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ORIGINAL ARTICLE

Influence factors and survival outcomes of different invasion sites in locally advanced thyroid cancer and new site-based risk stratification system

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Abstract

Purpose Locally advanced thyroid cancer (LATC) has gained increased attention, yet factors influencing invasion patterns and their prognostic impact remain poorly understood.

Methods Patients with LATC were identified from the Surveillance, Epidemiology, and End Results (SEER) program. Invasion patterns were visualized using bar graphs. Kaplan-Meier method and log-rank test analyzed outcomes by different invasion sites. Multivariable Cox regression analysis was conducted to adjust confounding factors and establish a new site-based risk stratification.

Results Papillary thyroid carcinoma (PTC) predominantly invaded esophagus or larynx (21.0%) and trachea (26.3%), while follicular thyroid carcinoma/oncocytic thyroid carcinoma (FTC/OTC) mainly invaded blood vessel (31.3%). Anaplastic thyroid carcinoma (ATC) exhibited the highest rate of trachea invasion (33.3%) and multi-invasion (8.1%). Age, tumor size significantly influenced the proportion of trachea invasion ($p < 0.001$). Locally advanced PTC patients with different invasion sites demonstrated significantly different prognoses: 10-year OS rate of each invasion site was: parathyroid or nerve (82.5%), bone or skeletal muscle (76.6%), esophagus or larynx (68.7%), blood vessel (58.0%), trachea (57.5%), multi-invasion (26.8%). Based on multivariable Cox regression, a novel site-based risk stratification was established for locally advanced PTC patients, with trachea invasion (HR = 1.83, $p < 0.001$), blood vessel invasion (HR = 2.64, $p < 0.001$), and multi-invasion (HR = 2.76, $p < 0.001$) categorized as medium and high risk of mortality, respectively, demonstrating better discrimination than 8th AJCC staging system.

Conclusion This study is the first to utilize population-based cohort to reveal factors influencing invasion sites and their prognostic differences. This study also proposed a new site-based risk stratification that builds upon 8th AJCC T staging for locally advanced PTC patients, which may facilitate more tailored clinical management strategies.

Keywords Locally advanced · Thyroid cancer · Extrathyroidal extension · SEER · Invasion · T4 stage

Introduction

Thyroid cancer (TC) is characterized by a high incidence rate (18.4 per 100,000 people annually in North America) but generally favorable prognosis (mortality rate of 0.3 per 100,000 people annually in North America) [1–4]. However, patients with locally advanced thyroid cancer (LATC) have garnered increasing attention due to their significantly poorer outcomes, with 10-year overall survival (OS) rate of 48.2–57.2% even in those with papillary thyroid carcinoma (PTC) [4–13]. LATC is defined by tumor invasion of vital neck organs, such as nerves, trachea, esophagus, larynx, and carotid artery, accounting for approximately 5–10% initial cases. Well-prepared surgical intervention with R0 (no

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tumor residue)/R1 (microscopic tumor residue) resection is typically the initial and crucial treatment for most of these patients.

However, preoperative identification of patients with LATC remains challenging, except in those with severe clinical symptoms. This difficulty can lead to missed diagnoses, inadequate surgical preparation, increased complication risks, and incomplete resection [14, 15]. These issues underscore the importance of identifying patients prone to locally advanced invasion and comprehensively understanding invasion patterns and their influence factors. For suspicious LATC patients, the combination of detailed preoperative imaging examinations and comprehensive knowledge of invasion patterns can help find specific invasion sites and decide the surgical procedures. While several studies have reported invasion patterns in locally advanced differentiated thyroid carcinoma (DTC), these reports were predominantly based on single-center cohorts with small sample sizes and needed validation by large sample cohorts. Additionally, due to the limitation of small sample, the influence factors of such invasion patterns, and the invasion patterns in other thyroid subtypes remain unclear and need further investigation [7, 12, 16].

Moreover, with the advancement of multidisciplinary approaches and neoadjuvant targeted/immunological therapies, developing a precise risk stratification system to guide preoperative treatment decisions has been crucial. However, the most commonly used risk stratification system for LATC patients, the 8th American Joint Committee on Cancer (AJCC) staging system, is considered inadequate by some clinicians because it only recognizes tumors encasing major neck vessels (Stage T4b) as an indication of worse survival [17]. While numerous studies have attempted to demonstrate varying survival outcomes based on different invasion sites, their results have been inconsistent [6, 16, 18], likely due to the influence of potential confounding factors and selection bias inherent in single-center cohorts. This uncertainty in risk stratification complicates clinical decision-making regarding surgical procedures and preoperative neoadjuvant treatments, necessitating the establishment of accurate site-based prognostic stratification through large-sample cohorts.

The Surveillance, Epidemiology, and End Results (SEER) program, a nationwide population-based retrospective cohort, encompasses detailed demographic and clinicopathological characteristics, invasion information, treatment-related data, and survival status of patients with malignancy from major cancer registries in the United States. Numerous studies have utilized the SEER program to address important clinical challenges. To our knowledge, no study has leveraged this essential large-sample cohort to address these critical issues in LATC patients.

This study, for the first time, utilizes the SEER database to demonstrate factors predicting locally advanced invasion and the unique invasion patterns influenced by different thyroid cancer subtypes, tumor size, age and sex. Additionally, this study systematically demonstrates significant prognostic differences across varying invasion sites, and propose a novel and more efficacious site-based risk stratification system based on the 8th AJCC T staging system for locally advanced PTC patients.

