2nd Bi-Annual UK Endocrine Pathology Society/RCPath Endocrine Pathology Update

Thursday 6th - Friday 7th February 2020

Held at

Royal College of Pathologists
6 Alie Street, London E1 8QT

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General Information

Certificates of attendance
Certificates of attendance will be emailed to all attendees, within a fortnight of the conference. This conference is eligible for 9 CPD credits

Speaker presentations
Where permission has been given, speaker presentations are included in this pack or will be uploaded to the RCPath website

Feedback
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Wi-Fi
There is free Wi-Fi available throughout the building. The network name is 'RCP_Guest' and the password is 2chtrcpath

Fire
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#rcpathdigipath @UEndopath

Programme

Thursday 6th February 2020

09.30	**Registration**
10.00	Introduction and welcome
10.05	The Thyroid Cancer 'Epidemic' – **Professor Manuel Sobrinho-Simoes, Porto**
10.30	WHO 2017- update on encapsulated follicular patterned lesions, NIFTP, FTUMP, WDTUMP, WDCa-NOS with emphasis on diagnostic pitfalls and how to avoid them – **Professor Giovanni Tallini, Bologna**
11.30	**Refreshments**
12.00	Reporting thyroid FNA using the UK Thy system with emphasis on practical application - **Dr Sarah Johnson, Newcastle**
12.40	Diagnosing papillary thyroid carcinoma with emphasis on non-encapsulated variants and illustrative cases - **Dr Mufaddal Moonim, London**
13.20	**Lunch**
14.00	Risk stratification of thyroid cancer with emphasis on high grade cases and illustrative examples - **Dr Ronald Ghossein, New York**
15.00	Surgical approaches to thyroid cancer and what the surgeon needs from the pathologist before and after surgery - **Mr Sabapathy Balasubramanian, Sheffield**
15.50	**Refreshments**
16.10	Unexpected pathology in the thyroid: case based discussions - **Professor Giovanni Tallini and Professor Manuel Sobrinho-Simoes**
17.10	Closing remarks

Friday 7th February 2020

09.00 Registration

09.30 Welcome

09.35 Pitfalls and medicolegal issues in thyroid diagnosis and how to avoid them, with illustrative cases - **Dr Ronald Ghossein, New York**

10.35 Refreshments

11.00 The thyroid cancer patient: what the oncologist needs from pathology and an update on new therapies and clinical trials - **Professor Jonathan Wadsley, Sheffield**

11.55 Why the Thyroid Multidisciplinary Team is so important with emphasis on common practical issues - **Dr David Poller, Portsmouth**

12.55 Closing remarks

13.00 Meeting close

Presenters

Dr Mufaddal Moonim, London

Dr Mufaddal Moonim is consultant Histopathologist at Guy's & St Thomas' Hospitals NHS Foundation Trust, London and prior to this worked for many years at the Tata Memorial Cancer center in Mumbai India. He is lead for Haematopathology and Endocrine Pathology at GSTT. He is also meetings secretary for the UK Endocrine Pathology Society (UKEPS) and co-author of the RCPath Adrenal tumour dataset. His interests include adrenal tumours, SDHB expression in Phaeochromocytoma, thyroid tumours, thyroid FNA and minimally invasive diagnostics.

Prof. Manuel Sobrinho-Simoes, Porto

Manuel Sobrinho Simões, MD, PhD is Professor of Pathology of the Medical Faculty/University Hospital S. João and Director of the Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP). MSS was President of the European Society of Pathology from 1999 to 2001, after having been Secretary from 1989 to 1997. MSS has co-authored many chapters of the 2nd, 3rd and 4th editions (1988, 2004 & 2017) of the WHO Book on Endocrine Tumours. 5th editions (1988, 2004 & 2017) of the WHO Book on Endocrine Tumours.

Dr Ronald Ghossein, New York

Dr Ronald Ghossein is Attending Pathologist and Director of Head and Neck Pathology at Memorial Sloan-Kettering Cancer Center in New York City. His research focuses on the histologic reclassification of thyroid carcinomas into clinically relevant entities. He was the senior author of the publication that renamed the non-invasive encapsulated follicular variant of papillary carcinoma as non-invasive follicular thyroid neoplasm with papillary like nuclei (NIFTP). He also published extensively on the predictive value of various histologic and molecular parameters such as extent of vascular invasion, extra-thyroid extension, nodal burden and BRAFV600E. He also analyses mouse models used in thyroid cancer pathogenesis.

Professor Giovanni Tallini

Giovanni Tallini, MD trained in Anatomic Pathology with Dr. J. Rosai in the US, was Faculty at the Department of Pathology of Yale University School of Medicine, and after 15 years in the US moved back to his native country to become Professor of Pathology at the University of Bologna School of Medicine. In addition to routine anatomic pathology commitments, he has set up and currently directs the Molecular Pathology Unit of the regional health care agency (Azienda USL di Bologna) for the Italian NHS. Over the years Dr. Tallini has developed an interest in thyroid gland pathology and pathobiology, a field to which he has made significant contributions. He has been President of the Endocrine Pathology Society, co-editor of the 2014 AFIP Tumor Pathology Atlas for the thyroid gland, working group member for the WHO books Tumors of Endocrine Organs (3d and 4th editions).

Dr D Poller, Portsmouth

Dr David Poller is a Consultant Pathologist & Reader in Pathology at The Queen Alexandra Hospital in Portsmouth. His interests are the pathology & cytology of thyroid & endocrine cancer with a number of publications in this area. Dr Poller is Treasurer and Membership Secretary of the UK Endocrine Pathology Society, and is a member of UK RCPath guideline and NCRI research groups that relate to diagnosis of thyroid cancer. He was member of The Endocrine Pathology Society's NIFTP working group in 2015/6 and frequently lectures on thyroid disease & FNA thyroid cytology.

Dr Sarah Johnson, Newcastle

Consultant Cyto/histopathologist at the Royal Victoria Infirmary in Newcastle upon Tyne. Lead for Endocrine Pathology and Lead for Cytology (cervical screening and nongynae cytology) for Newcastle upon Tyne Hospitals NHS Foundation Trust. Co-author of RCPath Endocrine Cancer Datasets, Thyroid Cytology Guidance document, Endocrine Tissue Pathways and Thyroid Cytology Audit Template. Author of publications on thyroid, parathyroid and NET pathology including ongoing thyroid cytology-histology correlation. Member of NCRI Thyroid Cancer Subgroup. President of UKEPS, previously Secretary.

Professor Saba Balasubramanian

Saba Balasubramanian is an endocrine surgeon and honorary professor at the University of Sheffield. He is lead clinician for thyroid cancer in Sheffield and educational lead for the British Association of Endocrine and Thyroid surgeons. In addition to numerous book chapters, he has published in peer reviewed journals on thyroid, parathyroid, adrenal surgery and breast cancer and is a chief investigator on several translational and clinical research projects. His current research interests include post-surgical hypoparathyroidism (PoSH), use of novel technology for parathyroid identification and preservation and thyroid cancer epidemiology.
He is currently the chief investigator for the NIHR EME funded multicentre trial on fluorescent imaging of parathyroids (the NIFTy - Near Infra Red Fluorescent Imaging in Thyroid surgery – trial) and co-investigator in the NIHR HTA funded multicentre trial on hemi versus total thyroidectomy in low risk differentiated thyroid cancer (the HoT trial).

Professor Jon Wadsley, Sheffield

Professor Wadsley was appointed as Consultant Clinical Oncologist at Weston Park Hospital, Sheffield in 2004. His clinical interests are in thyroid cancer, neuroendocrine tumours and pancreatic/biliary tract cancers, with a particular interest in molecular radiotherapy. His research mirrors these clinical interests, with a particular focus on thyroid cancer and neuroendocrine tumours. He currently chairs the NCRI Thyroid Cancer Subgroup and is Chief Investigator of the SELIMETRY trial. He is Clinical Director of the Sheffield Cancer Clinical Trials Centre, Cancer Specialty Lead for the Yorkshire and Humber Clinical Research Network and NIHR National Specialty Lead for Radiotherapy and Imaging.

Abstracts and References

The Thyroid Cancer “Epidemic”
Professor Manuel Sobrinho-Simões

Learning points

1.The existence of thyroid cancer “epidemic”: Relationship between obesity, diabetes, human development index and the risk of thyroid cancer
2. Discuss whether or not thyroid cancer “epidemic” also occurs in low- and middle-income countries and, if yes, what about the cancer histotypes?
3. Discuss the increasing incidence in USA, paying attention to differential trends of thyroid cancer, namely regarding classic PTC and follicular variant PTC
4. How to deal with subcentimeter non-invasive, encapsulated, follicular variant PTC in terms of cancer incidence?
5. How to deal, in general, with microcarcinomas (mPTC and mMTC) in terms of thyroid cancer incidence and mortality. The problem of so-called cancer overdiagnosis.

Abstract

There is an on-going discussion about the reasons underlying the increased thyroid cancer incidence (throughout the world?). I will not specifically address the (putative) role played by environmental and technological factors in the so-called thyroid cancer “epidemic”. Instead, I will concentrate on the following points: 1. Role played by the utilization of FNA with and/or without molecular data. 2. Is it true that increasing smaller sized thyroid carcinomas are seen in most institutions? And both regarding classic papillary carcinoma – PTC – and follicular variant of PTC? 3. Diagnosis of papillary microcarcinomas (mPTC).3a. Issues concerning histopathology, immunohistochemistry and genetics; 3b. mPTC inside benign lesions; 3c. Differential diagnosis of mPTC and microNIFTP; 3d. Evaluation of risk of mPTC displaying microscopical invasion of perithyroid adipose tissue.
4. Diagnosis of medullary microcarcinoma (mMTC): Histopathological, immunohistochemical and molecular features.

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Unexpected Pathology in the Thyroid: Case based discussions
Professor Manuel Sobrinho-Simões

Learning points

1. Whenever facing a difficult or questionable thyroid tumour, immunohistochemistry for thyroglobulin, TTF1 and calcitonin is mandatory.
2. The most important differential diagnosis, outside classic papillary carcinoma (cPTC) and metastatic carcinomas, is the demonstration of wide invasion and/or vascular (venous) invasion
3. The evaluation of encapsulation of any thyroid carcinoma is more important than the histopathological features *per se* (e.g. columnar cell PTC, hobnail variant of PTC, cribriform morular carcinoma).
4. The morphological appearance of the neoplastic cells fitting with the so-called "intermediate nuclei" usually lack any typical molecular alterations and lead to the diagnosis of well differentiated tumour or carcinoma.
5. Searching for molecular alterations in cytology specimens in useless for two main reasons: RAS mutations do not indicate malignancy (they are frequently detected in Follicular adenoma and NIFTP) and BRAF mutations are almost exclusively detected in classic PTC that can be readily diagnosed by cytology.

Abstracts

1. What to do in adenomas and NIFTPs in which the cytological study and/or the surgical specimen find a RAS mutation?
2. Is there room to use the diagnosis of "Well differentiated carcinoma" instead of pushing towards papillary or follicular thyroid carcinoma? The same applies to differentiated tumours of uncertain malignant potential?
3. How to diagnose tumours that look like fairly differentiated thyroid carcinomas that are negative for thyroglobulin and TTF1?
4. Is there room for diagnosing poorly differentiated carcinomas based upon high grade features?
5. How to deal with (very) aggressive histological features (e.g. hobnail variant of PTC) occurring in encapsulated tumours?

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WHO 2017- update on encapsulated follicular patterned lesions, NIFTP, FTUMP, WDTUMP, WDCa-NOS with emphasis on diagnostic pitfalls and how to avoid them

Professor Giovanni Tallini

Learning points

1. Encapsulated follicular patterned lesions (NIFTP, FTUMP, WDTUMP, WDCa-NOS): the context for the WHO 2017 update

2. Classification of well differentiated follicular patterned thyroid nodules

3. Criteria for the diagnosis of NIFTP (Non-invasive follicular thyroid neoplasm with papillary-like nuclear features)

4. Criteria for the diagnosis of Tumours of uncertain malignant potential

5. Understand the importance of accurate sampling and careful examination of thyroid nodules

6. Avoid pitfalls in the diagnosis of well differentiated follicular patterned thyroid nodules

Abstracts

In the routine practice of pathology a combination of four basic morphologic features is utilized to diagnose tumors of follicular cell derivation: i) papillary growth pattern; ii) follicular growth pattern iii); presence of a tumor capsule and of its invasion (capsular or vascular invasion); iv) presence of alterations of nuclear morphology typical of papillary carcinoma. The relative weight given to these four features has shifted considerably over the years: it has now become apparent that all of them need to be taken into account in a balanced manner. Some encapsulated thyroid nodules pose considerable diagnostic problems because of uncertainties whether the nuclear changes are sufficient to justify a diagnosis of papillary carcinoma, or whether there is bona fide capsular or vascular invasion.

The 2017 WHO classification promotes a pragmatic approach for these difficult cases. It has acknowledged the term of “Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)” for non-invasive neoplasms of thyroid follicular cells with a follicular growth pattern and nuclear features of papillary carcinoma that are well-developed (non-invasive follicular variant papillary carcinoma) or expressed incompletely. This new terminology includes many tumors that in the past have been diagnosed as encapsulated follicular variant papillary carcinoma. When non-invasive, the encapsulated follicular variant papillary carcinoma has an extremely low malignant potential, with a recurrence rate <1%. It is important to recognize that NIFTP is not a “new” tumor, but simply a new diagnostic term: the absence of the “carcinoma” label makes it easy to avoid aggressive forms of treatment for the patients.

The new WHO classification also endorses the concept of “tumors of uncertain malignant potential” to diagnose cases with equivocal signs of invasion (of the tumor capsule and/or of vessels):"Well differentiated tumor of uncertain malignant potential (WDT-UMP)" for tumors with well to incompletely expressed nuclear alterations of papillary carcinoma, and "Follicular tumor of uncertain malignant potential (FT-UMP)" if the nuclear features of papillary carcinoma are absent.
The consistent utilization of the NIFTP and UMP diagnostic terms is essential. Data are accumulating to support their use in the practice of thyroid pathology.

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Reporting thyroid FNA using the UK Thy system with emphasis on practical application

Dr Sarah J Johnson, Newcastle

Learning Points

1. To understand the role that FNA has in the investigation of thyroid nodules.
2. To understand the strengths and limitations of thyroid FNA.
3. To know how to improve adequacy, quality and accuracy of thyroid FNA cytology locally.
4. To know how to use the RCPath Thy categories for reporting thyroid FNAs.

Abstract

A thyroid nodule should initially be investigated by ultrasound scan (USS) by an experienced thyroid radiologist, with allocation of a score (eg BTA U score). Nodules with indeterminate or worse features (U3 and above) should also undergo USS-guided fine needle aspiration (FNA) for cytological examination by an experienced cytopathologist. Such FNA is a crucial part of the investigation of a thyroid nodule and can stratify the patients for reassurance and discharge, follow up with repeat USS +/- FNA, or for diagnostic or therapeutic surgery. The strengths of thyroid FNA are its ability to identify non-neoplastic lesions (eg colloid nodule) and to make definite diagnosis of certain malignancies (eg PTC, MTC, ATC, some metastases). There are, however, important limitations of thyroid FNA such as the often high unsatisfactory rates, varied usage nationally, interobserver variation in allocation of some Thy categories, and the inherent difficulty of follicular-patterned lesions. These will be discussed, with some practical pointers to assist in improving specimen quality and cytological diagnosis. There has been a recent meta-analysis published of the Risk of Malignancy after Thy categorisation of FNA and these data will be given, as well as a discussion of the Thy categories compared to other international systems. Brief mention will be made of molecular testing, still not routinely available in the UK, and of core biopsies of thyroid.

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Diagnosing papillary thyroid carcinoma with emphasis on non-encapsulated variants and illustrative cases.
Dr Mufaddal Moonim, London

Papillary thyroid carcinoma (PTC) is the commonest malignant tumour of the thyroid. The talk discusses the histologic criteria required for diagnosis, including architectural patterns, nuclear criteria and pitfalls associated with the use of these criteria. Papillary carcinoma has myriad morphologies and there are various variants, some of which are morphologic entities and others are associated with prognostic significance. The latter include Tall cell variant, columnar cell variant, cribriform-morular variant, diffuse sclerosing variant and hobnail cell variant. The diagnostic criteria of these are covered including relevant immunohistochemistry and molecular findings.

Risk stratification of thyroid cancer with emphasis on high grade cases and illustrative example.
Dr Ronald Ghossein, New York

The treatment of thyroid carcinoma of follicular cell origin has undergone important changes in the last two decades. The “one size fits all approach” to management has been abandoned for a therapy based on risk stratification. The pathologist has a key role in reporting on the numerous prognostically relevant histopathological features that will determine initial risk grouping. This in turn will guide the need for completion thyroidectomy and/or postoperative radioactive iodine therapy. Among these crucial parameters are the presence and extent of vascular invasion, extrathyroidal extension, surgical margin status, tumor size, grade and the characteristics of nodal metastasis. While molecular alterations are not currently required for prognostication, some are promising markers of outcome such as TERT promoter and BRAFV600E mutations. The latter is currently used to select patients for targeted therapies in radioactive iodine refractory thyroid carcinoma and most recently in anaplastic thyroid carcinoma with impressive responses. This lecture aims to summarize the diagnostic criteria, the controversies, the prognostic impact and the challenges of these pathological characteristics, focusing specifically on the parameters that are incorporated into the American Joint Committee on Cancer (AJCC) staging system, the College of American Pathologists (CAP) reporting template, the International Collaboration on Cancer Reporting (ICCR), the American Thyroid Association (ATA) and the National Comprehensive Cancer Network (NCCN) guidelines.

Pitfalls and medicolegal issues in thyroid diagnosis and how to avoid them, with illustrative cases.
Dr Ronald Ghossein, New York

There are numerous diagnostic pitfalls in the surgical pathology examination of thyroid tumors. Some lead to an erroneous diagnosis of carcinoma in a benign lesion such as pseudo-capsular invasion due to FNA related changes, reactive endothelial proliferation simulating vascular invasion, nuclear clearing in benign conditions such as lymphocytic thyroiditis mimicking the nuclear features of papillary carcinoma, parasitic nodules involved by chronic inflammation simulating metastatic thyroid carcinoma to lymph node and excessive reliance on immunohistochemical stains to diagnose papillary thyroid carcinoma. Other situations result in underdiagnosis or misclassification of thyroid malignancies. Poor sampling of an encapsulated lesion can lead to undertreatment of a carcinoma with extensive angioinvasion. Because of false positive immunostains in oncocytic lesions, Hurthle cell carcinomas can be misdiagnosed as medullary carcinoma. Passive diffusion of thyrogobulin can lead to a wrong diagnosis of carcinoma in a thyroid lymphoma. Very rare but clinically important variants of papillary carcinoma can be mistyped such as a cribriform morular variant being misdiagnosed as columnar cell variant depriving the patients of an early and life saving diagnosis of Familial Adenomatosis Polyposis (FAP). Overdiagnosis of anaplastic carcinoma is a particularly dramatic occurrence. The pathologist may mistake post-FNA reactive spindle cell proliferation, endocrine atypia in a Hurthle adenonma, spindle cell metaplasia and especially squamous metaplasia in papillary carcinoma as signs of anaplastic transformation. These errors often lead to wrong or

unnecessary treatments with their attached morbidity and in some instances a reduced chance of cure.

The thyroid cancer patient: what the oncologist needs from pathology and an update on new therapies and clinical trials

Professor Jon Wadsley

Learning Points

1.To understand evolving trends in the management of low risk differentiated thyroid cancer and requirements of pathological reporting to allow optimal clinical decision making.

2.To understand recent developments in treatment of iodine refractory differentiated thyroid cancer and how pathology might help better select patients for treatment.

3.To understand recent developments in treatment of advanced medullary thyroid cancer and how pathology can help select patients for treatment, with a particular focus on the development of RET specific inhibitors.

4.To understand recent developments in research and treatment in anaplastic thyroid cancer.

Abstract

Developments in thyroid cancer are occurring at both ends of the spectrum of disease aggressiveness. In low risk differentiated thyroid cancer the trend is to treatment de-escalation, to avoid the potential long term morbidities of unnecessary treatment. In advanced, aggressive diseases such as iodine refractory differentiated thyroid cancer, advanced medullary thyroid cancer and anaplastic thyroid cancer, new targeted treatments are being developed which are capable of significantly slowing the progression of the disease and improving patients' survival and quality of life.
All of these developments are dependent on detailed and accurate pathogical information to allow appropriate stratification and selection of patients for the correct treatment.
This session will review these developments and the information that an oncologist requires from pathology to allow optimal management of patients with thyroid cancer.

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Declaration of Interest

- Received research funding from AstraZeneca and Sanofi-Genzyme.
- Received honoraria from AstraZeneca, Sanofi-Genzyme, Eisai, Ipsen, Lilly, AAA, Novartis.

Importance of the Thyroid Multidisciplinary Team (MDT) Common Practical Problems
Dr David N. Poller Portsmouth

Multidisciplinary (MDT) working is mandatory in modern management of thyroid cancer. The majority of cancers & borderline tumours of the thyroid present little or no risk to life. The other major difference between thyroid cancer & most other tumours is that the intra/interobserver reproducibility of many of the diagnostic criteria is relatively poor & hence there is considerable subjectivity in diagnoses for both FNA cytology and histopathology at MDT's. Published studies show k statistics of ~0 .2 for capsular and vascular invasion in thyroid cancer & k statistics for NIFTP vs. adenoma of ~0.45. A brief review of the existing UK & international guidelines for histopathology & cytopathology relevant to thyroid cancer is presented, the diagnostic pitfalls of histopathology and cytopathology, problems of interobserver reproducibility of papillary carcinoma-type nuclei, capsular invasion and vascular invasion, NIFTP,WTUMP, & FTUMP. Risk stratification of thyroid carcinoma is discussed according to American Thyroid Association (ATA) 2015 guidance, describing the low-risk profile of majority of the cases discussed at typical thyroid MDT & also seen in requests for external thyroid histopathology opinions. In Portsmouth in 2019 88% of 25 external cases received were either final diagnosis benign, tumour of uncertain malignant potential/NIFTP, or ATA low risk thyroid cancer without vascular invasion. The results of a 2018 national peer review of thyroid cancer is presented as an example of some of the practical issues pathologists face working within the thyroid multidisciplinary teams with a series of recommendations for improving cytological & histopathology decision-making in MDT's.

PRESENTATIONS

Reporting thyroid FNA using the UK Thy system with emphasis on practical application

Dr Sarah J Johnson, Newcastle upon Tyne
Consultant Cyto/Histopathologist and Clinical Lead for Endocrine Pathology
President of UKEPS

Contents of presentation

- Place of FNA in investigation of thyroid nodules
- RCPath Thy categories and PPVs / ROMs
- Strengths and limitations of thyroid FNA
- Role of FNA report
- How can quality and accuracy be improved?
- Problem areas
- Additional or alternative approaches
- Summary

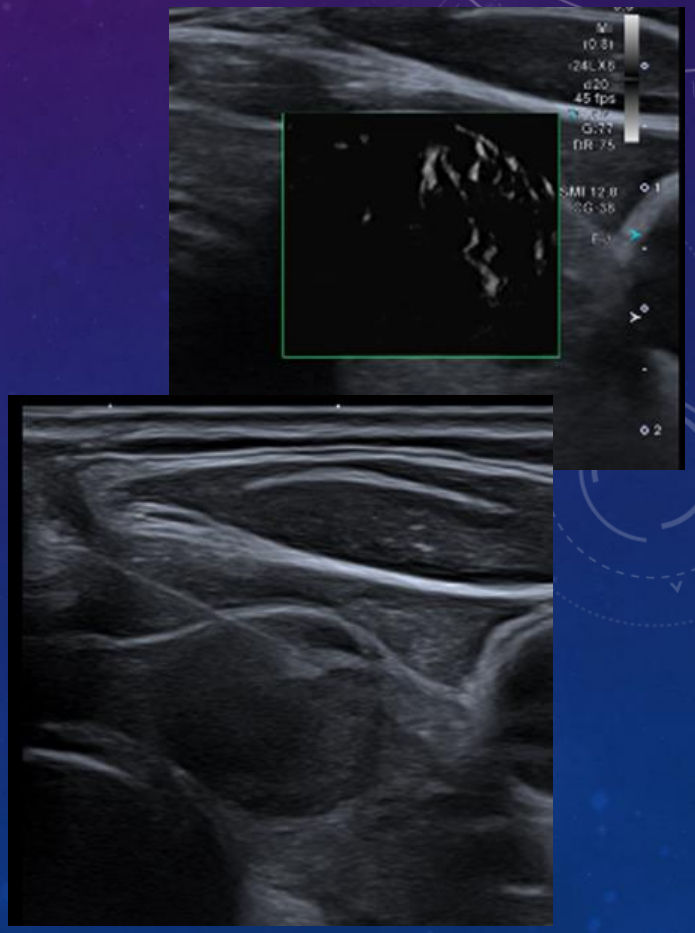
Place of FNA in investigation of a thyroid nodule

- All patients being investigated for thyroid cancer should have USS of neck in secondary care by appropriate competent practitioner

- Radiology should be scored
  eg U system or TIRADS
  (subjective)

- Then USS-guided FNA if U3, U4, U5

- And U1, U2 if statistically high risk
  of cancer



BTA Guidelines for the management of thyroid cancer
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RCPath Thy categories and PPVs / ROMs

RCPath categories		RCPath indicative PPV (2016) - all cases in category	Meta-analysis (2019) – only cases with histology
Thy1	Non-diagnostic for cytological diagnosis	**1%**	12% (95% CI 5%-22%)
Thy1c	Cystic, non-diagnostic		
Thy2	Non-neoplastic	**1.4%**	5% (95% CI 3%-9%)
Thy2c	Cystic, non-neoplastic		
Thy3a	Neoplasm possible – atypia	**17%**	**25%** (95% CI 20%-31%)
Thy3f	Neoplasm possible – suggesting follicular neoplasm	Up to 40%	**31%** (95% CI, 24%-39%); Thy3 22% (18-26%)
Thy4	Suspicious of malignancy	Up to 68%	**79%** (95% CI, 70%-87%)
Thy5	Malignant	Up to 100%	**98%** (95% CI, 97%-99%).

Guidance on the reporting of thyroid cytology specimens, 2nd ed 2016, RCPath

Poller *et al* *Cancer Cytopathol* 2020 Jan;128(1):36-42. doi: 10.1002/cncy.22201. Epub 2019 Nov 13.

