treatment of LATC, we recommend the application of a multi-disciplinary team (MDT) model, which uses multidisciplinary assessment to discuss the assessment of tumor resectability and the assessment of physical status prior to neoadjuvant therapy, if it is anticipated that it will be difficult to achieve R0 or R1 resection, or if it will be difficult to preserve the function of the adjacent structures or organs due to a large surgical extent, and the patient is in good physical condition, neoadjuvant therapy can be considered to improve the resection rate of subsequent surgery and the quality of life of patients. Due to the insensitivity of TC to radiotherapy, targeted therapy is currently

the main neoadjuvant treatment modality [38], and targeted therapy plus immunotherapy or chemotherapy can be used for poorly differentiated LATC [39].

It is important to note that the MDT model for the treatment and management of LATC patients is throughout the whole process, and patients can further develop follow-up treatment and follow-up plans based on the surgical situation and postoperative examination and pathology results in collaboration with multidisciplinary departments, so that tumor recurrence and DM can be detected as early as possible and treated, thus improving the quality of life and prolonging the survival time of the patients. Nevertheless, in clinical practice, clinicians choose the treatment for LATC based on their own experience, and no effective consensus has been reached on the treatment plan. We believe that the choice of treatment plan for LATC and the development of the follow-up mode should be individualized. The goal is to further increase the resection rate, reduce the risk of surgery, decrease the incidence of postoperative complications and death rates, prolong survival, and ensure the quality of life, rather than abandoning the treatment or operating blindly without regard to the consequences of the surgery, and at the same time, the appropriate application of preoperative neoadjuvant therapy and postoperative adjuvant therapy in the cooperation of the MDT team will make the patients greatly benefit from the LATC. The survival rate of the patients can be obtained by adding all the scores of the nomograms to obtain a total risk score. In addition, the risk stratification of the patients can be obtained according to the total score. It is suggested that the high-risk patients should adopt the MDT model actively, formulate personalized treatment plan, and increase the frequency of review and follow-up physical examination to improve the prognosis as much as possible. Although the prognostic model in this research has good predictive performance and clinical applicability, the research still has some limitations. Firstly, our study was retrospective, which means that there may be an inherent selection bias. Also, the SEER database does not contain information about the molecular biology of the patient's genes, family history, specific details of radiotherapy and chemotherapy, and other relevant information, all of which are clinical information that may affect the prognosis of the LATC patients. Secondly, although the prevalence of LATC is not high, external validation from more than two mechanisms centers is more convincing for the assessment of model performance, and future studies could carry out joint external validation from multiple centers. Finally, the definition of LATC by TNM staging was limited to TC primary foci, and future studies are recommended to include patients with cervical metastatic lymph nodes invading the surrounding structures and organs in the assessment of LATC. In addition, this study only analyzed the prognosis of LATC patients, but LATC is more susceptible to recurrence, and future studies could be carried out to address the risk of recurrence of LATC.

5. Conclusions

In summary, our study analyzed data on demographics, clinicopathological characteristics and survival information of LATC patients, and finally identified independent predictors of their prognosis and developed the first nomograms to predict CSS and OS in LATC patients at 3, 5, and 10 years. The model evaluation and validation demonstrated that the nomograms had outstanding discrimination, calibration ability, and clinical applicability. In addition, we proposed a risk stratification for the prognostic situation of LATC patients to help clinicians create the postoperative treatment and follow-up plan for their each patient.

Funding

"Four Batch" Shanxi Medical Science and Technology Innovation Team Construction Project (Clinical Diagnosis and Treatment and Basic Research Innovation Team of Thyroid Cancer) (2020TD16).

Ethics approval and consent

Because the SEER database does not release personally identifiable information, this study did not require the approval and consent of the Ethics Committee of the First Hospital of Shanxi Medical University.

Data availability

The data that support the findings of this study are available from the Surveillance, Epidemiology, and End Results (SEER) database at http://www.seer.cancer.gov. The data associated with our study has been deposited into a publicly available repository.