Methods

Data source

This study utilized clinicopathological data from the Surveillance, Epidemiology, and End Results (SEER) program (SEER-17 Registry database 2000-2021), published in April 2024. The SEER program encompasses 17 high-quality, population-based registries covering 28% of the US population. Due to the availability of specific variable providing information about locally advanced invasion sites ('CS extension (2004-2015)'), this study identified thyroid cancer (TC) patients diagnosed between 2004 and 2015. The follow-up end point was December 2021. As all data were derived from a public database, this study was exempted from institutional ethics review board approval.

Inclusion criteria were: (1) 'Primary site label' variable set to C73.9: thyroid; (2) Pathological types identified using the 'ICD3-O-3' variable: papillary thyroid carcinoma (PTC: 8050, 8260, 8340-8344, 8350, 8450-8460), follicular thyroid carcinoma and oncocytic thyroid carcinoma (FTC/OTC: 8290, 8330-8335), medullary thyroid carcinoma (MTC: 8345, 8510-8513), anaplastic thyroid carcinoma (ATC: 8020-8035) [2]; (3) Patients with locally advanced invasion or strap muscle invasion; (4) Only microscopically confirmed cases, as per the "Diagnostic Confirmation" variable. Exclusion criteria were: (1) Cases identified through autopsy or death certificates, as per the "Type of reporting source" variable; (2) Patients lacking information about tumor size or invasion status; (3) Patients with previous malignant tumor history; (4) Patients diagnosed before January 2004 or after December 2015.

Cohort characteristics comprised demographic features (sex, race, and age at diagnosis), clinicopathological characteristics (tumor size, invasion, N stage, and M stage), therapeutic approaches (surgery and radiation) and survival status. Demographic variables such as 'Sex', 'Age recode with single ages and 85+', and 'Race recode (W, B, AI, API)' were used to determine sex, age, and race. Considering the relatively large sample size, age

was categorized as 0–44, 45–64, and ≥65 years, corresponding to young, middle-aged, and elderly patients, respectively, to demonstrate more detailed differences between age groups. Clinicopathological characteristics were identified and categorized using 'CS Tumor/lymph node/Mets (2004–2015)'. The classification of invasion sites was based on 'CS extension (2004-2015)'. All included patients were divided into seven categories, with the last six categories defined as locally advanced invasion: (1) Strap muscle invasion: only omohyoid, sternohyoid, sternothyroid, or thyrohyoid. (2) Parathyroid or nerve invasion: only parathyroid, recurrent laryngeal nerve, or vagus nerve with/without strap muscle invasion. (3) Esophagus or larynx invasion: Esophagus, larynx, cricoid cartilage, thyroid cartilage or sternocleidomastoid muscle with/without parathyroid or nerve invasion. (4) Bone or skeletal muscle invasion: bone or skeletal muscle (other than strap or sternocleidomastoid muscle) with/without parathyroid or nerve invasion. (5) Trachea invasion: trachea with/without parathyroid or nerve invasion. (6) Blood vessel invasion: carotid artery, jugular vein, or thyroid artery/vein with/without parathyroid or nerve invasion. (7) Multi-invasion: trachea plus thyroid cartilage, blood vessels, bone, or skeletal muscle with/without parathyroid or nerve invasion. Surgery data were extracted from the 'Rx Summ-Surg Prim site' variable. Previous tumor history was identified from 'First malignant primary indicator'. Outcome data were gathered from "Survival months", "Vital status recode" and "SEER case-specific death classification" variables. Ultimately, 7041 patients with strap muscles invasion thyroid cancer and 3262 patients with locally advanced invasion thyroid cancer were included in the study cohort.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation or median with percentiles, while categorical variables were expressed as percentages. The 'Mice' package was employed for multiple imputation of missing data (race, N stage and M stage), after consulting a statistical expert. Modified Poisson regression was utilized to investigate the factors predicting locally advanced invasion. The Kaplan-Meier method and pairwise log-rank test compared overall survival and cancer-specific survival (CSS) among different invasion sites. The Benjamini-Hochberg method was utilized to reduce type I error due to multiple comparisons. Cox regression analysis was employed to identify risk factors for mortality. Factors that were significant in the univariate regression ($p < 0.1$) and those with potential effects based on past studies were included in multivariable Poisson/Cox regression analysis. Considering the relatively small sample sizes of FTC/OTC, MTC and ATC, which may lead to over-stratification by invasion sites, the Kaplan-Meier method and Cox regression were calculated only for PTC. All statistical analyses

Table 1 Clinical characteristics of TC patients with strap muscle invasion and locally advanced invasion

