

CARCINOMA THYROID - EVALUATION

(1)

STATISTICS AND FACTS ABOUT CARCINOMA THYROID

1973 - 3.6 PER 100,000 POPULATION
2002 - 8.7 PER 100,000 POPULATION
2012 - 10.4 PER 100,000 POPULATION

GRADUALLY INCREASING

(2)

T.C. - 1% OF ALL CANCER - WORLDWIDE VARYING FROM 0.6 TO 2.2%
IN ENDEMIC GOITER AREA / BLACK COMMUNITY

(3)

INCREASE NUMBER IS MOSTLY T. PAPILLARY CARCINOMA, WHILE
NO SIGNIFICANT CHANGE IN OTHER HISTOLOGICAL TYPE
(FOLLICULAR, MEDULLARY, ANAPLASTIC)

(4)

- T. - PAPILLARY CARCINOMA - 2.73 TO 7.7 PER 100,000
- MORTALITY RATE STABLE - 0.5 PER 100,000

REASON - RISE IN PAPILLARY CARCINOMA - LOW MALIGNANT
CHARACTER

(5)

HARACH, ET.AL. (2014) - AUTOPSY FINDINGS

- PAPILLARY CARCINOMA - LESS THAN 1 CM
36% OF 1250 PATIENTS

(SUBCLINICAL VARIANT - REMAINS SILENT FOR YEARS)

(6)

- MEDIAN AGE 45 YEARS
- MALE/FEMALE - 2.7 TO 1
- MALE AGE 52 (AGGRESSIVE NATURE)

(7)

INDIA (2016)

- THIRUVANANTHAPURAM - HIGHEST NUMBERS OF 7 CENTRES

1.9% - MALES
5.7% - FEMALES

NATIONAL - 0.1% TO 0.2%
FEMALE - 1 PER 100,000 POPULATION
MALE - 1.8 PER 100,000 POPULATION

65% PAPILLARY
20% FOLLICULAR

(8)

THYROIDS - HETEROGENEOUS GROUP OF NEOPLASM

- PAPILLARY (MOST FREQUENT)
 - FOLLICULAR
 - MEDULLARY
- } ORIGINATES FROM NEURO
ENDOCRINE CALCITONIN
PRODUCING C-CELLS
- LYMPHOMA - INTRA THYROID LYMPHATIC TISSUE
 - SARCOMA - CONNECTIVE TISSUE
 - ANAPLASTIC -

(GOOGLE SCHOLAR AND PUBMED DATABASE)

(9)

PAPILLARY THYROID CA (P.T.C.) - 80% WORLDWIDE

HISTOLOGICAL VARIANT -

- TYPICAL PAPILLARY
- FOLLICULAR VARIANT
- MICRO CARCINOMA
- TALL CELL
- ONCOCYTIC
- COLUMNAR CELL
- DIFFUSE SCLEROSING
- SOLID CELL
- CLEAR CELL
- CRIBRIFORM - MORULAR
- INTRA FOLLICULAR
- PTC WITH FASCIITIS
- WARTHINS LIKE P.T.C.
- MIXED PAPILLARY
- MIXED MEDULLARY
- PAPILLARY WITH DE DIFFERENTIATION IN ANAPLASTIC

CHALLENGE - TPC - RISING STEADILY IN LAST 10 YEARS FROM 70% TO 80% WHILE DECLINE IN OTHER TYPES.

(10)

FOLLICULAR T.C. -

- MALIGNANT EPITHELIAL TUMORS WITH FOLLICULAR CELL DIFFERENTIATION
- POSSIBLE CAUSE - IODINE DEFICIENCY GOITERS
DECLINE NOW AS DECLINE IN IODINE DEFICIENCY DISORDER

RADIATION EXPOSITION

- CHILDREN (18-19 YEARS) 1940-1975 -
FOR VARIOUS REASONS (BENIGN) IN HEAD AND NECK
 - INSIGNIFICANT NUMBER BECAUSE OF LOW DOSE

(14)

