Evaluation of Risk Factors for Malignancy in A Solitary Thyroid Nodule

Dr. Fawzi Salah Fawzi and Rami Kamal Atiya Morcos

General Surgery Department, Faculty of Medicine - Ain Shams University, Cairo, Egypt
ramikamal1@live.com

Abstact: The incidence of malignancy in STNs is quite significant and it is not very low as was thought before. Thyroid cancer may be less frequent in MNG compared to STNs. No significant increase in the rate of carcinoma was observed in patients with STNs. Multinodularity does not increase the risk of thyroid malignancy. However, patients with MNG who develop PTC are at an increased risk of cancer multifocality. STNs with suspicious US criteria can be evaluated by elastography that seems to be a useful addition for the assessment of such indeterminate nodules. Taking individual risk factors in isolation is **not** always reliable. Using a predictive model, one can anticipate a patient's risk of malignancy when the diagnosis is unclear. Nodule size does not appear to be a reliable parameter to improve the clinical management of a nodular goiter because of a high variability between size of nodular area and tumor diameter. Clinical examination is not useful in assessing malignancy risk, as corroborated by previous studies. FNA is sensitive in clinical suspicion of PTC, according to our results it should be complemented with extemporaneous biopsy due to its higher Specificity. STNs should be investigated thoroughly with a high index of suspicion because there is a high probability of malignancy, more than 30%. US-detected thyroid calcifications are strongly associated with malignancy, especially in certain groups, such as young patients or patients with a STN. With age, the prevalence of clinically relevant STNs increases, whereas the risk that such nodules are malignant decreases. TSH alone is not as useful as US features in deciding whether or not to perform FNA in patients with STNs. FNAC is a simple, easy-to-perform, cost-effective, and easily-repeated procedure for the diagnosis of thyroid cancer. The overall prevalence of thyroid carcinoma in this study population with STNs was 12%. US characteristics are extremely important in evaluating STNs. Radiological evaluation of lesions for the differentiation of benign versus malignant nature is important because unnecessary surgical procedures may lead to complications. FNAC should be performed on **ALL** STNs classified as positive, regardless of palpability. It is concluded from the study that a remarkable proportion of STNs (12%) was malignant. **C**linical, **L**aboratory, and **U**ltrasound features of STNs can be used as predictors of malignancy in children. Although none has diagnostic accuracy as high as that of FNA. While malignancy is associated with positive family history of thyroid cancer and hypoechoic lesions, palpable lymphadenopathy had the greatest risk. There are significant predictors of malignancy in STNs such as: Male gender, Solitary nodules, Size between 2-4 cm, Microcalcifications, Hypoechogenic pattern, Solid pattern, Ill-defined edges and Increased intranodular vascularity. This study concluded female predominance was observed, peak incidence was in the age group 31-50 years. Most common presenting complaint was painless neck swelling. The management of a STN remains a clinical challenge despite guidelines. Clinically, STNs should be investigated thoroughly with a high index of suspicion because there is at least a 10–20% probability of malignancy.
[Fawzi Salah Fawzi and Rami Kamal Atiya Morcos. **Evaluation of Risk Factors for Malignancy in A Solitary Thyroid Nodule.** *Nat Sci* 2019;17(6):91-99]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 12. doi:10.7537/marsnsj170619.12.

Keywords: Evaluation; Risk; Factor; Malignancy; solitary Tudate Thyroid; Nodule

1. Introduction

Enlargements of the thyroid gland include a variety of disorders such as the endemic goiter of iodine deficiency, Primary hyperthyroidism (Graves' disease), STNs, MNGs, several varieties of thyroiditis (acute, subacute, and chronic), and thyroid neoplasms either benign or frank malignancies **(Lawrence and Kaplan, 2002).**

The differential diagnosis of an apparent thyroid nodule includes thyroidal and non-thyroidal conditions. Subacute thyroiditis and chronic lymphocytic thyroiditis may result in a nodular appearance; in rare cases, infiltrative disorders (e.g., hemochromatosis) or a metastatic tumor, parathyroid cyst, lipoma, or paraganglioma can mimic a thyroid nodule. **(Burman and Wartofsky, 2015).**

A proper history of the present illness represents an important part of the clinical assessment. This should be targeted to search for risk factors for thyroid cancer and other useful information that would help to formulate a diagnosis and start a management strategy. Special investigations are required in suspected cases of familial disease such as familial MTC, MEN II, familial PTC, FAP, Cowden Disease, Gardner's Syndrome and Carney's Syndrome **(Galatà and Schulte, 2014).**

