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A Preoperative Nomogram for the Prediction of Ipsilateral Central Compartment Lymph Node Metastases in Papillary Thyroid Cancer

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Background: Central compartment lymph node metastases in papillary thyroid carcinoma (PTC) are difficult to detect preoperatively, and the role of routine or prophylactic central compartment lymph node dissection (CLND) in managing PTC remains controversial. The aim of this project was to create a nomogram able to predict the occurrence of central compartment lymph node metastasis using readily available preoperative clinical characteristics.

Methods: Records from patients undergoing total thyroidectomy and lymph node dissection for PTC in the period 1968–2012 were analyzed. Nodal status was based on results of serial hematoxylin and eosin (H&E) examination. Age, sex, tumor size, tumor site, and multifocality were included in a multivariable logistic regression model to predict lymph node metastasis. A coefficient-based nomogram was developed and validated using an external patient cohort.

Results: The study population included 914 patients (80% females) with an average central compartment nodal yield of eight per patient. Central compartment lymph node metastases were present in 390 patients (42.7%). The variables with the strongest predictive value were age ($p < 0.001$), male sex ($p < 0.001$), increasing tumor size ($p < 0.001$), and tumor multifocality ($p < 0.05$). The nomogram had good discrimination with a concordance index of 76.4% [95% confidence interval 73.3–79.4], supported by an external validation point estimate of 61.5% [95% confidence interval 49.5–73.6]. An online calculator and smartphone application were developed for point of care use.

Conclusions: A validated nomogram utilizing readily available preoperative variables has been developed to give a predicted probability of central lymph node metastases in patients presenting with PTC. This nomogram may help guide surgical decision making in PTC.

Introduction

PAPILLARY THYROID CANCER (PTC) occurs in two to three people per 100,000 and is the most common endocrine malignancy. The rate of cervical lymph node spread in PTC is in the order of 20–50%. The pattern of lymph node spread is well established and typically involves the central (level VI) lymph nodes before the lateral neck compartments (1).

Total thyroidectomy is generally considered the gold-standard surgical treatment of the primary tumor in clinically significant PTC (2–4). When cervical lymph node metastases are detected (cN1), by either clinical or radiological means, the decision to perform concurrent lymphadenectomy is well founded. Ongoing controversy exists regarding the optimal management of clinically and sonographically uninvolved (cN0) central (level VI) lymph nodes. Minimization of the morbidity of local recurrence and reoperation (5) is weighed against the potential for increased harm and perceived lack of benefit.

In institutions where prophylactic central compartment lymph node dissection (CLND) is not performed routinely, the decision to perform lymphadenectomy is dependent on

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clinical and radiological assessment. Due to the poor reliability of these modalities in assessing the level VI lymph nodes, a tool that helps to quantify the risk of nodal disease may facilitate preoperative decision making and help inform the discussion between the surgeon and patient.

The purpose of this study was to create a validated nomogram tool able to quantify the likelihood of central compartment lymph node metastases in patients with PTC based on preoperatively determinable clinical and radiological findings. An online interface and smartphone application were then created to aid point of care decision making.

Materials and Methods

Data were obtained from a retrospective analysis of a prospectively maintained thyroid cancer database kept within a tertiary thyroid cancer service. All patients consented to the anonymous use of their data for research prior to surgery. Approval for data collection and storage was provided by the Northern Health Human Research Ethics Committee.

Study patients

Patients undergoing first-time surgery for PTC within the University of Sydney Endocrine Surgical Unit in the period 1968–2012 were studied. A total of 1589 patients with histologically proven PTC were identified.

Patients were excluded who had no lymph nodes removed ($n=597$), who had lateral but not central lymph nodes removed ($n=70$), and who had inadequate covariate information ($n=8$). The population used in the analyses consisted of 914 patients who all underwent thyroidectomy and CLND. Tumors found incidentally in patients undergoing thyroidectomy were included only if nodal dissection was also performed. Papillary microcarcinomas may metastasize in 20–60% of cases (6,7) and were included in the analysis.

CLND and pathological evaluation

CLND was performed as previously described (8). The typical approach was to perform ipsilateral CLND. However, bilateral CLND was also performed in 16% of cases. All operations were performed by surgeons within the University of Sydney Endocrine Surgery Unit.

