The Role of Surgery in Small Differentiated Thyroid Cancer

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Research Article

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Abstract

Introduction

The incidence of small, differentiated thyroid cancer (DTC) cases has been increasing in the United States and the world mainly due to incidental detection because of widespread use of diagnostic modalities. While the option of active surveillance instead of surgical resection is getting more popular, there is still an open discussion about the best approach in these cases.

Materials and Methods

The National Cancer Database was queried for patients diagnosed with non-metastatic small T1/N0 DTC between 2004 and 2016, who have known surgical status and Charlson comorbidity index of two or less. We evaluated the overall survival (OS) based on the surgery status using Kaplan-Meier estimates and multivariable cox regression analyses.

Results

A total of 98,501 patients with non-metastatic small DTC were included, within which 96,612 (98.1%) were treated with surgery, and 1,889 (1.9%) were not treated with surgery or other ablative modalities. We found that patients who were treated with surgery had better OS compared to patients who were not treated with surgery (mean OS 171 months vs 134.1 months, P<0.001, median OS was not reached). This difference was still statistically significant even after we used propensity score matching for age, gender, race, Charlson-Deyo score, tumor size, and histology. On multivariate analysis, surgery was associated with better OS (HR 0.218; 95% CI: 0.196 - 0.244; P<0.001).

Same trend was found in subgroup analysis when we split the cohort according to tumor size (<1cm and ≥1cm), histology (follicular, papillary and Hurthle cell carcinoma), and age (< 55 years vs ≥ 55 years).

Conclusion

Patients with non-metastatic small DTC who were treated with surgery had significant improvement in OS compared to patients who were not treated with surgery. Notwithstanding the limitations of the current analysis, these results call for caution prior to recommending routine surveillance for all patients with small DTC.

Article Highlights

- Thyroid cancer is the most common endocrine malignancy.
- Thyroid cancer incidence rate is increasing, especially small thyroid tumors.
- The oncologic safety of active surveillance versus surgical resection in small, differentiated thyroid cancer is still controversial.
- Surgical resection improves the OS in small DTC.

- The survival benefit of surgical treatment is seen in all histologic types of DTC.

1. Introduction

Thyroid cancer is the most common endocrine malignancy with an estimated 44,280 new cases and 2,200 deaths in the United States (US) alone in 2021 and 586,202 new cases and about 43,000 deaths worldwide in 2020. The majority of thyroid cancer cases diagnosed in the US are differentiated thyroid cancer (DTC) which include papillary, follicular and Hurthle cell carcinoma[1–4]. The widespread use of diagnostic modalities including ultrasonography and fine-needle aspiration (FNA) has led to a rapid increase of thyroid cancer incidence rate in the US and worldwide in the last few decades. This increase is largely due to the rise in the diagnosis of small thyroid tumors, (mainly small papillary thyroid cancers[5–7]).

In recent years, active surveillance has been adopted more frequently as an acceptable option in managing small papillary thyroid cancer (PTC) as more studies showed comparable outcomes between active surveillance and surgical resection approaches[8, 9]. Despite the rapid adoption of active surveillance approach, there is still an open debate about the best approach in small thyroid cancer cases. This debate is getting ground for two main reasons. First, majority of the studies that compared between AS and surgical resection focused on assessing the difference in tumor size increase and developing regional or distant metastases, but very few studies compared the survival outcomes between these two approaches. Second, there is a lack of large randomized controlled trials that compared the outcomes between the two approaches[10–14].

In this study, we aimed to evaluate the difference in overall survival (OS) in patients with small DTC who had surgical resection vs the patients who did not have surgical resection.

2. Patients And Methods

2.1. Data source

The National Cancer Database (NCDB) is a nationwide database supported by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. About 70% of all cancer cases diagnosed in the United States from more than 1,500 cancer centers are included in this database. Details of patients' demographics, malignancy staging, and histological characteristics in addition to treatment and outcome information are provided in this database[15]. The CoC's NCDB and the hospitals participating in the CoC's NCDB are the sources of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors of the current study.

After we obtained the approval on our proposed protocol and the letter of support from the cancer committee chair at Cleveland Clinic, the NCDB was queried for patients diagnosed with non-metastatic

small DTC between 2004 and 2016. Survival follow-up for the studied cohort is available till December 2016.

2.2. Patient selection

For our study, we selected the patients who were diagnosed with histologically proven non-metastatic differentiated thyroid cancer at age of 18 or older. We included patients with tumor size of 2cm or less with clinical stage T1, N0, M0 only. We excluded patients with unknown surgical status to the primary site in addition to patients with Charlson-Deyo score of 3 and above. Also, we excluded patients with lost follow up which is defined by patients with missing details about their last contact status as alive or dead, and those with missing information about their time from diagnosis to the last contact.

We defined the differentiated thyroid cancer cases by using the International Classification of Diseases for Oncology-Third Edition (ICD-O-3) histology codes (8050, 8260, 8290, 8330, 8331, 8332, 8335, 8340, 8341, 8342, 8343, 8344)[16].

2.3. Variables

Using the NCDB, we included the following patient demographic variables: Age, gender, race, median income, education level, insurance status, facility type (which includes community cancer program, comprehensive community cancer program, academic/research program, and integrated network cancer program) in addition to the geographic area which was classified as metropolitan, urban, or rural location. Also, we collected the following disease-related variables: tumor size, histological type, surgery status and Charlson-Deyo comorbidity score.

2.4. Outcome

The primary outcome of this study was overall survival (OS) in months defined as the time from diagnosis to the time of death for any reason.

