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Prognostic Indicators and Comparative Treatment Outcomes in High-Risk Thyroid Cancer with Laryngotracheal Invasion

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Background: Laryngotracheal invasion occurs in a subset of patients with well-differentiated thyroid cancer (WDTC) and is associated with a poor prognosis. We aimed to analyze patterns and predictors/outcomes related to this high-risk manifestation.

Methods: This population-based analysis utilized the Surveillance, Epidemiology, and End Results (SEER) registry (2000 to 2015) to identify WDTC patients. Temporal trends and geographic variation in invasion rates were assessed. Logistic regression and propensity score matching were employed to identify predictors of secondary malignancy, mortality, and treatment impact on overall and thyroid cancer (TC)-specific survival.

Results: Of 131,721 WDTC patients, 1,662 (1.3%) had tracheal invasion and 976 (0.7%) had laryngeal invasion at diagnosis. Tracheal and laryngeal invasion rates declined from 3.7%–0.7% and 1.5%–0.6%, respectively, from 2000 to 2015. Compared to 98,835 noninvasive cases, patients with laryngotracheal invasion were older and more often male, Asian, and Hispanic (all $P<0.001$). This group had larger tumors with higher rates of nodal (N1: 61.8% vs. 15.1%) and distant metastases (M1: 9.3% vs. 0.4%). Age ≥55 years (hazard ratio [HR], 1.19; $P=0.004$) and metastases (HR, 1.75; $P<0.001$) increased TC-specific mortality, whereas the converse pattern was found for Asian race (HR, 0.63; $P=0.002$) and surgery (HR, 0.35; $P<0.001$). In rigorously matched groups to control confounding, adding radioactive iodine to surgery reduced mortality by 30% ($P<0.001$). However, external beam radiation and systemic therapy did not improve survival over surgery alone.

Conclusion: Laryngotracheal invasion is present in 0.7% to 1.3% of cases, conferring over double the mortality risk. Radioactive iodine with surgery improves outcomes in this aggressive WDTC subset.

Keywords: Prognostication; Thyroid neoplasms; Precision medicine; Extrathyroidal extension; Mortality predictors; Risk stratification

INTRODUCTION

Thyroid cancer is the fastest-growing cancer diagnosis worldwide, marked by an alarming increase in incidence over the past few decades [1,2]. In the United States (US), it is now the fifth most common cancer among women, with more than 43,700 new cases reported annually (https://seer.cancer.gov/statfacts/html/thyro.html). Although improved imaging and diagnostic

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techniques have played a role in this rise, changes in tumor biology might also be contributing factors [3,4].

The prognosis for well-differentiated papillary and follicular subtypes is generally favorable, largely due to their responsiveness to standard treatments [5]. Specifically, the 10-year relative survival rate exceeds 90%, primarily due to the effectiveness of surgery and radioactive iodine therapy following diagnosis [6-8]. However, approximately 20% of patients develop regional extrathyroidal extension (ETE) and distant metastases, which significantly increase the risks of recurrence and mortality [9,10].

Of particular concern is the invasion of the thyroid capsule into adjacent laryngotracheal structures, a pathway that indicates poor differentiation and an advanced T3/T4 stage designation [11-13]. The incidence of laryngotracheal invasion is reported to range from 1% to 16% among those with well-differentiated thyroid cancers (WDTCs) [14,15]. This extensive invasion often necessitates high-risk surgeries, such as laryngectomy or tracheal resection, which are associated with significant morbidity [16,17]. Furthermore, laryngotracheal invasion is associated with a 5-year disease-specific survival rate as low as 63% and a mortality rate up to five times higher than that of noninvasive disease [15].

While detrimental to prognosis, quality of life, and survival, significant gaps remain in our comprehensive understanding of the patterns, optimal prognostication, and evidence-based management strategies for laryngotracheal invasion [18]. Many studies have limitations due to small, retrospective samples that lack diversity and generalizability [19]. In this study, we utilized the extensive Surveillance, Epidemiology, and End Results (SEER) registry, which includes data from over 130,000 US thyroid cancer patients diagnosed over nearly three decades. Our goal was to definitively analyze the demographic and clinical factors that influence outcomes throughout the disease course. It is anticipated that the findings of this study will provide insights into enhancing tools for personalized risk stratification and therapeutic decisions in cases of aggressive thyroid cancer by extensively characterizing geographic distribution, temporal trends, pathological patterns, and prognostic factors, ultimately contributing to improvements in patient care.

METHODS

Data source

Our study utilized data from the SEER program's 17 registries, which cover approximately 28% of the US population from 2000 to 2019. The SEER database is a nationally representative, comprehensive source of population-based information, encompassing cancer incidence and survival data across various geographic areas and demographics.

Study population

The study involved a retrospective analysis of a database containing de-identified subjects, which exempted it from requiring Institutional Review Board approval (#2023-449). The initial registry included 203,728 patients diagnosed with thyroid cancer, after excluding 278 patients diagnosed incidentally at autopsy and 37 identified through death certificates. Our focus was on the 131,721 patients who had histologically confirmed cancer, comprising 123,918 with papillary thyroid cancer (PTC) and 7,803 with follicular thyroid cancer (FTC). ETE data were categorized into three groups: no ETE, confined to the thyroid (n=98,835); minimal ETE, extending to the sternothyroid muscle or perithyroid soft tissues (n=14,237); and gross ETE, involving capsular invasion, subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve, prevertebral fascia, major blood vessels, and mediastinum (n=18,649) [20,21]. The current study compared 2,329 patients with laryngeal (n=976) or tracheal invasion (n=1,662) to the group without ETE (n=98,835), excluding those with minimal ETE. Data of interest spanned from 2000 to 2015. Our study specifically targeted T4a tumors with laryngotracheal invasion, representing a distinct group where aggressive surgical intervention is both feasible and potentially advantageous. T4a tumors are classified as stage III disease, where aggressive surgical resection followed by adjuvant therapy is typically recommended. In contrast, T4b tumors, classified as stage IV disease, are generally deemed unresectable, with treatment shifting towards non-surgical options such as systemic therapy (e.g., tyrosine kinase inhibitors and radiation). In some instances, near-total gross resection may be considered for palliative purposes [22,23].

We identified laryngotracheal ETE using two variables from the SEER database: (1) T stage and (2) extent of invasion to adjacent structures. This was applied to 722 cases where the T stage was missing, as shown in Table 1. This method ensured the inclusion of all instances of laryngotracheal invasion in T4a tumors, capturing cases that might have been overlooked if only the T stage were considered.

Study variables

The parameters examined in our study included a broad range of demographic, clinical, and therapeutic factors. These covered

