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Overall survival is improved with total thyroidectomy and radiation for male patients and patients older than 55 with T2N0M0 Stage 1 classic papillary thyroid cancer



Erin C. MacKinney, MD^{a,b}, Kristine M. Kuchta, MS^c, David J. Winchester, MD^{a,b}, Amna M. Khokar, MD^b, Simon A. Holoubek, DO^d, Tricia A. Moo-Young, MD^{a,b}, Richard A. Prinz, MD^{a,b,*}

- ^a Department of Surgery, NorthShore University HealthSystem, Evanston, IL
- ^b Department of Surgery, University of Chicago, Chicago, IL
- ^c Bioinformatics and Research Core, NorthShore University HealthSystem, Evanston, IL
- ^d Augusta University, Otolaryngology Department, Head and Neck Surgery, Augusta, GA

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ABSTRACT

Background: We examine whether surgery extent and radiation administration affect overall survival for cT2N0M0 classic papillary thyroid cancer according to age and sex.

Methods: Patients with cT2N0M0 classic papillary thyroid cancer tumors in the National Cancer Data Base (2004–2016) were selected. Multivariable Cox regression analysis compared patients (combined male + female cohorts) having lobectomy to those having total thyroidectomy with or without radiation (primarily radioactive iodine) for ages: 18 to 45, 46 to 55, and >55 years. In addition, 1:1 propensity score matching and Kaplan-Meier curves with 10-year overall survival estimates, and log-rank test were stratified by age and sex.

Results: Lobectomy had equivalent overall survival to total thyroidectomy without and with radiation for patients (combined male + female cohorts) aged 18 to 45 and 46 to 55 years on multivariable analysis. On propensity score matching there was overall survival advantage for total thyroidectomy with radiation over both lobectomy and total thyroidectomy for men (ages 18-90+ combined) and overall survival advantage in patients (combined male + female cohort) aged >55 years having total thyroidectomy with radiation versus lobectomy. On propensity score matching there were no overall survival differences in women (ages 18-90+ combined) or patients (combined male + female cohort) aged 18 to 45 and 46 to 55 years having either lobectomy, total thyroidectomy, or total thyroidectomy with radiation.

Conclusion: For cT2N0M0 classic papillary thyroid cancer, total thyroidectomy with radiation improves 10-year overall survival for patients (combined male + female cohort) aged >55 years and men (ages 18 -90+ combined).

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Introduction

Thyroid cancer is one of the most rapidly increasing cancers in the United States with approximately 44,280 patients expected to be diagnosed in 2021 with 2,200 deaths expected according to the American Cancer Society. Differentiated thyroid cancer represents

E-mail address: rprinz@northshore.org (R.A. Prinz).

the majority of these cancers with only 10% to 15% of deaths occurring with more aggressive thyroid cancers.²

The appropriate extent of surgery for papillary thyroid cancer has been a subject of debate for decades. In 2007, Bilimoria et al published a study from the National Cancer Database (1985–1998) comparing lobectomy to total thyroidectomy for papillary thyroid cancer (PTC), concluding that total thyroidectomy had improved survival rates compared with lobectomy for tumors $\geq\!1$ cm. 3 However, a subsequent study of the National Cancer Data Base (NCDB) (1998–2006) published in 2014 by Adam et al found on multivariable adjustment, there was no survival advantage to total thyroidectomy compared with lobectomy for low-risk PTC. 4 We

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^{*} Reprint requests: Richard A. Prinz, MD, Ridge Ave, Walgreen Suite 2507, Evanston, IL 60201.

more recently published findings based on the NCDB (2004–2008) further clarifying the question of the appropriate extent of resection, showing that total thyroidectomy was associated with improved survival for classic PTC (2–3.9 cm) but not for patients with follicular-variant of papillary thyroid cancer.⁵

Thyroid cancer is the only adult cancer that uses age as a prognostic factor in the TNM staging system. The current American Joint Committee on Cancer (AJCC) 2017 guidelines have the age of 55 years as the age cut-off for upstaging older patients or downstaging younger patients with a differentiated thyroid cancer. This was an update from the age cut-off of 45 years in the previous guidelines. The change was based on 10-year disease specific survival rates showing that younger patients had improved disease specific survival compared with patients greater or equal to 55 years of age. Although there have been subsequent studies confirming worse prognosis for patients older than 55 years, there are few studies assessing whether age should be a factor in determining extent of treatment for differentiated thyroid cancer.

