The History and Histology of Follicular Lesions of Thyroid

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Differential Diagnosis: Follicular Lesions of Thyroid

Non-neoplastic

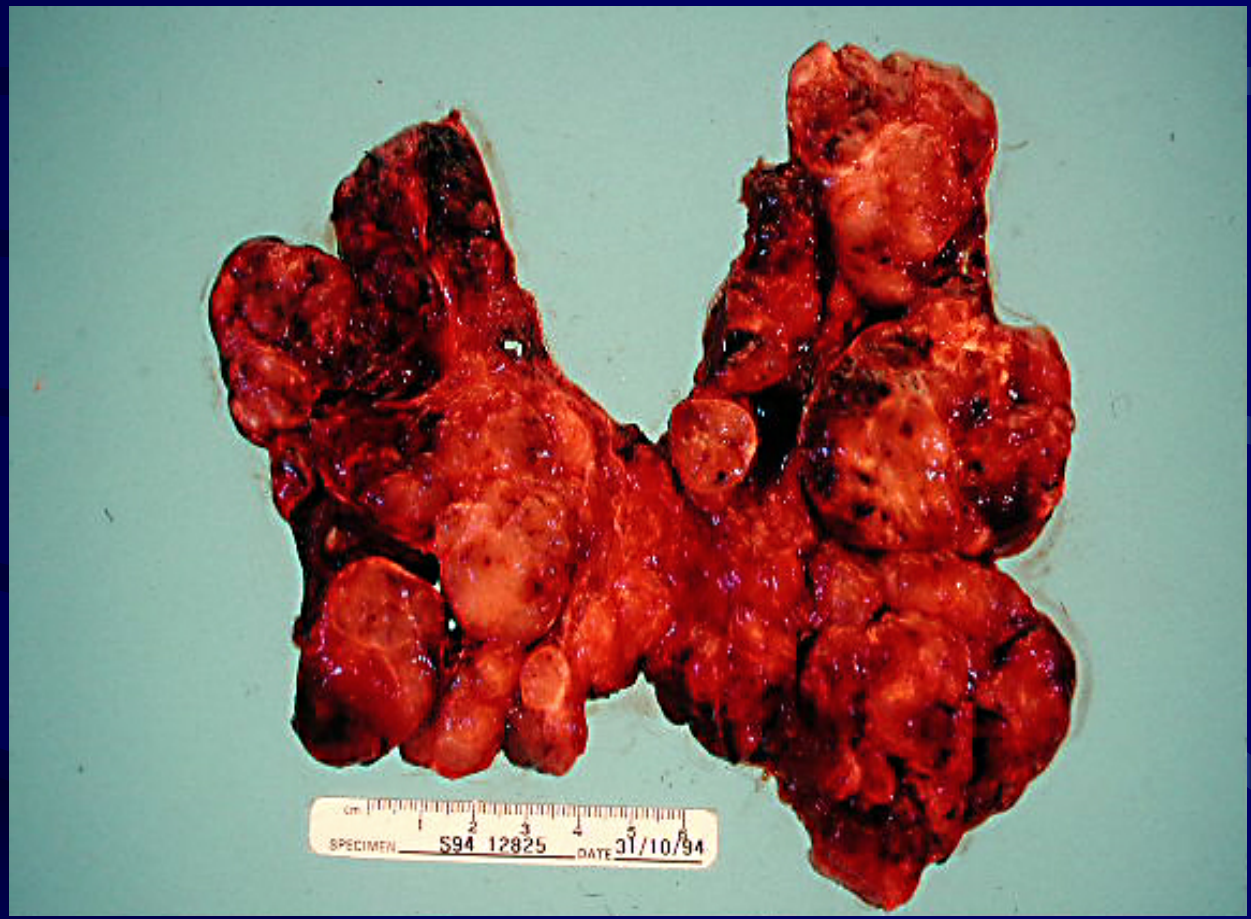
- Inflammatory Lesions
  - Inflammatory foci
  - Compensatory regenerative nodules (?TSH, ?TGI)
- Hyperplasia

Neoplastic

- Follicular epithelial neoplasms
  - Follicular adenoma
  - Differentiated Carcinoma: Papillary, Follicular

Sporadic Nodular Goiter

- Multinodular "colloid" goiter
- Occasionally associated with hyperthyroidism
  - "Plummer's disease"
- Etiology and pathogenesis NOT understood



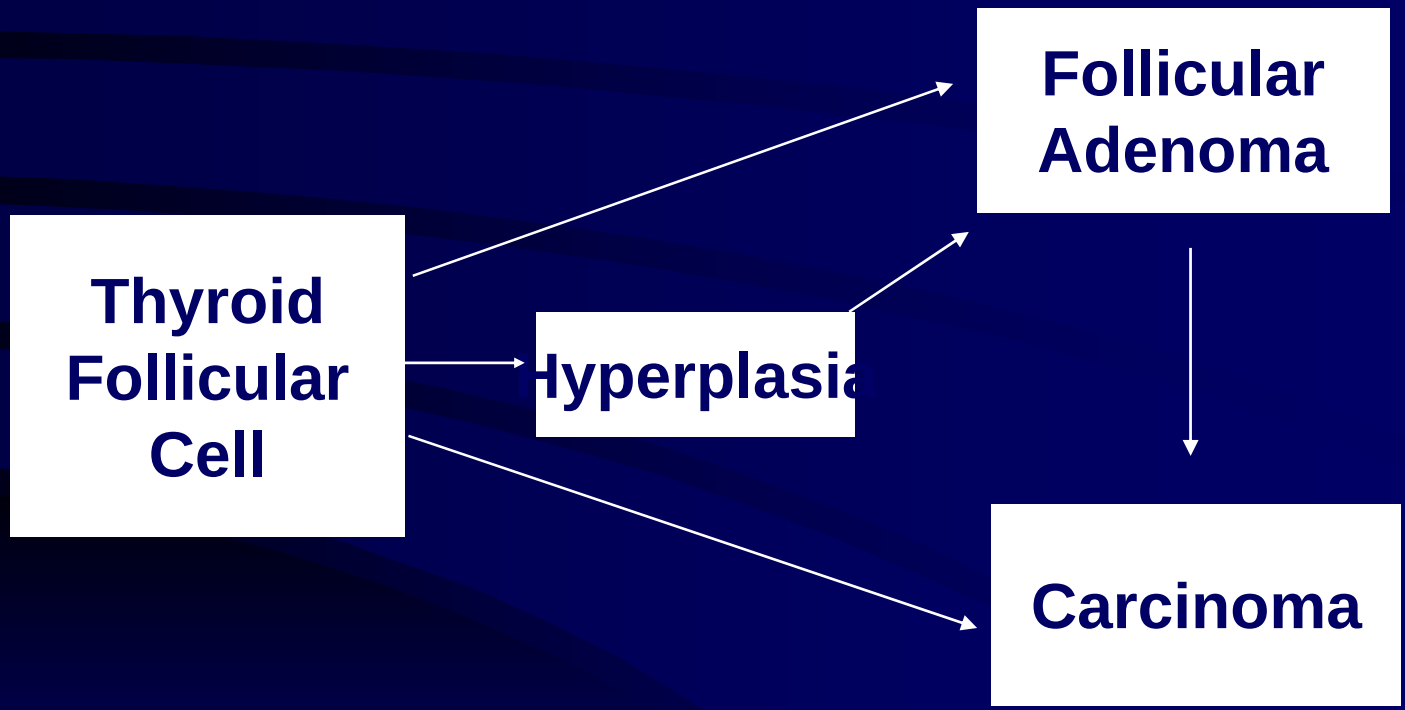
Clonality Studies of Sporadic Nodular Goiter

- Dominant nodules often monoclonal
- Nodules may show LOH or aberrant methylation
- Multiple nodules from a single goiter exhibit activation of the same allele

?Diagnostic criteria

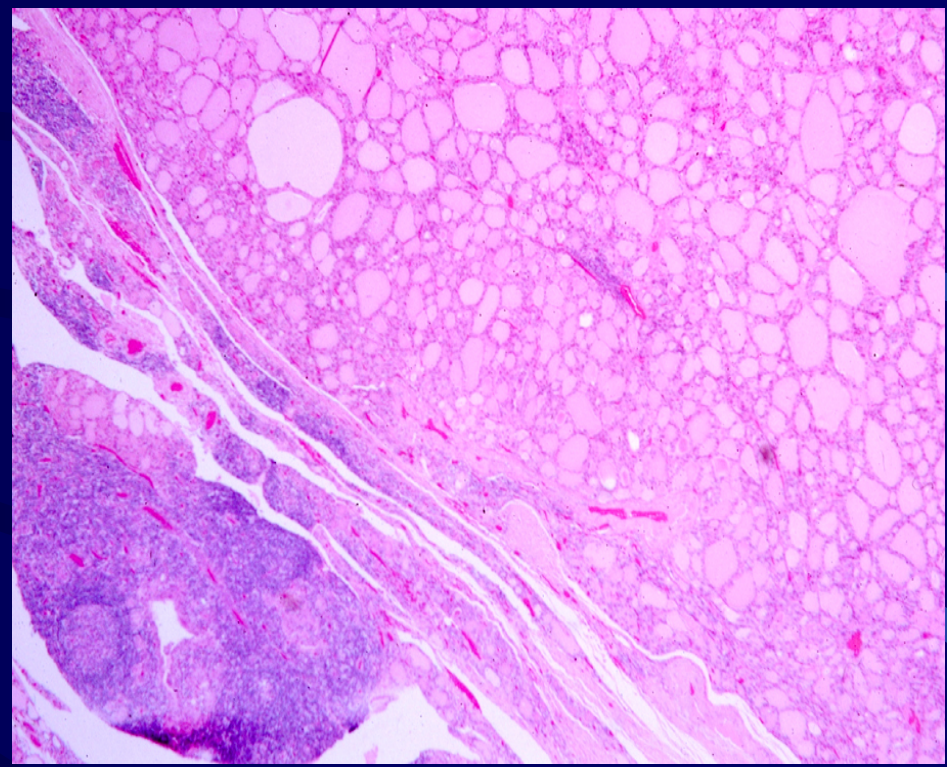
Apel et al; Diagn. Mol. Pathol. 1995; 42:113-121

Diagnostic Implications: Hyperplasia-Neoplasia Sequence



Immunologic Basis of Follicular Nodules: TSH Receptor Antibodies

- TSI stimulate hormone synthesis
- TGI stimulate cell division



Does TGI cause nodules in thyroiditis?