HIROSHIMA / NAGASAKI - JAPAN EXPOSURE 1945 ONWARDS

- FURUKAWA et.al. (2007) STUDY 1958 - 2005
 - RELATIVE RISK IS HIGH EVEN AFTER 40 YEARS

(15)

CHALLENGE

- T. FOLLICULAR CA - 10%
- **HOW TO DISCRIMINATE** -
 - FOLLICULAR ADENOMA
 - FOLLICULAR CA-MINIMAL INVASIVE
 - ENCAPSULATED FOLLICULAR VARIANT OF
PAPILLARY T.C.
 - HURTHLE CELL CA

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MORALITY RATE -

- HIGHEST IN - ASIA, CENTRAL AMERICA, EAST, CENTRAL
EUROPE
- LOWEST IN - WESTERN EUROPE, NORTH AMERICA
- OVERALL RISE IN THYROID CA IN ALL COUNTRIES
- OVERALL DECREASES

(17)

CHERNOBYL (RUSSIA)

- RELATIVE RISK HIGH AFTER 20 YEARS
- EXPOSITION DOSE OF 10 Gy TO 1500 Gy RELATIVE RISK ONLY
- ABOVE 1500 Gy - REDUCTION IN RELATIVE RISK, DUE TO TOXIC EFFECT ON CELLS

(18)

IMPORTANT CONSTITUTIONAL FACTOR - AGE

ABOVE 15 YEARS - EXPOSITION -

REDUCED RISK

(19)

IODINE INTAKE

- LOW OR HIGH - TSH CHANGES
- EXPERIMENTAL - ANIMAL STUDY
- IN BOTH CASES - EFFECT IS CARCINOGENIC

(20)

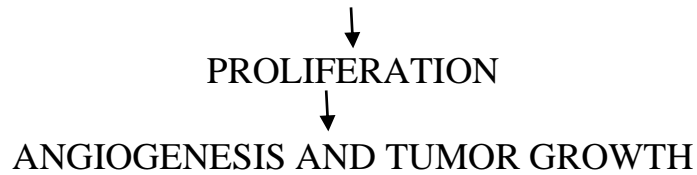
IODINE DEFICIENCY



PROMOTER - THROUGH INCREASE T.S.H.



STIMULATES - THYROID E.G.F. (EPIDERMAL GROWTH FACTOR)



(21)

MANY STUDIES -

- IODINE DEFICIENCY
↓
FOLLICULAR CA AND ANAPLASTIC CA
 - HIGH IODINE INTAKE
↓
RESULT IN CONCLUSIVE
-

(22)

ROSSING, et.al. (2013) AND 20 OTHER STUDIES

- HIGHER INCIDENCE OF T.MALIGNANCY IN - ASIAN BORN FEMALES, MAY HAVE MIGRATED TO USA - DUE TO

**DIET DEFICIENCY
(IODINE)**

(23)

PRE EXISTING BENIGN THYROID DISORDERS

- ARE RISK FACTOR FOR THE THYROID CANCER
- THYROID ADENOMA, SINGLE / MULTIPLE NODULAR GOITRE, AUTOIMMUNE DISORDER (GRAVE'S DISEASE/HASHIMOTO DISEASE)

(24)

CHENG G.G. et.al.

OESTROGEN EFFECT IN DEVELOPMENT OF THYROID CA IS
DETECTED WITH PRESENCE OF OESTROGEN RECEPTORS - ON
THYROID CANCER CELL LINES

(25)

OBESITY

INCREASE TSH



TSH + INSULIN LIKE GROWTH FACTOR-1

INACTIVATION OF MARK AND P13K PATHWAYS MAY BE A
CAUSE OF THYROID MALIGNANCY

(26)

GENE - BASIC PHYSICAL AND FUNCTIONAL UNIT OF
HEREDITY

(27)

- GENES ARE MADE UP OF DNA/RNA
 - GENES VARY IN SIZE FROM FEW HUNDREDS DNA BASES TO
MORE THAN 2 MILLIONS BASES
-

(28)

