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**SERUM IgG4 LEVEL FOR MALIGNANCY PREDICTION IN
INDETERMINATE THYROID NODULES AMONG PATIENTS WITH
OR WITHOUT AUTOIMMUNE THYROID DISEASE**

Thesis

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In Internal Medicine

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او بدون المرض المناعي للغده الدرقية

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قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العليم

صدقة الله العظيم

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LIST OF ABBREVIATIONS

Abb.	Full term
ACR-TIRADS	American collage or radiology thyroid imaging reporting and data system.
Anti TG	Anti thyroglobulin antibodies.
Anti TPO	Anti thyroid peroxidase antibodies.
ATA	American thyroid association
AUC	Area under the curve.
AUS	Atypia of undetermined significance
BSRTC	Bethesda system for reporting thyroid cytopathology.
CTL	Cytotoxic T lymphocytes
DSPTC	Diffuse sclerosing papillary thyroid carcinoma.
DW-MRI	Diffusion weighted- magnetic resonance imaging.
EFVPTC	Encapsulated follicular variant of papillary thyroid carcinoma.
ELISA	Enzyme-linked immunoassay.
FA	Follicular adenoma.
FDG-PET	Fludeoxyglucose- positron emission tomography.
FLUS	Follicular lesion of undetermined significance.
FN/SFN	Follicular neoplasm/suspicious for follicular neoplasm.
FNAC	Fine needle aspiration cytology.
FT3	Free triiodothyronine.
FT4	Free thyroxine.
FTC	Follicular thyroid carcinoma.
FVPTC	follicular variant of papillary thyroid carcinoma.
HPV	Human papilloma virus.
HT	Hashimoto's thyroiditis.
IFN-γ	Interferon- γ .
IgG4	immunoglobulin g4.
IgG4-RD	Immunoglobulin g4-related disease.
IgG4-TRD	Immunoglobulin g4-thyroid related disease.
IL	Interleukin.
IQRs	Medians with interquartile ranges.
K-TIRADS	Korean thyroid imaging reporting and data system.
MEN	multiple endocrine neoplasia

List of Abbreviations

Abb.	Full term
MRI	Magnetic resonance imaging.
n	Number.
ND-BSRTC	Non-diagnostic, Bethesda system for reporting thyroid cytopathology.
NI-FVPTC	Noninvasive follicular variant of papillary thyroid carcinoma.
NPV	Negative predictive value
PTC	Papillary thyroid carcinoma
PPV	Positive predicted value
r	Correlation coefficient.
REC	Research ethics committee.
Sig.	Significance.
SPSS	Statistical package for the social sciences.
SWE	The shear wave elastography.
TC	Thyroid carcinoma.
TG	Thyroglobulin.
TGF-β	Tumor growth factor β .
Th	T helper.
TNF-α	Tumor necrosis factor- α .
Treg	Regulatory t cells.
TSH	Thyroid stimulating hormone.
Tx	Thyroidectomy.
US	Ultrasonography

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INTRODUCTION

Nodular thyroid disease is one of the most common thyroid pathology detected in clinical practice. More than 50% of the population has at least one thyroid nodule. (*Ali., 2011*).

Although nodule prevalence is very high, only 5-10% of the nodules are malignant and require intervention either surgical and /or medical (*Aru et al., 2015*).

FNAC (Fine needle aspiration cytology) has a high sensitivity usually more than 90%. It was recommended by international experts as an initial or screening test to detect thyroid cancer (*Fatemeh, 2015*).

However, Thyroid FNAC has low specificity usually 50% to 65% which leads to many unnecessary surgical interventions. Only 20% to 30% of all indeterminate cases by FNAC were found malignant on histology, with high variability in determining risk of malignancy (*Miller et al., 2004*).

The major concern is to differentiate the malignant lesions from the benign lesions preoperatively. Fine-needle aspiration cytology (FNAC) for thyroid nodules is the key standard test used for this purpose. Although it is a rapid, cost-effective, safe, and reliable test, the non-diagnostic or the indeterminate results may require re-biopsy are the limitations of this method. The indeterminate cytology defined as the “gray zone “(*Bongiovanni et al., 2012*).