CRediT authorship contribution statement

Yonghao Li: Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Huiqiang Zhang:** Visualization, Resources, Methodology. **Yifan Cao:** Validation, Supervision, Resources, Methodology, Investigation. **Ningyu He:** Methodology, Investigation, Formal analysis. **Weichao Li:** Resources, Project administration, Methodology. **Xuefei Gao:** Investigation. **Tiantian Guo:** Writing – review & editing, Formal analysis. **Jing Liu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgments

"Four Batch" Shanxi Medical Science and Technology Innovation Team Construction Project(Clinical Diagnosis and Treatment and Basic Research Innovation Team of Thyroid Cancer) (2020TD16)

All of us authors are grateful for the SEER data because it provides very valuable clinical data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24798.

References

[1] R.L. Siegel, K.D. Miller, N.S. Wagle, A. Jemal, Cancer statistics, 2023, Ca - Cancer J. Clin. 73 (1) (2023) 17–48.
[2] S. Ortiz, J.M. Rodríguez, T. Soria, D. Pérez-Flores, A. Piñero, J. Moreno, P. Parrilla, Extrathyroid spread in papillary carcinoma of the thyroid: clinicopathological and prognostic study, Otolaryngology–head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 124 (3) (2001) 261–265.
[3] B.R. Haugen, E.K. Alexander, K.C. Bible, G.M. Doherty, S.J. Mandel, Y.E. Nikiforov, F. Pacini, G.W. Randolph, A.M. Sawka, M. Schlumberger, K.G. Schuff, S. I. Sherman, J.A. Sosa, D.L. Steward, R.M. Tuttle, L. Wartofsky, 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer, Thyroid : official journal of the American Thyroid Association 26 (1) (2016) 1–133.
[4] L.Y. Wang, I.J. Nixon, S.G. Patel, F.L. Palmer, R.M. Tuttle, A. Shaha, J.P. Shah, I. Ganly, Operative management of locally advanced, differentiated thyroid cancer, Surgery 160 (3) (2016) 738–746.
[5] A. Metere, V. Aceti, L. Giacomelli, The surgical management of locally advanced well-differentiated thyroid carcinoma: changes over the years according to the AJCC 8th edition Cancer Staging Manual, Thyroid Res. 12 (2019) 10.
[6] S. Moritani, Impact of gross extrathyroidal extension into major neck structures on the prognosis of papillary thyroid carcinoma according to the American Joint Committee on Cancer eighth edition, Endocr. J. 67 (9) (2020) 941–948.
[7] J. Tang, C. Zhanghuang, Z. Yao, L. Li, Y. Xie, H. Tang, K. Zhang, C. Wu, Z. Yang, B. Yan, Development and validation of a nomogram to predict cancer-specific survival in middle-aged patients with papillary thyroid cancer: a SEER database study, Heliyon 9 (2) (2023 Feb 10) e13665.
[8] T.V. McCaffrey, E.J. Bergstralh, I.D. Hay, Locally invasive papillary thyroid carcinoma: 1940-1990, Head Neck 16 (2) (1994) 165–172, https://doi.org/10.1002/hed.2880160211.
[9] M. Dell'Aquila, P. Tralongo, G. De Ruggieri, et al., Does locally advanced thyroid cancer have different features? Results from a single academic center, J. Personalized Med. 12 (2) (2022) 221.
[10] M. Xu, Z. Xi, Q. Zhao, et al., Causal inference between aggressive extrathyroidal extension and survival in papillary thyroid cancer: a propensity score matching and weighting analysis, Front. Endocrinol. 14 (2023) 1149826.
[11] H. Kim, H.J. Jung, S.Y. Lee, T.K. Kwon, K.H. Kim, M.W. Sung, J. Hun Hah, Prognostic factors of locally invasive well-differentiated thyroid carcinoma involving the trachea, Eur. Arch. Oto-Rhino-Laryngol. : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 273 (7) (2016) 1919–1926.
[12] D.H. Shin, E.J. Mark, H.C. Suen, H.C. Grillo, Pathologic staging of papillary carcinoma of the thyroid with airway invasion based on the anatomic manner of extension to the trachea: a clinicopathologic study based on 22 patients who underwent thyroidectomy and airway resection, Hum. Pathol. 24 (8) (1993) 866–870.