- ALLELES - ARE FORMS OF SAME GENE WITH SLIGHT DIFFERENCE IN SEQUENCE OF DNA BASE.
- DEFINE INDIVIDUAL'S CHARACTER

(29)

- GENES ARE NAMED, WITH ALPHABETS, AND NUMBERS FOR IDENTIFICATION PURPOSE

(30)

GENES - COMPOSED OF DNA
DOUBLE HELIX SHAPE, SPIRAL LADDER CONSISTS OF TWO PAIRED
CHEMICALS CALLED BASES

FOUR TYPES OF BASES (AMINO ACIDS)

- ADENINE (A)
- THYMINE (T)
- CYTOSINE (C)
- GUANINE (G)

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- HIGH INCIDENCE OF PAPILLARY CA
 - FAMILIAL ADENOMATOUS POLYPOSIS
 - COWDEN'S DISEASES (MULTIPLE - HEMARTOMA - SYNDROME)
- THYROID CA - SPORADIC BUT 5% FAMILIAL WITH GENETIC CHANGES - RAS MUTATION

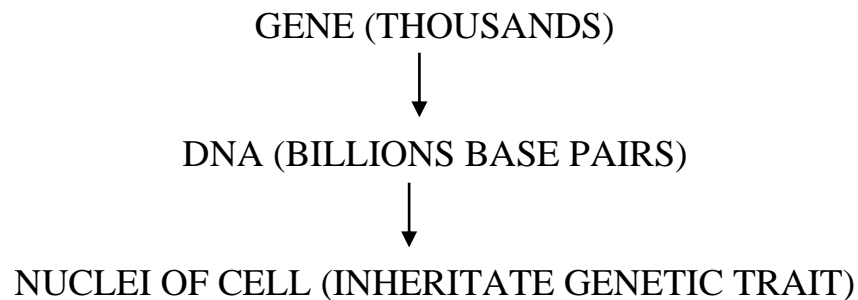
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MOLECULAR BIOLOGY

(33) DNA STRUCTURE - HELIX WITH CURVE BANDS WITH INTER
CONNECTING BASES FORMED BY PROTEINS / AMINOACIDS

- BASES MOSTLY PRESENT IN PAIRS OF -
- ADENOSINE + THYMINE AND GC GYANINE + CYTOSINE
- DIFFERENT SEQUENCES OF BASES FOR CODED MESSAGES ARE
FUNCTIONAL CODES

(34)



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CHROMOSOMES (23 PAIRS)

(1+1 - FATHER + MOTHER)

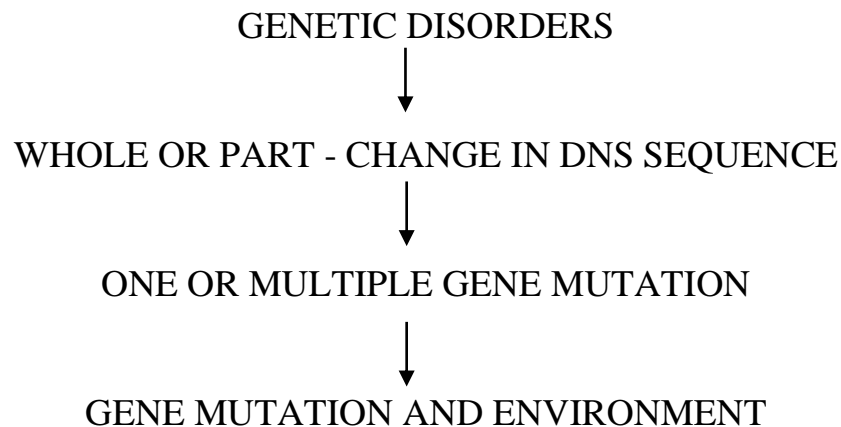
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BASIC FUNCTIONAL UNIT IS A GENE

BASE PAIR - CONSISTS OF NUCLEOTIDE / AMINO ACID/ PROTEIN

AND GUIDE CELL FUNCTION

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- ENDOCRINE GLANDS - FORM A GROUP - TO FUNCTION WITH - EACH OTHER GENETIC CODE AS NO DUCT IS INVOLVED FOR ITS SECRETION TO BODY CIRCULATION

