

Contents

Subjects	Page
List of abbreviations.....	II
List of Figures	VIII
List of Tables	IX
• Introduction	1
• Aim of the work	7
• Review of Literature	
♦ Chapter (1): Introduction	8
♦ Chapter (2): Molecular Pathology of Thyroid Cancer.....	30
♦ Chapter (3): Management of Thyroid Carcinoma.....	64
♦ Chapter (4): Target Therapy for Advanced Thyroid Carcinoma.....	85
• Summary	162
• References	166
• Arabic Summary	

List of Abbreviations

ADP	Adenosine diphosphate
AJCC	American Joint Committee on Cancer
AKT	Protein kinase b
ALT	Alanine transaminase
AST	Asparate transaminase
ATA	American Thyroid Association
ATC	Anaplastic thyroid carcinoma
ATP	Adenosine triphosphate
ATPase	Adenosine triphosphatase
BCR-Abl	Ableson and breakpoint cluster region fusion gene
b.i.d	Bis in die which means twice a day
BRAF	B- type RAF kinase
BRAF 600E	Valine to glutamic acid substitution of BRAF gene
CAMP	Cyclic adenosine monophosphate
C cells	Parafollicular (clear) cell
CDKN2A	Cycline dependant kinase inhibitor 2 A
CEA	Carcino embryonic antigen
CGY	Cent Gray
CI	Confidence interval
COX-2	Cyclo oxygenase 2
CPG	cytoplasmic GTPase activating proteins
CR	Complete response
C.T	Computed Tomography

List of Abbreviations

CT	Calcitonin
CTNNB 1	Catenin β 1
DAPK	Death associated protein kinase
DCI	Histone deacetylase inhibitors
DIT	Diiodotyrosine
DLT	Dose limiting toxicity
DNA	Deoxy Ribonucleic acid
DTC	Differentiated thyroid carcinoma
EBRT	External beam radiotherapy
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ERK	Extra cellular signal regulated protein kinase
ETA	European Thyroid Association
FA	Follicular adenoma
FAB	Familial adenomatous polyposis
FDA	Food and Drug administration
FDG	Fluorodeoxy glucose
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FMTC	Familial medullary thyroid carcinoma
FNAC	Fine needle aspiration cytology
FNMTc	Familial non medullary thyroid carcinoma
FTC	Follicular thyroid carcinoma
GDNF	Glial cell line derived neutrophic factor
GDP	Guanosine diphosphate

List of Abbreviations

GTP	Guanosine triphosphate
GTPase	Guanosine triphosphatase
GY	Gray
HATs	Histone acetyl transferase
HDAC	Histone deacetylase
HER 2	Human epidermal growth factor receptor
HGF	Hepatocyte growth factor
HR	Hazard ratio
HSP	Heat shock protein
I⁻	Iodide
I 123	Radioiodine 123
I 131	Radioiodine 131
IC 50 value	Half maximal inhibitory concentration of a substance
IGF-R	Insulin like growth factor receptor
K⁺	Potassium
KIT	V- Kit Hardy-Zukerman 4 feline sarcoma viral oncogene
KRAS	Kirsten rat sarcoma
LT4	Levothyroxine
MAPK	Mitogen activated protein kinase
MEK	Mitogen activated ERK kinase
MEN	Multiple endocrine neoplasia
MET	Mesenchymal epithelial transition factor
miR	Micro RNA
MIT	Monoiodotyrosine
MRI	Magnetic resonance imaging

List of Abbreviations

MTC	Medullary thyroid carcinoma
mTOR	Mammalian Target of rapamycin
Na⁺	Sodium
NCI	National Cancer Institute
NF-κB	Nuclear factor κ B
NIS	Sodium iodide symporter
NOS	Non otherwise specified
NTRK	Neutrophic tyrosine kinase
ORR	Overall response rate
OS	Overall survival
Onf FN	Oncofoetal Fibronectin
PAX8	Paired box gene 8
PD	Progressive disease
PDGFR	Platelet derived growth factor receptor
PDTC	Poorly differentiated thyroid carcinoma
PET	Positron emission tomography
PFS	Progression free survival
PI3K	Phosphoinositide 3 kinase
PIK3CA	Phosphatidyl inositol 3 kinase
PKA	Protein kinase A
PLC	phospholipase C cascade
PPAR-γ	Peroxisome proliferator activated receptor gamma
PR	Partial response
PTC	Papillary thyroid carcinoma
PTEN	Phosphate and tensin enzyme
P. value	Probability value

