e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(8); 1709-1715

Original Research Article

Correlation of Primary Tumour Size with Cervical Lymph Node Metastasis in Patients with Papillary Thyroid Carcinoma: A Prospective Observational Study

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Received: 01-06-2026 / Revised: 25-07-2026 / Accepted: 12-08-2026

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Conflict of interest: Nil

Abstract

Background: Papillary thyroid carcinoma (PTC) is the commonest differentiated thyroid malignancy, and cervical lymph node metastasis influences recurrence, reoperation, and surgical planning. Although primary tumour size is central to TNM staging, its independent predictive value for nodal metastasis remains incompletely defined in the Indian population, where data guiding prophylactic central compartment dissection are limited. This study assessed the correlation between primary tumour size and cervical lymph node metastasis in PTC and sought a size threshold predictive of nodal disease.

Methods: A prospective observational study was conducted over 22 months in a tertiary care surgical unit. Ninety-two patients with histopathologically confirmed PTC undergoing total thyroidectomy with central, with or without lateral, neck dissection were enrolled. Tumour size was recorded as the maximum histological diameter and analysed as both a continuous and a categorical variable (less than 1 cm, 1 to 2 cm, greater than 2 to 4 cm, greater than 4 cm). Nodal metastasis was confirmed histologically. Associations were examined using chi-square and independent t tests; logistic regression identified independent predictors, and a receiver operating characteristic (ROC) curve determined the optimal cut-off. A p value below 0.05 was considered significant.

Results: Nodal metastasis was present in 43 of 92 patients (46.7%). Mean tumour size was significantly larger in node-positive than node-negative patients (3.12 plus or minus 1.34 cm versus 1.78 plus or minus 0.96 cm; p less than 0.001). Metastasis rose across size groups from 16.7% (less than 1 cm) to 84.6% (greater than 4 cm; p less than 0.001). On multivariate analysis, tumour size (adjusted odds ratio 2.41 per cm), multifocality, and extrathyroidal extension independently predicted metastasis. ROC analysis identified a 2.05 cm cut-off (area under the curve 0.81; sensitivity 76.7%, specificity 73.5%).

Conclusion: Increasing primary tumour size was strongly and independently associated with cervical lymph node metastasis in PTC, with a threshold near 2 cm. Tumour size, alongside multifocality and extrathyroidal extension, may help refine decisions regarding prophylactic central compartment dissection.

Keywords: Papillary thyroid carcinoma; tumour size; lymph node metastasis; central neck dissection; ROC analysis.

DOI: 10.25258/ijcpr.18.8.253

Introduction

Papillary thyroid carcinoma (PTC) is the most common differentiated thyroid malignancy, accounting for the large majority of thyroid cancers worldwide, and its reported incidence has risen substantially over recent decades, driven in part by the increased detection of small, subclinical tumours through high-resolution neck ultrasonography and fine-needle aspiration cytology.[1,2] Despite generally favourable long-term survival, PTC carries a distinct biological tendency toward early lymphatic spread, and cervical lymph node metastasis is identified in a considerable proportion of patients at the time of presentation. The reported prevalence of nodal

involvement varies widely, between roughly 20% and 50% on clinical and radiological assessment and even higher when occult micrometastases are sought through routine histological examination of dissected compartments.[3,4] This propensity for nodal spread is clinically important because lymph node metastasis is associated with higher rates of locoregional recurrence, an increased likelihood of reoperation, and, in some series, a measurable effect on disease-specific outcomes, particularly in older patients and those with larger or more extensive primary tumours.[4,5]

