Lymphovascular invasion is associated with survival for papillary thyroid cancer

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Abstract

Data are limited regarding the association between tumor lymphovascular invasion and survival for patients with papillary thyroid cancer (PTC). This study sought to examine lymphovascular invasion as an independent prognostic factor for patients with PTC undergoing thyroid resection. The National Cancer Data Base (2010–2011) was queried for patients with PTC who underwent total thyroidectomy or lobectomy. Patients were classified into two groups based on the presence/absence of lymphovascular invasion. Demographic, clinical and pathological features were evaluated for all patients. A Cox proportional hazards model was utilized to identify factors associated with survival. Results show that 45,415 patients met inclusion criteria; 11.6% had lymphovascular invasion. Patients with lymphovascular invasion were more likely to have larger tumors (2.8 cm vs 1.5 cm, $P<0.01$), metastatic lymph nodes (74.1% vs 32.5%, $P<0.01$), and distant metastases (3.0% vs 0.5%, $P<0.01$). They were also more likely to receive radioactive iodine (69.3% vs 44.9%, $P<0.01$). Unadjusted overall 5-year survival was lower for patients who had tumors with lymphovascular invasion (86.6% vs 94.5%) (log-rank $P<0.01$). After adjustment, increasing patient age (HR = 1.06, $P<0.01$), male gender (HR = 1.68, $P<0.01$), presence of metastatic lymph nodes (HR = 1.77, $P<0.01$), distant metastases (HR = 3.49, $P<0.01$), and lymphovascular invasion (HR = 1.88, $P<0.01$) were associated with compromised survival. For patients with lymphovascular invasion, treatment with RAI was associated with reduced mortality (HR = 0.43, $P<0.01$). The presence of lymphovascular invasion among patients with PTC is independently associated with compromised survival. Patients who have PTC with lymphovascular invasion should be considered higher risk, and adjuvant RAI should be more strongly considered.

Key Words
- lymphovascular invasion
- papillary thyroid cancer
- thyroidectomy
- lymph nodes
- survival

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Introduction

Thyroid cancer is the fastest increasing cancer in the United States among both men and women, largely as a result of an increase in the incidence of papillary thyroid cancer (PTC), which now represents approximately 90% of all new cases (Sosa & Udelsman 2006, Jillard *et al.* 2015). PTC has an excellent prognosis, with a cause-specific 10-year survival rate of over 90% (Biersack & Grünwald 2005). In general, optimal treatment includes thyroid resection, with or without administration of postoperative radioactive iodine (RAI).

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The impact of lymphovascular invasion on survival is important for several cancers; it is an independent risk factor for survival in colorectal, urothelial and breast cancers (Lotan *et al*. 2005, Meguerditchian *et al*. 2005, Rovera *et al*. 2013). Data regarding the impact of lymphovascular invasion (LVI) on patient outcomes in PTC have been limited, based primarily on small, retrospective institutional studies (Kim *et al*. 2006, Girardi *et al*. 2013). One single institution study by Kim *et al*., including 662 PTC patients, of whom 33 (5%) had LVI, found that there was a significant association between LVI and both lateral cervical lymph node metastases and an increased risk of disease recurrence.

The primary aim of this study was to look for a potential association between tumor LVI and survival for patients with PTC undergoing thyroid resection. Such an association is not recognized in current differentiated thyroid cancer staging systems, including UICC/AJCC TNM (Union for International Cancer Control/American Joint Commission on Cancer tumor,

Table 1 Patient demographic, clinical and pathological features by the presence and absence of lymphovascular invasion.