List of Abbreviations

RAF	Rapidly accelerated fibrosarcoma kinase related oncogene
RAI	Radioactive iodine
RARb2	Retinoic acid receptor b2
RAS	Rat sarcoma oncogene
RASSF 1A	RAS- association domain family 1 splicing isoform A
RECIST	Response Evaluation Criteria in Solid Tumor
RET	Glial cell line derived neutrophic factor receptor
rhTSH	Recombinant human thyroid stimulating hormone
RNA	Ribonucleic acid
RTK	Receptor tyrosine kinase
SCL	Scleroderma oncogene
SD	Stable disease
SEER	Surveillance Epidemiology and End Results cancer registration program
T3	Triiodothyronine
T4	Thyroxine (tetraiodothyronine)
TBG	Thyroid binding globulin
Tc	Technetium
THW	Thyroid hormone withdrawal
TK	Tyrosine kinase
TTF-1	Thyroid transcription factor- 1
TFTs	Thyroid function tests
TG	Thyroglobulin
TIMP3	Tissue inhibitor of metalloproteinase 3

List of Abbreviations

Tie.2	Tyrosine kinase with immunoglobulin-like and EGF-like domain 2
TKI	Tyrosine kinase inhibitor
TNM	Tumor size, lymph node involvement, distant spread
TP53	Tumor suppressor protein 53 gene
TRH	Thyrotropin releasing hormone
TRK	Tyrosine kinase
TSH	Thyroid stimulating hormone
TSHR	Thyroid stimulating hormone receptor
U.S	Ultrasound
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VPA	Valporic acid
WBS	Whole body scan
WNT	Wingless and Integration signaling pathway

List of Figures

<u>No.</u>	Figure	<u>Page</u>
<u>1</u>	Evaluation of thyroid nodules.	12
<u>2</u>	Multi-step model of thyroid cancer.	14
<u>3</u>	Signaling pathways in differentiated thyroid cancer.	19
<u>4</u>	Diagnostic algorithm based on the measurement of both basal and rhTSH-stimulated serum thyroglobulin after initial treatment in patients with DTC.	27
<u>5</u>	MAP kinase and PI3K/AKT/mTOR pathways are both involved in thyroid proliferation: TKI molecular targets and specific drugs able to inhibit them are shown.	28
<u>6</u>	Progression Free Survival among vadetanib and placebo.	34
<u>7</u>	Progression Free Survival among cometriq and placebo.	50
<u>8</u>	Progression free survival among sorafinib and placebo.	52
<u>9</u>	Progression Free Survival among lenvatinib and placebo.	
<u>10</u>	Protocol Design and Changes in Iodine Uptake with selumetinib treatment.	

List of Tables

No.	Figure	Page
<u>1</u>	The Bethesda System for Thyroid Cytopathology.	12
<u>2</u>	Average Prevalence of Mutations in Various Types of Thyroid Cancer.	14
<u>3</u>	Risk stratification according to the ATA guidelines.	19
<u>4</u>	Risk stratification according to the ETA guidelines.	27
<u>5</u>	Indication for remnant radioiodine ablative therapy.	28
<u>6</u>	Thyroid cancer: tumor type, age, prevalence and survival.	34
<u>7</u>	IC50 values for the most important tyrosine kinase inhibitors and different targets.	50
<u>8</u>	The primary results of combined everolimus and sorafenib in RAI refractory thyroid cancer.	52



Introduction





Aim of the Work





Chapter (1)

Introduction





Chapter (2)

Molecular Pathology of Thyroid Cancer





Chapter (3)

Management of Thyroid Carcinoma





Chapter (4)

Target Therapy for Advanced Thyroid Carcinoma