Characteristics	No. of patients (%)	
	Strap muscle	Locally advanced
Total	7041 (100.0)	3262 (100.0)
Age at diagnosis, years		
0–44	2904 (41.2)	855 (26.2)
45–64	3064 (43.5)	1283 (39.3)
≥65	1073 (15.3)	1124 (34.5)
Sex		
Male	1856 (26.4)	1092 (33.5)
Female	5185 (73.6)	2170 (66.5)
Race (N = 10,222)		
White	5554 (78.9)	2559 (78.4)
Black	258 (3.7)	151 (4.6)
Others	1165 (16.5)	535 (16.4)
Tumor size, mm		
1–10	1161 (16.5)	207 (6.3)
11–20	2519 (35.8)	711 (21.8)
21–39	2078 (29.5)	1072 (32.9)
≥40	1283 (18.2)	1272 (39.0)
N stage (N = 9562)		
N0	3317 (47.1)	1128 (34.6)
N1a	2070 (29.4)	901 (27.6)
N1b	1279 (18.2)	867 (26.6)
M stage (M = 10,101)		
M0	6772 (96.2)	2713 (83.2)
M1	154 (2.2)	462 (14.2)
Subtypes		
PTC	6660 (94.6)	2699 (82.7)
FTC/OTC	283 (4.0)	166 (5.1)
MTC	80 (1.1)	100 (3.1)
ATC	18 (0.3)	297 (9.1)
Treatment		
No treatment or radiotherapy only	14 (0.2)	230 (7.1)
Surgery only	1853 (26.3)	724 (22.2)
Surgery and radiotherapy	5173 (73.5)	2308 (70.7)
Cancer-specific survival status		
Dead of TC	262 (3.7)	924 (28.3)
Alive or dead of other reasons	6779 (96.3)	2338 (71.7)

PTC papillary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *OTC* oncocytic thyroid carcinoma, *MTC* medullary thyroid carcinoma, *ATC* anaplastic thyroid cancer, *TC* thyroid cancer

Table 2 Modified Poisson regression for factors predicting locally advanced invasion progressing from strap muscle invasion

Characteristics	Univariable analysis[a]			Multivariable analysis[a]		
	RR	95% CI	P-value	RR	95% CI	P-value
Age at diagnosis, 45–64 years	**1.30**	**1.20–1.40**	**<0.001**	**1.33**	**1.23–1.43**	**<0.001**
Age at diagnosis, ≥65 years	**2.25**	**2.09–2.42**	**<0.001**	**1.91**	**1.77–2.05**	**<0.001**
Sex, Male	1.26	1.18–1.33	<0.001	0.99	0.94–1.05	0.805
Race, Black	1.17	1.03–1.33	0.018	1.04	0.92–1.17	0.508
Race, Others	1.00	0.92–1.08	0.969	1.03	0.96–1.10	0.469
Tumor size, 11–20 mm	**1.45**	**1.26–1.68**	**<0.001**	**1.41**	**1.23–1.62**	**<0.001**
Tumor size, 21–39 mm	**2.25**	**1.97–2.57**	**<0.001**	**2.03**	**1.77–2.31**	**<0.001**
Tumor size, ≥40 mm	**3.30**	**2.89–3.75**	**<0.001**	**2.48**	**2.16–2.83**	**<0.001**
N stage, N1	**1.39**	**1.31–1.48**	**<0.001**	**1.32**	**1.24–1.40**	**<0.001**
M stage, M1	**2.59**	**2.46–2.74**	**<0.001**	**1.52**	**1.42–1.63**	**<0.001**
Subtypes, FTC/OTC	1.28	1.13–1.45	<0.001	0.94	0.83–1.07	0.366
Subtypes, MTC	**1.93**	**1.68–2.20**	**<0.001**	**1.31**	**1.13–1.50**	**<0.001**
Subtypes, ATC	**3.27**	**3.14–3.41**	**<0.001**	**1.56**	**1.46–1.67**	**<0.001**

Values in bold indicated statistical significance

RR Risk ratio, *CI* Confidence interval, *PTC* Papillary thyroid carcinoma, *FTC* Follicular thyroid carcinoma, *OTC* Oncocytic thyroid carcinoma, *MTC* Medullary thyroid carcinoma, *ATC* Anaplastic thyroid carcinoma

[a]The reference for variable: Age at diagnosis (0–44 years), Sex (Female), Race (White), Tumor size (1–10 mm), N stage (N0), M stage (M0), Subtypes (PTC)

were conducted using R (version 4.3.3). All tests were two-tailed with α defined as 0.05.

Results

Baseline characteristics and factors predicting locally advanced invasion

Table 1 illustrates the baseline characteristics of patients with strap muscle invasion (Stage T3b according to 8th AJCC T staging) and locally advanced invasion (Stage T4 according to 8th AJCC staging). Modified Poisson regression was employed to investigate factors predicting progression from strap muscle invasion to locally advanced invasion (Table 2). Multivariable analysis revealed that age at diagnosis, tumor size, N stage, M stage and thyroid cancer subtypes were significant independent risk factors.

Table 3 further highlights significantly difference in baseline distributions among various thyroid cancer subtypes. Locally advanced FTC/OTC and ATC patients exhibited a significantly higher proportion of elderly patients and those with tumor sizes ≥40 mm, while locally advanced MTC patients had the highest rate of lateral lymph node metastasis (52.0%). Notably, locally advanced ATC, MTC, and FTC/OTC patients all demonstrated substantially higher rates of distant metastasis than locally advanced PTC patients (PTC vs. FTC/OTC vs. MTC vs. ATC: 9.4% vs. 27.7% vs. 30.0% vs. 44.4%, $p < 0.001$).

Influence of thyroid cancer subtypes, age, size and sex on locally advanced invasion patterns

Figure 1 depicts significantly different distribution of invasion sites across thyroid cancer subtypes. Locally advanced PTC primarily invaded parathyroid or nerve (27.8%), esophagus or larynx (21.0%) and trachea (26.3%), showing the highest proportion of parathyroid or nerve invasion among all subtypes. FTC mainly invaded trachea (24.1%) and blood vessel (31.3%), exhibiting the highest proportion of blood vessel invasion. MTC displayed invasion patterns similar to PTC but with higher rate of trachea invasion (28.0%) and blood vessel (17.0%) invasion. ATC emerged as the most aggressive subtype, showing the highest rate of trachea invasion (33.3%) and multi-invasion (8.1%) among all subtypes.