	LVI present $n=5284$ (%)	**LVI absent** $n=40,131$ (%)	**All patients** $n=45,415$	***P* value**
Age (years) (mean ± S.D.)	47.6 ± 16.4	50.2 ± 14.5	49.9 ± 14.7	<0.01
Gender (female)	3645 (69.0)	31,459 (78.4)	35,104 (77.3)	<0.01
Race				0.01
White	4434 (85.8)	33,941 (86.0)	38,375 (86.0)	
Black	343 (6.6)	3043 (7.7)	3386 (7.6)	
Asian	316 (6.2)	1964 (5.0)	2280 (5.1)	
Unknown/other	73 (1.4)	496 (1.3)	569 (1.3)	
Insurance status				<0.01
None	208 (4.0)	1146 (2.9)	1354 (3.0)	
Private	3610 (69.3)	28,185 (71.1)	31,795 (70.9)	
Government	1390 (26.7)	10,292 (26.0)	11,682 (26.1)	
Annual income				0.04
≤$35,999	1329 (26.1)	9462 (24.5)	10,791 (24.7)	
≥$36,000	3764 (73.9)	29,099 (75.5)	32,863 (75.3)	
Distance traveled to treatment facility (miles) (mean ± S.D.)	28.1 ± 94.7	25.8 ± 97.3	26.1 ± 97.0	0.05
Charlson/Deyo score				0.543
0	4402 (83.3)	33,338 (83.1)	37,740 (83.1)	
1	724 (13.7)	5669 (14.1)	6393 (14.1)	
≥2	158 (3.0)	1124 (2.8)	1282 (2.8)	
Facility type				<0.01
Academic	2573 (48.7)	17,112 (42.6)	19,685 (43.4)	
Comprehensive	2371 (44.9)	20,255 (50.5)	22,626 (49.8)	
Community	337 (6.4)	2757 (6.9)	3094 (6.8)	
Geographic region				<0.01
Northeast	1466 (27.7)	10,641 (26.5)	12,107 (26.7)	
South	1822 (34.5)	13,468 (33.6)	15,290 (33.7)	
Midwest	1042 (19.7)	9116 (22.7)	10,158 (22.3)	
West	954 (18.1)	6906 (17.2)	7860 (17.3)	
Tumor size (cm) (mean ± S.D.)	2.8 ± 2.4	1.5 ± 1.5	1.7 ± 1.7	<0.01
Metastatic cervical lymph nodes	2991 (74.1)	6853 (32.5)	9844 (39.1)	<0.01
Distant metastases	142 (3.0)	179 (0.5)	321 (0.8)	<0.01
Stage-NCDB				<0.01
I	2592 (51.5)	28,719 (76.0)	31,311 (73.1)	
II	429 (8.5)	3174 (8.4)	3603 (8.4)	
III	1235 (24.5)	4378 (11.6)	5613 (13.2)	
IV	775 (15.5)	1502 (4.0)	2277 (5.3)	
Lobectomy	263 (5.0)	4828 (12.0)	5091 (11.2)	<0.01
Length of stay (days) (mean ± S.D.)	2.1 ± 6.0	1.4 ± 4.9	1.5 ± 5.0	<0.01
Readmission	266 (5.1)	1533 (3.9)	1799 (4.0)	<0.01
Positive surgical margins	1427 (27.8)	3658 (9.2)	5085 (11.3)	<0.01
Extrathyroidal extension	405 (7.6)	547 (1.3)	952 (2.1)	<0.01
RAI	3660 (69.3)	18,023 (44.9)	21,683 (47.7)	<0.01

Data presented as *n* (%) unless otherwise specified. Percentages were calculated from patients with non-missing data, which may be less than the total number of patients in each category.

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nodes, metastases) (Edge *et al.* 2010), the National Thyroid Cancer Treatment Cooperative Study (NTCTCS) (Sherman *et al.* 1998), the European Organization for Research and Treatment of Cancer (EORTC) (Byar *et al.* 1979), AGES (age, grade, extent, size) (Hay *et al.* 1987), AMES (age, metastases, extent, size) (Cady & Rossi 1988), and MACIS (metastases, age, completeness of resection, invasion locally, size) (Hay *et al.* 1993, Dean & Hay 2000, Adam *et al.* 2015). Our secondary aim was to describe the treatment patterns employed in the United States for patients with PTC whose tumors have LVI. We hypothesized that LVI would be associated with patient outcomes and that more aggressive treatment for these tumors would be warranted.

