Prognostic implications of strap muscle invasion in differentiated thyroid cancer: a retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) database

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Directed by Professor Jin Young Kwak

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ABSTRACT

Prognostic implications of strap muscle invasion in differentiated thyroid cancer: a retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) database

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The American Joint Committee on Cancer (AJCC) 8th TNM staging system defined gross strap muscle invasion as the T3b stage in differentiated thyroid cancer. However, the prognostic impact of strap muscle invasion alone on disease-specific survival (DSS) remains unclear. This study aimed to explore the impact of strap muscle invasion, minimal and gross collectively, on the DSS of differentiated thyroid cancer patients using the Surveillance, Epidemiology, and End Results (SEER) database.

The SEER database (1973-2018) was queried for differentiated thyroid cancer patients in July 2019. Survival and staging data on differentiated thyroid cancer only patients were retrospectively reviewed. Excluding patients with incomplete data on staging, treatment, or survival, a total of 19,914 patients who underwent surgical treatment remained for final analysis. The 10-year DSS of T stages according to the 8th staging schema were compared to that of the proposed "modified" staging schema, which discarded strap muscle invasion, using Cox proportional hazard analysis and competing risk analysis. The measure of discrimination and goodness-of-fit for survival prediction was estimated using Harrell's C concordance index (C-index) and proportion of variance explained (PVE), respectively.

The restaged T3b group per the modified staging schema showed

significantly different 10-year DSS between the reallocated T stages ($p < 0.001$). In tumors equal to or smaller than 40 mm in size, strap muscle invasion alone was not a significant prognostic factor for DSS on adjusted Cox proportional hazard analysis (hazard ratio (HR) = 1.620 [95% confidence interval (CI) 0.917 – 2.860]; $p = 0.097$). In addition, strap muscle invasion alone was not a significant prognostic factor for DSS in both cancer-caused deaths (subdistribution HR (SDHR) = 1.567 [95% CI 0.984 – 2.495]; $p = 0.059$) and deaths due to other causes (SDHR = 1.155 [95% CI 0.842 – 1.585]; $p = 0.370$) on multivariable competing risk analysis, regardless of tumor size. The predictive power of the modified staging schema (C-index 0.941, PVE 4.43%) was slightly lower than that of the AJCC 8th staging schema (C-index 0.942, PVE 4.45%), but the difference was not statistically significant ($p = 0.220$). In addition, the modified staging schema showed better 10-year DSS distinction between T stages.

In conclusion, strap muscle invasion alone in differentiated thyroid cancer may not be a significant prognostic factor for DSS. The “modified” staging schema discarding strap muscle invasion as a T stage criterion may better reflect cancer-caused death risk and may help prevent potential over-staging.

Key words: thyroid neoplasms, SEER program, differentiated thyroid cancer, disease-specific survival, neoplasm staging.

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I. INTRODUCTION

Extrathyroidal extension (ETE) is defined as the direct extension of the primary thyroid cancer into the adjacent structures such as strap muscles, trachea, larynx, esophagus, recurrent laryngeal nerve, or major vasculature.[1,2] It is considered a significant prognostic factor for differentiated thyroid cancer, and is incorporated in the many staging systems that had been developed over time including AGES (age, grade, extent, size),[3] AMES (age, metastases, extent of disease, size),[4] and MACIS (metastases, age, completeness of resection, invasion locally, size),[5-7] the European Organization for Research Thyroid Cancer Treatment Cooperative Study (EORTC),[8] the National Thyroid Cancer Treatment Cooperative Study (NTCTCS),[9] as well as the American Joint Committee on Cancer (AJCC) TNM staging schema,[10] which has become the most widely used staging schema nowadays.[11]

In the recent versions of the AJCC TNM staging schemas, strap muscle invasion was further sub-classified into either minimal or gross. Unlike the 6th and 7th editions, the AJCC 8th edition TNM staging schema discarded the minimal ETE category entirely while defining gross strap muscle invasion alone as the T3b stage.[12] Validation studies have corroborated the new staging system by

showing better allocation of relatively low-risk patients into lower stages with excellent survival outcomes, and high-risk patients into more advanced stages.[11,13-16]

The newly introduced staging factor of gross strap muscle invasion alone (T3b) has been associated with higher risk of positive resection margin, bigger tumor size, higher recurrence rate, and lower disease survival rate.[17-19] However, studies have reported that strap muscle invasion alone, both minimal and gross, may not have significant influence on overall survival,[20,21] particularly in tumors equal to or smaller than 40 mm.[22] A recent study has also suggested similar disease-free survival between the minimal ETE group and gross strap muscle invasion alone group in papillary thyroid cancer with tumor size between 10 mm and 40 mm.[23] With advances in surgical techniques and adjuvant therapies,[22] it is possible that tumors with strap muscle invasion alone may indeed have better prognosis than previously anticipated. Therefore, the impact of strap muscle invasion alone, both minimal and gross, on the survival of differentiated thyroid cancer patients needs to be elucidated to accurately allocate patients into appropriate staging groups according to individual risk, which will ensure longer disease-free survival and prevent overtreatment.

The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute (NCI) collects cancer incidence and survival information from population-based cancer registries encompassing nearly 34.6% of the total population of the United States.[24] The SEER program is regarded as a critical database for cancer survival surveillance in the United States, with openly accessible data on cancer incidence and survival compiled since 1973. Accordingly, it is an ideal database for analyzing the effect of ETE on survival in thyroid cancer.

Therefore, the purpose of this study was to explore the impact of strap muscle invasion alone, both minimal and gross, on the disease-specific survival (DSS) of differentiated thyroid cancer patients using the SEER database, and to

potentially improve the survival prediction power of the TNM staging schema.

II. MATERIALS AND METHODS

1. The SEER database

The SEER database (SEER 18 Regs excluding AK Custom Data (with additional treatment fields), Nov 2018 Sub (2000-2016) <Katrina/Rita Population Adjustment>) was accessed on July 4th, 2019, and queried for all patients diagnosed with differentiated thyroid cancer.[25,26] This database encompassed approximately 27.8% of the United States population and included records since 2000. Earlier registries include records since 1973, but they did not include detailed information on the extent of ETE in differentiated thyroid cancer and were not considered to be appropriate.

The SEER cancer staging schema for thyroid cancer has evolved over the years, and the staging data available in the SEER database were heterogeneous. The earlier data on ETE—*i.e.*, SEER Extent of Disease (EOD) 3rd edition announced on 1988, and the SEER Summary Staging Manual 2000—did not differentiate between pericapsular thyroid extension and ETE involving strap muscle and beyond (Table 1).[27,28] Differentiation between perithyroidal/pericapsular soft tissue invasion and invasion of strap muscle or beyond were applied after the Collaborative Stage Data Collection System (CS), which encodes tumor ETE based on pathologic and/or clinical information, came into effect for cases diagnosed since 2004. Although the latest CS system (version 02.05.50) does not explicitly distinguish between minimal or gross strap muscle invasion,[29] invasion of pericapsular soft tissue/connective tissue and minimal ETE including strap muscle invasion was differentiated. Since more advanced organ invasion (*i.e.*, recurrent laryngeal nerve, vagus nerve, major organ, major vessels or prevertebral fascia) is clearly distinguished, the invasion of omohyoid, sternohyoid, sternothyroid, or thyrohyoid muscles was considered to include both

minimal and gross strap muscle invasion collectively (Table 2).

Table 1. Codes for extrathyroidal extension of thyroid cancer in the SEER database.

EOD 3rd edition (1988)[27]		Staging Summary 2000[28]	
00	IN SITU: Noninvasive	0	In situ: Noninvasive; intraepithelial
10	Single invasive tumor confined to thyroid	1	Localized only Single or multifocal invasive tumor(s) confined to thyroid Into or through thyroid capsule, but not beyond Localized, NOS
20	Multiple foci confined to thyroid		
30	Localized, NOS		
40	Into thyroid capsule, but not beyond		
50	Pericapsular soft/connective tissue Parathyroid Strap muscle(s): Sternothyroid, omohyoid, sternohyoid Nerves: Recurrent laryngeal, vagus	2	Regional by direct extension only Extension to: – Blood vessel(s) (major): Carotid artery, jugular vein, thyroid artery or vein – Cricoid cartilage – Esophagus – Larynx – Nerves (recurrent laryngeal, vagus) – Parathyroid – Pericapsular soft/connective tissue – Sternocleidomastoid muscle – Strap muscle(s): omohyoid, sternohyoid, sternothyroid – Thyroid cartilage – Tumor is described as "FIXED to adjacent tissues"
60	Extension to: – Major blood vessel(s): Carotid artery, jugular vein, thyroid artery or vein – Sternocleidomastoid muscle – Esophagus – Larynx, including thyroid and cricoid cartilages Tumor is described as "FIXED to adjacent tissues"		
70	Trachea, skeletal muscle (other than strap muscle or sternocleidomastoid muscle), bone		
80	FURTHER contiguous extension, Mediastinal tissues		

Earlier codes utilized for extrathyroidal extension in the SEER database utilized the Extension of disease (EOD) 3rd edition and Staging Summary 2000. Adapted and edited from respective references.[27,28] *NOS*, not otherwise specified.

Table 2. Codes for Collaborative Staging for SEER database (CS version 02.05.50).

Codes for Collaborative Staging (CS, version 02.05.50)	
0	In situ, intraepithelial, noninvasive
100	Single invasive tumor confined to thyroid
200	Multiple foci confined to thyroid
300	Localized, NOS
400	Into thyroid capsule, but not beyond
450	Minimal extrathyroid extension including: Strap muscle(s) (omohyoid, sternohyoid, sternothyroid, thyrohyoid)
480	Pericapsular soft tissue/connective tissue
500	Parathyroid, nerves (recurrent laryngeal, vagus)
520	Cricoid cartilage, esophagus, larynx, sternocleidomastoid muscle
550	Trachea
600	Thyroid cartilage
620	Major blood vessel(s): Carotid artery (encased), jugular vein, thyroid artery or vein
700	Bone, skeletal muscle other than strap or sternocleidomastoid muscle
800	Further contiguous extension including mediastinal tissues, prevertebral fascia

Adapted and edited from the CS Extension webpage.[29] *NOS*, not otherwise specified.