Furthermore, the influence of tumor size, age and sex was explored in locally advanced PTC patients (Fig. 1). Our results aligned with common understanding: as tumor size increased, the proportion of parathyroid or nerve invasion (39.5–19.7%) consistently decreased, while the proportions of esophagus or larynx (17.5–21.9%), trachea (17.5–31.1%), and blood vessel (4.3–8.9%) invasion significantly increased. Similarly, with increasing age, comparable changes were observed in the proportions of parathyroid or nerve invasion (36.1–20.8%) and trachea invasion (18.3–39.1%). However,

Table 3 Clinical characteristics of LATC patients by different thyroid cancer subtypes

Characteristics	No. of patients (%)			
	PTC	FTC/OTC	MTC	ATC
Total	2699 (100.0)	166 (100.0)	100 (100.0)	297 (100.0)
Age at diagnosis, years				
0–44	804 (29.8)	21 (12.7)	25 (25.0)	5 (1.7)
45–64	1065 (39.5)	67 (40.4)	48 (48.0)	103 (34.7)
≥65	830 (30.8)	78 (47.0)	27 (27.0)	189 (63.6)
Sex				
Male	841 (31.2)	74 (44.6)	56 (56.0)	121 (40.7)
Female	1858 (68.8)	92 (55.4)	44 (44.0)	176 (59.3)
Race (N = 3245)				
White	2,113 (78.3)	129 (77.7)	88 (88.0)	229 (77.1)
Black	104 (3.9)	13 (7.8)	6 (6.0)	28 (9.4)
Others	465 (17.2)	24 (14.5)	6 (6.0)	40 (13.5)
Tumor size, mm				
1-10	200 (7.4)	2 (1.2)	3 (3.0)	2 (0.7)
11–20	680 (25.2)	10 (6.0)	15 (15.0)	6 (2.0)
21–39	957 (35.5)	36 (21.7)	42 (42.0)	37 (12.5)
≥40	862 (31.9)	118 (71.1)	40 (40.0)	252 (84.8)
N stage (N = 2896)				
N0	910 (33.7)	105 (63.3)	8 (8.0)	105 (35.4)
N1a	803 (29.8)	13 (7.8)	30 (30.0)	55 (18.5)
N1b	708 (26.2)	26 (15.7)	52 (52.0)	81 (27.3)
M stage (N = 3175)				
M0	2378 (88.1)	118 (71.1)	69 (69.0)	148 (49.8)
M1	254 (9.4)	46 (27.7)	30 (30.0)	132 (44.4)
Treatment				
No treatment or radiotherapy only	78 (2.9)	13 (7.8)	5 (5.0)	134 (45.1)
Surgery only	580 (21.5)	35 (21.1)	41 (41.0)	68 (22.9)
Surgery and radiotherapy	2,041 (75.6)	118 (71.1)	54 (54.0)	95 (32.0)
Cancer-specific survival status				
Dead of TC	540 (20.0)	73 (44.0)	47 (47.0)	264 (88.9)
Alive or dead of other reasons	2159 (80.0)	93 (56.0)	53 (53.0)	33 (11.1)

There were 17 patients with unknown race, 265 patients with N1x, 101 patients with unknown N stage, and 87 patients with unknown M stage in this table

LATC locally advanced thyroid cancer, *PTC* papillary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *OTC* oncocytic thyroid carcinoma, *MTC* medullary thyroid carcinoma, *ATC* anaplastic thyroid cancer, *TC* thyroid cancer

unlike the changes associated with tumor size, the proportions of esophagus or larynx invasion and blood vessel invasion remained stable across age groups.

Survival disparities among different invasion sites in locally advanced PTC patients and new site-based risk stratification based on 8th AJCC T staging

Figure 2 illustrates the significant stratified prognostic impact of various locally advanced invasion sites on locally advanced PTC patients. The 10-year OS rates for each invasion site, in descending order, were: parathyroid or nerve (82.5%), bone or skeletal muscle (76.6%), esophagus or larynx (68.7%), blood vessel (58.0%), trachea (57.5%), multi-invasion (26.8%). Stratified log-rank test revealed statistically significant differences among all invasion sites, except between trachea and blood vessel invasion. These markedly different survival outcomes suggested the need for more precise risk stratification based on invasion sites.

To account for the confounding factors, such as age, tumor size, treatment and so on, multivariable Cox regression analysis was employed (Fig. 3). After adjustment, different locally advanced invasion sites remained independent prognostic factors for OS and CSS. Based on the