Table 1. Characteristics of the Study Population

Characteristic	Total (*n*=101,164)	No ETE (*n*=98,835)	Laryngotracheal ETE (*n*=2,329)	*P* value
Demographics				
Age				
Median age, yr	49 (38–60)	49 (38–59)	59 (46–71)	<0.001[a]
≤55	64,675 (63.9)	63,720 (64.5)	955 (41.0)	<0.001[a]
>55	36,489 (36.1)	35,115 (35.5)	1,374 (59.0)	
Sex				<0.001[a]
Female	79,111 (78.2)	77,607 (78.5)	1,504 (64.6)	
Male	22,053 (21.8)	21,228 (21.5)	825 (35.4)	
Race				<0.001[a]
White	83,344 (83.2)	81,501 (83.3)	1,843 (79.4)	
Black	6,516 (6.5)	6,405 (6.5)	111 (4.8)	
Asian or Pacific Islander	9,756 (9.7)	9,411 (9.6)	345 (14.9)	
American Indian/Alaska native	601 (0.6)	578 (0.6)	23 (1.0)	
Hispanic/Latino				<0.001[a]
No	86,891 (85.9)	85,115 (86.1)	1,776 (76.3)	
Yes	14,273 (14.1)	13,720 (13.9)	553 (23.7)	
Marital status				<0.001[a]
Married/domestic partner	63,730 (66.1)	62,334 (66.2)	1,396 (61.9)	
Single	19,612 (20.4)	19,232 (20.4)	380 (16.8)	
Separated/divorced	8,098 (8.4)	7,903 (8.4)	195 (8.6)	
Widowed	4,923 (5.1)	4,637 (4.9)	286 (12.7)	
Residency				0.510
Rural	10,158 (10.1)	9,915 (10)	243 (10.5)	
Urban	90,909 (89.9)	88,828 (90)	2,081 (89.5)	
Household income				0.560
≥$75,000	67,547 (66.8)	65,970 (66.7)	1,577 (67.7)	
<$75,000	33,607 (33.2)	32,855 (33.2)	752 (32.3)	
Presentation				
Histological type				0.150
Papillary	96,481 (95.4)	94,245 (95.4)	2,236 (96)	
Follicular	4,683 (4.6)	4,590 (4.6)	93 (4.0)	
Prior cancer before TC				<0.001[a]
Negative	89,397 (88.4)	87,427 (88.5)	1,970 (84.6)	
Positive	11,767 (11.6)	11,408 (11.5)	359 (15.4)	
T staging				<0.001[a]
T1	60,973 (73.7)	60,973 (75.2)	0	
T2	15,227 (18.4)	15,227 (18.8)	0	
T3	4,828 (5.8)	4,828 (6.0)	0	
T4a	1,425 (1.7)	53 (0.1)	1,372 (85.4)	
T4b	235 (0.3)	0	235 (14.6)	
N staging				<0.001[a]
N0	82,553 (83.9)	81,719 (84.9)	834 (38.2)	
N1	15,895 (16.1)	14,547 (15.1)	1,348 (61.8)	
M staging				<0.001
M0	100,506 (99.3)	98,393 (99.6)	2,113 (90.7)	
M1	658 (0.7)	442 (0.4)	216 (9.3)	

Values are expressed as median (interquartile range) or number (%). Two-sided chi-square and Fisher exact tests were used. A tumor of any size that invades the subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve is staged as T4a, while a tumor that invades prevertebral fascia, mediastinal vessels, or carotid artery is staged as T4b, according to the International Union Against Cancer.
ETE, extrathyroidal extension; TC, thyroid cancer.
[a]*P*<0.05.

age, sex, racial background, Hispanic/Latino ethnicity, urban or rural residency, household economic status, histopathological subtype, tumor size, and tumor-node-metastasis (TNM) staging. We also assessed factors such as tumor laterality, surgical interventions targeting the cancer, radiation therapy, and systemic therapeutic approaches.

Study outcomes

Our study outcomes were multifaceted, reflecting the aim to provide a comprehensive understanding of WDTC with laryngotracheal invasion. Initially, we conducted a longitudinal analysis to assess trends in the incidence of laryngotracheal invasion in WDTC, identifying any annual increases or decreases over time. Second, we compared demographic and clinical characteristics between patients with and without laryngotracheal invasion. Third, we focused on prognostic indicators by analyzing disease recurrence rates, the prevalence of second primary malignancies, overall survival, and thyroid cancer-specific survival rates across different groups. We defined a second primary malignancy as any new primary cancer that occurs in a patient with a history of thyroid cancer, using the SEER multiple primary codes and confirming through a review of site-specific factors.

We also identified independent predictors of second malignancies and mortality. Fourth, we examined the therapeutic modalities employed, including the type of surgery, use of adjuvant radiation, radioactive iodine, and systemic therapy. We analyzed the impact of treatment decisions and delays on patient survival outcomes. Fifth, we accounted for potential confounding using propensity score matching to compare survival between treatment groups, specifically for surgery alone versus surgery combined with radiation or systemic therapy. Lastly, we reported on common non-cancer causes of mortality among laryngotracheal invasion patients over long-term follow-up.

Propensity score matching

To account for potential confounding factors, we implemented 1:1 nearest neighbor propensity score matching without replacement. This method was based on a range of covariates, including age, sex, race, ethnicity, income, residence, tumor size, nodal stage, metastases, and histology. The matching process involved the following treatment groups: (1) 25 patients receiving no management were matched to 25 undergoing only surgery; (2) 345 patients treated with surgery and radioactive iodine were matched to 345 receiving surgery alone; (3) 253 patients receiving external beam radiation (EBR) in addition to surgery were matched to 253 undergoing surgery alone; (4) 48 patients treated with systemic therapy and surgery were matched to 48 undergoing surgery alone; (5) 346 patients receiving triple therapy (surgery, radioactive iodine, and systemic therapy) were matched to 346 undergoing surgery alone; and (6) 64 patients treated with systemic therapy, surgery, and EBR were matched to 64 undergoing surgery alone.

Statistical analysis

All analyses were conducted using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria; 2022) on macOS Ventura 13.3.1 (Apple Inc., Cupertino, CA, USA) and SPSS version 27.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as frequencies and percentages, while continuous variables were reported as mean with standard deviation or median with interquartile range (IQR). The chi-square and Fisher exact tests were used to compare groups for categorical data. For continuous variables, the Student *t* test or Mann-Whitney *U* test was applied, with a two-sided significance level set at 0.05. Trends in the incidence of laryngotracheal invasion over time were assessed using joinpoint regression. Logistic regression was used to identify independent predictors of recurrence and second malignancy, adjusting for confounders; odds ratio (OR) and 95% confidence interval (CI) were reported. Kaplan-Meier curves were drawn to depict survival outcomes, and the log-rank test with Bonferroni adjustment for multiple comparisons was used to assess survival differences between groups. Cox proportional hazards regression was employed to identify prognostic factors for survival, presenting hazard ratio (HR) and 95% CI.

RESULTS

Overall analysis of the study population

The workflow of patient selection is demonstrated in Fig. 1. The study examined data on 131,721 patients diagnosed with WDTC from the SEER database. Among these, 123,918 had PTC and 7,803 were diagnosed with FTC. Between 2000 and 2015, tracheal invasion occurred in 1,662 cases, while laryngeal invasion was noted in 976 cases, accounting for 1.30% and 0.70% of all WDTC patients, respectively. Notably, 309 of these patients experienced both laryngeal and tracheal invasions (Fig. 2A).

Temporal analysis of laryngotracheal invasion in WDTC cases

The age-adjusted incidence rate of thyroid cancer consistently increased over time. In 2000, the rate was 7.67 new cases per