Are they regenerative?

Or are they neoplastic?

Are they papillary ca?

Definitions: Hyperplasia vs Neoplasia

- An increase in the number of cells in an organ or tissue that is induced by known stimuli
- A controlled process that stops when the environmental stimulus is removed

- A proliferation of cells that exceeds and is uncoordinated with that of normal tissues
- An uncontrolled process that persists independent of environmental stimulation

Classical Criteria:
Hyperplasia *vs* Neoplasia

- Multiple
- Poorly encapsulated
- Architectural heterogeneity
- Cytological heterogeneity
- Comparable areas in adjacent gland
- No compression of surrounding gland

- Solitary
- Encapsulated
- Uniform architecture
- Cytological homogeneity
- Different from surrounding gland
- Compresses surrounding gland

Thyroid Follicular Cell Lesions: Hyperplasia *vs* Neoplasia

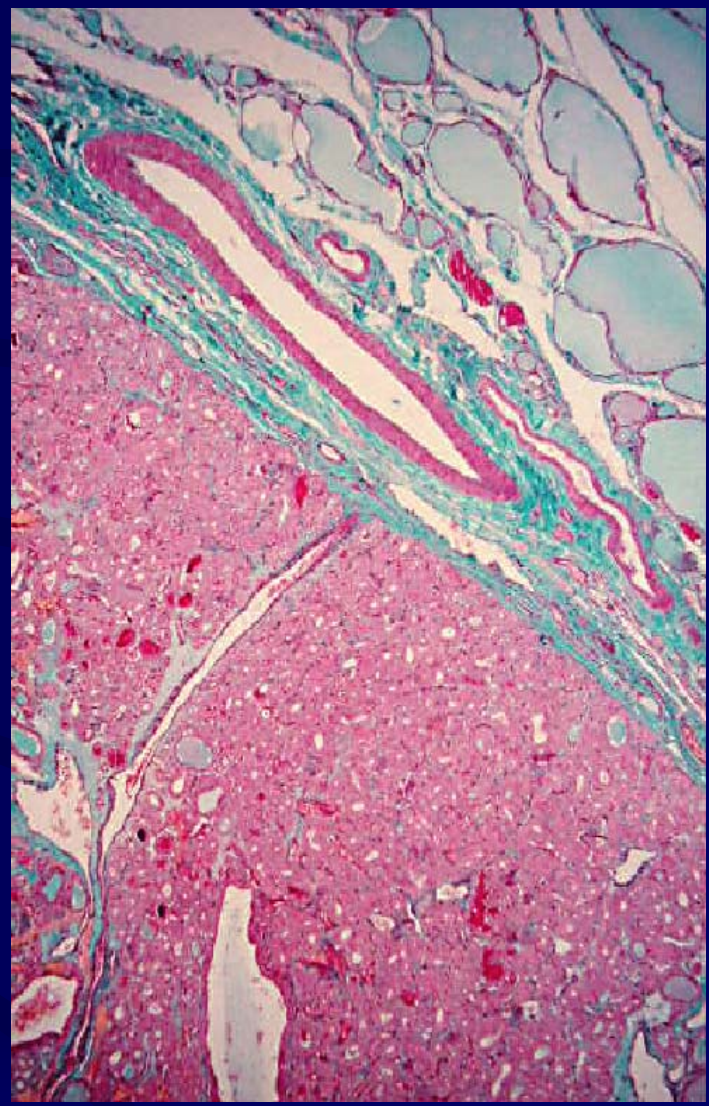
- Nodular goiter
- Hashimoto's thyroiditis

Which nodules are reactive/hyperplastic and which are neoplasms, benign or malignant?

Classification: Follicular Adenomas

- Simple
- Microfollicular
- Trabecular
- Oxyphil
- Atypical
- Papillary
- Signet ring cell

*no prognostic significance



Criteria for Diagnosis of Follicular Carcinoma

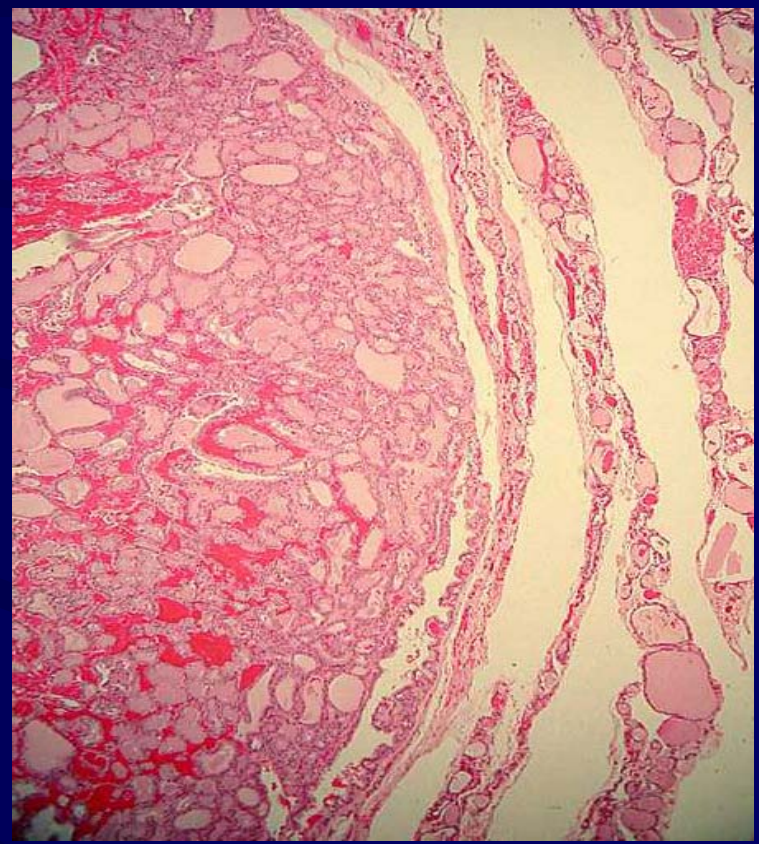
- As per criteria of follicular adenoma

and

- Capsular or vascular invasion

What If There Is NO Tumor Capsule?

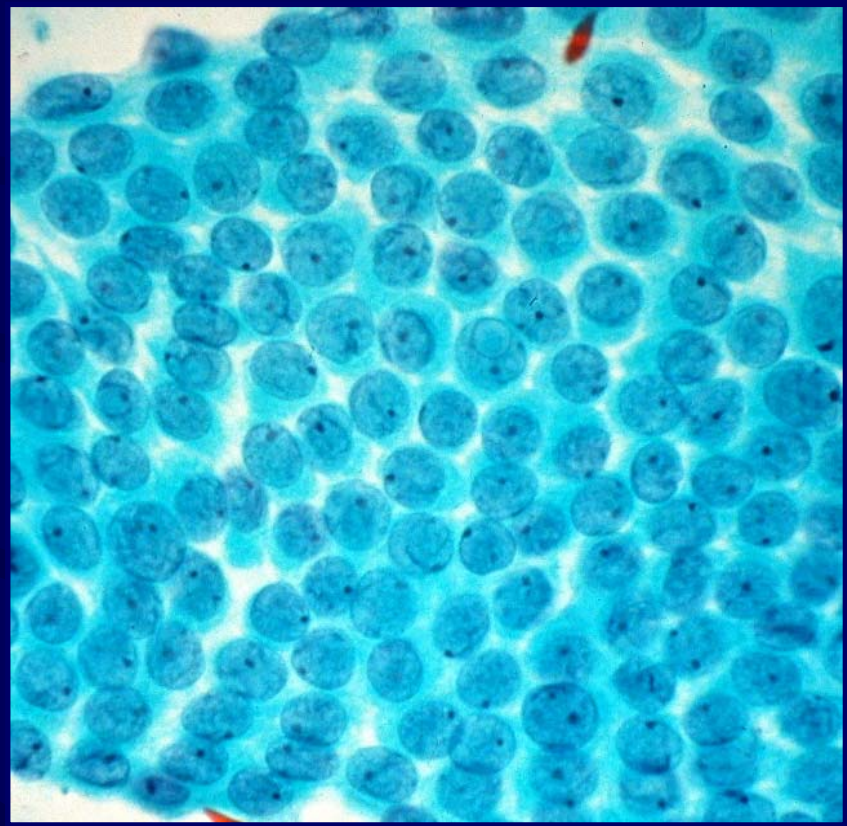
- Capsular invasion cannot be evaluated
- Invasion must be assessed as infiltration into surrounding parenchyma, perineural or vascular involvement