Thyroid function testing, including serum TSH measurement, should be performed to identify

underlying thyroid dysfunction but not to differentiate benign from malignant nodules **(Carling and Udelsman, 2014).**

Thyroid ultrasound is the first-line tool for the evaluation of patients with nodular thyroid disease. Evidence-based guidelines recommend thyroid ultrasound for all patients suspected of having thyroid nodules by either physical examination or another imaging study **(Jameson et al., 2017).**

Thyroid FNA has high sensitivity and specificity in the diagnosis of papillary thyroid carcinoma, as well as other thyroid malignancies, including medullary and anaplastic thyroid carcinoma. The sensitivity, specificity, and accuracy of thyroid FNAC are significantly improved when FNAC is performed under ultrasound guidance **(Ogilvie et al., 2012).**

The incidence of thyroid cancer continues to rise worldwide, mostly as a result of increased use of diagnostic imaging modalities and surveillance tools **(Cabanillas et al., 2016).**

Medical and/or surgical management strategies of the thyroid nodules should be guided by clinical data together with the results of ultrasound evaluation and FNAC analysis if appropriate **(Gharib et al., 2016).**

Aim of the Work

The aim of this study is to evaluate the predictivity of different preoperative clinical findings compared to postoperative histopathological data of malignancy in patients presenting with Solitary Thyroid Nodules (STNs).

2. Patients and Methods

This study is a prospective study to evaluate the predictivity of different preoperative clinical findings compared to postoperative histopathological data of malignancy in **25** patients with clinically-palpable STNs presenting to the outpatient clinics in El-Demerdash Hospital from July 2018 to December 2018.

Selected patients had clinically-palpable STNs who succeeded to fulfill the inclusion criteria set for the study. Patients presenting with STNs and fulfilling the inclusion criteria will be randomly selected, informed, included, categorized and recorded for demographic variables.

❖ **Ethical Considerations:** This study was conducted according to the standards approved by the Ain Shams University's Research Ethics Committee. All participants signed the informed consent after full explanation of the study details.

**** Inclusion Criteria:**

(1) Age: 10 – 70 years old.

(2) Gender: Both genders.

(3) Patients presenting with STN arising from any lobe of the thyroid selected by clinical palpation.

**** Exclusion Criteria:**

(1) Patients with diffuse thyroid swelling.

(2) Patients with toxic manifestations and/or MNGs clinically.

(3) Patients with history of any type of thyroid surgery (lobectomy or total thyroidectomy).

❖ **The selected patients were subjected to some or all of the following tools and/or procedures.**

(A) Clinical Evaluation: This includes a detailed history taking including a full range of the patient's symptomatology, history of head and neck irradiation, history of childhood malignancy, history of thyroid medication and family history for endocrine disorders in general and thyroid diseases and malignancy specifically. It also includes physical examination including both general examination for signs of any thyroid functions abnormality and local examination of the neck region including the thyroid compartment and lymph node groups of the neck bilaterally.

(B) Laboratory Evaluation: Serum TSH, Free T^3 and T^4were routinely estimated in **all** participants to confirm and document that all patients are in the euthyroid state to begin with. Patients exhibiting thyroid hyperfunction or hypofunction were excluded from the study.

(C) Thyroid Ultrasound: Thyroid ultrasound was used **extensively** in this study for many purposes, e.g. to confirm that the thyroid swelling is actually solitary or only a part of a MNG. It was used to assess the status of the nodule whether solid, cystic or mixed. It was also used to guide in US-guided FNAC using both the longitudinal and transverse probe techniques. **Only** patients with true STNs confirmed by US were selected to participate in this study.

(D) Thyroid Scintigraphy: Isotope scanning was **not** a part of the routine assessment for patients in this study. It was used in some cases to evaluate the functional status of the nodule.

(E) Fine-Needle Aspiration Cytology: FNAC is considered the cornerstone diagnostic and/or evaluation tool in this study. The cytology was carried out by cytopathologists expert in performing and explaining thyroid cytology. The puncture technique consists of the following steps:

1. Local disinfection of the puncture area with povidone iodine.
2. Location of the suspected nodule by palpation. It was guided by ultrasound using the "Free-hand" technique.
3. Injection of the local anesthesia.
4. Puncture with a Cameco syringe holder using 20-ml disposable syringes and 22-gauge needles.
5. Suction was applied while the puncture was moved in the nodule to mobilize cell material.