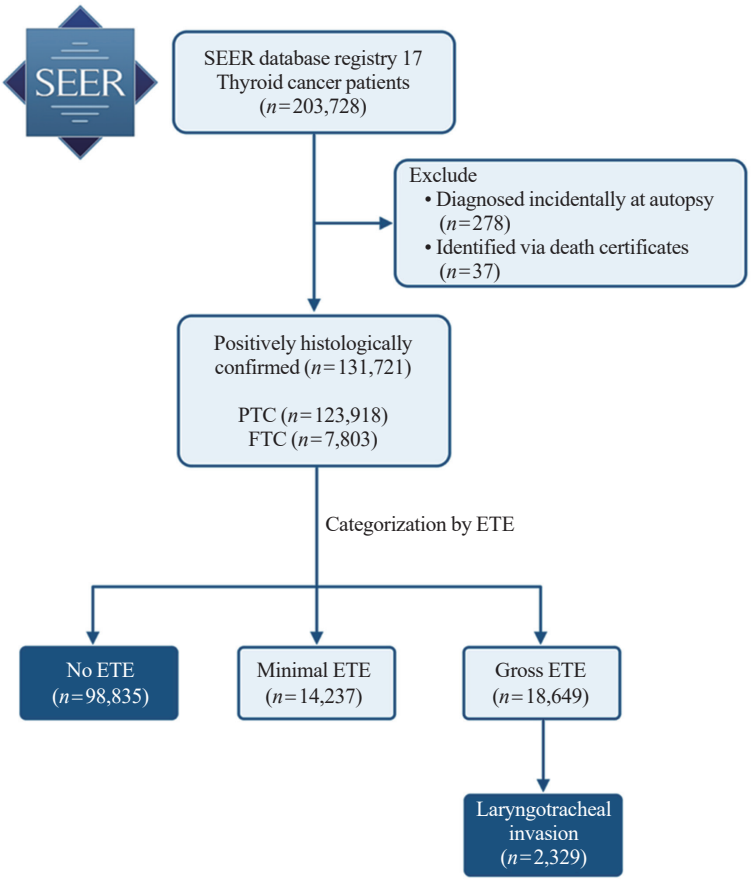

Fig. 1. Patient selection flowchart. From an initial pool of 203,728 thyroid cancer patients in the Surveillance, Epidemiology, and End Results (SEER) database, we excluded 315 cases (278 diagnosed at autopsy, 37 from death certificates). Of the remaining 131,721 histologically confirmed cases (123,918 papillary thyroid cancer [PTC] and 7,803 follicular thyroid cancer [FTC]), patients were categorized by extrathyroidal extension (ETE): 98,835 without ETE, 14,237 with minimal ETE (excluded), and 18,649 with gross ETE. Among gross ETE cases, 2,329 had laryngotracheal invasion (976 laryngeal, 1,662 tracheal, and 309 both). The final study population comprised 101,164 patients: 98,835 without ETE and 2,329 with laryngotracheal invasion. The image was created using BioRender (www.biorender.com).

100,000 people. It doubled by 2015, reaching 14.89 new cases per 100,000 people (Fig. 2B). Conversely, the rates of tracheal and laryngeal invasion showed a steady decline during the same period. The incidence of tracheal invasion peaked at 3.7% in 2000 but gradually decreased to 0.7% by 2015 ($P<0.001$). Laryngeal invasion followed a similar pattern, starting at 1.5% in 2000 and decreasing to 0.6% by the end of the study period ($P<0.001$), as illustrated in Fig. 2C.

When classifying the data by cancer type, tracheal invasion was observed in 1.3% of PTC patients ($n=1,587$) and 1% of FTC patients ($n=75$). Laryngeal invasion was less common, occurring in 0.7% of PTC patients ($n=928$) and 0.6% of FTC patients ($n=48$) (Fig. 2D). The incidence of tracheal invasion in PTC patients peaked in 2000 at 3.80% and then progressively declined, reaching 0.70% by 2015. A similar decreasing trend was noted in FTC, with the highest incidence at 3.30% in 2001, decreasing to the lowest point of 0.20% by 2009, despite some fluctuations in the intervening years (Fig. 2E). Laryngeal invasion in both PTC and FTC also showed an overall downward trend. The incidence rate of laryngeal invasion in PTC decreased from 1.50% in 2000 to 0.60% in 2015. Notably, FTC exhibited a more pronounced decline, from 2.20% in 2000 to no reported cases of laryngeal invasion in 2015 (Fig. 2F).

Spatial analysis for laryngotracheal invasion in WDTC cases

The geospatial analysis of laryngotracheal invasion in WDTC patients across the US revealed significant disparities among different states, as shown in Supplemental Fig. S1. Alaska reported the highest incidence, with laryngotracheal invasion oc-

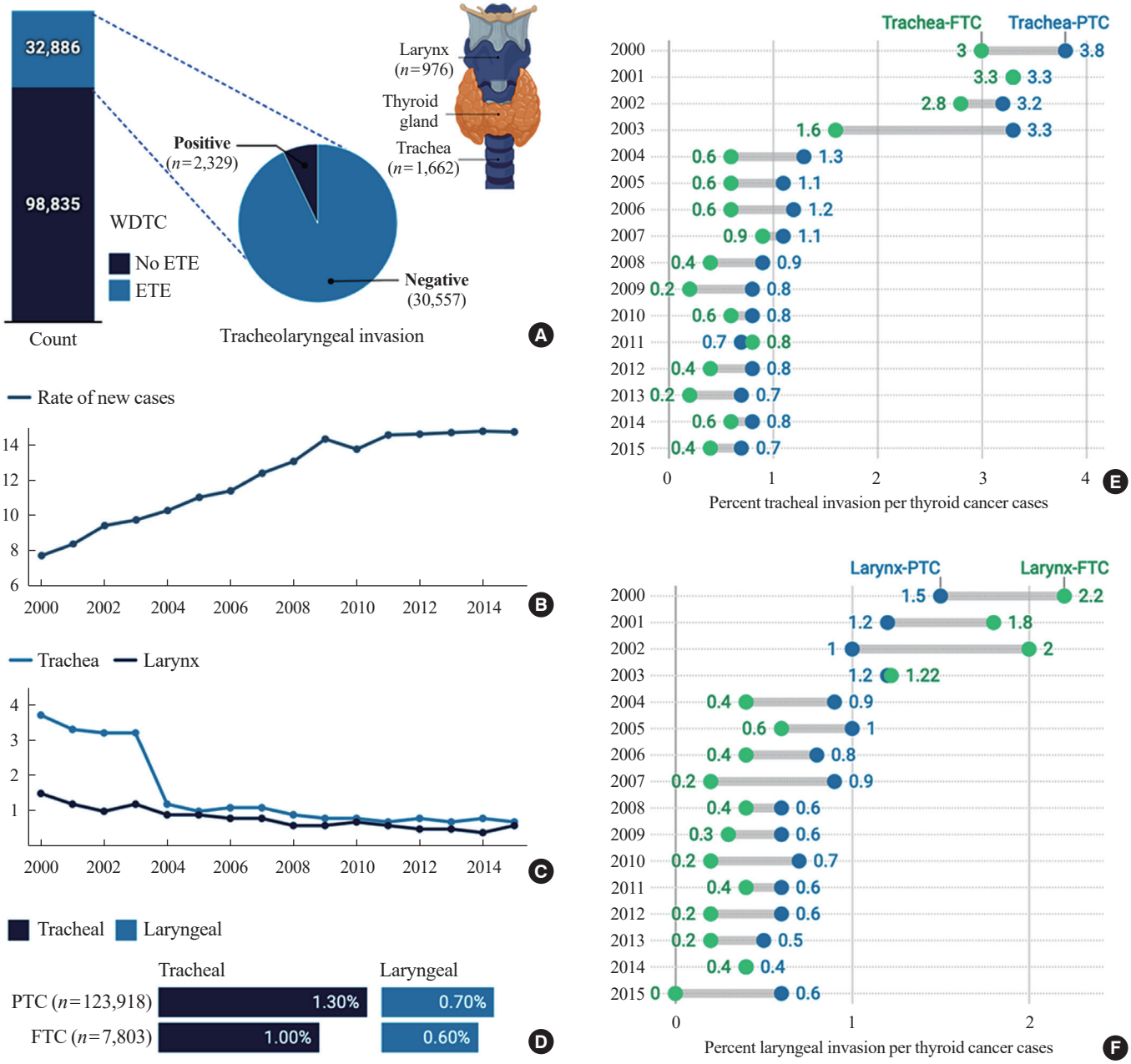

Fig. 2. Temporal trends and patterns in the incidence and invasion characteristics of well-differentiated thyroid cancer (WDTC), papillary thyroid cancer (PTC), and follicular thyroid cancer (FTC) in the United States over 15 years. (A) A bar chart representing the total study population of 131,721 WDTC patients, of whom 123,918 had PTC and 7,803 had FTC. Of those with extrathyroidal extension (ETE), 2,329 cases presented with laryngotracheal invasion. These included 1,662 patients with tracheal invasion and 976 cases with laryngeal invasion. (B) Age-adjusted incidence rates of thyroid cancer per 100,000 people. The line graph shows a consistent increase in the age-adjusted incidence rate of WDTC over time from 2000 to 2015, demonstrating. (C) Trends of laryngotracheal invasion in WDTC patients (n=131,721). Two-line graphs overlaid on each other represent the declining rates of tracheal and laryngeal invasion in WDTC patients over the years. (D) Prevalence of tracheal and laryngeal invasion in well-differentiated thyroid cancer. A bar chart illustrating the prevalence of tracheal and laryngeal invasion in PTC and FTC patients. The bars are categorized by cancer type and invasion location. (E) A range plot detailing the yearly incidence of tracheal invasion in PTC and FTC patients from 2000 to 2015, showing a decreasing trend over time. (F) Similar to Fig. 1E, this range plot shows the yearly incidence of laryngeal invasion in PTC and FTC patients, demonstrating a declining trend.

curring in 5.7% of the diagnosed WDTC patients (n=87) within the state. In contrast, Connecticut recorded the lowest incidence, with only 1.4% of the diagnosed patients in the area (n=6,313) experiencing this complication. Additionally, California, despite having the highest number of cases (n=39,731), reported an invasion rate of 3.0%.