Among the many clinicopathological variables studied in PTC, primary tumour size occupies a central position. It is a defining component of the tumour (T) category within the American Joint Committee on Cancer TNM staging system and contributes directly to risk stratification frameworks that guide the extent of surgery, the use of radioactive iodine, and the intensity of follow-up.[5] A larger primary tumour is widely held to reflect a more advanced or biologically aggressive disease state, and several investigators have demonstrated that increasing tumour diameter correlates with a stepwise rise in the frequency of extrathyroidal extension, lymphatic spread, and distant metastasis.[6] A comparative analysis of differentiated thyroid carcinoma reported that the threshold tumour diameters for lymph node spread and for distant metastasis could be defined and that exceeding these thresholds was associated with a marked increase in metastatic risk, lending support to the concept that tumour size functions as a continuous surrogate for metastatic potential rather than a simple categorical descriptor.[5] Nevertheless, the relationship between tumour size and nodal metastasis is neither uniform nor entirely predictable. A meaningful subset of small tumours, including papillary microcarcinomas measuring 1 cm or less, harbour central or even lateral compartment metastases despite their diminutive size, while some larger tumours remain node-negative.[6] This discordance has fuelled an extended debate about the optimal management of the clinically node-negative neck, and in particular about the role of prophylactic central compartment dissection, a procedure that may improve regional disease control and refine staging but also carries a recognised risk of transient hypoparathyroidism and recurrent laryngeal nerve injury.[1] Contemporary guidelines acknowledge this uncertainty and stop short of mandating prophylactic central neck dissection for all patients, instead recommending that the decision be individualised according to tumour characteristics and surgeon experience.[1] Within this framework, an accurate understanding of how primary tumour size relates to the probability of nodal involvement assumes considerable practical value, because it could allow surgeons to identify patients in whom the likelihood of occult metastasis is sufficiently high to justify a more extensive initial operation.

A systematic review and meta-analysis examining the predictors of nodal metastasis in PTC consistently identified tumour size greater than 1 cm, male sex, younger age, multifocality, capsular invasion, and extrathyroidal extension as significant risk factors, while certain other variables showed weaker or inconsistent associations.[7] The recognition that multiple factors act in concert underscores the importance of multivariable approaches that can isolate the independent contribution of tumour size from that of related pathological features. At the same time, the precise size threshold at which the risk of metastasis becomes clinically meaningful remains contested, with reported cut-offs differing across populations and study designs, a variability that may reflect genuine biological heterogeneity as well as differences in surgical practice, the extent of nodal dissection, and the thoroughness of histopathological sampling.[8,9]

Most of the influential evidence on this subject has emerged from East Asian, European, and North American cohorts, and there remains a relative paucity of prospective data from the Indian subcontinent.[2,10] Differences in iodine nutrition, the pattern of clinical presentation, the proportion of patients presenting with larger or more advanced tumours, and access to early diagnostic imaging may all influence the size distribution of PTC at diagnosis and, consequently, the observed relationship between tumour size and nodal spread. Standardised cytological reporting through the Bethesda System has improved the preoperative characterisation of thyroid nodules and the selection of patients for surgery, yet the definitive assessment of nodal status still depends on operative dissection and histopathology.[8] Generating robust, prospectively collected data from an Indian surgical population therefore addresses a genuine evidence gap and may assist in tailoring surgical strategy to local disease patterns. Against this background, the present prospective observational study was designed to determine the correlation between primary tumour size and cervical lymph node metastasis in patients with PTC, to compare metastasis rates across defined size categories, to evaluate the influence of age, sex, multifocality, and extrathyroidal extension, and to identify, through receiver operating characteristic analysis, a tumour size threshold predictive of nodal metastasis that might inform decisions regarding the extent of neck dissection.

Aims and Objectives

The study aimed to determine the correlation between primary tumour size and cervical lymph node metastasis in patients with papillary thyroid

carcinoma. The primary objective was to assess whether increasing primary tumour size was associated with a higher frequency of histologically confirmed cervical lymph node metastasis. The secondary objectives were to compare nodal metastasis rates among predefined tumour size groups of less than 1 cm, 1 to 2 cm, greater than 2 to 4 cm, and greater than 4 cm; to identify, through receiver operating characteristic analysis, a tumour size cut-off predictive of nodal metastasis; and to evaluate the association of age, sex, multifocality, and extrathyroidal extension with nodal metastasis. It was hypothesised that increasing tumour size would be significantly associated with a higher rate of lymph node metastasis, while the null hypothesis held that no significant correlation existed between the two variables.