6. Once the aspirate had been obtained, aspiration was stopped and the needle is removed.

After aspiration a dry spread of the material was examined using May-Grünwald–Giemsa staining (Diff-Quick® rapid variant). In cases which a papillary carcinoma was suspected, Hematoxylin–Eosin and/or Papanicolaou staining was used.

The Cytological Diagnosis was performed based upon the BETHESDA Classification System: (Haugen et al., 2016)

1. Inadequate/Unsatisfactory: Smear with very few follicular cells and no colloid.

2. Benign or Colloid: Smear with a large amount of colloid but with few or no small-sized isolated follicular cells.

3. Indeterminate Nodules (FLUS/AUS or FN/SFN):

- Follicular proliferation: Smear with minimal or no colloid, with a hematic background and a major predominance of follicular cells measuring 2–3 times more than usual arranged in follicular structures or leaves.
- Hürthle cell proliferation: follicular proliferation with Hürthle or oncocytic cells.

4. Suggestive of Malignancy and/or Malignant: This category is subdivided into four groups as follows,

A. Papillary: Cells with a metaplastic appearance or formation of papillae with connective axes with typical nuclear alterations and occasionally the presence of Psammoma bodies.

B. Follicular: Follicular, aciniform or microfollicular cells, with large nuclear irregularities, and the presence of prominent nucleoli.

C. Medullary: Plasmocytoid appearance of the cells generally isolated and intermingling with the amyloid.

D. Anaplastic/Undifferentiated: Pleomorphic cells with an anaplastic appearance and multinucleated.

- **In this study, Inadequate and/or Indeterminate FNAC results were excluded.**

❖ **Study Interventions:** All patients were subjected to further surgical intervention whether hemithyroidectomy, subtotal or total thyroidectomy and then evaluated for definitive diagnosis postoperatively. Histopathological Examination is the Golden Standard in this study, which all preoperative input from clinical and workup data was compared to.

Data Management and Statistical Analysis of the Study:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical Package for Social Science (SPSS version 15.0 for windows; SPSS Inc., Chicago, IL, 2001). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

I. Descriptive Statistics:

- Mean.
- Standard Deviation (± SD).
- Minimum and Maximum Values for numerical data.
- Frequency and Percentage of non-numerical data.

II. Analytical Statistics:

1. **The Independent Samples t-Test:** it was used to assess the statistical significance of the difference between two study group means.
2. **Chi-Square Test:** it was used to examine the relationship between two qualitative variables.
3. **Fisher's Exact Chi-Square Test:** this test is computed when a table that does not result from missing rows or columns in a larger table has a cell with an expected frequency of less than 5.
4. **Kappa Test:** Cohen's Kappa coefficient measures the agreement between the evaluations of two raters when both are rating the same object. A value of **"1"** indicates perfect agreement. A value of **"0"** indicates that agreement is no better than a chance.

❖ **P. Value: The Level of Significance**

* P. > 0.05 means **N**on-**S**ignificant (NS).
* P. ≤ 0.05 means **S**ignificant (S).
* P. ≤ 0.01 means **H**ighly **S**ignificant (HS).

3. Results

This study is a prospective cross-sectional study to evaluate the predictivity of different preoperative clinical findings compared to postoperative histopathological data of malignancy in patients with clinically-palpable STNs presenting to outpatient clinics in El-Demerdash Hospital from July 2018 to December 2018.

A total of 25 patients were available for the study.

- The overall mean age of the study cohort was 42.5±9 years with an age range from 22 to 63 years (N= 25).
- The majority of the patients were females 92% (N= 23).
- All patients presented with a unilateral neck swelling (either painless or painful) that move up and dawn with deglutition. No pressure symptoms or symptoms of thyrotoxicosis were present.
- The majority of patients presented with painless neck swelling 92% (N= 23). All patients had preoperative US to confirm that the nodule is actually a true STN followed later by US-guided FNA.
- 56% of the STNs were located in the left lobe (N= 14) while the rest of nodules 44% located in the right lobe (N= 11).