Demographic and clinical characteristics of patients presenting with laryngotracheal invasion

Table 1 presents an analysis of 2,329 patients diagnosed with thyroid cancer who exhibited laryngotracheal invasion, comparing them to a control group of 98,835 patients without ETE. The study revealed distinct demographic characteristics in patients with laryngotracheal invasion. These patients were more likely to be over 55 years old (59% vs. 35.5%, P<0.001), male (35.4% vs. 21.5%, P<0.001), of Asian or Pacific Islander descent (14.9% vs. 9.6%, P<0.001), Hispanic/Latino (23.7% vs. 13.9%, P<0.001), widowed (12.7% vs. 4.9%, P<0.001), and to have a history of cancer prior to the diagnosis of thyroid cancer (15.4% vs. 11.5%, P<0.001). However, there were no significant differences in residency status (P=0.51) or household income (P=0.56) between the two groups.

In the context of pathological presentation, the classical variant of PTC exhibited a higher incidence of laryngotracheal invasion (3.80%) at the time of cancer diagnosis compared to its follicular variant (1.40%). Similarly, in FTC cases, the widely invasive variant demonstrated a higher prevalence of laryngotracheal invasion (2.50%) than the minimally invasive variant (0.60%). Intriguingly, patients with laryngotracheal invasion showed a markedly higher incidence of T4a tumors (85.4%) followed by T4b tumors (14.6%). These patients also had significantly higher rates of N1 (61.8% vs. 15.1%, P<0.001) and M1 staging (9.3% vs. 0.4%, P<0.001). Additionally, a strikingly high rate of coexisting esophageal invasion (35% vs. 0%) and distant metastasis to the lungs (10.7% vs. 0.2%) was identified in these patients.

Therapeutic strategies

Table 2 compares clinical outcomes and treatment strategies for patients with laryngotracheal invasion versus those without ETE. Regarding surgical management, although a high percentage of patients in both groups underwent cancer-directed surgery, those with laryngotracheal invasion were slightly less likely to receive this treatment compared to those without ETE (95.1% vs. 98.8%, P<0.001). Total thyroidectomy was the predominant surgical approach in both groups, yet it occurred more frequently among patients with laryngotracheal invasion (81.2% vs. 75.7%). In terms of additional therapies, patients with laryngotracheal invasion more commonly received radiation therapy (75.1% vs. 43.2%, P<0.001) and systemic therapy (54.6% vs. 47.2%, P<0.001) than those without ETE.

Clinical outcomes

Clinical outcomes were significantly worse for patients with laryngotracheal invasion compared to those without ETE. Although the recurrence rates were similar between the groups (0.6% with invasion vs. 0.4% without, P=0.07), the incidence of second primary cancers was markedly higher in patients with invasion (26.7% vs. 20.6%, P<0.001) (Table 2).

Predictors of second primary malignancies

Multivariate binary logistic regression analysis identified advanced age and non-Hispanic ethnicity as significant predictors of an increased likelihood of developing second primary malignancies in patients with laryngotracheal invasion (Supplemental Table S1). Specifically, patients aged 55 years or older were more than twice as likely to develop another malignancy compared to their younger counterparts (OR, 2.078; 95% CI, 1.551 to 2.785; P<0.001). Conversely, Hispanic patients exhibited lower odds of developing additional malignancies than non-Hispanics (OR, 0.605; 95% CI, 0.433 to 0.846; P=0.003). Other variables assessed, such as sex, race, income level, residence location, tumor histology, treatment modalities, and cancer stage, did not show significant predictive value.

Survival outcomes

Among 101,164 thyroid cancer patients included in the analysis, 10,794 (10.7%) died over a median follow-up period of 14.25 years (IQR, 12.88 to 15.61). Of these deceased patients, thyroid cancer was explicitly identified as the cause of death in 1,716 (15.8%) cases. Mortality rates were significantly higher in patients with laryngotracheal invasion compared to those without ETE. Specifically, the mortality rate for patients with laryngotracheal invasion was 44.0%, versus only 9.9% for patients without such invasion (P<0.001). Additionally, 25.8% of the deaths in the laryngotracheal invasion group were directly attributed to thyroid cancer, compared to just 1.1% in the noninvasive group (P<0.001) (Table 2).

Regarding survival outcomes, the estimated 5-year overall survival rate was 96% among patients without ETE, which slightly decreased to 91% at 10 years post-diagnosis. In contrast, for those with laryngotracheal invasion, the 5-year surviv-

Table 2. Clinical Outcomes and Management Strategies Employed for Patients with Laryngotracheal Invasion Compared to Those without ETE

Characteristic	Total (n=101,164)	No ETE (n=98,835)	Laryngotracheal ETE (n=2,329)	P value
Management				
Cancer-directed surgery				<0.001[a]
Overall	99,846 (98.7)	97,632 (98.8)	2,214 (95.1)	
Lobectomy and/or isthmectomy	17,011 (16.8)	16,860 (17.1)	151 (6.5)	
Subtotal thyroidectomy	5,314 (5.3)	5,177 (5.2)	137 (5.9)	
Total thyroidectomy	76,672 (75.8)	74,782 (75.7)	1,890 (81.2)	
Surgery, NOS	813 (0.8)	36 (1.5)	849 (0.8)	
Surgery at other sites				<0.001[a]
Regional sites or lymph nodes	366 (3.1)	310 (2.7)	56 (10.6)	
Distant lymph nodes	666 (5.6)	624 (5.5)	42 (8.0)	
Distant sites	376 (3.2)	294 (2.6)	82 (15.5)	
Adjuvant therapy				<0.001[a]
Radioactive ablation	41,244 (40.8)	39,887 (40.4)	1,357 (58.3)	
Radiation therapy	44,470 (44.0)	42,720 (43.2)	1,750 (75.1)	
Systemic therapy	33,833 (47.3)	33,143 (47.2)	690 (54.6)	
Outcomes				
Recurrence				
Positive	408 (0.4)	393 (0.4)	15 (0.6)	0.070
Second primary cancers				
Positive	20,966 (20.7)	20,345 (20.6)	621 (26.7)	<0.001[a]
Survival status				<0.001[a]
Alive	90,370 (89.3)	89,066 (90.1)	1,304 (56.0)	
Dead	10,794 (10.7)	9,769 (9.9)	1,025 (44.0)	
Cause of death				<0.001[a]
Alive	90,370 (89.3)	89,066 (90.1)	1,304 (56.0)	
Dead, other cancer	9,078 (9.0)	8,655 (8.8)	423 (18.2)	
Dead, TC	1,716 (1.7)	1,114 (1.1)	602 (25.8)	

Values are expressed as number (%). Two-sided chi-square and Mann-Whitney U tests were used.
ETE, extrathyroidal extension; NOS, not otherwise specified; TC, thyroid cancer.
[a]P<0.05.

al rate was 75%, which dramatically declined to 60% at 10 years. Kaplan-Meier survival curves illustrated that the mean overall survival time was 216.3±0.22 months in the noninvasive group, compared to 149.9±2.04 months for those with invasion (P<0.001). Similarly, the mean thyroid cancer-specific survival was 236.1±0.09 and 172.1±2.24 months in the two groups, respectively (P<0.001) (Fig. 3).