In the study population of 914 patients, 744 (81%) had CLND performed routinely in the period after 2003. The remainder had CLND performed selectively at the discretion of the surgeon. To investigate further the applicability of the series to CLND, sensitivity testing was performed on patients undergoing surgery after 2003 ($n=744$), when the practice of prophylactic or routine CLND was introduced at this unit, and on patients who underwent CLND without any form of lateral lymphadenectomy ($n=566$).

The key outcome measure was the presence of PTC lymph node metastases as determined on histopathological examination. Lymph nodes were evaluated by step-sectioning with hematoxylin and eosin (H&E) staining. Pathology reporting was undertaken by three dedicated endocrine pathologists.

Predictive variables considered both likely to influence the rate of central compartment metastases and available in the

preoperative period included clinical factors (age and sex) and tumor features (size, site within the thyroid, and multifocality).

Statistical methods

Descriptive statistics for the sample were calculated to show the number of patients for each predictive factor: (i) age, grouped as less than or greater than 45 years; (ii) sex; (iii) tumor size, grouped according to TNM criteria (9); (iv) tumor site, grouped as superior, mid, inferior, isthmic, or other; and (v) tumor multifocality, grouped as absent or present. The positive outcome variable was the number of patients (and percent) who had one or more positive nodes.

For the predictive model, we restricted one patient's tumor size of 100 mm to 70 mm to ensure that this value did not have undue influence as an outlier.

Logistic regression was used to model the association between each variable and the presence of PTC lymph node metastases. All candidate variables (age, sex, site of primary tumor, tumor multifocality) were included in the multivariable model regardless of significance to ensure the model's generalizability. Sex, tumor site (inferior, mid, superior, isthmus, and other/no data), and tumor multifocality (absent or present) were included in the models as categorical variables. Preliminary analysis showed that the best functional form for age was through a quadratic function. Tumor size was modeled using a fractional polynomial, and the best-fitting fractional polynomial was obtained from the full multivariable model. In multifocal cases, the largest diameter of the largest tumor focus was used to determine tumor size. Likelihood ratio p-values were used to assess the incremental value of each variable, and $p<0.05$ was considered statistically significant. For each patient, we calculated their probability of PTC lymph node metastases. The ability of the model to discriminate between patients with and without lymph node metastases was assessed using the area under the ROC curve (AUC), also known as the concordance index.

Ten thousand random bootstrap resamples were used for internal validation of the model and to assess the degree of sampling error in the estimates. This method, used to assess internal validation for risk prediction models, involves creating multiple (in this case 10,000) new samples from the existing data, and using the variability in the model estimates to ascertain sampling variability. Confidence intervals were estimated from the percentiles of the bootstrap distributions.

Sensitivity analyses were performed to assess the impact of the surgical unit's change in practice from 2003 onwards (routine prophylactic CLND for cN0 patients) and of lateral lymph node dissection on the model. This was done by refitting the model on the subset of patients from 2003 onwards and separately on the subset of patients with no lateral lymph node dissection (CLND alone).

External validation was performed using 87 patients who underwent thyroidectomy and CLND for PTC at the University of California Los Angeles Endocrine Surgery Unit between September 2000 and December 2010. As this data set did not document tumor site, two versions of the model were assessed. First, we used the original model and categorized all tumor sites as "unknown," and second, a new model was fitted to the original sample with the tumor site variable excluded. The performances of these models were assessed on

the external sample. The discrimination of the model in the external validation sample was assessed using the AUC. The calibration of the model was assessed by modeling the predicted probabilities from the model versus the true outcomes using logistic regression. Boxplots of the predicted probabilities in the original and external validation samples were plotted according to the presence or absence of PTC lymph node metastases (Fig. 1).

All statistical analyses were performed in SAS v9.2 and Stata v11.2.

Software development

An online interface (Supplementary Fig. S1; Supplementary Data are available online at www.liebertpub.com/thy) and a smartphone application were created to calculate the probability of central lymph node metastases for individual patients.

Results

Demographics

The study population consisted of 733 females and 181 males with a mean age of 46.3 years. The overall rate of nodal metastases detected by H&E sectioning was 42.7% (Table 1). The mean nodal yield from the central compartment was 7.7 lymph nodes. Lateral compartment lymph nodes were removed in 348 (38.1%) patients and were positive in 173 patients (Table 1). Skip metastases occurred in 5.6% of patients who had cancer in the lymph nodes (23 of 413) and were considered "node negative" for the purposes of the central compartment predictive model.

The mean maximum diameter of the primary tumor was 17.4 mm (median = 15.0 mm), with sizes ranging from 0.2 mm to 100 mm. A total of 36.2% of the study population had papillary microcarcinomas (T1a).