It is also debated on whether sex is a prognostic factor in PTC with some studies suggesting male sex is an independent, poor prognostic factor, ^{8,9} while other studies shown sex does not influence survival. ^{10,11} We sought to determine if extent of surgery and use of radiation (radioactive iodine primarily) affect overall survival (OS) for patients with PTC T2 tumors (2–3.9 cm) according to age and sex.

Methods

The NCDB was used for this study to be able to compare findings of previous studies addressing similar questions with our results. The NCDB is a database sponsored by the American College of Surgeons and the American Cancer Society sourced from hospital registry data from 1,500 Commission on Cancer-accredited facilities. The data represent more than 70% of newly diagnosed cancers across the United States. ¹²

Using the 2016 NCDB participant user file, all patients who underwent thyroid surgery for thyroid cancer from 2004 to 2016 were identified. Using the International Classification of Disease for Oncology, Third Edition (ICD-O-3), codes for classic papillary cancer were identified: 8050/3 (papillary carcinoma, not otherwise specified), 8260/3 (papillary adenocarcinoma, not otherwise specified), and 8343/3 (papillary carcinoma, encapsulated). Papillary microcarcinoma and other variants of papillary thyroid cancer were excluded.

Patients were included if they were 18 years of age or older, had a tumor size of 2.0 to 3.9 cm, clinical stage NO or Nx, and had a lobectomy without radiation (lobectomy), total thyroidectomy without radiation (TT), or total thyroidectomy with radiation (TT+R). Patients with radiation included those having RAI (99.4%) and external beam radiation (0.6%). Lobectomy patients included those who underwent lobectomy with or without isthmusectomy. Total thyroidectomy patients included those who underwent total, near-total, or subtotal thyroidectomy. Patients who had a lobectomy followed by completion thyroidectomy were included in the total thyroidectomy group. Patients were excluded if they had more than one primary malignancy, distant metastases, received chemotherapy, unknown radiation history, or clinical N1 disease. Patients with distant metastases or those receiving chemotherapy were excluded.⁵ Patients having lobectomy and radiation were excluded (762 patients).

Patient characteristics analyzed were age at diagnosis (grouped by 18–45, 46–55, and >55), sex, race, insurance status, annual income, tumor size, extent of disease, tumor multifocality, surgical margins, Charlson-Deyo comorbidity index (CCI), and extent of surgical treatment and radioactive iodine therapy. Comparisons

were made of lobectomy versus TT+R; TT versus TT+R; and lobectomy versus TT.

Patient variables were reported using frequency with percentage. These variables were compared across groups using the Pearson χ^2 test, with the Bonferroni correction for multiple comparisons. Kaplan-Meier analysis and 10-year overall survival estimates were compared across groups using the log-rank test with the Tukey-Kramer method for multiple comparisons.

A multivariable Cox proportional hazards model was used to determine whether the extent of surgery and or radioactive iodine administration contributed to an overall survival advantage at various age ranges (18–45, 46–55, and >55) in cohorts of combined male and female patients. The model adjusted for the effects of patient characteristics and clinical factors, including sex, race, insurance status and type, tumor size (2.0–2.9 cm vs 3.0–3.9 cm), extrathyroidal extension (ETE), multifocality, surgical margins, CCI score, and facility type.