Causes of death in patients with laryngotracheal invasion

Among the 2,329 patients with laryngotracheal invasion, 602 (25.8%) died from thyroid cancer during the follow-up period, while 423 (18.2%) died from other causes. The primary causes of non-cancer-related deaths included other malignant cancers (n=134 out of 423, 31.68%), heart diseases (n=93, 21.99%), cerebrovascular events (n=23, 5.44%), chronic lower respiratory diseases (n=16, 3.78%), and diabetes (n=14, 3.31%) (Supplemental Fig. S2). At the initial diagnosis of thyroid cancer, the median age for those with laryngotracheal invasion was 59 years (IQR, 46 to 71). For those who died during the follow-up, the median age at death was significantly higher, at 73.3 years (IQR, 58.9 to 86.6).

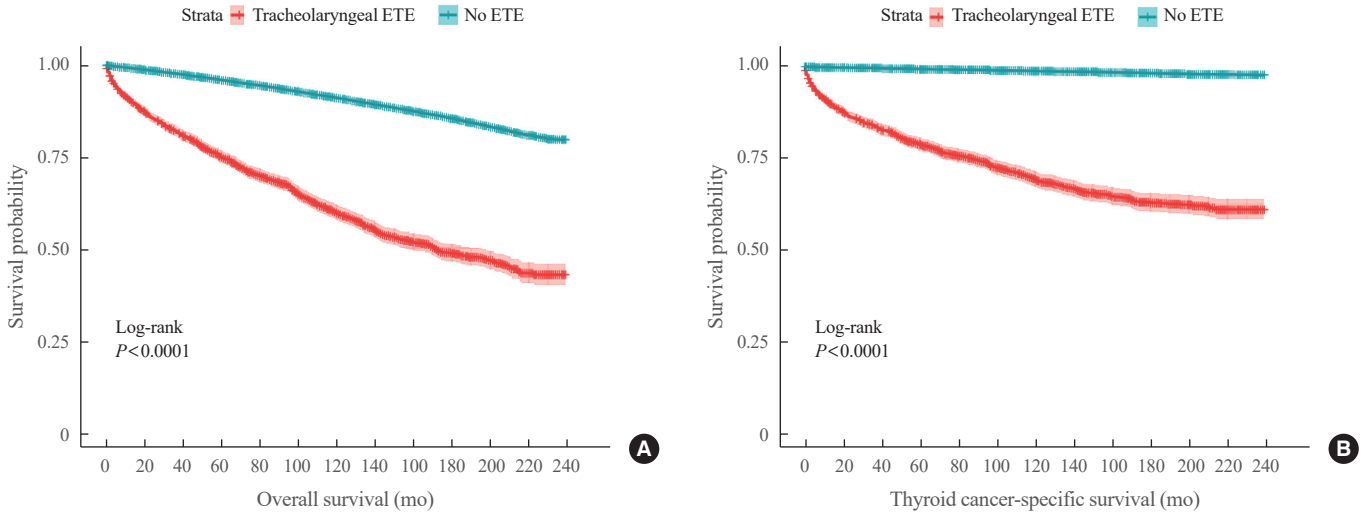

Fig. 3. Kaplan-Meier survival curves comparing patients with and without extrathyroidal extension (ETE). (A) Overall survival. The mean overall survival time was 216.3±0.22 months in the noninvasive group versus 149.9±2.04 months for those with laryngotracheal invasion (P<0.001). (B) Thyroid cancer-specific survival. The mean thyroid cancer-specific survival was 236.1±0.09 and 172.1±2.24 months in the two groups, respectively (P<0.001). The log-rank test was used for comparison.

Independent predictors of mortality in laryngotracheal invasion patients

Table 3 outlines the key demographic, clinical, and treatment factors that independently predict mortality outcomes in the thyroid cancer cohort with laryngotracheal invasion. Notably, being over the age of 55 emerged as the most significant risk factor, increasing the hazard of overall mortality by 18% (HR, 1.18; 95% CI, 1.05 to 1.33; P=0.005) and cancer-specific mortality by nearly six times (HR, 5.92; 95% CI, 4.69 to 7.48; P<0.001) compared to younger patients. Additionally, male sex slightly increased the hazard of cancer-specific mortality by 29% compared to females (HR, 1.29; 95% CI, 1.08 to 1.54; P=0.005).

In terms of race/ethnicity, individuals identified as Asian/Pacific Islander experienced a 38% lower hazard of cancer mortality than Caucasian individuals (HR, 0.62; 95% CI, 0.48 to 0.84; P=0.001). Conversely, Hispanic ethnicity was associated with a 32% increase in the hazard of overall mortality, though it did not affect cancer-specific mortality (HR, 1.32; 95% CI, 1.16 to 1.52; P<0.001). Neither annual household income nor urban versus rural residence significantly influenced mortality outcomes.

T4b tumors were associated with higher overall mortality (HR, 1.38; 95% CI, 1.14 to 1.67; P=0.001) and cancer-specific mortality (HR, 1.62; 95% CI, 1.28 to 2.05; P<0.001) than T4a tumors. Consistent with the biological behavior of the tumors, the presence of nodal metastases increased the hazard by 44% (HR, 1.44; 95% CI, 1.22 to 1.78; P<0.001), and distant metastases more than doubled the mortality hazard (HR, 2.52; 95% CI, 2.04 to 3.21; P<0.001).

Undergoing primary tumor resection (HR, 0.34; 95% CI, 0.26 to 0.52; P<0.001) and radioactive iodine therapy (HR, 0.50; 95% CI, 0.41 to 0.65; P<0.001) each independently conferred a reduction in cancer-specific mortality hazard by approximately 50% to 66%. EBR and systemic therapy, however, did not significantly affect mortality outcomes in this analysis.

Impact of treatment strategies on survival

As outlined in Table 4 and depicted in Kaplan-Meier plots (Fig. 4), the choice of adjuvant treatments significantly influenced both overall and cancer-specific mortality in patients with laryngotracheal invasive thyroid cancer. The addition of radioactive iodine ablation to primary surgery significantly increased mean overall survival by 17% (167.7 months vs. 133.2 months) and cancer-specific survival by 21% (189.8 months vs. 157.1 months) compared to surgery alone (both P<0.001). In contrast, EBR did not enhance either overall or cancer-specific survival when compared to surgery alone. Similarly, systemic therapies following surgery showed no survival advantage over surgery alone, and their combination with radioactive iodine did not further improve the benefits achieved with radioiodine and surgery (P=1.0). This suggests that surgery combined with radioactive iodine provides sufficient and optimal survival outcomes. Among non-surgical options, declining all treatments significantly reduced survival (both P<0.001), highlighting the importance of definitive local-regional treatment. Regarding treatment

Table 3. Predictors of Mortality in Thyroid Cancer Patients with Laryngotracheal Invasion

