

Clinicopathological Profile, Histopathological Spectrum, Prevalence, and Factors Associated with Malignancy in Solitary Thyroid Nodules

Resham Ali, Syed Shafqatullah, Ghansham Rawlani, Amna Farid, Raja Jawad Ali, Sarkhail Ahmed Sayar

ABSTRACT

Objective: To determine the frequency and histopathological spectrum of malignancy among surgically treated solitary thyroid nodules (STNs) and assess associated clinical, sonographic, and cytological features.

Study Design & Setting: Descriptive cross-sectional study. Department of General Surgery, Surgical Ward 2, Jinnah Postgraduate Medical Centre (JPMC), Karachi, from 25 August 2025 to 25 February 2026.

Methodology: Fifty-eight consecutive patients aged 16–70 years with STNs who underwent thyroid surgery were included. Clinical and ultrasonographic findings, preoperative Bethesda cytology, and final histopathology were recorded. Categorical variables were analysed using Fisher's exact or Fisher-Freeman-Halton exact tests, as appropriate. A p-value < 0.05 was considered significant. Data were analysed using SPSS version 26.

Results: Of 58 patients, 45 (77.6%) were female and 13 (22.4%) were male; mean age was 43.24 ± 16.46 years. Malignancy was found in 22 (37.9%) patients. Papillary carcinoma was most common (72.7%), followed by follicular (18.2%), medullary (4.5%), and poorly differentiated carcinoma (4.5%). Female sex was associated with malignancy ($p = 0.001$); microcalcifications, irregular margins, and Bethesda category were also associated (all $p < 0.001$). Malignancy occurred in 6/17 (35.3%) Bethesda IV nodules and all Bethesda V and VI nodules.

Conclusion: Malignancy was found in 22/58 (37.9%) surgically treated STNs. Microcalcifications, irregular margins, and higher Bethesda categories were strongly associated with malignant histopathology. Female sex was an observed association and should be interpreted cautiously.

Keywords: Solitary Thyroid Nodule; Thyroid Malignancy; Papillary Carcinoma; Bethesda System

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Resham Ali

Post Graduate, Department of General Surgery,
Jinnah Postgraduate Medical Centre (JPMC), Karachi
Email: reshamali20@gmail.com

Syed Shafqatullah

Head, Department of General Surgery,
Jinnah Postgraduate Medical Centre (JPMC), Karachi
Email: drsyedshafqat@yahoo.com

Ghansham Rawlani

Assistant Professor, Department of General Surgery,
Jinnah Postgraduate Medical Centre (JPMC), Karachi
Email: drsham84@hotmail.com

Amna Farid

Post Graduate, Department of General Surgery,
Jinnah Postgraduate Medical Centre (JPMC), Karachi
Email: amnafarid222@gmail.com

Raja Jawad Ali

Post Graduate, Department of General Surgery,
Jinnah Postgraduate Medical Centre (JPMC), Karachi
Email: drrajawad@gmail.com

Sarkhail Ahmed Sayar

Post Graduate, Department of General Surgery,
Jinnah Postgraduate Medical Centre (JPMC), Karachi
Email: sarkhail.ahmed123@gmail.com

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INTRODUCTION

Although thyroid nodules are relatively common, a large majority are clinically silent but disease burden is high both clinically and financially, leading to inappropriate investigations and surgery, and to appropriate risk stratification for timely diagnosis of possible thyroid malignancy.¹⁻³ Most thyroid nodules are non-cancerous but those with malignant thyroid disease pose a significant diagnostic challenge. In unselected patients, the incidence of malignancy is reported the proportion of malignancy is reported to be in the range of 5–15% and is significantly increased in patients referred for surgery due to referral and selection bias. In the past, solitary thyroid nodules were considered more likely to be malignant than a multinodular goitre but based on current evidence, the risk of malignancy depends more on the individual characteristics of each sonographically and reported cytologically abnormal thyroid nodule.⁴⁻⁶ With this change, management was changed from solely clinical examination to evidence-based risk stratification using standardized imaging and cytology reporting systems.⁷

Thyroid disease has been steadily rampant for the last three

decades, with thyroid cancer as one of the fastest-growing malignancies globally, especially in women of reproductive age. Population-based screening studies using high-resolution ultrasonography have shown rates of up to 50–60% of adults had at least one thyroid nodule, and only a small proportion of these even came to clinical attention.¹ The central clinical question has now thus become the ability to reliably identify thyroid nodules with significant risk of malignancy and those suitable for surgical intervention.⁷ This has broad public health implications in Pakistan that is a low to middle income country, where diagnostic resources and follow up infrastructure were unevenly distributed and access to specialised thyroid surgery is still not widespread.