- 12% of cases had clinically-palpable ipsilateral lymph nodes (N= 3).
- 12% of cases gave a history of voice changes as an additional complaint besides the neck swelling (N= 3). These patients were evaluated using flexible laryngoscopy to assess the vocal folds. The test was **negative** for vocal fold paralysis in all three subjects.
- 52% of the patients were diagnosed with a single chronic disease (N= 13) and are being treated for it, e.g. Hypertension or Diabetes Mellitus.
- 8% of the patients were diabetics (N= 2) and on treatment with Insulin injections or Oral hypoglycemic medications, and their Random Blood Sugar was within normal just before and during the operation.
- 24% of the patients were hypertensive (N= 6) and being treated with the corresponding antihypertension treatment, and their blood pressure levels were within normal just before and during the operation.
- 4% of cases complained of chronic renal insufficiency (N= 1). 4% complained of a long-term history of SLE (N= 1). 4% gave a history of chronic chest disease (bronchial asthma) (N= 1).
- 20% patients only were subjected to isotope scan (N= 5). This scan was done to confirm the physiological status of the nodule whether "Hot," "Cold," or "Normal," and the whole gland as well. Only one patient yielded a "Cold" scan result, while the remaining four cases yielded "Normal" scan results.

All patients were investigated preoperatively for:

- Thyroid hormones (Free T3, T4 and TSH) and all patients were in the euthyroid state just before the operation.
- HBV, HCV and HIV and all patients' results were negative for viral infections.
- Random Blood Sugar.
- Blood Urea, Serum Creatinine and BUN.
- Serum AST and ALT.
- Serum Na^{+}, K^{+}, and Ca^{++}.
- CBC, PT, PTT and INR. Only one patient had microcytic hypochromic anemia that required blood transfusion before surgery.

Postoperative Workout:

The final histopathology report for the postoperative specimen was used to define the overall incidence of malignancy, and confirm the incidence of clinically significant cancers. In this study we compared the usefulness of different clinical and workup parameters such as findings from patient's history, clinical examination, thyroid US, and FNAC against the results of histopathology in the management of STNs.

Table (1): Comparison between pre-op. data and post-op. HP regarding Age.

Age	N	Mean	SD	Median	Range	t	P. Value	Sig.
Malignant	3	35.7	20.2	25.0	23-59	1.41	0.172	NS
Benign	22	46.6	11.6	50.0	22-63			

Independent Samples Test. There was no statically significant difference between pre-op. data and post-op. HP regarding Age.

Table (2): Comparison between pre-op. data and post-op. HP regarding Gender.

Gender	Malignant	Benign	Total	X^2	P Value	Sig.
Male	1(50.0%)	1(50.0%)	2(100%)	2.97	0.230	NS
Female	2(8.7%)	21(91.3%)	23(100%)			
Total	3(12.0%)	22(88.0%)	25(100%)			

Fisher's Exact Chi-Square Test. There was no statistically significant difference between pre-op. data and post-op. HP as regards the gender.

Table (3): Comparison between pre-op. data and post-op. histopathology regarding residence

Residence	Malignant	Benign	Total	X2	P. Value	Sig.
Urban	3(25%)	9(75%)	12(100%)	3.69	0.096	NS
Rural	0	13(100%)	13(100%)			
Total	3(12%)	22(88.0%)	25(100%)			

Fisher's Exact Chi-Square Test. There was no statically significant difference between pre-op. data and post-op. HP as regards residence.

Table (4): Comparison between pre-op. data and post-op. HP as regards special habits.

Special Habits	Malignant	Benign	Total	X^2	P. Value	Sig.

Smoking	**1(50%)**	**1(50%)**	**2(100%)**	**2.97**	**0.230**	**NS**
No Smoking	**21(91.3%)**	**2(8.7%)**	**23(100%)**			
Total	**22(88%)**	**3(12%)**	**25(100%)**			

Fisher's Exact Chi-Square Test. There was no statically significant difference between pre-op. data and post-op. HP regarding special habits.

Table (5): Comparison between pre-op. data and post-op. HP as regards the Main Complaint.

Main Compliant	Malignant	Benign	Total	X^2	P Value	Sig.
Neck swelling	**2(8.7%)**	**21 (91.3%)**	**23(100%)**	**2.97**	**0.230**	**NS**
Painful swelling	**1(50%)**	**1(50%)**	**2(100%)**			
Total	**3(12%)**	**22(88%)**	**25(100%)**			

Fisher's Exact Chi-Square Test. There was no statically significant difference between pre-op. data and post-op. HP as regards the main complaint.