…which map to international categories

RCPath categories		TBS categories		Italian	Australian	Japanese
Thy1	Non-diagnostic for cytological diagnosis	I	Non-diagnostic / unsatisfactory	TIR 1 non-diagnostic TIR1c Non-diagnostic, cystic	1 Non-diagnostic	1 Inadequate
Thy1c	Cystic, non-diagnostic					
Thy2	Non-neoplastic	III	Benign	TIR 2 Non-malignant	2 Benign	2 Normal or benign
Thy2c	Cystic non-neoplastic					
Thy3a	Neoplasm possible – atypia	III	Atypia of undetermined significance / follicular lesion of undetermined significance (AUS / FLUS)	TIR 3A Low risk indeterminate lesion (LRIL)	3 Indeterminate or follicular lesion of undetermined significance	3 Indeterminate B others
Thy3f	Neoplasm possible, suggesting follicular neoplasm	IV	Follicular neoplasm / suspicious for follicular neoplasm (FN / SFN)	TIR 3B High risk indeterminate lesion (HRIL)	4 Suggestive of follicular neoplasm	3 Indeterminate A Follicular neoplasms A-1 favour benign A-2 borderline A-3 favour malignant
Thy4	Suspicious of malignancy	V	Suspicious for malignancy	TIR 4 Suspicious of malignancy	5 Suspicious of malignancy	4 Malignancy suspected
Thy5	Malignant	VI	Malignant	TIR 5 Malignant	6 Malignant	5 Malignancy

Strengths and limitations of thyroid FNA

- Is very useful for
  - Colloid nodules
  - Diagnosis of some malignancies
    - PTC, MTC, ATC, (lymphoma)

- But has some major problems:
  1. varied use nationally
  2. can have high unsatisfactory rate
  3. interobserver variation
  4. limited value for follicular lesions

Limitations of thyroid FNA

1. **Huge variation in use of categories nationally**
2. **Plus some high rates of inadequacy**

UKEPS audit

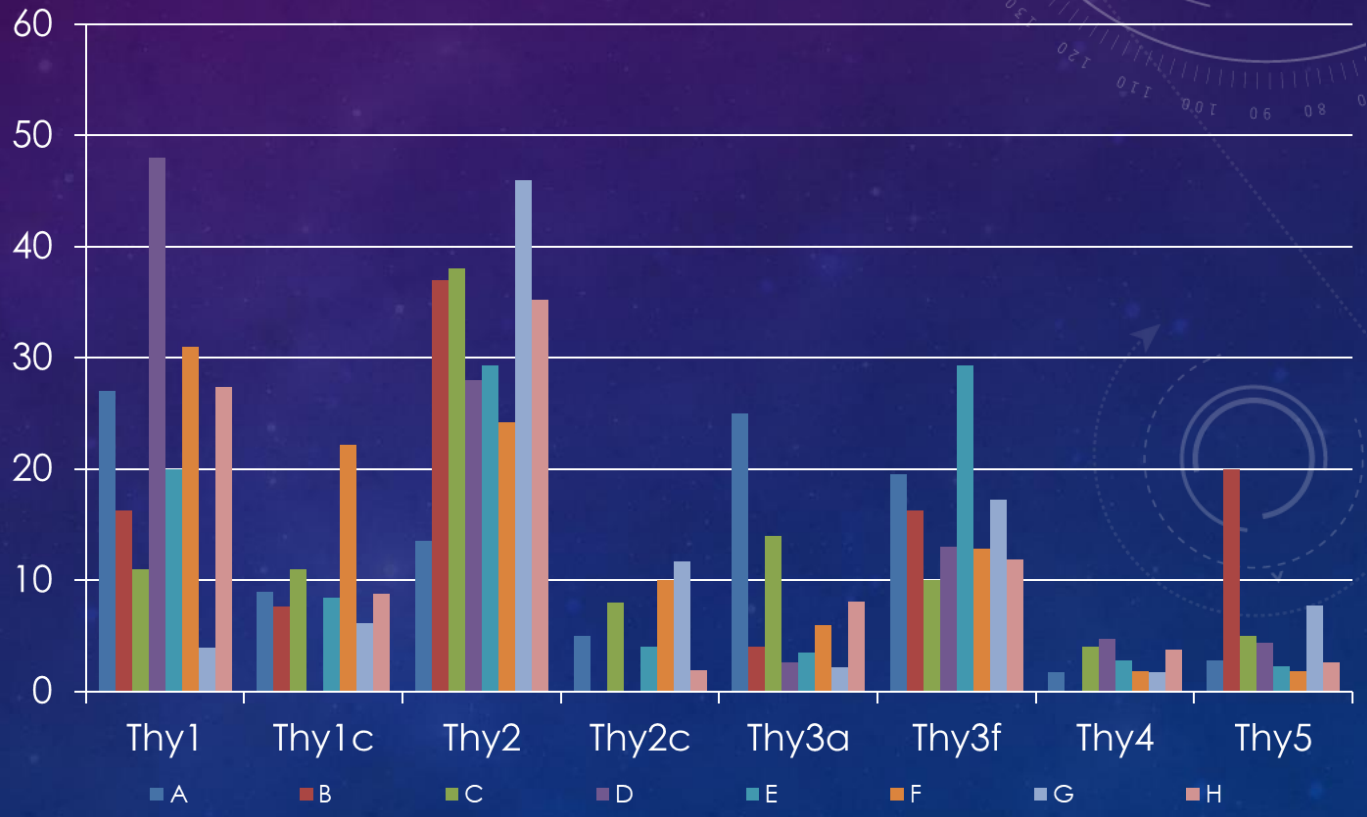
7941 cases from 9 centres

Years

- 2013 – 2015 from most
- 2008 – 2014 from two

Cases per year per centre

- mostly 150-400 (12–571)



3. Interobserver variation, especially Thy3a and Thy4

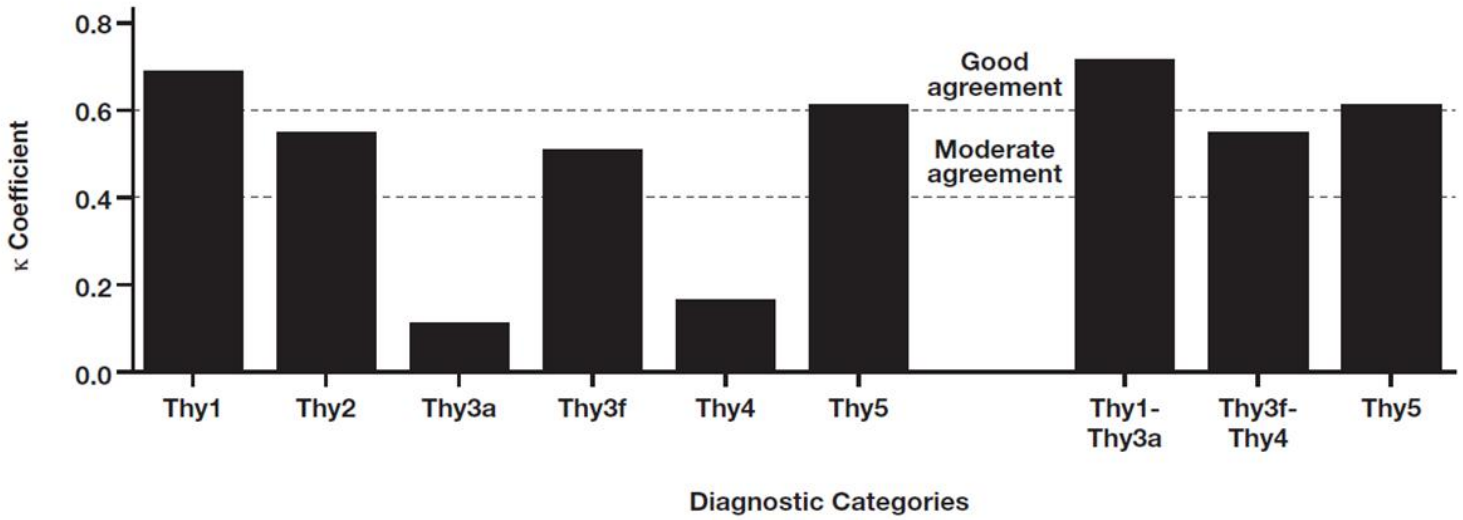


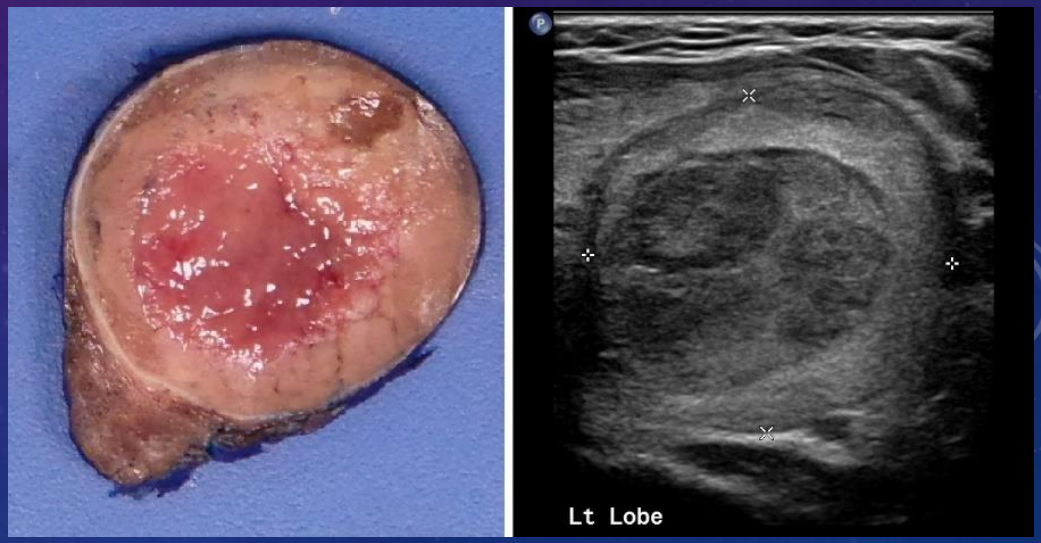
Figure 1 Interobserver agreement for various UK Royal College of Pathologists individual and combined reporting categories. For an explanation of the categories, see Table 2.

Kocjan *et al* *Am J Clin Pathol* 2011;135:852-859.

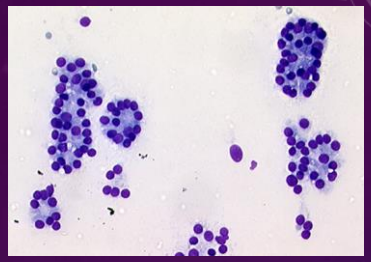
4. limited use in follicular lesions

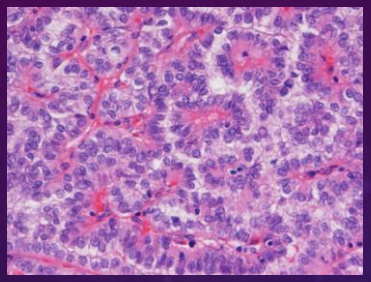
Differential diagnosis of follicular lesions includes:

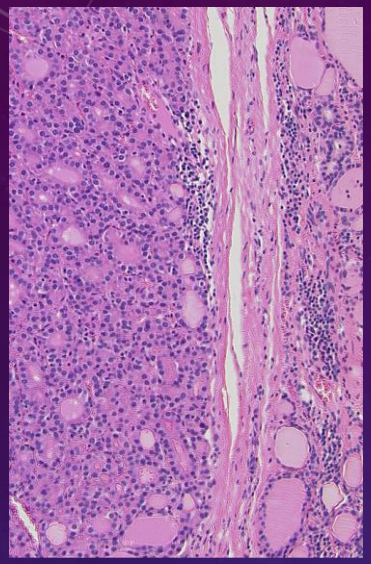
- non-neoplasms, eg hyperplastic nodules
- encapsulated follicular-patterned neoplasms
  - follicular adenomas
  - follicular carcinoma
  - encapsulated FVPTC
  - WDCa-NOS
  - NIFTP
  - WDTUMP
  - FTUMP
  - oncocytic adenoma
  - oncocytic carcinoma

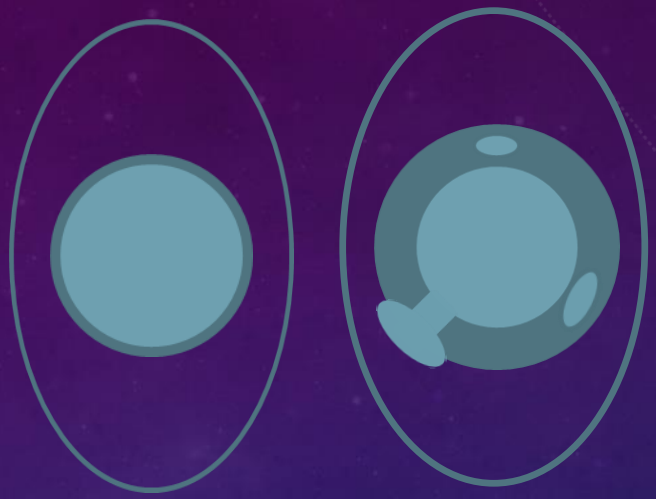


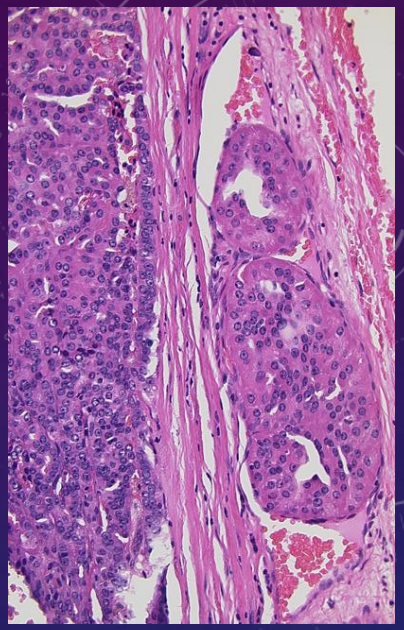
Which all need a HISTOLOGICAL diagnosis











WHO 2017		Invasion		
		Absent	*Questionable*	Present
PTC nuclei	Absent	Follicular adenoma	FT-UMP	Follicular carcinoma
	Questionable	NIFTP*	WDT-UMP	WDCa-NOS
	Present			Invasive eFVPTC

In practice, role of thyroid FNA report

Stratifying nodule for further clinical action:

- Reassurance as to high likelihood of benignity, no further action needed (if asymp, benign USS, no clinical concern)
  - Thy2
- More investigations needed - usually repeat USS +/- FNA
  - Thy1
  - Thy3a
  - Thy4 - if repeat likely to help
  - (Thy5 if lymphoma and core biopsy needed to subtype)
- Needs diagnostic surgery (hemithyroid or isthmus)
  - Thy3f
  - Thy4 – if repeat unlikely to help
- Diagnosis of malignancy made – needs therapeutic surgery or other treatment
  - Thy5 – PTC, MTC, ATC, (lymphoma)

How can quality and accuracy be improved?

- Experienced staff – aspirators, cytopathologists, clinicians
- Maximise quality of specimens
- Communicate with aspirators
- Adequacy and ROSE?
- Consider relevant clinical and radiological findings
- MDT discussion pre-surgery with central review of cytology
- Ongoing audit of cytology / histology correlation
- Understand limitations of cytology and manage expectations

Poller *et al* in press in *Cancer Cytopathol.*

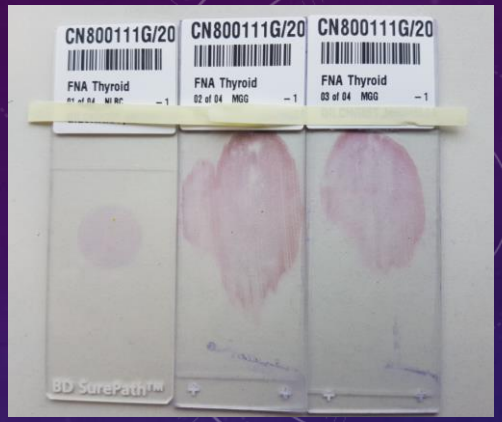
Maximise quality of specimens

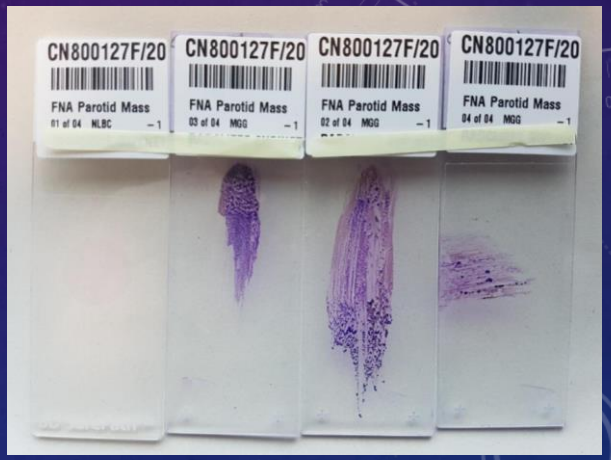
Not standardised across UK

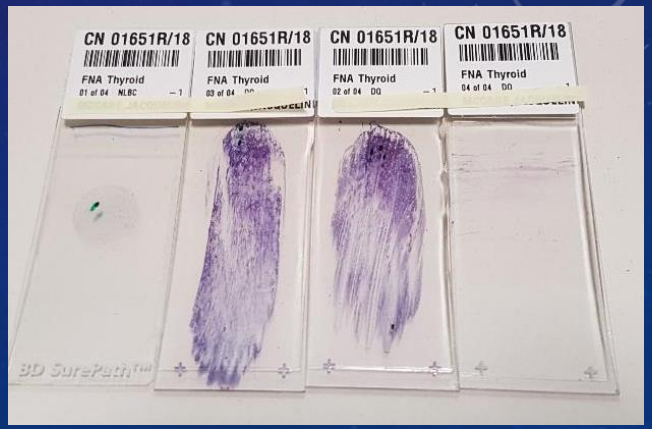
Specimens
- Thyroid - FNA and/or cyst fluid
- Lymph node - FNA

May be mix of
- Direct spreads
  - Airdried then Giemsa
  - Fixed then Pap
- LBC
  - Surepath™
  - Thinprep™
- Cell blocks or clots – FFPE, H&E

In Newcastle upon Tyne
- direct spreads all airdried, stained with MGG
- needle washout for Surepath™ LBC
- very rarely a spontaneous clot present – processed for H&E





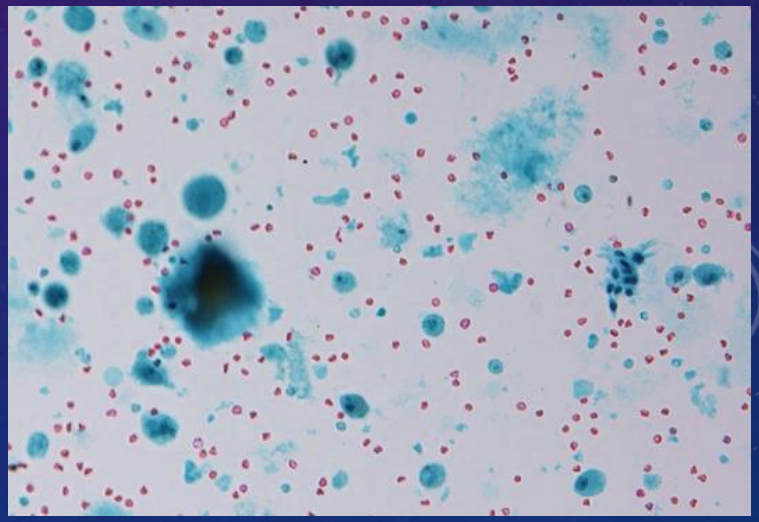


Communicate with aspirators

- Provision of information on request form
- Liaise about individual cases
- Essential to give feedback on quality so can improve

Adequacy

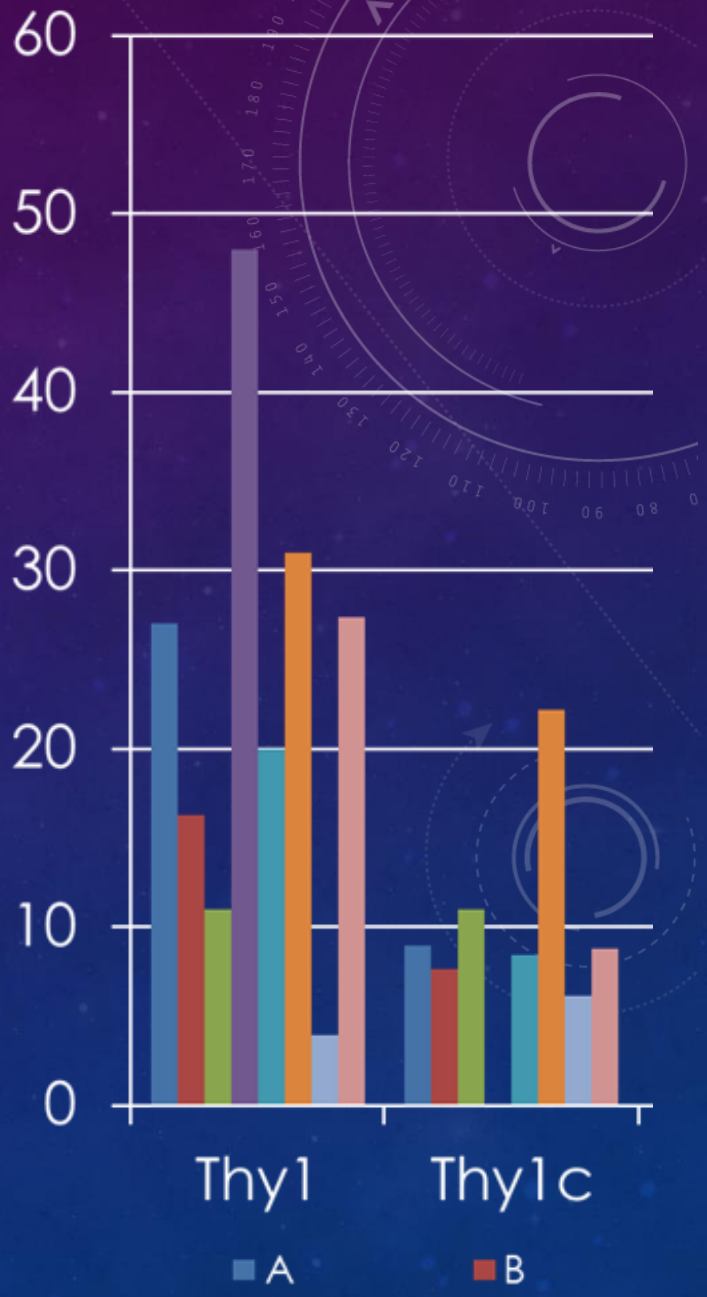
- Solid lesions – need at least 6 groups of thyroid follicular epithelial cells, each with at least 10 well visualised cells
- Report should state reason for inadequacy
  - Related to technique – Thy1
    - acellular
    - just blood or blood obscures cells
    - too few epithelial cells or badly preserved cells
  - Related to lesion
    - cyst macrophages without abundant colloid - Thy1c



- Aspirators should audit their adequacy rates

Adequacy (cont)

	Thy1	Thy1c
UKEPS audit	4 - 48%	7 - 22%
NuTH		
2008-10	16.1%	10.6%
2011-14	9.8%	10.7%
2015	11.9%	9.6%
2016	9.6%	4.5%
2017	7.6%	8.6%
2018	4.9%	9.9%



Parkinson *et al J Clin Pathol* 2017;70:648-655.
Unpublished NuTH audit by SJ Johnson.

To ROSE or not to ROSE?

- ROSE can help if non-diagnostic rate is high
- Done by BMS or cytopathologist
- Current review of 25 published articles:
  - Overall 13.6% Thy1 (3.0-43.3)
  - Only 3 separated out Thy1c which reduced overall Thy1 rate
  - ROSE, 6 articles – Thy1 6.0% (3.0-10.9)
  - No ROSE, 17 articles – Thy1 18.5% (7.9 – 43.3)

Poller *et al* in press in *Cytopathology.*

Central review of cytology for MDTM

MDTM discussion

- All Thy4 and Thy5, with review of cytology
- Others by local arrangement and clinical need

Central review of cytology – NuTH audits 2014-15:

- Often changes Thy category – up to 65%
- Changes usually add clinical value
  - Reduces nondiagnostic (Thy1)
  - Increases non-neoplastic (Thy2)
  - Reduces nonspecified Thy3
  - Reduces Thy3a
  - Increases suspicious and malignant (Thy4 and Thy5)
- Improves accuracy compared to histology
- Better pre-op diagnosis of malignancy
- Increases clinician confidence

Guidance on the reporting of thyroid cytology specimens, 2nd ed 2016, RCPath.
Unpublished audits by SJ Johnson.

Ongoing audit of cytology / histology correlation

- Need to know frequency of use and ROM for each category locally
  - Local clinicians need to know ROM – send them audits or include in reports
- ROM = probability lesion is malignant on histology
  - Need to know calculation
    - Only cases with surgery (= PPV) – more relevant for Thy3a, Thy3f, Thy4, Thy5
    - All cases in that cytology category – more relevant for Thy1, Thy2
  - Remember subjectivity in histology diagnoses
- Audit can inform reporting

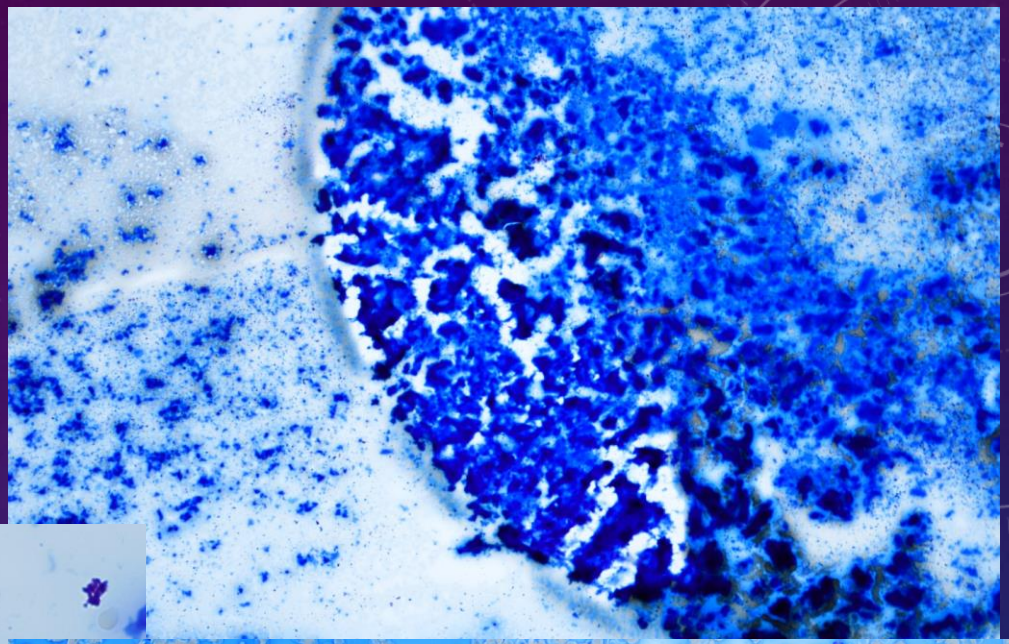
Parkinson *et al J Clin Pathol* 2017;70:648-655.
Poller *et al* in press in *Cancer Cytopathol*.
Audit template, RCPath, 2019.