Methods

The National Cancer Data Base (NCDB) is a joint collaboration of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. It is a national database that contains more than 29 million cancer cases from more than 1500 Commission on Cancer accredited cancer programs. More than 85% of all new thyroid cancer cases in the USA are captured in the database (Raval *et al.* 2009).

Data were coded according to the Commission on Cancer Registry Operations and Data Standards Manual, the American Joint Committee for Cancer (AJCC) Manual for Staging of Cancer, and the International Classification of Disease for Oncology. Data were de-identified and submitted to the NCDB in compliance with the Health Insurance Portability and Accountability Act (HIPAA) (Phillips 2015). The institutional review board at our institution granted this study an exempt status.

The NCDB (2010–2011) was queried for all adult patients (age ≥18 years) with a diagnosis of papillary thyroid cancer. We limited our study cohort to patients who underwent total thyroidectomy or lobectomy. The cohort was divided into two principle study groups based on the presence or absence of LVI on surgical pathology. Patient variables extracted from the database included age at diagnosis, gender, race, annual income, insurance, year of diagnosis, distance traveled to treating institution, and comorbidity score. Annual income levels were assigned by the NCDB by linking a patient's zip code to the U.S. Census data for the year 2000. Comorbidity was represented by the modified Charlson/Deyo scoring system (Deyo *et al.* 1992). Clinical and pathological variables of interest included tumor size, histological subtype, presence of multifocality, lymph node involvement, and NCDB cancer stage according to the AJCC/TNM system. All variables were summarized based on the presence or absence of LVI.

Statistical analysis

Baseline characteristics were reported using frequencies and proportions for categorical variables and mean and standard deviation for continuous variables. Data were compared using χ^2 and Student's *t*-tests. Overall survival was defined as the time from diagnosis to death or the last follow-up visit. Survival time was censored for patients alive at the end of the study period. Patients with zero months of follow-up evaluation were excluded from the study. Estimates and 95% confidence intervals (95% CI) of overall survival proportions were computed using the Kaplan–Meier method, and survival distributions were compared between study groups using the log-rank test.

A multivariate Cox proportional hazards model was used to examine the adjusted association of LVI with overall survival. The model adjusted for the effects of patient age, gender, race, annual income, insurance status, facility type, tumor size, lymph node involvement, and treatment with radioactive iodine. To examine the effect of RAI use in combination with LVI on survival, a separate model was conducted that also included a RAI*LVI interaction term. A multivariate logistic regression model

Table 2 Patient and tumor factors associated with the presence of lymphovascular invasion ($n=41347$).

	Odds ratio	95% CI	*P* value
Age (years)	0.98	0.98–0.98	<0.01
Male gender	1.58	1.48–1.69	<0.01
Race (reference-white)*			
Black	0.94	0.83–1.06	0.03
Asian	1.10	0.97–1.25	0.13
Insurance status (reference-private)			
None	1.20	0.98–1.47	0.08
Government	1.20	1.08–1.33	<0.01
Annual income ≤$35,999	0.92	0.81–1.04	0.19
Facility type (reference-academic)			
Comprehensive	0.83	0.78–0.88	<0.01
Community	0.86	0.76–0.98	<0.02
Tumor size (cm)	1.00	1.00–1.01	<0.01
Metastatic cervical lymph nodes	3.00	2.67–3.35	<0.01
Distant metastases	3.65	2.85–4.67	<0.01
Extrathyroidal extension	4.61	3.99–5.32	<0.01
Multifocality	1.61	1.52–1.71	<0.01
Follicular variant	0.99	0.93–1.06	0.81
Aggressive variant	3.27	2.76–3.88	<0.01

*Patients with unknown/other race were excluded from this model.