Table (6): Comparison between pre-op. data and post-op. HP as regards Other Complaints

Other Complaints	Malignant	Benign	Total	X^2	P. Value	Sig.
NO	**3(14.3%)**	**18(85.7%)**	**21(100%)**	**0.65**	**0.723**	**NS**
Chest Problems	**0**	**1(100%)**	**1(100%)**			
Voice Changes	**0**	**3(100%)**	**3(100%)**			
Total	**3(12%)**	**22(88%)**	**25(100%)**			

Fisher's Exact Chi-Square Test. There was no statically significant difference between pre-op. data and post-op. HP regards other complaints.

Table (7): Comparison between pre-op. data and post-op. HP regarding Medical History.

Medical History	Malignant	Benign	Total	X^2	P. Value	Sig.
NO	**0**	**12(100%)**	**12(100%)**	**14.11**	**0.01**	**S**
Hypertension	**0**	**6(100%)**	**6(100%)**			
Diabetes Mellitus	**0**	**2(100%)**	**2(100%)**			
Renal Insufficiency	**0**	**1(100%)**	**1(100%)**			
Chest Infections	**1(50%)**	**1(50%)**	**1(100%)**			
SLE	**1(100%)**	**0**	**1(100%)**			
Bronchial Asthma	**1(100%)**	**0**	**1(100%)**			
Total	**3(12.0%)**	**22(88.0%)**	**25(100%)**			

Fisher's Exact Chi-Square Test. There were statically significant differences between pre-op. data and post-op. HP regards medical history.

The highest percentage was the patients with NO medical history, patients with hypertension came second in place. Each of the three malignant cases gave a previous medical history, namely bronchial asthma, SLE and repeated chest infections. From that, it appears that a significant relationship is present between medical history and thyroid malignancy.

Table (8): Comparison between pre-op. data and post-op. HP regarding family history of thyroid disease.

Family History	Malignant	Benign	Total	X^2	P Value	Sig.
Positive	**3(60%)**	**2(40.0%)**	**5(100%)**	**13.64**	**0.004**	**HS**
Negative	**0**	**20(100%)**	**20(100%)**			
Total	**3(12%)**	**22(88%)**	**25(100%)**			

Fisher's Exact Chi-Square Test.

The percentage of patients with negative or positive family history of thyroid disease compared to their final HP results has shown the following:

1. Benign cases with negative family history came first followed by malignant cases with positive family history for and then benign cases with positive family history.

2. This difference was statistically highly significant for the presence of a strong relationship between having a positive family history of thyroid

disease and the potential for development of thyroid malignancy.

Table (9): Comparison between Nodule Dimensions on US and postoperative histopathology

Nodule Dimensions	Malignant	Benign	Total	X^2	P. Value	Sig.
Group 2	3(12.5%)	21(87.5%)	24(100%)	0.14	0.880	NS
Group 1	0	1(100%)	1(100%)			
Total	3(12.0%)	22(88.0%)	25(100%)			

Fisher's Exact Chi-Square Test.

There was no statically significant difference between pre-op. data and post-op. HP as regards nodule dimensions on ultrasound. All malignant cases came within the same group, from 1 to 3 cm. This means that nodule size (i.e. the largest nodule dimension) on ultrasound is **neither** a reliable indicator or a rule-out factor for malignancy in STNs.

N.B.: "**Group 1**" is the group in which the largest nodule dimension is between 1 – 3 cm, while "**Group 2**" is the group in which the Largest nodule dimension is 1 cm or less.

Table (10): Measurement of agreement between Nodule Echogenicity and Postoperative Histopathology.

Nodule Echogenicity	Malignant	Benign	Total	Kappa	P. Value	Sig.
Hypoechoic	3(100%)	0	3(100%)	1.0	<0.001	HS
Hyperechoic	0	22(100%)	22(100%)			
Total	3(12.0%)	22(88.0%)	25(100%)			

Measure of Agreement (Kappa test).

There was a statistically highly-significant agreement between nodule echogenicity detected by ultrasound and postoperative histopathology. Nodule echogenicity gave the same results as histopathology. Nodule echogenicity on US was a **"Highly Valid"** test as it detected three cases as malignant which were **"Hypoechoic"**, the same as histopathology.

Table (11): Measurement of Agreement between Local Examination for Cervical Lymphadenopathy and post-op. HP.

Cervical Lymphadenopathy	Malignant	Benign	Total	Kappa	P. Value	Sig.
Palpable LNs	3(100%)	0	3(100%)	1.0	<0.001	HS
No Palpable LNs	0	22(100%)	22(100%)			
Total	3(12.0%)	22(88.0%)	25(100%)			

Measure of Agreement (Kappa test).