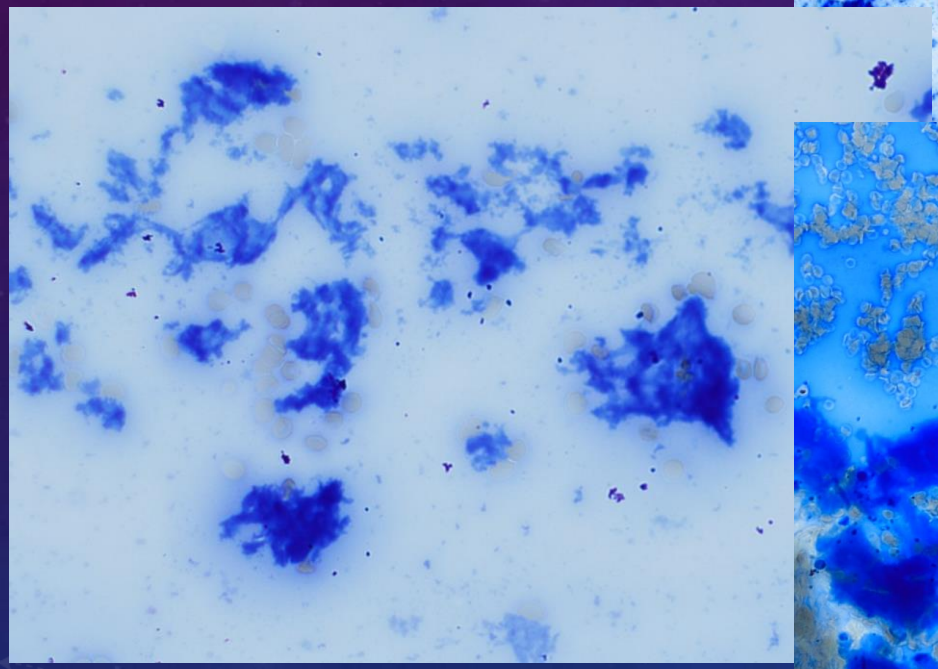
Problem areas – personal view

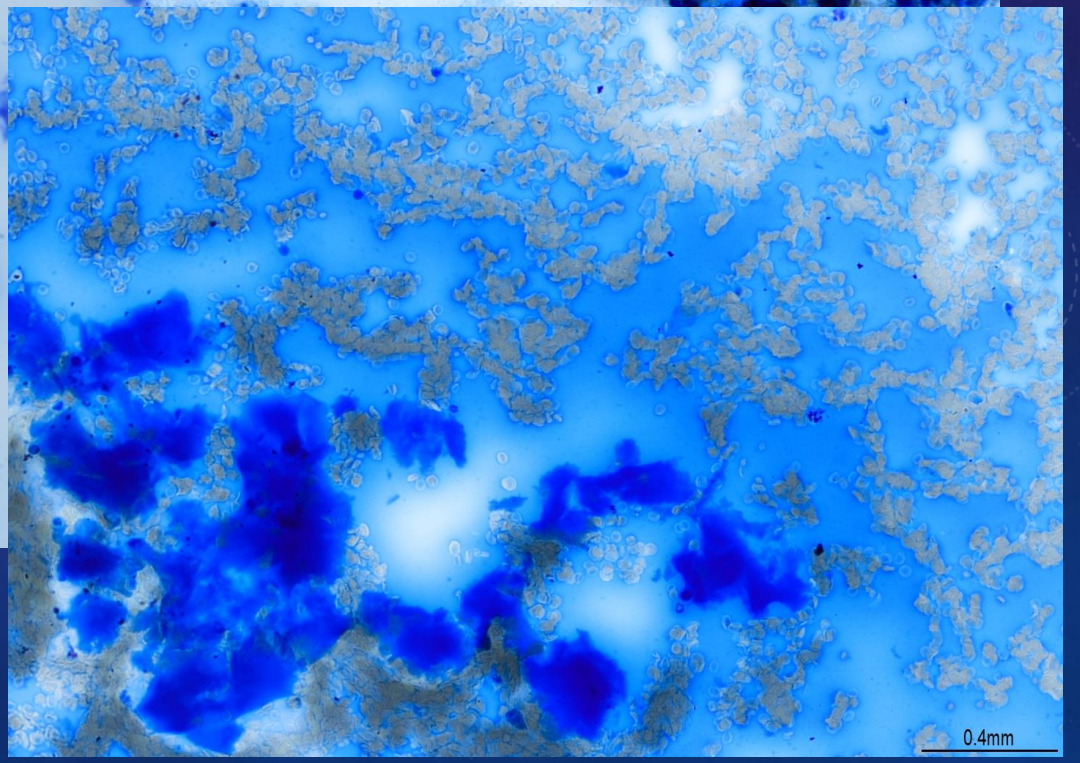
- Colloid – present or not?
- What can be accepted in “non-neoplastic”
- When to use “atypia” or Thy3a
- When to suggest follicular-patterned lesion / neoplasm
- When to be suspicious of malignancy
- Diagnosing malignancy

Colloid – present or not?

- MGG - thick colloid

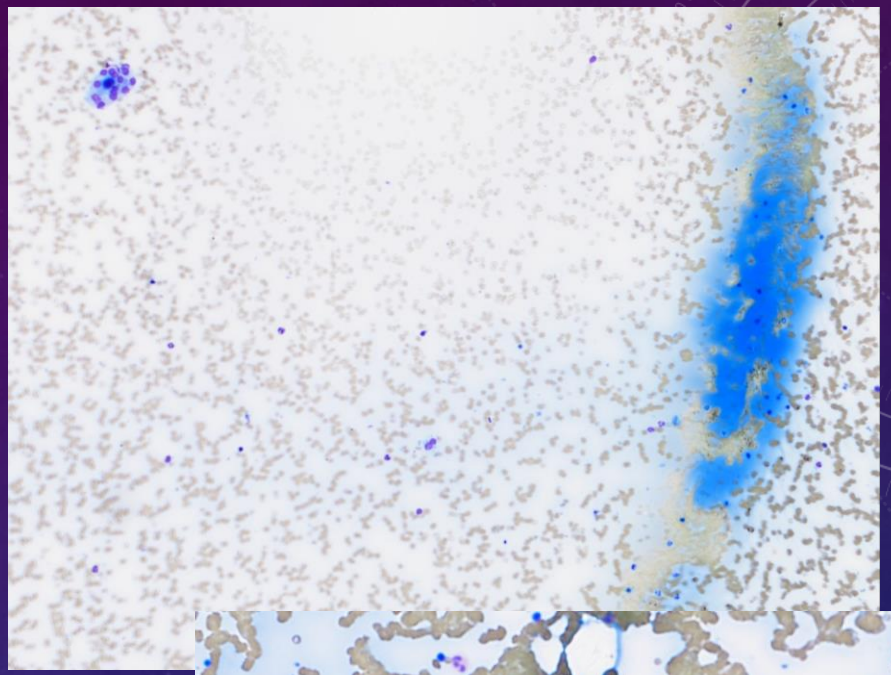


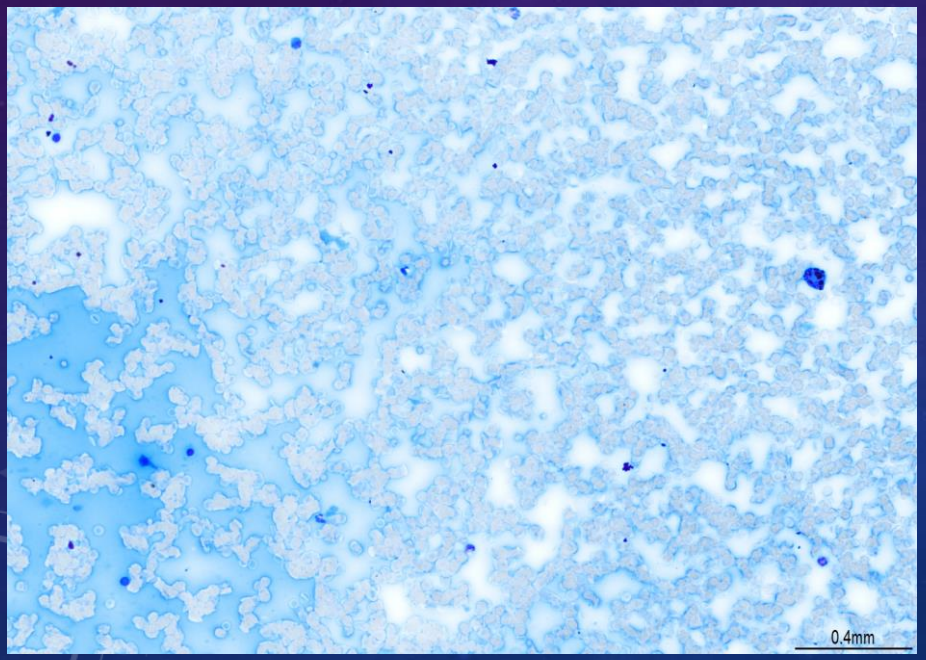


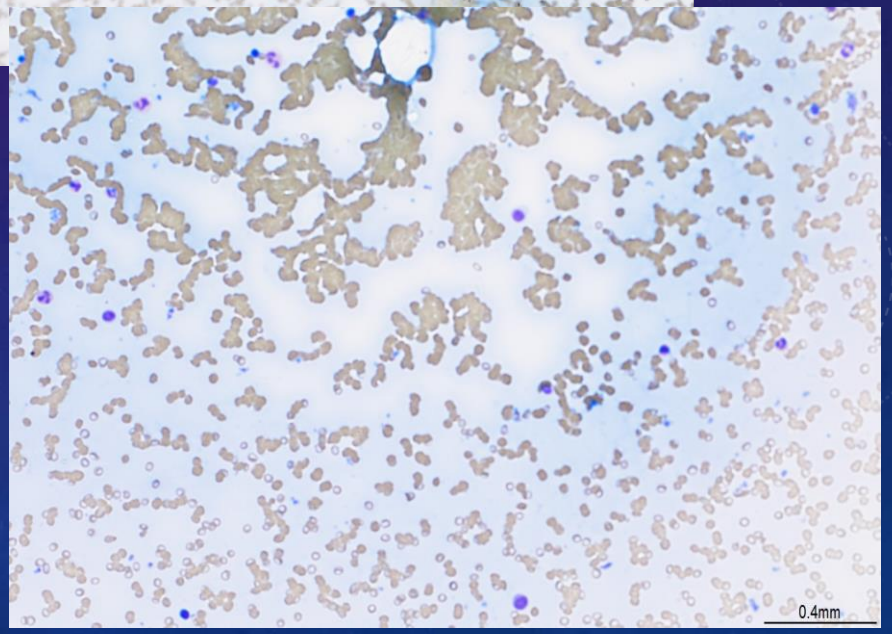


Colloid? (cont)

- MGG - thin colloid

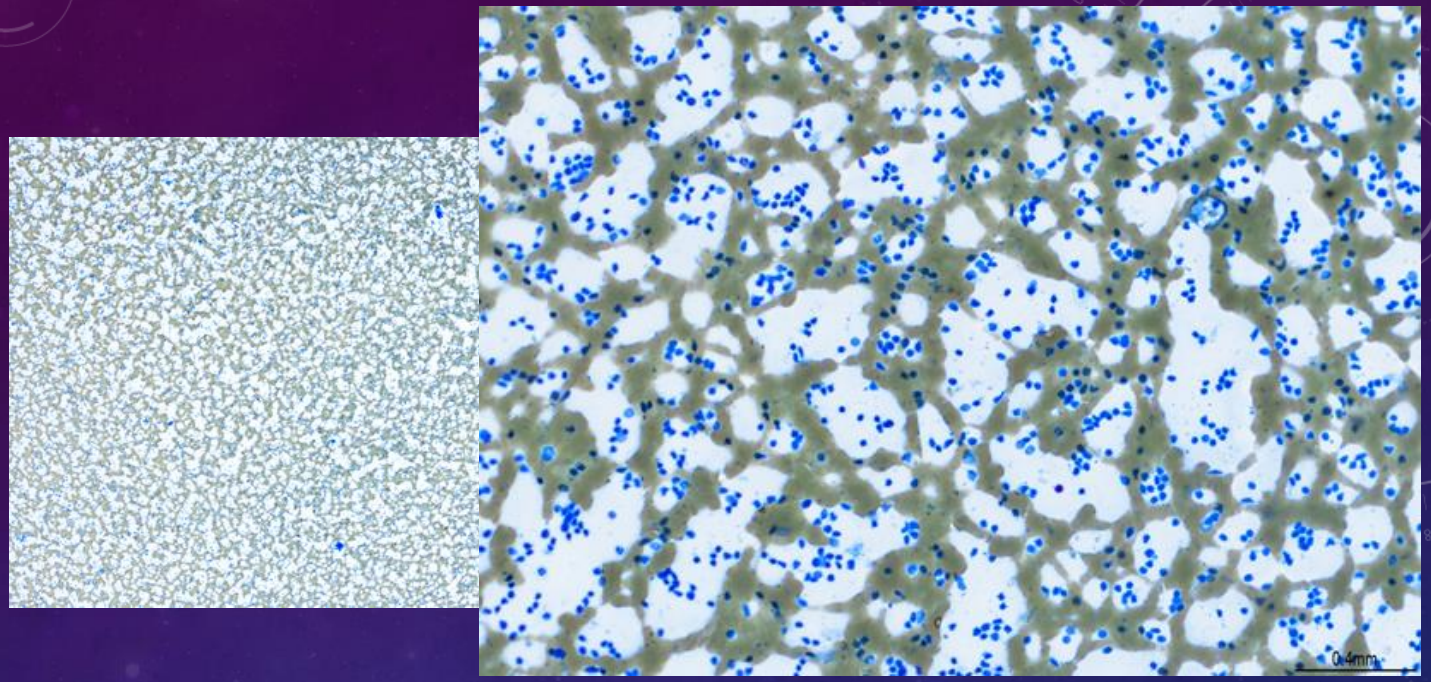




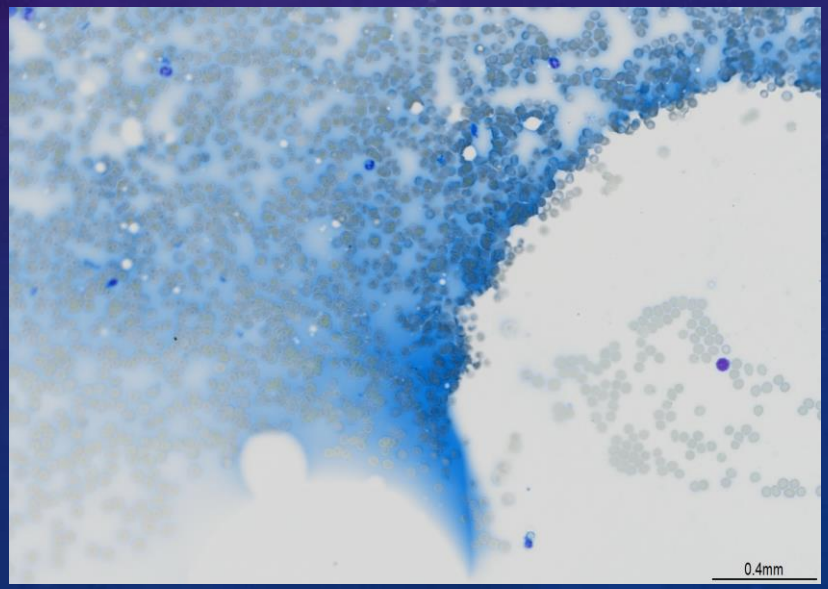


Often mimicked

eg LN FNA

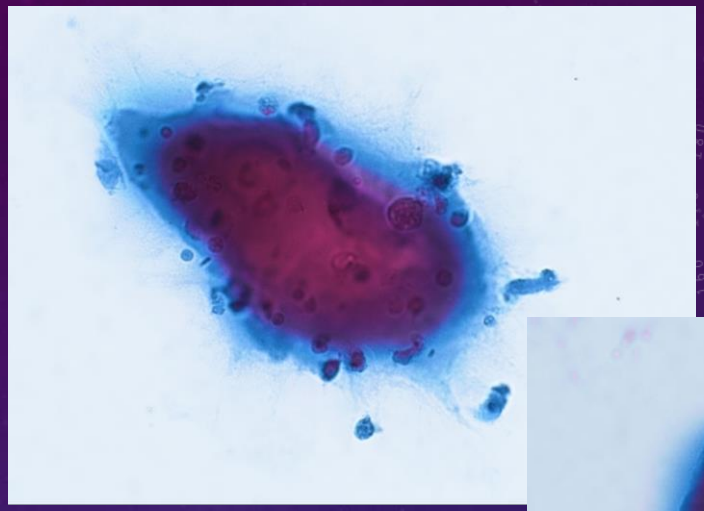


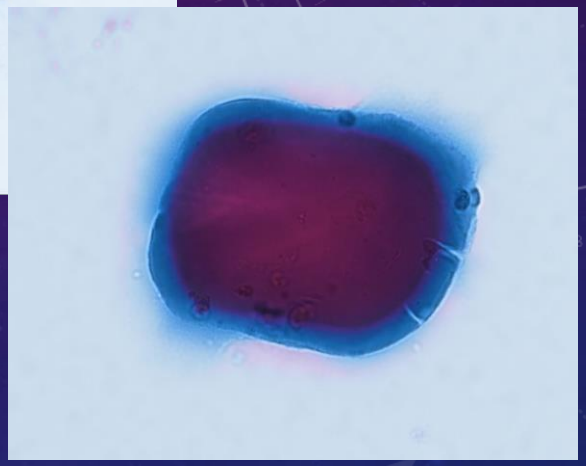
Breast FNA



Colloid? (cont)

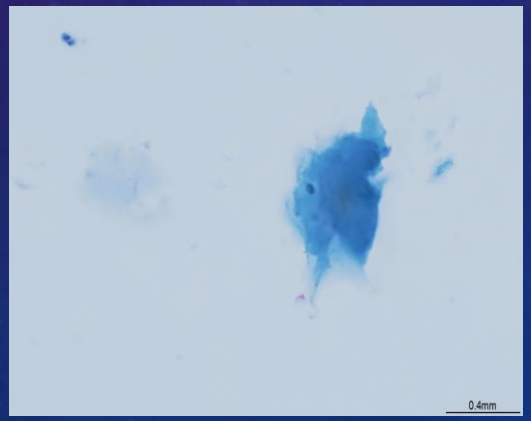
- Pap
  - Surepath LBC – thick colloid

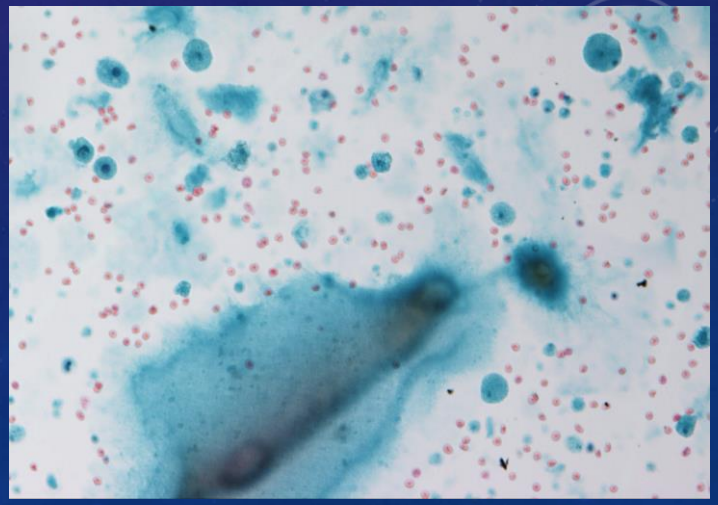




Can crack and mimic psammoma bodies

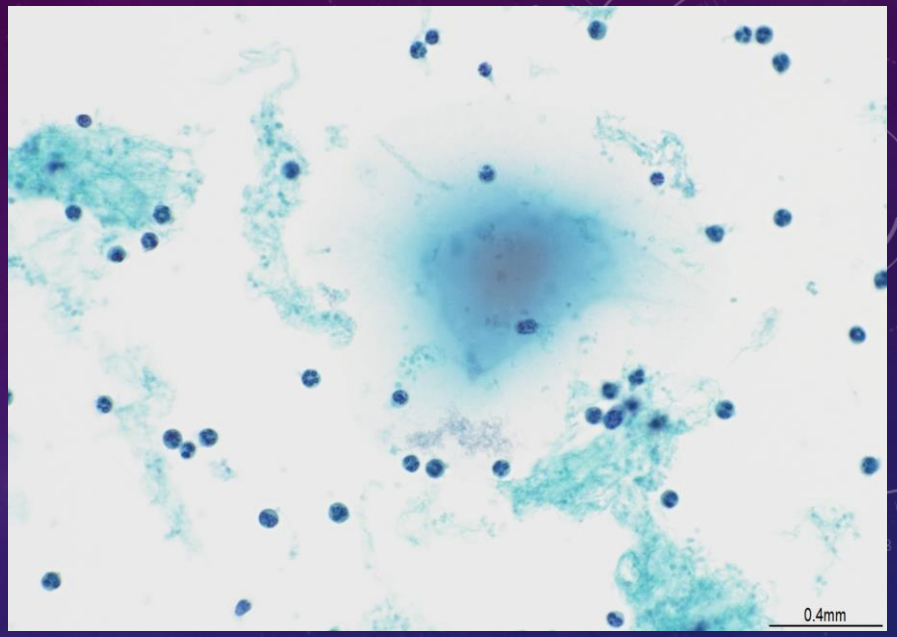
- Surepath – thick and thin colloid





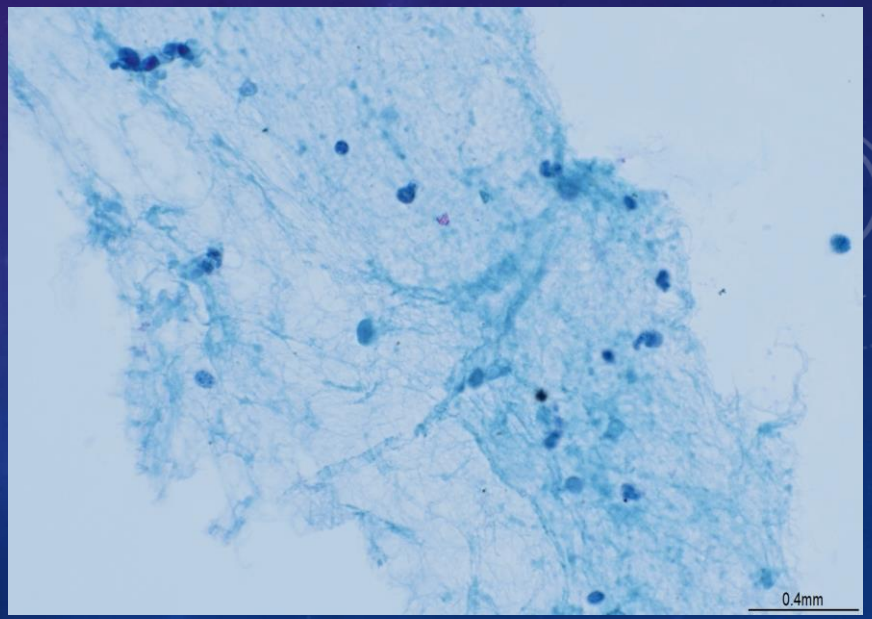
Colloid? (cont)

- Pap
  - Surepath LBC – thin colloid



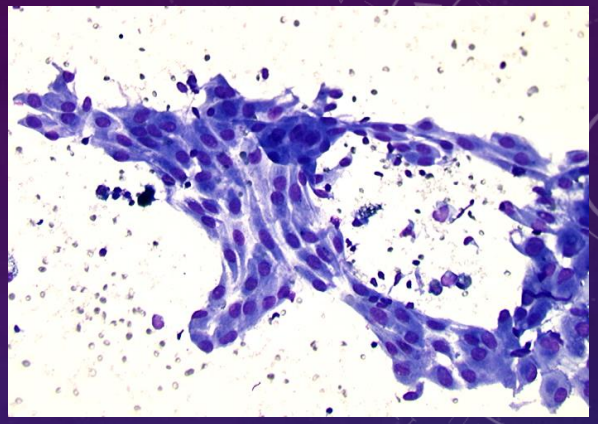
- Direct spreads and
- Thinprep LBC

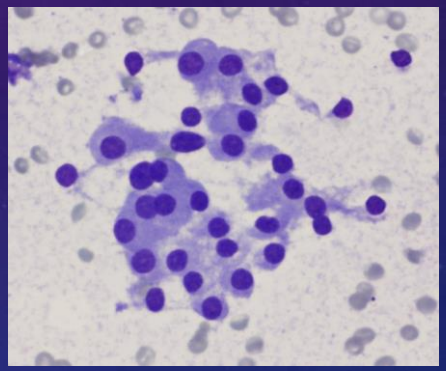
- both very difficult!