2. Study population inclusion and exclusion criteria

The flow diagram of the SEER database search is shown on Figure 1. Data on 135,824 patients with thyroid cancer as the only malignancy were obtained. Inclusion criteria were as follows: 1) patients older than 18 years old, 2) patients diagnosed with only differentiated thyroid cancer according to the International Classification of Disease for Oncology third edition (ICD-O-3) codes (Table 3), and 3) patients who underwent surgery with or without adjuvant radiation therapy or chemotherapy. Patients with medullary carcinoma, mixed medullary carcinoma component, insular carcinoma, and anaplastic thyroid cancer were excluded. Patients with unknown race, unknown tumor grade, unknown ETE, unavailable or incomplete TNM staging data, death certificate or autopsy alone, or unknown cause of death were excluded.

Notably, only data recorded since 2004 were included for final analysis since earlier records did not differentiate between pericapsular soft tissue/connective tissue and strap muscle invasion. The extension item of the CS version 02.05.50 differentiated pericapsular soft tissue/connective tissue (code 480), strap muscle invasion (code 450), and ETE beyond strap muscle (*i.e.*, recurrent laryngeal nerve, vagus nerve, major vessels, major organ, or prevertebral fascia, codes 500 – 800) which were utilized for appropriate TNM re-staging according to the AJCC 8th TNM staging schema and the "modified" staging schema.[29] The invasion of omohyoid, sternohyoid, sternothyroid or thyrohyoid muscles (code 450) was considered to include both minimal and gross strap muscle invasion collectively. This code was regarded as the T3b stage per the AJCC 8th TNM staging schema in this study.

A total of 19,914 patients were included in the final analysis. Demographic variables included age at diagnosis, race, sex, year of diagnosis, and survival status. Pathologic characteristics included single or multifocal disease, tumor size, ETE, lymph node metastasis, and distant metastasis. Treatment methods included surgery, with or without adjuvant chemotherapy or

adjuvant radiation therapy. Surgery included either partial or total thyroidectomy. Radiation therapy included beam radiation, radioactive implants or radioisotopes, a combination of beam radiation with implants or isotopes, and radiation therapy not otherwise specified.

This retrospective study utilized a publicly available database with de-identified records, and did not require informed consent from the SEER registered cases. The requirement for the approval by the Institutional Review Board was formally waived.

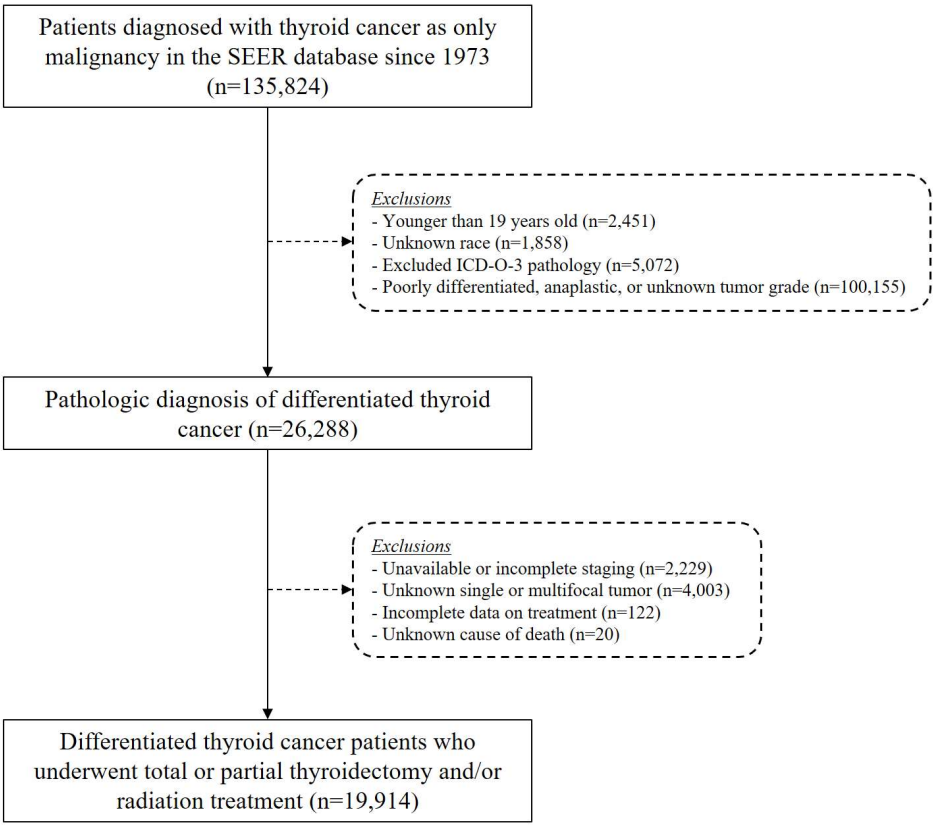

Figure 1. Flow diagram of the SEER database search. Among the total 135,824 patients who were diagnosed with only differentiated thyroid cancer since 1973, adult patients with complete data on race, staging, treatment, and outcome were included. A total of 19,914 patients remained for final analysis.

Table 3. Histopathologic diagnosis of differentiated thyroid cancer according to ICD-O-3.

ICD-O-3 Histology/ behavior code	Histopathology	n	(%)
8050/3	Papillary carcinoma, NOS	603	(3.0)
8260/3	Papillary adenocarcinoma, NOS	10,865	(54.6)
8330/3	Follicular adenocarcinoma, NOS	781	(3.9)
8331/3	Follicular adenocarcinoma well differentiated	273	(1.4)
8332/3	Follicular adenocarcinoma trabecular	31	(0.2)
8335/3	Follicular carcinoma, minimally invasive	321	(1.6)
8340/3	Papillary carcinoma, follicular variant	5,568	(28.0)
8341/3	Papillary microcarcinoma	680	(3.4)
8342/3	Papillary carcinoma, oxyphilic cell	39	(0.2)
8343/3	Papillary carcinoma, encapsulated	124	(0.6)
8344/3	Papillary carcinoma, columnar cell	205	(1.0)
8350/3	Nonencapsulated sclerosing carcinoma	64	(0.3)
8290/3	Oxyphilic adenocarcinoma	355	(1.8)
8310/3	Clear cell adenocarcinoma, NOS	4	(0.0)
8450/3	Papillary cystadenocarcinoma, NOS	1	(0.0)

Histopathologic diagnosis of differentiated thyroid cancer according to ICD-O-3 included in this study. *ICD-O-3*, International Classification of Diseases for Oncology, 3rd edition; *NOS*, not otherwise specified.

3. Primary outcome

The primary outcome of this study was cancer-caused death due to differentiated thyroid cancer, or disease-specific survival (DSS). DSS was defined as the time from date of diagnosis until cancer-caused death or last censoring.

4. Tumor staging

Because the currently available SEER database only provides TNM staging according to the AJCC 7th or previous staging schemas, the included 19,914 patients were restaged according to the AJCC 8th TNM staging schema using the recorded pathologic characteristics (Table 4). Strap muscle invasion alone was categorized as T3b stage, while pericapsular soft tissue or connective tissue invasion was categorized according to tumor size only. Major organ invasion including gross invasion of the subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve from any tumor size was classified as T4a stage per the AJCC 8th TNM staging schema. Likewise, major vessel or prevertebral fascia invasion including the encasement of carotid artery or mediastinal vessels from tumor of any size were classified as T4b stage.

Based on our hypothesis that minimal and gross strap muscle invasion collectively does not significantly impact DSS in the absence of other risk factors, we suggested a “modified” staging schema discarding strap muscle invasion of any degree from the T staging criteria. Therefore, the T3b stage according to the AJCC 8th TNM staging schema were reallocated according to tumor size only, into T1a, T1b, T2, or T3 stages per the modified staging schema (Table 4). The staging of ETE involving major adjacent structures (*i.e.,* T4a or T4b stages) remained unchanged.

Table 4. Tumor stage according to the AJCC 8th TNM staging schema (edited and adapted from source)[12] and the proposed "modified" TNM staging schema.

AJCC 8th TNM staging			"Modified" TNM staging		
T stage	**Size (mm)**	**Extent**	**T stage**	**Size (mm)**	**Extent**
TX		Primary tumor cannot be assessed	**TX**		Primary tumor cannot be assessed
T0		No evidence of primary tumor	**T0**		No evidence of primary tumor
T1a	≤ 10	Limited to thyroid	**T1a**	≤ 10	
T1b	10< ≤20	Limited to thyroid	**T1b**	10< ≤20	・Limited to thyroid ・Minimal perithyroidal/pericapsular invasion ・Minimal or gross strap muscle invasion
T2	20< ≤40	Limited to thyroid	**T2**	20< ≤40	
T3a	> 40	Limited to thyroid	**T3**	> 40	
T3b	Any	Gross strap muscle invasion only			
T4a	Any	Invasion of subcutaneous tissue, larynx, trachea, recurrent laryngeal nerve, esophagus	**T4a**	Any	Invasion of subcutaneous tissue, larynx, trachea, recurrent laryngeal nerve, esophagus
T4b	Any	Invasion of mediastinal vessels, carotid artery or prevertebral fascia	**T4b**	Any	Invasion of mediastinal vessels, carotid artery or prevertebral fascia

5. Statistical analysis

Statistical analyses were performed using commercially available R software, version 3.6.1 (*http://www.R-project.org*, R Foundation for Statistical Computing, Vienna, Austria) with the application of appropriate packages (survival, survminer, cmprsk, compareC, ggplot2, and alluvial).[30-35] The Kruskal-Wallis test with post-hoc Dunn's procedure was performed to compare median tumor size according to the extent of the ETE. The Cox proportional hazard analysis was used to examine the effects of clinical factors and histopathologic characteristics of differentiated thyroid cancer on DSS. Competing risk analysis by proportional subdistribution hazards regression (SDHR) modeling was performed.[35,36] In this study, competing risk was considered death due to other causes since deaths unrelated to differentiated thyroid cancer may obscure the ability to observe cancer-caused deaths.[37] Kaplan-Meier estimation and the log rank test were used to assess the 10-year DSS probability and to obtain survival curves for DSS according to T stages based on either the AJCC 8th TNM staging schema or the modified TNM staging schema. The measure of discrimination for survival prediction was estimated using Harrell's C concordance index (C-index), and goodness-of-fit for survival prediction was estimated using the proportion of variance explained (PVE) for both staging schemas.[38]

$$\mathrm{PVE} = 1 - e^{-(\frac{\mathrm{LRT}}{\mathrm{N}})},$$

LRT: log likelihood ratio test statistic, *N*:sample size

All tests were two-sided, and a *p*-value of less than 0.05 was considered statistically significant.

