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Facility Volume as a Prognosticator of Survival in Locally Advanced Papillary Thyroid Cancer

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Abstract

Objectives: To evaluate the influence of facility case-volume on survival in patients with locally advanced papillary thyroid cancer (PTC), and to identify prognostic case-volume thresholds for facilities managing this patient population.

Study Design: Retrospective database study.

Methods: The 2004–2017 National Cancer Database was queried for patients receiving definitive surgery for locally advanced PTC. Using K-means clustering and multivariable Cox proportional-hazards (CPH) regression, two groups with distinct spectrums of facility case-volumes were generated. Multivariable CPH regression and Kaplan-Meier analysis assessed for the influence of facility case-volume and the prognostic value of its stratification on overall survival (OS).

Results: Of 48,899 patients treated at 1,304 facilities, there were 34,312 (70.2%) females and the mean age was 48.0±16.0 years. Increased facility volume was significantly associated with reduced all-cause mortality (HR 0.996; 95% CI, 0.992–0.999; p=0.008). Five facility clusters were generated, from which two distinct cohorts were identified: low (LVF; <27 cases/year) and high (HVF; ≥27 cases/year) facility case-volume. Patients at HVFs were associated with reduced mortality compared to those at LVFs (HR 0.791; 95% CI, 0.678–0.923, p=0.003). Kaplan-Meier analysis of propensity score-matched N0 and N1 patients demonstrated higher OS in HVF cohorts (all p<0.001).

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Conflicts of Interest: ECK is a consultant for Stryker ENT (Kalamazoo, MI).

Level of Evidence: 4

Conclusions: Facility case-volume was an independent predictor of improved OS in locally advanced PTC, indicating a possible survival benefit at high-volume medical centers. Specifically, independent of a number of sociodemographic and clinical factors, facilities that treated ≥27 cases per year were associated with increased OS. Patients with locally advanced PTC may, therefore, benefit from referrals to higher-volume facilities.

Keywords

Papillary thyroid cancer; hospital volume; prognosis; survival; quality improvement

Introduction

Papillary thyroid carcinoma (PTC) accounts for approximately 80% of all thyroid cancers in the United States, and its incidence has been increasing over the past several decades.[1] Although non-metastatic PTC generally has an excellent prognosis, morbidity and mortality are significantly higher in patients with locally advanced disease.[2,3] Extrathyroidal extension, in which the tumor penetrates beyond the thyroid capsule into surrounding tissues, has been reported in approximately 13% of PTC cases.[4] The recurrent laryngeal nerves, esophagus, and trachea are common sites of invasion,[5] and involvement of these structures places the patient at high risk of local complications like airway obstruction, hoarseness, and hemoptysis.[6] Surgery is a critical first step in disease management; although, adjuvant therapy like radioiodine ablation is often indicated to establish local control and prevent tumor recurrence.[6,7]

A growing body of literature suggests that high hospital case volume is associated with superior clinical outcomes and longer patient survival. This relationship has been established for a variety of malignancies, including testicular cancer,[8] non-small cell lung cancer,[9] and nasopharyngeal carcinoma,[10] among others.[11,12] However, the underlying mechanism for the relationship between case volume and quality of care is still under debate. Possible explanations include greater adherence to clinical guidelines, utilization of specialized multidisciplinary care teams, and greater access to advanced technologies and treatments at high volume "centers of excellence" compared to community hospitals.[10,13–16] Since locally advanced PTC requires a high level of surgical expertise and effective coordination of care between different medical specialists, patients may benefit from treatment at high volume institutions. However, to date, no study has investigated the impact of facility case-volume on survival outcomes in this patient population. Furthermore, the current literature lacks systematically formulated case volume stratifications that could be applied to clinical decision making and assessments of facility quality of care. Therefore, in this study, we evaluated the influence of facility volume on survival in patients with locally advanced PTC and aimed to identify prognostic case volume thresholds for facilities managing this patient population.

Methods

Study Population

The 2004–2017 NCDB is a deidentified and publicly available database that reports more than 70% of newly diagnosed cancer cases nationwide from over 1500 Commission on Cancer (CoC)-accredited facilities throughout the U.S.[17] Due to the anonymized nature of the NCDB, this study was exempt from University of California, Irvine Institutional Review Board approval.