Variable	Overall mortality		Thyroid cancer-specific mortality	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age ≥55 years vs. <55 years	1.18 (1.05–1.33)	0.005[a]	5.92 (4.69–7.48)	<0.001[a]
Sex: male vs. female	1.05 (0.91–1.18)	0.450	1.29 (1.08–1.54)	0.005[a]
Race: Black vs. White	1.16 (0.88–1.53)	0.310	0.97 (0.63–1.52)	0.880
Race: Asian or Pacific Islander vs. White	1.10 (0.94–1.29)	0.260	0.62 (0.48–0.84)	0.001[a]
Race: American Indian/Alaska Native vs. White	1.13 (0.56–2.30)	0.740	2.04 (0.91–4.64)	0.090
Ethnicity: Hispanic/Latino vs. none	1.32 (1.16–1.52)	<0.001[a]	0.83 (0.67–1.04)	0.090
Income: ≥$75,000 vs. <$75,000	1.09 (0.97–1.24)	0.170	1.18 (0.98–1.47)	0.100
Residence: urban vs. rural	0.99 (0.82–1.20)	0.910	0.86 (0.66–1.23)	0.290
Histological type: FTC vs. PTC	0.64 (0.42–0.95)	0.023[a]	1.26 (0.82–2.2)	0.270
T staging: T4b vs. T4a	1.38 (1.14–1.67)	0.001[a]	1.62 (1.28–2.05)	<0.001[a]
N staging: N1 vs. N0	1.03 (0.90–1.16)	0.680	1.44 (1.22–1.78)	<0.001[a]
M staging: M1 vs. M0	1.75 (1.30–2.29)	<0.001[a]	2.52 (2.04–3.21)	<0.001[a]
Cancer-directed surgery vs. none	0.78 (0.42–1.43)	0.400	0.34 (0.26–0.52)	<0.001[a]
Radioactive iodine vs. none	1.13 (0.94–1.34)	0.200	0.50 (0.41–0.65)	<0.001[a]
External beam radiation vs. none	1.05 (0.85–1.27)	0.710	0.99 (0.80–1.29)	0.950
Systemic therapy vs. none	0.77 (0.65–1.02)	0.060	0.83 (0.68–1.03)	0.090

Multivariate Cox proportional hazards regression analysis was conducted, adjusting for potential demographic and clinical confounders, which included age, sex, race, ethnicity, income, residence, histological type, tumor staging, nodal staging, metastasis staging, and treatment modalities. HR and 95% CI were reported using surgery only as a reference.
HR, hazard ratio; CI, confidence interval; FTC, follicular thyroid cancer; PTC, papillary thyroid cancer.
[a]*P*<0.05.

Table 4. Survival Times of Thyroid Cancer Patients with Laryngotracheal Invasion

Treatment received	Overall mortality, mo			Thyroid cancer-specific mortality, mo		
	Mean	SD	*P* value	Mean	SD	*P* value
Cancer-directed surgery only	133.2	5.41	Ref	157.1	6.57	Ref
Surgery+RAI	167.7	2.61	<0.001[a]	189.8	2.69	<0.001[a]
Surgery+EBR	109.2	5.85	0.150	124.0	6.88	0.033[a]
Surgery+systemic therapy	86.9	8.64	0.990	99.3	10.5	0.990
Surgery+RAI+systemic therapy	156.7	5.63	0.004[a]	184.5	5.78	0.001[a]
Surgery+EBR+systemic therapy	84.9	10.9	0.008[a]	88.8	12.6	0.001[a]
No treatment	40.1	14.2	<0.001[a]	45.6	17.7	<0.001[a]

The log-rank test was used with the Bonferroni adjustment method.
SD, standard deviation; RAI, radioactive iodine ablation; EBR, external beam radiation.
[a]*P*<0.05.

timing, initiating therapy more than 1 month after diagnosis did not adversely affect multivariate-adjusted survival compared to earlier initiation (*P*>0.05).

Propensity-matched analyses reveal survival benefit differs by radiation modality

The characteristics of patients after propensity score matching are demonstrated in Supplemental Tables S2-S7. After matching, survival was compared between treatment pairs. The combination of radioactive iodine with surgery significantly reduced mortality hazard by 30% overall (HR, 0.70; 95% CI, 0.56 to 0.86; *P*<0.001) and 33% for cancer-specific mortality (HR, 0.67; 95% CI, 0.50 to 0.89; *P*=0.007) versus surgery alone. However, EBR with surgery showed no survival advantage over surgery,

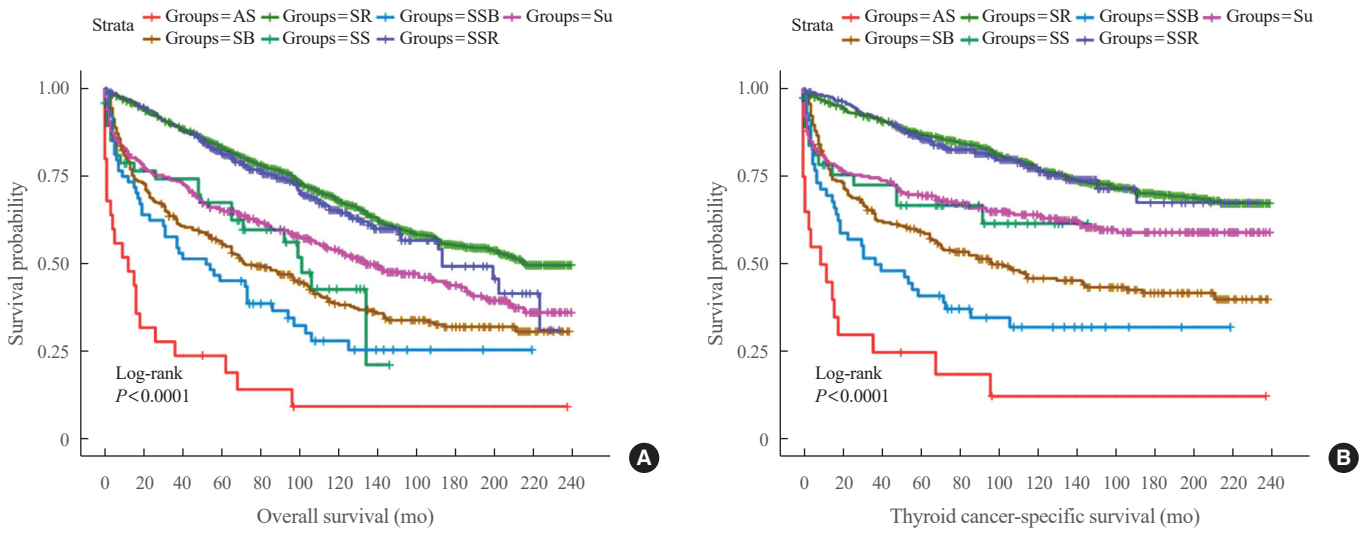

Fig. 4. Kaplan-Meier survival curves comparing patients who received different treatment modalities. (A) Overall survival. The curve depicts the probability of survival over time for all causes of death, comparing the different treatment modalities. (B) Thyroid cancer-specific survival. The curve shows the probability of survival without dying from thyroid cancer, highlighting the effectiveness of treatment modalities specifically against the cause of death of thyroid cancer. The log-rank test was used for comparison with the Bonferroni adjustment method. AS, active surveillance; SR, surgery+radioactive iodine ablation; SSB, surgery+systemic therapy+external beam radiation; Su, cancer-directed surgery only; SB, surgery+external beam radiation; SS, surgery+systemic therapy; SSR, surgery+systemic therapy+radioactive iodine ablation.