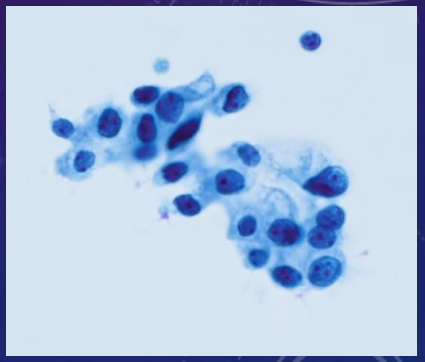


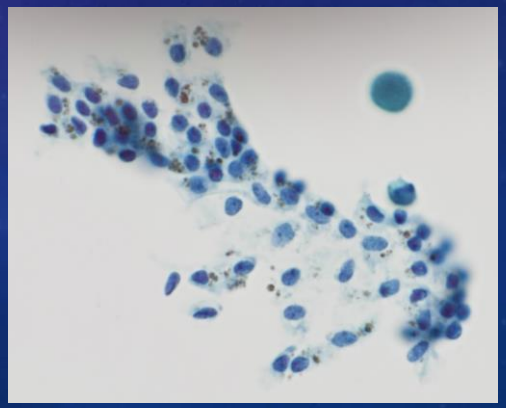
What can be accepted in “non-neoplastic”, ie Thy2

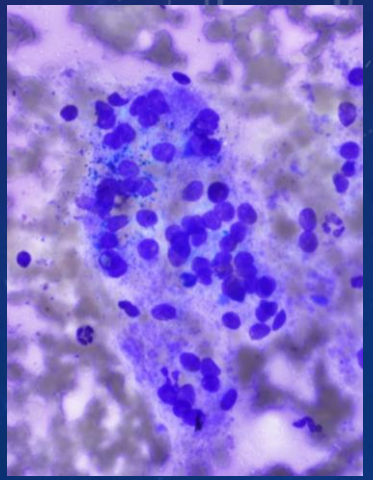
- Can be cellular with a few microfollicles but not prominent microfollicles
- Can have plump cyst lining cells if nuclei bland
- Or slight nuclear changes
- Can have some oncocytic cells, in fact a mixture is reassuring
- May have cytoplasmic lipofuscin granules (I find reassuring)











When to use “atypia” or Thy3a?

- Definition: cytological features raising possibility of neoplasia but not enough for another category
- Text should indicate problem
- Should be a minority
  - TBS1 <7%, TBS2 <10%
  - RCPath suggests 5-10%

Easy to over-use

- Instead of Thy2
- Instead of Thy4 – increases ROM of Thy3a & Thy4

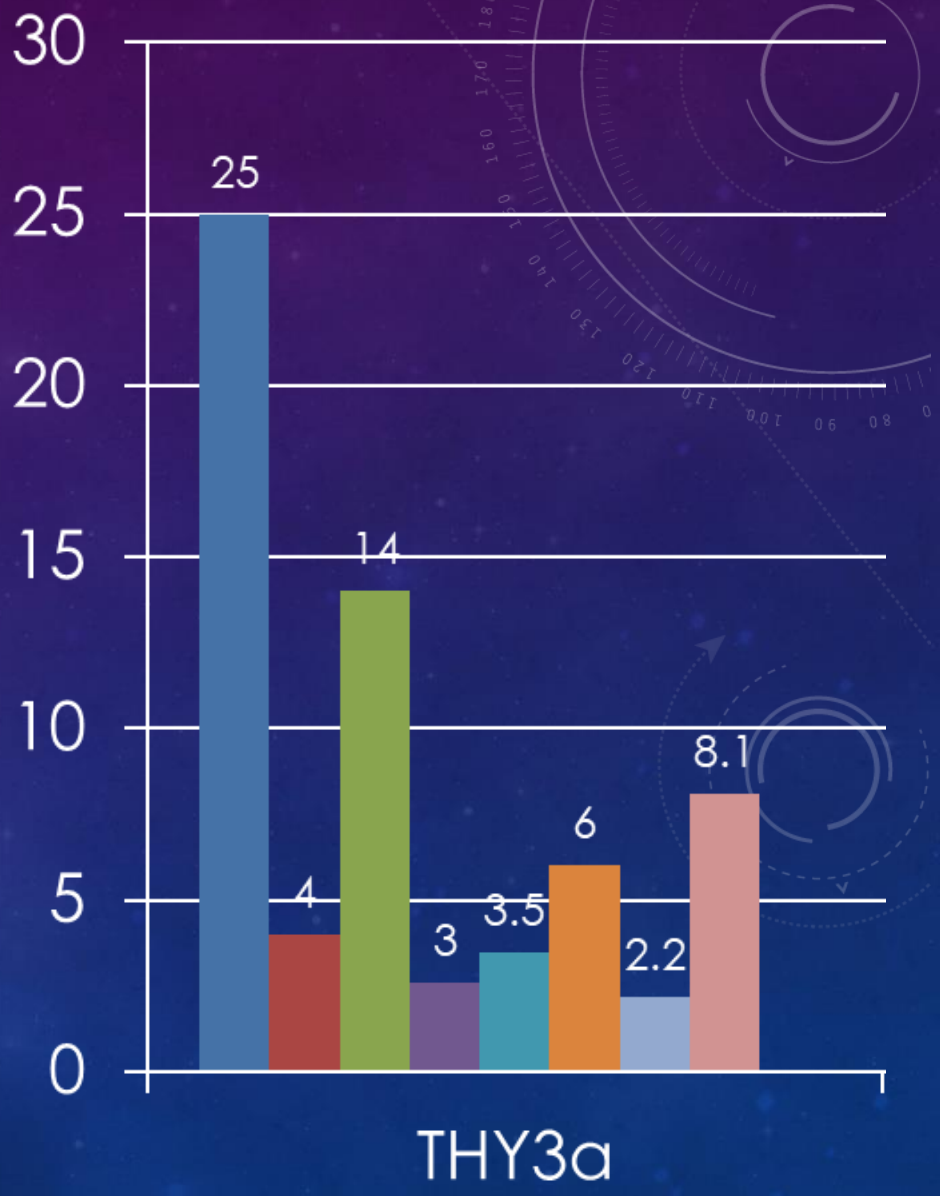
Report should be very clear on interpretation, possibilities and limitations

Thy3a (cont)

Highly variable frequency of use nationally:

UKEPS audit 2.2 – 25%

NuTH	Thy3a	Thy3a/Thy5 ratio (1.0-3.0)
2008-10	11%	
2011-14	14.4%	2.73
2015	11.4%	2.0
2016	9.6%	1.13
2017 provisional	18.4%	4.25
2018 provisional	19.3%	3.9

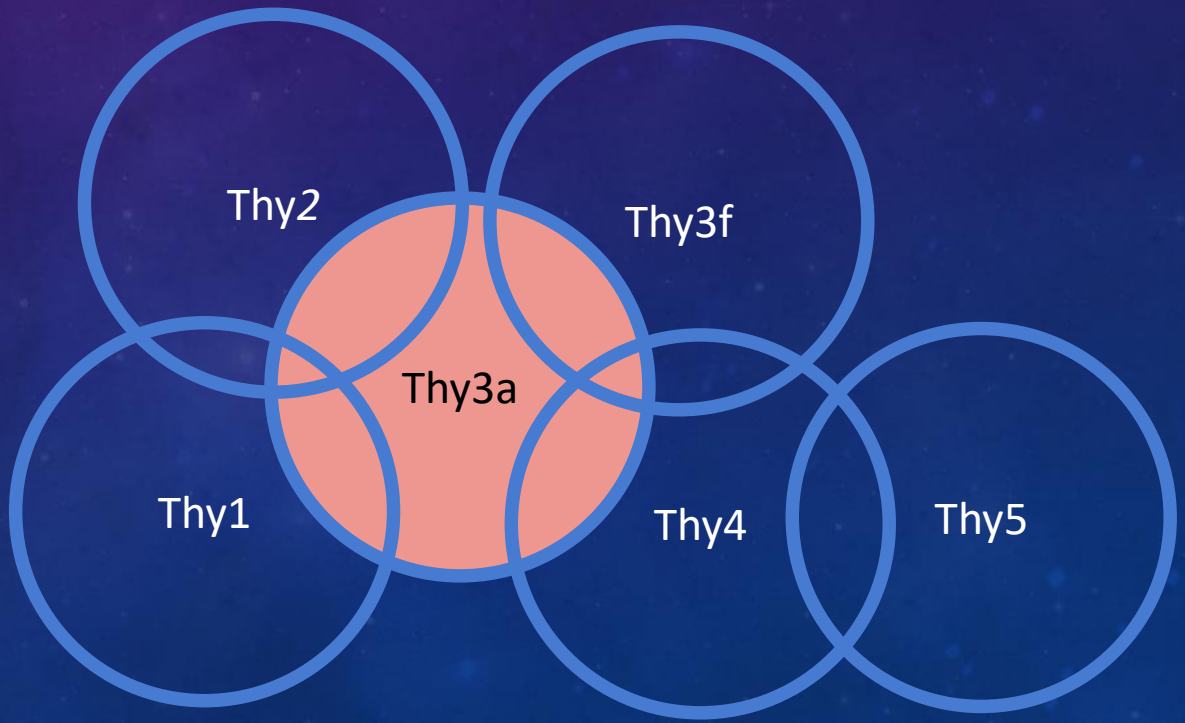


Thy3a (cont)

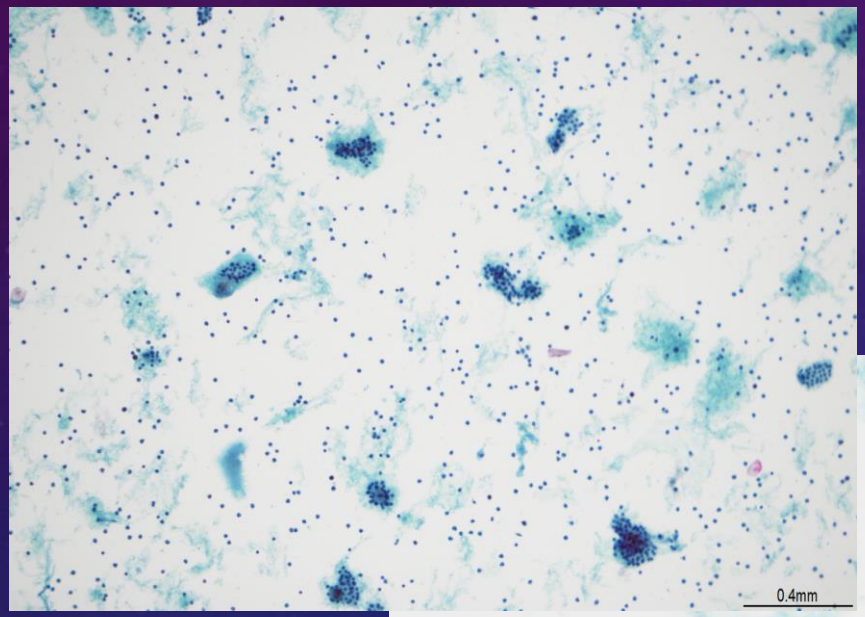
Conceptually:

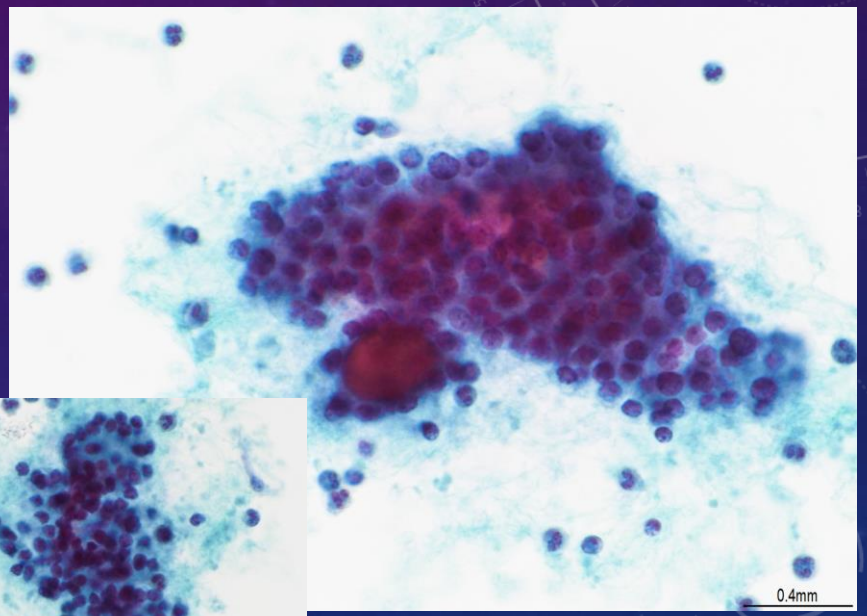
<u>Not</u> a progression

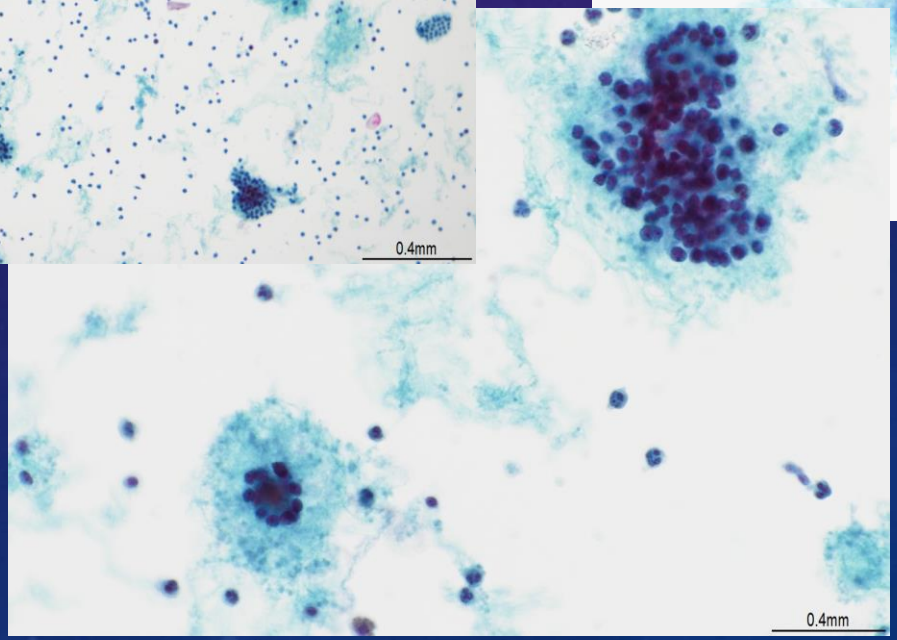
More an overlap …with subjectivity at all the intersections…



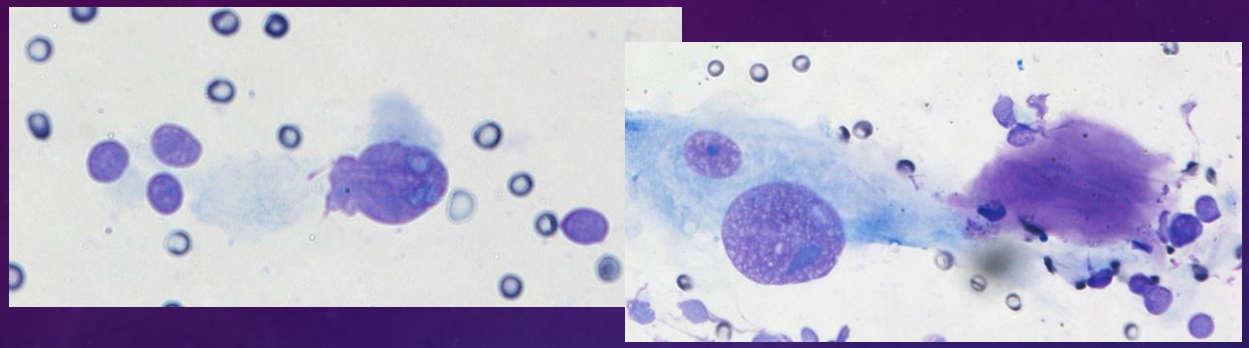
- Should be subcategorised, examples
  - architectural atypia - too many microfollicles and/or too little colloid - cannot exclude FN



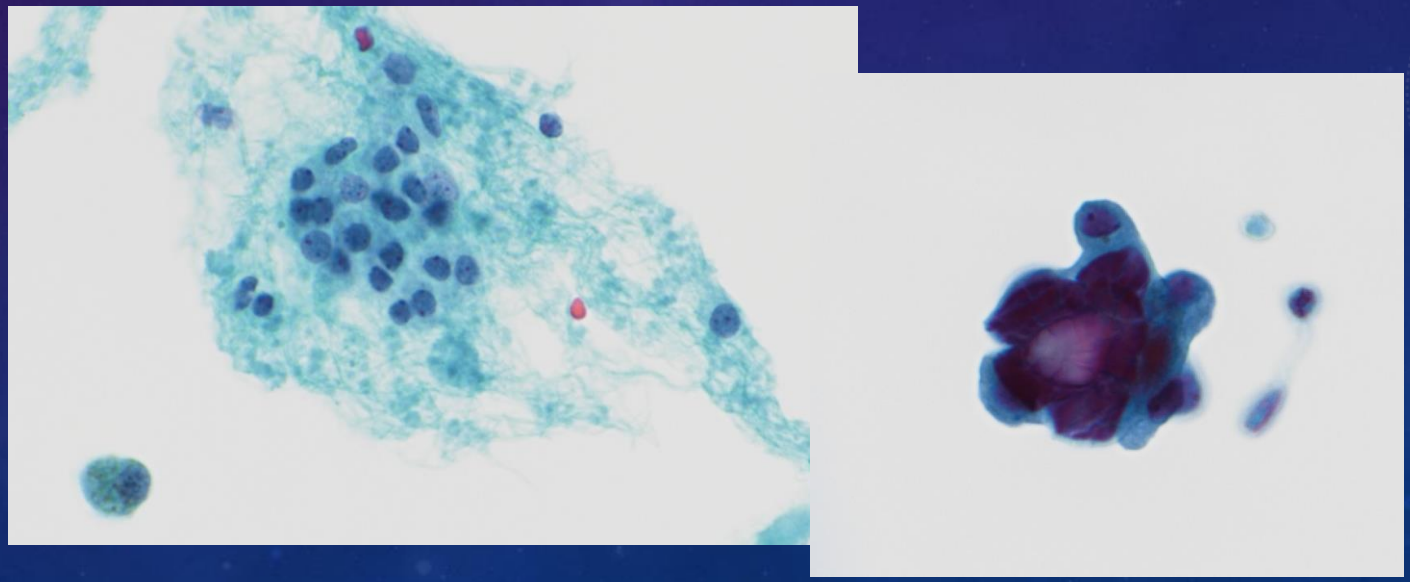




- Scanty focal nuclear/cytological atypia – higher ROM

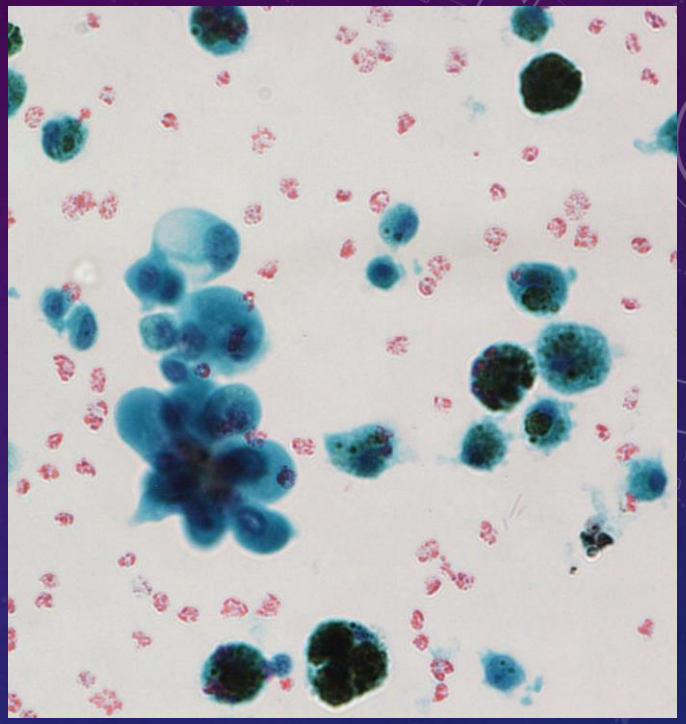


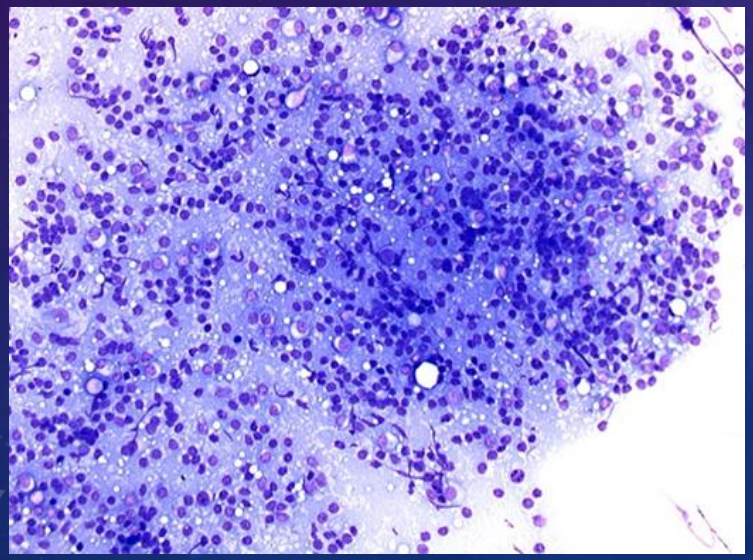
- other features when cannot exclude PTC, eg psammoma body-like



- atypical cyst lining cells

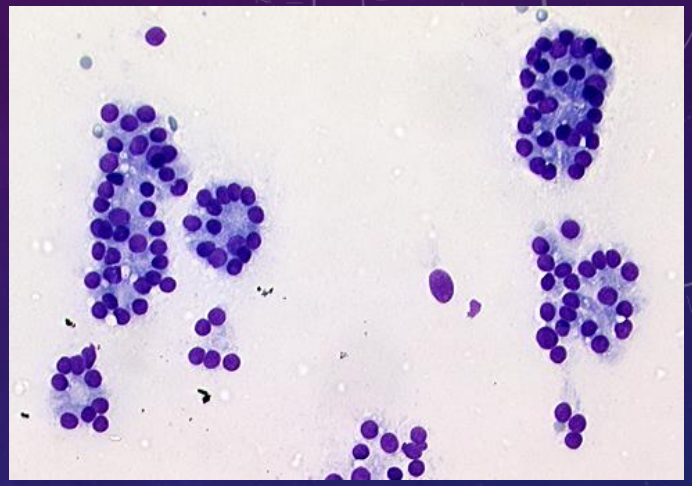
- predominance of lymphoid cells - cannot exclude lymphoma



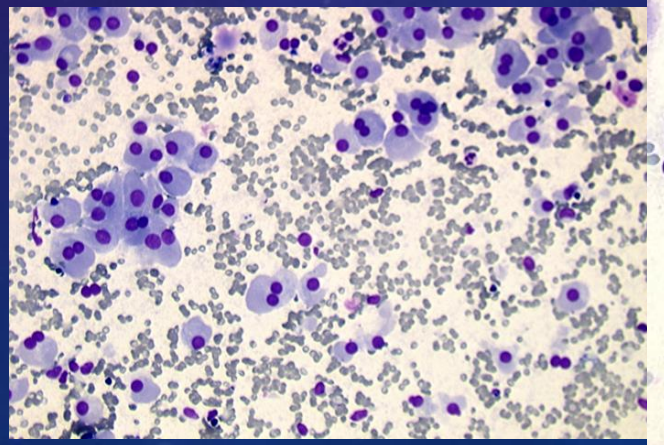


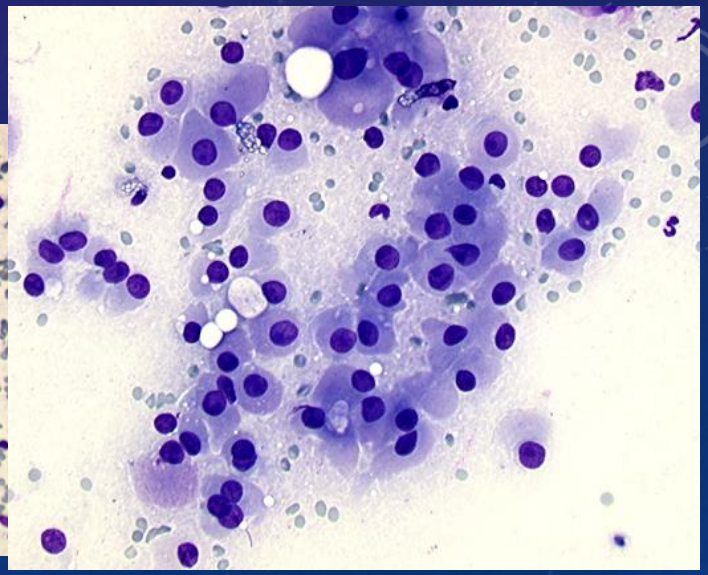
When to suggest follicular lesion / neoplasm, ie Thy3f = surgery

- Cytological features
  - Reduced / no colloid
  - High cellularity with frequent microfollicles and/or cell clusters
    or
  - Predominance of oncocytes
    (beware MTC and metastatic RCC)