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Table 3 Patient demographic, clinical and pathological features in patients with lymphovascular invasion by gender ($n = 5284$).

	Males $n = 1639$ (%)	Females $n = 3645$ (%)	*P* value
Age (years) (mean ± S.D.)	51.6 ± 16.3	45.9 ± 16.1	<0.01
Race			<0.01
White	1425 (88.6)	3009 (84.6)	
Black	72 (4.5)	271 (7.6)	
Asian	88 (5.4)	228 (6.4)	
Other	24 (1.5)	49 (1.4)	
Insurance			<0.01
None	48 (3.0)	160 (4.5)	
Private	1077 (66.7)	2533 (70.5)	
Government	490 (30.3)	900 (25.0)	
Income			0.55
≤$35,999	426 (27.0)	903 (25.7)	
≥$36,000	1150 (73.0)	2614 (74.3)	
Distance traveled to treatment facility (miles) (mean ± S.D.)	25.3 ± 51.0	29.4 ± 108.7	0.15
Charlson/Deyo score			<0.01
0	1322 (80.7)	3080 (84.5)	
1	256 (15.6)	468 (12.8)	
≥2	61 (3.7)	97 (2.7)	
Facility type			0.75
Academic	815 (49.8)	1758 (48.3)	
Comprehensive	724 (44.2)	1647 (45.2)	
Community	99 (6.0)	238 (6.5)	
Geographic region			0.99
Northeast	457 (27.9)	1009 (27.7)	
South	559 (34.1)	1263 (34.7)	
Midwest	331 (20.2)	711 (19.5)	
West	292 (17.8)	662 (18.1)	
Tumor size (cm) (mean ± S.D.)	3.3 ± 2.7	2.6 ± 2.2	<0.01
Metastatic cervical lymph nodes	988 (80.1)	2003 (71.5)	<0.01
Distant metastases	72 (5.1)	70 (2.2)	<0.01
Stage-NCDB			<0.01
I	593 (38.3)	1999 (57.4)	
II	148 (9.6)	281 (8.1)	
III	445 (28.7)	790 (22.7)	
IV	363 (23.4)	412 (11.8)	
Lobectomy	88 (5.4)	175 (4.8)	0.38
Length of stay (days) (mean ± S.D.)	2.2 ± 5.2	2.0 ± 6.3	0.29
Readmission	81 (5.0)	185 (5.2)	0.79
Positive surgical margins	465 (29.0)	1000 (27.9)	0.21
Extrathyroidal extension	165 (10.1)	240 (6.6)	<0.01
RAI	1160 (70.8)	2500 (68.6)	0.11

Data presented as *n* (%) unless otherwise specified. Percentages were calculated from patients with non-missing data, which may be less than the total number of patients in each category.

was used to examine which factors were associated with the presence of LVI. This model included patient age, gender, race, insurance, income level, facility type, tumor size, histological subtype, presence of multifocality, presence of lymph node metastases, presence of distant metastases, and presence of extrathyroidal extension.

All analyses were performed using SPSS 22 statistical software (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM). Two-sided statistical tests were specified in all analyses, with *P*-values <0.01 considered statistically significant.

Results

In total, 45,415 patients met the inclusion criteria. Of these, 5284 (11.6%) patients had tumors with LVI. Overall, patients were more likely to be female than male, to be white rather than other races, and to have private insurance; the majority of patients were treated at academic and comprehensive facilities. Patients with LVI were more likely to be male and to have larger tumors (mean size of 2.8 vs 1.5 cm for patients without LVI, $P < 0.01$), metastatic cervical lymph nodes,

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and distant metastases (Table 1). They also had more advanced cancers (stages 3 and 4) and were more likely to undergo treatment at an academic medical center. Patients with LVI were also more likely to receive postoperative RAI.