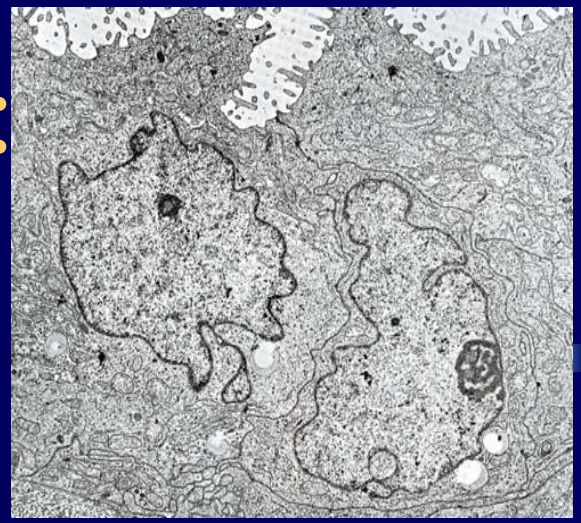
Papillary Carcinoma: A History

Lindsay 1960:

- Papillary carcinoma is recognized to have a “delicate, often indented nuclear membrane” and “opaque, ground-glass appearance”
- A tumor with such nuclei would behave biologically like papillary tumors, even if the structure were follicular



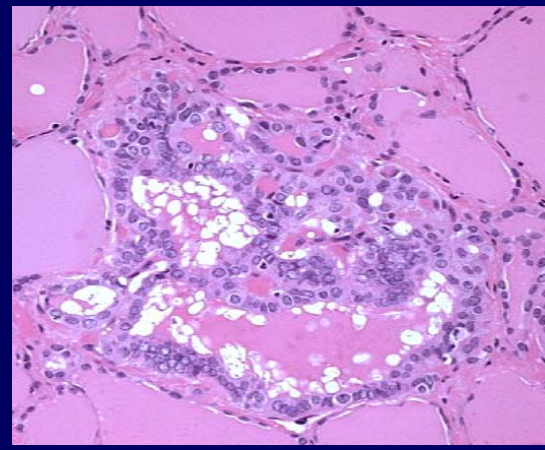
Papillary Carcinoma: A History



Meissner 1983:

- “The concept that follicular cancers with clear nuclei represent papillary carcinomas has been generally accepted and has led to the awkward term ‘follicular variant of papillary carcinoma.’ Fortunately, such tumors are infrequent.”

Papillary Carcinoma: A History



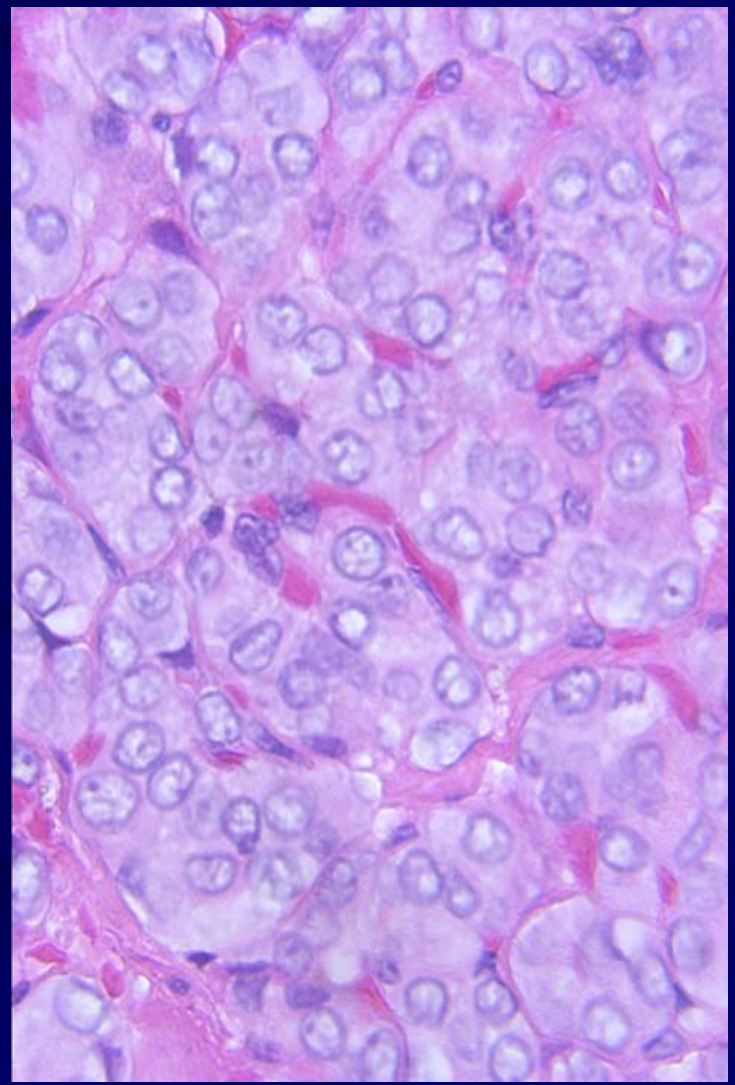
Rosai et al 1992:

- “The two morphologic features that best characterize typical papillary carcinoma are the papillae and the nuclear changes
- “The nuclei of the papillary carcinoma cells usually have a distinctive appearance, which in recent years has acquired a diagnostic significance at least comparable to that of the papillae”
- Follicular variant “Regardless of follicle size, the nuclei of the lining cells have features analogous to those of conventional papillary carcinoma”

Papillary Carcinoma: A History

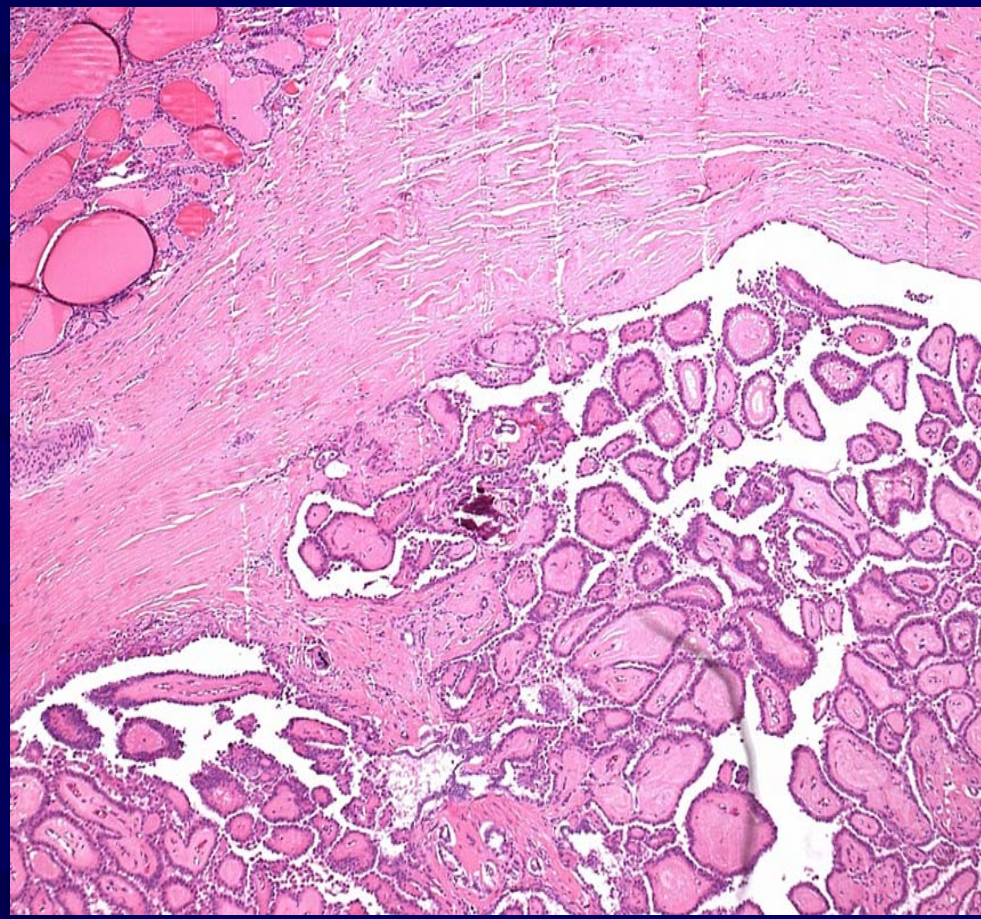
WHO 2004:

- “A malignant epithelial tumour showing evidence of follicular cell differentiation and characterized by distinctive nuclear features”