2.5. Statistical analysis

We compared the baseline demographics and characteristics between patients who had surgical resection to the primary tumor versus patients who did not have surgery using the Pearson Chi-square test.

For OS comparisons, we split the cohort into two separate groups according to the surgical status, the first group who had surgical resection to the primary tumor and the second group who did not have surgery or other ablative modalities. Then, we compared the OS between the two groups.

We also did subgroup analyses. In the first subgroup analysis, we split the cohort according to the tumor size into < 1cm and ≥ 1cm groups and compared the OS between patients who had surgical resection and patients who did not have surgery in each group. In the second subgroup analysis, we split the cohort according to the histological type into follicular, papillary, Hurthle and combined papillary & follicular groups and compared the OS between patients who had surgical resection and patients who did not have

surgery in each group. In the third subgroup analysis, we split the cohort according to age cutoff of < 55 years vs ≥ 55 years. The reason for selecting this age cutoff is the use of this cutoff in the current American Joint Committee on Cancer (AJCC) Cancer Staging Manual for DTC. Moreover, giving that most of the previous studies evaluated the active surveillance in papillary microcarcinoma (PMC), and that the NCCN thyroid cancer guideline specifically recommended active surveillance as an optional approach for low-risk PMC, we did a subgroup analysis that included only patients with papillary thyroid cancer, diagnosed at age less than 75 with tumor size < 1cm and Charlson-Deyo score of 0–1.

OS analyses were evaluated using the Kaplan-Meier survival method. A log-rank test was used to evaluate survival differences between groups. We used Cox regression analysis to conduct multivariable analyses to evaluate the factors associated with improved OS; hazard ratios (HRs) with associated 95% confidence intervals (CI) were accordingly generated, statistical significance was defined as a P value less than 0.05 for all analyses. The following factors were included in the multivariable model: facility type, age, gender, race, median household income, education level, insurance status, area, Charlson score, histology type, tumor size, and surgery status.

All the above statistical analyses were performed using the SPSS Statistics (Version 27.0, SPSS Inc.)

To further reduce any potential biases related to the variation in baseline characteristics between the patient group that had surgical resection and the one that did not have surgery, we used nearest neighbor, 1:1, propensity score matching using RStudio Version 1.3.1093 (MA, USA).

3. Results

3.1. Baseline characteristics

(Figure-1) provides a flowchart for patient selection within the current study. The initial cohort had 428,178 patients who were diagnosed with differentiated thyroid cancer between 2004 and 2016. Patients were excluded if they had tumor size > 2cm or clinical T stage other than T1 (N = 312,038). We also excluded patients if they had clinical metastatic disease or unknown clinical metastatic status or had clinical N1 stage or unknown N stage (N = 15,625).

We then excluded patients with Charlson-Deyo score of 3 (N = 665), patients with unknown surgery status (N = 76) and patients who lost the follow up for OS (N = 1,273). We ended up with 98,501 patients who had non-metastatic small DTC with known surgery status; 96,612 (98.1%) had surgery and 1,889 (1.9%) did not have surgery. The baseline characteristics comparison between the two groups is summarized in Table 1.

We also checked the percentage of patients who had surgery and patients who did not have surgery between 2004–2016 in yearly basis. We found the percentage of patients who did not have surgery increased over the years which could be a reflection on the increase adoption of active surveillance approach (supplementary Fig. 1).

3.2. Survival outcome

3.2.1. The entire cohort

We compared OS between patients who were treated with surgery versus patients who did not have surgery and found that patients who were treated with surgery had better OS compared to patients who did not have surgery (mean OS 171 months vs 134.1 months, $P < 0.001$, median OS was not reached) as illustrated in the Kaplan-Meier survival curves (Fig. 2).

Propensity score matching yielded 3,778 patients for analysis: 1,889 patients in the surgery group and 1,889 patients in the no surgery group. Comparison of baseline characteristics between the groups after propensity score matching is shown in Table 2.

Table 1
Baseline characteristics of non-metastatic small DTC patients according to surgery status as found in the National Cancer Database between 2004 and 2016

Characteristics	All cases (N = 98,501)	Surgery (N = 96,612) (98.1%)	No surgery (N = 1,889) (1.9%)	P value and test
Mean age in years	50.44 ± 14.21	50.36 ± 14.15	54.54 ± 16.52	< 0.001[1]
Sex				< 0.001[2]
Female	79,756 (81.0%)	78,370 (81.1%)	1,386 (73.4%)	
Male	18,745 (19.0%)	18,242 (18.9%)	503 (26.6%)	
Race				< 0.001[2]
White	84,373 (85.7%)	82,859 (85.8%)	1,514 (80.1%)	
African American	6,465 (6.6%)	6,337 (6.6%)	128 (6.8%)	
Others	6,122 (6.2%)	5,948 (6.2%)	174 (9.2%)	
Unknown	1,541 (1.6%)	1,468 (1.5%)	73 (3.9%)	
Facility type				< 0.001[2]
Community cancer program	4,768 (4.8%)	4,686 (4.9%)	82 (4.3%)	
Comprehensive Community Cancer Program	28,997 (29.4%)	28,488 (29.5%)	498 (26.4%)	
Academic/Research Program	30,957 (31.4%)	30,236 (31.3%)	721 (38.2%)	
Integrated Network Cancer Program	10,188 (10.3%)	9,979 (10.3%)	209 (11.1%)	
Unknown	23,591 (24.0%)	23,212 (24.0%)	379 (20.1%)	
Median household income 2012–2016				0.226[2]
Less than $40,227	11,466 (11.6%)	11,259 (11.7%)	207 (11.0%)	