A one-to-one propensity score matched (PSM) analysis was then performed on 1,189 patients per treatment group (men and women combined). Propensity scores were computed based on a logistic regression model including age, sex, race, CCI score, insurance status, income, facility type, tumor size, tumor focality, extrathyroidal extension, and surgical margins. The treatment groups consisted of lobectomy, TT and TT+R. Matching was performed using propensity scores without replacement with a greedy, nearest-neighbor algorithm. Kaplan-Meier curves with 10-year overall survival estimates and conditional Cox proportional hazards modeling stratified by age were used to determine whether extent of surgery affected overall survival on PSM analysis. A similar analysis was performed stratified by sex, with 299 patients per treatment group for men (ages 18-90+ combined) and 890 for women (ages 18-90+ combined). All statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

There were 32,147 patients in the National Cancer Data Base from 2004 to 2016 with cT2N0M0 Stage I cPTC tumors meeting exclusion and inclusion criteria. There were 1,189 patients (men and women combined) treated with lobectomy, 9,314 treated with TT, and 21,644 treated with TT+R (Table I). Patients having radiation included 99.4% having radioactive iodine and 0.6% with external beam radiation. There were significant differences comparing age groups composed of combined male and female patients aged 18 to 45, 46 to 55, and >55 years with regard to sex, white race, insurance status, income, CCI score >2, margin status, and extrathyroidal extension. Younger patients (both sexes combined) were more likely to have solitary tumors versus multifocal tumors compared with patients aged 46 to 55 or older than 55 years. A higher percentage of combined male and female patients >55 compared with ages 18 to 45 or 46 to 55 years had lobectomy (4.4% vs 3.4% and 3.6%, respectively with both comparisons P <.0001) and a higher percentage of patients >55 compared with ages 18 to 45 or 46 to 55 years had no radiation (34.3% vs 32.3% and 31.6%, respectively).

On multivariable Cox proportional hazards modeling for overall survival, men had poorer survival within every age group compared to women (Table II). Patients (men and women combined) aged >55 had worse survival with lobectomy compared to TT+R. This difference was not seen within the age groups 18 to 45 or 46 to 55 years. In the 18 to 45 age group (men and women combined) as well as the oldest age group, patients having TT compared with TT+R had poorer survival. Survival was similar for all 3 treatments in the age 46 to 55 group. There was no difference in overall survival in any age group with lobectomy compared with TT.