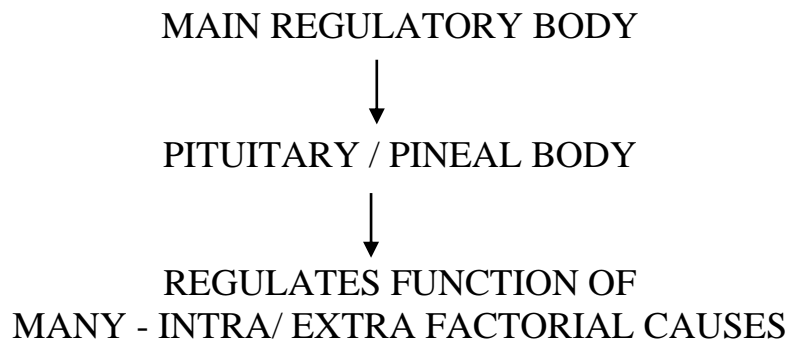
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- OTHER FUNCTIONING GLANDS WITH DUCTS HAS ONE ETIOLOGY FACTOR FOR CARCINO GENESIS

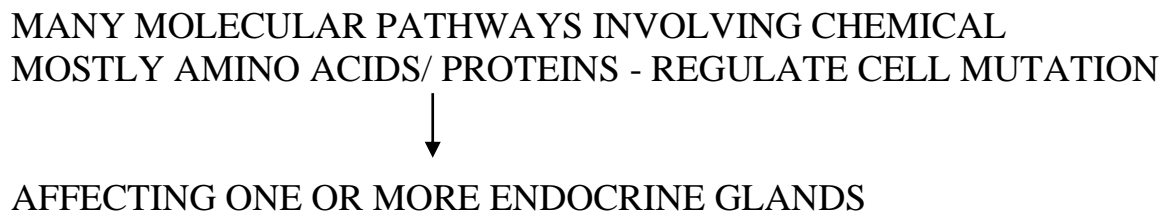
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OBSTRUCTION

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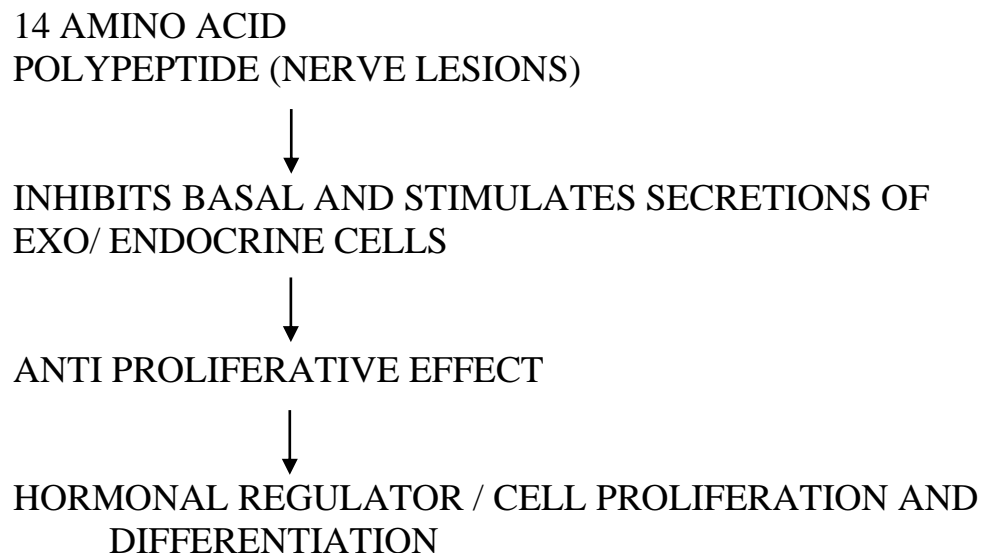
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MOLECULAR BIOLOGY OF ENDOCRINE TUMORS