There was a statistically highly-significant agreement between local examination for cervical lymphadenopathy and post-op. HP. Local examination for cervical lymphadenopathy detected the same results as post-histopathology. Local examination was a **"Highly Valid"** test as it detected three cases as malignant; the same as histopathology.

Table (12): Measurement of agreement between FNAC and postoperative histopathology results.

FNAC	Malignant	Benign	Total	Kappa	P. Value	Sig.
Malignant	3(100%)	0	3(100%)	1.0	<0.001	HS
Benign	0	22(100%)	22(100%)			
Total	3(12.0%)	22(88.0%)	25(100%)			

Measure of Agreement (Kappa test).

There was a statistically highly-significant agreement between FNAC results and postoperative histopathology results. FNAC detected the same results as histopathology. FNAC was a **"Highly Valid"** as it detected three cases as malignant; the same as histopathology.

❖ **Summary of the Study Results:**

1. Many variables appeared to have **NO** statistically significant correlation with either increased or decreased risk of malignancy among patients of this study. These variables include: Patient's Age, Gender, Residence, Special Habits, Main Complaint, and Other Complaints.

2. Previous medical history of a chronic disease appears to have a relationship with the susceptibility of a patient to develop thyroid malignancies. We can consider medical history for long-term and/or chronic diseases to be a **Relative Risk Factor** of some sort to develop thyroid cancer. This point may require further studies to elaborate what disease may be strongly correlated with an elevated risk for thyroid cancer.

3. All malignant cases (100%) reported a positive family history of thyroid disease; either benign or malignant. This gives a hint on the fact that a positive family history of thyroid disease is a **Highly Significant Risk Factor** for thyroid malignancy.

4. Nodule Dimension on ultrasound didn't appear to be of any statistically significant value in this study. This come in accordance with the international literature in this point, which consider that nodule size (expressed by the largest nodule diameter) is of a **Minor Predictive Value** as a risk factor for malignancy in STNs.

5. Two variables, namely Nodule Echogenicity and Cervical Lymphadenopathy on local examination have shown to be of an utmost importance among patients of this study. Considering nodule hypoechogenicity on ultrasound and the presence of unexplained cervical lymphadenopathy as red-flag signs for malignant thyroid disease, we can say that this study corroborated the reliability of both signs as **Reliable Risk Factors**. The three malignant cases in this study had cervical lymphadenopathy and shown to be hypoechogenic on ultrasound, this helps to elaborate the strong predictive value of both variables.

6. FNAC, the most important diagnostic tool for STNs, was of a major help in this study. FNAC detected successfully the three malignant cases preoperatively as did histopathology postoperatively. FNAC results were **100% accurate** in concordance with postoperative histopathology. In this study, FNAC Sensitivity and Specificity were both 100% and its **Diagnostic Accuracy** was **1** (**excellent**).

4. Discussion

Politary thyroid nodules represent a fairly common clinical problem, and differentiated thyroid cancer is becoming increasingly prevalent **(Anuradha Kapali et al., 2016).**

The clinical importance of STNs lies in the need to exclude thyroid cancer which occurs in 5-15% depending on age, gender, radiation exposure history, family history, and other factors **(Zubair Baloch et al., 2014).**

Generally, only STNs over 1 cm should be evaluated, since they have a greater potential to be clinically significant cancers **(Alexandra Inman et al., 2017).**

It is recommended that every patient with a palpable STN should undergo an FNAC **(Hewitt and Srivatsa, 2016).**

Some clinical variables have been associated with a greater risk of malignancy, e.g. age, male gender, previous radiotherapy, a positive family history of thyroid cancer **(Liora Lazar et al., 2016).**

Increasing prevalence of thyroid cancer worldwide is partly attributed to increased detection by advanced diagnostic techniques **(Rajesh Kakkeri, 2016).**

In a study of 300 patients, 46.2% of STNs were malignant compared to 22.5% of MNGs. This was not the case in several other studies **(Zi Wei Liu et al., 2017).**

Genetic and/or environmental factors, such as living in an endemic goiter region and variations in iodine exposure, may have an effect on thyroid cancer rates **(Remonti et al., 2014).**

US may help guide FNA, follow thyroid nodule size, and detect small nodules that are not palpable **(Rago et al., 2015).**