Table ICharacteristics of patients by age for Ct2n0m0 stage I classic PTC

	All N (%)	18-45 y N (%)	46-55 y N (%)	>55 y N (%)	P value
Total patients	32,147	16,534	7,203	8,410	_
Sex					<.0001*,†,‡
Male	8,089 (25.2)	3,304 (20.0)	2,076 (28.8)	2,709 (32.2)	
Female	24,058 (74.8)	13,230 (80.0)	5,127 (71.2)	5,701 (67.8)	
Race					<.0001*,†,‡
White	23,991 (74.6)	11,845 (71.6)	5,477 (76.0)	6,669 (79.3)	
Black	1,743 (5.4)	856 (5.2)	439 (6.1)	448 (5.3)	
Hispanic	3,380 (10.5)	2,071 (12.5)	669 (9.3)	640 (7.6)	
Asian/Pacific Islander	1,973 (6.1)	1,155 (7.0)	372 (5.2)	446 (5.3)	
Other/unknown	1,060 (3.3)	607 (3.7)	246 (3.4)	207 (2.5)	
Insurance					<.0001*,†,‡
Private	23,603 (73.4)	13,472 (81.5)	6,076 (84.4)	4,055 (48.2)	
Medicare	4,311 (13.4)	293 (1.8)	302 (4.2)	3,716 (44.2)	
Medicaid/other government	2,619 (8.1)	1,792 (10.8)	463 (6.4)	364 (4.3)	
Unknown/uninsured	1,614 (5.0)	977 (5.9)	362 (5.0)	275 (3.3)	
Income					<.0001*,†,‡
<\$38,000	3,940 (12.3)	1,975 (11.9)	823 (11.4)	1,142 (13.6)	
\$38,000-\$62,999	15,008 (46.7)	7,733 (46.8)	3,232 (44.9)	4,043 (48.1)	
≥\$63,000	13,047 (40.6)	6,747 (40.8)	3,122 (43.3)	3,178 (37.8)	
Unknown	152 (0.5)	79 (0.5)	26 (0.4)	47 (0.6)	
Charlson Comorbidity Index					<.0001*,†,‡
0	27,899 (86.8)	15,181 (91.8)	6,146 (85.3)	6,572 (78.1)	
1	3,561 (11.1)	1,225 (7.4)	920 (12.8)	1,416 (16.8)	
≥2	687 (2.1)	128 (0.8)	137 (1.9)	422 (5.0)	
Facility type					<.0001*,†
Community cancer program	1,190 (3.7)	240 (1.5)	431 (6.0)	519 (6.2)	
Comprehensive Community Cancer Program	7,857 (24.4)	1,716 (10.4)	2,791 (38.7)	3,350 (39.8)	
Academic/research program	8,182 (25.5)	1,905 (11.5)	2,957 (41.1)	3,320 (39.5)	
Integrated network cancer program	2,894 (9.0)	649 (3.9)	1,024 (14.2)	1,221 (14.5)	
Unknown/patient age <40 y	12,024 (37.4)	12,024 (72.7)	0 (0.0)	0 (0.0)	
Tumor size					0.0657
2.0-2.9 cm	22,215 (69.1)	11,439 (69.2)	5,038 (69.9)	5,738 (68.2)	
3.0-3.9 cm	9,932 (30.9)	5,095 (30.8)	2,165 (30.1)	2,672 (31.8)	
Surgery					<.0001 ^{†,‡}
Lobectomy without radiation	1,189 (3.7)	559 (3.4)	260 (3.6)	370 (4.4)	
Total thyroidectomy without radiation	9,314 (29.0)	4,786 (28.9)	2,016 (28.0)	2,512 (29.9)	
Total thyroidectomy with radiation	21,644 (67.3)	11,189 (67.7)	4,927 (68.4)	5,528 (65.7)	
Surgical margins					<.0001*,†,‡
Negative	25,676 (79.9)	13,564 (82.0)	5,769 (80.1)	6,343 (75.4)	
Positive	5,312 (16.5)	2,391 (14.5)	1,168 (16.2)	1,753 (20.8)	
Unknown	1,159 (3.6)	579 (3.5)	266 (3.7)	314 (3.7)	
Tumor focality					<.0001*,†
Solitary	17,918 (55.7)	9,598 (58.1)	3,775 (52.4)	4,545 (54.0)	
Multifocal	13,423 (41.8)	6,545 (39.6)	3,252 (45.1)	3,626 (43.1)	
Unknown	806 (2.5)	391 (2.4)	176 (2.4)	239 (2.8)	
Extrathyroidal extension					<.0001*,†,‡
None	19,741 (61.4)	10,763 (65.1)	4,407 (61.2)	4,571 (54.4)	
Micro	2,232 (6.9)	1,263 (7.6)	479 (6.7)	490 (5.8)	
Minimal	3,228 (10.0)	1,456 (8.8)	792 (11.0)	980 (11.7)	
Macro	4,013 (12.5)	1,620 (9.8)	908 (12.6)	1,485 (17.7)	
Unknown	2,933 (9.1)	1,432 (8.7)	617 (8.6)	884 (10.5)	

^{* 18–45} y vs 46–55, *P* < .05

PSM analysis

There were no differences in patient or tumor characteristics including age, sex, race, insurance type, income range, CCI score, facility type, tumor size, surgical margin status, tumor focality, or ETE extent between the 1,189 patients having lobectomy and the 1,189 having TT or the 1,189 selected having TT+R after PSM (men and women combined in these groups).

In the patients within age group 18 to 45 years, there was no difference in survival with lobectomy compared to TT+R or lobectomy compared with TT or TT compared with TT+R. In the patient age group 46 to 55, there was also no difference in survival with lobectomy compared to TT+R, lobectomy compared with TT, or TT

compared with TT+R. In the >55 age group, patients having lobectomy compared with TT+R had worse survival, but those having lobectomy compared to TT had no difference in survival. Those having TT compared with TT+R had no difference in survival (Table III).