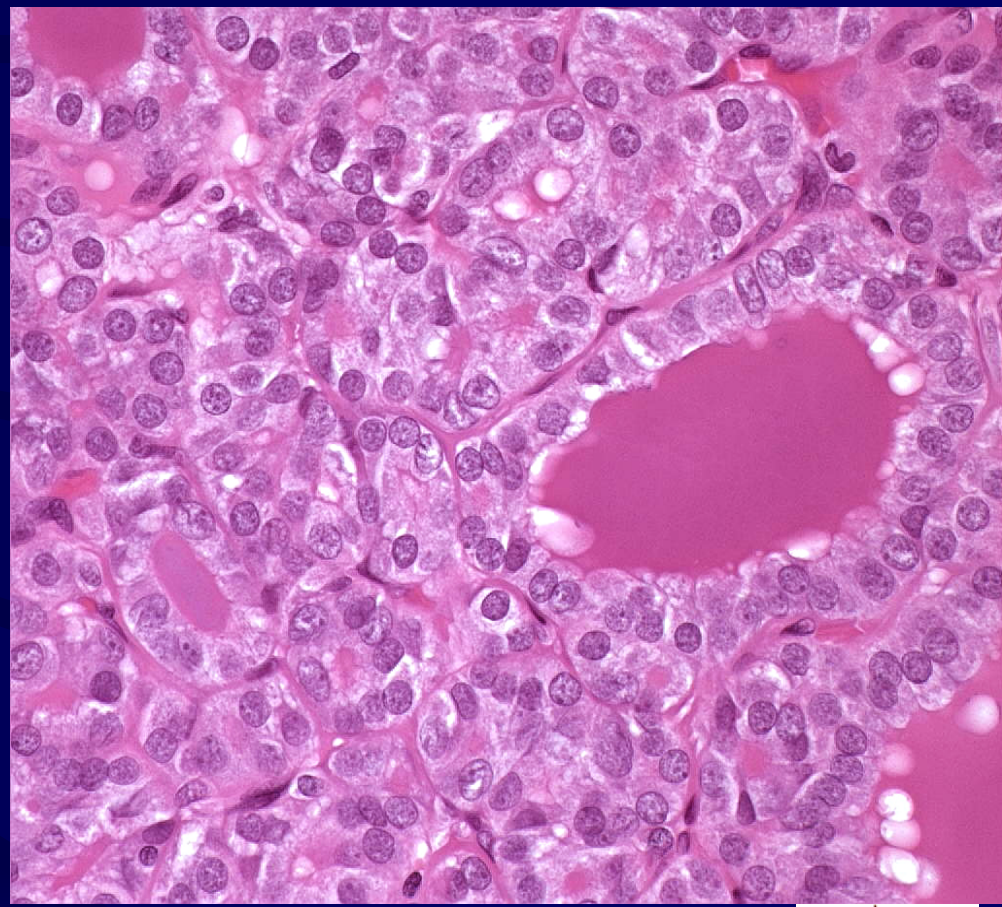
Papillary Carcinoma: Today

- Case 1: 32 y/o female
  - 2 year history of neck mass, stable in size
  - No thyroid dysfunction, otherwise well
  - Thyroidectomy
  - 2 cm papillary lesion; 2/5 lymph nodes positive for metastatic carcinoma



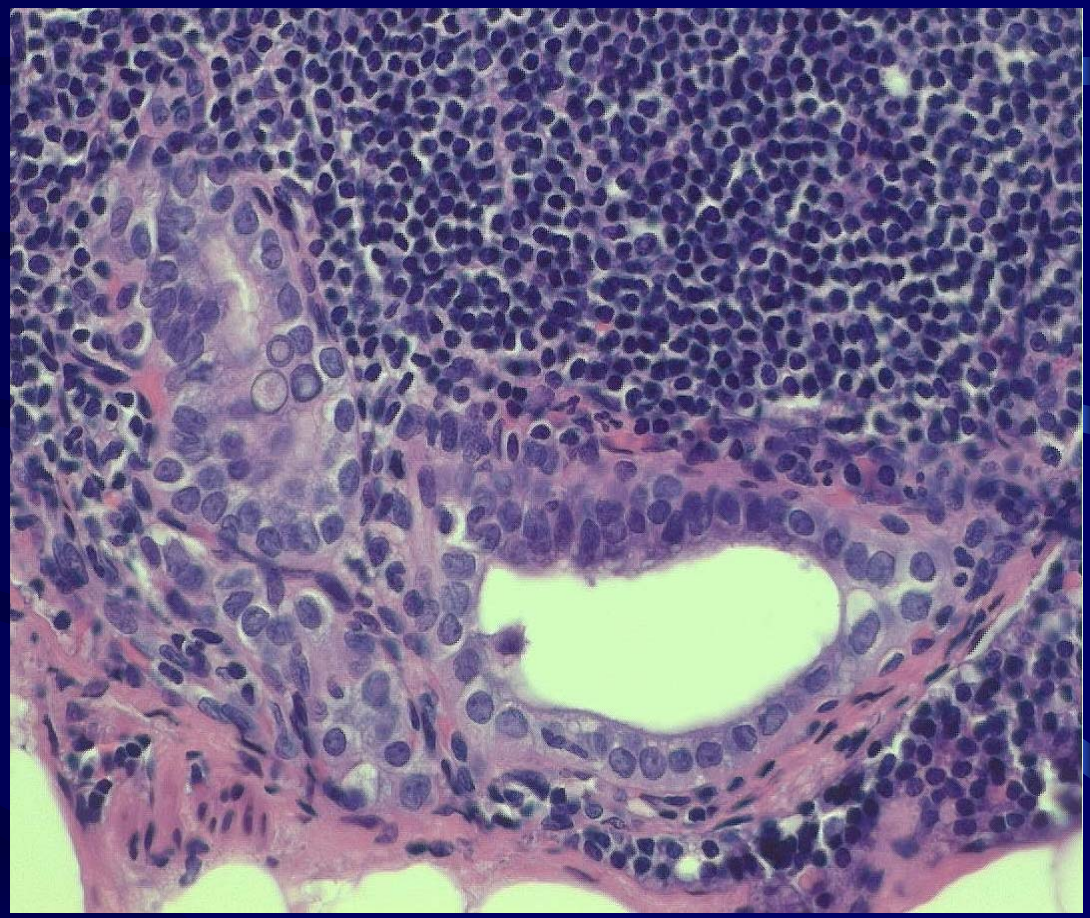
Papillary Carcinoma: Today

- Case 2: 28 y/o female
  - 18 month history of neck mass
  - No thyroid dysfunction, otherwise well
  - Thyroidectomy
  - 2.4 cm papillary lesion; 1/3 lymph nodes positive for metastatic carcinoma



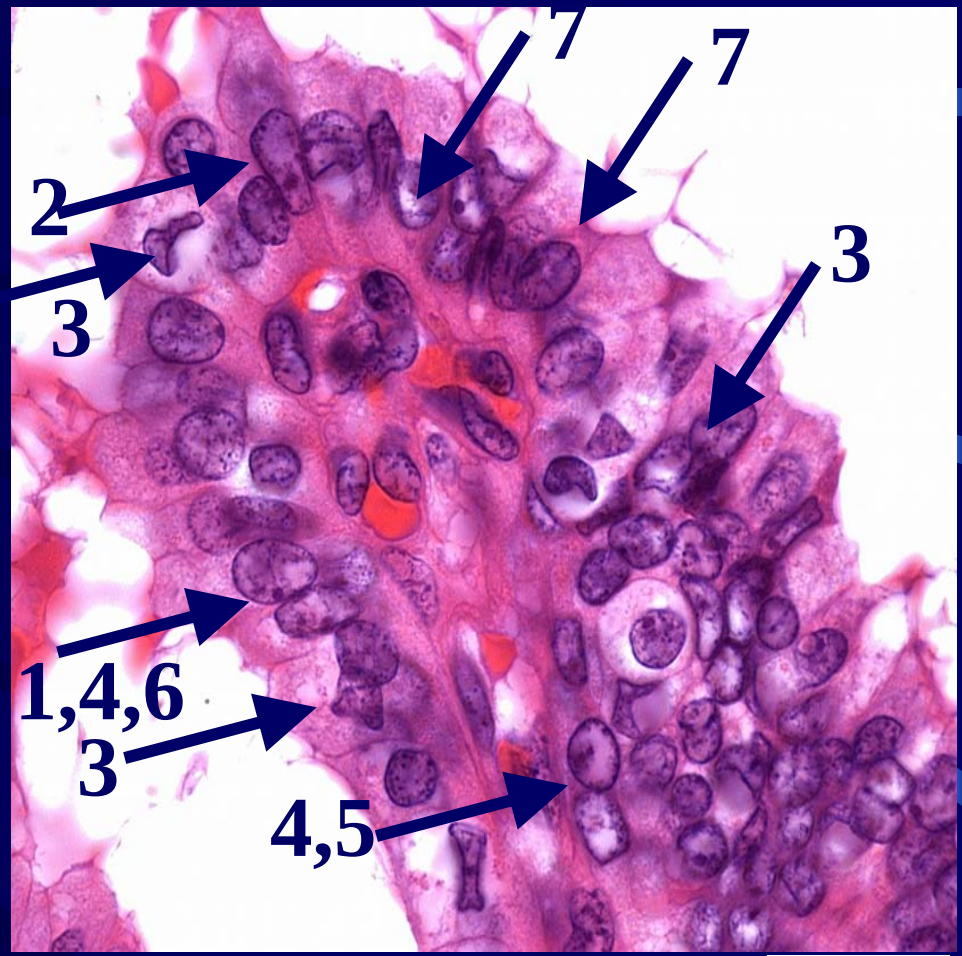
What is the Biology of These Two Lesions?