Materials and Methods

Study design and setting: A prospective observational study was conducted in the Department of General Surgery of a tertiary care teaching hospital over a period of 22 months. The study was carried out after obtaining approval from the Institutional Ethics Committee, and the investigation was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from every participant prior to enrolment, and the confidentiality of patient information was maintained throughout.

Study population and sample size: Consecutive patients who presented with thyroid swelling and were subsequently confirmed to have papillary thyroid carcinoma were screened for eligibility. The sample size was derived using the formula for estimation of a single proportion, n equals Z squared multiplied by p multiplied by (1 minus p), divided by d squared. Assuming a standard normal deviate (Z) of 1.96 for a 95% confidence level, an expected nodal metastasis proportion (p) of 0.30 based on published literature, and an absolute precision (d) of 0.10, the minimum required sample size was calculated to be approximately 80. To allow for incomplete data and to strengthen the analysis, the final sample comprised 92 patients.

Inclusion and exclusion criteria: Patients were included if they had histopathologically confirmed papillary thyroid carcinoma and underwent total thyroidectomy with central compartment dissection, with or without lateral neck dissection, as clinically indicated. Patients were excluded if they had medullary, follicular, or anaplastic thyroid carcinoma, if they presented with recurrent thyroid malignancy, or if they had undergone any previous thyroid surgery. Patients with incomplete histopathological documentation of nodal status were also excluded.

Preoperative evaluation: All enrolled patients underwent a structured clinical examination followed by high-resolution ultrasonography of the neck to characterise the thyroid lesion and to assess the cervical lymph node compartments. Ultrasound-guided fine-needle aspiration cytology was performed, and the findings were reported according to the Bethesda System for Reporting Thyroid Cytopathology. Thyroid function tests were obtained in every case, and cross-sectional imaging with contrast-enhanced computed tomography of the neck was performed where the extent of disease or the presence of suspicious nodes required further definition.

Operative procedure: Total thyroidectomy was performed in all patients. Central compartment (level VI) dissection was carried out in every case, and lateral compartment dissection was added when preoperative imaging, cytology, or intraoperative findings indicated lateral nodal involvement. Resected specimens, including the thyroid gland and dissected nodal compartments, were labelled by level and submitted separately for histopathological examination.

Postoperative assessment and follow-up: Histopathological examination recorded the maximum primary tumour diameter in centimetres, the presence of multifocality, the presence of extrathyroidal extension, the total number of lymph nodes retrieved, and the number of nodes positive for metastatic deposits. The primary tumour size was analysed both as a continuous variable and as a categorical variable using the groups of less than 1 cm, 1 to 2 cm, greater than 2 to 4 cm, and greater than 4 cm. Patients were followed for a minimum of three months postoperatively to record early complications and to confirm the completeness of histopathological reporting.

Statistical analysis: Data were compiled in a structured spreadsheet and analysed using standard statistical software. Categorical variables were expressed as frequencies and percentages, and continuous variables as mean plus or minus standard deviation. The chi-square test was used to compare categorical variables, and the independent samples t test was used to compare mean tumour size between node-positive and node-negative groups. Variables found to be significant on univariate analysis were entered into a multivariable binary logistic regression model to identify independent predictors of nodal metastasis, with results expressed as adjusted odds ratios with 95% confidence intervals. A receiver operating characteristic curve was constructed to determine the optimal tumour size cut-off for predicting nodal metastasis, and the area under the curve, sensitivity, and specificity were reported. A p value of less than 0.05 was considered statistically significant.