FNA is still the gold standard for determining the preoperative diagnosis and is reported universally in line with the Bethesda System for Reporting Thyroid Cytopathology (BSBT). The Bethesda 2023 update offers easy-to-follow discrete diagnostic categories and risk for malignancy, as well as suggested management options. The Bethesda categories II and VI are usually associated with the ability to make easy and efficient clinical decisions regarding subsequent clinical assessment. The indeterminate categories III and IV remain therapeutic nightmares due to the range of risk for malignancy. In developed countries, molecular diagnostics have helped risk-stratify and saved unnecessary surgery for indeterminate nodules. However, this testing is still costly and not readily available in many low and middle-income countries, such as Pakistan. Thus, clinical evaluation and ultrasonographic and Bethesda cytological data, remain the primary factors for surgical decision-making in resource-limited clinical care settings.^{8,9}

Many tertiary referral centres including the Jinnah Postgraduate Medical Centre (JPMC), Karachi, have reported a higher incidence of malignancy a higher frequency of malignancy among the surgically treated solitary thyroid nodules, presumably a reflection of the referral system, the selection of cases for surgery, different iodine nutrition, and population differences.¹⁰⁻¹² Although several regions have been the focus of study, there is still limited local evidence to support correlation of clinical presentation, ultrasonographic characteristics, Bethesda cytology, and final histopathology. Such data are critical in the development of pre-counselling for surgery, narrowing down patient selection, more effective utilization of resources, and also in the development of an informed surgical management strategy, of course, in resource-deprived healthcare settings. Most published series in the Pakistani context report the experience of single institutions, use a variable definition, have non-uniform cytology reporting practices, and fail to adhere to consistent reporting standards, such as a standard scoring system like the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS). This heterogeneity has made it challenging to generate risk categorisation specific to each thyroid nodule

and has, combined with this variability, meant that the threshold for intervention to treat a thyroid nodule varies between centres. Moreover, factors which are the independent predictors of malignancy in Pakistani patients with thyroid-alone surgery are not well delineated in preoperative clinical, sonographic or cytological parameters. To alleviate this evidence gap will be vital to rationalising the referral pathway to surgery, maximising theatre utilisation and minimising avoidable morbidity and lifelong requirement for levothyroxine in those patients who turn out to have benign disease.

Therefore, the present study was conducted to determine the frequency and histopathological spectrum of malignancy among surgically managed solitary thyroid nodules at Jinnah Postgraduate Medical Centre, Karachi, and to evaluate the association of clinical, sonographic, and cytological variables with malignant histopathology. The findings are expected to provide locally relevant evidence that may improve preoperative risk stratification and guide surgical decision-making in patients with solitary thyroid nodules. Therefore, a comprehensive institutional audit of the clinicopathological spectrum of surgical patients with solitary thyroid nodules and assessment of the prognostic factors for malignancy before surgery is appropriate and of clinical significance. Such audits produce data about practice that can be used to develop local guidelines for practice, to drive quality improvement processes and to permit meaningful comparisons to be made with local and international series.

METHODOLOGYS

This is a descriptive cross-sectional study in Surgical Ward 2 of a tertiary care teaching hospital in the public sector (Jinnah Postgraduate Medical Centre). Research was carried out for six months. The study design is prospective because data will be collected from 25 August, 2025 until 25 February 2026. The study was approved by the Institutional Review Board of JPMC with IRB#F.2-81/2025-GENL/413/JPMC dated 22 August 2025. All participants gave their written informed consent. This descriptive cross-sectional study was conducted in Surgical Ward 2, Jinnah Postgraduate Medical Centre, a public-sector tertiary care teaching hospital, over six months from 25 August 2025 to 25 February 2026. The study was approved by the Institutional Review Board of JPMC (IRB No. F.2-81/2025-GENL/413/JPMC; 22 August 2025). All participants provided written informed consent.