III. RESULTS

1. Baseline population characteristics

Baseline demographics of the included population are presented in Table 5. The median age at diagnosis was 47.0 years old (interquartile range (IQR), 36.0 – 57.0 years old), with a median follow-up of 55.0 months (IQR, 32.0 – 85.0 months; range, 1.0 – 155.0 months). The majority of patients were white (80.7%). 'Other' race included American India/AK Native, Asian/Pacific Islander. A total of 18,085 (90.8%) patients were diagnosed with papillary carcinoma and its variants, while 1,406 (7.1%) patients were diagnosed with follicular carcinoma and its variants. Other pathologies included oxyphilic adenocarcinoma (n=355), non-encapsulated sclerosing carcinoma (n=64), and clear cell adenocarcinoma (n=4). Most patients underwent total thyroidectomy (n=16,874, 84.7%). Median tumor size was 15 mm (IQR, 8 – 26 mm). The median tumor size showed a positive relationship according to ETE groups (Figure 2). Most patients underwent total thyroidectomy (n=16,874, 84.7%). Adjuvant radiation therapy was performed in over half of the patients (n=10,165, 51.0%), which included radioactive iodine (RAI) (n=9,740), radioactive implants (n=120), beam radiation (n=195), a combination of beam radiation with implants or isotopes (n=66), and radiation therapy not otherwise specified (n=44). Adjuvant chemotherapy was performed in 57 (0.3%) patients.

10-year DSS was significantly different according to the T stage per the AJCC 8th TNM staging criteria (Table 6), except for T1b stage. There was a trend for decreasing 10-year DSS with higher T stage. However, T3b stage showed better 10-year DSS than T3a stage (T3a 93.1% versus T3b 96.4%).

Table 5. Baseline demographics.

Patient characteristics	Value	
Age at diagnosis*	47.0	(36.0, 57.0)
< 55 years old	13,688	(68.7)
≥ 55 years old	6,226	(31.3)
Sex		
Male	4,658	(23.4)
Female	15,256	(76.6)
Race		
White	16,063	(80.7)
Black	1,371	(6.9)
Other	2,480	(12.4)
Tumor size (mm)*	15	(8.0, 26.0)
Pathology according to ICD-O-3		
Papillary carcinoma	18,085	(90.8)
Follicular carcinoma	1,406	(7.1)
Other	423	(2.1)
Multifocal	8,213	(41.2)
Extrathyroidal extension		
No or minimal perithyroidal/pericapsular invasion	17,703	(88.9)
Strap muscle invasion only	1,552	(7.8)
Major organ invasion	464	(2.3)
Major vessel or prevertebral fascial invasion	195	(1.0)
Lymph node metastasis	4,897	(24.6)
Distant metastasis	229	(1.1)
Type of surgery		
Partial thyroidectomy	3,040	(15.3)
Total thyroidectomy	16,874	(84.7)
Radiation therapy†	10,165	(51.0)
Chemotherapy	57	(0.3)
Follow-up months*	55.0	(32.0, 85.0)
range	1.0 – 155.0	

Data are presented as numbers (%) unless indicated otherwise. *Data are shown as medians (1st quartile, 3rd quartile). †Radiation therapy included radioactive iodine (RAI) (n=9,740), radioactive implants (n=120), beam radiation (n=195), a combination of beam radiation with implants or isotopes (n=66), and radiation therapy not otherwise specified (n=44). *ICD-O-3*, International Classification of Diseases for Oncology, 3rd edition.

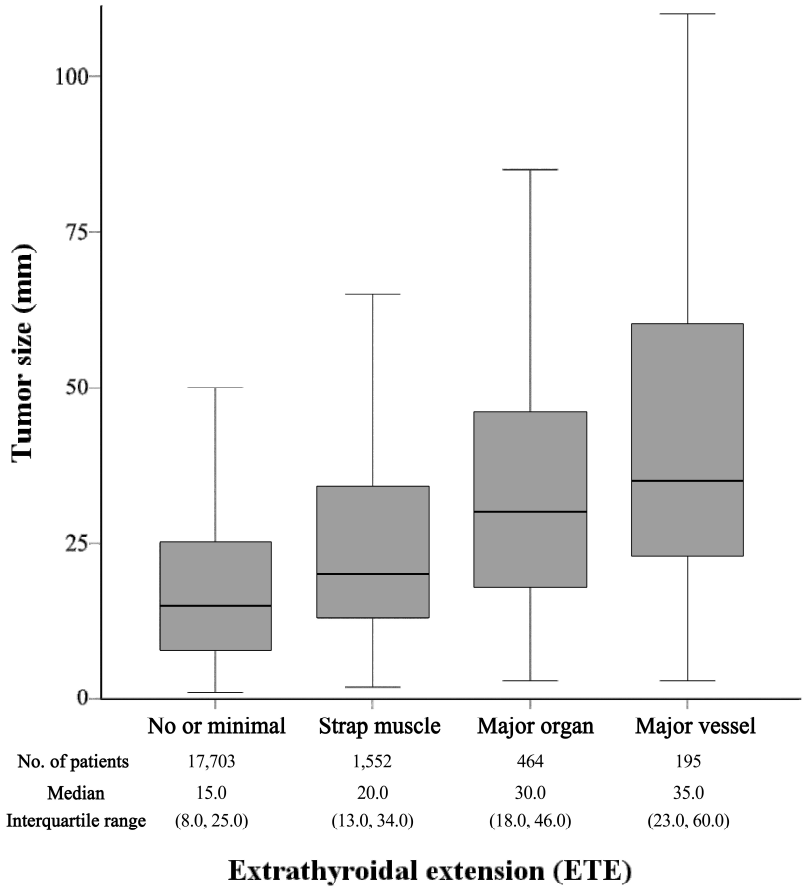

Figure 2. Difference in median tumor size according to extrathyroidal extension (ETE) groups. Pairwise comparison of median tumor size according to the ETE group is presented. Dark horizontal line indicates the median tumor size, and the upper and lower limits of the box indicate the 1st and 3rd quartile. The whiskers at the top and bottom of the boxes indicate minimal and maximal values. The Kruskal-Wallis test and post-hoc Dunn's procedure revealed statistically significant differences in the pairwise comparison of median tumor size between all ETE groups ($p < 0.05$).

Table 6. 10-year DSS and T stage distribution according to the AJCC 8th TNM staging or the "modified" TNM staging schema.

	n (%)		10-year DSS (%)	HR	95% CI	*p*-value
AJCC 8th TNM staging*						**<0.001**
T1a	6610	(33.2)	99.4	1	Reference	
T1b	5258	(26.4)	99.4	2.008	0.920 – 4.386	0.080
T2	4249	(21.3)	98.0	5.381	2.676 – 10.821	**<0.001**
T3a	1586	(8.0)	93.1	19.144	9.685 – 37.839	**<0.001**
T3b	1552	(7.8)	96.4	13.177	6.442 – 26.955	**<0.001**
T4a	464	(2.3)	86.2	65.291	32.946 – 129.388	**<0.001**
T4b	195	(1.0)	70.0	146.927	74.023 – 291.632	**<0.001**
Modified TNM staging†						**<0.001**
T1a	6848	(34.4)	99.4	1	Reference	
T1b	5801	(29.1)	99.3	1.900	0.957 – 3.772	0.067
T2	4755	(23.9)	97.8	4.810	2.599 – 8.904	**<0.001**
T3	1851	(9.3)	92.6	16.802	9.232 – 30.579	**<0.001**
T4a	464	(2.3)	86.2	52.082	28.137 – 96.408	**<0.001**
T4b	195	(1.0)	70.0	117.250	63.230 – 217.418	**<0.001**

Statistically significant values are shown in bold. *DSS*, disease-specific survival; *HR*, hazard ratio; *CI*, confidence interval. *Staging according to the American Joint Committee on Cancer (AJCC) 8th edition of TNM staging schema. †Modified TNM staging schema, which discards the strap muscle invasion factor from the T staging criteria.

2. Prognostic impact of strap muscle invasion alone

Univariable and multivariable Cox proportional hazard analysis and competing risk analysis were performed to evaluate the prognostic impact of strap muscle invasion alone on DSS.

In all patients (n=19,914), univariable and multivariable Cox proportional hazard analyses revealed that strap muscle invasion alone, as well as age, tumor size, major organ invasion, major vessel or major prevertebral fascial invasion, lymph node metastasis, distant metastasis, and chemotherapy were significant prognostic factors for survival (Table 7). On the other hand, strap muscle invasion alone did not impact neither death due to cancer nor death due to other causes on multivariable competing risk analysis (Table 9), despite its significance for DSS on death due to any causes on univariable competing risk analysis (Table 8). Other significant factors for DSS included age, tumor size, major organ invasion, major vessel or prevertebral fascial invasion, lymph node metastasis, distant metastasis, and chemotherapy.

In the subgroup of patients with tumor size equal to or smaller than 40 mm (n=17,837), univariable and multivariable Cox proportional hazard analyses showed that although strap muscle invasion alone was a significant prognostic factor for DSS on univariable Cox proportional hazard analysis, it was not a significant prognostic factor for DSS on multivariable Cox proportional hazard analysis (Table 10). On univariable competing risk analysis, strap muscle invasion alone was a significant risk factor for cancer-caused death but not for other caused death (Table 11). However, on multivariable competing risk analysis, strap muscle invasion alone was not a significant factor for DSS in both cancer-cause death and other caused death (Table 12).