Characteristics	All cases (N = 98,501)	Surgery (N = 96,612) (98.1%)	No surgery (N = 1,889) (1.9%)	P value and test
$40,227 - $50,353	16,063 (16.3%)	15,772 (16.3%)	291 (15.4%)	
$50,354- $63,332	19,818 (20.1%)	19,455 (20.1%)	363 (19.2%)	
$63,333+	41,743 (42.4%)	40,893 (42.3%)	850 (45.0%)	
Unknown	9,411 (9.6%)	9,233 (9.6%)	178 (9.4%)	
Education level 2012–2016 (percentage of not graduated from high school)				0.003[2]
17.6% or more	14,603 (14.8%)	14,269 (14.8%)	334 (17.7%)	
10.9% – 17.5%	20,535 (20.8%)	20,186 (20.9%)	349 (18.5%)	
6.3%-10.8%	25,813 (26.2%)	25,326 (26.2%)	487 (25.8%)	
Less than 6.3%	28,280 (28.7%)	27,736 (28.7%)	544 (28.8%)	
Unknown	9,270 (9.4%)	9,095 (9.4%)	175 (9.3%)	
Insurance status				< 0.001[2]
No	2,094 (2.1%)	2,031 (2.1%)	63 (3.3%)	
Yes	95,127 (96.6%)	93,348 (96.6%)	1,779 (94.2%)	
Unknown	1,280 (1.3%)	1,233 (1.3%)	47 (2.5%)	
Area				< 0.001[2]
Metro counties	84,598 (85.9%)	89,943 (85.9%)	1,655 (87.6%)	
Rural counties	1,204 (1.2%)	1,187 (1.2%)	17 (0.9%)	
Urban counties	9,910 (10.1%)	9,769 (10.1%)	141 (7.5%)	

Characteristics	All cases (N = 98,501)	Surgery (N = 96,612) (98.1%)	No surgery (N = 1,889) (1.9%)	P value and test
Unknown	2,789 (2.8%)	2,713 (2.8%)	76 (4.0%)	
Tumor size				< 0.001[2]
< 1cm	49,387 (50.1%)	48,856 (50.6%)	531 (28.1%)	
≥ 1cm	49,114 (49.9%)	47,756 (49.4%)	1,358 (71.9%)	
Histology type				< 0.001[2]
Follicular	2,093 (2.1%)	2,052 (2.1%)	41 (2.2%)	
Papillary	68,003 (69.0%)	66,272 (68.6%)	1,731 (91.6%)	
Hurthle cell	995 (1.0%)	961 (1.0%)	34 (1.8%)	
Follicular & Papillary combined	27,410 (27.8%)	27,327 (28.3%)	83 (4.4%)	
Charlson-Deyo score				< 0.001[2]
0	82,604 (83.9%)	80,900 (83.7%)	1,704 (90.2%)	
1	13,634 (13.8%)	13,486 (14.0%)	148 (7.8%)	
2	2,263 (2.3%)	2,226 (2.3%)	37 (2.0%)	
Footnotes 1. T-test 2. Chi-squared				

We compared the OS between patients who had surgery versus patients who did not have surgery using Kaplan-Meier analysis on the propensity score-matched groups and found that patients who had surgery had better OS than those who did not have surgery (mean OS 165.8 months vs 134.1 months, P < 0.001, median OS was not reached) as illustrated in the Kaplan-Meier survival curves (Fig. 3).

3.2.2. Subgroup analysis

We did four subgroup analyses:

3.2.2.1. Based on tumor size; we split the cohort according to the tumor size into < 1cm and ≥ 1cm groups to compare OS between patients who had surgery and patients who did not have surgery in each tumor size group. We found patients who had surgery had a statistically significant better OS than those who did not have surgery in both groups; <1cm and ≥ 1cm tumor size (mean OS 169.3 months vs 138.3 months, P < 0.001, and mean OS 171.6 months vs 131 months, P < 0.001, respectively. median OS was not reached) as illustrated in the Kaplan-Meier survival curves (supplementary Fig. 2a-b).

In the patient group with tumor size < 1cm, propensity score matching yielded 1,062 patients for analysis: 531 in the surgery group and 531 patients in the no surgery group. We compared the OS between patients who had surgery and patients who did not have surgery using Kaplan-Meier analysis on the propensity score-matched groups and found that patients who had surgery had statistically significant better OS compared to patients who did not have surgery (mean OS 155.5 months vs 138.3 months, P < 0.001, median OS was not reached) as illustrated in the Kaplan-Meier survival curves (supplementary Fig. 3a).

In the patient group with tumor size ≥ 1cm, propensity score matching yielded 2,716 patients for analysis: 1,358 in the surgery group and 1,358 patients in the no surgery group. We compared the OS between patients who had surgery and patients who did not have surgery using Kaplan-Meier analysis on the propensity score-matched groups and found that patients who had surgery had statistically significant better OS compared to patients who did not have surgery (mean OS 175.2 months vs 131 months, P < 0.001, median OS was not reached) as illustrated in the Kaplan-Meier survival curves (supplementary Fig. 3b).

3.2.2.2. Based on histology; we split the cohort according to the histological type into follicular, papillary, Hurthle and papillary & follicular combined groups to compare the OS between patients who had surgery and patients who did not have surgery in each histology type group. We found patients who had surgery had a statistically significant better OS than those who did not have surgery in each group (for Follicular mean OS 166.7 months vs 106.8 months, for Papillary mean OS 170.8 months vs 136.3 months, for Hurthle cell mean OS 166.5 months vs 72.5 months, for Papillary/Follicular OS 169.9 months vs 116.7 months, P < 0.001 for all, median OS was not reached) as illustrated in the Kaplan-Meier survival curves (supplementary Figs. 4a-d).