The rates of lymph node metastases according to each of the predictive variables are shown in Table 2. The database did not contain sufficient detail to define the size of the metastatic deposits within the lymph nodes and therefore included both micro- and macrometastases.

Our database recorded tumor focality according to the number of tumor foci seen (1, 2, 3, ≥ 4). When modeled in this
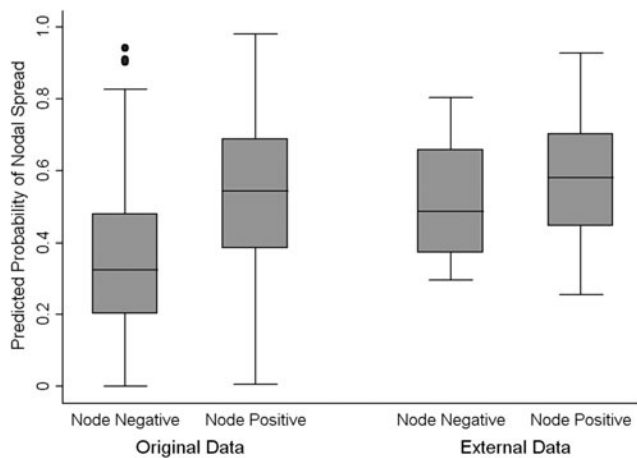
FIG. 1. Distribution of predicted probabilities by pathologically determined nodal involvement for the original and external data sets.

TABLE 1. COMPARISONS BETWEEN STUDY
AND EXTERNAL VALIDATION POPULATIONS

	Database	External validation
Demographics		
Number of patients	914	87
Female	733 (80.2%)	72 (82.8%)
Male	181	15
Mean age in years	46.3	40.1
Tumor characteristics		
Mean tumor size (greatest diameter, mm)	17.4	22.2
Multifocal tumor present	413 (45.3%)	48 (55.2%)
Extrathyroidal spread present	421 (46.1%)	16 (18.4%)
Lymph-node characteristics		
Nodal yield per patient (mean, median)	9.8, 6	7.8, 7
Number of patients with nodal metastases present[a]	390 (42.7%)	56 (64.4%)

[a]23 patients with skip metastases are not included.

TABLE 2. NUMBER AND PERCENTAGE OF PATIENTS
WITH LYMPH-NODE METASTASES
ACCORDING TO PATIENT AND TUMOR CHARACTERISTICS

	Number of patients [n (%)]	Number of patients with one or more positive nodes [n (%)]
Age group		
≤ 45 years	448 (49.0)	234 (52.2)
> 45 years	466 (51.0)	156 (33.5)
Sex		
Male	181 (19.8)	107 (59.1)
Female	733 (80.2)	283 (38.6)
Tumor size (mm)[a]		
T1a	331 (36.2)	77 (23.3)
T1b	312 (34.1)	151 (48.4)
T2	207 (22.6)	122 (58.9)
≥ T3	64 (7.0)	40 (62.5)
Extrathyroidal spread[b]		
1	493 (53.9)	121 (24.5)
2	139 (15.2)	63 (45.3)
3	222 (24.3)	160 (72.1)
4	54 (5.9)	43 (79.6)
5	6 (0.7)	3 (50.0)
Tumor multifocality		
Absent	501 (54.8)	196 (39.1)
Present	413 (45.2)	194 (47.0)
Total	914 (100.0)	390 (42.7)

[a]T1a (≤ 10 mm), T1b (> 10 mm and ≤ 20 mm), T2 (> 20 mm and ≤ 40 mm), ≥ T3 (> 40 mm) (9).
[b]Categorization of extrathyroidal spread: 1, Tumor is completely confined to the thyroid parenchyma; 2, tumor directly underlies the junction of the thyroid and adjacent soft tissue; 3, tumor extends focally out of the thyroid and adjacent perithyroidal fibroadipose tissue; 4, widespread extrathyroidal spread into soft tissue and skeletal muscle; 5, unknown.

way, multifocality was also a significant risk factor ($p < 0.001$) and improved the concordance index to 77.2%. As preoperative ultrasound is not sensitive to this level of measurement, multifocality was remodeled to be either "present" (number of foci = 2, 3, or ≥4) or "absent" (number of foci = 1). Significance was preserved under the less detailed classification system in both the univariable ($p = 0.017$) and multivariable ($p < 0.05$) models.

Of the study population, 63.2% had insufficient detailing of tumor site, in most cases having it defined as "left lobe" or "right lobe" only.

