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Review Article

The molecular pathology of thyroid neoplasms

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ABSTRACT

The Bethesda system of reporting thyroid cytology is being currently adopted worldwide. Rapid advances have been made in the understanding of the genetics of thyroid cancers. Common genetic mutations include RAS, BRAF, p53, B Catenin, and PAX8/PPARγ, genes. BRAF mutations tumours are often aggressive. BRAF mutations commonly affect papillary carcinomas in the BRAF MEK ERF intracellular pathway, whereas RAS mutations commonly affect follicular carcinoma in the PL3 kinase pathway. TK inhibitors, RAS, RET, non RET, PL3, HDAC, DNMT etc. inhibitors are also being considered for therapy against these tumours.

INTRODUCTION

Historically thyroid cancers have always intrigued pathologists and clinicians alike by their seemingly unpredictable and sometimes perplexing nature.[1] They have long known to comprise of a very heterogeneous group of tumours that shows marked diversity in biological behavior. Those active in this field have inevitably had unexpected surprises while dealing with them. Though they form a meager 1% of all cancers, they are the most common endocrine cancers, and the overall incidence especially that of papillary microcarcinomas is increasing over the last few decades.[2] Most of the follicle derived neoplasms are low grade with very good 10 years survival rates. The rarer high grade neoplasms are some of the most aggressive tumours known to afflict mankind.

REVIEW

About 5-10% of the general population has thyroid nodules, many are asymptomatic or the lesions are detected incidentally.[3] Of these nodules, however only 8-19% proves eventually to be malignant. These findings prompted a surge in preliminary assessment of thyroid nodules by fine needle aspiration cytology in an attempt to reduce unwarranted radical surgery for benign lesions. However inherent limitations of cytology resulted in unacceptable false negative or rarely false positive cases even in expert hands. About 20-30% of patients currently generate an "indefinite for malignancy" report on cytology resulting in a clinical management quagmire. And this fact has virtually remained unchanged for the last two decades. The Bethesda System of grading thyroid cytology has been developed to address some of these issues with some success (Table. 1).[4]

For better clinico-pathological correlation, both the pathologist and clinician need to be familiar with the terminology, categorization and limitations of the Bethesda System, and the cancer risk involved for each cytology category. The management for each category is specified in the classification, and both should also be aware of them. For example a "benign" category still carries up to 3% cancer risk, and hence still calls for clinical follow up (Table.2). A "malignant" category implies up to 3%

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Table 1: The Bethesda System of reporting thyroid cytology with the implied cancer risk for each category

S.N.	Category	Implied cancer risk	Management
1	Non-diagnostic or Unsatisfactory	-	Repeat FNAC under USG guidance
2.	Benign	0-3%	Clinical follow up
3	Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	5-15%	Repeat FNAC
4	Follicular Neoplasm or Suspicious for a Follicular Neoplasm	15-30%	Lobectomy
5	Suspicious for Malignancy	60-75%	Lobectomy +/- frozen section, total thyroidectomy
6	Malignant	97-99%	Total thyroidectomy

*Lobectomy can also be considered on the basis of clinical or USG findings.

Tumour	Prevalence	F:M ratio	Age	LN mets	Distant mets	5Yrs survival
Papillary	85-90%	2-4:1	20-50	<50 %	5-7%	>90%
Follicular	<10%	2-3:1	40-60	<5%	20%	>90%
PD ca	0-7%	0.4-2.1:1	50-60	30-80%	30-80%	50%
UD ca	2%	1.5:1	60-80	40%	20-50%	1-17%
Medullary	3%	1.1:1	30-60	50%	15%	80%

Table 2: *Common thyroid tumours and their behavior*

Tumour	Prevalence	F:M ratio	Age	LN mets	Distant mets	5Yrs survival
Papillary	85-90%	2-4:1	20-50	<50 %	5-7%	>90%
Follicular	<10%	2-3:1	40-60	<5%	20%	>90%
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UD ca	2%	1.5:1	60-80	40%	20-50%	1-17%
Medullary	3%	1.1:1	30-60	50%	15%	80%

Table 3: *Genetic mutations in common thyroid tumours*

chances of a non malignant pathology. Therefore the role of the pathologist is limited to interpretation of the cytology and the decision of performing a two step thyroid surgery or one step total thyroidectomy in a "malignant" cytology category should rest with the clinician, as other variables need to be considered like clinical features, other laboratory data and imaging findings. Intraoperative frozen sections, if available, can solve some of these problems.

Till of late study of the pathology of thyroid tumours has been largely limited to morphological analysis of cytology and histological specimens. Efforts were made in the past to categorize the lesions on the basis of whether the neoplastic cells were derived from follicular, para-follicular or other cell origin. Even the differences between papillary and follicular carcinomas were found to be imprecise with the follicular variant of papillary carcinomas showing nuclear features of papillary carcinomas, but showing follicle formations and genetic changes reminiscent of follicular carcinomas (Table.3). And although appearing morphologically similar, many of these tumours seem to show different grades of biological behavior depending on the nature of genetic changes,

Interests in genetics of thyroid tumours started with low grade tumours like papillary carcinomas often showing RET/PTC gene rearrangement (fig. 1).[5] More recent studies show mutations of the RAS gene and BRAF genes.[6,7] The higher grade tumours like undifferentiated or poorly differentiated carcinomas show p52 gene and B catenin (CTBNN1) gene mutations.[8] And the distinction between different thyroid lesions become blurred as even some nodules of multinodular goiters show TSH R gsp suggesting clonality. Some of thyroid cancers show alterations of cellular key signally MAPK receptor effectors (fig.2). Abnormal DNA methylation histone modification and disorders of microRNA have also been noted. Genetic study has resulted in further identification of a subset of more aggressive papillary carcinomas: the tall cell, columnar cell, diffuse sclerosing, solid and follicular variants of PTC. The diffuse variant of follicular PTC has a worse prognosis than an encapsulated variant.