3.2.2.3. Based on age; we split the cohort according to age, into two groups: patients under 55 years at diagnosis and patients 55 years and older at diagnosis to compare the OS between patients who had surgery and patients who did not have surgery in each group. We found patients who had surgery had a statistically significant better OS than those who did not have surgery in both groups. For those under 55 years at diagnosis, mean OS 178.4 months vs 163.2 months, P < 0.001 (median OS was not reached). For those 55 years and older at diagnosis, mean OS 158.4 months vs 101.5 months, P < 0.001 as illustrated in the Kaplan-Meier survival curves (supplementary Figs. 5a-b).

3.2.2.4. Papillary microcarcinoma group; We had total 33,448 patients included in this cohort. We compared the OS between patients who had surgery (N = 33,013) versus patients who did not have surgery (N = 435). We found patients who had surgery had a statistically significant better OS than those who did not have surgery (mean OS 172.6 months vs 152.8 months, P < 0.001, median OS was not reached) as illustrated in the Kaplan-Meier survival curves (supplementary Figs. 6). Also, on multivariate analysis we found that surgery was associated with better OS (HR 0.204, 95% CI 0.153–0.273, P < 0.001).

3.3. Multivariable analysis

Multivariate analysis was done to assess factors affecting OS. Factors associated with worse OS were older age (HR 1.077, 95% CI 1.075–1.080, P < 0.001), male gender (HR 1.624, 95 CI 1.533–1.721, P < 0.001), African American compared to Caucasian race (HR 1.208, 95% CI 1.090–2.340, P < 0.001), no health insurance (HR for having health insurance vs not having insurance 0.787, 95% CI 0.629–0.985, P = 0.036), urban area compared to metro area (HR 1.123, 95% CI 1.033–1.221, P = 0.007), community cancer program (HR for Comprehensive Community Cancer Program and Academic/Research Program compared to community cancer program was 0.893; 95% CI 0.799–0.998, P = 0.045 and HR 0.876; 95% CI 0.782–0.980, P = 0.021, respectively), follicular compared to papillary histology (HR for papillary vs follicular 0.847, 95% CI 0.721–0.994, P = 0.042), Charlson-Deyo scores 1 and 2 compared to the Charlson-Deyo score of 0 (HR 1.544, 95% CI 1.447–1.647, P < 0.001) and (HR 2.625, 95% CI 2.366–2.914, P < 0.001), respectively and no surgery (HR for surgery vs no surgery 0.218, 95% CI 0.196–0.244, P < 0.001) (Table 3).

Table 2
Baseline characteristics of non-metastatic small DTC patients according to surgery status after propensity score matching.

Characteristics	All cases (N = 3,778)	Surgery (N = 1,889) (50%)	No surgery (N = 1,889) (50%)	P value and test
Mean age in years	46.0 ± 16.73	37.46 ± 11.86	54.54 ± 16.52	< 0.001[1]
Sex				< 0.001[2]
Female	3,193 (84.5%)	1,807 (95.7%)	1,386 (73.4%)	
Male	585 (15.5%)	82 (4.3%)	503 (26.6%)	
Race				< 0.001[2]
White	3,329 (88.1%)	1,815 (96.1%)	1,514 (80.1%)	
African American	191 (5.1%)	63 (3.3%)	128 (6.8%)	
Others	185 (4.9%)	11 (0.6%)	174 (9.2%)	
Unknown	73 (1.9%)	0 (0.0%)	73 (3.9%)	
Facility type				< 0.001[2]
Community cancer program	129 (3.4%)	47 (2.5%)	82 (4.3%)	
Comprehensive Community Cancer Program	804 (21.3%)	306 (16.2%)	498 (26.4%)	
Academic/Research Program	956 (25.3%)	235 (12.4%)	721 (38.2%)	
Integrated Network Cancer Program	308 (8.2%)	99 (5.2%)	209 (11.1%)	
Unknown	1,581 (41.8%)	1,202 (63.6%)	379 (20.1%)	
Median household income 2012–2016				< 0.001[2]
Less than $40,227	456 (12.1%)	249 (13.2%)	207 (11.0%)	

Characteristics	All cases (N = 3,778)	Surgery (N = 1,889) (50%)	No surgery (N = 1,889) (50%)	P value and test
$40,227 - $50,353	608 (16.1%)	317 (16.8%)	291 (15.4%)	
$50,354- $63,332	804 (21.3%)	441 (23.3%)	363 (19.2%)	
$63,333+	1,555 (41.2%)	705 (37.3%)	850 (45.0%)	
Unknown	355 (9.4%)	177 (9.4%)	178 (9.4%)	
Education level 2012–2016 (percentage of not graduated from high school)				0.017[2]
17.6% or more	633 (16.8%)	299 (15.8%)	334 (17.7%)	
10.9% – 17.5%	774 (20.5%)	425 (22.5%)	349 (18.5%)	
6.3%-10.8%	986 (26.1%)	499 (26.4%)	487 (25.8%)	
Less than 6.3%	1,037 (27.4%)	493 (26.1%)	544 (28.8%)	
Unknown	348 (9.2%)	173 (9.2%)	175 (9.3%)	
Insurance status				0.027[2]
No	113 (3.0%)	50 (2.6%)	63 (3.3%)	
Yes	3,591 (95.1%)	1,812 (95.9%)	1,779 (94.2%)	
Unknown	74 (2.0%)	27 (1.4%)	47 (2.5%)	
Area				< 0.001[2]
Metro counties	3,266 (86.4%)	1,611 (85.3%)	1,655 (87.6%)	
Rural counties	39 (1.0%)	22 (1.2%)	17 (0.9%)	
Urban counties	357 (9.4%)	216 (11.4%)	141 (7.5%)	
Unknown	116 (3.1%)	40 (2.1%)	76 (4.0%)	