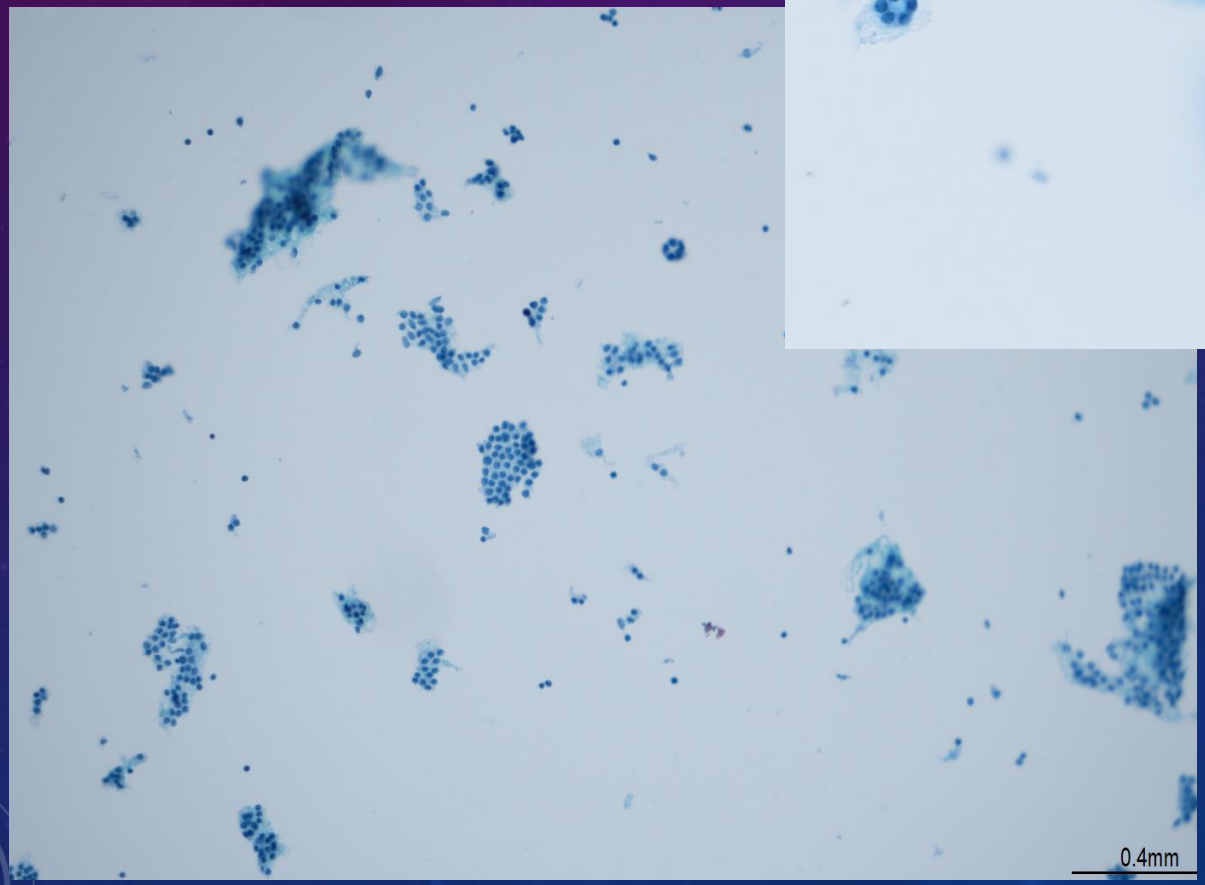
(Remember intrathyroidal parathyroids)





Thy2 vs Thy3 in follicular setting? – my approach

Amount of colloid				Cellularity and microfollicles	
Colloid nodule	Cellular colloid nodule	Favour cellular colloid nodule but cannot exclude follicular neoplasm	Differential diagnosis is between follicular neoplasm and cellular colloid nodule	Favour follicular neoplasm but cannot exclude cellular colloid nodule	Suggests follicular neoplasm
Thy2	Thy2	Thy3a	Thy3f	Thy3f	Thy3f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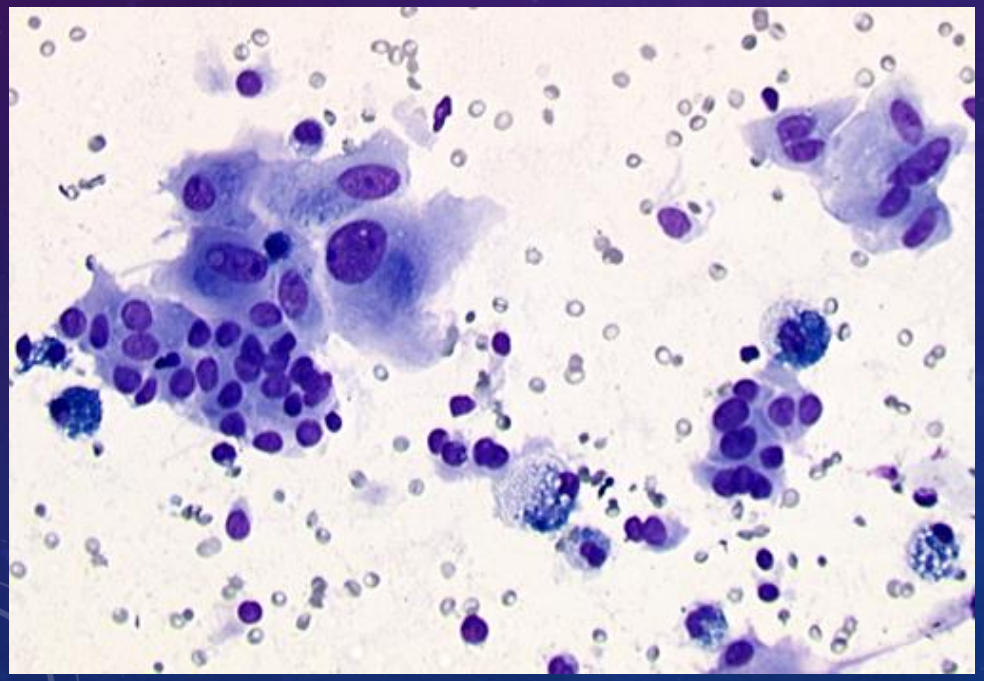
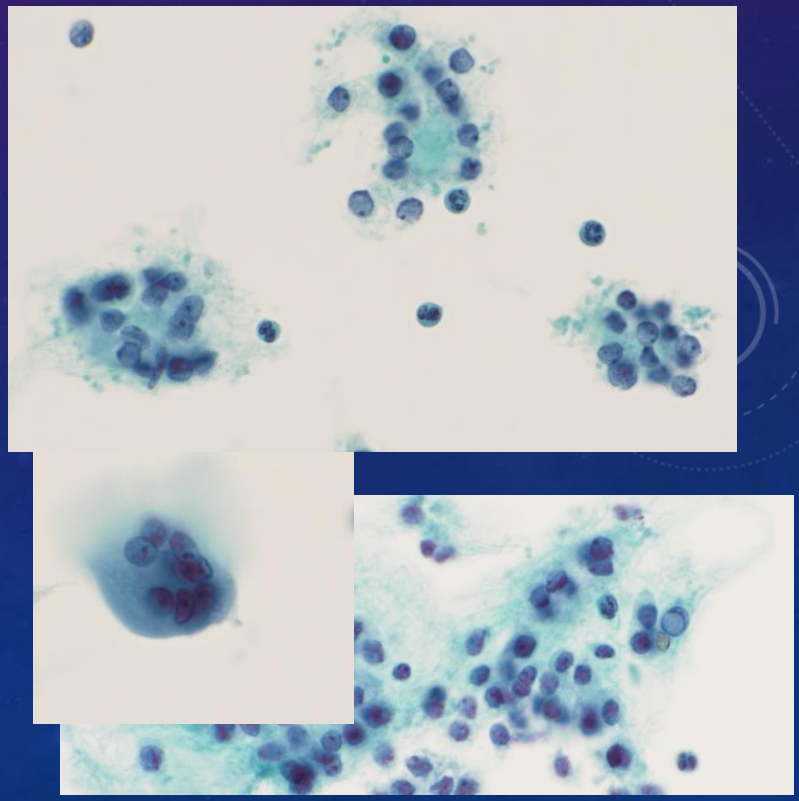
When to be suspicious of malignancy, ie Thy4 vs Thy3a

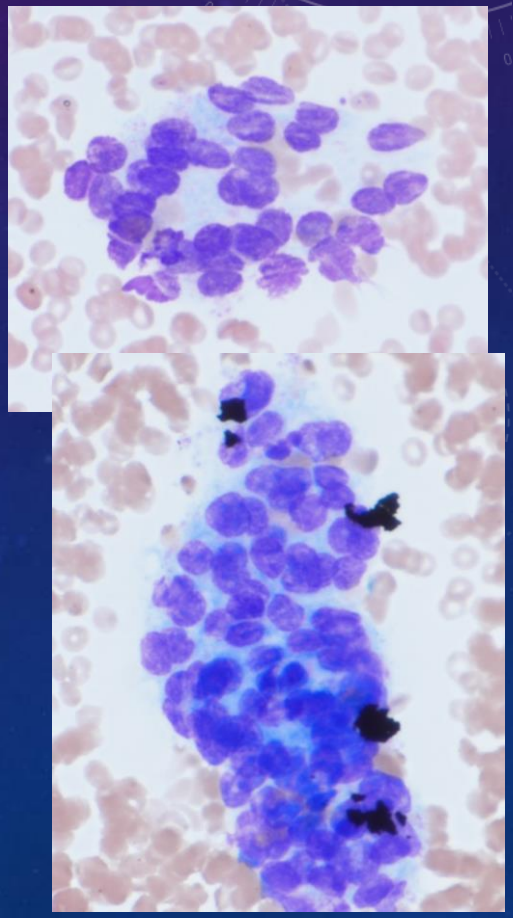
- Subjective
- Comes with experience and review of cases once have histology
- Usually for PTC, so features falling short of diagnostic (Thy5) but more marked than atypical (Thy3a)

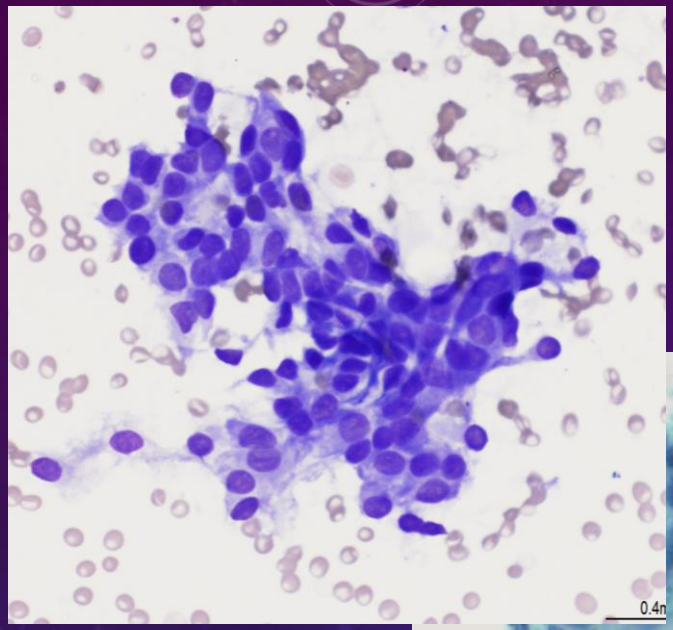


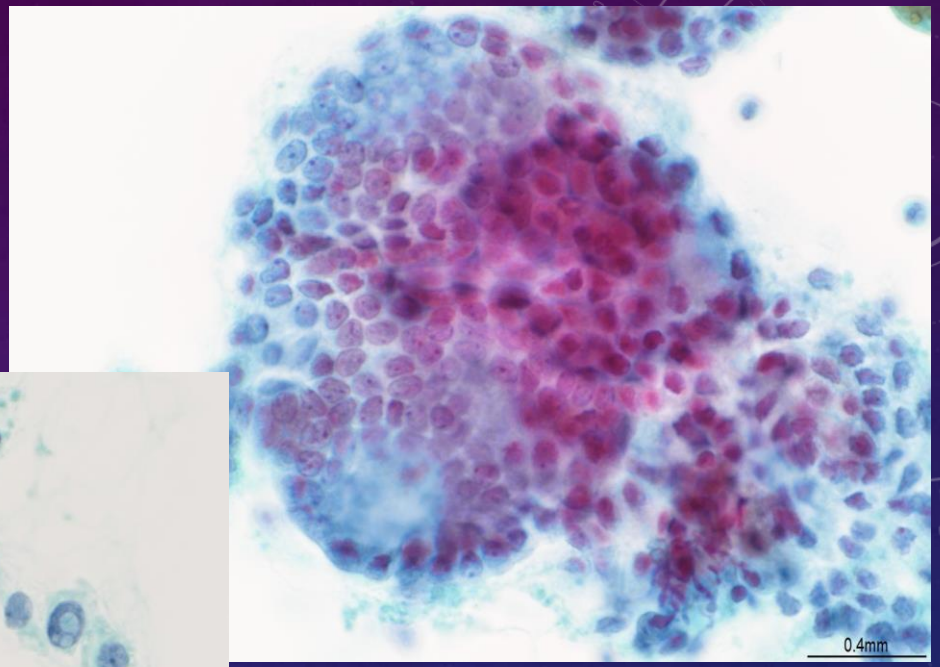


Diagnosing malignancy, ie Thy5

- **Papillary thyroid carcinoma**
  - No cytological features are pathognomic of PTC
    - Need qualitative and quantitative judgement
  - Complicated by recent entity of NIFTP
    - Use Thy4 if
      - Significant follicular architecture with nuclear abnormalities but not too many intranuclear inclusions
      - Especially if U3 on radiology
      - Flag in report that it may be a lower risk lesion such as NIFTP or eFVPTC
    - Go to Thy5 if
      - Papillary structures
      - Psammoma bodies
      - Multiple intranuclear inclusions



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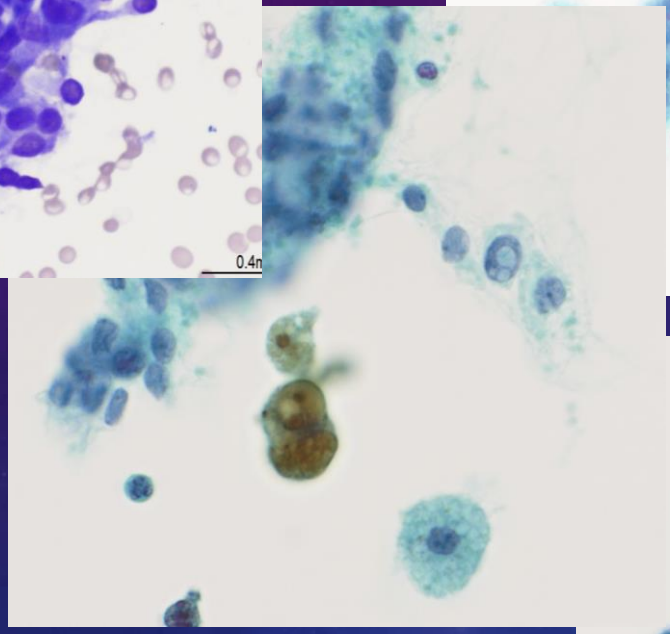

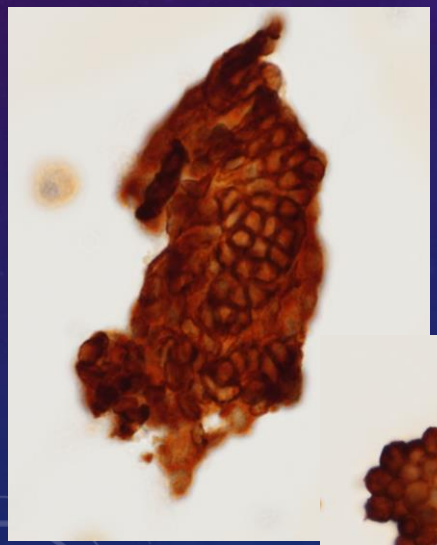

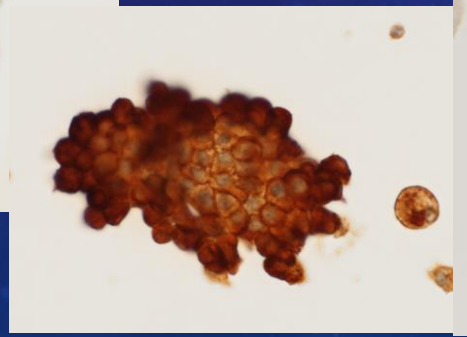

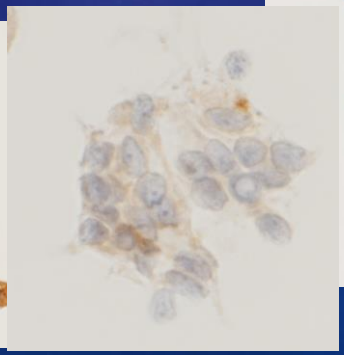

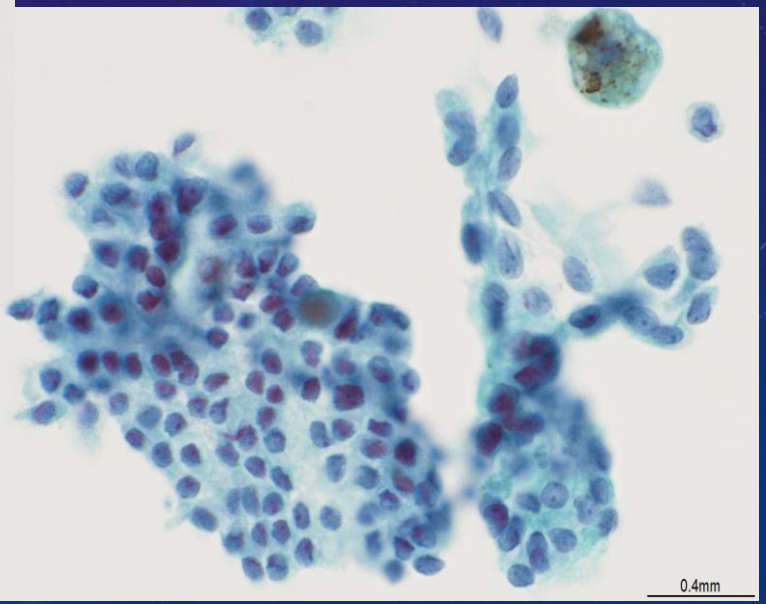
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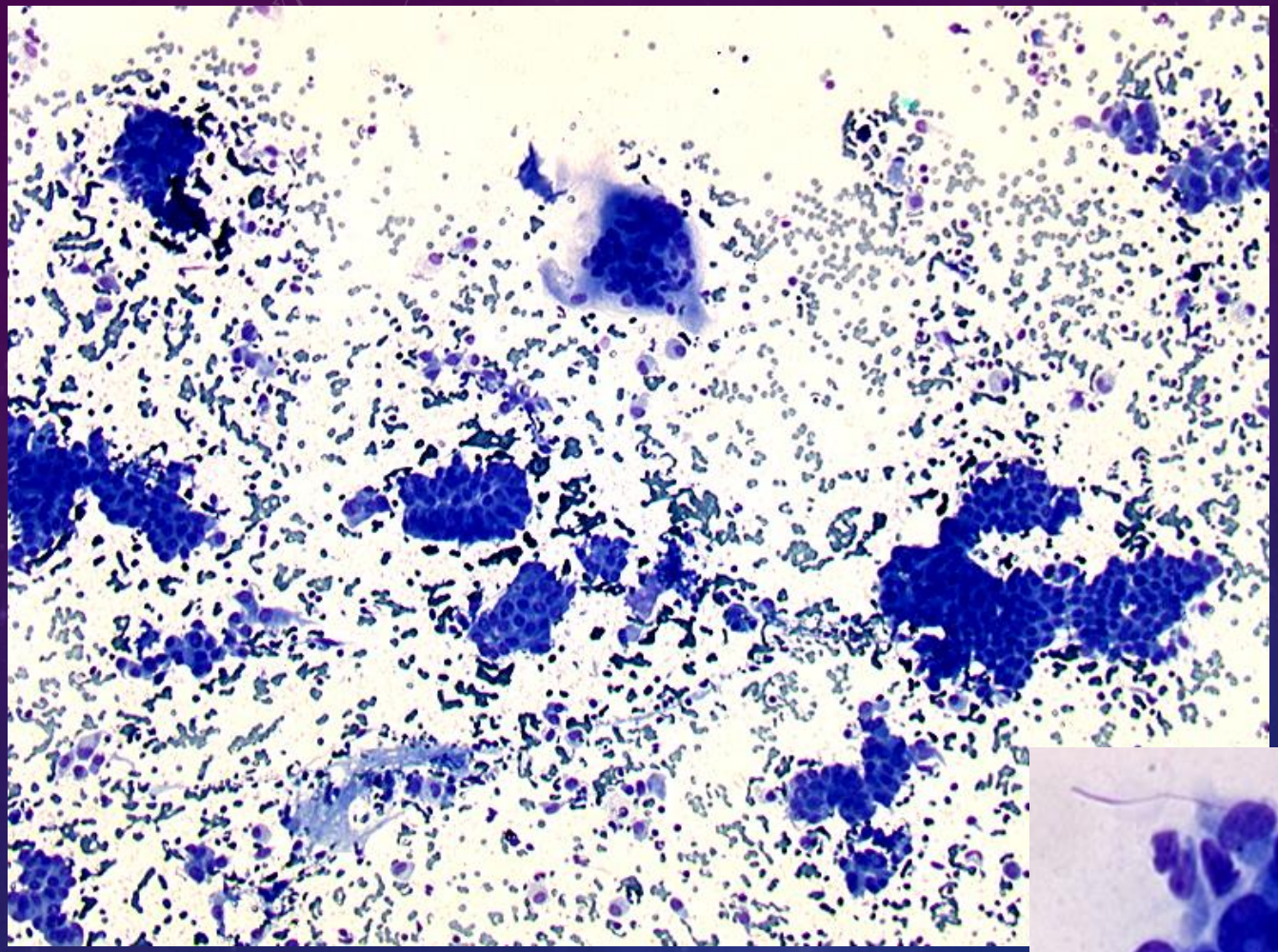
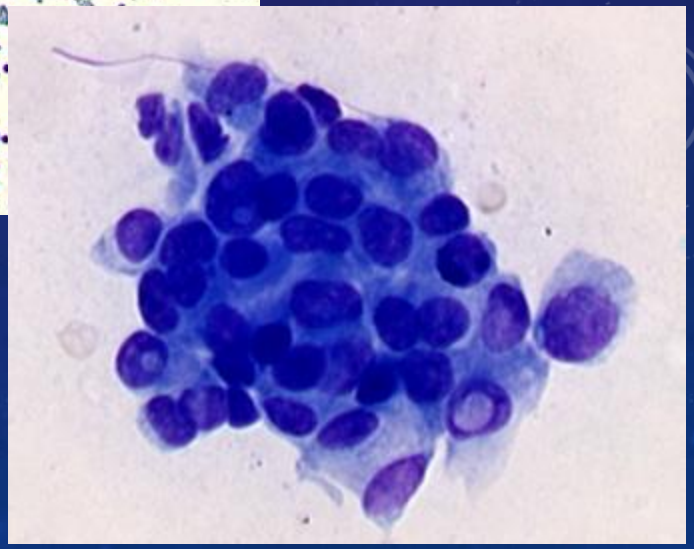
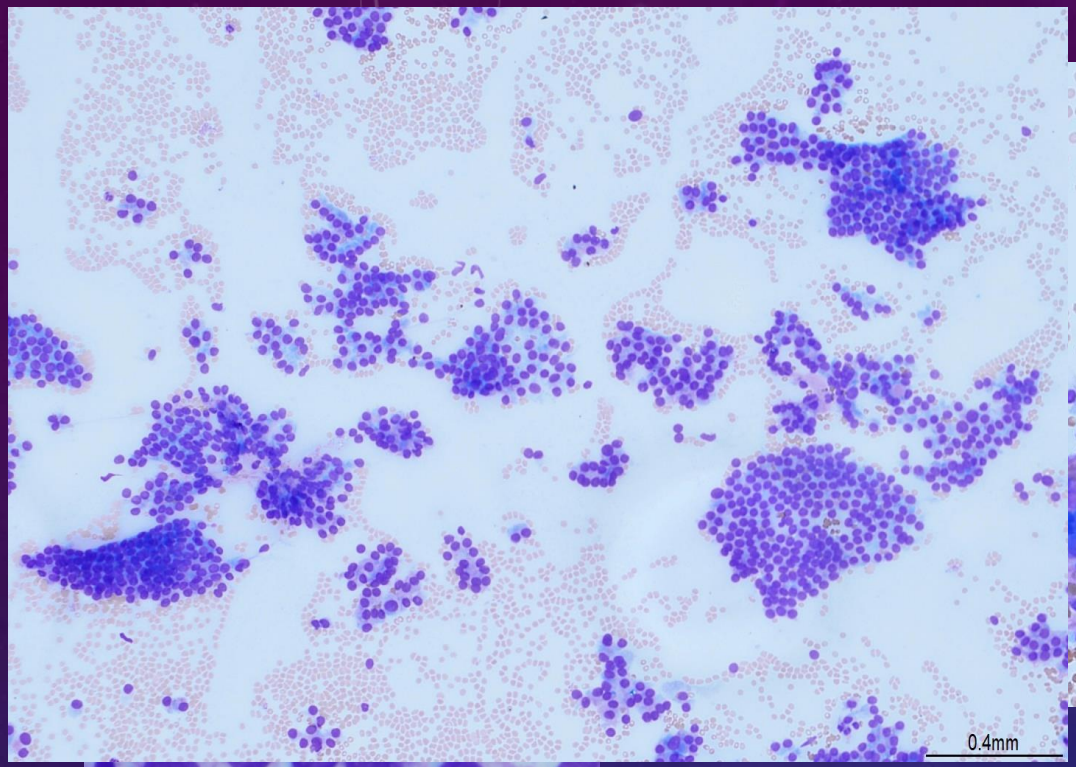
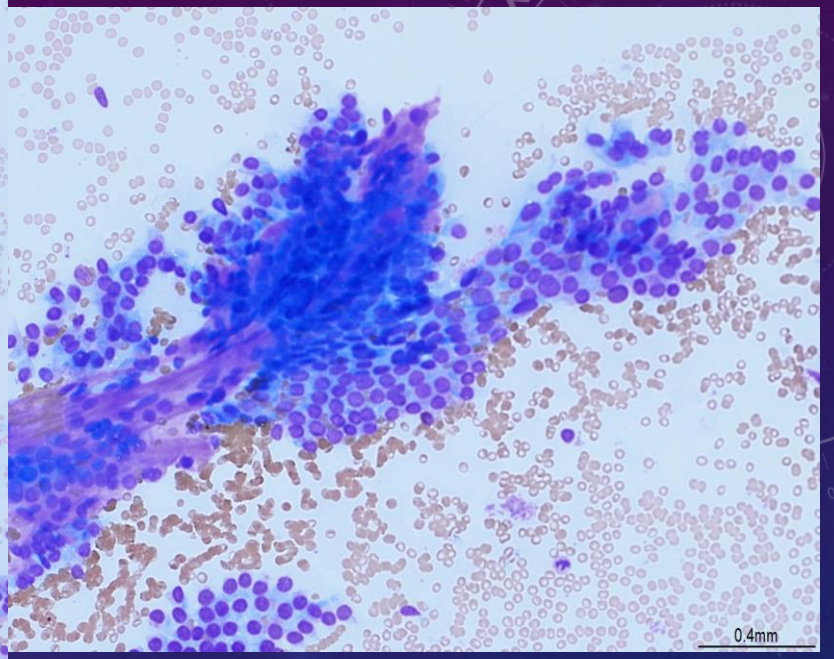
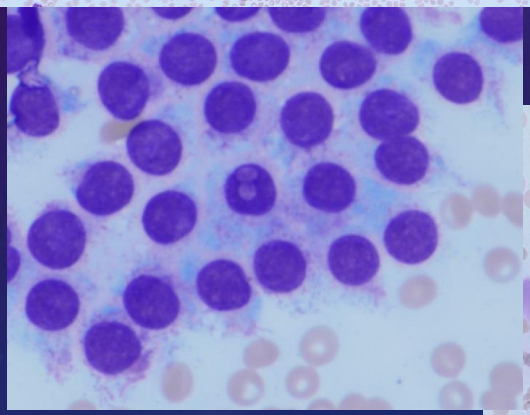
PTC