SOMATOSTATIN -



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GROWTH HORMONES (ANT PITUITARY)
(TWO G PROTEINS)



REGULATED BY GROWTH HORMONE REGULATORY FACTOR/
INHIBITING FACTORS



TUMEROGENESIS

(44)

GROWTH HORMONE

SOMATIC MUTATION

CONVERTING GENE BY ALPHA PEPTIDE CHAIN OF G_s (CELL PHASE)
INTO PUTATIVE ONCOGENES - TERMED *gsp*

(45)

G - PROTEIN - ACTIVATION



G. PROTEIN ALPHA CHAIN GENE - MUTATION



REPLACES ARGININE 179



CYSTEINE / HISTIDINE



RESULTS INTO

↓
CA OVARY / ADRENAL CORTEX
THYROID ?

(46)

ALPHA 12 GENE AND gsp MUTATION FOUND IN 18 OF 42
GROWTH HORMONE (GH)

↓ SEEN IN
PITUITARY TUMOR AND THYROID ADENOMA

(47)

SUGGESTION

G- PROTEIN ALPHA CHAIN PRODUCES MUTATION IN MANY HUMAN
TUMORS/ MORE IN ENDOCRINE TUMORS

(48)

CARCINOID / NEURO ENDOCRINE TUMOR

THYROID TRANSCRIPTION FACTOR-2 IS POSITIVE IN FORE GUT, AND
ABSCENT IN MID AND HIND GUT CARCINOIDS

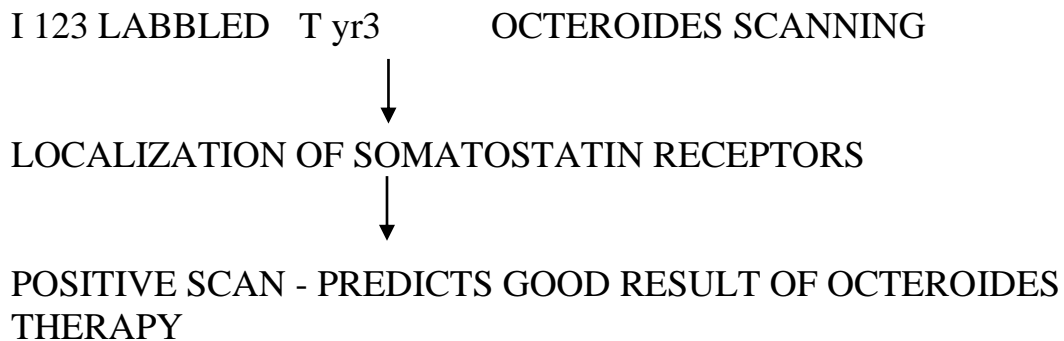
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SOMATOSTATIN ANALOGUE CHOICE OF TREATMENT IN
SYMPTOMATIC CARCINOIDS

(50)

SOMATOSTATIN RECEPTORS

IMAGING - LOCALIZATION OF ENDOCRINE TUMORS



(51)

THYROID NODULE

- FOUND IN 50% OF PEOPLE - MORE THAN 6 YEARS AGE (10 STUDIES 1992-2014)

 - 5% ARE MALIGNANT
 - PAPILLARY - 75%
 - FOLLICULAR - 20%

 - SURVIVAL- 98% - WELL DIFFERENTIATED - I/II STAGE
 - SUBSET - RECURRENCE (MORE III-IV STAGE)
 - POORLY DIFFERENTIATED
 - UN DIFFERENTIATED
 - ANAPLASTIC
- } HIGH MORTALITY

(52)

NEED - ACCURATE IDENTIFICATION OF SUBSET WITH HIGH RISK FACTORS TO GUIDE

- (1) TREATMENT / MANAGEMENT
- (2) PREVENT OVER TREATMENT IN LOW RISK GROUP

(53)

THYROID NODULE
MOST RELIABLE DIAGNOSTIC TOOLS

- U.S.G.
- FNAC/ FNAB

(54)

NATIONAL CANCER INSTITUTE - BETHESDA U.S.D.