Characteristics	All cases (N = 3,778)	Surgery (N = 1,889) (50%)	No surgery (N = 1,889) (50%)	P value and test
Tumor size				< 0.001[2]
< 1cm	2,405 (63.7%)	1,874 (99.2%)	531 (28.1%)	
≧ 1cm	1,373 (36.3%)	15 (0.8%)	1,358 (71.9%)	
Histology type				< 0.001[2]
Follicular	41 (1.1%)	0 (0.0%)	41 (2.2%)	
Papillary	1,731 (1.0%)	0 (0.0%)	1,731 (91.6%)	
Hurthle cell	34 (0.9%)	0 (0.0%)	34 (1.8%)	
Follicular & Papillary combined	1,972 (52.2%)	1,889 (100.0%)	83 (4.4%)	
Charlson-Deyo score				< 0.001[2]
0	2,672 (70.7%)	968 (51.2%)	1,704 (90.2%)	
1	802 (21.2%)	654 (34.6%)	148 (7.8%)	
2	304 (8.0%)	267 (14.1%)	37 (2.0%)	
Footnotes 1. T-test 2. Chi-squared				

Table 3

Multivariate analysis for non-metastatic small DTC patients

Variables	HR	95%CI	P value
Facility type			
Community cancer program	Reference		
Comprehensive Community Cancer Program	0.893	0.799 - 0.998	0.045
Academic/Research Program	0.876	0.782 - 0.980	0.021
Integrated Network Cancer Program	1.036	0.913 – 1.176	0.582
Unknown	1.181	0.983 - 1.419	0.075
Age	1.077	1.075 - 1.080	<0.001
Gender			
Male	1.624	1.533 - 1.721	<0.001
Female	Reference		
Race			
African American	1.208	1.090 - 1.340	<0.001
Others	0.640	0.540 - 0.758	<0.001
Unknown	0.706	0.533 - 0.937	0.016
White	Reference		
Median household income 2012-2016			
Less than $40,227	Reference		
$40,227 - $50,353	0.900	0.821 – 0.987	0.026
$50,354- $63,332	0.837	0.759 - 0.923	<0.001
$63,333+	0.687	0.618 - 0.765	<0.001
Unknown	1.218	0.703 - 2.110	0.483

Education level 2012-2016 (percentage of not graduated from high school)			
17.6% or more	Reference		
10.9% - 17.5%	1.043	0.956 - 1.138	0.341
6.3%-10.8%	1.069	0.972 - 1.175	0.167
Less than 6.3%	0.942	0.846 - 1.049	0.275
Unknown	0.313	0.178 – 0.550	<0.001
Insurance status			
Yes	0.957	0.695 - 1.316	0.785
Unknown	0.787	0.629 – 0.985	0.036
No	Reference		
Area			
Metro counties	Reference		
Rural counties	1.051	0.849 - 1.302	0.647
Urban counties	1.123	1.033 - 1.221	0.007
Unknown	1.090	0.925 - 1.284	0.303
Charlson score			
0	Reference		
1	0.928	0.694 - 1.240	0.613
2	1.299	0.940 - 1.796	0.113
Histology			
Follicular	Reference		
Hurthle cell	0.844	0.653 - 1.091	0.195
Papillary	0.847	0.721 – 0.994	0.042

Follicular & papillary combined	0.834	0.708 – 0.983	0.030
Tumor size			
≥1cm	Reference		
<1cm	0.960	0.909 - 1.014	0.144
Surgery			
No	Reference		
Yes	0.218	0.196 - 0.244	<0.001

4. Discussion

While active surveillance is being considered an option in managing low-risk small PTC, there is still a debate about the best treatment approach in these cases. And despite this debate, there is a lack of large and controlled trials that compared the outcomes between surgical management and active surveillance, especially in the US.

To our knowledge, this is the largest real-world study that compared the survival outcome in small DTC between patients who had surgical resection versus patients who did not have surgical resection. And while most of the studies that looked at the active surveillance in DTC focused on papillary thyroid cancer, in our study we evaluated the survival benefit of surgical resection in all histologic types of DTC. We found that patients who were treated with surgical resection had better OS compared to the ones who did not have surgery. The survival benefit of surgery was seen in all histologic types of DTC and different tumor sizes (< 1cm and 1-2cm).

The active surveillance (AS) approach was first introduced by Akira Miyauchi and his team after his observation of increase thyroid cancer incidence rate without an increase in mortality rate around the world, in addition to having different studies showing frequent detection of PMC, defined as well-differentiated tumors 1 cm or less in size with no lymph node or distant metastasis and no extrathyroidal involvement, on autopsy studies of patients who died of other reasons than thyroid cancer[14, 17, 18]. This proposal was a trigger to start experimental observation with no surgical resection for low risk PMC in two hospitals in Japan and multiple studies reported very low percentage of tumor size increase and lymph node metastases development[11–13, 19].