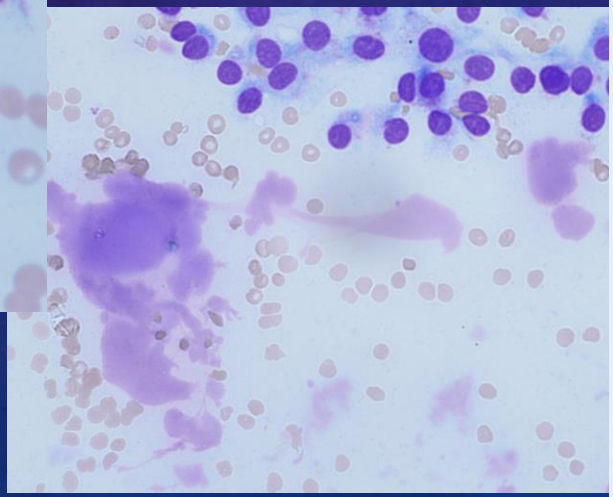


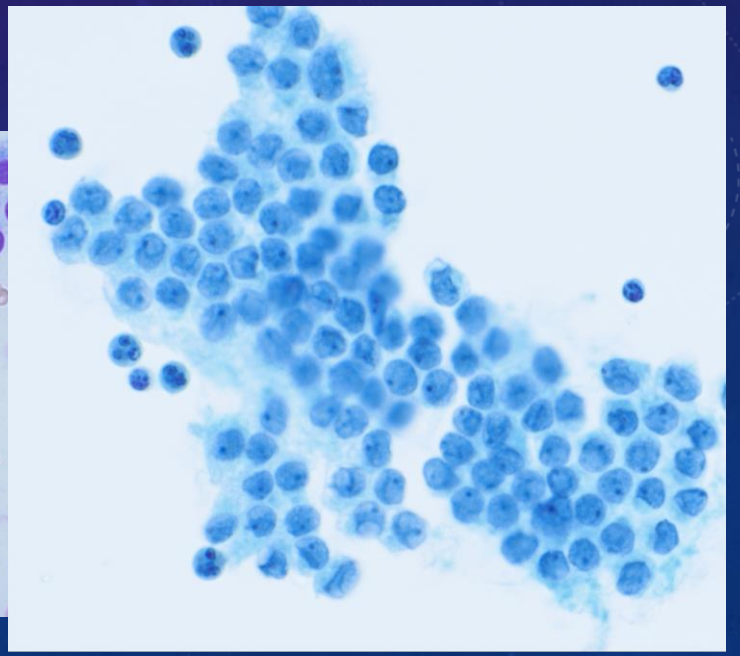








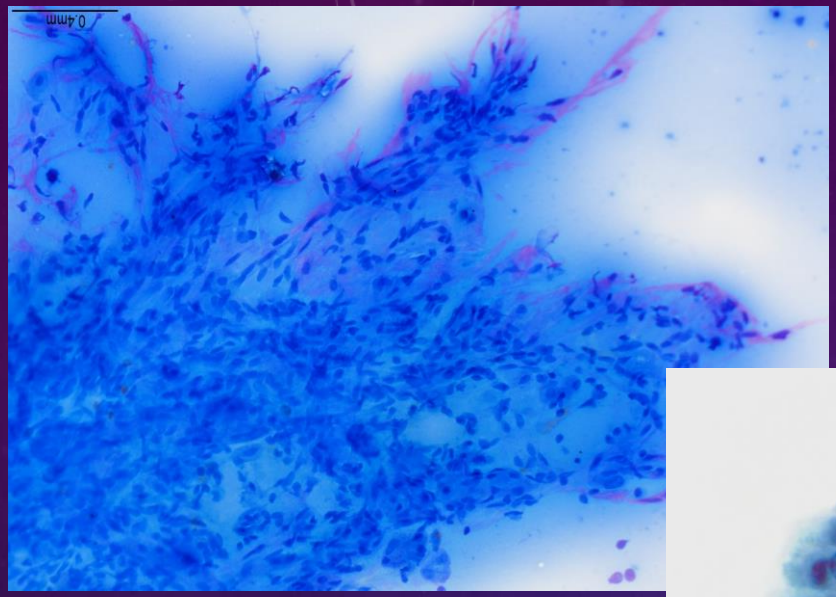


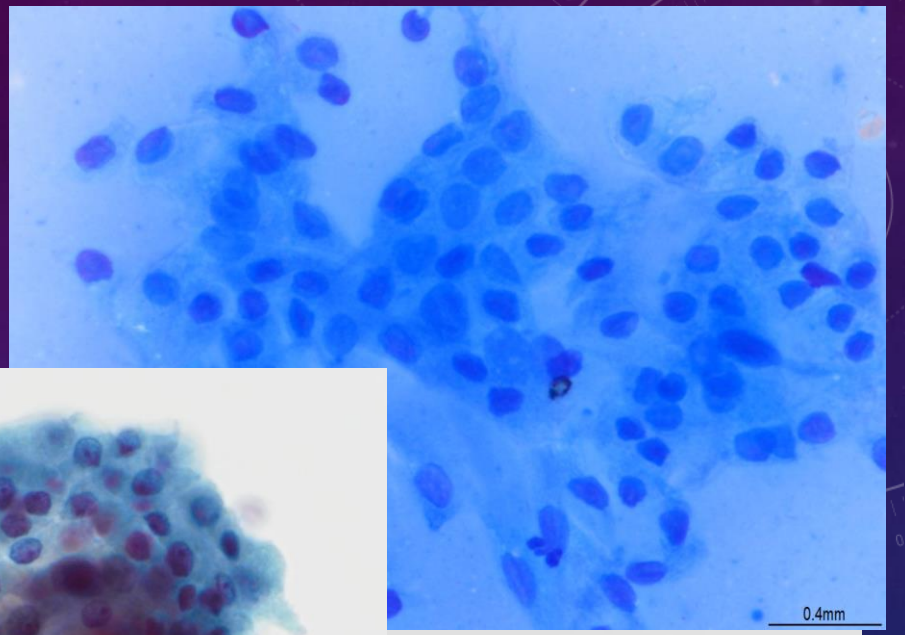


PTC

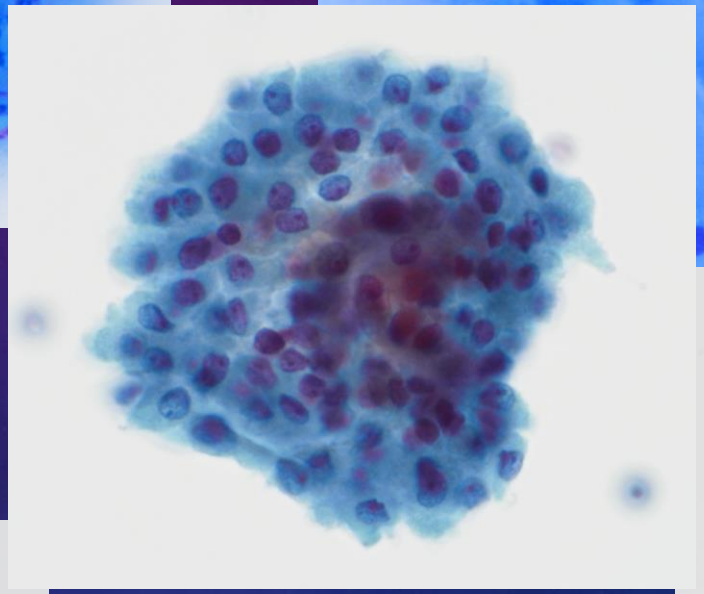
Problem of PTC vs oncocytes

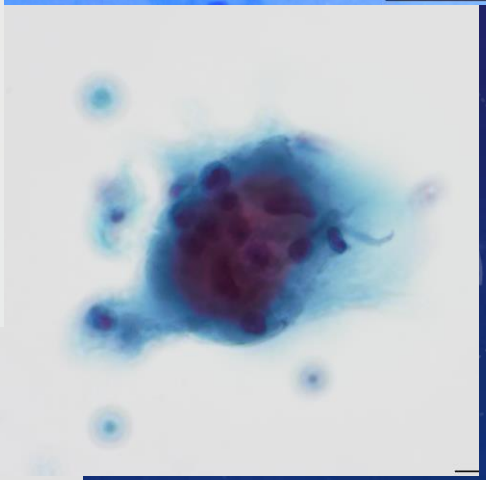
Both can have	Differences
Large cells with dense well demarcated cytoplasm	PTC – smooth Oncocytes - granular
n/c ratios	PTC – high (usually, beware TCV) Oncocytes – low
Large cell sheets with vessels	PTC – papillary structures Oncocytic neoplasm – traversing vessels
Thick or inspissated colloid can mimic psammoma bodies	
Both can have giant cells with dense cytoplasm especially in Hashimoto's	
Nuclei – large nucleoli of oncocytes can mimic intranuclear inclusions of PTC	

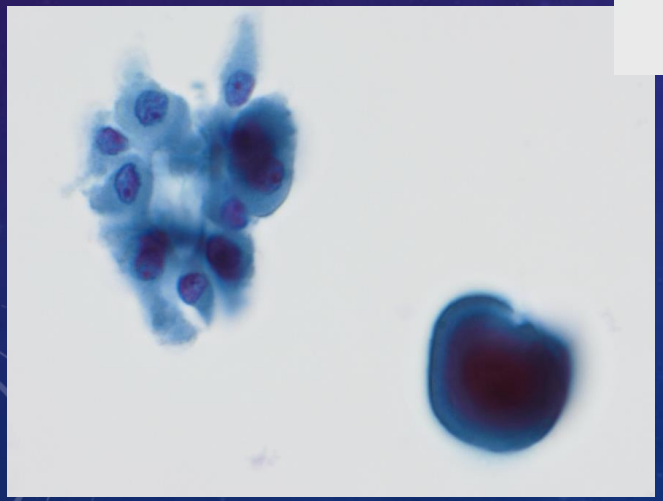


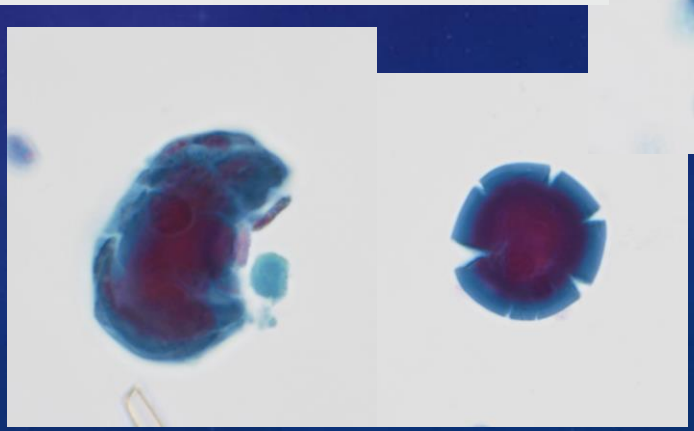


Thy3f oncocytic neoplasm

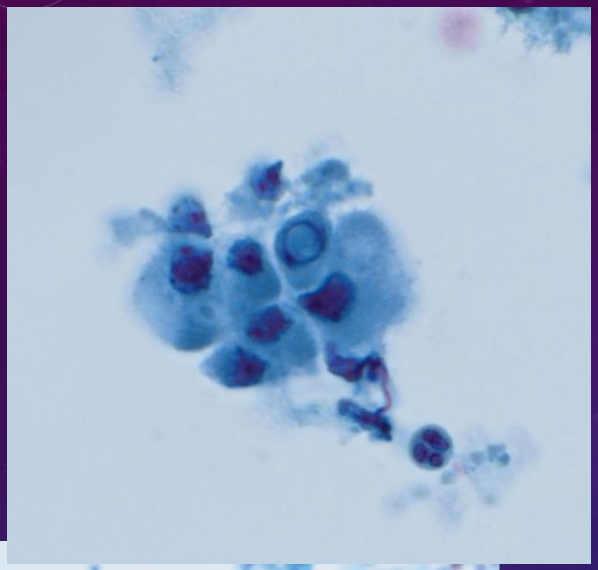


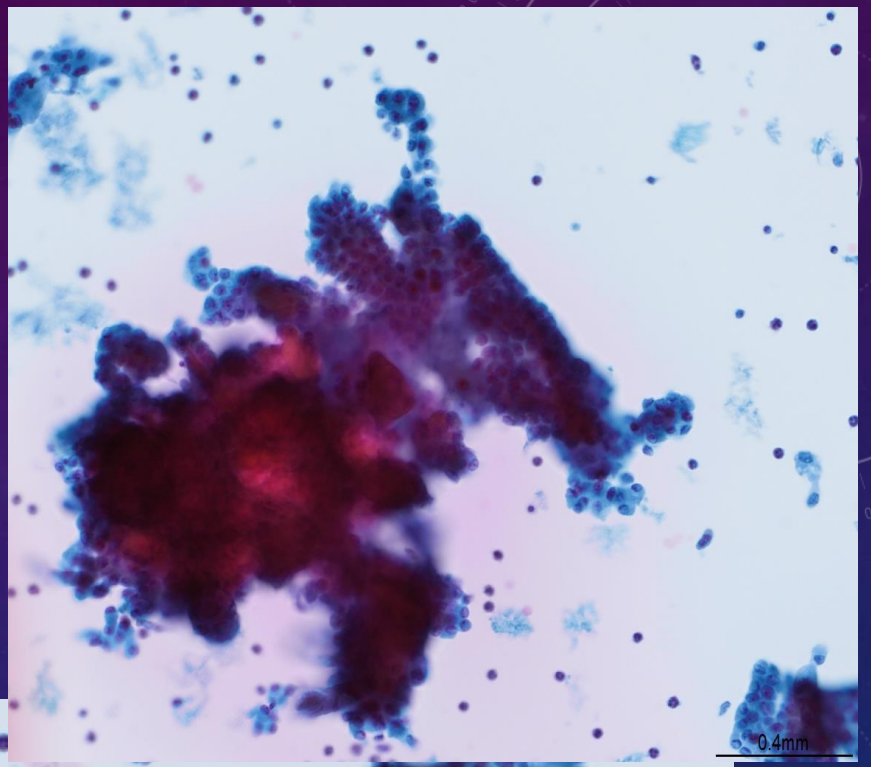


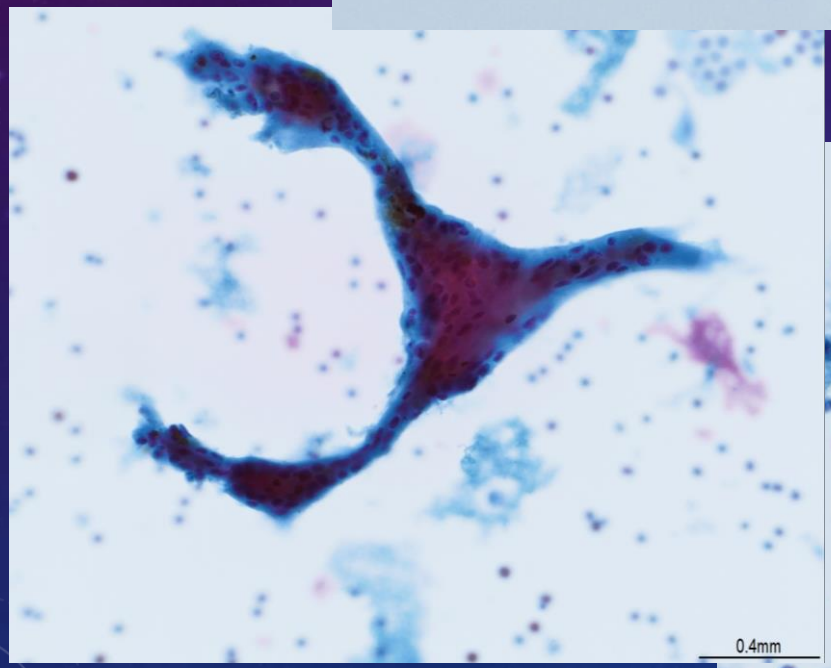


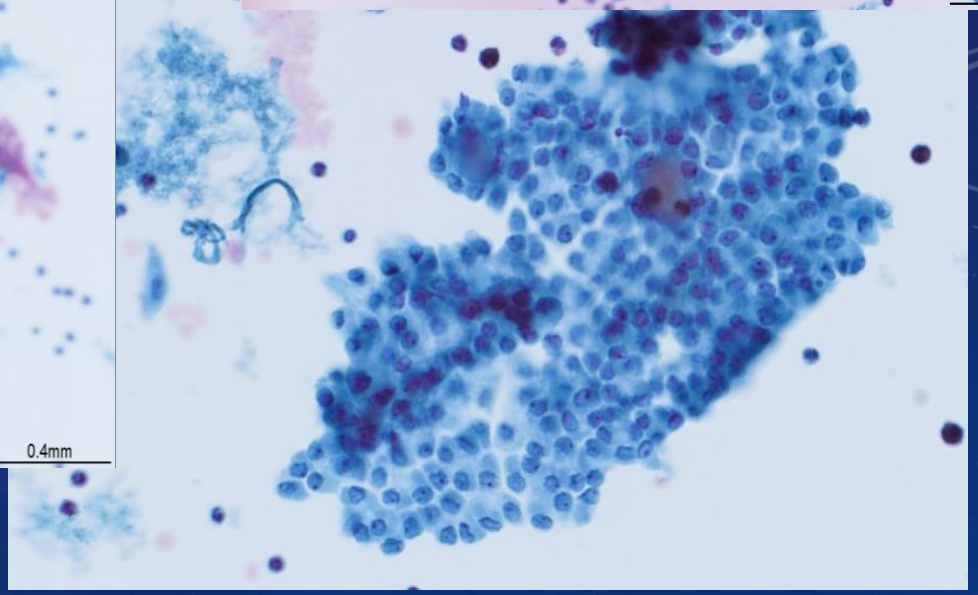


Thy5 PTC (Histol = PTC, 30% TCV)



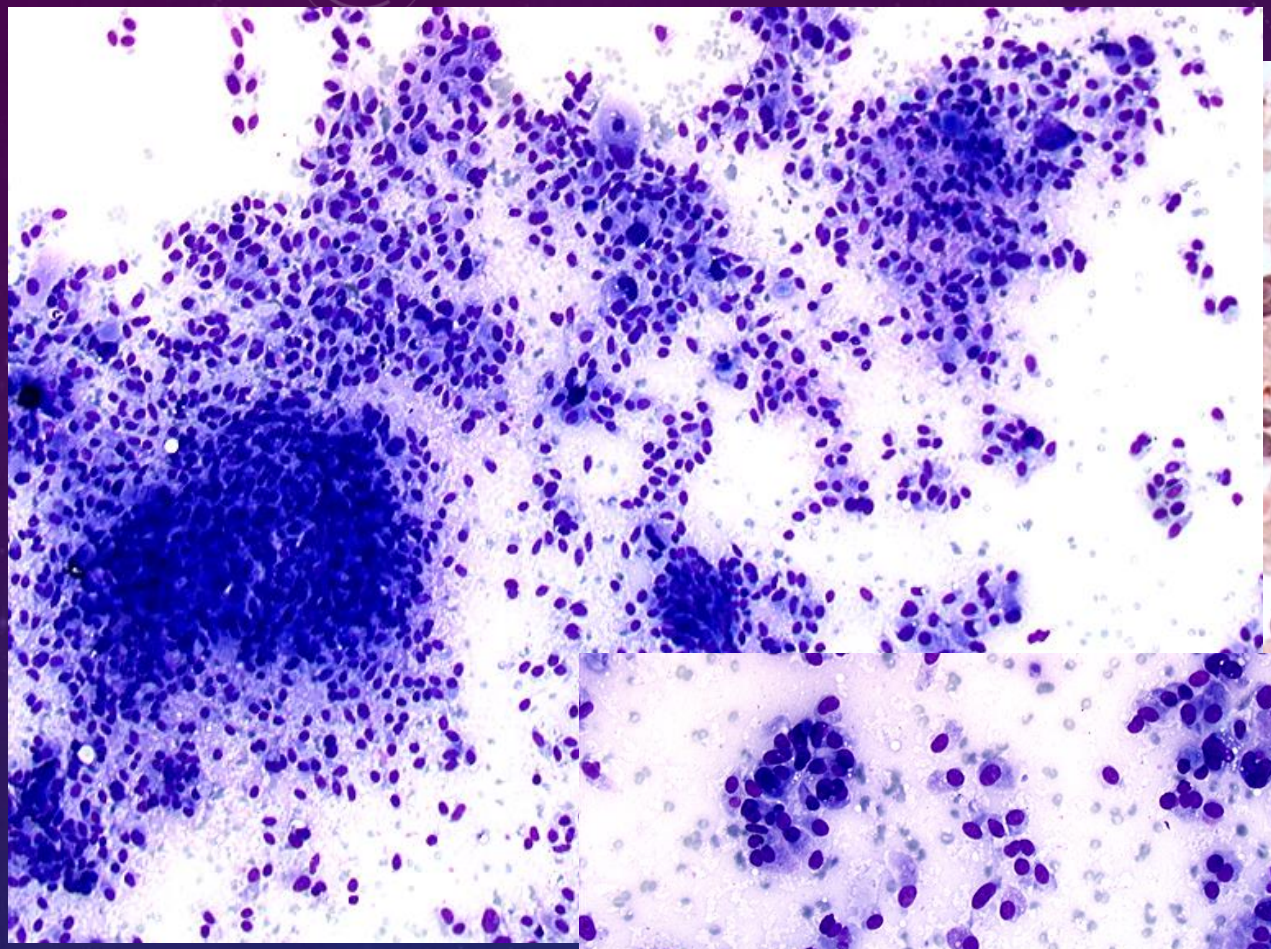


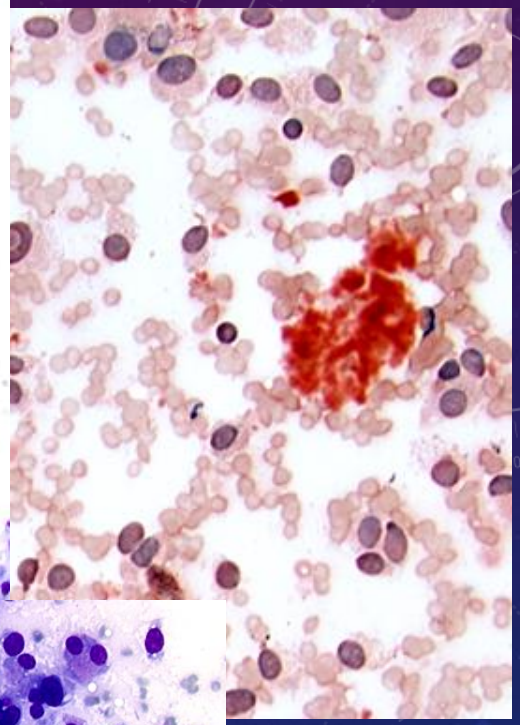


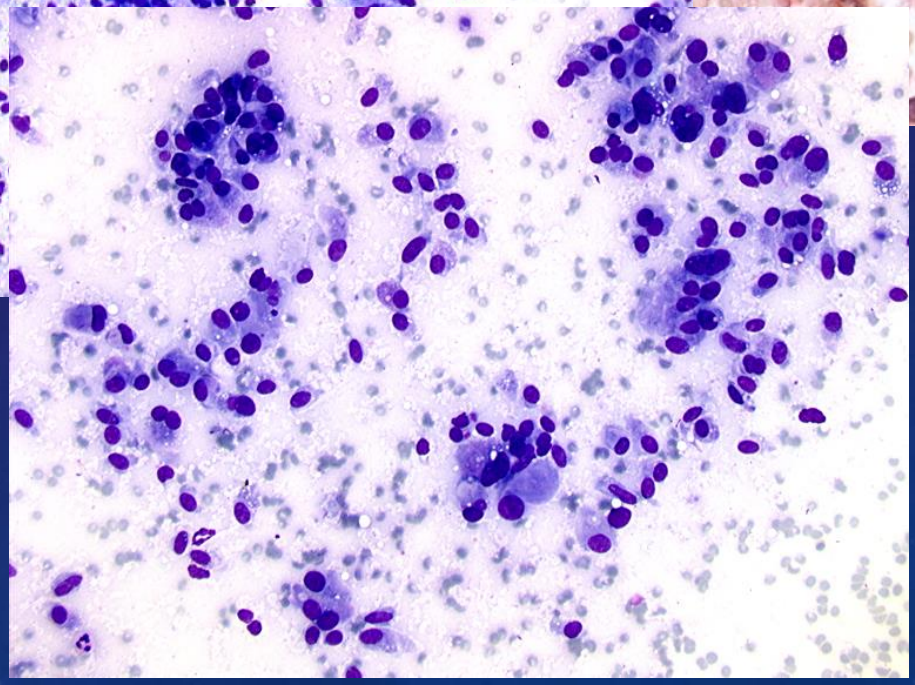


- **Medullary thyroid carcinoma**
  - Less common so can be overlooked unless considered
  - Remember possibility of MTC with oncocytic lesions
  - Immunostaining is useful
    - Positive for TTF1, CEA, calcitonin
    - Negative for thyroglobulin
  - If cellular, and many features present, but some uncertainty (eg no confirmation on immunostaining), could report as Thy4 but state could be regarded as diagnostic in clinical context of a significantly raised serum calcitonin