No single clinical or US characteristics is solely predictive of malignancy **(Alaa Al Nofal et al., 2016).**

Papini et al. evaluated the relative risk of malignancy of the main US features and showed that the presence of microcalcifications presented a higher specificity for malignancy **(Rebecca Brown et al., 2015).**

Capelli et al. evaluated nodule shape (taller-than-wide or anteroposterior/transverse ratio>1) as a predictor of malignancy **(Sophia Kamran et al., 2013).**

Absent halo combined with the presence of spot microcalcifications and/or hypoechogenicity were the most predictive of malignancy (sensitivity 60% and specificity 93.5%) **(Shyam Keshri et al., 2015).**

Hypoechogenic STNs with irregular margins and microcalcifications increased the probability of malignancies **(Gerald Kangelaris et al., 2015).**

Nodule vascularity has also been proposed to be of a diagnostic value, but many authors question this proposal **(Sheila Sheth et al., 2014).**

Solid composition, central vascularity, greater stiffness, and taller greater than wider in a transverse dimension are US characteristics having predictive value for malignancy on a lesser scale **(Knudsen and Brix, 2014).**

FNA is considered to be the most accurate, sensitive, specific, and cost-effective diagnostic tool

in the preoperative evaluation of STNs **(Melinda Ukrainski et al., 2016).**

Clinical features such as nodule size and rapid growth rate giving rise to compression symptoms are also associated with an increased risk **(Cibas and Ali, 2015).**

Workup of patients with STNs includes both US and FNA. Information obtained on US includes tumor size, presence of solid versus cystic components, nodule definition, and calcifications **(Janjua and Wreesmann, 2018).**

US-detected calcifications were found to be a significant independent cancer predictor **(Kaliszewski et al., 2016).**

Taking individual risk factors in isolation and applying their risk of malignancy to patients is not always reliable **(Lingbin Du et al.,2018).**

A strong association is of note between calcifications and thyroid malignancy, particularly in patients with STNs **(Park and Coorough, 2015).**

Patients younger than 45 who have calcified STNs constitute a high-risk group, with a probability of harboring thyroid malignancy **(Edgar Alfonso et al., 2015).**

Lee et al. concluded that diagnostic lobectomy is associated with improved outcomes at an acceptable cost in the management of large benign STNs. **(Rowe et al., 2017).**

Although the most common age group of STNs is the third and fourth decades of life, but interestingly the malignancy is more common in the second decade **(Liao and Shindo, 2015).**

❖ Our series was a prospective cross-sectional study to evaluate the predictivity of different preoperative findings compared to postoperative histopathological data for malignancy in **(25)** patients with clinically-palpable STNs presenting to the outpatient clinics in El-Demerdash Hospital from July 2018 to December 2018.

❖ Our series is one of the few that analyze Solitary Thyroid Nodules exclusively; others include **Cibas and Ali (2015) and Enrico Papini et al (2014).**

✓ In our study, factors such as age, gender, place of residence, and any personal habits e.g. smoking failed to describe any relationship with the tendency to anticipate a subject's potential to develop malignancy in a patient with a solitary thyroid nodule.

✓ Findings from patient's history and previous medical history gave a little information about any relationship between malignancy in STNs and any individual or family history except for cases with positive family history for thyroid disease either benign or malignant. 16% of patients reported positive family history for thyroid disease (N= 4). 75% of this group of patients appeared to have thyroid malignancy (N= 3) and this could only be explained by the fact that a strong relationship is present between having a positive family history for thyroid disease and the susceptibility to develop thyroid malignancy especially in patients over 50 years of age.

✓ In our study, findings on local examination were not very specific to relate for malignancy, except for cases with cervical lymphadenopathy which appeared in 12% of patients (N= 3) and was later found to harbor malignancy by histopathological diagnosis.

✓ Thyroid ultrasound was able to detect signs of malignancy (e.g. nodule hypoechogenicity) with great accuracy in 12% of patients (N= 3). Malignancy was later confirmed in these 3 cases by histopathological diagnosis postoperatively.

✓ The FNAC results indicated malignancy in 3 patients (12%), benign in 22 patients (88%). The final histopathological diagnosis confirmed malignancy in 3 patients (12%), the three of which had PTC.

✓ Among the rest, 22 patients (88%) had benign thyroid pathology on FNAC. Out of the 22 cases identified to be benign lesion by FNAC, only 48% of patients were found to be adenoma (N= 12). While 24% were found to have Colloid Goiter (N= 6), and 12% were found to have Hashimoto's Thyroiditis (N= 3).