Inclusion criteria were either male or female patients aged 16–70 years clinically and ultrasonographically diagnosed with solitary thyroid nodules and who underwent surgery on the thyroid gland during the study period. The inclusion criteria were clinically and ultrasonographically confirmed solitary thyroid nodules in patients of either sex aged 16–70 years who were receiving thyroid surgery during the study period. Multinodular goitre, previous thyroid malignancy, recurrent thyroid disease, previous thyroid surgery, pregnancy,

or refusal of written informed consent were excluded. Patients of either sex aged 16–70 years with a clinically and ultrasonographically confirmed solitary thyroid nodule who underwent thyroid surgery during the study period were included. Patients with multinodular goitre, previous thyroid malignancy, recurrent thyroid disease, previous thyroid surgery, pregnancy, or refusal to provide written informed consent were excluded. A minimum sample size of 54 was determined using the calculation formula for the single proportion used by WHO, expecting 27% of the surgical series in Pakistan to be malignant; absolute margin of error of +12%, and confidence level of 95%. Eligible patients were consecutively sampled using non-probability sampling which included 58 consecutive patients.

Patients were evaluated clinically, with data for age, gender, location, duration, degree of swelling, associated pain, relevant symptoms (dysphagia, dyspnoea and hoarseness), cervical lymphadenopathy, family history of thyroid cancer, and a history of prior irradiation of the neck. A consultant radiologist performed the sonographic evaluation using a linear-array ultrasound probe (7 – 12 MHz). The features documented were site (right lobe, left lobe and isthmus), maximum diameter of nodules, nodule echogenicity, the presence or absence of micrometastases/microcalcifications, nodule margin (regular or irregular), nodule shape (taller-than-wide versus wider-than-tall) and presence of suspicious cervical lymph nodes. Each of the patients had ultrasound-guided fine needle aspiration which was reported pre-operatively using the Bethesda System for Reporting Thyroid Cytopathology (BSTC) categories (I – VI).⁸ The surgical procedure was hemithyroidectomy or total thyroidectomy, depending on the size of the nodules, sonographic and cytological risk category, and patient preference, and in accordance with current international guidelines.^{13,14} For Bethesda II and III nodules, surgery was undertaken for clinical indications including large nodule size, pressure or compressive symptoms, concerning sonographic features, or patient preference. The main outcome was the presence of malignancy as determined by formal histopathological evaluation of the excised specimen, which served as the reference standard. Malignant lesions were additionally distinguished into papillary, follicular, medullary, or poorly differentiated thyroid carcinoma according to classic histological characteristics.

Data analysis was done using SPSS V.26 statistical software. Normal quantitative data were presented as mean and standard deviation and non-normal qualitative data were represented as frequencies and percentages. The association between categorical clinical, sonographic, and cytological variables was evaluated between the benign and malignant groups by the chi-square test. Amid the counts found to be below five, Fisher's exact test was used. A p-value of < 0.05 was defined as statistically significant and actual p-values were reported for each comparison. Data were analysed using SPSS

version 26. Quantitative variables were summarised as mean and standard deviation when approximately normally distributed or as median and range otherwise; categorical variables were presented as frequencies and percentages. Associations between categorical clinical, sonographic, and cytological variables and histopathology were assessed using exact tests because several cells had small or zero expected counts. Fisher's exact test was used for 2 × 2 tables, and the Fisher-Freeman-Halton exact test was used for the Bethesda II–VI distribution. A p-value < 0.05 was considered statistically significant. Operational definitions were standardised prior to data collection to ensure consistency. A solitary thyroid nodule was defined as a single-focally defined lesion in a normal-appearing gland with no other nodules over 5 mm diameter identified on the high-resolution ultrasound exam.¹⁴ Microcalcifications were defined as punctate echogenic foci smaller than 1 mm that did not show acoustic shadowing.⁴ Irregular margins were noted when the margins of the nodule were ill-defined, lobulated, or infiltrative, rather than smoothly circumscribed. All fine needle aspiration specimens were classified in accordance with the Bethesda System for Reporting Thyroid Cytopathology,⁷ and all histopathology specimens were reviewed by consultant histopathologists unaware of the fine needle aspiration biopsy results, and any conflicting reports were re-reviewed and confirmed. The participants' confidentiality was protected during the study period, and the patient data was reported anonymously, assigning unique study identifiers instead of the individual identities on the data collection form.