LVI was associated with other aggressive tumor characteristics, such as metastatic cervical lymph nodes (odds ratio (OR) = 3.00, 95% CI: 2.67–3.35, $P<0.01$), distant metastases (OR = 3.65, 95% CI: 2.85–4.67, $P<0.01$), extrathyroidal extension (OR = 4.61, 95% CI: 3.99–5.32, $P<0.01$), multifocality (OR = 1.61, 95% CI: 1.52–1.71, $P<0.01$), and aggressive histological variants (OR = 3.27, 95% CI: 2.76–3.88, $P<0.01$). Other characteristics associated with LVI included male gender and government insurance (Table 2).

Among patients with LVI, males were older than females (age 51.6 vs females 45.9 years, $P<0.01$) and had a larger average tumor size (mean size of 3.3 vs 2.6 cm, $P<0.01$). Males were also more likely to have metastatic cervical lymph nodes (80.1% of males vs 71.5% of females, $P<0.01$) and distant metastases (5.1% of males vs 2.2% of females, $P<0.01$) (Table 3). When the presence of LVI was analyzed by age (decade of life), younger and older patients had a higher rate of LVI than middle-aged patients in the fifth to seventh decade of life (Fig. 1).

LVI and survival in unadjusted analyses

The overall 5-year survival for PTC was 93.6%. A Kaplan–Meier analysis was performed, and unadjusted overall survival was examined for patients with LVI compared with patients without LVI (log-rank $P<0.01$, 5-year survival 86.6% vs 94.5%, respectively) (Fig. 2). The 5-year survival among patients aged >45 years was superior for patients without LVI (92.6%) compared with patients with LVI (76.2%, $P<0.01$), and among patients aged ≤45 years, survival was similar (97.9% without LVI and 99.5% with LVI, $P=0.91$; data not shown).

LVI and survival in adjusted analyses

After adjusting for patient demographic, clinical and pathological factors, including age, gender, race, insurance status, income, facility type, tumor size, lymph node status, presence of distant metastases, lobectomy, positive surgical margins, and extrathyroidal extension, the presence of LVI was associated with compromised survival (Hazard ratio (HR) = 1.88, 95% CI: 1.56–2.27, $P<0.01$). Other factors associated with survival included increasing patient age (HR = 1.06 per year, 95% CI: 1.05–1.07, $P<0.01$), male gender (HR = 1.68, 95% CI: 1.45–1.95, $P<0.01$), presence of metastatic cervical lymph nodes (HR = 1.77, 95% CI: 1.35–2.32, $P<0.01$), extrathyroidal extension (HR = 3.80, 95% CI: 2.94–4.91, $P<0.01$), and distant metastases (HR = 3.49, 95% CI: 2.60–4.69, $P<0.01$) (Table 4). In a subgroup analysis of tumors <1 cm in size, LVI was not associated with compromised survival (HR = 1.76, 95% CI: 1.00–3.10, $P=0.05$). When using an interaction model, there was a significant interaction effect between LVI and RAI (interaction HR = 0.48, 95% CI: 0.41–0.56, $P<0.01$). Patients with LVI in the presence of RAI (HR = 0.43, CI: 0.33–0.58, $P<0.01$) had a greater reduction in mortality

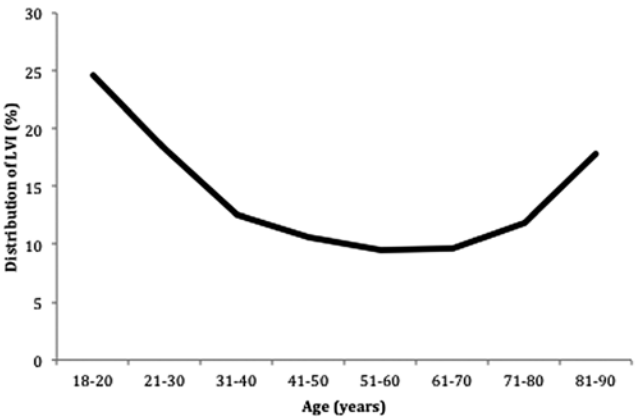

Figure 1
Distribution of patients with LVI by age.