Yasuhiro Ito and Akira Miyauchi, along with other researchers, conducted several studies evaluating the outcome of AS in PMC in Japan. Ito et al.[13] between 1993 and 2004 followed a total of 1,395 patients with PMC; 340 patients underwent observation and 1,055 patients had immediate surgical treatment for an average of 74 months. Both groups had the same rate of lymph node metastases. It was noted that

32% of the observation group patients required surgery during the study period for various reasons mainly due to tumor enlargement or tumor location, but none of these patients had disease recurrence after surgery. More recently, Ito et al.[20] conducted a study of 1235 low-risk PMC patients who were followed with AS between 1993 and 2011. It was reported that 8.0% of the patients had tumor enlargement and 3.8% developed lymph node metastases at 10 years (more significant in less than 60 years old patients), but there was no death or distant metastases in any of the study patients. Sugitani et al.[12] followed 230 patients with asymptomatic PMC for a mean time of 5 years. They found only 7% of tumors increased in sizes with no extrathyroidal invasion or distant metastasis. Oda et al.[21] also compared the outcomes between AS and surgical resection in 2,153 patients with low-risk PMC (defined as < 1cm tumor size with no nodal or distant metastasis, macroscopic extrathyroidal extension, high-grade malignancy on cytology, or evidence of progression) in Japan. There was no significant difference in developing lymph node metastases between the two groups (0.5% in AS group and 0.2% in surgical treatment group) and none of the 2,153 patients developed distant metastases or died of thyroid cancer. In addition to that, few studies found AS to be cost-effective compared to early surgical resection in PMC[22, 23]. The reported findings of the mentioned studies played a significant role in adopting AS approach in Japan in 2010 by the Japanese Association of Endocrine Surgeons and the Japanese Society of Thyroid Surgeons[24, 25].

In the US, very few studies evaluated the AS approach. In 2017, Tuttle et al.[26] in a study of 291 patients with low-risk PTC (defined as intrathyroidal tumors < 1.5 cm) were followed for a median time of 25 months. The findings were very similar to the Japanese studies, 3.8% of the patients had tumor growth of 3mm or more and no regional or distant metastases reported during the active surveillance. Wang et al.[27] on the other had reported a retrospective study of 29,512 patients with PTMC using SEER database. They split the cohort into three groups according to the treatment approach they had: 1.4% did not have surgery, 25.2% had partial thyroidectomy and 73.4% had total thyroidectomy. There was no significant difference between the two surgical approaches, but patients who did not have surgery had lower disease specific survival. Also 5-year OS was 25% in the observation group compared to 97.6% for patients who underwent either partial or total thyroidectomy ($p < 0.001$). In the last few years, the AS approach started getting more popular in the US and the 2015 ATA guideline mentioned active surveillance as an option in selected patients with PMC who have low-risk tumors (no metastases or local extension and no cytological indication of aggressive disease)[28–31].

Our study has some limitations that are worth mentioning. First, lack of details if patients who did not have surgical resection were followed with active surveillance or not. Second, other than overall survival, NCDB doesn't have details about other oncologic endpoints like disease-free survival and cancer-specific survival. Therefore, one might argue that higher mortality in the no surgery group is derived by non-thyroid cancer deaths rather than thyroid cancer deaths (particularly given the imbalance in baseline characteristics between both groups with older age and more comorbidity in the no surgery group). It is possible that factors like age and comorbidity were part of the reason why some of those patients did not have surgery in the first place. In order to mitigate the impact of this limitation, we conducted multivariable analyses (to adjust for age, comorbidity and other non-thyroid cancer factors), propensity

score matching, as well as multiple subgroup analyses. Third, we did not have the details about all high-risk features, like aggressive histological subtypes or history of prior neck irradiation. Fourth, the retrospective nature of the study and data collection within the NCDB carry different types of bias that might affect the accuracy of the analyses and result interpretation. Despite these limitations, this study represents the largest observational study to compare the survival outcomes in small DTC between patients who were managed with surgical resection and patients who did not have surgical resection. Further prospective randomized studies and/or multi-center studies are needed to further compare the outcomes between surgical approach and active surveillance in small DTC.

5. Conclusion

Patients with non-metastatic small DTC who were treated with surgical resection had statistically significant improvement in OS compared to patients who did not have surgical resection. The benefit of the surgical approach is seen in all histologic types, size and age categories. We cannot confirm though whether this excess mortality associated with an observation strategy for those patients is totally related to thyroid cancer or is caused by other non-thyroid cancer factors.

While the limitations of this retrospective analysis are acknowledged, these results raise the importance of conducting further studies to compare the outcomes between active surveillance and surgical resection in patients with small DTC.

Further large-scale studies that look at disease-specific survival are needed to evaluate the benefit of active surveillance compared to surgical resection in small DTC.

Abbreviations

AJCC
American Joint Committee on Cancer
AS
active surveillance
CI
confidence intervals
CoC
commission on cancer
DTC
differentiated thyroid cancer
FNA
fine-needle aspiration
HR
Hazard Ratio
NCDB

National Cancer Database
OS
overall survival
PMC
papillary microcarcinoma
PTC
papillary thyroid cancer
US
United States

Declarations

Author contributions:

Firas Baidoun: data analysis, data interpretation, manuscript writing.

Omar Abdel-Rahman: study concept, manuscript editing, critical revision.

Disclosures

Firas Baidoun: no conflict of interest or financial interest to disclose.

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Data Availability Statement

The data we used in this study is available from the National Cancer Database.

Consent

Not required.