We queried the database for patients with well-differentiated thyroid cancer (DTC) using the *International Classification of Disease for Oncology, 3rd Edition* (ICD-O-3) topography code for the thyroid (C73.9) and histology/behavior codes for locally advanced (T3/T4, any N, M0) papillary thyroid cancer (8050/3, 8260/3, 8340–8344/3, 8350/3). Only patients who had undergone surgery as part of their treatment course were included. Patients who received palliative care or had more than one primary malignancy were excluded. Additionally, those who had undergone chemotherapy as part of their treatment course were excluded, as less than 0.1% of patients had reportedly received chemotherapy. Finally, cases with unknown or missing treatment information were excluded.

Study Variables

Independent covariates included patient age, sex, race, insurance type, Charlson/Deyo (CD) comorbidity index, facility type (non-academic, academic), facility volume (cases per year), T classification, N classification, extent of surgery, radioiodine therapy (RAI), or thyroid-stimulating hormone suppression therapy (THST). CD indices were binarized as 0 and ≥1 to indicate the absence or presence of comorbidities, respectively. Extent of surgery was dichotomized as lobectomy (lobectomy ± isthmectomy) and total thyroidectomy (total, near-total, or subtotal resection) per previously published studies.[18,19] The primary measured outcomes were all-cause mortality and overall survival (OS) starting at the time of diagnosis.

Facility Volume Calculation and Threshold Determination

Mean annual facility volume was calculated based on the cases of locally advanced PTC that were treated at each facility. The number of cases per facility was summed and divided by the number of years that the NCDB reported data on the institution. These values represented actual case volume, as the NCDB collects data on all cancer cases from its contributing facilities.[20]

After applying the exclusion criteria, K-means clustering was performed to group facilities into 1 to 10 clusters according to their case volumes. For each round of clustering, the sum of square within a cluster was calculated, which represented the variance of the values (i.e., facility case volumes) in that cluster. The elbow curve method[21] was used to determine the optimal number of clusters to be 5, with a compactness of 90.9% (Figure 1). The clusters were sorted in order of increasing facility volume, with the ranges of the first and last cluster being 1–5 and 57–103 cases per year, respectively. Each cluster's OS was visualized on univariate Kaplan-Meier survival curves (Supplementary Figure 1) and, subsequently, mortality risk was compared with the preceding two clusters via multivariable cox proportional hazards (CPH) regression (Supplementary Table 1). A case volume threshold was created whenever a cluster had significantly lower mortality than both of the preceding clusters. The clusters were then collapsed according to the identified thresholds to generate volume-stratified groups that could be used in further analyses. Thus, this method served as an objective way to minimize differences within volume-stratified patient cohorts and maximize differences between cohorts.

Statistical Analysis

All statistical analyses were performed via R (version 3.6.1; The R Foundation for Statistical Computing) in RStudio (version 1.2.1335). A *p*-value of <0.05 was considered statistically significant. Kruskal-Wallis and Chi-square tests were used to evaluate differences among continuous and categorical variables, respectively. CPH regression was performed to identify significant associations between sociodemographic or clinical factors and mortality risk. Variables that were found to be significantly associated with mortality on univariate analysis were included as covariates in multivariable CPH models. A lack of multicollinearity in multivariable CPH models was ensured by confirming that all covariates possessed variance inflation factors less than 10.[22] OS was modeled with Kaplan Meier analysis and compared between patient cohorts using log-rank tests. To account for confounding factors in Kaplan-Meier analyses, propensity score matching was performed to create propensity-matched cohorts with statistically nonsignificant differences in the sociodemographic and clinical factors that were previously found to be statistically different on univariate analysis. Propensity scores were calculated using logistical regression, and 1-to-1 propensity matching without replacement was performed utilizing the nearest neighbor method. A caliper width equal to 0.2 of the standard deviation of the logit of the propensity score was utilized to eliminate at least 98% of bias.[23]

Results

Overall, 48,899 patients with locally advanced PTC were treated at 1,304 facilities, with 34,312 (70.2%) being female and a mean age of 48.0±16.0 years. Using the case-volume threshold identified from analyzing the five facility clusters, patients were assigned to one of two distinct cohorts according to their treatment at a low (LVF, <27 cases/year) or high (HVF, ≥27 cases/year) case-volume facility. Thus, HVFs (N=16) represented approximately the top 1.2% of facilities by case-volume. Patient demographic and clinical characteristics in each cohort were compared and summarized in Table 1.