RESULTS

A total of 58 patients were included in the study with solitary nodular goitres who underwent surgery. The mean age was 43 with a standard deviation (SD) of 16.46 (range 16–70 years). Most of the participants (45, 77.6%) were female. There was an imbalance of 3.5 females for every male. Of all who participated in this study, 25 (43.1%) participants were from urban areas and 56.9% from rural areas. 39.7% of the nodules were reported on the left lobe; 37.9% were on the right lobe; and 22.4% of the nodules were on the isthmus. 41.4% of participants complained of pain and cervical lymphadenopathy was clinically found in 15 (25.9%) of the participants. 43 reported pressure symptoms (Table I1).

The median period of symptoms was 18 months, with, at the longest, 7 years of symptoms. The family history of thyroid disease was reported by 6 (10.3%) patients, and external neck irradiation was reported in 2 (3.4%) patients who experienced a history of prior neck irradiation. Hoarseness of voice was reported by 5 (8.6%) patients, dysphagia by 12 (20.7%), and dyspnoea by 4 (6.9%). Among the 43 patients with pressure symptoms, hoarseness was reported by 16 (37.2%), dysphagia by 14 (32.6%), and dyspnoea by 13 (30.2%). At the time of surgery, there was

Table 1: Demographic and clinical characteristics of the study population (n = 58)

Variable	Category	n (%)
Age (years), mean $\pm$ SD	Range 16–70	43.24 $\pm$ 16.46
Gender	Female	45 (77.6)
	Male	13 (22.4)
Residence	Urban	25 (43.1)
	Rural	33 (56.9)
Site of nodule	Right lobe	22 (37.9)
	Left lobe	23 (39.7)
	Isthmus	13 (22.4)
Pain	Present	24 (41.4)
	Absent	34 (58.6)
Pressure symptoms (n = 43)	Hoarseness	16 (37.2)
	Dysphagia	14 (32.6)
	Dyspnoea	13 (30.2)
Cervical lymphadenopathy	Present	15 (25.9)
	Absent	43 (74.1)

Table 2: Sonographic features of solitary thyroid nodules (n = 58)

Feature	Category	n (%)
Echogenicity	Hyperechoic	22 (37.9)
	Hypoechoic	20 (34.5)
	Isoechoic	16 (27.6)
Microcalcifications	Present	34 (58.6)
	Absent	24 (41.4)
Margin	Regular	36 (62.1)
	Irregular	22 (37.9)
Shape	Wider-than-tall	48 (82.8)
	Taller-than-wide	10 (17.2)
Suspicious cervical nodes	Present	15 (25.9)
	Absent	43 (74.1)

Table 3: Pre-operative Bethesda category and final histopathological outcome (n = 58)

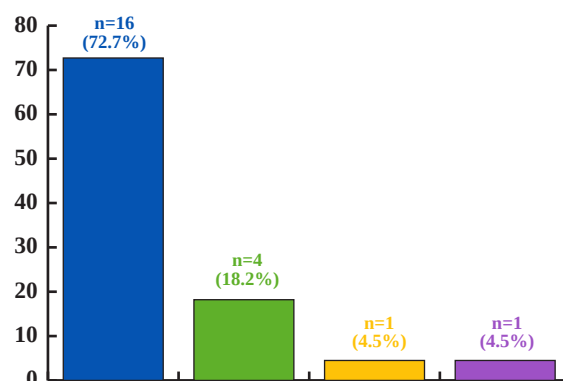
Bethesda category	Total n	Benign n (%)	Malignant n (%)	Malignancy frequency (%)
II (Benign)	11	11 (100.0)	0 (0.0)	0.0
III (AUS/FLUS)	14	14 (100.0)	0 (0.0)	0.0
IV (FN/SFN)	17	11 (64.7)	6 (35.3)	35.3
V (Suspicious)	7	0 (0.0)	7 (100.0)	100.0
VI (Malignant)	9	0 (0.0)	9 (100.0)	100.0
Total	58	36 (62.1)	22 (37.9)	37.9

Table 4: Comparison of clinical, sonographic and cytological variables between benign and malignant nodules (n = 58)

Variable	Benign (n = 36)	Malignant (n = 22)	Exact test	p-value
Female gender, n (%)	23 (63.9)	22 (100.0)	Fisher's exact	0.001*
Microcalcifications present, n (%)	12 (33.3)	22 (100.0)	Fisher's exact	<0.001*
Irregular margin, n (%)	0 (0.0)	22 (100.0)	Fisher's exact	<0.001*
Bethesda V–VI, n (%)	0 (0.0)	16 (72.7)	Fisher's exact	<0.001*