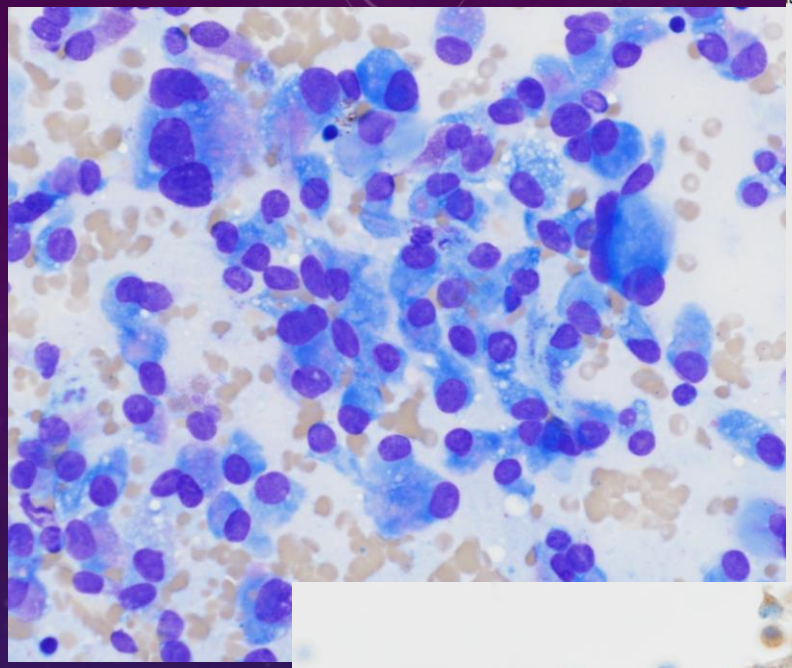
MTC

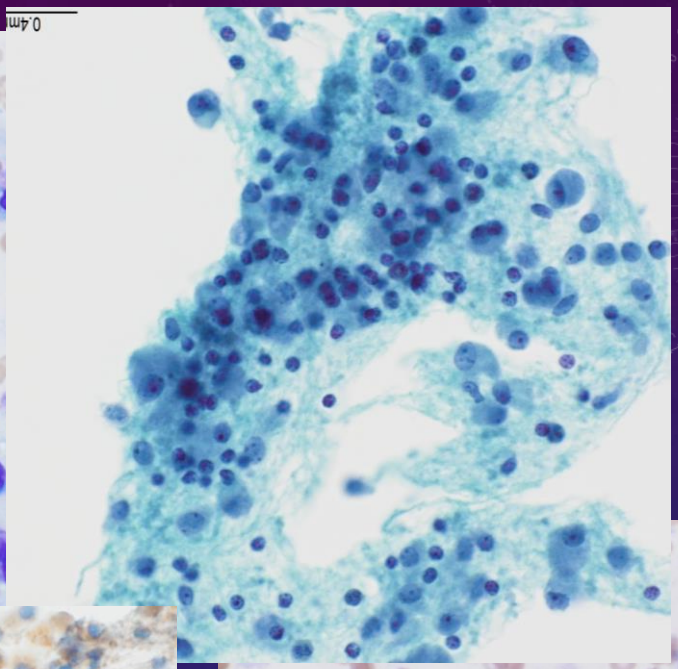


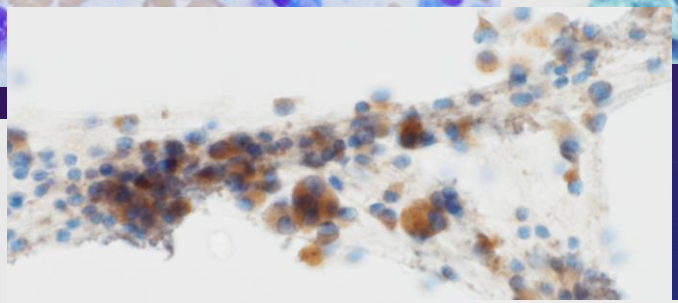


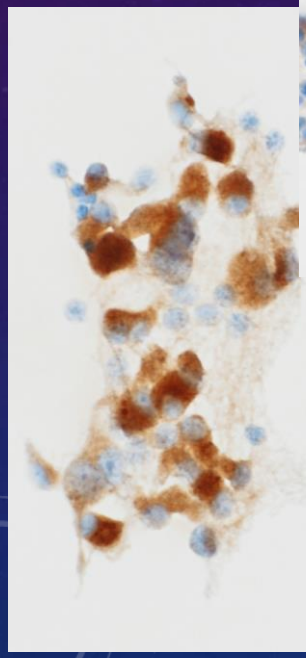


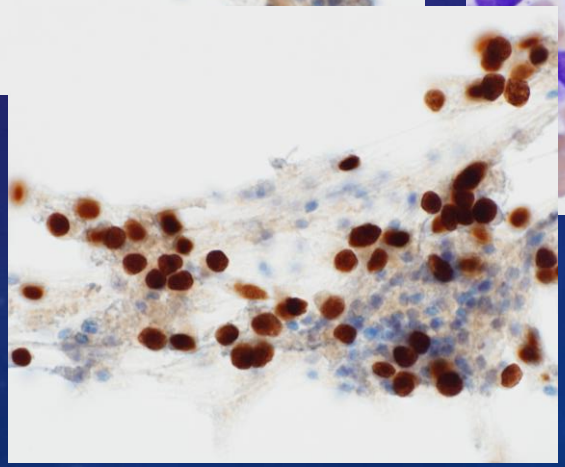
MTC in LN

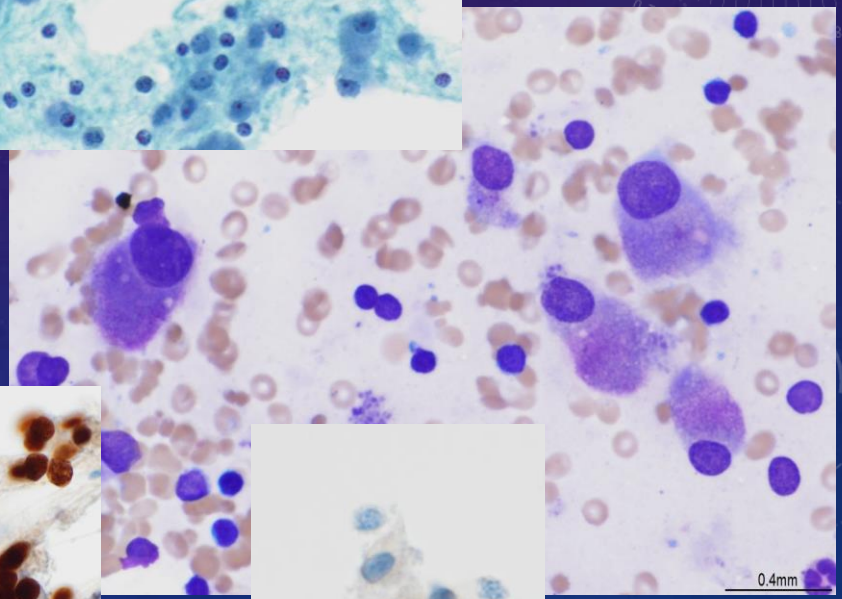




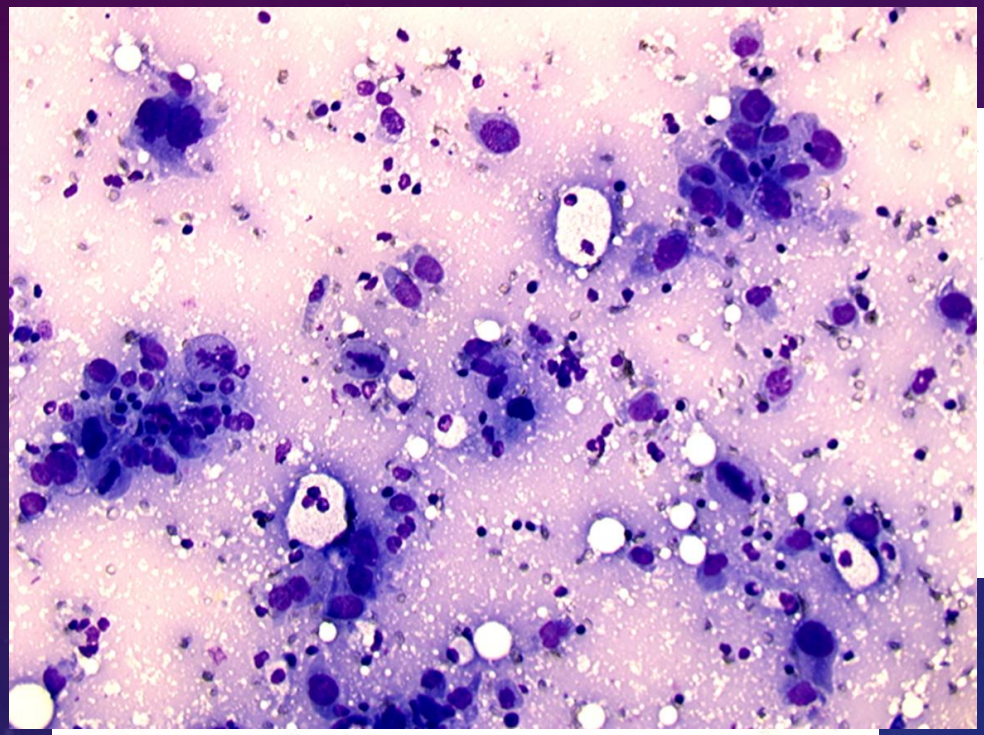


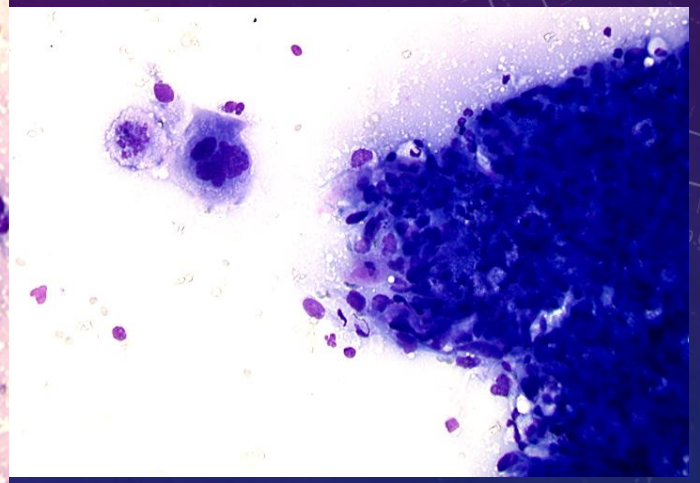


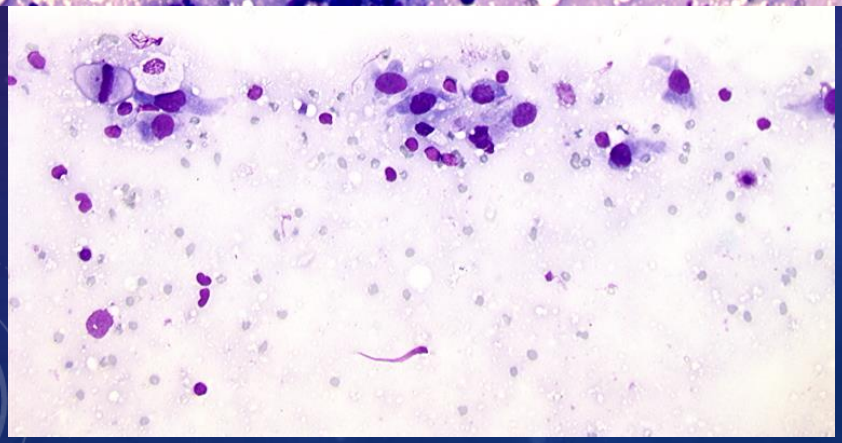


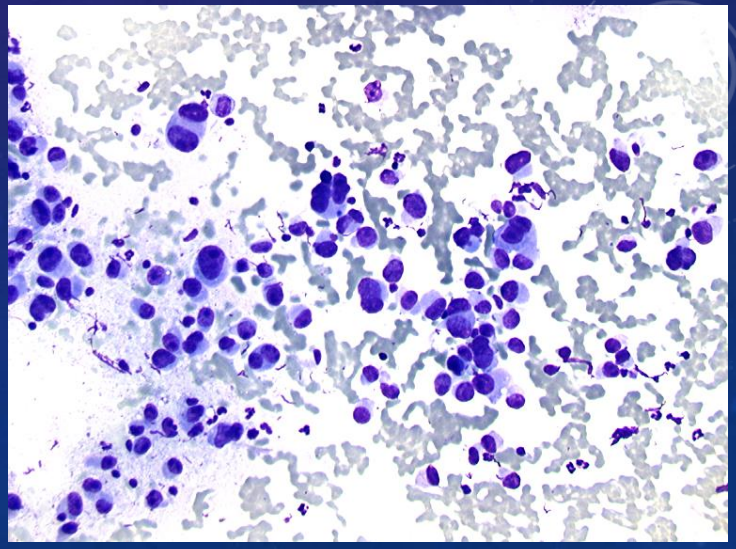


- **Anaplastic thyroid carcinoma**

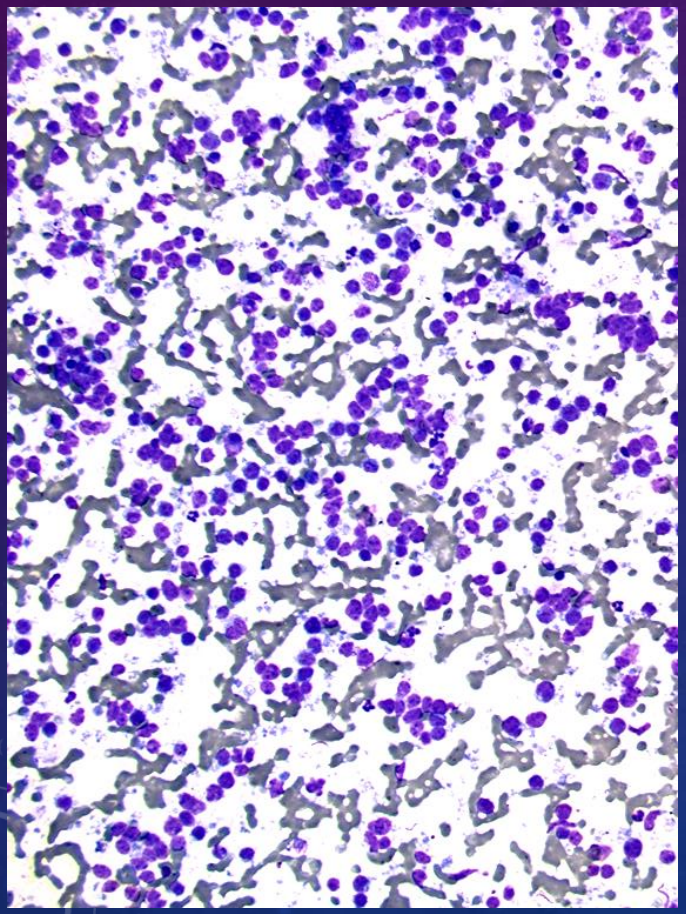


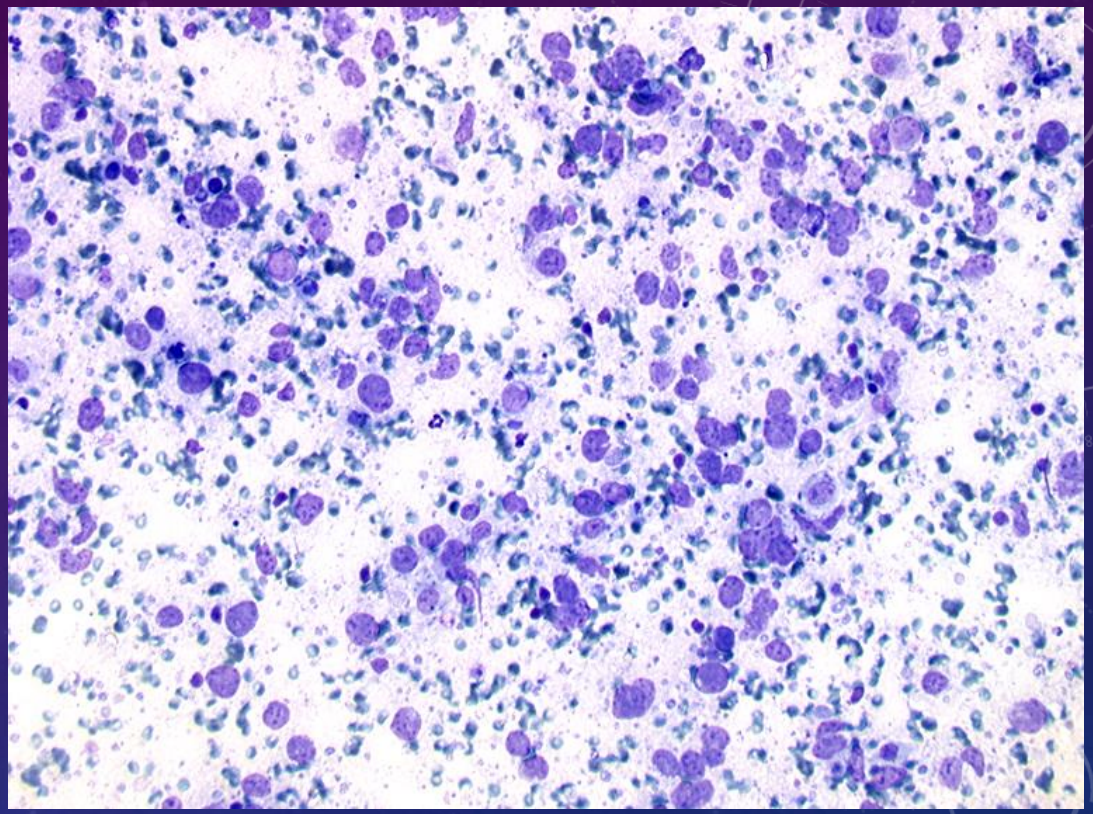






- High grade lymphoma

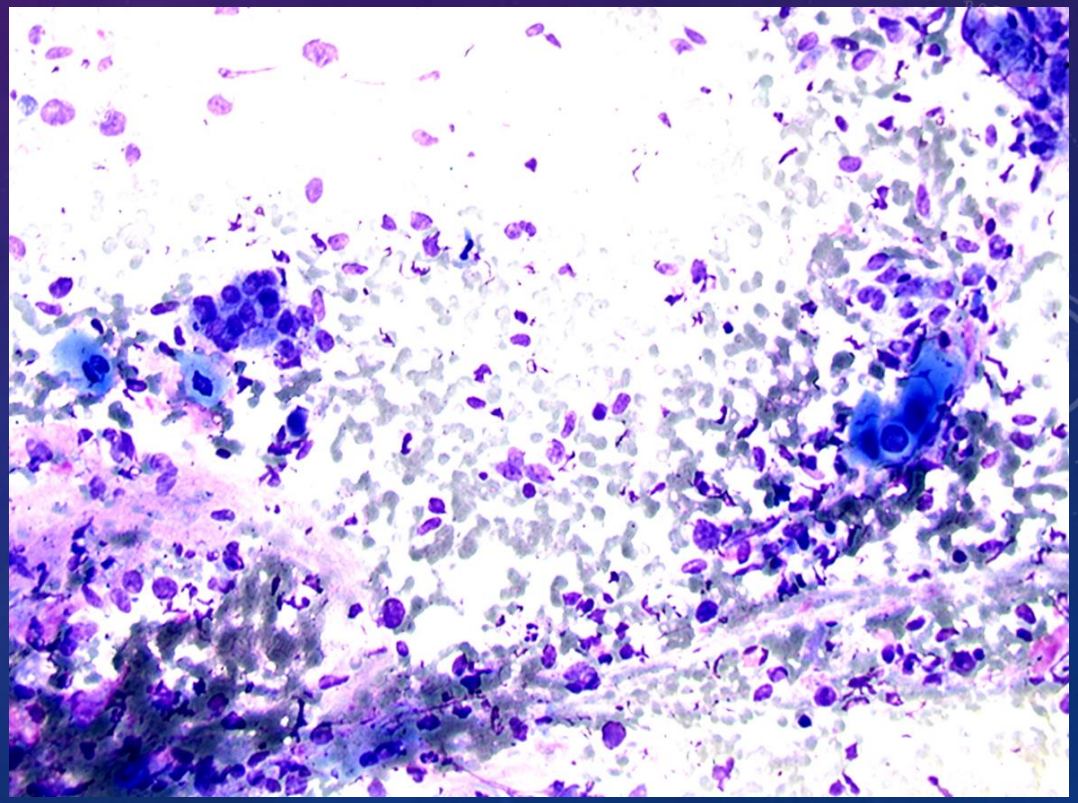




- **Metastatic carcinoma**

- Also counts as Thy5
- Check patient history and imaging
- Beware metastatic RCC – mimics oncocytic neoplasm

- Metastatic SCC



Additional or alternative approaches

1. Immunocytochemistry

- PTC – careful – CK19, HBME1, CD56, (BRAF)
- MTC – CEA, calcitonin, TTF1, thyroglobulin
- ATC vs lymphoma
- Intrathyroidal parathyroid gland – PTH, TTF1, thyroglobulin
- Metastases

2. Molecular testing

- Huge increase in understanding of genetics of TC
- Could refine diagnosis of indeterminate cytology
- Point mutation testing for BRAF V600E mutation – 99% PPV PTC, but not sensitive
- "rule in" – to therapeutic surgery for malignancy
  - 7 mutation panel – also RET/PTC, PAX8/PPARG, RAS
  - NGS, eg Thyroseq3 and other panels in development
- "rule out" – to avoid diagnostic surgery
  - Affirma by Veracyte
  - NGS, eg Thyroseq3 and other panels in development

3. Core biopsies

- No UK guidelines
- Useful guidance from Korea, suggests categories for reporting:
  I. Non-diagnostic
  II. Benign lesion
  III. Indeterminate lesion – IIIA nuclear atypia, IIIB architectural atypia
  IV. Follicular neoplasm – IVA without nuclear atypia, IVB with nuclear atypia
  V. Suspicious for malignancy
  VI. Malignant
- And indications:
  - Previous unsatisfactory FNA, or cystic change
  - Previous AUS/FLUS
  - FN vs non-neoplastic but not for FA vs FC
  - Calcified nodules
  - Uncommon eg lymphoma vs ATC
- Low rate of inadequate samples
- Facilitates ancillary tests

Jung *et al J Pathol Trans Med* 2015;49:288-299.

Summary

- Thyroid FNA is a valuable pre-operative investigation but has limitations, many can be reduced, some are inherent
- Essential to
  - Maximise quality of specimens
  - Use prose and categories for reporting
  - Use additional tests and second opinions appropriately
  - Be aware of limitations
  - Audit so know ROMs locally
  - Have experienced staff throughout
    - aspirators
    - cytopathologists
    - clinicians

Thankyou for listening

And enjoy reporting thyroid cytology!

NHS
Sheffield Teaching Hospitals
NHS Foundation Trust

The thyroid cancer patient: what the oncologist needs from pathology and an update on new therapies and clinical trials

Prof Jon Wadsley
Consultant Clinical Oncologist, Weston Park Hospital
Chair of NCRI Thyroid Cancer Subgroup
2nd Bi-Annual UKEPS/RCPath Endocrine Pathology Update
7th February 2020

Weston Park Cancer Centre
excellence in cancer care and research

The University Of Sheffield.

Overview

- Low risk differentiated thyroid cancer
  - Trend to de-escalate treatment
  - On going trials
- Iodine refractory differentiated thyroid cancer
  - Treatment options
  - Biomarkers and further research
- Medullary thyroid cancer
  - Treatment options
  - RET mutations and further research
- Anaplastic thyroid cancer
  - iNATT
  - BRAF mutations

Low risk differentiated thyroid cancer

- What is low risk?
- Questions about management
- Trend to de-escalation
  - HiLo
  - IoN
  - HoT
- What does the oncologist need from pathology?

What is low risk? TNM staging

Tumour

- **T0:** There is no evidence of a tumor.
- **T1:** The tumor is 2 centimeters (cm) or smaller and limited to the thyroid.
- **T1a:** The tumor is 1 cm or smaller.
- **T1b:** The tumor is larger than 1 cm but less than 2 cm.
- **T2:** The tumor is larger than 2 cm but smaller than 4 cm and is limited to the thyroid.
- **T3:** The tumor is larger than 4 cm, but the tumor does not extend beyond the thyroid gland.
- **T4:** The tumor is any size and has extended beyond the thyroid.
- **T4a**: The tumor has spread beyond the thyroid to nearby soft tissues, the larynx, trachea, esophagus, or recurrent laryngeal nerve.
- **T4b**: The tumor has spread beyond the regions in T4a (above).

Node

- **NX:** The regional lymph nodes cannot be evaluated.
- **N0:** There is no evidence of cancer in the regional lymph nodes.
- **N1:** Cancer has spread to the lymph nodes.
- **N1a:** Cancer has spread to the lymph nodes around the thyroid (called the central compartment; the pretracheal, paratracheal, and prelaryngeal lymph nodes).
- **N1b:** Cancer has spread beyond the central compartment, including unilateral cervical (lymph nodes on 1 side of the neck), bilateral cervical (lymph nodes on both sides of the neck), contralateral cervical (the opposite side of the tumor), or mediastinal (the chest) lymph nodes.

Metastasis

- **MX:** Distant metastasis cannot be evaluated.
- **M0:** Cancer has not spread to other parts of the body.
- **M1:** Cancer has spread to other parts of the body.