In the subgroup of patients aged 55 years or older (n=6,226), univariable and multivariable Cox proportional hazard analysis showed that strap muscle invasion alone did not significant impact DSS (Table 13). Multivariable competing risk analysis showed that strap muscle invasion alone did not

significantly impact death due to any cause (Table 15), despite its significance on univariable competing risk analysis (Table 14).

Table 7. Univariable and multivariable Cox proportional hazard analysis of clinical and pathologic variables for DSS in all patients (n=19,914), according to the AJCC 8th TNM staging schema.

All patients (n=19,914)	Univariable		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	1.089 (1.079 – 1.100)	**<0.001**	1.068 (1.058 – 1.078)	**<0.001**
Male sex	2.396 (0.322 – 0.541)	**<0.001**	1.197 (0.636 – 1.098)	0.196
Race (reference: White)		0.300		
Black	0.688 (1.453 – 0.364)	0.250	-	-
Others	1.192 (0.827 – 1.717)	0.346	-	-
Primary tumor size (reference: ≤ 10 mm)		**<0.001**		
10 < ≤ 20 mm	2.421 (1.315 – 4.457)	**0.005**	2.021 (1.088 – 3.756)	**0.026**
20 < ≤ 40 mm	5.886 (3.365 – 10.296)	**<0.001**	3.821 (2.146 – 6.803)	**<0.001**
> 40 mm	25.546 (14.923 – 43.732)	**<0.001**	7.613 (4.276 – 13.554)	**<0.001**
Extrathyroidal extension		**<0.001**		**<0.001**
No or minimal perithyroidal/pericapsular invasion	Reference		Reference	
Strap muscle invasion only	3.278 (2.191 – 4.904)	**<0.001**	1.592 (1.044 – 2.427)	**0.031**
Major organ invasion	16.228 (11.513 – 22.875)	**<0.001**	2.933 (1.925 – 4.467)	**<0.001**
Major vessel or prevertebral fascial invasion	36.492 (25.812 – 51.592)	**<0.001**	4.284 (2.824 – 6.500)	**<0.001**
Multifocality	1.078 (0.713 – 1.207)	0.576	-	-
Lymph node metastasis	3.628 (2.804 – 4.693)	**<0.001**	1.783 (1.307 – 2.431)	**<0.001**
Distant metastasis	50.060 (37.600 – 66.663)	**<0.001**	6.439 (4.590 – 9.034)	**<0.001**
Total thyroidectomy	1.124 (0.781 – 1.617)	0.529	-	-
Radiation therapy	2.486 (1.856 – 3.330)	**<0.001**	1.177 (0.864 – 1.605)	0.301
Chemotherapy	30.070 (17.814 – 50.755)	**<0.001**	4.945 (2.719 – 8.995)	**<0.001**

Statistically significant values are shown in bold. *DSS*, disease-specific survival; *HR*, hazards ratio; *CI*, confidence interval.

Table 8. Univariable competing risk analysis of clinical and pathological variables for cancer-caused death in all patients (n=19,914), according to the AJCC 8th TNM staging schema.

All (n=19,914)	Cancer-caused death (n=233)		Other caused death (n=409)	
	SDHR (95% CI)	*p*-value	SDHR (95% CI)	*p*-value
Age	1.085 (1.075 – 1.095)	**<0.001**	1.092 (1.083 – 1.100)	**<0.001**
Male sex	0.423 (0.326 – 0.549)	**<0.001**	0.404 (0.332 – 0.492)	**<0.001**
Race (reference: White)				
Black	0.682 (0.361 – 1.289)	0.240	1.514 (1.082 – 2.118)	**0.016**
Others	1.198 (0.831 – 1.725)	0.330	0.647 (0.453 – 0.924)	**0.017**
Primary tumor size (reference: ≤ 10 mm)				
10 < ≤ 20 mm	2.425 (1.315 – 4.470)	**0.004**	0.996 (0.755 – 1.314)	0.980
20 < ≤ 40 mm	5.883 (3.360 – 10.301)	**<0.001**	1.272 (0.970 – 1.668)	0.082
> 40 mm	25.034 (14.608 – 42.901)	**<0.001**	3.098 (2.360 – 4.068)	**<0.001**
Extrathyroidal extension				
No or minimal perithyroidal/pericapsular invasion	Reference		Reference	
Strap muscle invasion only	3.259 (2.180 – 4.874)	**<0.001**	1.162 (1.162 – 2.204)	**0.004**
Major organ invasion	15.734 (11.080 – 22.344)	**<0.001**	3.255 (2.216 – 4.780)	**<0.001**
Major vessel or prevertebral fascial invasion	35.019 (24.505 – 50.043)	**<0.001**	3.747 (2.246 – 6.252)	**<0.001**
Multifocality	0.927 (0.712 – 1.205)	0.570	1.064 (0.875 – 1.295)	0.530
Lymph node metastasis	3.620 (2.799 – 4.682)	**<0.001**	1.083 (0.868 – 1.352)	0.480
Distant metastasis	45.281 (33.966 – 60.364)	**<0.001**	5.705 (3.721 – 8.746)	**<0.001**
Total thyroidectomy	1.127 (0.782 – 1.624)	0.520	0.844 (0.658 – 1.084)	0.180
Radiation therapy	2.499 (1.867 – 3.343)	**<0.001**	0.775 (0.639 – 0.941)	**0.010**
Chemotherapy	28.048 (15.819 – 49.730)	**<0.001**	4.320 (1.738 – 10.737)	**0.002**

Statistically significant values are shown in bold. *DSS*, disease-specific survival; *SDHR*, subdistribution hazard ratio; *CI*, confidence interval.

Table 9. Multivariable competing risk analysis of clinical and pathological variables for cancer-caused death in all patients (n=19,914), according to the AJCC 8th TNM staging schema.

All (n=19,914)	Cancer–caused death (n=233)		Other caused death (n=409)	
	SDHR (95% CI)	*p*-value	SDHR (95% CI)	*p*-value
Age	1.063 (1.053 – 1.074)	**<0.001**	1.085 (1.077 – 1.094)	**<0.001**
Male sex	1.124 (0.831 – 1.520)	0.450	1.835 (1.499 – 2.245)	**<0.001**
Primary tumor size (reference: ≤ 10 mm)				
10 < ≤ 20 mm	1.990 (1.060 – 3.736)	**0.032**	1.219 (0.916 – 1.621)	0.170
20 < ≤ 40 mm	3.736 (2.058 – 6.784)	**<0.001**	1.360 (1.024 – 1.807)	**0.034**
> 40 mm	7.085 (3.810 – 13.173)	**<0.001**	1.951 (1.448 – 2.628)	**<0.001**
Extrathyroidal extension				
No or minimal perithyroidal/pericapsular invasion	Reference		Reference	
Strap muscle invasion only	1.567 (0.984 – 2.495)	0.059	1.155 (0.842 – 1.585)	0.370
Major organ invasion	2.823 (1.676 – 4.753)	**<0.001**	1.328 (0.872 – 2.021)	0.190
Major vessel or prevertebral fascial invasion	4.427 (2.632 – 7.445)	**<0.001**	0.921 (0.508 – 1.667)	0.790
Lymph node metastasis	1.730 (1.185 – 2.526)	**0.004**	1.173 (0.926 – 1.485)	0.190
Distant metastasis	5.962 (3.850 – 9.234)	**<0.001**	1.672 (1.032 – 2.709)	**0.037**
Radiation therapy	1.268 (0.902 – 1.782)	0.170	0.702 (0.570 – 0.864)	**0.001**
Chemotherapy	4.506 (2.022 – 10.041)	**<0.001**	2.720 (0.978 – 7.563)	0.055

Statistically significant values are shown in bold. *SDHR*, subdistribution hazard ratio; *CI*, confidence interval.

Table 10. Univariable and multivariable Cox proportional hazard analysis of clinical and pathologic variables for DSS in patients with tumor size ≤ 40 mm (n=17,837), according to the AJCC 8th TNM staging schema.

Tumors ≤40 mm (n=17,837)	Univariable		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	1.101 (1.086 – 1.116)	**<0.001**	1.084 (1.068 – 1.099)	**<0.001**
Male sex	1.949 (0.350 – 0.752)	**<0.001**	1.203 (0.563 – 1.228)	0.354
Race (reference: White)		0.257		
Black	0.624 (0.229 – 1.698)	0.356	-	-
Others	1.375 (0.839 – 2.252)	0.206	-	-
Primary tumor size (reference: ≤10 mm)		**<0.001**		
10 < ≤ 20 mm	2.414 (1.311 – 4.444)	**0.005**	1.676 (0.895 – 3.137)	0.107
20 < ≤ 40 mm	5.886 (3.365 – 10.296)	**<0.001**	3.821 (2.146 – 6.803)	**<0.001**
> 40 mm				
Extrathyroidal extension		**<0.001**		**<0.001**
No or minimal perithyroidal/pericapsular invasion	Reference		Reference	
Strap muscle invasion only	3.580 (2.097 – 6.112)	**<0.001**	1.620 (0.917 – 2.860)	0.097
Major organ invasion	15.010 (9.081 – 24.810)	**<0.001**	2.429 (1.327 – 4.447)	**0.004**
Major vessel or prevertebral fascial invasion	30.001 (17.083 – 52.689)	**<0.001**	6.195 (3.392 – 11.316)	**<0.001**
Multifocality	1.158 (0.803 – 1.670)	0.400	-	-
Lymph node metastasis	3.379 (2.348 – 4.863)	**<0.001**	2.150 (1.406 – 3.287)	**<0.001**
Distant metastasis	76.920 (51.083 – 115.810)	**<0.001**	14.532 (9.232 – 22.875)	**<0.001**
Total thyroidectomy	1.210 (0.714 – 2.052)	0.479	-	-
Radiation therapy	2.804 (1.841 – 4.270)	**<0.001**	1.423 (0.907 – 2.233)	0.125
Chemotherapy	16.706 (6.162 – 45.297)	**<0.001**	6.459 (2.231 – 18.694)	**<0.001**

Statistically significant values are shown in bold. *DSS*, disease-specific survival; *HR*, hazards ratio; *CI*, confidence interval.