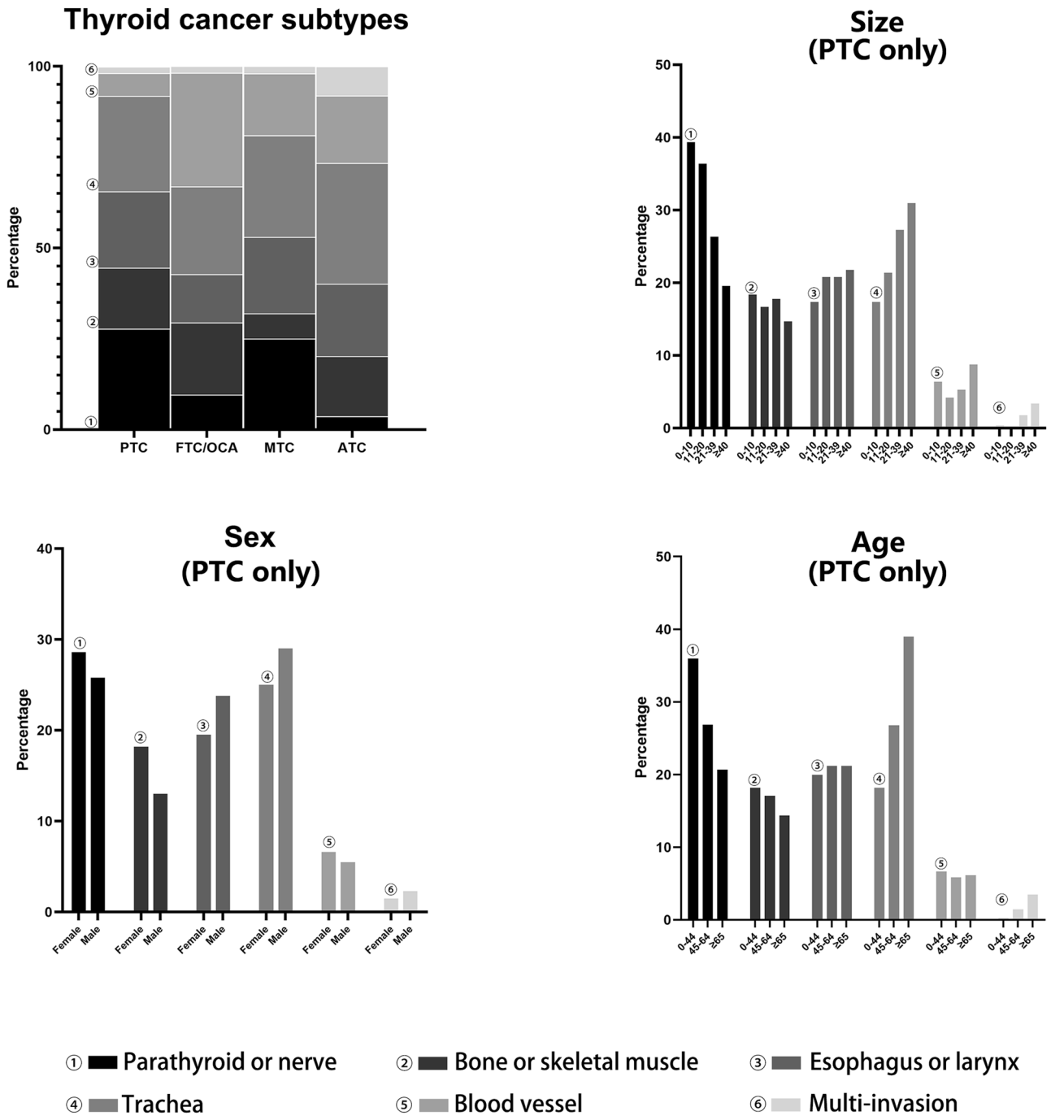

Fig. 1 Locally advanced invasion patterns by thyroid cancer subtypes, age, tumor size and sex. PTC papillary thyroid carcinoma, FTC follicular thyroid carcinoma, OTC oncocytic thyroid carcinoma, MTC medullary thyroid carcinoma, ATC anaplastic thyroid cancer

8th AJCC T staging and hazard ratio of cancer-specific mortality, different locally advanced invasion sites were categorized into a new site-based risk stratification with four layers: (1) Extremely low risk: Parathyroid or nerve invasion (HR = 1); (2) Low risk: Esophagus or larynx invasion (HR = 1.50) and bone or skeletal muscle invasion (HR = 1.50); (3) Medium risk: Trachea invasion (HR = 1.83); (4) High risk: Blood vessel invasion (HR = 2.64) and multi-invasion (HR = 2.76). Figure 4 demonstrates the survival curves based on this novel site-based risk stratification and 8th AJCC T staging, with the new risk stratification showing better discrimination in survival outcomes. The 15-year CSS rates of new prognostic stratification system were 88.8, 79.3, 68.9 and 57.1% for four layers, respectively, while those of 8th AJCC staging system were 76.6 and 62.1% for stage T4a and stage T4b.