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Figures

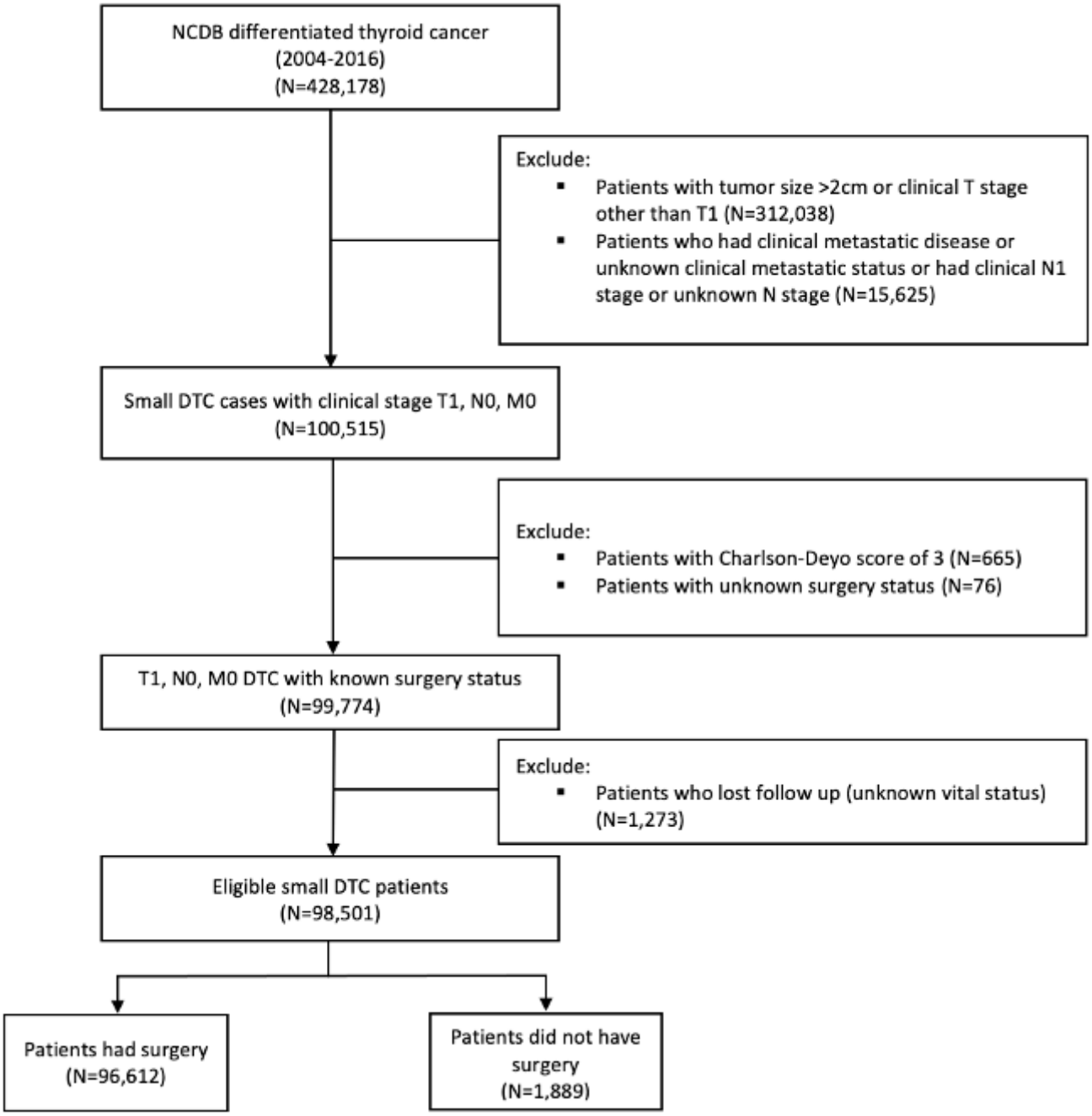

Figure 1

Consort diagram of study population

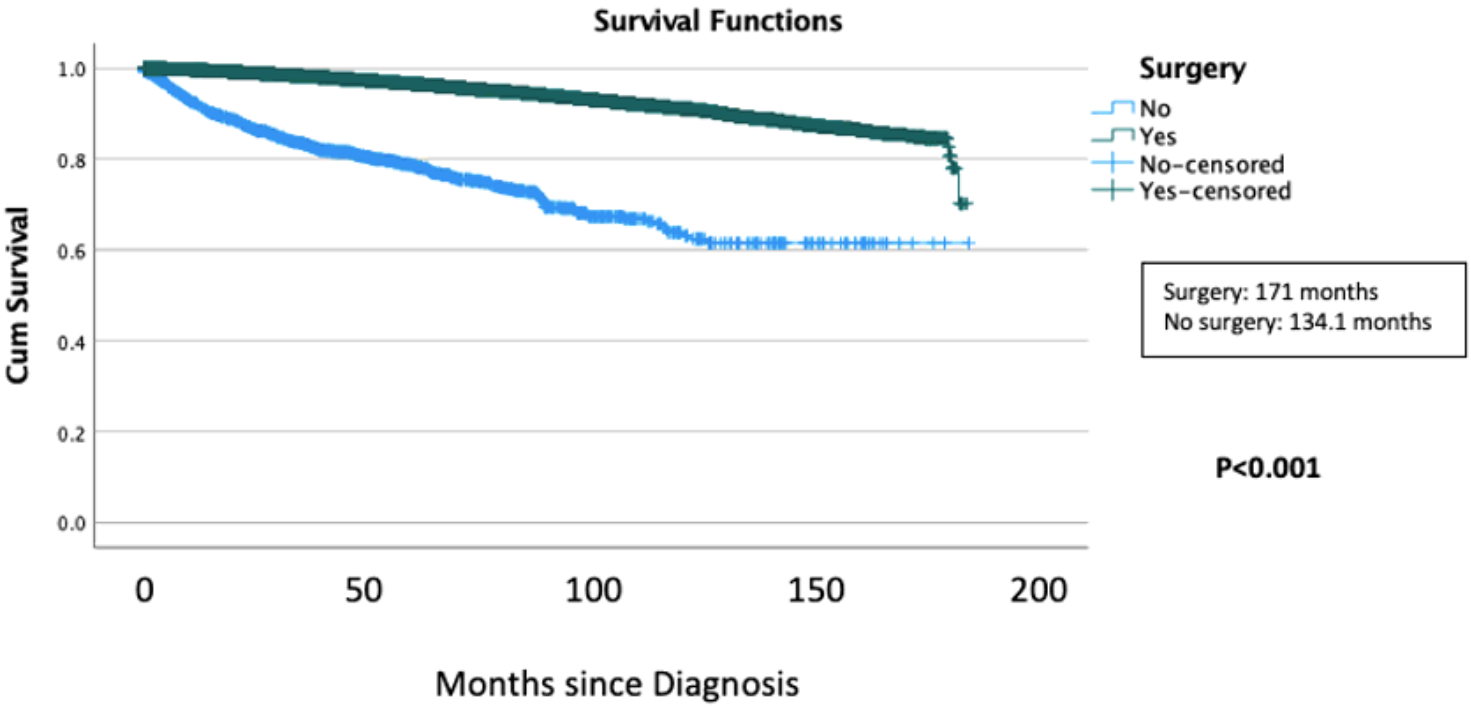

Figure 2

Mean overall survival in the whole cohort of non-metastatic small DTC patients according to surgery status - the median overall survival was not reached