Table 11. Univariable competing risk analysis of clinical and pathological variables for cancer-caused deaths in patients with tumor size ≤ 40 mm (n=17,837), according to the AJCC 8th TNM staging schema.

Tumor size ≤ 40 mm (n=17,837)	Cancer-caused death (n=116)		Other caused death (n=305)	
	SDHR (95% CI)	*p*-value	SDHR (95% CI)	*p*-value
Age	1.097 (1.081 – 1.113)	**<0.001**	1.091 (1.080 – 1.101)	**<0.001**
Male sex	0.519 (0.354 – 0.762)	**0.001**	0.400 (0.318 – 0.503)	**<0.001**
Race (reference: White)				**0.008**
Black	0.624 (0.229 – 1.698)	0.356	1.457 (0.966 – 2.200)	0.073
Others	1.375 (0.839 – 2.252)	0.206	0.603 (0.394 – 0.924)	**0.020**
Primary tumor size (reference: ≤ 10 mm)				
10 < ≤ 20 mm	2.416 (1.309 – 4.461)	**0.005**	1.458 (0.966 – 2.200)	0.072
20 < ≤ 40 mm	5.860 (3.342 – 10.276)	**<0.001**	0.602 (0.393 – 0.922)	**0.020**
Extrathyroidal extension				
No or minimal perithyroidal/pericapsular invasion	Reference		Reference	
Strap muscle invasion only	3.575 (2.096 – 6.096)	**<0.001**	1.253 (0.825 – 1.901)	0.290
Major organ invasion	14.800 (8.862 – 24.718)	**<0.001**	2.057 (1.146 – 3.694	**0.016**
Major vessel or prevertebral fascial invasion	29.079 (16.198 – 52.206)	**<0.001**	3.898 (1.994 – 7.622)	**<0.001**
Multifocality	1.156 (0.803 – 1.666)	0.440	1.102 (0.879 – 1.241)	**0.400**
Lymph node metastasis	3.378 (2.348 – 4.861)	**<0.001**	0.948 (0.725 – 1.241)	0.700
Distant metastasis	71.143 (47.026 – 107.629)	**<0.001**	5.389 (2.854 – 10.176)	**<0.001**
Total thyroidectomy	1.212 (0.713 – 2.061)	0.480	0.895 (0.667 – 1.201)	0.460
Radiation therapy	2.817 (1.854 – 4.281)	**<0.001**	0.764 (0.611 – 0.956)	**0.019**
Chemotherapy	15.919 (5.731 – 44.219)	**<0.001**	4.334 (1.342 – 13.995)	**0.014**

Statistically significant values are shown in bold. *SDHR*, subdistribution hazard ratio; *CI*, confidence interval.

Table 12. Multivariable competing risk analysis of clinical and pathological variables for cancer-caused deaths in patients with tumor size ≤ 40 mm (n=17,837), according to the AJCC 8th TNM staging schema.

Tumor size ≤ 40 mm (n=17,837)	Cancer–caused death (n=116)		Other caused death (n=305)	
	SDHR (95% CI)	*p*-value	SDHR (95% CI)	*p*-value
Age	1.080 (1.064 – 1.098)	**<0.001**	1.088 (1.077 – 1.098)	**<0.001**
Male sex	1.168 (0.761 – 1.793)	0.480	1.995 (1.580 – 2.519)	**<0.001**
Primary tumor size (reference: ≤ 10 mm)				
10 < ≤ 20 mm	1.632 (0.846 – 3.149)	0.140	1.205 (0.903 – 1.609)	0.210
20 < ≤ 40 mm	2.692 (1.432 – 5.061)	**0.002**	1.323 (0.990 – 1.769)	0.059
Extrathyroidal extension				
No or minimal perithyroidal/pericapsular invasion	Reference		Reference	
Strap muscle invasion only	1.588 (0.831 – 3.035)	0.160	1.025 (0.676 – 1.556)	0.910
Major organ invasion	2.720 (1.298 – 5.702)	**0.008**	1.007 (0.531 – 1.910)	0.980
Major vessel or prevertebral fascial invasion	6.001 (3.104 – 11.603)	**<0.001**	1.343 (0.638 – 2.827)	0.440
Lymph node metastasis	2.027 (1.235 – 3.327)	**0.005**	1.180 (0.880 – 1.583)	0.270
Distant metastasis	13.190 (7.718 – 22.542)	**<0.001**	1.666 (1.848 – 3.273)	0.140
Radiation therapy	1.534 (0.933 – 2.520)	0.091	0.746 (0.582 – 0.956)	**0.021**
Chemotherapy	5.661 (2.213 – 14.481)	**<0.001**	3.212 (0.856 – 12.054)	0.084

Statistically significant values are shown in bold. *SDHR*, subdistribution hazard ratio; *CI*, confidence interval.

Table 13. Univariable and multivariable Cox proportional hazard analysis of clinical and pathological variables for cancer-caused death in patients aged 55 years or older (n=6,226), according to the AJCC 8th TNM staging schema.

Age ≥ 55 years old (n=6,226)	Univariable		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	1.106 (1.095 - 1.117)	**<0.001**	1.089 (1.078 - 1.100)	**<0.001**
Male sex	0.549 (0.458 - 0.657)	**<0.001**	0.706 (0.585 - 0.852)	**<0.001**
Race (reference: White)		0.919		
Black	1.029 (0.717 - 1.475)	0.878	-	-
Others	1.057 (0.801 - 1.396)	0.693	-	-
Primary tumor size (reference: ≤10 mm)		**<0.001**		**<0.001**
10 < ≤ 20 mm	1.485 (1.109 - 1.987)	**0.008**	1.321 (0.976 - 1.787)	0.072
20 < ≤ 40 mm	2.424 (1.849 - 3.177)	**<0.001**	1.716 (1.284 - 2.292)	**<0.001**
> 40 mm	6.197 (4.789 - 8.018)	**<0.001**	2.295 (1.635 - 3.222)	**<0.001**
Extrathyroidal extension		**<0.001**		**<0.001**
No or minimal perithyroidal/pericapsular invasion	Reference		Reference	
Strap muscle invasion only	1.965 (1.476 - 2.617)	**<0.001**	1.280 (0.946 - 1.732)	0.110
Major organ invasion	5.458 (4.150 - 7.178)	**<0.001**	1.971 (1.426 - 2.724)	**<0.001**
Major vessel or preverteberal fascial invasion	7.733 (5.753 - 10.394)	**<0.001**	2.295 (1.635 - 3.222)	**<0.001**
Multifocality	1.102 (0.920 - 1.319)	0.290	-	-
Lymph node metastasis	2.619 (2.173 - 3.157)	**<0.001**	1.458 (1.159 - 1.833)	**0.001**
Distant metastasis	11.574 (9.040 - 14.820)	**<0.001**	4.298 (3.265 - 5.657)	**<0.001**
Total thyroidectomy	1.002 (0.796 - 1.261)	0.969	1.159 (0.909 - 1.480)	0.234
Radiation therapy	1.292 (1.081 - 1.546)	**0.005**	1.261 (1.031 - 1.544)	**0.024**
Chemotherapy	10.343 (6.175 - 17.323)	**<0.001**	5.508 (3.133 - 9.681)	**<0.001**

Statistically significant values are shown in bold. *SDHR*, subdistribution hazard ratio; *CI*, confidence interval.

Table 14. Univariable competing risk analysis of clinical and pathological variables for cancer-caused death in patients aged 55 years or older (n=6,226), according to the AJCC 8th TNM staging schema.

Age ≥ 55 years old (n=6,226)	Cancer-caused death (n=178)		Other caused death (n=308)	
	SDHR (95% CI)	*p*-value	SDHR (95% CI)	*p*-value
Age	1.080 (1.062 – 1.098)	**<0.001**	1.109 (1.096 – 1.123)	**<0.001**
Male sex	0.614 (0.454 – 0.831)	**0.002**	0.529 (0.421 – 0.664)	**<0.001**
Race (reference: White)				
Black	0.610 (0.286 – 1.301)	0.200	1.291 (0.852 – 1.956)	0.230
Others	1.578 (1.059 – 2.352)	0.025	0.802 (0.541 – 1.189)	0.270
Primary tumor size (reference: ≤ 10 mm)				
10 < ≤ 20 mm	2.800 (1.445 – 5.426)	**0.002**	1.206 (0.860 – 1.692)	0.280
20 < ≤ 40 mm	6.076 (3.301 – 11.184)	**<0.001**	1.791 (1.302 – 2.462)	**<0.001**
> 40 mm	18.387 (10.244 – 33.005)	**<0.001**	3.245 (2.363 – 4.457)	**<0.001**
Extrathyroidal extension				
No or minimal perithyroidal/pericapsular invasion	Reference		Reference	
Strap muscle invasion only	2.914 (1.821 – 4.662)	**<0.001**	1.449 (1.040 – 2.162)	**0.030**
Major organ invasion	10.724 (7.137 – 16.112)	**<0.001**	2.496 (1.624 – 3.839)	**<0.001**
Major vessel or prevertebral fascial invasion	20.175 (13.533 – 30.078)	**<0.001**	1.941 (1.095 – 3.441)	**0.023**
Multifocality	1.065 (0.789 – 1.438)	0.680	1.126 (0.896 – 1.414)	0.310
Lymph node metastasis	5.672 (4.216 – 7.631)	**<0.001**	1.427 (1.093 – 1.865)	**0.009**
Distant metastasis	22.594 (16.400 – 31.129)	**<0.001**	2.836 (1.788 – 4.498)	**<0.001**
Total thyroidectomy	1.226 (0.812 – 1.851)	0.330	0.936 (0.702 – 1.248)	0.650
Radiation therapy	2.564 (1.852 – 3.550)	**<0.001**	0.872 (0.696 – 1.093)	0.230
Chemotherapy	16.675 (8.446 – 32.921)	**<0.001**	3.128 (1.106 – 8.849)	**0.032**

Statistically significant values are shown in bold. *SDHR*, subdistribution hazard ratio; *CI*, confidence interval.