- Usually indolent
- Lymph node metastases
- Response to I^{131}
- Occasional systemic spread



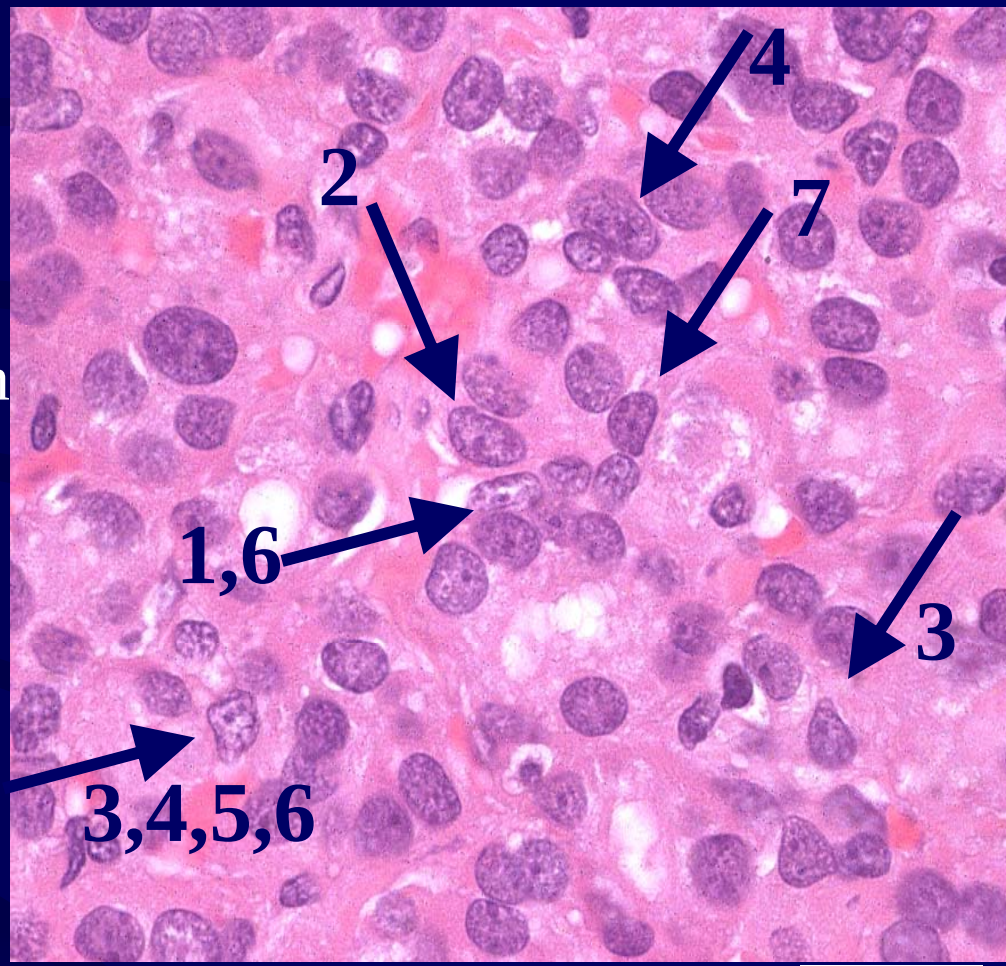
Cytology: Case 1

1. Crowded overlapping nuclei
2. Enlarged, elongated nuclei
3. Irregular nuclear membrane
4. Pale vacuolated nucleoplasm
5. Peripheral margination of chromatin
6. Multiple micronucleoli
7. Nuclear grooves
8. (Nuclear pseudoinclusions)



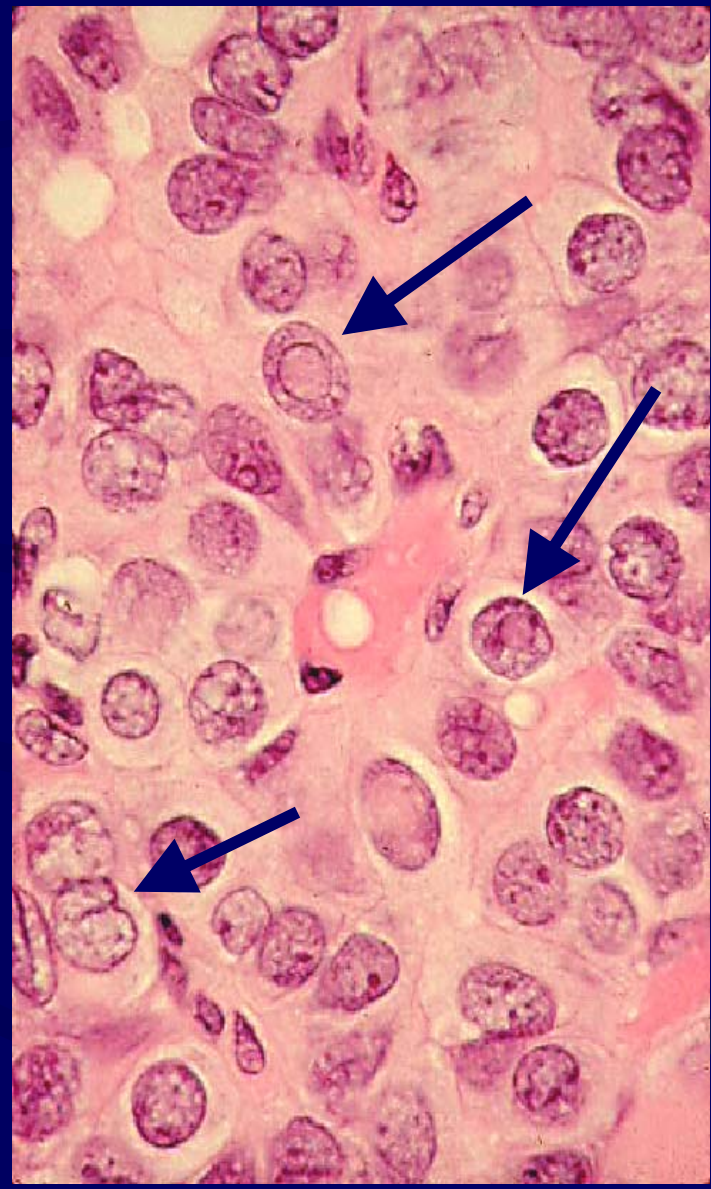
Cytology: Case 2

1. Crowded overlapping nuclei
2. Enlarged, elongated nuclei
3. Irregular nuclear membrane
4. Pale vacuolated nucleoplasm
5. Peripheral margination of chromatin
6. Multiple micronucleoli
7. Nuclear grooves
8. (Nuclear pseudoinclusions)



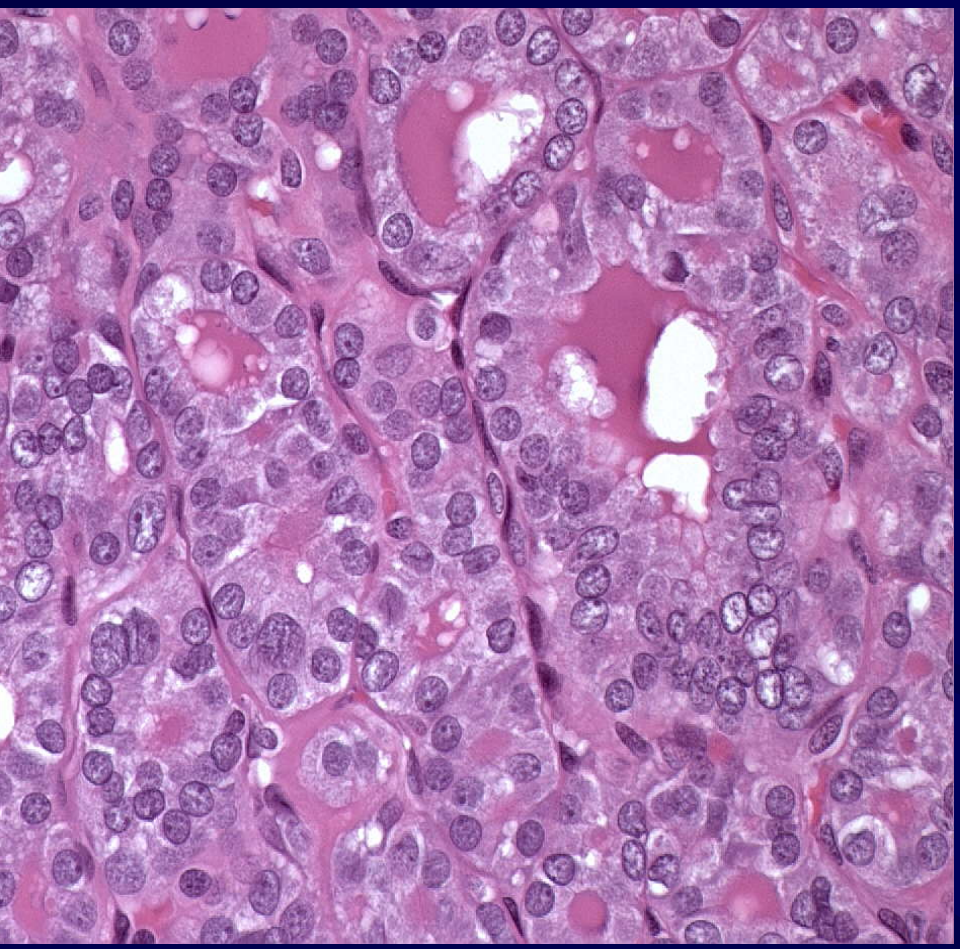
Cytologic Features of Papillary Carcinoma