Associations between various sociodemographic or clinical factors and all-cause mortality were evaluated using CPH regression and are listed in Table 2. On univariate CPH regression, higher facility volume (as a continuous variable) was associated with lower mortality (HR 0.988; 95% CI, 0.985–0.991; *p*<0.001). After accounting for a number of variables, multivariable CPH regression continued to reveal an association between increased facility volume and reduced all-cause mortality (HR 0.996; 95% CI, 0.992–0.999; *p*=0.008).

On univariate CPH regression, patients treated at HVFs were associated with lower mortality risk than those treated at LVFs (HR 0.617; 95% CI, 0.538–0.707; *p*<0.001). Multivariable analysis demonstrated patients in the HVF cohort to be associated with reduced mortality (HR 0.791; 95% CI, 0.678–0.923; p=0.003). Since histogram analysis (Supplementary Figure 2) identified two very high-volume facilities, a sub-analysis was done excluding these two facilities to ensure that our case-volume threshold was still prognostically significant. Indeed, multivariable CPH analysis of this trimmed patient cohort continued to demonstrate an association between HVF patients and reduced mortality (HR 0.797; 95% CI, 0.673–0.944; p=0.008).

Further stratification according to nodal metastasis similarly demonstrated patients with N0 (HR 0.793; 95% CI, 0.634–0.993; p=0.041) or N1 (HR 0.785; 95% CI, 0.635–0.970; p=0.024) cancer to be associated with decreased mortality if they were treated at an HVF. Moreover, Kaplan Meier analysis of propensity score-matched patients demonstrated significantly greater OS among patients treated at HVFs, regardless of the presence of nodal metastasis (Figure 2, all p<0.001). To ensure that the effect of facility volume could be compared between the two Kaplan Meier analyses, we performed two layers of propensity score matching, first by node status and second by facility volume designation, such that the N0 and N1 sub-cohorts consisted of patients with similar characteristics. Among N0 patients, the 10-year OS rate of patients in the HVF cohort (89.9% [86.8–93.0]) was greater than that of those in the LVF cohort (82.7% [79.7–85.8]; p<0.001). Similarly, among N1 patients, those in the HVF cohort (90.2% [87.8–92.7]) were associated with a higher 10-year OS rate than patients in the LVF cohort (80.9% [77.6–84.5]; p<0.001).

Discussion

Prognostic associations between facility volume and various outcome measures of head and neck malignancies have been previously reported.[10,12,24–26] However, to our knowledge, this study is the first to determine a systematic, data-driven facility case-volume threshold informed by population-based patient survival data for locally advanced PTC. Using LVF (<27 cases/year) and HVF (≥27 cases/year) as prognostic case-volume designations, our analysis demonstrated that high facility case-volume, representing approximately the top 1.2% of facilities in our cohort, was an independent predictor of overall survival in locally advanced PTC. This was an association that remained statistically significant after adjusting for an array of potentially confounding demographic, socioeconomic, and clinical variables in a multivariable regression model. Specifically, rates of both 5- and 10-year OS were significantly higher for patients treated at HVFs compared to those receiving care at LVFs. Further validating this observation, a Kaplan-Meier analysis of propensity score-matched N0 and N1 patients demonstrated that, regardless of the presence of nodal metastasis, treatment at higher case-volume centers was significantly associated with improved survival.