➢ According to our study results, we can state that some variables, e.g. **F**amily history of thyroid disease, **N**odule hypoechogenicity and **FNAC** assessment are considered reliably **"Valid Tests"** to evaluate patients presenting with STNs for malignancy.

Conclusion

- The utmost clinical importance of a solitary thyroid nodule is exclusion of malignancy.
- STNs are fairly common lesions, frequently detected by modern imaging methods (mainly ultrasonography).
- These data substantively expand our un-worsening knowledge of STNs in adults by showing that advancing age clearly increases the risk of thyroid nodule formation.
- The combination of FNA with clinical and US parameters may improve diagnostic definition of palpable STNs.
- US has a sensitivity and specificity of 100% and 95% respectively, while FNAC has sensitivity, specificity, diagnostic accuracy and positive predictive value of 94%, 99%, 99.2% and 88.9% respectively.
- It is concluded from the present series that 12% of STNs are malignant, with female preponderance and a mean age of STN is 31-40 years.

- US findings should be the primary criterion used to decide the management of asymptomatic STNs.
- STNs and MNGs carry almost the same risk of thyroid malignancy.

References

1. Alaa Al Nofal, Michael R. Gionfriddo, Asma Javed, Qusay Haydour, Juan P. Brito, Larry J. Prokop, Alam T, Khattak YJ, Beg M, Raouf A, Azeemuddin M, Khan AA. Diagnostic accuracy of ultrasonography in differentiating benign and malignant thyroid nodules using fine needle aspiration cytology as the reference standard. Asian Pac J Cancer Prev (2016); 15(22):10039-43.
2. Alexander EK, Marqusee E, Orcutt J, Benson CB, Frates MC, Doubilet PM, Cibas ES, Atri A. Thyroid nodule shape and prediction of malignancy. Thyroid 2004; 14(11):953-8.
3. Cibas ES. Fine-needle aspiration in the work-up of thyroid nodules. Otolaryngologic Clinics of North America. (2010); 43(2):257-71.
4. Edgar Alfonso, Alvaro Sanabria, Maho Castillo Surgeons overestimate the risk of malignancy in thyroid nodules, evaluation of subjective estimates using a bayesian analysis Biomédica (2011); 31:590-8.
5. Gharib H, Papini E. Thyroid nodules: clinical importance, assessment, and treatment. Endocrinology and metabolism clinics of North America (2007); 36(3):707-35.
6. Janjua N, Wreesmann VB. Aggressive differentiated thyroid cancer. European Journal of Surgical Oncology (2018); 44(3):367-77.
7. Kaliszewski K, Diakowska D, Wojtczak B, Strutyńska-Karpińska M, Domosławski P, Sutkowski K, Głód M, Balcerzak W, Forkasiewicz Z, Łukieńczuk T. Fine-needle aspiration biopsy as a preoperative procedure in patients with malignancy in solitary and multiple thyroid nodules. PloS one (2016); 11(1): e0146883.
8. Knudsen N, Brix TH. Genetic and non-iodine-related factors in the aetiology of nodular goitre. Best Practice & Research Clinical Endocrinology & Metabolism. (2014) Aug 1;28(4):495-506.
9. Liao S, Shindo M. Management of well-differentiated thyroid cancer. Otolaryngologic Clinics of North America (2012); 45(5):1163-79.
10. Park JM, Choi Y, Kwag HJ. Partially cystic thyroid nodules: ultrasound findings of malignancy. Korean journal of radiology (2012); 13(5):530-5.
11. Rago T, Vitti P. Diagnostic role of ultrasound and elastosonography in nodular goiter. Best Practice & Research Clinical Endocrinology & Metabolism (2014); 28(4):519-29.
12. Rebecca S. Bahn and Regina M. Castro Approach to the Patient with Nontoxic Multinodular Goiter J Clin Endocrinol Metab (2011): 96: 1202–1212.
13. Remonti LR, Kramer CK, Leitao CB, Pinto LC, Gross JL. Thyroid ultrasound features and risk of carcinoma: a systematic review and meta-analysis of observational studies. Thyroid (2015); 25(5):538-50.
14. Rowe ME, Osorio M, Likhterov I, Urken ML. Evaluation of ultrasound reporting for thyroid cancer diagnosis and surveillance. Head & Neck (2017); 39(9):1756-60.

3/25/2019