What is low risk? Stage

Papillary or follicular* under 55 years

Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1

Papillary or follicular 55 years or over

Stage I	T1a, T1b, T2	N0	M0
Stage II	T3	N0	M0
	T1, T2, T3	N1	M0
Stage III	T4a	Any N	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1

What is low risk? ATA Postoperative risk stratification

Low risk	Intermediate risk	High risk
No local or distant metastases All macroscopic tumour resected No tumour invasion of loco-regional tissues or structures No aggressive histology (eg tall cell, insular) or vascular invasion No I131 uptake outside the thyroid bed on post RAI scan *Clinical N0 or </=5 N1 pathological micrometastases- <0.2cm* *Intrathyroidal encapsulated FVPTC* *Intrathyroidal well differentiated follicular cancer with capsular but no (or minimal) vascular invasion*	Microscopic invasion of tumour into perithyroidal soft tissue I131 uptake in the neck but outside the thyroid bed on post RAI imaging Tumour with aggressive histology or vascular invasion *Clinical N1 or >5 pathologic nodes, all nodes <3cm* *Intrathyroidal papillary cancer 1-4cm with V600E BRAF mutation*	Macroscopic tumour invasion Incomplete tumour resection Distant metastases Raised thyroglobulin out of proportion to what is seen on post RAI scan *Pathologic N1 with a node >3cm* *Follicular cancer with extensive vascular invasion (>4 foci)*

What is low risk? Dynamic risk stratification

Excellent response	Indeterminate response	Incomplete response
Suppressed and stimulated Thyroglobulin<1mcg/l No evidence of disease on neck ultrasound scan Cross-sectional and/or nuclear imaging clear (if done)	Suppressed thyroglobulin <1 and stimulated thyroglobulin 1-10mcg/l Neck ultrasound with non-specific changes or stable sub-cm lymph nodes Cross-sectional and/or nuclear imaging not completely normal but non-specific findings	Suppressed thyroglobulin>1 or Stimulated thyroglobulin>10mcg/l Rising thyroglobulin Persistent or new disease on imaging

What about molecular pathology? Comments from ATA 2015 Guidelines

'While not routinely recommended for initial post-operative risk stratification in DTC, the mutational status of *BRAF*, and potentially other mutations such as *TERT*, have the potential to refine risk estimates when interpreted in the context of other clinico-pathologic risk factors.'

'The role of molecular testing in guiding post-operative RAI use has yet to be established, therefore no molecular testing to guide post-operative RAI use can be recommended at this time.'

Not currently universally available in the UK.

Likely to be addressed in NICE Thyroid Cancer Guidelines

Questions about management

- What extent of surgery is necessary- lobectomy vs total thyroidectomy?
- Is radioiodine ablation required?
- If so what activity of I131 is required?
- Is subsequent TSH suppression necessary?
- How long should patients be followed up?

Trend to de-escalate treatment

Drivers-

1. Generally excellent outcomes with very high overall survival
2. Concerns about morbidity of treatment
   - -vocal cord palsy
   - -hypothyroidism
   - -hypoparathyroidism
   - -second malignancy

HiLo trial

- HiLo recruited patients with well-differentiated thyroid cancer requiring radioiodine (RAI) ablation therapy after total thyroidectomy
- Randomised to receive (factorial trial)
  - 1.1GBq vs 3.7GBq I131
  - Thyroid hormone withdrawal (THW) vs recombinant TSH (rhTSH)
- Primary endpoint was ablation success rate at 6-9 months defined by both:
  - Stimulated thyroglobulin
  - RAI uptake scan
- Longer term follow up recently reported- median follow up 78 months (maximum 127 months)

HiLo Trial Results-Ablation Success Rate

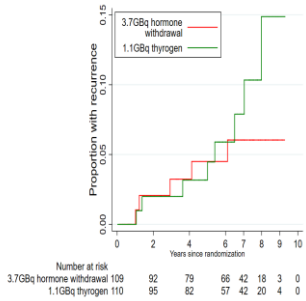
- 438 patients from 29 UK centres randomised 2007-2010
- 421 had both Tg and RAI scan at 6-9 months post-ablation
- Tumour stage T1-T3; N1a or N1b; no metastatic disease
- Trial objective of non-inferiority achieved for both main comparisons

	1.1 GBq (n=214)	3.7 GBq (n=207)
% ablation success	85%	89%

	Thyrogen (n=210)	Hormone withdrawal (n=211)
% ablation success	87%	87%

HiLo Trial Results- Recurrence

High dose RAI and THW versus
Low dose RAI and recombinant TSH



HiLo Trial Results-Summary

- Overall thyroid cancer recurrence rate 5% (21/434)
- Risk of thyroid cancer recurrence not higher in patients having
  (i) 1.1GBq RAI compared with 3.7GBq RAI
  (ii) recombinant TSH compared with THW
- These findings were consistent across T- and N- stages
- Several recurrences were seen after more than 5 years follow up
- Confirmed second malignancy found in 3 patients in 1.1GBq RAI group and 4 patients in 3.7GBq RAI group, diagnosed 6 months-7 years post ablation
- This has led to change in BTA Guidelines and UK practice

IoN Trial

- Patients are randomly assigned to receive radioiodine ablation or not following total thyroidectomy
- Close follow up with annual USS neck
- Primary endpoint- progression free survival at 5 years
- Target of 450 patients has been reached but on going recruitment agreed due to lower than anticipated event rate

IoN Trial- Eligibility Criteria

- INCLUSION CRITERIA

Papillary thyroid cancer (PTC):
- Non aggressive histological features (small foci of aggressive histology allowed
- at the discretion of the MDT)
- VI lymph nodes (pN1a)
- pT1a(m): all individual foci 1cm
- pT1b and pT1b(m): >1-2cm
- pT2 and pT2(m): >2-4cm
- pT3 and pT3(m): >4cm confined to the thyroid
- pT3 R0 +/- (m): any size with minimal ETE if recommended by the MDT
- pN0
- pN1a
- pNX

Follicular thyroid cancer (FTC) (including oncocytic or Hürthle cell cancer):
- minimally invasive FTC which are considered low risk and are
- recommended by the specialist MDT based on overall clinico-pathological
- assessment
- pT1b and pT2: >1-4cm intrathyroidal
- pT3 R0:any size up to 4 cm with minimal ETE if recommended by the MDT

- EXLUSION CRITERIA
- pT1a -without any positive nodes or unfavourable clinical features, treated by lobectomy.
- Up to 4cm non-invasive Encapsulated Follicular Variant of Papillary Thyroid
- Cancer (eFVPTC) with no capsular or vascular invasion (>4 cm can be included at
- the discretion of the MDT)
- non-invasive follicular tumour with papillary-like nuclei (NIFTP)
- Anaplastic, poorly differentiated or medullary carcinoma
- R1 or R2 thyroidectomy
- Patients with:
- pN1b
- M1
- Aggressive Papillary thyroid cancer with any of the following features:
- Widely invasive
- Poorly differentiated
- Anaplastic
- Tall cell
- Columnar cell
- Diffuse sclerosing variants
- Follicular thyroid cancer/Hürthle cell cancer with any of the following features:
- Tumours greater than 4cm
- Widely invasive
- Poorly differentiated
- Anaplastic
- Incomplete resection or lobectomy
- pT4a and pT4b or macroscopic and microscopic tumour invasion of loco-regional tissues or structures

HoT Trial (Dae Kim)

- Lobectomy vs thyroidectomy for patients with low-risk thyroid cancer
- Extensive engagement with surgical community and patient groups
- NIHR HTA grant application successful
- Final protocol currently in development
- Hoping to be open to recruitment mid 2020
- Will have strict eligibility criteria

Summary- what does the oncologist need from pathology?

- Increased importance of detailed pathological staging because this does now affect what further treatment is given
  - Extent of surgery
  - Whether to give I131 and what activity
  - Duration of TSH suppression and follow up
  - Eligibility for clinical trials
- Possible emerging role for molecular pathology- BRAF and TERT- but currently to guide prognosis rather than treatment

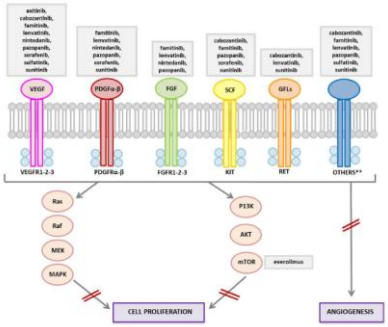
Iodine refractory differentiated thyroid cancer

- Overview
- Currently available treatments
- Recent Trials
- Future role of biomarkers

Iodine Refractory Differentiated Thyroid Cancer

- Relatively uncommon- develops in 5-10% of differentiated thyroid cancer patients
- Some variation in criteria
  - One or more measurable lesions that do not demonstrate iodine uptake on a previous radioiodine scan (diagnostic uptake or post therapy)
  - One or more measurable lesions that have progressed within 12 months of I-131 therapy, despite demonstrable radioiodine avidity at the time of that treatment
- Some include FDG-PET positive lesions
- Poor prognosis- 10 years survival <10%
- Until recently few treatment options
  - Single agent Doxorubicin
- More recent interest in multi-targeted kinase inhibitors

Potential molecular targets



Agents tested in iodine refractory differentiated thyroid cancer

- Sorafenib
- Sunitinib
- Pazopanib
- Vandetanib
- Axitinib
- Motesanib
- Lenvatinib

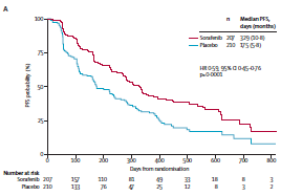
Sorefenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial

Brose M et al Lancet 2014; 384:319-28

- Phase 3 sorafenib vs placebo
- 417 patients randomised
- Papillary, follicular (hurtle cell), poorly differentiated thyroid cancer
- Evidence of radiological progression (RECIST) within last 14 months
- At least one measurable lesion
- Crossover allowed at progression

Sorafenib- Outcomes

- Primary endpoint: progression free survival
- Median Progression Free Survival 10.8 vs 5.8 months in favour of Sorafenib
- 6 month disease control rate 54.1% vs 33.8%
- Objective response rate 12.2% vs 0.5%
- No significant difference in overall survival (median not reached at time of reporting)
- BRAF and RAS mutations not predictive of PFS benefit from Sorafenib

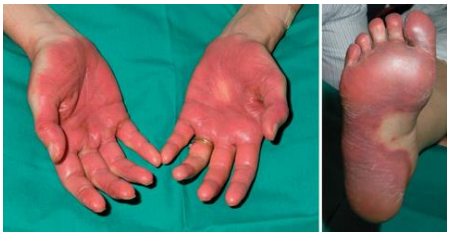


Sorafenib (contd)
Toxicity

- Hand foot syndrome (76.3%)
- Diarrhoea (68.6%)
- Alopecia (67.1%)
- Rash or desquamation (50.2%)
- Fatigue (49.8%)
- Weight loss (46.9%)
- Hypertension (40.6%)
- Squamous cell carcinoma of the skin (7 patients)

- 18.8% patients had to discontinue Sorafenib due to toxicity

Sorafenib (contd)

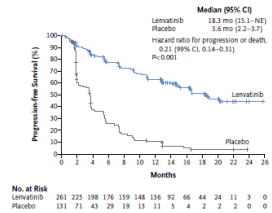


Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer
Schlumberger et al NEJM Feb 2015

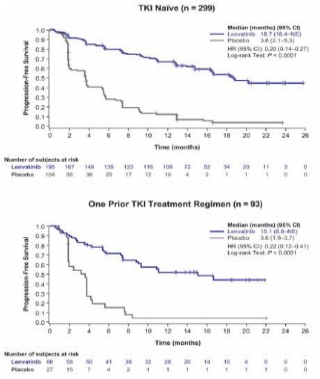
- Phase 3 lenvatinib vs placebo
- 392 patients randomised (2:1)
- Papillary, poorly differentiated, follicular, Hurtle cell included
- Independently reviewed evidence of radiological progression within the previous 13 months
- At least 1 measurable lesion
- Crossover allowed at progression
- Primary endpoint: PFS

Lenvatinib- Outcomes

- Median Progression Free Survival 18.3 vs 3.6 months in favour of lenvatinib
- 6 month PFS 77.5% vs 25.4%
- PFS benefit maintained in all subgroups
  - previous tyrosine kinase inhibitor
  - Histology
  - BRAF or RAS mutation status
- Response rate 64.8% vs 1.5%
- 4 complete responses to Lenvatinib
- Overall survival HR 0.73, p=0.10



PFS by prior TKI exposure



Lenvatininb- Toxicity

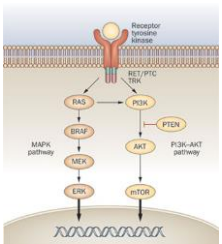
- Toxicity
  - Hypertension (67.8%)
  - Diarrhoea (59.4%)
  - Fatigue (59.0%)
  - Weight loss (46.4%)
  - Hand foot syndrome (31.8%)
  - Proteinuria (31.0%)
- Treatment related deaths
  - 6 deaths considered to be drug-related
  - 1 pulmonary embolism, 1 haemorrhagic stroke

Re-differentiation therapy

- Since I-131 is such an effective treatment for iodine-avid advanced thyroid cancer, several attempts have been made to re-instate iodine uptake in iodine-refractory cells
  - Lithium
  - Retinoids
  - Recent targeted approaches

A more targeted approach to increasing iodine uptake

- Expression of NaI symporter regulated by MAPKinase signalling pathway
- Mutations leading to activation of the pathway switches off NaI expression in thyroid cells
- Inhibiting the pathway might therefore allow re-expression of NaI



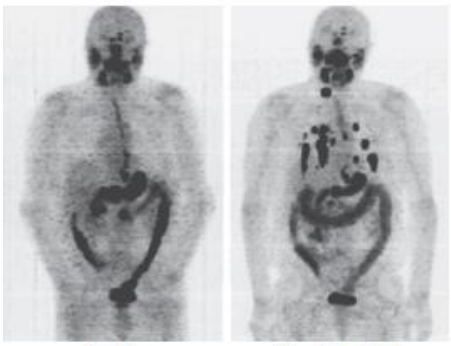
Selumetinib

- MEK inhibitor
- Blocks MAPK pathway signalling
- Early phase trials show little evidence of direct cytotoxic activity on thyroid cancer cells
- Preclinical work in mice demonstrated that iodine refractory thyroid cancer cells with BRAF mutations treated with a MEK inhibitor regain the ability to accumulate radioiodine

Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer

Ho et al NEJM 2013

- Pilot study
- 20 patients with iodine refractory DTC
- Given selumetinib 75mg bd for 4 weeks
- 12/20 had increased iodine uptake as assessed by I124 PET
- 8 received further I131 therapy
- 5 had partial radiological response to treatment
- All 8 patients had a fall in serum thyroglobulin



Baseline After Selumetinib

SELIMETRY

- UK multicentre single arm phase 2 trial
- Aiming to replicate findings of the pilot study
- Aiming to recruit 60 patients
- Currently open at
  - Royal Marsden
  - Guildford
  - Oxford
  - Bristol
  - Southampton

Summary- what does the oncologist need from pathology?

- Multi-kinase inhibitors demonstrate improvements in progression free survival
- Significant costs in terms of toxicity
- Novel approaches being explored to allow further I131 therapy
- **Better biomarkers are needed to predict benefit from treatment**
- ?role for circulating tumour DNA

Medullary thyroid cancer

- Overview
- Currently available treatments
- The development of RET specific inhibitors

Advanced Medullary Carcinoma of the thyroid

- Arises from parafollicular C cells
- 5% of thyroid cancers
- 25% hereditary- RET mutations
- In locally advanced/metastatic disease
  - 10 year overall survival 40%
- Neither radiotherapy nor conventional chemotherapy demonstrate durable responses

Treatment Approaches in Advanced Medullary Thyroid Cancer

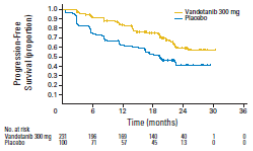
- Historical
  - Cytotoxic chemotherapy
  - IFN
  - Somatostatin analogues
- Current
  - **Tyrosine kinase inhibitors**
  - Radioisotope therapies- MIBG, Dotatate

Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomised, double blind, phase III trial
Wells et al, JCO 2011

- Phase 3 Vandetanib 300mg/day vs placebo
- 2:1 randomisation
- 331 patients with advanced MTC recruited
- No progression criteria prior to trial entry
- Crossover allowed at progression
- Primary endpoint- progression free survival

Vandetanib- outcomes

- Significant improvement in Progression Free Survival demonstrated
  - HR 0.46 (0.31-0.69)
- Benefits consistent across all pre-specified subgroups
  - Performance status 0 vs 1
  - Metastatic vs locally advanced disease
  - Hereditary vs sporadic
  - Prior therapy
- Higher response rate noted in tumours RET M918T mutation positive (but too many unknown mutation status cases to comment on significance of RET mutation status)

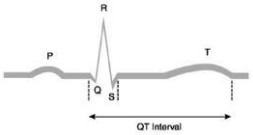


Vandetanib- toxicity

- Median duration of treatment 90.1 months
- 12% stopped Vandetanib due to toxicity
- Most common toxicities
  - Diarrhoea
  - Rash
  - Nausea
  - Hypertension
  - Asthenia
  - QTc prolongation
  - Increased thyroxine requirement

Vandetanib- toxicity

- QTc interval prolongation
- Single measurement >550ms or >100ms above baseline
- Repeated measurements 500-550ms or 60-100ms above baseline
- Dose reduction required in 35% patients

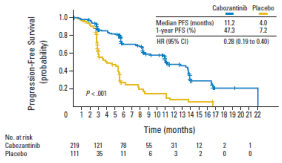


Cabozantanib in progressive medullary thyroid carcinoma
Elisei et al JCO 2013

- Phase 3 Cabozantinib 140mg/day vs placebo
- 2:1 randomisation
- Required to have evidence of progression within previous 14 months at screening
- No cross over allowed
- Primary endpoint- progression free survival

Cabozantinib- outcomes

- Median PFS 4.0 vs 11.2 months in favour of Cabozantinib
  - PFS HR 0.28 (0.19-0.40)
- Benefit seen in all pre-specified subgroups
  - Prior therapy
  - RET mutation status
- Greater evidence of benefit if known RET mutation positive

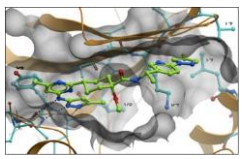


Cabozantinib- Toxicity

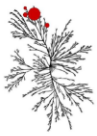
- 16% patients stopped Cabozantinib due to toxicity
- Most common toxicities
  - Diarrhoea
  - Palmar-plantar syndrome
  - Fatigue
  - Hair colour change
  - Hypertension
  - Stomatitis
- VEGF related effects
  - Fistula and haemorrhage
  - 4 treatment related deaths

RET-specific inhibitors

- RET point mutations are common drivers, both of hereditary and sporadic medullary thyroid cancer
- RET fusions can be drivers in other cancers- non-small cell lung cancer (2%), papillary thyroid cancer (10-20%)
- A number of highly specific RET inhibitors are currently in development, showing significant promise



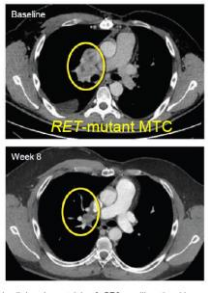
BLU-667



BLU-667 potently inhibits RET alterations and resistance mutants while sparing VEGFR2

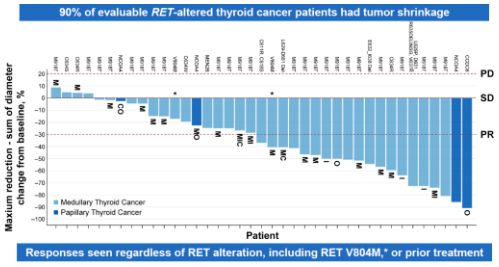
	Biochemical IC50 (nM)			
	RET M918T Most common in MTC	RET V804M Gatekeeper resistance in MTC	CCDC6-RET Occurs in PTC	VEGFR2
BLU-667	0.4	0.4	0.4	35
Cabozantinib	8	45	34	2
Vandetinib	7	3597	20	4
Sorafenib	23	32	ND	21
Lenvatinib	3	360	4	0.7

BLU-667

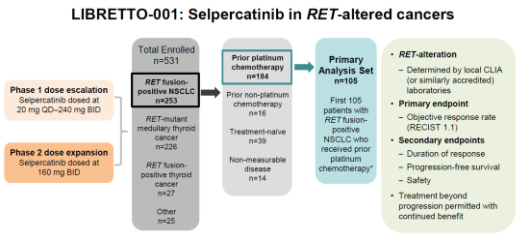


- 69 patients with RET alterations treated to date
- Some impressive responses seen
- Generally very well tolerated with only mild (G1/2) toxicity

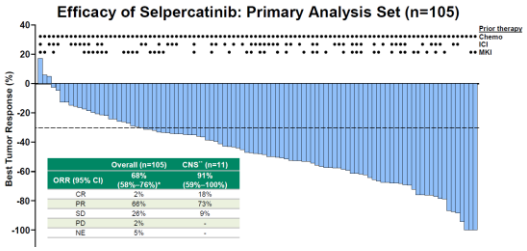
BLU-667



LOXO-292 (Selpercatinib)



LOXO-292 (Selpercatinib)



RET-specific inhibitors

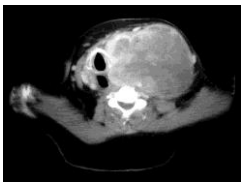
- Phase 3 trials of both BLU-667 and LOXO-292 are in development and likely to open in the UK within the next 12 months
- Will require testing for somatic RET mutations in MTC patients with advanced progressive disease

Summary- what does the oncologist need from pathology?

- Germline RET mutation testing already standard for new diagnoses of MTC
- Will be increasingly important to be able to access somatic RET mutation status for non-inherited cases
  - Prognostic information
  - To select patients for treatment
- Genomics England test directory

Anaplastic thyroid cancer

- Rare (1-2% of thyroid cancers- estimated approx 150 cases in UK pa)
- Highly aggressive, undifferentiated
- Important differential- thyroid lymphoma
- Rarely operable, current treatments generally ineffective
- Median survival only 5-12 months
- 20-50% have BRAF V600E mutations

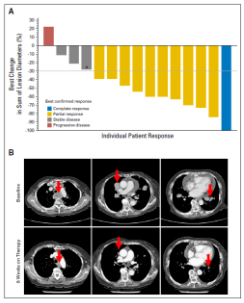


iNATT

- Anaplastic thyroid cancer tissue bank
- 114 samples collected so far
- A number of projects using the tissue underway
- Contact: Dr Laura Moss, Velindre Hospital, Cardiff

The *inter*National Anaplastic Thyroid Cancer Tissue Bank and Database Project (***i*NATT**)

Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600–Mutant Anaplastic Thyroid Cancer.
Subbiah et al JCO 2017



- 28 patients with ATC screened
- 16 found to be eligible
- 15/16 had BRAF V600E mutations
- Durable responses seen- estimated 1 year survival rate 80%
- Significant toxicity- fatigue, pyrexia, nausea

BRAF- Dabrafenib/Tametinib

- UK Compassionate access scheme has been negotiated to allow patients of good performance status with BRAF mutation to access these drugs
- Immunohistochemical testing is sufficient in the first instance, but ideally should be confirmed by NGS

Summary- what does the oncologist need from pathology?

- Important to distinguish from other more treatable conditions (eg lymphoma)
  - Core biopsy may be preferable to FNA
- Rapid turnaround is essential
- BRAF testing may lead to additional treatment options in fitter patients

Overall Summary

- Low risk thyroid cancer
  - Trend to treatment de-escalation
  - Requirement for detailed pathological reporting to ensure appropriate stratification
- Advanced disease
  - Increasing treatment options available
  - Need for molecular testing to determine suitability for treatment likely to increase

FORTHCOMING EVENTS

Specialist Head and Neck Pathology Conference

IAOP2020

20th International Congress on Oral Pathology and Medicine

June 17th – 20th, 2020

Day 1:	Wednesday 17 June
09.00	Opening Ceremony
09.30	Symposium I: **Cancer Immunology and Immunotherapy** • **Immunotherapy for squamous cell cancer of the head and neck** Kevin Harrington • **Phase I evaluation of pan-ErbB targeted CAR T-cell immunotherapy of locally advanced/ recurrent head and neck cancer.** John Maher • **Improving immunotherapy: targeting the tumour microenvironment** Gareth Thomas • **Using 'omics data to study the HNSCC immune microenvironment** Tim Fenton
12.30	Lunch and poster session
14.00	**Keynote Lecture** **Updates on sinonasal tract pathology: nothing to sneeze at!** Justin Bishop
15.00	**BSOMP Slide Seminar: Sinonasal pathology** Chair: Bill Barrett Panel: Justin Bishop, Ketan Shah
17.00	Finish

Day 2:	Thursday 18 June
08.30	Symposium II: **Precursor lesions of the head and neck** • **Premalignancy of the oral cavity: from molecular profiling to personalized prevention strategies** Pierre Saintigny • **Inflaming progression: understanding the role of inflammation in oral malignant transformation** Marco Magalhaes • **The use of non-invasive optical and molecular tests in management of an oral lesion** Catherine Poh • **Human papillomavirus associated oral epithelial dysplasia** Selvam Thavaraj • **Grading laryngeal dysplasia: order from chaos?** Eddy Odell
12.30	Lunch and poster session
14.00	**Keynote Lecture** **Newly defined (and recently refined) salivary gland tumors** Justin Bishop
15.00	**IAOP Debate: Ameloblastic fibro-odontoma is a neoplasm** Chair: Takashi Takata **Against:** John Wright, TJ Li **For:** Marilena Vered, Merva Soluk Tekkesin
16.15	IAOP AGM

Day 3:	Friday 19 June	
08.30	**Free papers I**	**Free papers II**
11.00	Slide seminar: **Pitfalls in oral & maxillofacial pathology** Chair: Brendan Conn Alison Rich, Ioannis Koutlas, Seamus Napier	**Free papers III**
12.30	Lunch	
13.30	**Keynote Lecture** **IAOP President's Prize lecture**	
14.30	Symposium III: **Digital pathology and artificial intelligence: Friends or foes** • **AI based cancer histology image analytics** Nasir Rajpoot • **Digital pathology for routine clinical practice - The Leeds experience** Gordon Hutchins • **Digital microscopy in the diagnoses of oral diseases** Alan Santos Silva • **Artificial Intelligence in Oral and Maxillofacial Pathology. Man vs Machine or Man + Machine?** Syed Ali Khurram	Symposium IV: **Clinical trials** • **Cancer clinical trials – what is the role of pathology and the pathologist?** Richard Jordan • **Training and accreditation for pathologists undertaking clinical trials research** Nick West • **Integrated pathology practice in an era of precision medicine** Jackie James • **SEND from Glasgow to Nice: the sentinel node biopsy trials** Keith Hunter • **PATHOS: a trial of reduced intensity adjuvant treatment HPV-positive oropharyngeal cancer** Max Robinson
16.15	BSOMP AGM	SFOPOM AGM
18.00	**Presidents' Reception and Awards Ceremonies**	

Day 4:	Saturday 20 June
09.00	**Keynote Lecture** **SFOPOM Pindborg Lecture**
10.00	**Clinico-pathology Conference** Chairs: Mark Lingen, Camilla Kragelund
12.00	**Closing Ceremony**

More info:

https://www.iaoplondon2020.com

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