Table 15. Multivariable competing risk analysis of clinical and pathological variables for cancer-caused death in patients aged 55 years or older (n=6,226), according to the AJCC 8th TNM staging schema.

Age ≥ 55 years old (n=6,226)	Cancer-caused death (n=178)		Other caused death (n=308)	
	SDHR (95% CI)	*p*-value	SDHR (95% CI)	*p*-value
Age	1.56 (1.036 – 1.076)	**<0.001**	1.102 (1.087 – 1.117)	**<0.001**
Male sex	0.949 (0.668 – 1.348)	0.770	1.770 (1.397 – 2.243)	**<0.001**
Primary tumor size (reference: ≤ 10 mm)				
10 < ≤ 20 mm	1.963 (0.985 – 3.912)	0.055	1.243 (0.876 – 1.763)	0.220
20 < ≤ 40 mm	3.086 (1.583 – 6.018)	**0.001**	1.549 (1.106 – 2.169)	**0.011**
> 40 mm	5.004 (2.484 – 10.082)	**<0.001**	2.004 (1.408 – 2.851)	**<0.001**
Extrathyroidal extension				
No or minimal perithyroidal/pericapsular invasion	Reference		Reference	
Strap muscle invasion only	1.447 (0.835 – 2.508)	0.190	1.121 (0.780 – 1.610)	0.540
Major organ invasion	2.411 (1.314 – 4.422)	**0.004**	1.260 (0.784 – 2.026)	0.340
Major vessel or prevertebral fascial invasion	4.202 (2.372 – 7.444)	**<0.001**	0.760 (0.391 – 1.477)	0.420
Lymph node metastasis	2.061 (1.310 – 3.243)	**0.002**	1.067 (0.799 – 1.425)	0.660
Distant metastasis	5.957 (3.754 – 9.454)	**<0.001**	1.659 (0.998 – 2.759)	0.051
Radiation therapy	1.105 (0.749 – 1.630)	0.610	0.704 (0.552 – 0.899)	**0.005**
Chemotherapy	3.445 (1.344 – 8.828)	**0.010**	3.295 (1.038 – 10.463)	**0.043**

Statistically significant values are shown in bold. *SDHR*, subdistribution hazard ratio; *CI*, confidence interval

3. 10-year DSS according to the AJCC 8th TNM staging schema and the modified TNM staging schema

Table 6 showed the 10-year DSS and the number of patients in each T stage according to the AJCC 8th TNM staging schema and the modified TNM staging schema. While there was grossly linear correlation between higher T stage and lower 10-year DSS per the AJCC 8th TNM staging schema, the T3b stage showed better 10-year DSS than the T3a stage (Figure 3a). Restaging of the T3b stage (*i.e.*, $T3bN_{any}M_{any}$) according to the modified TNM staging schema resulted in a total of 1,552 patients assigned to T1a (n=238, 15.3%), T1b (n=543, 35.0%), T2 (n=506, 32.6%), and T3 (n=265, 17.1%) stages with significant difference in DSS (Figure 3b). T staging per the modified TNM staging schema showed poorer 10-year DSS with higher T stage (Table 7). Among the 1,518 patients without distant metastasis (*i.e.*, $T3bN_{any}M0$, stage II), 589 patients (38.8%) were down-staged to stage I, and there was significant difference in DSS after reallocation into either stage I or stage II per the modified staging schema (Figure 3c-d).

The number of patients with reallocated T stage and overall stage according to the modified staging schema is shown in Figure 4.

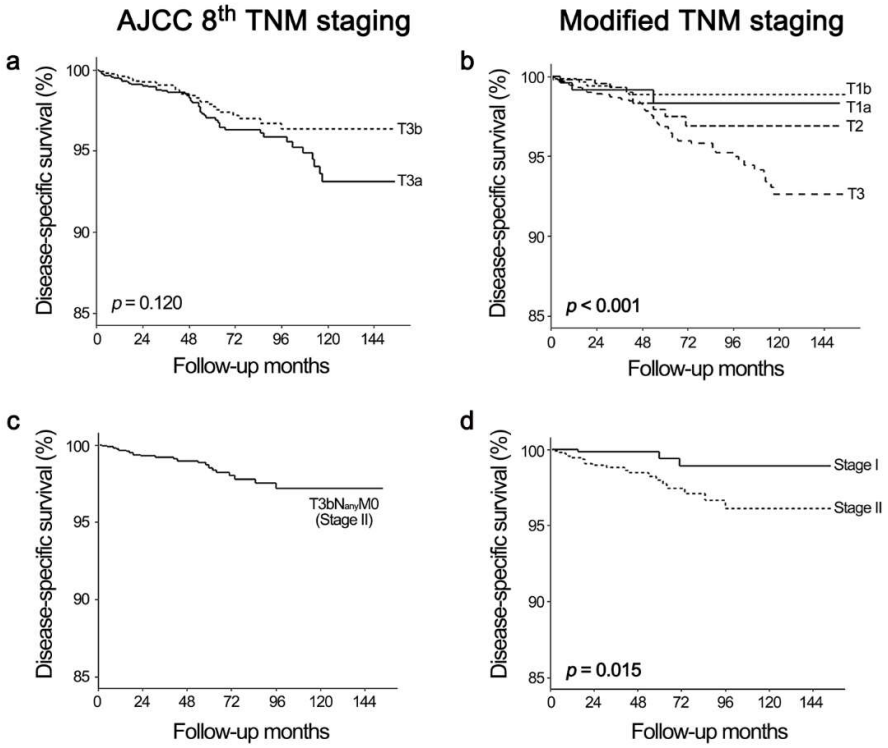

Figure 3. Comparison of disease-specific survival (DSS) of the T3b subgroup according to the AJCC 8th TNM staging schema and the modified TNM staging schema. (a-b) Comparison of the disease-specific survival (DSS) between the T3a and T3b stages according to the AJCC 8th TNM staging schema (a) and the modified TNM staging schema (b). Reallocation of the T3a and T3b stages according to the modified TNM staging schema (b) showed significantly different DSS according to tumor size only (p <0.001). (c-d) Comparison of DSS of the T3bN$_{any}$M0 group according to the AJCC 8th TNM staging schema (c) and the modified TNM staging schema (d). The T3bN$_{any}$M0 group (stage II) (c) according to the AJCC 8th TNM staging schema was reallocated to either stage I or stage II according to the modified TNM staging schema (d), with statistically significant difference in DSS (p = 0.015).

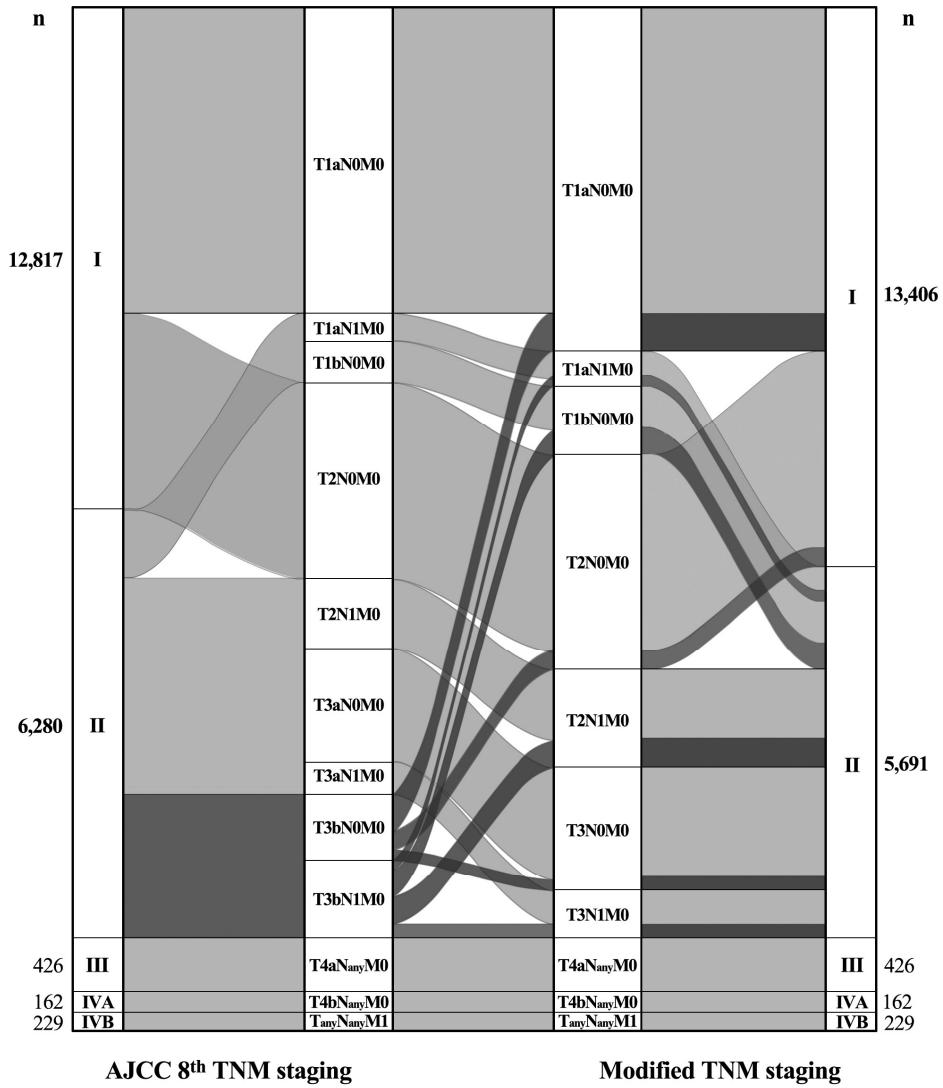

Figure 4. Reallocation of the AJCC 8th TNM stages according to the modified TNM staging schema. The alluvial plot shows the reallocation flow for T stages and overall stages according to the modified TNM staging schema. Dark-grey bands indicate the reallocation of patients with strap muscle invasion (T3bN$_{any}$M0) according to tumor size (*i.e.*, per the modified TNM

staging schema). The number of patients in each T stage of the AJCC 8th TNM staging schema or the modified TNM staging schema are presented along the left and right margins.