RECOMMEND - USG/FNAC
- ADD ALL RISK FACTOR
AND CATEGORIZE CLINICALLY
(BALOCHET.AL. 2008, ALI AND CIBAS 2010)

(55)

STATISTICS - IN THIS GROUP (USG+FNAC+CLINICAL)

FNAC/FNAB - BENIGN (LOW RISK OF MALIG< 0.03
- MALIGNANT - 97% - 99% - RISK OF CA
- INDETERMINATE NODULE 20% - 30%
- ATYPIA
- FOLLICULAR / ONCOCYTIC

HURTHEL CELL - ?

- SUSPICIOUS - FOLLICULAR
MALIGNANCY RISK - 5% - 15%
(BALOCHET.AL.-2008, OHORI AND SCHODET- 2011)

(56)

INDETERMINATE NODULE

REPEAT - FNAC / FNAB - CHANCES OF MALIGNANCY - 5% - 15%

TREATMENT -

- SAME REPORT - LOBECTOMY
- SUSPICIOUS - NEAR TOTAL
(RISK OF MALIGNANCY - 60%-75%)
(IN 25%-30% - OVER TREATMENT)

(57)

INDETERMINATE NODULE

- NODULE EXCISED - BENIGN (DIAGNOSTIC SURGERY) - 10% - 40%
- SURGICAL LOBECTOMY - CASES
- **IF TUMOUR IS LARGER THEN 1CM - SECOND SURGERY
NEAR TOTAL**

(58)

**ADDITIONAL MARKERS
NEEDED TO GUIDE MANAGEMENT
IN INDETERMINATE NODULE - STEPS TO IMPROVE DIAGNOSIS**

- IMMUNO HISTOCHEMICAL STAINS
- MICRO RNA
- GENE EXPRESSION PANEL

BARTOLAZZI et.al. 2008, KENTGEN et.al.-2014

(60)

PANEL AVAILABLE

- GENE MUTATION PANEL
- GENE EXPRESSION PANEL

- INFORMATION - USEFUL IN PROGNOSTIC PREDICTION AND TARGET THERAPY

(61)

ABOVE MARKERS - EVALUATION BASED ON -
SENSITIVITY, SPECIFICITY -

- MOLECULAR TEST - NEGATIVE

(62)

INDETERMINATE NODULE

NEGATIVE TEST (NEGATIVE MOLECULAR TEST)

- HIGH VALUE % FOR BENIGN
 - TREATMENT - SURVEILLANCE

POSITIVE TEST (MOLECULAR TEST)

- HIGH VALUE % - MALIGNANCY
- TREATMENT - NEAR TOTAL THYROIDECTOMY

(64)

MOLECULAR TESTS HAS INSTITUTIONAL DIFFERENCES

CORRELATION WITH USG, FNAC, AND CLINICAL
RESULTS SENSITIVITY GOES UPTO 97%-99 %

(65)

MOLECULAR GENETICS OF THYROID CANCER

- 1990 - 25% OF THYROID CANCER WERE OF GENETIC ORIGIN
 - 2000 - 35% OF RAS/PET/PTC/TP53TRK, PTEN, B CATEMIN PAY
 - 2005 - 70% OF BRAF/PIKCCA/BRAPAKA19
 - 2014 - 90% OF AKT/ETV6/NT RKS/STRN/ALK
-

(66)

IS IT A GENETIC DISORDER OF FAMILIAL TYPE ?

(67)

BIOLOGICAL - PATHWAY - LEADING TO POINT MUTATION IS

MAPK PATHWAYS

MAPK PATHWAYS IS A MOLECULAR PROCESS LEADING TO MUTATION IN THYROID CELL CAUSING - MALIGNANCY (98%-99%)

- Kimura et.al. - 2003
 - Soares et.al. - 2004
 - Fratinine et.al. - 2007
-

(68)

MAPK CYCLE

MITOGEN ACTIVATED PROTEIN KINASE

+

PHOSPHYTIDYLNESTRAL - 3 KINASE (P13K)

+

A.K.T.