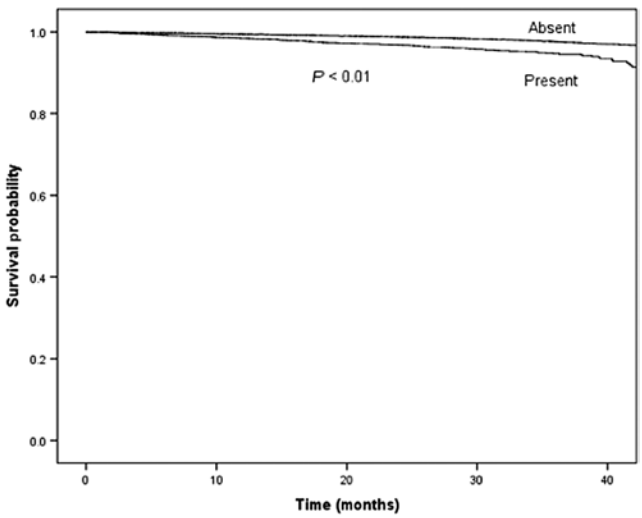

Figure 2
Unadjusted overall survival for patients with papillary thyroid cancer undergoing total thyroidectomy based on the presence or absence of LVI (n = 45,415).

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Table 4 Multivariate analysis for all-cause mortality for patients with papillary thyroid cancer undergoing thyroid lobectomy and total thyroidectomy (n = 42,276).

	Hazard ratio	CI (95%)	*P* value
Lymphovascular invasion	1.88	1.56–2.27	<0.01
Age	1.06	1.05–1.07	<0.01
Male gender	1.68	1.45–1.95	<0.01
Race (reference-white)*			
Black	1.16	0.90–1.51	0.25
Asian	0.60	0.39–0.93	0.02
Insurance status (reference-private)			
None	2.09	1.22–3.60	0.01
Government	2.24	1.69–3.01	<0.01
Annual income ≤$35,999	1.21	0.89–1.65	0.23
Facility type (reference-academic)			
Comprehensive	0.93	0.80–1.08	0.36
Community	1.17	0.90–1.52	0.25
Tumor size (cm)	1.00	0.99–1.00	0.25
Metastatic cervical lymph nodes	1.77	1.35–2.32	<0.01
Distant metastases	3.49	2.60–4.69	<0.01
Lobectomy	0.77	0.61–0.97	0.03
Positive surgical margins	1.21	0.99–1.48	0.06
Extrathyroidal extension	3.80	2.94–4.91	<0.01
RAI	0.48	0.41–0.56	<0.01

*Patients with unknown/other race were excluded from this model.

compared with patients with LVI in the absence of RAI (HR = 0.49, CI: 0.41–0.58, P < 0.01).

Discussion

To date, published data about the importance of LVI for outcomes among patients with PTC have been limited to small, retrospective, single institution studies (Kim *et al.* 2006, Girardi *et al.* 2013). This is the first study to examine the association between LVI and mortality for PTC in a nationwide database and to demonstrate that the presence of tumor LVI is associated with compromised patient survival. However, it is not included as a criterion to measure prognosis in any current thyroid staging systems.

Most studies to date assessing LVI have focused on disease recurrence (Kim *et al.* 2006, Girardi *et al.* 2013). In an analysis of 517 patients with PTC undergoing thyroidectomy at a single institution over 11 years, Girardi and coworkers reported LVI as an important risk factor for disease recurrence, as well as cervical lymph node metastasis (Girardi *et al.* 2013). They also demonstrated that LVI was associated with more aggressive histological subtypes of PTC, such as the diffuse sclerosing, tall cell, and solid variants. In another study performed by Soydal and coworkers, 357 patients with papillary thyroid microcarcinomas (or PTC <1 cm) from a single institution underwent thyroidectomy (Soydal *et al.* 2015); 89 of these patients had LVI and/or capsular invasion. They demonstrated that LVI was associated with an increased risk of disease recurrence and metastasis (2.2% rate without LVI/capsular invasion, 9.2% rate with LVI/capsular invasion, P<0.01). Although this study demonstrated an association between LVI and disease recurrence, it was limited to PTC <1 cm in diameter, and did not distinguish LVI as a separate prognostic factor from capsular invasion. Additionally, there are no known studies to date examining LVI as a predictor of mortality. Our study represents not only the largest cohort but also the only cohort, to date analyzing the association between LVI and survival using a large national dataset. It demonstrates that LVI is independently associated with compromised patient survival, observed even at relatively short follow-up times.