Papillary microcarcinomas are frequently seen in up to 37% of autopsy specimens.[9] They are being increasingly picked up due to better thyroid imaging techniques, and the use of USG guided FNAC. They are usually incidentolomas and mostly of little clinical significance. They usually show more than 99% 10-15 years survival rates. Risk factors of mortality from microcarcinomas include: age older than 45 years, male sex, minority racial group, lymph node metastases, extra thyroidal extension or superficial location, intra glandular spread or multifocality, peritumoral fibrosis, and BRAF positivity.

BRAF V600E mutation correlates with tumours showing aggressive characteristics, extra thyroidal extension, advanced stage at presentation, lymph node or distant

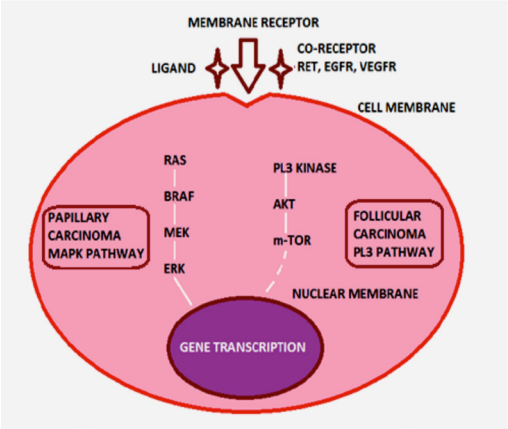
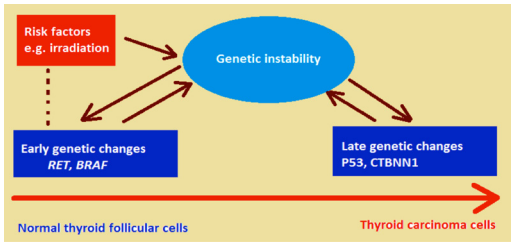


Figure 1: Cellular pathways of papillary and follicular thyroid tumours.



Figures 2: Early and late genetic changes in thyroid tumours.

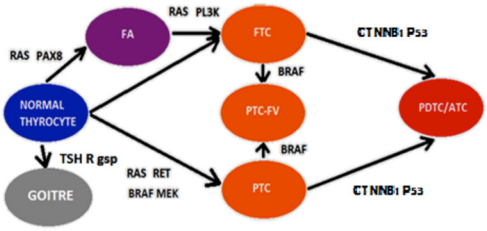


Figure 3: The spectrum of genetic changes in thyroid tumours.

metastases, increased tumor recurrence and tumor-related mortality. BRAF mutation is also a useful prognostic indicator.[10-13] The presence of a BRAF mutation in an FNA sample indicates more than 99% probability of thyroid cancer, and it serves as a marker of aggressive behavior. Thus preoperatively detected BRAF positive nodules should be extensively excised with more aggressive treatment and follow-up.

RAS (NRAS, HRAS, KRAS) point mutations are found in the follicular variant of papillary carcinomas[14], follicular carcinomas, and follicular adenomas. Papillary carcinomas with RAS mutations are usually encapsulated with a low rate of lymph node metastases. The presence of RAS mutations in cold adenomatous nodules and goiter nodules suggests that these lesions are likely true neoplasms, and they should be categorized as follicular adenomas. Follicular and oncocytic carcinomas also show PAX8/PPARγ rearrangement (fig.3).[15] The tumours in these cases are small, occur in younger people and tend to show vascular invasion.

Genetics in the management of thyroid neoplasm:

Conventional therapy for thyroid cancer at present include total thyroidectomy, ablative radioactive iodine use, TSH suppression, follow up with thyroglobulin levels and treatment of recurrent disease with radiation. Phase I and II clinical trials are underway to evaluate the role of tyrosine kinase inhibitors for thyroid cancers.[16] Sorafenib and vandetenib are some of the newer drugs undergoing trials. There are a host of other potential RET and non RET tyrosine kinase inhibitors, RAS, RAF, and MEK inhibitors,17 PL3, ATK, mTOR inhibitors, and DNMT and HDAC inhibitors all awaiting future usage. Understanding the molecular biology of these tumours could mean improvement in our understanding of the disease process and help better diagnose, prognosticate and manage them.

CONCLUSION

As with many other cancers recent genetic research has vastly improved our understanding of these once mystifying tumours. At present this knowledge is helping in our understanding of their behavior. This could translate in better diagnoses, categorization into meaningful groups, and help manage even advanced stage or resistant disease by therapy based on genetic lines in the future.

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