Table 5. Hazard Ratios for Mortality Comparing Treatment Groups after Propensity Score Matching

Pairwise comparison	Subject per arm	Overall mortality			Thyroid cancer-specific mortality		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Surgery+RAI vs. surgery only	345	0.70	0.56–0.86	<0.001[a]	0.67	0.50–0.89	0.007[a]
Surgery+EBR vs. surgery only	253	1.11	0.89–1.39	0.360	1.21	0.91–1.61	0.200
Surgery+systemic therapy vs. surgery only	48	0.81	0.47–1.41	0.460	0.60	0.29–1.26	0.180
Surgery+RAI+systemic therapy vs. surgery only	346	0.69	0.53–0.90	0.006[a]	0.62	0.43–0.88	0.009[a]
Surgery+EBR+systemic therapy vs. surgery only	64	1.58	1.01–2.47	0.046[a]	2.08	1.17–3.71	0.013[a]
No management vs. surgery only	25	0.97	0.53–1.76	0.910	1.01	0.48–2.12	0.980

Matching was performed using 1:1 nearest neighbor propensity score matching without replacement. Propensity scores were calculated using logistic regression based on the following covariates: age, sex, race, ethnicity, income, residence, tumor size, nodal stage, metastases, and histology. Matches were made using a caliper width of 0.2 of the standard deviation of the logit of the propensity score. The balance between matched pairs was assessed using standardized mean differences, with values <0.1 considered to indicate good balance. Univariate Cox regression models were conducted for each comparison. HR and 95% CI were reported using surgery only as a reference.
HR, hazard ratio; CI, confidence interval; RAI, radioactive iodine ablation; EBR, external beam radiation.
[a]*P*<0.05.

with non-significant HRs of 1.11 (95% CI, 0.89 to 1.39; *P*=0.36) for overall mortality and 1.21 (95% CI, 0.91 to 1.61; *P*=0.20) for cancer death. Systemic therapy combined with surgery also failed to improve survival, with non-significant HRs of 0.81 (95% CI, 0.47 to 1.41; *P*=0.46) and 0.60 (95% CI, 0.29 to 1.26; *P*=0.18) for overall and disease-specific metrics. Moreover, triple therapy regimens demonstrated diverging survival patterns by radiation type. Adding RAI reduced the mortality hazard by 31% overall (HR, 0.69; 95% CI, 0.53 to 0.90; *P*=0.006) and 38% for cancer-specific mortality (HR, 0.62; 95% CI, 0.43 to 0.88; *P*=0.009). However, substituting EBR raised the hazard by 58% (HR, 1.58; 95% CI, 1.01 to 2.47; *P*=0.046) and 108% (HR, 2.08; 95% CI, 1.17 to 3.71; *P*=0.013) (Table 5).

DISCUSSION

Our extensive analysis of more than 130,000 thyroid cancer patients revealed a declining trend in the incidence of laryngotracheal invasion, yet there remained a persistent, disproportionate mortality burden. In addition to uncovering dynamic geospatial and longitudinal patterns, we identified a comprehensive range of prognostic indicators and demonstrated significant survival benefits associated with the selective use of adjuvant radioactive iodine after surgery for high-risk invasive disease.

Despite thyroid cancer being identified as the most rapidly increasing malignancy in the US [2], our data clearly shows that the rates of tracheal and laryngeal invasion have decreased by over 50% since their peak in 2000. However, with 1,662 (1.3%) tracheal and 976 (0.7%) laryngeal invasive cases recorded among our 131,721 patients from 2000 to 2015, this phenotype remains clinically significant. This is due to its association with more than double the mortality risk compared to noninvasive disease and a 5-year survival rate below 60%, indicating a persistently poor prognosis. The decline in incidence rates likely reflects the delayed effects of increased screening and earlier detection at premalignant stages [24-26].

We also discovered substantial state-level variation in invasion, with rates of 1.4% to 5.7%. This likely reflects the impact of factors such as access to diagnostics and care, socioeconomic status, and environmental triggers on the detection of occult invasion and subsequent outcomes [27-29]. Our data provide a basis for reallocating resources to enhance early-stage diagnosis in demographics at higher risk. Further investigation into facility-level contributors could reveal actionable disparities and inform health policy initiatives aimed at targeting the highest-risk demographics [30].

Our regression models demonstrated prognostic utility for guiding frontline risk stratification. Factors such as advanced age, male sex, Hispanic ethnicity, nodal involvement, and distant metastases independently predicted the highest mortality risks, even after adjusting for confounders. Tailoring screening and management strategies based on these factors could enhance triage to specialty care and reduce adverse outcomes [30]. Interestingly, income and urban residency had negligible predictive value when controlling for nodal involvement and metastatic spread. This indicates that socioeconomic barriers to accessing specialty oncologic care might be overcome in the current healthcare environment [31]. Additionally, a 37% reduction in cancer-specific mortality among Asian patients has emerged as a novel, previously unrecognized protective factor. This finding warrants further investigation to determine whether environmental, genetic, or lifestyle factors are involved [32,33]. Elucidating the underlying factors in these ethnicities could significantly shape preventative and therapeutic approaches [34].

However, the most important finding from our up-to-date dataset and rigorous propensity-matched analysis is the significant 30% survival advantage derived solely from supplemental radioactive iodine following surgery for invasive disease. While previous studies were limited by small sample sizes and lacked appropriate comparison groups to definitively demonstrate the benefits of radioactive iodine [35-37], our latest evidence addresses these gaps. Given the high 10-year mortality rate, which exceeds 25%, this 30% reduction in hazard with radioactive iodine prevents early deaths during the initial high-risk years when locoregional progression peaks, before the survival curves gradually converge. This intervention also results in meaningful gains in quality-adjusted life years, as previously noted [38]. In our real-world data, neither EBR therapies nor systemic agents provided additional benefits beyond those achieved with radioactive iodine and surgery, unlike findings from earlier studies [39,40]. Collectively, these latest data strongly endorse updated guidelines [41] recommending surgery with radioactive iodine remnants ablation as the optimized evidence-based standard of care for regionally invasive thyroid cancer.

Despite the extensive contemporary dataset, several limitations must be acknowledged. Residual confounding due to unmeasured variables, the retrospective nature of the SEER data, and potential coding errors are inherent limitations. The SEER database, being a population-based registry, may exhibit different reporting patterns for ETE compared to institution-based studies, which could affect the proportion of cases without ETE in our analysis. Additionally, the database lacks detailed information on certain clinical variables, which limits our ability to conduct more comprehensive multivariate analyses. The generalizability to less common histological variants requires further investigation. Nonetheless, our multi-pronged analysis of population-based data, covering 16 years and involving over 130,000 patients, provides a robust assessment of this rare outcome. Future studies that include emerging mutational, transcriptomic, and radiographic predictors could further clarify which subgroups might benefit from adjuvant systemic therapies or EBR.

In conclusion, our contemporary analysis of over 130,000 thyroid cancer patients highlights a decline in laryngotracheal invasion, focusing on 2,329 residual cases of papillary and follicular types. In addition to identifying diverse prognostic indicators, we found a significant 30% survival benefit when radio-

active iodine was added to surgical treatment for this invasive disease, potentially reducing early mortality in this high-risk group. We aim for our real-world data to inform risk-adjusted guidelines that optimize the selection of adjuvant therapies and enhance patient outcomes. Advancing meaningful progress in the treatment of rare and aggressive cancer manifestations requires a thorough examination of uncommon histological types that are often neglected due to a gradual increase in less aggressive subtypes. Equally important is the need for future research to explore the generalizability and biological mechanisms of these findings. Continuing to translate population-level analytics into clinical practice to better manage these high-risk variants remains a top priority.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: E.A.T., J.A.J., M.H.H., A.A.M.S., M.S.F., E.K. Acquisition, analysis, or interpretation of data: E.A.T., J.A.J., M.H.H. Drafting the work or revising: E.A.T., J.A.J., M.H.H., A.A.M.S., M.S.F., E.K. Final approval of the manuscript: E.A.T., J.A.J., M.H.H., A.A.M.S., M.S.F., E.K.