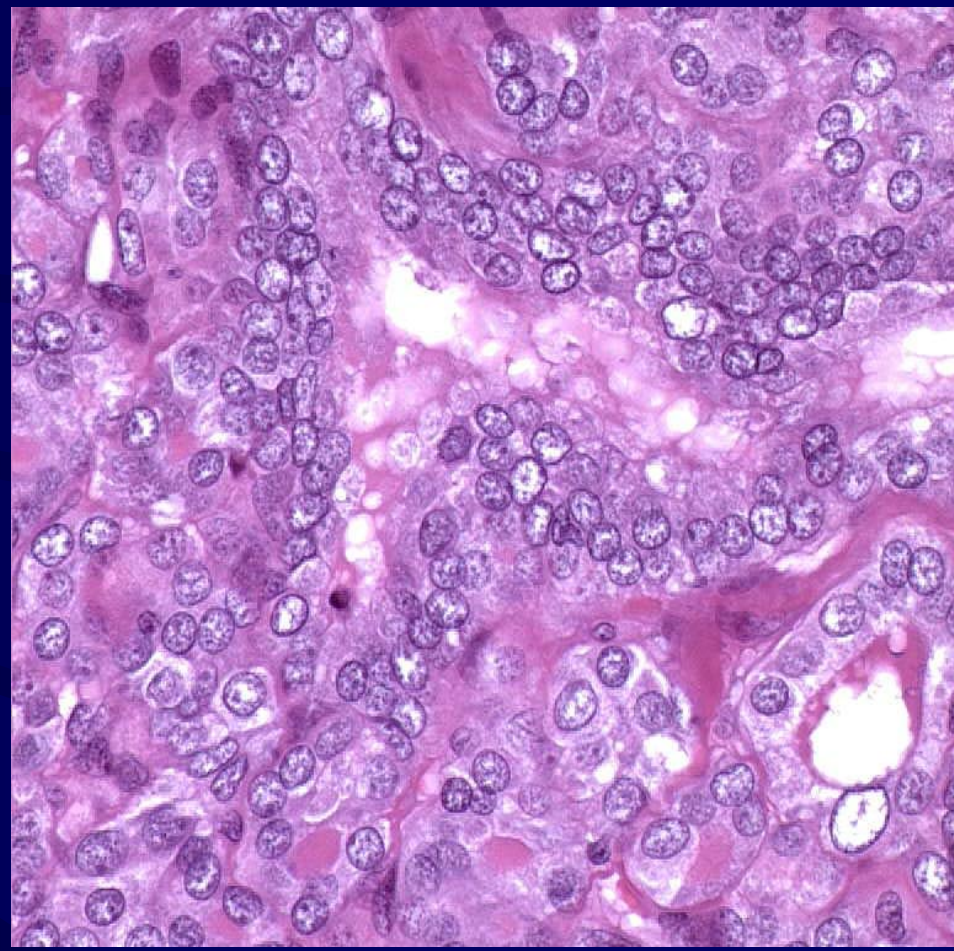
1. Crowded overlapping nuclei
2. Enlarged, elongated nuclei
3. Irregular nuclear membrane
4. Pale vacuolated nucleoplasm
5. Peripheral margination of chromatin
6. Multiple micronucleoli
7. Nuclear grooves
8. Nuclear pseudoinclusions