The persistence of the observed benefit of HVF treatment on patient outcomes across a spectrum of non-thyroidal malignancies has drawn a number of probable explanations.[8–12] High case volumes at the facility level may translate into high case volumes at the provider level, which has been demonstrated to be a significant predictor of high-quality oncologic management, sensitive and specific radiologic detection and diagnoses, improved surgical tumor control and post-operative outcomes, as well as lower complication and recurrence rates post-radiation therapy—all effects that have been established to, in turn, directly influence patient outcomes in numerous cancers.[13,14,27–32] In addition to experience via ample case volume, physicians at HVFs may also be more likely to be subspecialized, more extensively trained, and better resourced to comply with the most recent evidence-based clinical guidelines.[33–36] Of course, this does not imply that all physicians at high-volume facilities are necessarily better trained than their colleagues at lower-volume facilities, but rather that the higher surgeon case-volume that inherently results from working at a high-volume facility may produce an “average” effect that contributes to a positive correlation between facility volume and patient outcomes. Studies suggest that patients treated at HVFs are also more likely to access a diverse array of ancillary services such as dieticians, social services, palliative care, and oncologic psychiatry, all of which have the potential to improve patient outcomes and quality of life.[37–40] As such, facility volume emerged as an increasingly useful prognostic variable and marker of treatment quality. To further that end, this study derived a specific and statistically meaningful case-volume threshold that can be used to prognosticate locally advanced PTC and inform improvement of care.

Mechanisms offered in previous studies to explain their findings of improved thyroid cancer outcomes in relation to facility case volume were similarly varied in nature. Many studies examined extent of surgery as a potentially expounding factor and demonstrated a positive association between rates of total thyroidectomies and facility volume. In 2009, a multicenter study in France that categorized facilities into three groups by case volume found that the odds of receiving a unilateral thyroid lobectomy, as opposed to total thyroidectomy, for thyroid cancer increased by a factor of 2.85 in low-volume and 2.03 in medium-volume centers relative to high-volume centers.[41] A more recent study examining the proportion of medullary thyroid patients receiving neck dissections found a positive relationship between the incidence of neck dissection and hospital volume (low-volume: 23.8%, low-medium-volume: 47.7%, medium-volume: 60.3%, high-volume: 65.9%) to accompany their findings of a positive relationship between 5-year OS rate and hospital volume.[25] The authors went on to hypothesize that high-volume centers have a greater capacity to update their practices and comply with changing care guidelines, thus contributing to their superior patient outcomes.[25] Not surprisingly then, in an effort to develop a composite measure of quality of hospital management of thyroid cancers, Megwalu *et al.* included a case volume threshold (≥10 thyroid cancer cases per year) as one of their two combined criteria.[24] Using these criteria, they identified high quality centers where patients with DTC experienced significantly improved OS and disease-specific survival.[24]

While our study focused on the association between facility volume and patient survival, other investigations have previously also evaluated the relationship between avoidable re-admissions and hospital volume. In a retrospective study, Mitchell *et al.* derived a set of criteria from 2006 thyroid disease management guidelines categorizing thyroid surgeries as avoidable or unavoidable, and found that 50% of all thyroid surgeries at low-volume centers were avoidable compared to 14% at high-volume centers.[42] Operations for thyroid cancers specifically led to avoidable reoperations significantly more often when performed at a low-volume center. These conclusions, however, may have been limited by the study not accounting for patient election for surgery and availability of services. In a 2013 study, Youngwirth *et al.* found that pediatric thyroid cancer patients treated at LVFs were more likely to be readmitted after thyroid surgery than patients treated at HVFs.[43] The authors based their analysis on a case-volume threshold (<39 vs. ≥ 39 cases over the study period), revealing a significantly higher percentage of patients receiving total thyroidectomy (as opposed to lobectomy or no surgery) at HVFs compared to LVFs (90.8% vs. 86.3%). However, the authors noted that this case-volume threshold was, in of itself, fairly low and was likely expounded by the fact that the analyzed high-volume facilities treating pediatric thyroid cancer were also frequently high-volume facilities treating adult thyroid cancer.[43]

Differences in facility volume have also been previously associated with varying postoperative complication rates. Pieracci et al. found increasing hospital volume of substernal thyroidectomies in the treatment of substernal thyroid goiters, to be a significant predictor of decreased risk of overall complications, postoperative bleeding, blood transfusion, respiratory failure, and mortality.[26] Similar trends have also been demonstrated at the provider level. A study of the Nationwide Inpatient Sample found that thyroidectomies, when performed by low-volume surgeons, were associated with an elevated risk of complications compared with high-volume surgeons (15.8% vs 7.7%).[44] Similarly, recent meta-analyses found that care provided by higher volume thyroid surgeons resulted in decreased surgical and medical complications, fewer recurrences, and shorter length of hospital stay when compared to care under lower volume surgeons, especially for patients with advanced stage disease.[45,46] Granted, associating outcomes with surgeon volume as opposed to hospital volume provides a distinct analysis by nature. Indeed, one study of 2002 New York and Florida discharge data on endocrine surgeries found that, while high surgeon volume was associated with decreased risk of complications and reduced length of hospital stay, hospital volume had a negligible influence on patient outcomes.[47] Nonetheless, the theme remains relatively consistent—a positive relationship between patient outcomes and case volume, at both provider and hospital levels.