4. Power of survival prediction of TNM staging schemas

The C-indices of the AJCC 8th TNM staging schema and the modified TNM staging schema was estimated as 0.942 and 0.941, respectively, but without statistically significant difference (p = 0.220). The PVE for DSS prediction with the AJCC 8th TNM staging schema and the modified TNM staging schema was estimated as 4.45% and 4.43%, respectively.

IV. DISCUSSION

This study suggested that strap muscle invasion alone of any degree was not a statistically significant prognostic factor of DSS in differentiated thyroid cancer regardless of tumor size. This finding may particularly impact tumors equal to or smaller than 40 mm, which may be over-staged by the current AJCC 8th TNM staging schema. In addition, the survival analysis of the T3b group according to the AJCC 8th TNM staging schema showed that it consists of a heterogeneous group of patients with significantly different 10-year DSS according to tumor size (Figure 3). In our study, T3b patients showed significantly better DSS compared to the T3 stage, and they were reallocated to either the T1 or T2 stage with statistical significance.

In our study, Cox proportional hazard analysis and competing risk analysis revealed discrepant results for the prognostic impact of strap muscle on multivariable analysis. Unlike Cox proportional hazard analysis, competing risk analysis accounted for the possibility that death due to causes other than cancer may have obscured the ability to observe cancer-caused deaths.[37] Multivariable competing risk analysis consistently showed that strap muscle invasion alone was not a significant factor for DSS in all patients, as well as subgroups according to tumor size or older patient age.

Historically, ETE was assumed to have a positive correlation with compromised survival in differentiated thyroid cancer,[39,40] but with some

controversy.[41,42] Minimal ETE was totally discarded from the AJCC 8th TNM staging schema, gross strap muscle invasion was introduced as the new T3b stage regardless of tumor size. However, there have been suggestions that even gross strap muscle invasion does not impact survival in patients with differentiated thyroid cancer.[17-19,21,22,43] Indeed, even the AJCC 8th TNM staging schema contains in-stage heterogeneity in regards to DSS prediction, which is consistent with the findings of this study.[44] One potential source of this heterogeneity may be the prognostic impact of strap muscle invasion. A recent study of a total of 2,804 patients and demonstrated that perithyroidal soft tissue or strap muscle invasion showed disease-free survival, overall survival, and DSS comparable to those of intrathyroidal tumors equal to or smaller than 40 mm (median follow-up 59 months [range, 12 – 192 months]), although with small number of strap muscle invasion cases (n=61).[22] Another study on 3,104 patients with either papillary or follicular thyroid carcinoma revealed that gross strap muscle invasion does not significantly impact DSS in tumors equal to or smaller than 40 mm, and that DSS of the T3b stage did not significantly differ from that of the T2 stage (median follow-up 10 years; interquartile range, 8.1 – 12 years).[21]

This population-based study utilized the SEER database[25,26] to reveal that strap muscle invasion alone does not significantly impact DSS, regardless of tumor size or cause of death. This may have particular clinical impact on tumors equal to or smaller than 40 mm which may be appropriately down-staged. Although the estimated C-indices and PVE did not reveal statistically significant differences in the predictive power of the current AJCC 8th TNM staging schema and the suggested modified TNM staging schema, better survival curve separation was observed per the modified staging schema with statistical significance. Given these results, it can be suggested that the modified staging schema shows non-inferior predictive power for prognosis prediction of differentiated thyroid cancer with a more consistent trend of lower 10-year DSS with higher T stage.

Invasion of strap muscle in any degree may not have significant survival impact due to the relative complexity of posterior anatomical structures such as trachea, recurrent laryngeal nerve, and prevertebral fascia. Critical laryngo-tracheal structure invasion leads to a higher possibility of incomplete resection and therefore to higher clinical recurrence and poorer prognosis.[18] On the other hand, strap muscles can be relatively easily resected in the presence of tumor invasion,[22,45] accounting for their lack of significant impact on DSS. Consequently, anterior or posterior ETE have been suggested as more appropriate staging factors than gross strap muscle invasion, with poorer prognosis with posterior ETE.[22,46] Therefore, the dismissal of both minimal and gross strap muscle invasion may lead to better allocation by the TNM staging schema and better reflection of DSS, as suggested by the modified staging schema, particularly for tumors equal to or smaller than 40 mm.

There are several limitations to our study. First, the retrospective nature of this study may have caused an inherent bias. For example, a large portion of the data were discarded due to changes in tumor staging schema, and only data since 2004 were included. Second, the SEER database did not explicitly distinguish between minimal and gross strap muscle invasion, and an inference on the code for strap muscle invasion, both minimal and gross, was made. This may be construed as subjective, but since ETE beyond strap muscle invasion was explicitly distinguished, we believe this interpretation is reasonable. In addition, due to such inference, the purpose of this study was limited to exploring the potential changes in TNM staging with the collective dismissal of both minimal and gross strap muscle invasions. Third, the SEER database did not include recurrence data, which limited the analysis of the impact of strap muscle invasion alone on disease-free survival. Finally, the utilization of a predominantly Caucasian population may limit the applicability of our results to other ethnicities or populations, including Koreans. However, previous studies conducted in Korea with large number of subjects had also yielded similar results that tumors

equal to or smaller than 4 cm in size with gross strap muscle invasion may be downgraded to T2 stage, with better survival predictability.[21]

Strengths of the present study include the use of a national, comprehensive database with analyses of prognostic variables in all tumor size groups as well as tumor size and age subgroups. Moreover, competing risk analysis offered a more accurate evaluation of potential prognostic variables relative to other causes of death.

V. CONCLUSION

Strap muscle invasion alone of any degree does not significantly impact DSS in differentiated thyroid cancer patients, regardless of tumor size. The "modified" TNM staging schema disregarding strap muscle invasion as a T staging criteria was proposed with a more consistent trend of DSS according to T stage, with non-inferior prognosis predictive power compared to that of the currently used AJCC 8th TNM staging schema. Therefore, the modified TNM staging schema suggests potential modification of the TNM staging schema to better reflect the risk of cancer-caused death and to prevent potential over-staging of tumors, particularly those equal to or smaller than 40 mm in size.

REFERENCES

1. Andersen PE, Kinsella J, Loree TR, Shaha AR, Shah JP. Differentiated carcinoma of the thyroid with extrathyroidal extension. Am J Surg 1995;170:467-70.
2. Ortiz S, Rodriguez J, Soria T, Perez-Flores D, Pinero A, Moreno J, et al. Extrathyroid spread in papillary carcinoma of the thyroid: clinicopathological and prognostic study. Otolaryng Head Neck 2001;124:261-5.
3. Hay ID, Grant CS, Taylor WF, McConahey WM. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery 1987;102:1088-95.
4. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery 1988;104:947-53.
5. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993;114:1050-8.
6. Dean DS, Hay ID. Prognostic indicators in differentiated thyroid carcinoma. Cancer control 2000;7:229-39.
7. Adam MA, Pura J, Goffredo P, Dinan MA, Reed SD, Scheri RP, et al. Presence and number of lymph node metastases are associated with compromised survival for patients younger than age 45 years with papillary thyroid cancer. Journal of Clinical Oncology 2015;33:2370-5.
8. Byar DP, Green SB, Dor P, Williams ED, Colon J, van Gilse HA, et al. A prognostic index for thyroid carcinoma. A study of the EORTC Thyroid Cancer Cooperative Group. European Journal of Cancer 1979;15:1033-41.
9. Sherman SI, Brierley JD, Sperling M, Ain KB, Bigos ST, Cooper DS, et

al. Prospective multicenter study of thyroid carcinoma treatment: initial analysis of staging and outcome. Cancer 1998;83:1012-21.

10. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Annals of surgical oncology 2010;17:1471-4.
11. Pontius LN, Oyekunle TO, Thomas SM, Stang MT, Scheri RP, Roman SA, et al. Projecting Survival in Papillary Thyroid Cancer: A Comparison of the Seventh and Eighth Editions of the American Joint Commission on Cancer/Union for International Cancer Control Staging Systems in Two Contemporary National Patient Cohorts. Thyroid 2017;27:1408-16.
12. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. AJCC Cancer Staging Manual. Eighth edition. New York: Springer; 2017.
13. Lamartina L, Grani G, Arvat E, Nervo A, Zatelli MC, Rossi R, et al. 8th edition of the AJCC/TNM staging system of thyroid cancer: what to expect. Endocrinology 2017;25:L7-L11.
14. Suh S, Kim YH, Goh TS, Lee J, Jeong DC, Oh SO, et al. Outcome prediction with the revised American Joint Committee on Cancer staging system and American Thyroid Association guidelines for thyroid cancer. Endocrine 2017;58:495-502.
15. Perrier ND, Brierley JD, Tuttle RM. Differentiated and anaplastic thyroid carcinoma: Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2018;68:55-63.
16. Shteinshnaider M, Muallem-Kalmovich L, Koren S, Or K, Cantrell D, Benbassat C. Reassessment of Differentiated Thyroid Cancer Patients Using the Eighth TNM/AJCC Classification System: A Comparative Study. Thyroid 2018;28:201-9.
17. Jin BJ, Kim MK, Ji YB, Song CM, Park JH, Tae K. Characteristics and significance of minimal and maximal extrathyroidal extension in

papillary thyroid carcinoma. Oral Oncol 2015;51:759-63.