Prediction model for lymph node metastases

In the multivariable model, patient age, sex, tumor size, and multifocality were all associated with the presence of lymph node metastases ($p < 0.001$; Table 3). Males had 2.27 times increased odds of lymph node metastases compared to females [95% confidence interval (CI) 1.56–3.23] adjusted for all other variables in the model (Table 3). The risk related to age was U-shaped with increased odds of metastases in younger and older patients (Fig. 2B). Increasing tumor size was also highly predictive of lymph node metastases, with tumors > 50 mm having an estimated 60% predicted probability of involved lymph nodes (Fig. 2A).

This model showed good discrimination of lymph node metastases with an AUC of 76.4% [CI 73.3–79.4]. Internal validation, performed on 10,000 bootstrap resamples, produced an AUC of 76.4% [CI 73.6–79.7]. The bootstrap confidence intervals for the odds ratios were similar but slightly wider, as expected, than the original model.

Sensitivity analysis

Although the database was unable to discern if CND was performed with prophylactic or therapeutic intention, it was known that the prophylactic approach became routine at the start of 2003. A sensitivity analysis of the 744 patients operated on since 2003 had similar precision (AUC = 76.5%) compared to the full data set, with model coefficients similar to that obtained in the full model (Supplementary Table S1).

External validation

The external validation population comprised 87 patients (72 females) with a 64% overall rate of nodal metastases. The mean age was 40.1 years with a range of 13–75 years. Tumor and lymph node characteristics were again determined by histopathology and were comparable overall to the original data set (Table 1). The site of primary tumor was not recorded in this data set.

When applied to the original model, the external validation data set (assuming tumor site unknown for the 87 cases) produced an AUC of 61.5% [CI 49.5–73.6]. Tumor site was then excluded from both data sets (Fig. 3; "original reduced model" and "external reduced model") and the model refitted on the original sample. A comparison of ROC was produced (Fig. 3).

Figure 1 shows the distribution of predicted probabilities of nodal metastases for the original sample and external validation sample by whether lymph node metastases were present at histopathological examination.

To check the calibration of the model, the predicted probabilities from the model were used as predictor variables against the true outcomes. A calibration slope of 1 would

TABLE 3. UNIVARIABLE AND MULTIVARIABLE LOGISTIC REGRESSION MODELS ACCORDING TO PATIENT AND TUMOR CHARACTERISTICS

	Univariable models					*Multivariable model*[b]				
	Model coefficients	*Odds ratio [CI]*	*Wald p-value*	*Likelihood ratio p-value*	*AUC*	*Model coefficients*	*Odds ratio [CI]*	*Wald p-value*	*Likelihood ratio p-value*	*AUC*
Age				< 0.0001	65.3				< 0.001	
Linear term	−0.037		< 0.0001			−0.042		< 0.0001		
Quadratic term	0.001		< 0.0001			0.001		< 0.0001		
Sex				< 0.0001	56.7				< 0.001	
Male[a]										
Female	−0.833	0.44 [0.31–0.61]	< 0.0001			−0.881	0.44 [0.31–0.64]	< 0.0001		
Tumor size (mm)				< 0.0001	69.2				< 0.001	
Fractional[a]										
Polynomial	−1.523		< 0.0001			−1.351		< 0.0001		
Tumor site				0.25	53.8				0.08	
Inferior[a]										
Superior	0.543	1.72 [0.97–3.06]	0.06			0.568	1.76 [0.94–3.30]	0.08		
Mid	0.408	1.50 [0.86–2.62]	0.15			0.578	1.78 [0.98–3.25]	0.06		
Isthmus	−0.092	0.91 [0.42–2.00]	0.82			−0.396	0.67 [0.28–1.59]	0.37		
Other/no data	0.200	1.22 [0.79–1.89]	0.37			0.312	1.37 [0.85–2.19]	0.19		
Multifocality				0.02	54.0				0.05	
Absent[a]										
Present	0.321	1.38 [1.06–1.79]	0.02			0.304	1.36 [1.01–1.83]	0.05		76.4