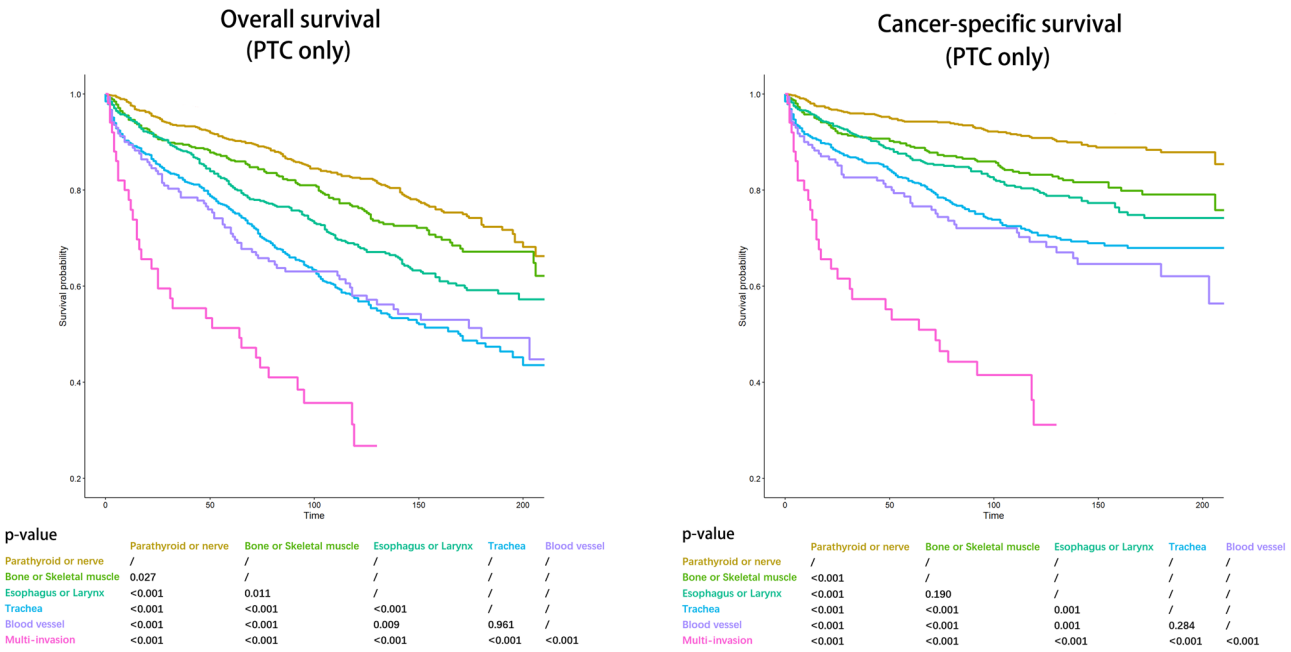

Fig. 2 Outcomes of locally advanced PTC patients stratified by invasion sites

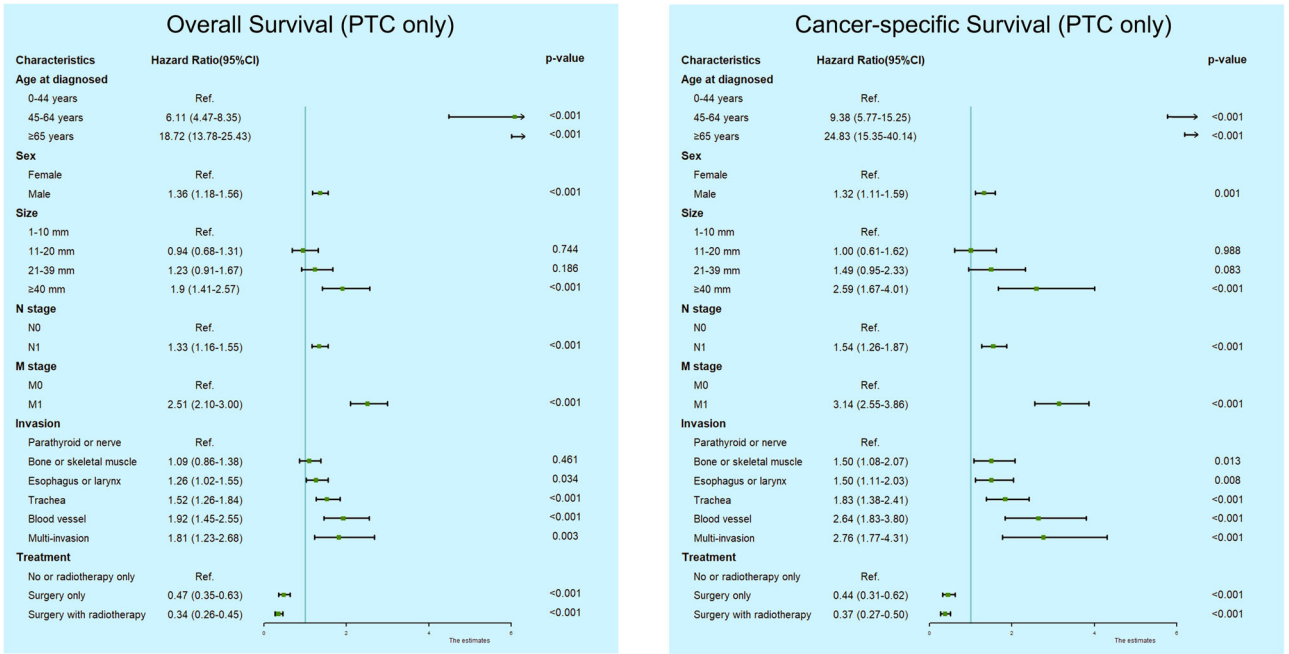

Fig. 3 Multivariable Cox regression analyses of OM and CSM in locally advanced PTC patients. OM overall mortality, CSM cancer-specific mortality, PTC papillary thyroid carcinoma

Discussion

Recent epidemiological studies have suggested a real increase in the incidence of LATC patients [2, 19]. The stark contrast between poor prognosis and increased incidence underscores the critical need for heightened clinical attention to patients with locally advanced disease. However, current literature on locally advanced thyroid cancer is predominantly based on small sample cohorts, which may introduce potential selection bias and confounding factors [6, 7, 10, 12, 16, 20, 21]. This study is the first to utilize the SEER database, a nationwide large sample cohort, to provide comprehensive data on the factors predicting locally advanced invasion and influencing invasion