ACTIVATES POINT MUTATION OF GENES

- BRAF/RAS
 - RET/PTC/TRK
- } PAPILLARY CA 98-99%

(69)

FOLLICULAR CA -

- RAS GENES (ALL GROUP) - ENCODE
- G-PROTEINS - SURFACE OF CELL MEMBRANE
- SIGNALS - P13K/AKT PATHWAYS
- RESULT IN CELL MUTATION

- 40-50% (FOLLICULAR)
- 20% (FOLLICULAR VARIANTS)
- 20% (FOLLICULAR ADENOMA)
- 10% (MEDULLARY + FOLLICULAR) FAMILIAL TYPE

(70)

FOLLICULAR CA -

PAX8 - GENE PAIRED DOMAIN TRANSCRIPTION FACTOR

PPARY - PEROXISOME PROLIFERATION ACTIVATED RECEPTOR GENE

- RESULTS IN CELL MUTATION TO
- FOLLICULAR CA 35%
- HURTHLE CELL CA LOW PREVALENCE

(71)

MEDULLARY CA

- RET - PROTO ONCO GENE - ACTIVATED BY POINT MUTATION (GERM LINE MUTATION) - ALL CASES OF FAMILIAL - MEDULLARY CA
-

(72)

ANAPLASTIC CA, |POORLY DIFF CA

AGGRESSIVE FOLLICULAR -

SOMATIC MUTATION OF PTEN/AKT1/CT NNB (GENES)

REGULATE TUMEROGENESIS

(73)

TP-53 (SUPPRESSOR GENE)

- REGULATES CELL CYCLE, AND DNA REPAIR
 - **IT IS MARKER FOR PROGNOSTIC VALUE**
-

(74)

UTILITY MUTATION MOLECULAR MARKER -

- **PRE OP DIAGNOSIS + TREAT STRATEGY**
 - **PROGNOSTIC FACTOR**
-

(75)

MULTI NODULAR GOITRE AND MALIGNANCY

- SAME INCIDENCE AS SOLITARY NODULE
 - **FNAC/FNAB - LIMITED ROLE DUE TO MULTIPLE NODULES**
-

(76)

-ONE INSTITUTION STUDY (1994-2004)

TOTAL CASES UNDERWENT THYROIDECTOMIES

- 1791- CASES
 - 838 - M.N. GOITRE LABELLED AS CA
 - **113 - SINGLE NODULE <1 CMS (44%) not detected preoperative**

- 140 - CASES NOT RECOGNIZED BY PREOPERATIVE
EVALUATION, NODULE / NODULES > 1CM
VALUE OF FNAC/FNAB - **LOW PREDICTIVE VALUE**

- NEED BETTER PREDICTIVE VALUE FACTORS
- INADEQUATE SURGERY-**31%**, REOPERATION -**36%**

(79)

- FNAC - NEGATIVE RESULT DOES NOT RULE OUT
MALIGNANCY

STILL THE BEST BET

CHALLENGES AND DIAGNOSTIC DILEMMA
ASSOCIATED WITH INDETERMINATE CYTOLOGY OF THYROID
NODULE SINGLE - MULTIPLE

(81)

THYROID TOXICOSIS AND THYROID MALIGNANCY

WORLD JOURNAL OF SURGERY (2004)

- 10 DIFFERENT STUDIES
- ANALYTICAL DATAS -
- | | |
|----------------------------|---------------|
| - % OF MALIGNANCY | |
| - TOXIC GOITERS | - 2.6% |
| - MULTI NODULAR TOXIC G | - 3.3% |
| - UNI NODULAR TOX.G | - 2.9% |
| - DIFFUSE TOX. G. (GRAVES) | - 1.1% |

(82)

ANALYSIS OF THYROID CANCER OPERATED
(One Example)

- 554 - PATIENTS
Associated Thyroid Conditions
 - HYPERTHYROIDISM - 4.2%
 - NON TOXIC COLLOID GOITRE - 2.2%
 - TOXIC DIFFUSE G (GRAVES D) - 21.2%
-

(84)