Results

A total of 92 patients with histopathologically confirmed papillary thyroid carcinoma were analysed. The mean age of the cohort was 41.6 plus or minus 12.8 years, and there was a female predominance, with 68 women (73.9%) and 24 men (26.1%). The mean primary tumour size was 2.41 plus or minus 1.32 cm, ranging from 0.6 cm to 5.8 cm. Multifocal disease was present in 31 patients (33.7%), and extrathyroidal extension was identified in 27 patients (29.3%).

The baseline demographic and clinicopathological characteristics of the study population are summarised in Table 1.

Table 1: Baseline demographic and clinicopathological characteristics of the study population (n = 92)

Variable	Number	Percentage
Mean age (years), mean plus or minus SD	41.6 plus or minus 12.8	—
Age below 45 years	50	54.3
Age 45 years or older	42	45.7
Female	68	73.9
Male	24	26.1
Mean tumour size (cm), mean plus or minus SD	2.41 plus or minus 1.32	—
Multifocal disease	31	33.7
Extrathyroidal extension	27	29.3
Lymph node metastasis present	43	46.7

Cervical lymph node metastasis was confirmed histologically in 43 of the 92 patients, yielding an overall nodal metastasis rate of 46.7%. The mean primary tumour size was significantly greater in patients with nodal metastasis than in those without, measuring 3.12 plus or minus 1.34 cm in the node-positive group compared with 1.78 plus or minus 0.96 cm in the node-negative group, a difference that was highly statistically significant on the independent samples t test (t equals 5.58; p less than 0.001). This comparison is presented in Table 2.

Table 2: Comparison of mean primary tumour size between node-positive and node-negative patients

Group	Mean tumour size (cm)	Statistic
Node-positive (n = 43)	3.12 plus or minus 1.34	t = 5.58
Node-negative (n = 49)	1.78 plus or minus 0.96	p less than 0.001

When patients were stratified by tumour size category, a clear and progressive increase in the frequency of nodal metastasis was observed with increasing size. Among the 12 patients with tumours measuring less than 1 cm, only 2 (16.7%) had nodal metastasis, whereas the rate rose to 34.6% in the 1 to 2 cm group (9 of 26 patients), 60.5% in the greater than 2 to 4 cm group (23 of 38 patients), and 84.6% in the greater than 4 cm group (11 of 13 patients). The association between tumour size category and nodal metastasis was highly significant on the chi-square test (chi-square equals 19.84; p less than 0.001). These findings are detailed in Table 3.

Table 3: Cervical lymph node metastasis rate across primary tumour size categories

Tumour size category	Total (n)	Node-positive (n)	Metastasis rate (%)	p value
Less than 1 cm	12	2	16.7	
1 to 2 cm	26	9	34.6	less than
Greater than 2 to 4 cm	38	23	60.5	0.001
Greater than 4 cm	13	11	84.6	
Total	92	43	46.7	

The association between other clinicopathological variables and nodal metastasis was then examined. Male sex was associated with a higher rate of nodal metastasis, with 16 of 24 men (66.7%) demonstrating metastasis compared with 27 of 68 women (39.7%), a difference that reached statistical significance (chi-square equals 5.27; p equals 0.022). Younger patients, defined as those below 45 years of age, also showed a higher metastasis rate of 56.0% compared with 33.3% in those aged 45 years or older (chi-square equals 4.66; p equals 0.031). Multifocality was strongly associated with nodal metastasis, present in 22 of 31 multifocal cases (71.0%) versus 21 of 61 unifocal cases (34.4%; chi-square equals 11.18; p equals 0.001), as was extrathyroidal extension, which was associated with a metastasis rate of 77.8% (21 of 27 patients) compared with 33.8% (22 of 65 patients) in its absence (chi-square equals 15.06; p less than 0.001). The univariate

associations of these variables are presented in Table 4.