Sex PSM analysis

There were no differences in patient or tumor characteristics including age, sex, race, insurance type, income range, CCI score, facility type, tumor size, surgical margin status, tumor focality, or ETE extent between the 299 male patients (ages 18–90+ combined) having lobectomy and the 299 male patients having TT or

[†] 18-45 y vs > 55, P < .05

 $^{^{\}ddagger}$ 46–55 y vs > 55, P < .05

Table IIMultivariable Cox PH modeling for overall survival

	Age 18-45 y	Age 46-55 y	Age >55 y	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Sex, male vs female	2.53 (1.72-3.73)	1.53 (1.12-2.10)	1.31 (1.15-1.51)	
Tumor size, 3.0-3.9 vs 2.0-2.9 cm	1.17 (0.79-1.72)	1.36 (0.99-1.86)	1.28 (1.12-1.46)	
Surgical margins				
Positive vs negative	0.93 (0.54-1.61)	0.88 (0.57-1.36)	1.37 (1.16-1.61)	
Unknown vs negative	1.13 (0.48-2.63)	0.96 (0.45-2.08)	1.52 (1.14-2.02)	
Tumor focality				
Multifocal vs solitary	1.00 (0.68-1.49)	0.76 (0.55-1.05)	0.88 (0.76-1.01)	
Unknown vs solitary	1.57 (0.66-3.73)	1.35 (0.70-2.62)	0.91 (0.65-1.26)	
Extrathyroidal extension				
Micro vs none	1.37 (0.73-2.60)	1.48 (0.86-2.52)	0.96 (0.72-1.30)	
Minimal vs none	1.08 (0.53-2.20)	0.66 (0.34-1.29)	1.33 (1.08-1.65)	
Macro vs none	2.21 (1.32-3.72)	2.13 (1.44-3.15)	1.78 (1.51-2.11)	
Unknown vs none	1.28 (0.17-9.83)	0.69 (0.09-5.09)	0.52 (0.16-1.63)	
Surgery type				
Lobe w/o rad* vs total w/ rad†	1.75 (0.70-4.38)	1.61 (0.77-3.35)	1.95 (1.46-2.60)	
Total w/o rad‡ vs total w/ rad†	1.80 (1.22-2.66)	1.20 (0.85-1.68)	1.60 (1.38-1.85)	
Lobe w/o rad* vs total w/o rad‡	1.01 (0.40-2.57)	0.74 (0.35-1.58)	0.82 (0.61-1.10)	

CI, confidence interval; HR, hazard ratio.

The following variables are accounted for in the model: race, insurance, Charlson Comorbidity Index, facility type:

- * Lobectomy without radiation.
- † Total thyroidectomy with radiation.
- [‡] Total thyroidectomy without radiation.

Table IIITen-year overall survival estimates from propensity score—matched patients

	Lobectomy	TT	TT+R	Lobectomy vs TT	Lobectomy vs TT+R	TT vs TT+R
Age 18–45, y	98.5	97.1	99.1	P = .81	P = .99	P = .25
Age 46-55, y	95.2	92.9	97.6	P = .29	P = .19	P = .07
Age >55, y	70.3	73	79.2	P = .10	P < .01	P = .19
Age $18-90+$ female, y	91.2	88.8	91.6	P = .60	P = .21	P = .06
Age 18–90+ male, y	80.6	78.5	86.7	P = .25	P = .02	P = .02

TT, total thyroidectomy; TT+R, total thyroidectomy with radiation.

the 299 male patients selected having TT+R after PSM. Similarly, there were no differences in patient variables or tumor characteristics between the 890 female patients (ages 18-90+ combined) having lobectomy and the 890 female patients having TT or the 890 female patients selected having TT+R after PSM.

For female patients (ages 18-90+ combined), there was no difference in 10-year overall survival comparing any of the treatments (Table III). Male patients (ages 18-90+ combined) had improved survival with TT+R compared with lobectomy and with TT+R compared with TT (Table III).