*Statistically significant ($p < 0.05$). Exact tests were used because small or zero expected cell counts occurred

Figure 1: Distribution of histological subtypes among malignant solitary thyroid nodules (n = 22)



no clinically apparent evidence of distant metastasis in any of the patients. On ultrasound, 37.9% (22) of the nodules were hyperechoic, 34.5% (20) hypoechoic, and 27.6% (16) isoechoic. Ten nodules (17.2%) had a shape other than being taller than wide. Of the patients surveyed ($n = 58$) suspicious cervical lymph nodes on ultrasound examination were noted in 15 (25.9%) (Table II). The mean diameter of maximum nodules on ultrasound was 3.4 ± 1.6 cm, ranging from 1.2 to 7.8 cm. At the time of surgery, the size of 34 (58.6%) nodules was larger than 3 cm. FNAC distribution according to the Bethesda category was similar to that listed in Table III3. While, hemithyroidectomy and total thyroidectomy were performed with the same frequency in 29 (50.0%) patients.

The results of bivariate analysis gave a significant association between female gender and malignant tumors. All 22 cancers were found in females, whereas none of the 13 males had malignant tumors ($\chi^2 = 10.240$, $p = 0.001$). This association was even greater for sonographic microcalcifications. All malignancies (22) demonstrated microcalcifications, as opposed to 33.3% (12 of 36) of the benign nodules ($\chi^2 = 25.020$, $p < 0.001$). Irregular margins completely separated the two groups: all 22 malignant nodules had irregular margins, whereas all 36 benign nodules had regular margins ($\chi^2 = 58.000$, $p < 0.001$). Bivariate analysis showed an association between female sex and malignant histopathology. All 22 cancers occurred in females, whereas none of the 13 males had malignant histopathology (Fisher's exact $p = 0.001$). All 22 malignant nodules had microcalcifications, compared with 12 of 36 (33.3%) benign nodules (Fisher's exact $p < 0.001$). Irregular margins completely separated the groups: all 22 malignant nodules had irregular margins, whereas all 36 benign nodules had regular margins (Fisher's exact $p < 0.001$). Preoperative Bethesda category was also highly correlated with Malignancy ($\chi^2 = 41.510$, $p < 0.001$). The results of all of the revealed Bethesda II (0/11) and III (0/14) nodules were non-malignant. All of the Bethesda V (7/7) and Bethesda VI (9/9) cases were found to be present as malignant cases on histopathology, with 35.3% (6/17) malignancy rate encountered in the Bethesda IV cases. (See Table III). Clinical, sonographic, and cytological variables are presented in detail, comparing the benign and malignant groups, in Table IV. Preoperative Bethesda category was associated with malignant histopathology (Fisher-Freeman-Halton exact $p < 0.001$). All Bethesda II (0/11) and III (0/14) nodules were benign. Malignancy was found in 6/17 (35.3%) Bethesda IV nodules and in all Bethesda V (7/7) and VI (9/9) nodules (Table III3). Clinical, sonographic, and cytological variables are compared between the benign and malignant groups in Table IV4.

Slightly more interesting is how many nodules were found to be malignant when split by nodule size, with 8 of 24 (33.3%) being malignant in nodules ≤ 3 cm and 14 of 34 (41.2%) of nodules > 3 cm being malignant, but this wasn't

significant ($p = 0.55$). There was no significant relationship detected between patient age and malignancy, rural vs city residence, laterality, or duration of symptoms. There were 6 (10.3%) postoperative complications in the series: transient hypocalcaemia (4 patients) and transient recurrent laryngeal nerve palsy (2 patients), all of which resolved by six weeks after surgery. Among the 22 malignant nodules, papillary carcinoma was the most common subtype (16/22, 72.7%), followed by follicular carcinoma (4/22, 18.2%), medullary carcinoma (1/22, 4.5%), and poorly differentiated carcinoma (1/22, 4.5%) (Figure 2).

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Authors Contribution:

Resham Ali: Concept, study design, data collection, manuscript writing
Syed Shafqatullah: Supervision Manuscript review
Ghansham Rawlani: Data Collection
Amna Farid: Data Collection
Raja Jawad Ali: Data Collection
Sarkhail Ahmed Sayar: Data Collection

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