Besides facility case volume, our multivariable analysis revealed other factors, both oncologic and non-clinical, that independently predicted mortality. These have the potential to further widen the survival differences between HVF and LVF locally advanced PTC patients, whether in complementation or opposition to the influences of facility case-volume. Indeed, a significantly lower proportion of patients aged ≥55 years comprised our HVF cohort compared to our LVF cohort, a notable observation as the ≥55 age group was found to be at particularly higher risk for mortality than the younger patient population. This observation would be consistent with the well-reported phenomenon of regionalization of health services as living at a distance from HVFs presents logistical, socioeconomic, and psychosocial barriers to patients seeking their care, particularly those vulnerable due to elderly age.[48,49] A significantly lower proportion of patients enrolled in government insurance programs were treated at HVFs, which may explain this group's higher associated risk for mortality relative to patients with private health insurance. Assuming HVFs do indeed provide higher quality care through their specialized and experienced providers, compliance to the latest clinical guidelines, and access to greater ancillary resources, the higher mortality experienced by these nonprivate insurance holders may be partly attributed to their lack of access to HVFs. Our analysis also showed that HVFs treated a significantly higher ratio of T3 to T4 diseases compared to LVFs, suggesting that HVFs may potentially be detecting disease earlier and/or pursuing more aggressive treatment compared to LVFs.

An alternative explanation would be the sizable body of evidence that demonstrates more advanced disease upon presentation for patients from low socioeconomic backgrounds, corroborating with higher rates of T4 disease at facilities that care for a higher proportion of these populations.[50,51] Additionally, HVFs treated a significantly lower proportion of their patients with RAI compared to LVFs, a finding that builds upon past literature demonstrating the associations between surgeon case-volume and RAI decision making as well as between specialized surgical training and lower proportions of well-differentiated thyroid cancer patients receiving RAI after total thyroidectomy.[52,53] Thus, our analysis suggests that some attribution of favorable survival outcomes at HVFs to various demographic, social, and clinical factors is plausible and warrants further investigation.

While the present study offers evidence for a novel prognostic quality threshold for facilities treating locally advanced PTC, certain considerations should be made when interpreting these results. Since patients were extracted from a de-identified national database, selection and information bias is possible. Moreover, due to NCDB limitations, we were restricted to using OS as our primary outcome measure and could not evaluate recurrence-free or disease-free survival. Additionally, T classification was not based on the recent 8th edition of the American Joint Committee on Cancer (AJCC) staging guidelines, which removed microscopic extrathyroidal extension from the definition of T3 disease.[54] Lastly, while we accounted for a wide variety of clinical and sociodemographic variables via multivariable regression and propensity score matching, certain variables (e.g., family support, adequate follow-up, treatment regimen adherence, etc.) were not captured by the NCDB and could not be controlled for in our analyses.