Discussion

Surgeons have long debated whether a lobectomy or a TT for well-differentiated papillary thyroid cancer without ETE or lymph node metastases is the most appropriate operation. In 2007, Bilimoria et al reported their NCDB-based study on patients from 1985 to 1998 that demonstrated a higher 10-year overall survival for patients with PTC $\geq \! 1$ cm having TT compared to lobectomy. The NCDB database at that time did not include factors such as ETE, multifocality, comorbidities, or completeness of resection. In a subsequent study using the NCDB database performed by Adam et al in 2014 showed that there was no survival difference in patients with lobectomy compared to TT with 1 to 4 cm PTC when adjustments were made for variables regarding tumor factors and patient comorbidities. Similarly, studies based from patients in the SEER database did not show survival differences based on extent of thyroid resection. 14,15 In 2005, Haigh et al analyzed 1,030 high-risk

patients with PTC. This group included young patients with tumors having ETE, older patients with cancers 5 cm or greater, any cancer with ETE, or patients with distant metastases and they found no difference in survival on multivariate analysis when comparing lobectomy to TT.¹⁴ Mendelsohn et al in 2010 examined patients from the SEER database from 1988 to 2001 with tumors <1 cm to >4 cm and included classic PTC as well as variants (follicular variant, oxyphilic cell, encapsulated, columnar cell, and papillary cystadenocarcinoma). They found no difference in overall survival or disease-specific survival comparing treatments of lobectomy to TT.¹⁵ We recently published findings based on patients from 2004 to 2008 in the NCDB clarifying the question of the appropriate extent of resection. We showed that TT was associated with improved survival for classic PTC (2–3.9 cm) but not for patients with follicular-variant of PTC.⁵

Age is an important factor in the outcome of PTC. The current AJCC 2017 guidelines have increased the age from 45 to 55 for upstaging older patients with differentiated thyroid cancer.^{6,7} This change was based on 10-year disease specific survival rates showing that younger patients had improved disease specific survival compared with patients aged 55 and older.^{7,16} A subsequent study done based on patients with PTC in the California Cancer Registry found that patients 60 years of age and older have worse disease-specific survival and disease-free survival in every stage of the disease, and patients older than 45 years have progressively worse survival. They suggested 3 age groups 18 to 44 years of age, 45 to 59 years, and 60 years and older as independent predictors of survival and recurrence.¹⁷

Although subsequent studies have confirmed worse prognosis for patients over 55 years of age, ^{18,19} few studies assess the outcomes of various surgical treatments for different age groups. We chose 3 age groups of ages 18 to 45, 46 to 55, and older than 55 years to assess and validate the recent change in age for staging. We included only classic PTC in this study as previous studies identified improved overall survival with TT over lobectomy. ⁵ If age is an important factor in various treatment outcomes, examining only this type may better stratify outcomes. Our initial hypothesis was that patients aged younger than 55 years with T2N0M0 stage I classic PTC have no significant survival difference with lobectomy compared to TT but patients 55 and older improved overall survival with TT.

We found that age is a significant factor in 10-year overall survival for cPTC for different surgical treatments. In the multivariate analysis of combined male and female patients, the youngest age group of 18 to 45 and the oldest of age >55 years had worse survival with TT compared with TT+R and the oldest age group also had worse survival with both lobectomy compared to TT+R and TT compared with TT+R. The survival advantage for TT+R compared with TT in the youngest age group was not seen in the PSM patients. Similarly, in the PSM in the >55 years age group there was no difference in survival between TT and TT+R. Necessarily there is a smaller "n" in the PSM compared with the multivariable analysis, which could account for the differences between the analyses. However, as PSM is a more rigorous method of excluding confounding variables, there were likely a combination of factors other than the treatments themselves causing the survival differences in the multivariate analysis.

Younger patients (men and women combined) of age 18 to 45 and 45 to 55 years in the PSM had no difference in 10-year survival when comparing 3 treatment modalities of lobectomy, TT, and TT+R in the PSM. Patients (men and women combined) older than 55 years did have improved survival with TT+R over lobectomy. However, there was no survival difference in this older age group when comparing lobectomy to TT or when comparing TT with TT+R. The added treatment effect of total thyroidectomy and radiation did improved survival in patients older than 55 years but not in younger patients. These findings support the change of age in staging well differentiated thyroid cancers and support for less aggressive treatments in younger patients.