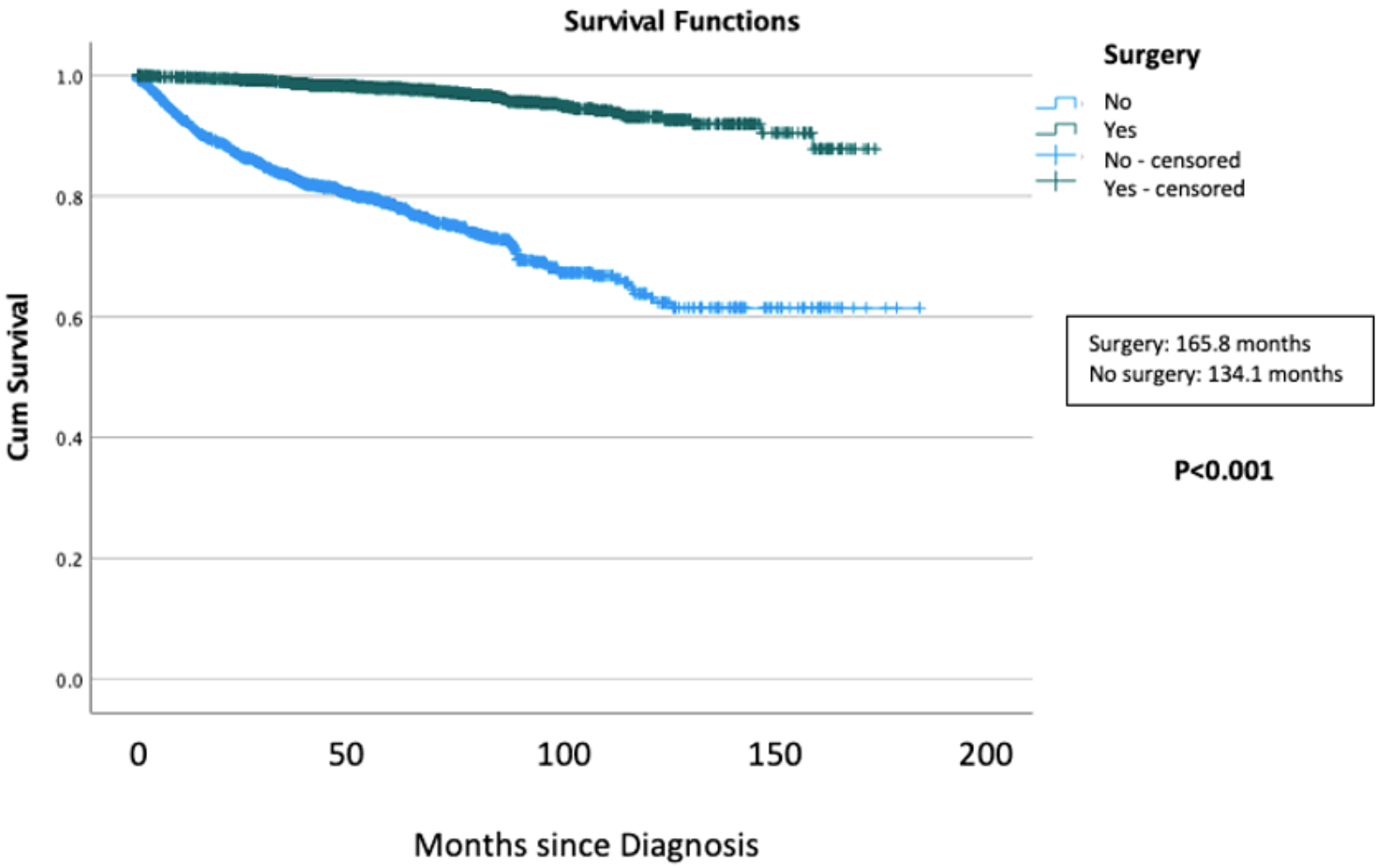

Figure 3

Mean overall survival in the whole cohort of non-metastatic small DTC patients according to surgery status after propensity score matching- the median overall survival was not reached

Supplementary Files

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