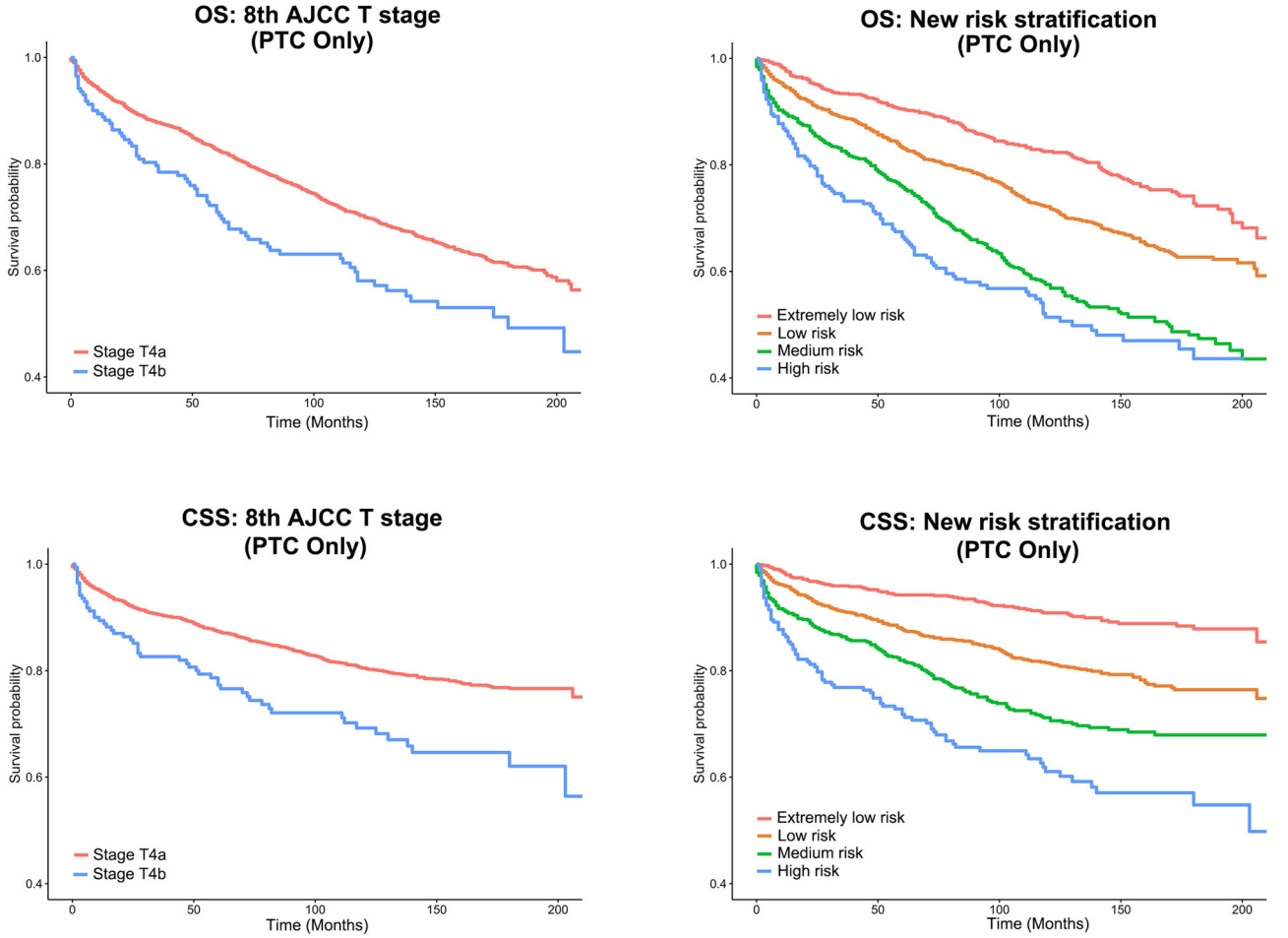

Fig. 4 Cancer-specific survival curves comparing the 8th AJCC staging system and the new site-based risk stratification system in locally advanced PTC patients. Extremely low risk: parathyroid or nerve invasion (15-year CSS rate: 88.8%); Low risk: bone or skeletal muscle invasion and esophagus or larynx invasion (15-year CSS rate: 79.3%); Medium risk: trachea invasion (15-year CSS rate: 68.9%); High risk: blood vessel invasion and multi-invasion (15-year CSS rate: 57.1%); Stage T4a: (15-year CSS rate: 76.6%); Stage T4b: (15-year CSS rate: 62.1%)

patterns in LATC patients. Furthermore, this study explored the significant different survival outcomes across various invasion sites and established a novel site-based risk stratification based on 8th AJCC T staging for locally advanced PTC patients, which demonstrated better discrimination than 8th AJCC T staging.

Previous researches have reported that LATC patients with R0 resection (no tumor residue) or R1 resection (microscopic tumor residue) have better prognoses than those with R2 resection (macroscopic tumor residue) [10, 12]. One of the challenges in surgical intervention is distinguishing LATC patients and their invasion sites preoperatively to avoid R2 resection due to inefficient preoperative preparation. Ultrasound is the most common examination for screening suspicious LATC patients and consequent computerized tomography or magnetic resonance imaging are employed in these patients to identify specific invasion sites. However, considering the sensitivity and specificity of ultrasound, understanding the factors predicting locally advanced invasion and influencing invasion patterns may help decide further imaging examinations, find specific invasion sites and improve surgery performance. Xu et al. suggested that the distribution of age, sex, tumor size, N stage and M stage significantly changed from no extrathyroidal extension to extrathyroidal extension [22]. Similarly, this study further found that patients aged≥65 years ($HR = 1.91$, $p < 0.001$), those with tumor size ≥40 mm ($HR = 2.48$, $p < 0.001$), those with lymph node metastasis ($HR = 1.32$, $p < 0.001$), those with distant metastasis ($HR = 1.52$, $p < 0.001$) and those with MTC ($HR = 1.31$, $p < 0.001$) or ATC ($HR = 1.56$, $p < 0.001$) were more likely to have locally advanced invasion progressing from strap muscle invasion. These findings indicate that more attention and further imaging examinations should be paid to potential LATC patients with these characteristics.