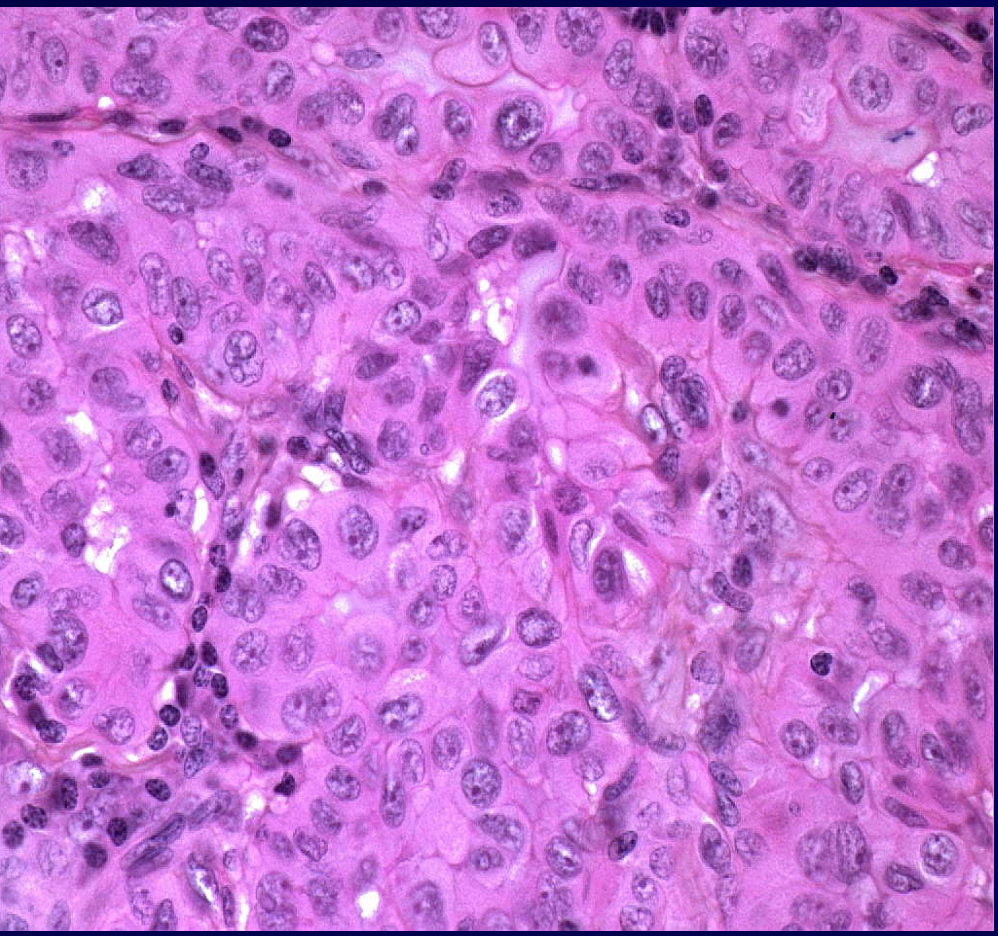
Papanicolaou Society of Cytopathology

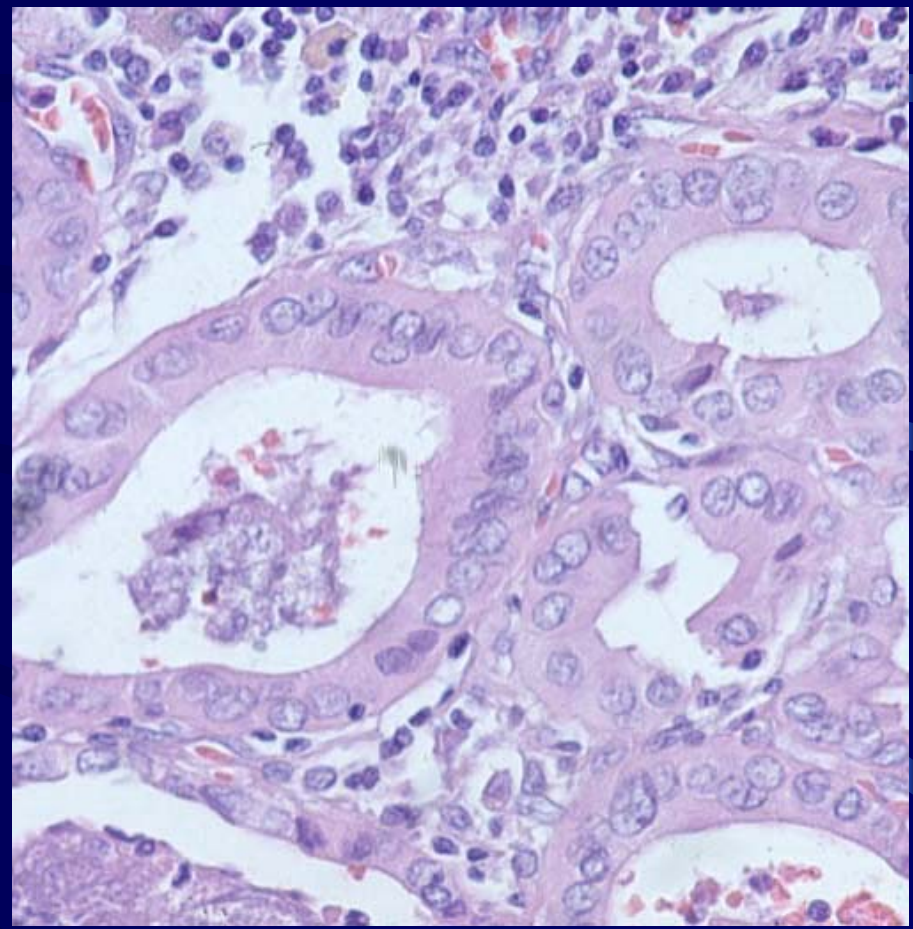
Follicular Variant



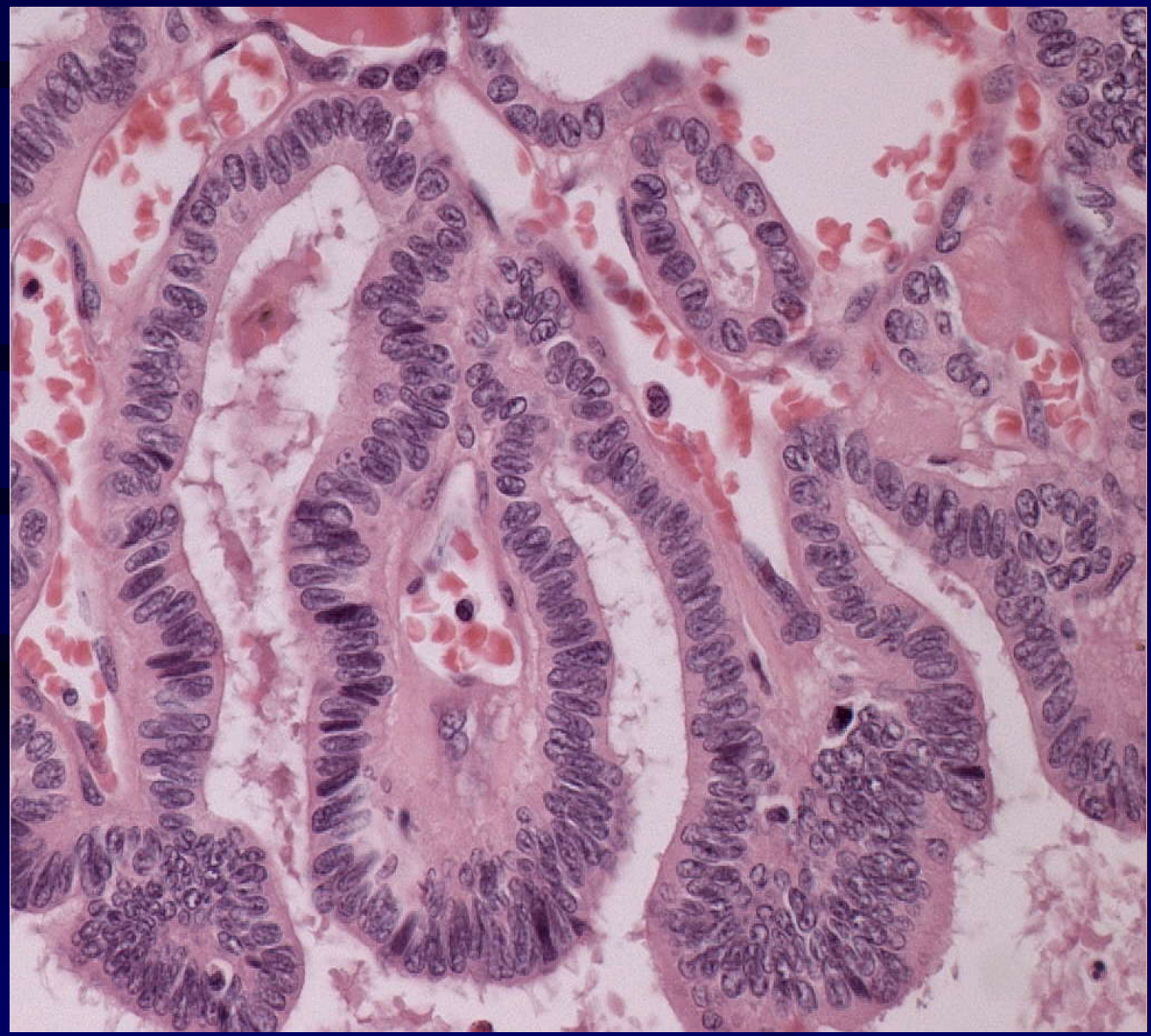


Oncocytic Variant





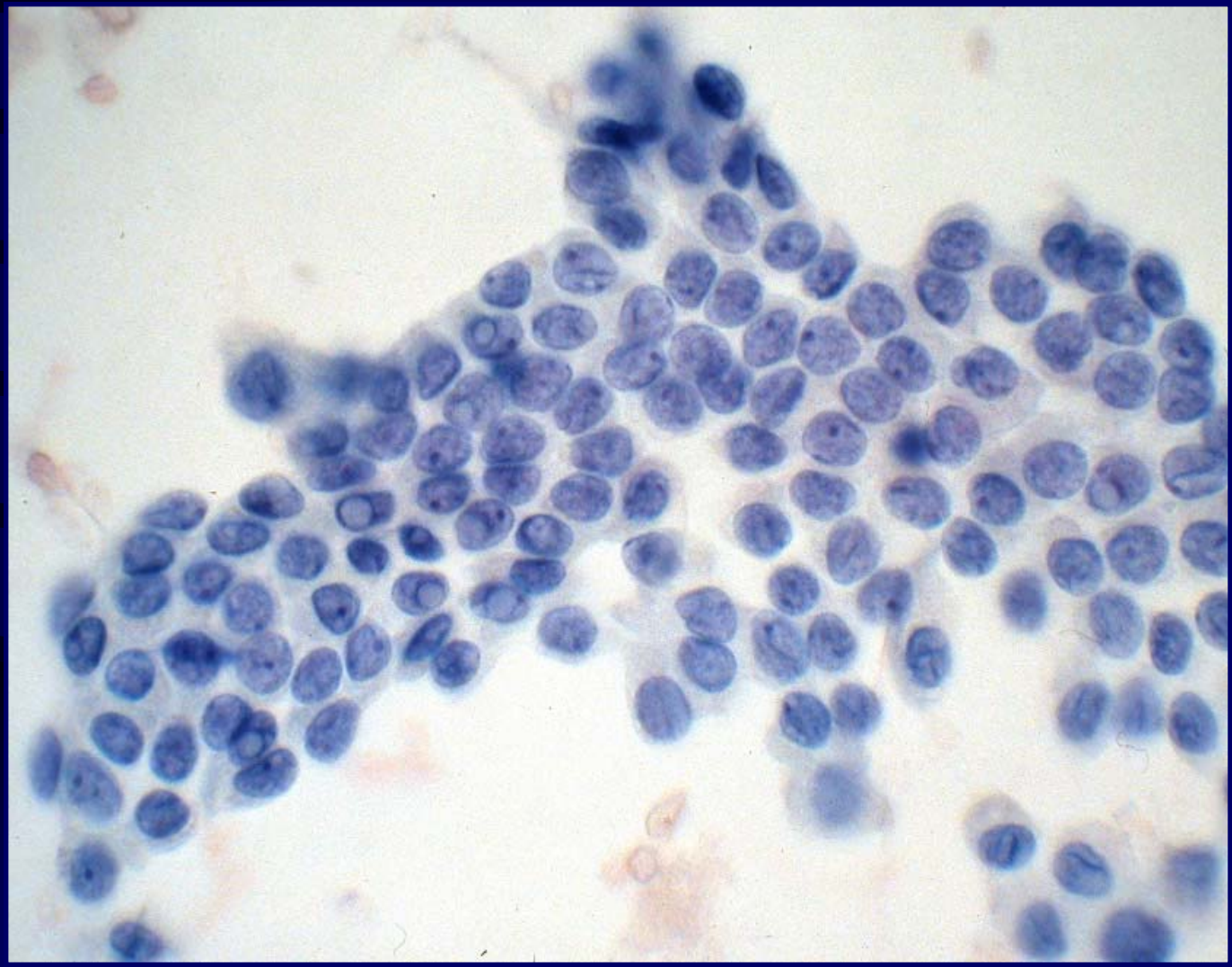
Tall Cell & Columnar Variant



Papillary Carcinoma: A Cytologic Diagnosis

- Architecture irrelevant
  - Papillary, Follicular, Mixed, Solid , Cystic
  - Diffuse sclerosis variant
- Invasion not a criterion
  - Encapsulated variant
- Nuclear features predict behavior

Cytology: Papillary Carcinoma



Papillary Carcinoma: Diagnostic Markers

- Cytologic as well as architectural features
- Psammoma bodies
- HLA-DR expression
- S100-positive Langerhans cells
- High molecular weight cytokeratins (CK19)
- HBME-1, Galectin-3
- Ret expression - ret/PTC rearrangements
- BRAF mutations

Papillary Carcinoma: A History….continued

Fischer et al, Am J Pathol 1998

- Ret/PTC-1 alters nuclear envelope and chromatin structure to account for nuclear features of papillary carcinoma

Differential Diagnosis: Follicular Lesions of Thyroid

Non-neoplastic

- Inflammatory Lesions
  - Inflammatory foci
  - Compensatory regenerative nodules (?TSH, ?TGI)
- Hyperplasia

Neoplastic

- Follicular epithelial neoplasms
  - Follicular adenoma
  - Differentiated Carcinoma: Papillary, Follicular

Thyroid Cytology: Usefulness *vs* Limitations

- *Benign*
  - Thyroiditis
  - “Colloid Nodule”
- *Malignant*
  - Papillary Carcinoma
  - Medullary Carcinoma
  - Lymphoma
  - Anaplastic Carcinoma
  - Metastatic Carcinoma

- *Indeterminate*
  - Insufficient Smear
  - Degenerating Lesion
  - Follicular lesion*
    - hyperplasia
    - neoplasia
      - benign
      - malignant

Adjuvant Methods in Cytology

- Immunocytochemistry
  - HBME-1, galectin-3 reported to indicate malignancy and are reliable on cytology
  - possibly CK19, on cell blocks
    - caution since reactive follicular cells and Hashimoto's thyroiditis are positive
- Molecular analysis
  - e.g ret/PTC rearrangements, BRAF mutations

These applications can improve diagnostic accuracy and enhance the role of cytology in patient management

Management Outcomes Related to Cytologic Diagnosis

- Total thyroidectomy *vs* hemithyroidectomy for known primary malignancy
- Rule out surgery for lymphoma or metastatic disease

The History and Histology of Follicular Lesions of Thyroid

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Thyroid nodules are common in the general population; it has been estimated that about 20% of the population has a palpable thyroid nodule and approximately 70% has a nodule that can be detected by ultrasound [(1)]. The prevalence of thyroid nodules is greater in women (72%) than in men (41%). Multiple nodules are more common than solitary nodules.