18. Dionigi G, Ieni A, Ferraù F, Sun H, Cannavò S, Tuccari G. Pitfalls in the 2017 TNM Classification of Thyroid Carcinoma. J Endocr Surg 2018;18:98-109.
19. Park S, Kim H, Kim JH, Kim J, Oh Y, Kim S, et al. Prognostic significance of gross extrathyroidal extension invading only strap muscles in differentiated thyroid carcinoma. Br J Surg 2018;105:1155-62.
20. Verburg FA, Mäder U, Tanase K, Thies E-D, Diessl S, Buck AK, et al. Life expectancy is reduced in differentiated thyroid cancer patients≥ 45 years old with extensive local tumor invasion, lateral lymph node, or distant metastases at diagnosis and normal in all other DTC patients. J Clin Endocr Metab 2013;98:172-80.
21. Song E, Lee YM, Oh HS, Jeon MJ, Song DE, Kim TY, et al. A relook at the T stage of differentiated thyroid carcinoma with a focus on gross extrathyroidal extension. Thyroid 2019;29:202-8.
22. Amit M, Boonsripitayanon M, Goepfert RP, Tam S, Busaidy NL, Cabanillas ME, et al. Extrathyroidal Extension: Does Strap Muscle Invasion Alone Influence Recurrence and Survival in Patients with Differentiated Thyroid Cancer? Ann Surg Oncol 2018;25:3380-8.
23. Song E, Kim WW, Jeon MJ, Sung TY, Song DE, Kim TY, et al. Clinical significance of gross invasion of strap muscles in patients with 1- to 4-cm-sized papillary thyroid carcinoma undergoing lobectomy. Ann Surg Oncol 2019;26:4466-71.
24. Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute. Available at: *https://seer.cancer.gov/*. Accessed July 4, 2019
25. Surveillance, Epidemiology, and End Results (SEER) Program (*www.seer.cancer.gov*) SEER*Stat Database: Incidence - SEER 18 Regs

excluding AK Custom Data (with additional treatment fields), Nov 2018 Sub (2000-2016) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2017 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2019, based on the November 2018 submission.

26. Surveillance Research Program, National Cancer Institute SEER*Stat software (*seer.cancer.gov/seerstat*) version <8.3.5>.
27. National Cancer Institute. SEER Registrar Staging Assistant. EOD data (v2.0) Available at *https://staging.seer.cancer.gov/eod_public/schema/2.0/thyroid/*. Accessed on July 4, 2019.
28. National Cancer Institute. SEER Summary Staging Manual 2000. Available at *https://seer.cancer.gov/tools/ssm/ssm2000/*. Accessed on July 4, 2019.
29. Collaborative Stage Data Collection System. Available at *http://web2.facs.org/cstage0205/thyroid/Thyroidschema.html*. Accessed on July 4, 2019.
30. Therneau TM. A Package for Survival Analysis in S. version 2.38 ed; 2015.
31. Kang L, Chen W, Petrick NA, Gallas BD. Comparing two correlated C indices with right-censored survival outcome: a one-shot nonparametric approach. Stat Med 2015;34:685-703.
32. Wickham H. ggplot2: Elegant Graphics for Data Analysis. New York: Springer-Verlag 2016.
33. Brunson JC. ggalluvial: Alluvial Diagrams in 'ggplot2'. R package version 0.9.1 ed; 2018.
34. Kassambara A, Kosinski M, Biecek P. survminer: Drawing Survival Curves using 'ggplot2'. R package version 0.4.5 ed; 2019.
35. Gray B. cmprsk: Subdistribution Analysis of Competing Risks. . R

package version 2.2-8. ed; 2019.

36. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
37. Han K, Kim EK, Kwak JY. 1.5–2 cm tumor size was not associated with distant metastasis and mortality in small thyroid cancer: A population-based study. Sci Rep 2017;7:46298.
38. Schemper M, Stare J. Explained variation in survival analysis. Stat Med 1996;15:1999-2012.
39. Chereau N, Buffet C, Tresallet C, Tissier F, Golmard JL, Leenhardt L, et al. Does extracapsular extension impact the prognosis of papillary thyroid microcarcinoma? Ann Surg Oncol 2014;21:1659-64.
40. Anderson KL, Jr., Youngwirth LM, Scheri RP, Stang MT, Roman SA, Sosa JA. T1a Versus T1b Differentiated Thyroid Cancers: Do We Need to Make the Distinction? Thyroid 2016;26:1046-52.
41. Hu A, Clark J, Payne RJ, Eski S, Walfish PG, Freeman JL. Extrathyroidal extension in well-differentiated thyroid cancer: macroscopic vs microscopic as a predictor of outcome. Arch Otolaryngol Head Neck Surg 2007;133:644-9.
42. Arora N, Turbendian HK, Scognamiglio T, Wagner PL, Goldsmith SJ, Zarnegar R, et al. Extrathyroidal extension is not all equal: Implications of macroscopic versus microscopic extent in papillary thyroid carcinoma. Surgery 2008;144:942-7; discussion 7-8.
43. Underwood HJ, Patel KN. The Clinical Significance of Strap Muscle Invasion in Papillary Thyroid Cancer on Local Recurrence: Is Less Surgery Warranted? Ann Surg Oncol 2018;26:4171-2.
44. Tam S, Boonsripitayanon M, Amit M, Fellman BM, Li Y, Busaidy NL, et al. Survival in differentiated thyroid cancer: comparing the AJCC cancer staging seventh and eighth editions. Thyroid 2018;28:1301-10.
45. Khan ZA, Mehta S, Sumathi N, Dhiwakar M. Occult invasion of

sternothyroid muscle by differentiated thyroid cancer. Eur Arch Otorhinolaryngol 2018;275:233-8.

46. Moran A, Boonsripitayanon M, Zafereo ME. ASO Author reflections: strap muscle invasion does not influence recurrence and survival in patients with differentiated thyroid cancer. Annals of surgical oncology 2018;25:892-3.

ABSTRACT(IN KOREAN)

분화갑상선암에서 띠근육 침범이 예후에 미치는 영향에 대한 고찰: 대규모 Surveillance, Epidemiology, and End Results (SEER) 데이터베이스를 이용한 후향적 연구

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배경: 분화갑상선암의 American Joint Committee on Cancer (AJCC) 8판 병기 설정 매뉴얼에서 육안적 띠근육 침범이 종양의 크기에 무관하게 T3b로 분류되었다. 그러나 분화갑상선암에서 질병특이생존률에 띠근육 침범이 미치는 영향은 뚜렷이 알려진 바가 없다. 본 연구는 대규모 Surveillance, Epidemiology, and End Results (SEER) 데이터베이스를 통해 분화갑상선암에서 띠근육 침범이 예후에 미치는 영향을 분석하고자 하였다.

방법: SEER 데이터베이스를 2019년 7월에 조회하여 1973년부터 2018년까지 분화갑상선암으로 진단된 환자의 데이터를 얻어 후향적으로 분석하였다. 분화갑상선암에 대해 수술적 치료를 받은 환자 중 병기, 치료, 또는 생존에 대한 기록이 불완전하거나 불충분한 경우를 제외한 후 총 19,914명의 데이터가 최종 분석에 포함되었다. 띠근육 침범 여부를 T 병기 설정 기준에서 제외한 “modified” 병기 설정 모델을 구상하였다. 콕스 비례위험모형과 경쟁위험분석을 이용하여 T 병기에 따른 10년 질병특이생존률을 AJCC 8판 매뉴얼과 “modified” 모델에 따라 비교하였다. 또한 두 병기 설정 모델에 따른 생존 예측 정확도를 Harrell의 일치 인덱스(C-index)와 설명변이비율(proportion of variation explained)를 이용해 비교하였다.

결과: 기존의 AJCC 8판 매뉴얼에 의한 T3b 병기를 “modified” 모델에

따라 재설정하였을 때 “modified” 모델에 의한 병기 설정 시 10년 질병특이생존률이 통계적으로 유의미한 차이가 났다 (p <0.001). 특히 종양의 크기가 40 mm 이하인 경우, 다변수 콕스 비례위험모형에서 띠근육 침범은 질병특이생존률에 대해 통계적으로 유의미하지 않은 요소로 나타났다 (위험비 1.620 [95% 신뢰구간 0.917- 2.860], p = 0.097). 또한 다변수 경쟁위험분석에서 띠근육 침범은 암에 의한 사망 (subdistribution hazard ratio (SDHR) 1.567 [95% 신뢰구간 0.984 - 2.495], p = 0.059))과 암 이외의 사망 (SDHR 1.155 [95% CI 0.842 - 1.585], p = 0.370) 모두에서 예후 예측에 통계적으로 유의미하지 않은 요소로 나타났으며, 이는 종양의 크기와 무관하게 나타났다. 55세 이상 환자군에서도 띠근육 침범은 다변수 콕스 비례위험모형에서 질병특이생존률에 대해 통계적으로 유의미하지 않은 요소로 나타났으며 (위험비 1.280 [95% CI 0.946 - 1.732], p = 0.110), 다변수 경쟁위험분석에서도 사망원인과 무관하게 예후 예측에 통계적으로 유의미하지 않은 요소로 나타났다 (암에 의한 사망, SDHR 1.447 [95% 신뢰구간 0.835 - 2.508], p = 0.190; 암 이외의 사망, SDHR = 1.121 [95% CI 0.780 - 1.610], p = 0.540). “Modified” 모델의 생존 예측 정확도 (C-index 0.941, PVE 4.43%)는 AJCC 8판 매뉴얼 (C-index 0.942, PVE 4.45%)과 비교해 약간 낮았으나 이 차이는 통계적으로 유의미하지 않았다 (p = 0.220). 또한 “modified” 모델에서 더 높은 T 병기에 따른 10년 질병특이생존률의 감소가 일관성 있게 관찰되었다.

결론: 분화갑상선암에서 띠근육 침범은 10년 질병특이생존률에 유의미한 영향을 끼치지 않았다. 따라서, AJCC 8판 병기 설정 매뉴얼에서 띠근육 침범을 제외한 “modified” 병기 설정 모델이 암에 의한 사망률을 더 잘 반영하며, 또한 종양의 크기가 40 mm 이하인 경우에서 과도하게 높은 병기 설정을 예방할 수 있을 것으로 예상된다.

핵심되는 말 : 갑상선 종양, SEER 프로그램, 분화갑상선암, 질병특이생존율, 암 병기 설정

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