Conclusion

Our analysis of 48,899 patients with locally advanced PTC demonstrated facility case-volume to be independently associated with reduced mortality. Furthermore, using a systematic and data-driven approach, we identified a novel prognostic facility case-volume threshold. Specifically, independent of a number of sociodemographic and clinical factors, we found centers that treated more than 26 cases per year to be associated with increased overall survival. Our findings, therefore, appear to support regionalization of care to higher-volume facilities where patients may have improved outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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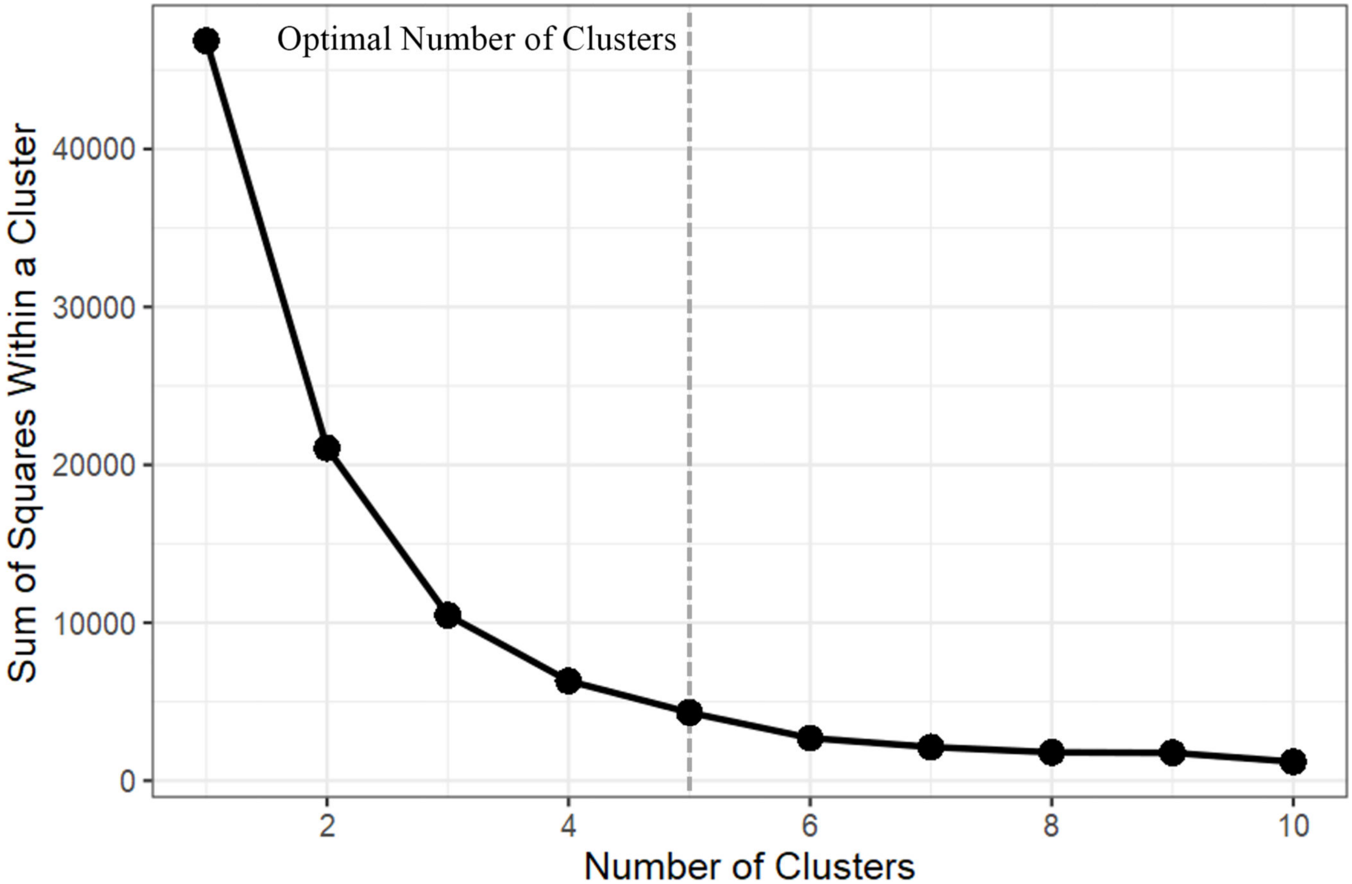

Figure 1:
Plot of the sum of squares within a cluster versus the number of clusters generated from K-means clustering, demonstrating five to be an appropriate number of clusters.