Follicular nodules are the most commonly encountered problems in the surgical pathology of the thyroid. These lesions can be classified along the full spectrum of thyroid pathology from hyperplastic nodules to benign follicular adenomas and malignant follicular carcinomas and follicular variant papillary carcinomas.

Sporadic nodular goiter is characterised by numerous follicular nodules with heterogeneous architecture and cytology, features that have suggested a hyperplastic rather than neoplastic pathogenesis [(2-5)]. The nodules are composed of follicles of variable size and shape. Some follicles are large, with abundant colloid surrounded by flattened, cuboidal or columnar epithelial cells, often with cellular areas composed of small follicles lined by crowded epithelium with scant colloid in a small lumen, alone or pushing into large colloid-filled follicles as "Sanderson's polsters". However, the morphologic classification of cellular microfollicular nodules in nodular glands can be extremely difficult. Molecular studies have indicated that the dominant nodules of multinodular goiters are monoclonal proliferations, and therefore represent benign neoplasms [(3,6)]. Moreoever, it is impossible to distinguish monoclonal from polyclonal nodules on the basis of histology or cytology. Since many of these nodules represent adenomas arising in the background of a hyperplastic process [(7)], the distinction is a dilemma. However, it is rather academic since clinical experience has shown us that the vast majority of these lesions remain entirely benign.

Follicular Adenomas are monoclonal nodules [(8,9)] that lack invasive behaviour or markers of papillary carcinoma, and are therefore considered to be benign. Follicular adenomas are generally considered to be solitary encapsulated follicular lesions that exhibit a uniform architectural and cytologic pattern, however, the inclusion of nodules in sporadic nodular goiter in this category alters these criteria. Follicular adenomas are subclassified histologically according the size or presence of follicles and degree of cellularity, each adenoma tending to have a consistent microscopic pattern. The subclassification of follicular adenomas into simple, microfollicular, trabecular, oxyphil, atypical, papillary and signet ring cell types has no prognostic significance. Atypical adenomas are highly cellular tumours with unusual gross and/or histologic appearances that suggest the possibility of malignancy but these tumours lack evidence of invasion. They may have necrosis, infarction, numerous mitoses or unusual cellularity. Many so-called "atypical adenomas" are indeed papillary carcinomas. The distinction of an encapsulated follicular variant papillary carcinoma from follicular adenoma relies on cytologic characteristics. The presence of the cytologic features of papillary carcinoma

described below should indicate that diagnosis, despite lack of invasion. Whether some follicular nodules classified histologically as adenomas have the biologic potential to become carcinoma is not clear; aneuploid cell populations have been described in a significant percentage of these lesions, suggesting that some of these may represent carcinoma in situ.

Follicular Carcinoma cannot be distinguished from follicular adenoma with respect to clinical presentation, radiographic appearance, cytologic findings and microscopic features. In most cases, the parenchymal component of both tumour types is essentially the same histomorphologically. The distinction between these two conditions has been considered possible only by recognition of invasion or metastasis. As indicated above, some encapsulated follicular adenomas exhibit evidence of aneuploidy and may in fact represent in situ follicular carcinomas. Nuclear and cellular atypia and mitotic figures may be present in adenomas as well as in carcinomas and therefore cytologic characteristics are not helpful. Most follicular tumours are composed of cells with nuclei that are round to oval with uniformly speckled chromatin; the nuclei are evenly spaced and lack the crowded, overlapping appearance found in papillary carcinoma. The concept of unencapsulated follicular carcinoma was raised by the identification of tumours that lack a capsule. In one report of four such cases, one patient developed metastases, and this gave rise to citations of a 25% metastatic rate by such lesions[10]. However, this has not been substantiated in larger series and this concept has largely been abandoned.

Papillary Carcinoma comprises at least 80% of thyroid epithelial malignancies diagnosed in regions of the world where goiters are not endemic. The terminology is misleading; papillary carcinomas can exhibit papillary architecture but they may also have follicular or mixed papillary and follicular patterns[11-18].

The history of the entity known as “follicular variant papillary carcinoma” is interesting. Papillary carcinoma was, as its name implies, originally recognized on the basis of its papillary architecture. However, in 1960, Lindsay made the observation that the nuclei of tumor cells in papillary carcinoma have a “delicate, often indented nuclear membrane” and “opaque, ground-glass appearance” and he suggested that a tumor with such nuclei would behave biologically like papillary tumors, even if the structure were follicular [19-21]. In 1983’s second series AFIP Fascicle on Tumors of the Thyroid Gland, Meissner indicated that “The concept that follicular cancers with clear nuclei represent papillary carcinomas has been generally accepted and has led to the awkward term ‘follicular variant of papillary carcinoma.’ Fortunately, such tumors are infrequent.”[22]. By 1992, Rosai et al published the following statements about papillary carcinoma in the third series AFIP fascicle: “The two morphologic features that best characterize typical papillary carcinoma are the papillae and the nuclear changes” and “The nuclei of the papillary carcinoma cells usually have a distinctive appearance, which in recent years has acquired a diagnostic significance at least comparable to that of the papillae”. In regard to follicular lesions, they stated that “Regardless of follicle size, the nuclei of the lining cells have features analogous to those of conventional papillary carcinoma”[12].

It is now recognised that the diagnosis of papillary carcinoma is based on what the WHO has described as "a distinctive set of nuclear characteristics" [23]. In contrast to true follicular carcinomas, these lesions are usually more indolent and most have an excellent prognosis with a 20 year survival rate of 90% or better [24,25]. The defining nuclear features are readily seen on cytology of fine needle aspirates as well as on histologic sections. They include an alteration of the size and the roundness of the normal follicular cell nucleus to one that is large and oval. Due

to peripheral margination of chromatin, the centre of the nucleus has an empty appearance, which when pronounced has been termed "ground glass" [26]. The chromatin and nucleolus are pushed to the edge of the nucleus. The nuclear contour is strikingly irregular, resulting in a "crumpled paper" appearance, intranuclear cytoplasmic pseudoinclusions and nuclear grooves [27,28,28]. No one specific feature is absolutely diagnostic of papillary carcinoma; a constellation or combination of nuclear features is required for the diagnosis[15,17,18,29,30]. Lesions with these nuclear features and follicular architecture have been recognized more frequently in the past 20 years [11,12,23,31,32,32,33]. This lesion comprises about more than 50% of papillary cancers in our experience. It has either been misdiagnosed as follicular carcinoma or underdiagnosed as follicular adenoma or atypical adenoma. Any lesion with follicular architecture and characteristic nuclear features of papillary carcinoma should be classified as this tumour. The presence of cytologic atypia may raise the possibility of papillary carcinoma without being sufficiently convincing for unequivocal diagnosis.

The Role of Cytology

The thyroid aspirate is extremely useful as a first line determinant of the pathology underlying a thyroid nodule [34-37]. The reason for this is that the most common thyroid malignancy is papillary carcinoma, and papillary carcinoma is a cytologic diagnosis. However, on FNA, the diagnosis of "follicular lesion" covers follicular hyperpalsia, adenoma and follicular carcinoma, which are difficult if not impossible to distinguish because the diagnostic criteria do not rest on cytologic characteristics. Any tumor that is composed of well differentiated follicular epithelial cells that do not exhibit the characteristic nuclear features of papillary carcinoma will fall into this category; these include hyperplastic lesions as well as neoplasms which may be benign (follicular adenomas) or malignant (follicular carcinomas). These diagnoses cannot be distinguished on the basis of cytology alone; in all of these lesions, the follicular cells generally have evenly-spaced round to oval nuclei with uniform speckled chromatin, nuclear or cellular atypia is not significant and does not reflect potential malignancy. Mitoses are also not significant.

These problems underly the limitation of cytology in these disorders and the management of patients with these lesions requires clinicopathologic correlation. If the patient is not thought to have a high likelihood of malignancy, for example those with multinodular disease that is most consistent with sporadic nodular goitre, the patient can be watched before proceeding to surgery; if there is no progression of disease or if thyroid hormone replacement results in regression of the nodule, surgery is usually not indicated. In contrast, a cellular follicular lesion that appears to be a solitary nodule or a lesion in a patient who has risk factors predisposing to thyroid tumor formation, such as previous head and neck irradiation, or a rapidly enlarging nodule, should proceed to surgery at this point. Resection of the lesion by thyroid lobectomy and histologic examination will yield a more definitive diagnosis concerning the benign or malignant nature of a follicular lesion. More recently, molecular techniques have been developed that hold promise in the more accurate evaluation of problematic thyroid aspirates [38,39].

The clinical management of these lesions can be difficult and controversial. The use of fine needle aspiration biopsy has significantly improved our ability to identify specific high-risk disorders and to facilitate their management in an expeditious and cost-effective manner.

Patients who require surgery for further confirmation of the disease process rely upon the pathologist to correctly characterise their nodule and pathologists are actively involved in research to clarify the pathogenesis of thyroid disease. Advances in our understanding of the molecular basis of thyroid cancer will allow more accurate characterisation of specific subtypes of neoplasia and malignancy even on single cells obtained at fine needle aspiration biopsy. This should further enhance the usefulness of this technique and better guide the management of patients with a thyroid nodule.

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