[13] V. Sharanappa, R.A. Bichoo, A. Mishra, P.K. Pradhan, S.K. Mishra, Circumferential laryngotracheal resection in thyroid cancer: experience and outcome in a single center, Indian J. Otolaryngol. : official publication of the Association of Otolaryngologists of India 74 (Suppl 2) (2022) 2629–2635.
[14] K. Tsukahara, I. Sugitani, K. Kawabata, Surgical management of tracheal shaving for papillary thyroid carcinoma with tracheal invasion, Acta Otolaryngol. 129 (12) (2009) 1498–1502.
[15] M.G. Chiofalo, R. D'Anna, F. Di Gennaro, S.V. Setola, V. Marotta, Great veins invasion in follicular thyroid cancer: single-centre study assessing prevalence and clinical outcome, Endocrine 62 (1) (2018) 71–75.
[16] Y.S. Lee, W.Y. Chung, H.S. Chang, C.S. Park, Treatment of locally advanced thyroid cancer invading the great vessels using a Y-shaped graft bypass, Interact. Cardiovasc. Thorac. Surg. 10 (6) (2010) 1039–1041.
[17] Z. Čolović, P. Ivanišević, C. Bulat, A. Barić, M. Kontić, H. Punda, N.K. Poljak, A. Punda, Treatment approach to follicular thyroid carcinoma tumor thrombus in the internal jugular vein and brachiocephalic vein, Acta Clin. Croat. 59 (Suppl 1) (2020) 149–152.
[18] S. Moritani, Appropriateness of subadventitial resection for invasion of the carotid artery by papillary thyroid carcinoma, World J. Surg. 43 (2) (2019) 519–526.
[19] H.S. Lee, S.W. Kim, J.C. Hong, K.D. Lee, Papillary thyroid carcinoma with exclusive involvement of a functioning recurrent laryngeal nerve may be treated using a shaving technique: reply, World J. Surg. 39 (7) (2015) 1853–1854.
[20] D.W. Chen, B.H.H. Lang, D.S.A. McLeod, K. Newbold, M.R. Haymart, Thyroid cancer, Lancet (London, England) 401 (10387) (2023) 1531–1544.
[21] Z. Wang, Q. Zhang, H. Ye, C. Jia, Z. Lv, J. Liu, Z. Yin, Tumor size IS an independent predictor of mortality RISK in differentiated thyroid cancer patients with T4 DISease, Endocr. Pract. : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 26 (5) (2020) 499–507.
[22] Y. Li, X. Gao, T. Guo, J. Liu, Development and validation of a nomogram for risk of pulmonary metastasis in non-papillary thyroid carcinoma: a SEER-based study, Medicine 102 (32) (2023) e34581.
[23] J.S. Lee, J.S. Lee, H.J. Yun, H. Chang, S.M. Kim, Y.S. Lee, H.S. Chang, C.S. Park, Prognosis of anaplastic thyroid cancer with distant metastasis, Cancers 14 (23) (2022) 5784.
[24] L.C. Tan, N.S. Huang, P.C. Yu, P.Z. Han, W.L. Liu, Z.W. Lu, R.L. Shi, X. Shi, Y. Wang, Q.H. Ji, N. Qu, W.J. Wei, Y.L. Wang, Different clinicopathologic features predispose to different patterns of distant metastasis with heterogeneous short-term prognosis in patients with differentiated thyroid cancer, Clin. Endocrinol. 96 (3) (2022) 402–412.
[25] N. Shukla, N. Osazuwa-Peters, U.C. Megwalu, Association between age and nodal metastasis in papillary thyroid carcinoma, Otolaryngology–head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 165 (1) (2021) 43–49.
[26] Y. Li, D. Huang, B. Wang, W. Mao, X. Chen, P. Dong, Socioeconomic factors are associated with the prognosis of Thyroid Cancer, J. Cancer 12 (9) (2021) 2507–2512.
[27] Y. Mao, Y. Huang, L. Xu, J. Liang, W. Lin, H. Huang, L. Li, J. Wen, G. Chen, Surgical methods and social factors are associated with long-term survival in follicular thyroid carcinoma: construction and validation of a prognostic model based on machine learning algorithms, Front. Oncol. 12 (2022) 816427.
[28] P. Li, Y. Ding, M. Liu, W. Wang, X. Li, Sex disparities in thyroid cancer: a SEER population study, Gland Surg. 10 (12) (2021) 3200–3210, https://doi.org/10.21037/gs-21-545.