AMERICAN THYROID ASSOCIATION GUIDELINE (2015) FOR SINGLE
NODULE AND DIFF. THYROID CANCER

- **GRAVES DISEASE -**
MALIGNANCY - MULTIFOCAL AND AGGRESSIVE
 - NEEDS PROPER EVALUATION
-

(85)

RADIO ACTIVE IODINE AND
THYROID CARCINOMA

131 - FOR THYRO TOXICOSIS -

REDUCES THE CHANCE OF MALIGNANCY BY DESTRUCTION OF
MUTATED CELL IN SMALL CANCEROUS FOCI (**MICRO CANCER,**
REMAIN IDEAL FOR YEAR)

(86)

NODAL METASTASIS IN THYROID CANCER

- EARLY AND FREQUENT NODAL METS IN DIFFERENTIATED CANCER
 - **OLD AGE, NUMBER, SIZE OF INVOLVED NODES AFFECT PROGNOSIS**
 - CONSISTENT PATTERN OF NODAL INVOLVEMENT
 - CENTRAL COMPARTMENT (6-7 Neck group) Primary Involvement
 - FOLLOWED BY LATERAL COMP. (2-5- group)
 - SKIP METS TO LATERAL - WITHOUT CENTRAL - SEEN IN - **20% CASES**
-

(87)

- **UNLIKE MOST OTHER SOLID CANCER**
 - **IN THYROID CANCER - METS TO REGIONAL NODES - NO IMPACT ON PROGNOSIS**
 - **MAJORITY OF PAPILLARY T.C. - NODAL METS HARBOR MICRO METS - WHICH ARE INDOLENT**
-

(88)

AMERICAN THYROID ASSOCIATION AND OTHER SCORING SYSTEM

- GAMES
 - MACIS
 - AMES
-
- DO NOT INCLUDE NODAL METASTASIS IN SYSTEM
-

(89)

PREDICTOR OF NODAL METS

- MULTI FOCALITY
 - LYMPHO VASCULAR INVASION
 - ABSENCE OF TUMOUR CAPSULE
 - EXTRA THYROID EXTENSION
-

(90)

AMERICAN THYROID ASSOCIATION SCORING SYSTEM

- LOW RISK Nodule - SIZE < 0.2CM
NUMBER ≤ 5
WILL BE CONSIDERED AS NO RISK NO GROUP
 - SUCH PATIENT - NO NODAL SURGERY AND NO ADJUVANT RADIO ACTIVE IODINE
-

(91)

AMERICAN THYROID ASSOCIATION GUIDELINE (2015)

- DIFFERENTIATE T.C. - CENTRAL COMPARTMENT NECK DISSECTION TO BE DONE IN THYROID CA - T3 - T4 ONLY
-

(92)

EUROPEAN / JAPANESE/OTHER
INTERNATIONAL BODIES

- **DO NOT RECOMMEND - PROPHYLACTIC CENTRAL NODE DISSECTION -**
 - NO ADJUVANT RAI
-

(93)

DIAGNOSTIC / PREDICTIVE FACTORS

- SO MANY CONTROVERSIES IN PREDICTIVE FACTORS HAS LEAD
 - GENOMIC STUDIES OR MOLECULAR BIOLOGICAL PATHWAYS /
CELLULAR GENOMIC - TO GIVE PROPER ANSWER - REGARDING
MANAGEMENT AND PREDICTION FOR SURVIVAL
-

(94)

MICRO RNA GENE - IN DIAGNOSIS AND PREDICTOR FACTOR IN
PAPILLARY CA

- ALTERATION IN RET/RAS/BRAF

PATHWAYS -

MICRO RAAS - TRANSCRIPTIONALLY UPGRADED IN
TUMOR CELLS

- **VERY HIGH POSITIVITY** - 99%
-

(95)

EVALUATION OF SERUM SOLUBLE INTRA CELLULAR ADHESION
MOLECULE (**S₁CAM**) - AS

PROGNOSTIC - FACTOR

(AVAILABLE IN USA/EUROPE/JAPAN)