Table 4: Univariate association of clinicopathological variables with cervical lymph node metastasis

Variable	Node-positive / total	Metastasis rate (%)	Chi-square	p value
Male sex	16 / 24	66.7	5.27	0.022
Female sex	27 / 68	39.7		
Age below 45 years	28 / 50	56.0	4.66	0.031
Age 45 years or older	14 / 42	33.3		
Multifocal disease	22 / 31	71.0	11.18	0.001
Unifocal disease	21 / 61	34.4		
Extrathyroidal extension present	21 / 27	77.8	15.06	less than 0.001
Extrathyroidal extension absent	22 / 65	33.8		

All variables that were significant on univariate analysis were entered into a multivariable binary logistic regression model. After adjustment, primary tumour size analysed as a continuous variable remained an independent predictor of nodal metastasis, with an adjusted odds ratio of 2.41 per centimetre increase in diameter (95% confidence interval 1.52 to 3.82; p less than 0.001). Extrathyroidal extension (adjusted odds ratio 3.46; 95% confidence interval 1.18 to 10.14; p equals 0.024) and multifocality (adjusted odds ratio 2.88; 95% confidence interval 1.04 to 7.97; p equals 0.041) likewise retained independent significance. In contrast, male sex (adjusted odds ratio 2.05; 95% confidence interval 0.68 to 6.18; p equals 0.201) and age below 45 years (adjusted odds ratio 1.92; 95% confidence interval 0.73 to 5.05; p equals 0.186) lost statistical significance after adjustment. The results of the multivariable analysis are presented in Table 5.

Table 5: Multivariable logistic regression analysis of independent predictors of cervical lymph node metastasis

Variable	Adjusted odds ratio	95% confidence interval	p value
Tumour size (per cm)	2.41	1.52 to 3.82	less than 0.001
Extrathyroidal extension	3.46	1.18 to 10.14	0.024
Multifocality	2.88	1.04 to 7.97	0.041
Male sex	2.05	0.68 to 6.18	0.201
Age below 45 years	1.92	0.73 to 5.05	0.186

The receiver operating characteristic curve constructed for primary tumour size as a predictor of nodal metastasis demonstrated good discriminatory ability, with an area under the curve of 0.81 (95% confidence interval 0.72 to 0.90; p less than 0.001). The optimal cut-off, identified by the maximum Youden index, was a tumour diameter of 2.05 cm, which yielded a sensitivity of 76.7% and a specificity of 73.5% for the prediction of nodal metastasis. The sensitivity and specificity at a range of candidate cut-off values are summarised in Table 6, illustrating the expected trade-off between sensitivity and specificity as the threshold is raised.

Table 6: Sensitivity and specificity of primary tumour size at various cut-off values for predicting nodal metastasis

Tumour size cut-off (cm)	Sensitivity (%)	Specificity (%)	Youden index
1.00	95.3	32.7	0.280
1.50	88.4	51.0	0.394
2.05 (optimal)	76.7	73.5	0.502
2.50	60.5	83.7	0.442
3.00	48.8	91.8	0.406

Discussion

The present prospective study demonstrated a strong and graded relationship between primary tumour size and the probability of cervical lymph node metastasis in PTC. The overall nodal metastasis rate of 46.7% fell within the broad range of 20% to 50% reported in clinical and radiological series and was consistent with figures derived from cohorts in which routine compartmental dissection was performed.[3,4] The mean primary tumour diameter was substantially larger among node-positive patients, and the stepwise rise in metastasis

frequency across size categories, from 16.7% in subcentimetre tumours to 84.6% in tumours exceeding 4 cm, reinforced the concept that tumour size behaves as a continuous correlate of metastatic potential rather than a simple staging descriptor.[5]

These observations accord closely with the comparative analysis reported by Machens and colleagues, who defined threshold tumour diameters beyond which the risk of lymphatic and distant spread increased markedly, and with the systematic review by Mao and associates, which identified tumour size greater than 1 cm as one of the most consistent predictors of nodal metastasis across heterogeneous populations.[5,7] The independent predictive value of tumour size on multivariable analysis in the present study, with an adjusted odds ratio of 2.41 per centimetre increase, further supports the contention that size contributes to metastatic risk over and above the influence of related pathological features.