[29] Y. Zhou, Y. Wang, Z. Zhang, X. Yin, J. Liu, W. Zheng, Male sex is not a risk factor for prognosis in postoperative thyroid cancer patients: a propensity score matching study, J. Clin. Endocrinol. Metab. 108 (12) (2023) 3330–3337.
[30] F. Yang, J. Wang, Y. Rao, Y. Feng, L. Meng, J. Fang, Predictive factors and risk analysis of recurrent laryngeal nerve invasion in papillary thyroid carcinoma ≤ 1 cm, Archives of endocrinology and metabolism 67 (3) (2023) 330–340.
[31] D.M. Hartl, J. Guerlain, I. Bresuskin, E. Baudin, L. Lamartina, J. Hadoux, S. Leboulleux, M. Schlumberger, Surgery in the context of kinase inhibitor therapy for locally invasive thyroid cancer, Eur. J. Surg. Oncol. : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 46 (4 Pt A) (2020) 650–655.
[32] R.I. Haddad, L. Bischoff, D. Ball, V. Bernet, E. Blomain, N.L. Busaidy, M. Campbell, P. Dickson, Q.Y. Duh, H. Ehya, W.S. Goldner, T. Guo, M. Haymart, S. Holt, J. P. Hunt, A. Iagaru, F. Kandeel, D.M. Lamonica, S. Mandel, S. Markovina, S. Darlow, Thyroid carcinoma, version 2.2022, NCCN clinical practice guidelines in oncology, J. Natl. Compr. Cancer Netw. : J. Natl. Compr. Cancer Netw. 20 (8) (2022) 925–951.
[33] F. Pacini, F. Basolo, R. Bellantone, G. Boni, M.A. Cannizzaro, M. De Palma, C. Durante, R. Elisei, G. Fadda, A. Frasoldati, L. Fugazzola, R. Guglielmi, C. P. Lombardi, P. Miccoli, E. Papini, G. Pellegriti, L. Pezzullo, A. Pontecorvi, M. Salvatori, E. Seregni, P. Vitti, Italian consensus on diagnosis and treatment of differentiated thyroid cancer: joint statements of six Italian societies, J. Endocrinol. Invest. 41 (7) (2018) 849–876.
[34] A. Bove, M. Farrukh, A. Di Gioia, V. Di Resta, A. Buffone, C. Melchionna, P. Panaccio, Surgical skills and technological advancements to avoid complications in lateral neck dissection for differentiated thyroid cancer, Cancers 13 (14) (2021) 3379.
[35] S. Filetti, C. Durante, D. Hartl, S. Leboulleux, L.D. Locati, K. Newbold, M.G. Papotti, A. Berruti, ESMO Guidelines Committee, Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. : official journal of the European Society for Medical Oncology 30 (12) (2019) 1856–1883. Electronic address: clinicalguidelines@esmo.org.
[36] L. Lamartina, Y. Godbert, C. Nascimento, C. Do Cao, S. Hescot, I. Borget, A. Al Ghuzlan, D. Hartl, J. Hadoux, E. Pottier, M. Attard, A. Berdelou, M. Terroir, E. Baudin, M. Schlumberger, S. Leboulleux, With the support of the TUTHYREF network (2020). Locally unresectable differentiated thyroid cancer: outcomes and perspectives, Endocrine 69 (1) (2020) 133–141.
[37] N. Besic, M. Auersperg, B. Gazic, M. Dremelj, I. Zagar, Neoadjuvant chemotherapy in 29 patients with locally advanced follicular or Hürthle cell thyroid carcinoma: a phase 2 study, Thyroid : official journal of the American Thyroid Association 22 (2) (2012) 131–137.
[38] E. Maurer, F. Eilsberger, S. Wächter, J. Riera Knorrenschild, A. Pehl, K. Holzer, A. Neubauer, M. Luster, D.K. Bartsch, Mutation-based, short-term "neoadjuvant" treatment allows resectability in stage IVB and C anaplastic thyroid cancer, Eur. Arch. Oto-Rhino-Laryngol. : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 280 (3) (2023) 1509–1518.
[39] K.C. Bible, E. Kebebew, J. Brierley, J.P. Brito, M.E. Cabanillas, T.J. Clark Jr., A. Di Cristofano, R. Foote, T. Giordano, J. Kasperbauer, K. Newbold, Y.E. Nikiforov, G. Randolph, M.S. Rosenthal, A.M. Sawka, M. Shah, A. Shaha, R. Smallridge, C.K. Wong-Clark, 2021 American thyroid association guidelines for management of patients with anaplastic thyroid cancer, Thyroid : official journal of the American Thyroid Association 31 (3) (2021) 337–386.