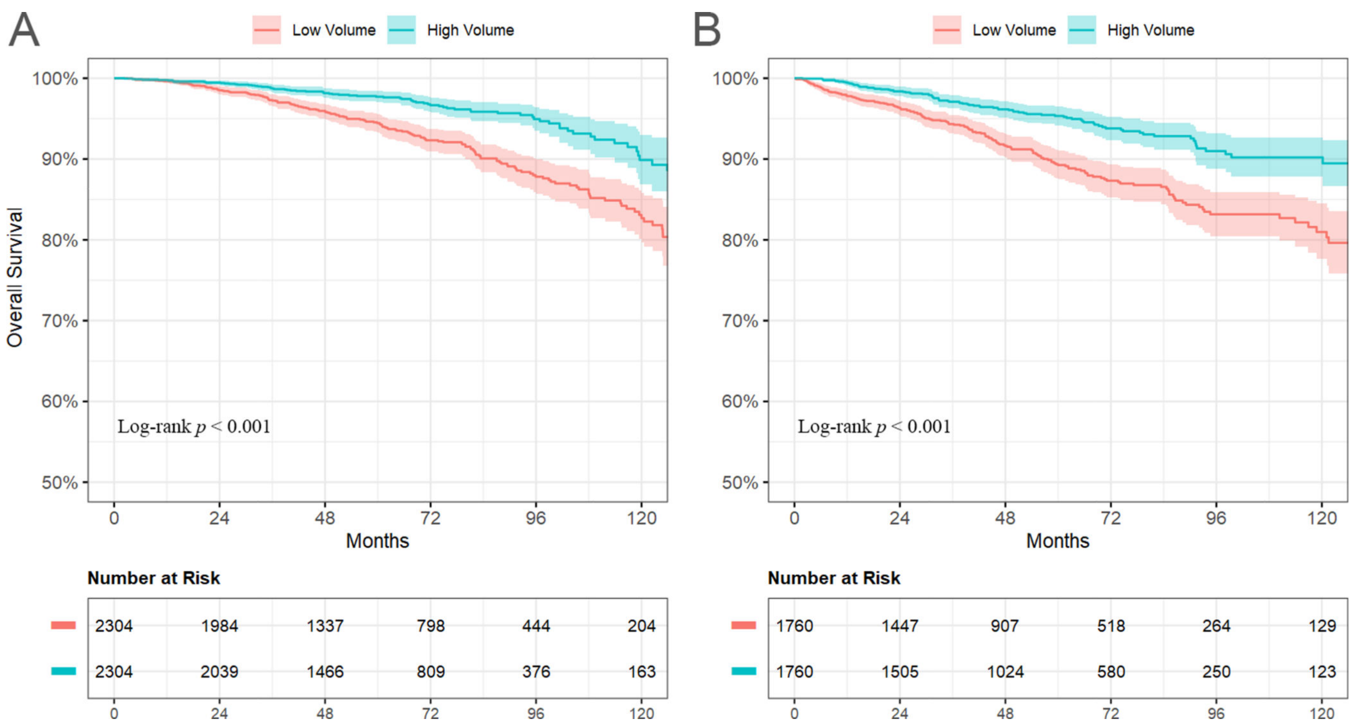

Figure 2:

Kaplan-Meier curves of overall survival in propensity score-matched (A) N0 patients (N=4,608) and (B) N1 patients (N=3,520) with locally advanced papillary thyroid cancer, demonstrating significantly improved survival in high volume facilities, regardless of the presence of nodal metastasis. Shaded areas represent 95% confidence intervals.

Table 1:

Demographics of patients with locally advanced papillary thyroid cancer (N=48,899).

Variables	Low Volume (N=42,048)	High Volume (N=6,851)	*P*-Value
Age, yr			
< 55	27,259 (64.8)	4,633 (67.6)	<0.001 *
≥ 55	14,789 (35.2)	2,218 (32.4)	
Sex			
Male	12,573 (29.9)	2,014 (29.4)	0.397
Female	29,475 (70.1)	4,837 (70.6)	
Race			
White	34,869 (86.4)	5,324 (83.9)	<0.001 *
Black	2,905 (7.2)	349 (5.5)	
Asian	2,565 (6.4)	669 (10.5)	
Insurance			
Private	28,333 (71.2)	5,182 (78.7)	<0.001 *
Government	11,458 (28.8)	1,404 (21.3)	
CD Score			
0	35,390 (84.2)	5,741 (83.8)	0.440
≥ 1	6,658 (15.8)	1,110 (16.2)	
Facility Type			
Non-Academic	25,194 (60.0)	373 (5.4)	<0.001 *
Academic	16,799 (40.0)	6,478 (94.6)	
Facility Volume, cases/yr †	5 (1–26)	35 (27–103)	<0.001 *
T Classification			
T3	37,027 (88.1)	6,407 (93.5)	<0.001 *
T4	5,021 (11.9)	444 (6.5)	
N Classification			
N0	21,129 (51.4)	3,195 (47.3)	<0.001 *
N1	19,985 (48.6)	3,562 (52.7)	
Extent of Surgery			
Lobectomy	2,141 (5.2)	416 (6.1)	0.001 *
Total Thyroidectomy	39,332 (94.8)	6,386 (93.9)	
RAI Therapy			
No	10,565 (25.1)	2,033 (29.7)	<0.001 *
Yes	31,483 (74.9)	4,818 (70.3)	
THST			
No	14,537 (35.2)	854 (12.6)	<0.001 *
Yes	26,797 (64.8)	5,898 (87.4)	