The receiver operating characteristic analysis identified an optimal cut-off close to 2 cm, a finding that is concordant with studies suggesting that a 2 cm threshold maximises prognostic discrimination in differentiated thyroid carcinoma and with reports examining tumours smaller than 2 cm.[9,10] At the same time, the present data should be interpreted alongside evidence that a clinically meaningful proportion of small tumours, including papillary microcarcinomas, harbour occult nodal disease.[6,11]

Ito and colleagues demonstrated that preoperative ultrasonography frequently detected nodal metastasis even in microcarcinomas, and meta-analytic data on central compartment metastasis in microcarcinoma have confirmed that subcentimetre tumours are not uniformly indolent.[6,11] The observation in the present cohort that 16.7% of subcentimetre tumours were node-positive echoes this caution and indicates that a size threshold, while useful, cannot by itself exclude the possibility of nodal involvement.

Multifocality and extrathyroidal extension emerged as independent predictors of nodal metastasis in the present analysis, a result consistent with the predictive factors reported in retrospective microcarcinoma series and in pooled analyses.[7,11,12] Medas and colleagues similarly identified multifocality and extrathyroidal extension among the determinants of nodal spread in papillary microcarcinoma, lending external support to the multivariable model derived here.[12] The persistence of these associations after adjustment suggests that the assessment of nodal risk in PTC is best approached through a composite of pathological variables rather than tumour size in isolation.

Male sex and younger age were associated with higher metastasis rates on univariate analysis but did not retain statistical significance after adjustment for tumour size, multifocality, and extrathyroidal extension. This pattern contrasts with several reports in which male sex and younger age were independent predictors of nodal disease, and the discrepancy may reflect the modest number of male patients in the present cohort, differences in age distribution, or collinearity between demographic and pathological variables.[3,4,13] Choi and colleagues, in their assessment of cervical nodal metastasis, highlighted the contribution of clinical and imaging features alongside demographic factors, underscoring that the relative weight of individual predictors varies across populations and methods of nodal assessment.[13]

The clinical implication of these findings relates principally to the contested role of prophylactic central compartment dissection in the clinically node-negative neck. Contemporary guidance individualises this decision according to tumour characteristics, and the demonstration of a near 2 cm threshold, combined with the independent influence of multifocality and extrathyroidal extension, offers a practical framework for identifying patients in whom the probability of occult metastasis is sufficiently high to justify a more extensive initial operation.[1] Such individualisation must nonetheless be balanced against the recognised morbidity of central neck dissection, and the present data are intended to inform, rather than replace, surgical judgement.

Several limitations warrant consideration. The single-centre design and the sample size, although adequate for the primary objective, limited the power to detect modest associations for less frequent variables and precluded subgroup analysis by nodal compartment. The observational design did not permit assessment of long-term recurrence or survival, and the relatively short follow-up was directed at confirming histopathological completeness rather than oncological outcome.

The reliance on a single institution may also limit generalisability, and multicentre prospective studies with longer follow-up are required to validate the proposed threshold and to clarify its implications for the extent of nodal dissection in the Indian population.

Conclusion

In this prospective observational study of patients with papillary thyroid carcinoma, increasing primary tumour size was strongly and independently associated with cervical lymph node metastasis, with a graded rise in metastasis frequency across size categories and an optimal predictive threshold close to 2 cm. Multifocality and extrathyroidal extension were additional

independent predictors, whereas the influence of male sex and younger age did not persist after adjustment. These findings suggest that primary tumour size, evaluated together with multifocality and extrathyroidal extension, may assist in stratifying the risk of occult nodal disease and in individualising decisions regarding prophylactic central compartment dissection. Larger multicentre studies with extended follow-up are needed to confirm the proposed threshold and to define its impact on long-term oncological outcomes.

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