Thyroid cancer is one of the most common endocrine malignancy, and the incidence has been increasing worldwide. Chronic inflammation can be involved in tumorigenesis. It is estimated that more than 20% of all tumors are caused by constant inflammatory state (*Blomberg et al., 2012*).

Thyroid nodules are usually accompanied by an increase in autoimmune thyroid diseases mainly Hashimoto’s thyroiditis (*Ruggeri et al., 2011*).

Immunoglobulin G4-related disease (IgG4-RD) is a new disease class involving many organs, including the endocrine system in general and the thyroid especially. It is a fibro-inflammatory disease with special histological features and frequently elevated serum IgG4 levels which are helpful in the diagnosis. Recent studies focused on the relation between IgG4-RD and malignancies. Thyroid cancer and thyroid autoimmunity are considered opposite extremes of immune responses. Although, several studies have proposed that thyroid cancer coexists with autoimmune thyroid diseases (*Tabata et al., 2011*).

IgG4-RD is diagnosed when the cut-off for serum IgG4 was set at greater than 135 mg/ dL there are sensitivity and specificity of 90 and 60%, respectively. The measurement of serum IgG4 is also helpful to determine treatment response and recurrence (*Motohisa et al., 2012*).

Malignancies occurred in 10.4% of IgG4-RD patients, approximately 3.5 times higher than the incidence of cancer in the general population. These results proposed that when diagnosing IgG4-RD, it is essential not only to differentiate between the enlarged organs and cancers but also to consider the possibility of cancer complications in other parts of the body. Malignancies as complications to IgG4-RD are categorized as lymphoma and non-lymphoid tumors (*Tabata et al., 2011*).

AIM OF THE WORK

We aim to detect the predictive value of serum IgG4 level for the diagnosis of malignancy in indeterminate thyroid nodules (FNAC result) among patients with and without autoimmune thyroid disease.

NODULAR THYROID DISEASE

Thyroid gland has a distinctive position among the endocrine organs. Its superficial location qualifies for an early detection of any abnormality. There are many spectrums of thyroid diseases ranges from inflammatory, hyperplastic to neoplastic disorders. Thyroid lesions can present as diffuse or nodular swellings and can be in any one of the following functional classes: Euthyroid, Hypothyroid or Hyperthyroid (*Barui et al., 2017*).

The normal thyroid gland lies in the anterior neck, anterior to the trachea, deep to the strap muscles, and lateral to it are the carotid arteries and jugular veins. Because thyroid malignancies most commonly present as focal nodules there are morphological and size criteria to recognize nodules most suspicious for malignancy (figure 1) (*Alexander et al., 2020*).

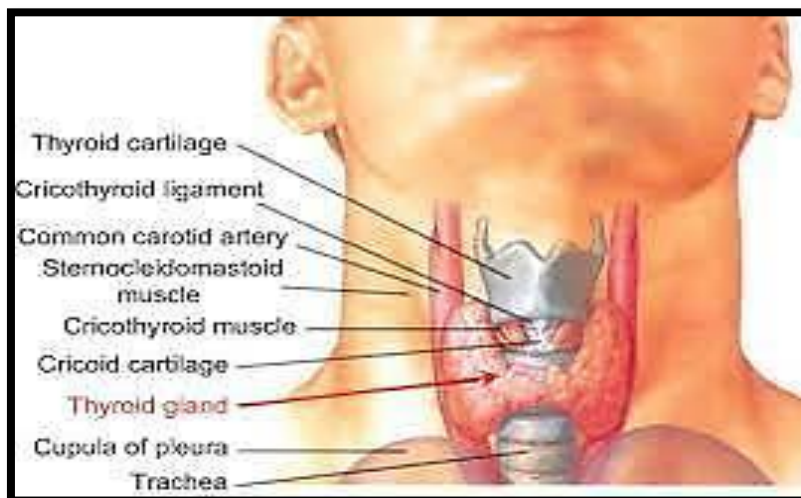


Figure (1): Anatomy of thyroid gland