EVALUATION OF RISK FACTORS FOR MALIGNANCY IN A SOLITARY THYROID NODULE

Thesis

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By

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Rami Kamal Atiya Morcos

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List of Abbreviations

Abb.	Full term
AACE	American Association of Clinical Endocrinologists; ATA, American Thyroid Association; ATC,
ANOVA	Analysis of variance
AP/T	Anteroposteriorntransverse diameter
APC	Annual percentage change
ASIRW	Age-standardized incidence rate by world population
ATA	American Thyroid Association
ATC	Anaplastic thyroid carcinoma
AUS	Atypia of undetermined significance
B	PBs,
BI-RADS	Breast imaging reporting and data system
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BRAF, BRAF	Protein (oncogene)
BST	Bilateral subtotal thyroidectomy,
Camp	Cyclic adenosine monophosphate
CCH	C-Cell hyperplasia
CEA	Carcinoembryonic antigen
CI	Confidence Interval
CT	Computed tomography
Ct	Calcitonin
CVPTC	Classical variant of papillary thyroid carcinoma
DM	Distant Metastasis
DO	Dunhill operation,
DTC	Differentiated thyroid carcinoma
E2	Estradiol
EANM	European Association of Nuclear Medicine
EDI	Electronic data interchange
EFC	Encapsulated follicular thyroid carcinoma

List of Abbreviations (Cont.)

Abb.	Full term
EFVPTC	Encapsulated follicular variant of papillary thyroid carcinoma
EREs	Estrogen response elements
ERK	Extracellular signal-regulated kinase
ETE	Extra thyroidal extension
ETT	Endotracheal tube
FA	Follicular adenomas
FACS	Fluorescent activated cell sorter
factor-1	HLAG, human leukocyte antigen
FC	Follicular thyroid cancer
FDG18	Fluoro-deoxy-glucose
FLUS	Follicular lesion of undetermined significance
FMTC	Familial medullary thyroid cancer
FN	Follicular neoplasm
FNA	Fine needle aspiration
FNAB	Fine-needle aspiration biopsy
FNAC	Fine needle aspiration cytology
FTA	Follicular adenoma
FTC	Follicular thyroid carcinoma;
FVPTC	Follicular variant of papillary thyroid carcinoma
GEC	Afirma Gene Expression Classifier
GEE	Generalized estimated equations
GP	General practitioner
GPCR	G protein-coupled receptor
hCG, human	Chorionic gonadothropin
HIF-1	Hypoxia inducible
HR	Hazard Ratio
HRT	Hormone replacement therapy,
HT	Hashimoto thyroiditis

List of Abbreviations (Cont.)

Abb.	Full term
ICD	International classification of diseases
ICD-O	The International Classification of Diseases for Oncology
IFP	Increased interstitial fluid pressure
IJV	Internal jugular vein
IMRT	Intensity modulated radiotherapy
ITN	Incidental thyroid nodule
LNM	Lymph node metastases
MACIS	Metastases, Age at presentation, Completeness of surgical resection, Invasion (extrathyroidal), Size
MALT	Mucosa associated lymphoid tissue
MAPK	Mitogen-activated protein kinase
MDL	Minimum detection level
MDT	Multidisciplinary team
MEK	Mitogen-activated protein kinase kinase
MEN	Multiple endocrine neoplasia
MEN2	Multiple endocrine neoplasia type 2
MIBG	Metaiodobenzylguanidine
MKIs	Multi kinase inhibitors
MNG	Multinodular goiter
MRI	Magnetic resonance imaging
MRND	Modified radical neck dissection
MTC	Medullary thyroid cancer
MTD	Maximum tumor diameter
NCCN	National Comprehensive Cancer Network
NF-b	Nuclear factor-kappa
NHI	National Health Insurance
NHIS	National Health Insurance Service
NPV	Negative Predictive value

List of Abbreviations (Cont.)

Abb.	Full term
OR	Odds Ratio
OS	Overall survival
PBDEs	Polybrominated diphenyl etherflame retardants
PDTC	Poorly differentiated thyroid carcinoma
PET	Positron emission tomography
PFS	Progression-free survival
PHEO	Pheochromocytoma
PHP	Primary hyperparathyroidism
PI3K	Phosphatidylinositol 3-kinase
PPV	Positive predictive value
PTC	Papillary thyroid carcinoma
PTH	Parathyroid hormone
PTMC	Papillary microcarcinoma
Ptnm	Pathologically staged according to Tumour size, Node metastases and distant Metastases
QIC	Quasi-likelihood under the independence criterion
QTc	Corrected QT interval (electrocardiogram)
RAI	Radioactive iodine
RAS	Ras proto-oncogene, GTPase
REC	research ethics committee
RET	Ret proto-oncogene
rhTSH	Recombinant human TSH
RIA	Radioimmunoassay
RLN	Recurrent laryngeal nerve
RR	Relative risk
RR-DTC	Radioiodine-refractory differentiated thyroid carcinoma
SAN	Spinal accessory nerve
SCM	Sternocleidomastoid muscle
SD	Standard deviation

List of Abbreviations (Cont.)

Abb.	Full term
SEER	Surveillance, Epidemiology, and End Results Program
SFN	Suspicious for follicular neoplasm
SNG	Solitary nodular goiter,
SUSP	Suspicious for malignancy
T3	Triiodothyronine (liothyronine)
TC	Thyroid cancer
TCGA	The Cancer Genome Atlas
TFT	Thyroid function test
Tg	Thyroglobulin
TgAb	Anti-thyroglobulin antibodies
TI-RADS	Thyroid imaging reporting and data system
TKIs	Tyrosine kinase inhibitors
TKs	Tyrosine kinases
TNM	Staged according to Tumour size, Node and Metastases
TSG	Tumour-specific group
TSH	Thyroid-stimulating hormone
TSVPTC	Papillary thyroid carcinoma with trabecular-solid pattern of growth
TT	Total thyroidectomy
US	Ultrasonography
US	United States of America
UT	Unilateral thyroidectomy
WBS	Whole-body scan

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).