[a]Reference group for Wald *p*-values.
[b]Intercept = −0.057
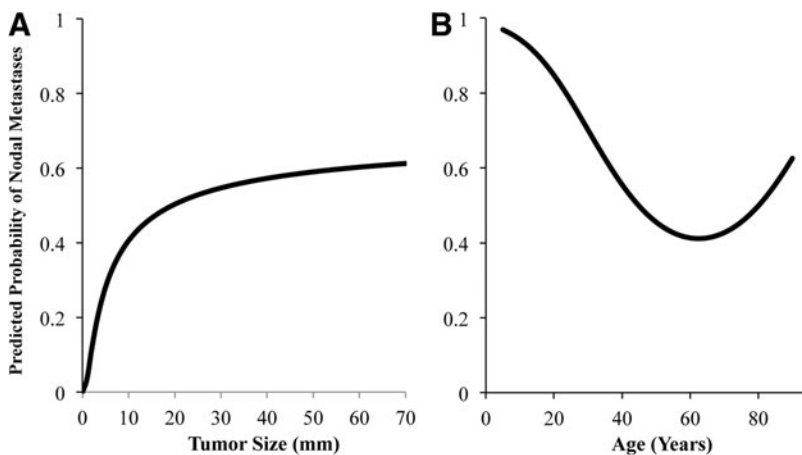AUC, area under the receiver operator curve, also known as the Concordance Index; CI, 95% confidence interval.

FIG. 2. Predicted probability of central lymph node disease compared to **(A)** tumor size (greatest diameter in mm) and **(B)** age in years (minimum = 5.5, maximum = 89).

indicate perfect calibration, and a slope less than 1 indicates the degree of shrinkage required for the model coefficients to be optimized to the new sample. We found that the calibration slope did not deviate significantly from 1 (full model: deviations from perfect calibration = 0.38, $p = 0.254$; reduced model: deviations from perfect calibration = 0.38, $p = 0.23$), indicating that there was little shrinkage of the model coefficients. The mean of the predicted values was similar to the mean of the true values (full model: difference = -0.02, $p = 0.94$; reduced model: difference = -0.01, $p = 0.96$).

Discussion

In the absence of randomized controlled data, the role of central lymph node dissection in PTC continues to be debated. Prophylactic level VI lymphadenectomy, which in the cN0 patient has become increasingly popular, is supported by evidence that suggests reduced local recurrence rates (2,10–12) and less potentially hazardous reoperative surgery. Advocates also point to an improved postoperative course as

FIG. 3. Receiver operator curves for original and external validation data sets, and reduced models (excluding site of primary tumor).

defined by a lower serum thyroglobulin (13) and potentially lower doses of radioactive iodine-131 (14,15). Survival benefit, although identified in several studies (16–18), has been difficult to prove, possibly because of the excellent overall prognosis seen in patients with PTC (19).

An alternate approach that many clinicians continue to adopt is a policy of therapeutic lymphadenectomy only. They cite a lack of evidence for the benefit of prophylactic CLND in terms of recurrence and survival (20), as well as the potential increased risks to the patient (21,22). Although many series have shown little or no adverse effect from CLND (23), there is concern that in low-volume centers, rates of permanent hypoparathyroidism and recurrent laryngeal nerve injury might increase if the procedure became the acceptable standard of care.

While upstaging of patients due to the detection of subclinical disease may change treatment (24), the impact of cN1a disease on the decision to use radioactive iodine is most often institutionally dependent (25) and variable.

Therapeutic rather than prophylactic management of the central compartment depends on detection of nodal metastases by clinical and radiological means. In contrast to the lateral neck, ultrasound, computed tomography (CT), and physical examination perform poorly in diagnosing nodal disease in level VI (26,27) due to the anatomical confines.

Given the limited ability to detect level VI nodal metastases clinically, attention might instead be turned to risk stratification, in order to select patients most likely to have locoregional nodal disease. The aim of this study was to develop a nomogram tool able to predict the risk of central compartment lymph node metastases, and thereby guide clinicians in regard to the need for prophylactic lymphadenectomy.

Our study identified central compartment nodal metastases in 42.9% of cases. Of the patients who had concurrent lateral nodes dissected, a 49.7% rate of lateral nodal metastases reflects our practice of therapeutic (rather than prophylactic) lateral neck dissection. The median number of lateral nodes (four per patient) is in keeping with selective node sampling of the medial aspects of levels III and IV in certain patients. Among patients with lymph node metastases, the rate of skip metastases (5.6%) was comparable to work by Roh *et al.* (28), but lower than that of Machens *et al.* (29).

Excluding patients who underwent lateral lymphadenectomy from our model had little or no impact on the significance of patient age ($p < 0.001$), sex ($p = 0.007$), and tumor

Author Disclosure Statement

The authors declare that no competing financial interests exist or have contributed to the production of this manuscript.

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