Wang et al. investigated the invasion patterns in locally advanced differentiated thyroid carcinoma patients, and found that recurrent laryngeal nerve and trachea invasion were most common [12]. Our study further explored the influence of thyroid cancer subtypes, tumor size, age and sex on invasion patterns. Consistent with Wang's findings, our results suggest that for the management of PTC patients, potential parathyroid or nerve invasion and trachea invasion should be emphasized, while potential blood vessel invasion should be more monitored in FTC/OTC patients and ATC patients. Additionally, elderly patients, those with large tumors, and male patients demonstrated higher rates of trachea invasion, rather than isolated parathyroid or nerve invasion. Integration of these parameters in suspicious LATC patients can inform the focus of imaging examinations and guide the selection of surgical procedures and comprehensive treatment planning. This may mitigate risks of intraoperative cessation, tumor residual (due to R1/R2 resection), or increased complication rates resulting from missed diagnoses of locally advanced invasion in clinical practice [14, 15, 23].

According to the 8th AJCC T staging system, invasion of subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve invasion is classified as T4a, while tumor encasement of the carotid artery or mediastinal vessels is defined as T4b. Some clinicians consider this risk stratification inadequate, as they have observed significantly different survival outcomes associated with various invasion sites and it does not take multi-invasion into account. Abraham et al. found that patients with multi-invasion had a fivefold increased risk of recurrence compared to those with single-site invasion [17]. Moreover, previous studies attempting to demonstrate the prognosis of specific invasion sites, but they reported significantly conflicting results, likely due to selection bias and confounding effects [6, 16, 18]. For instance, Sessa et al. reported a 5-year disease-free rate of approximately 65% for patients with trachea invasion, while Song et al. found it to be 80% [6, 16]. Our study is the first to utilize a large sample cohort to reveal prognostic variations by different invasion sites in locally advanced PTC patients. Our findings illustrated that almost every invasion site is associated with significantly different survival outcomes, suggesting the necessity for a new, detailed site-based risk stratification system. After adjusting for confounding factors by multivariable Cox regression, all LATC patients could be stratified into four risk layers based on CSS rates: (1) Extremely low risk: parathyroid or nerve invasion (15-year CSS rate: 88.8%); (2) Low risk: bone or skeletal muscle invasion and esophagus or larynx invasion (15-year CSS rate: 79.3%); (3) Medium risk: trachea invasion (15-year CSS rate: 68.9%); (4) High risk: blood vessel invasion and multi-invasion (15-year CSS rate: 57.1%). Survival curves comparing the 8th AJCC T staging and this new risk stratification showed that new site-based risk stratification offers better discrimination. This novel stratification enables tailored treatment strategies based on preoperatively identified invasion sites, with more aggressive approaches considered for sites associated with poorer prognosis. For instance, the implementation of neoadjuvant targeted or immunological therapy may be more strongly considered in patients with trachea invasion, blood vessel invasion, or multi-invasion to potentially improve prognostic outcomes in these patients.

Our study has several limitations. Firstly, since SEER database only registers initial LATC patients, the prognosis of patients with recurrent LATC, who may be more common in clinical practice, could not be assessed. Further studies containing both initial and recurrent LATC patients should be conducted in the real world to validate our findings. Secondly, our results revealed that LATC showed a significantly increased rate of distant metastasis, especially in patients with locally advanced FTC/OTC, MTC, and ATC. These patients may have unique prognostic profiles, but they were not the focus of this study. Further relevant studies are needed to address this subgroup. Thirdly, due to the limitation of SEER records ('CS extension'), the calculation of parathyroid or nerve invasion rates in our results only include patients with isolated parathyroid or nerve invasion (refer to the methods section), which may underestimate the true proportion of parathyroid or nerve invasion (refer to previous studies [6, 7, 12]). Finally, the lack of information about invasion depth in the SEER database made it difficult to further stratify prognosis among specific invasion sites, particularly in patients with trachea invasion. Future studies containing detailed invasion depth and different surgical procedures in single invasion site should be conducted.

Conclusion

This study is the first to utilize the SEER database to investigate the predictive factors of locally advanced invasion and influence of thyroid cancer subtypes, tumor size, age and sex on invasion patterns. These findings may help reduce the likelihood of incomplete surgical treatment due to preoperative misdiagnosis. Furthermore, this study systematically examined the significantly different survival outcomes among various invasion sites and proposed a novel site-based risk stratification system for locally advanced PTC patients, building upon the 8th AJCC T staging. This innovative risk stratification categorized LATC patients into 4 distinct risk layers: extremely low risk, low risk, medium risk, high risk. The new system demonstrated better discriminatory power than 8th AJCC T staging, providing robust evidence to support the implementation of tailored clinical management strategies based on survival outcomes.

Data availability

No datasets were generated or analysed during the current study.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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