Variables	Low Volume (N=42,048)	High Volume (N=6,851)	*P*-Value
5-Year OS Rate (%)	94.0 (93.3–94.7)	97.3 (96.9–97.8)	<0.001 *
10-Year OS Rate (%)	85.4 (83.7–87.2)	92.0 (90.5–93.6)	<0.001 *

CD: Charleson/Deyo; RAI: Radioactive Iodine; THST: Thyroid-Stimulating Hormone Suppression Therapy; OS: Overall Survival

Not all cases reported values for the collected variables, thus the percentages reflect the number of cases with available data.

† Reported as median (range)

* Statistically significant, $p<0.05$

Table 2:

Univariate and multivariable Cox proportional-hazards regression of patients with locally advanced papillary thyroid cancer, demonstrating reduced mortality risk with higher facility volume.

Covariates	Univariate		Multivariable	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Age, yr				
< 55	1 [Reference]		1 [Reference]	
≥ 55	9.012 (8.196–9.908)	<0.001 *	5.262 (4.698–5.894)	<0.001 *
Sex				
Male	1 [Reference]		1 [Reference]	
Female	0.537 (0.498–0.578)	<0.001 *	0.648 (0.597–0.703)	<0.001 *
Race				
White	1 [Reference]		1 [Reference]	
Black	1.147 (0.997–1.319)	0.055	1.274 (1.090–1.489)	0.039 *
Asian	0.667 (0.552–0.807)	<0.001 *	0.717 (0.586–0.879)	<0.001 *
Insurance				
Private	1 [Reference]		1 [Reference]	
Government	6.501 (5.995–7.051)	<0.001 *	3.087 (2.816–3.383)	<0.001 *
Facility Type				
Non-Academic	1 [Reference]		1 [Reference]	
Academic	0.846 (0.785–0.912)	<0.001 *	1.022 (0.934–1.119)	0.633
Facility Volume	0.988 (0.985–0.991)	<0.001 *	0.996 (0.992–0.999)	0.008 *
CD Score				
0	1 [Reference]		1 [Reference]	
≥ 1	2.785 (2.572–3.015)	<0.001 *	1.710 (1.568–1.864)	<0.001 *
T Classification				
T3	1 [Reference]		1 [Reference]	
T4	3.139 (2.899–3.400)	<0.001 *	2.232 (2.042–2.440)	<0.001 *
N Classification				
N0	1 [Reference]		1 [Reference]	
N1	1.163 (1.079–1.254)	<0.001 *	1.452 (1.335–1.580)	<0.001 *
Extent of Surgery				
Lobectomy	1 [Reference]		1 [Reference]	
Total Thyroidectomy	0.746 (0.643–0.866)	<0.001 *	0.875 (0.741–1.032)	0.113
RAI Therapy				
No	1 [Reference]		1 [Reference]	
Yes	0.524 (0.486–0.566)	<0.001 *	0.563 (0.515–0.614)	<0.001 *
THST				

Covariates	Univariate		Multivariable	
	HR (95% CI)	***P*-Value**	**HR (95% CI)**	***P*-Value**
No	1 [Reference]		1 [Reference]	
Yes	0.726 (0.673–0.783)	<0.001 *	0.958 (0.879–1.045)	0.334

HR: Hazard Ratio; CI: Confidence Interval; CD: Charlson/Deyo; RAI: Radioactive Iodine; THST: Thyroid-Stimulating Hormone Suppression Therapy

*Statistically significant, $p<0.05$

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