In addition, we sought to determine whether survival was influenced by sex with extent of surgery. Studies suggest that male sex is an independent, poor prognostic factor in PTC, 8,9 whereas other studies have shown gender does not influence survival. 10,11 We obtained survival estimates from patients in a sex-matched one-to-one PSM and found that women (ages 18–90+ combined) had no survival differences comparing any of the 3 treatments. In men (ages 18-90+ combined), there was a survival advantage to total thyroidectomy with radiation compared with lobectomy or total thyroidectomy alone. These findings suggest that treatment extent in women does not change survival outcome, but more aggressive treatments in men may have survival advantages. These findings also suggest that male patients are the driving factor in the survival advantage seen in patients age >55 years (male and female cohort combined) undergoing total thyroidectomy with radiation over lobectomy.

Our work has the limitations of any large database study. The data contained in large databases may not be entirely accurate. The NCBD does not contain data such as disease recurrence, or disease-specific survival, which would have been useful in our analysis. It also does not contain other pathologic variables such as lymphatic invasion, vascular invasion, or molecular markers such as BRAF positivity. There is also no way to tell from the data the reasons the patients underwent the various treatments or if a patient initially

had a lobectomy followed by a completion thyroidectomy. Patients were excluded that had chemotherapy in attempt to eliminated confounding factors; all potentially confounding factors cannot be excluded and for example patients having immunotherapy were retained (0.4% of patients). The database does have a very large number of patients which adds strength to analyses. In addition, performing one-to-one propensity score matching improves the validity of our outcomes.

In conclusion, survival outcomes for different treatment strategies vary based on age and sex in cT2N0M0 stage I classic papillary thyroid cancer. As this is a retrospective study, translating our findings to prospective treatment strategies should be approached with caution.

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Conflict of Interest/Disclosure

The authors have no related conflicts of interest to declare.

References

- American Cancer Society Cancer Facts & Figures 2021. Atlanta: American Cancer Society; 2021.
- Shah JP. Thyroid carcinoma: Epidemiology, histology, and diagnosis. Clin Adv Hematol Oncol. 2015;13(4 Suppl 4):3–6.
- **3.** Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS, Sturgeon C. Extent of surgery affects survival for papillary thyroid cancer. *Ann Surg.* 2007;246:375–381; discussion 381–384.
- Adam MA, Pura J, Gu L, et al. Extent of surgery for papillary thyroid cancer is not associated with survival: An analysis of 61,775 patients. *Ann Surg.* 2014;260:601–605; discussion 605–607.
- Rajjoub SR, Yan H, Calcatera NA, et al. Thyroid lobectomy is not sufficient for T2 papillary thyroid cancers. Surgery. 2018;163:1134–1143.
- American Cancer Society. Thyroid cancer stages. Available at: https://www.cancer.org/cancer/thyroid-cancer/detection-diagnosis-staging/staging.html. Accessed February 6, 2021.
- American Joint Committee on Cancer. Thyroid: Differentiated and anaplastic. In: AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017:873.
- Liu C, Chen T, Zeng W, et al. Reevaluating the prognostic significance of male gender for papillary thyroid carcinoma and microcarcinoma: A SEER database analysis. Scientific Reports. 2017;7:11412.
- Cunningham MP, Duda RB, Recant W, et al. Survival discriminants for differentiated thyroid cancer. *Am J Surg.* 1990:344–347.
 Akslen LA, Haldorsen T, Thoresen SO, et al. Survival and causes of death in
- Akslen LA, Haldorsen T, Thoresen SO, et al. Survival and causes of death in thyroid cancer: A population-based study of 2479 cases from Norway. Cancer Res. 1991:1234–1241.
- Nilubol N, Zhang L, Kebebew E. Multivariate analysis of the relationship between male sex, disease-specific survival, and features of tumor aggressiveness in thyroid cancer of follicular cell origin. *Thyroid*. 2013;23:695–702.
- American College of Surgeons. National Cancer Database. Available at: https:// www.facs.org/Quality-Programs/Cancer/NCDB. Accessed February 6, 2021.
- National Cancer Institute. Surveillance, Epidemiology, and End Results program. ICD-0-3 coding materials. ICD-0-3 SEER site/histology validation list. Available at: https://seer.cancer.gov/icd-o-3/. Accessed February 6, 2021.
 Haigh Pl, Urbach DR, Rotstein LE, Extent of thyroidectomy is not a major
- Haigh PI, Urbach DR, Rotstein LE. Extent of thyroidectomy is not a major determinant of survival in low- or high-risk papillary thyroid cancer. *Ann Surg Oncol.* 2005:81–89.
- Mendelsohn AH, Elashoff DA, Abemayor E, St John MA. Surgery for papillary thyroid carcinoma: Is lobectomy enough? *Arch Otolaryngol Head Neck Surg.* 2010;136:1055–1061.
- Nixon IJ, Wang LY, Migliacci JC, et al. An international multi-institutional validation of age 55 years as a cutoff for risk stratification in the AJCC/UICC staging system for well-differentiated thyroid cancer. *Thyroid*. 2016;26: 373–380.
- Kauffmann RM, Hamner JB, Ituarte PHG, Yim JH. Age greater than 60 years portends a worse prognosis in patients with papillary thyroid cancer: Should there be three age categories for staging? BMC Cancer. 2018;18:316.
- Trimboli P, Piccardo A, Signore A, et al. Patient age is an independent risk factor of relapse of differentiated thyroid carcinoma and improves the performance of the American Thyroid Association stratification system. *Thyroid*. 2020;30:713–719.
- van Velsen EFS, Stegenga MT, van Kemenade FJ, et al. Comparing the prognostic value of the eighth edition of the American Joint Committee on cancer/ tumor node metastasis staging system between papillary and follicular thyroid cancer. *Thyroid*. 2018;28:976–981.