We also demonstrated that more aggressive tumor characteristics were associated with LVI, including positive lymph nodes, extrathyroidal extension and distant metastases. This is in agreement with several other studies that have established an association between LVI and cervical lymph node metastases (Merdad *et al.* 2012, Sun *et al.* 2015). In a systematic review, Sun and coworkers reviewed 20 studies and 9084 patients with PTC who underwent thyroidectomy with prophylactic lymph node dissection (Sun *et al.* 2015). In this study, the authors found that there was an increased risk of central lymph node metastases in clinical N0 patients with LVI (OR = 4.35, 95% CI: 2.24–8.46, P<0.01). Other factors were independently associated with central lymph node metastases, such as tumor size >2 cm (OR = 2.98, 95% CI: 2.08–4.28, P<0.01), extrathyroidal extension (OR = 2.27, 95% CI: 1.76–2.94, P<0.01), and capsular invasion (OR = 1.72, 95% CI: 1.39–2.41, P<0.01); however, LVI had the greatest predictive value. LVI has also been shown to be associated with an increased risk of having lateral lymph node metastasis; Merdad et al. presented a series of 185 patients with PTC who underwent selective neck dissection and showed that tumor LVI (OR = 5.52, S.E.M. = 0.03, P = 0.03) was an independent risk factor for having level Vb nodal involvement (Merdad *et al.* 2012).

Our data have shown that patients with LVI had an overall greater risk of mortality compared with those without LVI, and patients in extremes of age had more tumors with LVI than those who were in their fifth to seventh decade of life. The improved survival of those

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without LVI continued to hold true when controlling for patient age. LVI is currently not part of any staging system for differentiated thyroid cancer. The UICC/AJCC TNM system is most widely used in the United States and includes tumor size, extrathyroidal extension, capsular invasion, vascular invasion, cervical and mediastinal lymph node involvement, and distant metastases (Edge *et al*. 2010). Our multivariate analysis demonstrated that LVI is associated with compromised survival.

The limitations of our study include those that are part of all studies involving large databases. There is a potential for coding errors, but the NCDB is standardized and highly audited. An additional limitation of this study is that NCDB only reports overall survival, without disease-specific survival or recurrence data. Also, the NCDB does not include novel predictors of outcomes, such as molecular markers. As this study is observational, it is impossible to conclude that LVI is the cause of compromised survival. The strengths of our study lie in the large volume of patient data evaluated, as well as the contemporary population-based data available.

Conclusion

In this study, we identified patients more likely to have PTC with LVI following total thyroidectomy or lobectomy, including males, patients in the extremes of age, larger tumor size, presence of metastatic cervical lymph nodes, and distant metastases. We further demonstrated that there is compromised survival for patients with LVI compared with patients without LVI. These results suggest that patients with LVI undergoing total thyroidectomy or lobectomy for PTC should be considered to be at higher risk for mortality, and LVI may be an important independent risk factor to include in future iterations of staging guidelines.

Declaration of interest

Dr Sosa is a member of the Data Monitoring Committee for the Medullary Thyroid Cancer Consortium Registry funded by Novo Nordisk, Astra Zeneca, GlaxoSmithKline and Eli Lilly.

The data used in this study are derived from a de-identified National Cancer Data Base (NCDB) file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigators.

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