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REFERENCES

1. Morris LG, Sikora AG, Tosteson TD, Davies L. The increasing incidence of thyroid cancer: the influence of access to care. Thyroid 2013;23:885-91.
2. Sanabria A, Kowalski LP, Shah JP, Nixon IJ, Angelos P, Williams MD, et al. Growing incidence of thyroid carcinoma in recent years: factors underlying overdiagnosis. Head Neck 2018;40:855-66.
3. Brito JP, Morris JC, Montori VM. Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours. BMJ 2013;347:f4706.
4. Wang C, Wu Z, Lei L, Dong X, Cao W, Luo Z, et al. Geographic disparities in trends of thyroid cancer incidence and mortality from 1990 to 2019 and a projection to 2030 across income-classified countries and territories. J Glob Health 2023;13:04108.
5. Liu W, Jiang B, Xue J, Liu R, Wei Y, Li P. Clinicopathological features of differentiated thyroid carcinoma as predictors of the effects of radioactive iodine therapy. Ann Diagn Pathol 2024;69:152243.
6. Handkiewicz-Junak D, Wloch J, Roskosz J, Krajewska J, Kropinska A, Pomorski L, et al. Total thyroidectomy and adjuvant radioiodine treatment independently decrease locoregional recurrence risk in childhood and adolescent differentiated thyroid cancer. J Nucl Med 2007;48:879-88.
7. Ciarallo A, Rivera J. Radioactive Iodine therapy in differentiated thyroid cancer: 2020 update. AJR Am J Roentgenol 2020;215:285-91.
8. Yang J, Zheng R, Liang M, Jia Y, Lin L, Geng J, et al. Association of the cumulative dose of radioactive iodine therapy with overall survival in patients with differentiated thyroid cancer and pulmonary metastases. Front Oncol 2019;9:558.
9. Anwar SL, Cahyono R, Suwardjo S, Hardiyanto H. Extrathyroidal extension and cervical node infiltration are associated with recurrences and shorter recurrence-free survival in differentiated thyroid cancer: a cohort study. Thyroid Res 2022;15:13.
10. Coca-Pelaz A, Shah JP, Hernandez-Prera JC, Ghossein RA, Rodrigo JP, Hartl DM, et al. Papillary thyroid cancer-aggressive variants and impact on management: a narrative review. Adv Ther 2020;37:3112-28.

11. Zhang J, Fu C, Cui K, Ma X. Papillary thyroid carcinoma with tracheal invasion: a case report. Medicine (Baltimore) 2019;98:e17033.
12. Nguyen QT, Lee EJ, Huang MG, Park YI, Khullar A, Plodkowski RA. Diagnosis and treatment of patients with thyroid cancer. Am Health Drug Benefits 2015;8:30-40.
13. Metere A, Aceti V, Giacomelli L. 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 2019;12:10.
14. Sharanappa V, Bichoo RA, Mishra A, Pradhan PK, Mishra SK. Circumferential laryngotracheal resection in thyroid cancer: experience and outcome in a single center. Indian J Otolaryngol Head Neck Surg 2022;74(Suppl 2):2629-35.
15. Piazza C, Lancini D, Tomasoni M, D'Cruz A, Hartl DM, Kowalski LP, et al. Tracheal and cricotracheal resection with end-to-end anastomosis for locally advanced thyroid cancer: a systematic review of the literature on 656 patients. Front Endocrinol (Lausanne) 2021;12:779999.
16. Piazza C, Del Bon F, Paderno A, Grazioli P, Mangili S, Lombardi D, et al. Complications after tracheal and cricotracheal resection and anastomosis for inflammatory and neoplastic stenoses. Ann Otol Rhinol Laryngol 2014;123:798-804.
17. Piazza C, Del Bon F, Barbieri D, Grazioli P, Paderno A, Perotti P, et al. Tracheal and crico-tracheal resection and anastomosis for malignancies involving the thyroid gland and the airway. Ann Otol Rhinol Laryngol 2016;125:97-104.
18. Wagner MM, Cure JK, Caudell JJ, Spencer SA, Nabell LM, Carroll WR, et al. Prognostic significance of thyroid or cricoid cartilage invasion in laryngeal or hypopharyngeal cancer treated with organ preserving strategies. Radiat Oncol 2012;7:219.
19. Nguyen HX, Le Trinh H, Nguyen HX, Nguyen HV, Le QV. Surgical treatment of advanced thyroid cancer with tracheal invasion. Case Rep Endocrinol 2021;2021:8823405.
20. Wang LY, Nixon IJ, Patel SG, Palmer FL, Tuttle RM, Shaha A, et al. Operative management of locally advanced, differentiated thyroid cancer. Surgery 2016;160:738-46.
21. Nishino M, Jacob J. Invasion in thyroid cancer: controversies and best practices. Semin Diagn Pathol 2020;37:219-27.
22. Agosto Salgado S, Kaye ER, Sargi Z, Chung CH, Papaleontiou M. Management of advanced thyroid cancer: overview, advances, and opportunities. Am Soc Clin Oncol Educ Book 2023;43:e389708.
23. Lamartina L, Grani G, Durante C, Filetti S. Recent advances in managing differentiated thyroid cancer. F1000Res 2018;7:86.
24. Furuya-Kanamori L, Bell KJ, Clark J, Glasziou P, Doi SA. Prevalence of differentiated thyroid cancer in autopsy studies over six decades: a meta-analysis. J Clin Oncol 2016;34:3672-9.
25. Kaliszewski K, Diakowska D, Miciak M, Jurkiewicz K, Kisiel M, Makles S, et al. The incidence trend and management of thyroid cancer-what has changed in the past years: own experience and literature review. Cancers (Basel) 2023;15:4941.
26. Park S, Oh CM, Cho H, Lee JY, Jung KW, Jun JK, et al. Association between screening and the thyroid cancer "epidemic" in South Korea: evidence from a nationwide study. BMJ 2016;355:i5745.
27. Kim J, Gosnell JE, Roman SA. Geographic influences in the global rise of thyroid cancer. Nat Rev Endocrinol 2020;16:17-29.
28. Brent GA. Environmental exposures and autoimmune thyroid disease. Thyroid 2010;20:755-61.
29. Wang X, Mo Z, Mao G, Zhu W, Xing M, Li X, et al. Geographical influences on thyroid abnormalities in adult population from iodine-replete regions: a cross-sectional study. Sci Rep 2021;11:994.
30. Lopez B, Fligor SC, Randolph GW, James BC. Inequities in thyroid cancer care: populations most at risk for delays in diagnosis and treatment. Thyroid 2023;33:724-31.
31. Ezeonwu MC. Specialty-care access for community health clinic patients: processes and barriers. J Multidiscip Healthc 2018;11:109-19.
32. Wu D, Yang Y, Jiang M, Yao R. Competing risk of the specific mortality among Asian-American patients with prostate cancer: a surveillance, epidemiology, and end results analysis. BMC Urol 2022;22:42.
33. Grippa WR, Dell'Antonio LS, Salaroli LB, Lopes-Junior LC. Incompleteness trends of epidemiological variables in a Brazilian high complexity cancer registry: an ecological time series study. Medicine (Baltimore) 2023;102:e34369.
34. Ellis L, Canchola AJ, Spiegel D, Ladabaum U, Haile R, Gomez SL. Racial and ethnic disparities in cancer survival: the contribution of tumor, sociodemographic, institutional, and neighborhood characteristics. J Clin Oncol 2018;36:25-33.
35. Carballo M, Quiros RM. To treat or not to treat: the role of adjuvant radioiodine therapy in thyroid cancer patients. J Oncol 2012;2012:707156.

36. Ruel E, Thomas S, Dinan M, Perkins JM, Roman SA, Sosa JA. Adjuvant radioactive iodine therapy is associated with improved survival for patients with intermediate-risk papillary thyroid cancer. J Clin Endocrinol Metab 2015;100:1529-36.
37. Wang X, Zhu J, Li Z, Wei T. The benefits of radioactive iodine ablation for patients with intermediate-risk papillary thyroid cancer. PLoS One 2020;15:e0234843.
38. Houten R, Fleeman N, Kotas E, Boland A, Lambe T, Duarte R. A systematic review of health state utility values for thyroid cancer. Qual Life Res 2021;30:675-702.
39. Matsumoto F, Ikeda K. Surgical management of tracheal invasion by well-differentiated thyroid cancer. Cancers (Basel) 2021;13:797.
40. Kim YS, Choi JH, Kim KS, Lim GC, Kim JH, Kang JW, et al. The role of adjuvant external beam radiation therapy for papillary thyroid carcinoma invading the trachea. Radiat Oncol J 2017;35:112-20.
41. Price DL, Shah JP. Surgery for locally extensive carcinomas of the thyroid gland. Oper Tech Otolayngol Head Neck Surg 2009;20:7-17.