Discussion



- **Dr. Elizabeth Grubbs (Houston):** I noticed you used clinical nodal status and not pathologic. Why did you choose that? Is that something based on the NCDB? Or was there another reason you wanted to use the clinical designation?
- **Dr. Erin MacKinney:** Yes, there is pathologic designation as well in NCDB. We chose to use clinical nodal status whenever we had this information as it related to tailoring future clinical decisions about these types of tumors.
- **Dr. Elizabeth Grubbs (Houston):** So the idea is you want to be able to use this to identify patients before you take them to surgery to be able to say, for example, that all men over 55 who have a T2 lesion, even with no obvious clinical nodal disease, should consider total thyroidectomy?
 - Dr. Erin MacKinney: Right.
- **Dr. Roger Tabah (Montreal):** Were you able to determine the mean dose of radioiodine with the National Cancer Database?
- **Dr. Erin MacKinney:** No, we were not able to look at that, but that is a good question.
- **Dr. Elizabeth Grubbs:** Because I think there are a lot of different variations of RAI. Do you think that is a potential weakness or limitation of the study that you would want to identify?
- **Dr. Erin MacKinney:** Yes, definitely. This would be something good to do in future studies.
- **Dr. Naris Nilubol (Bethesda):** Can you please confirm that cohorts of male patients and of patients greater than 55 years old

- have similar clinical features between the total thyroidectomy plus RAI group versus the lobectomy group?
- **Dr. Erin MacKinney:** We did match as best we could the clinical features available in the National Cancer Data Base (NCDB), so they had similar rates of extrathyroidal extension, tumor size, and surgical margin status.
- **Dr. Naris Nilubol (Bethesda):** Specifically, the rates of aggressive histology? Were you able to parse that out?
- **Dr. Erin MacKinney:** So we were just using patients with classic papillary thyroid cancer of a certain size (the 2-4 cm tumors). They were matched according to evidence of aggressiveness as well.
- **Dr. Elizabeth Grubbs (Houston):** With the NCDB, are you able to look at some of the more aggressive papillary variants and you just used classical?
- **Dr. Erin MacKinney:** Correct, yes. There are aggressive subtypes noted in the NCDB, but we just looked at the classical variant of papillary thyroid cancer.
- **Dr. Diana Diesen (Dallas):** What were your thoughts behind the age groups that you chose? Did you consider further age breakdown?
- **Dr. Erin MacKinney:** Yes, we chose age groups based on the AJCC staging for papillary thyroid cancer, and the change in that recently from 45 to 55 as being the cutoff for upstaging papillary thyroid cancer, which is why we included 45 to 55 age range and then older and younger than that. We could have broken down our age groups further, but we were already working with small numbers of patients.