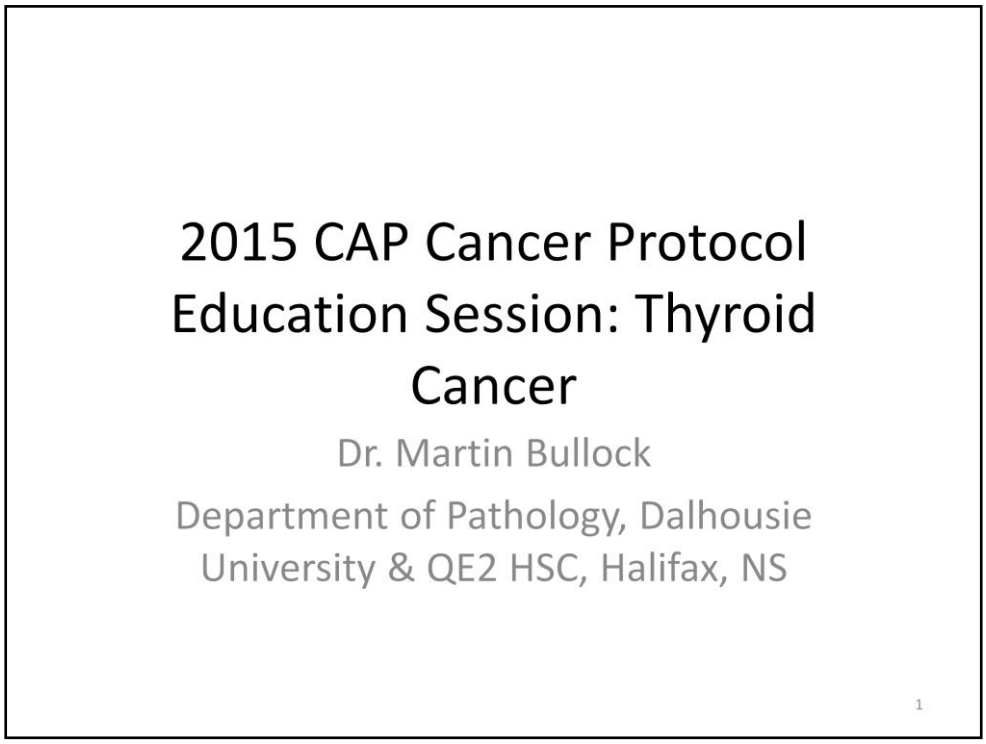


Dr. John Srigley:

Good afternoon everyone. I am Dr. John Srigley, the Expert Lead for Pathology at the Canadian Partnership Against Cancer.

On behalf of Cancer Care Ontario, the Canadian Partnership Against Cancer, and the Canadian Association of Pathologists, I would like to welcome everyone to today's CAP checklist education session on Cancer Biomarker Reporting Templates. Before I introduce our speaker and we get formally underway, I'd like to take care of a few housekeeping items first.

This session is being recorded and will be made available to all participants via e-mail links once the recording becomes available. Both the live presentation and the recorded presentation are eligible for CME credits. The information for obtaining credits was provided in the notice for this session previously distributed.

Please note: CME certificates for each of the CAP Checklist Education sessions will only be issued for one month from the presentation date. Please refer the session notice for the exact deadline date. Thirdly, please note that everyone's line has been automatically muted for today's presentation. We have a large number of participants and have difficulty troubleshooting WebEx issues as part of this call. If you have any

difficulties, please call the WebEx hotline at 1 866 229 3239. We encourage you to submit questions at any time during the presentation using the chat feature. The documentation previously distributed provides instructions for using the WebEx chat window.

During the question and answer portion of the presentation, in order to avoid question collisions, a CCO staff member will pose the submitted questions on your behalf, as long as time permits, and in the order in which they appear. In the chat window, please include the following information: your institutional name, the name of the individual posing the question and finally your question. Now it's my great pleasure to introduce Dr. Martin Bullock, today's speaker.

Dr. Bullock, originally from St. John's, Newfoundland, graduated from Memorial University in St. John's in 1988. Following a two-year stint in general practice in Ottawa, he trained in anatomical pathology at the University of Toronto, graduating in 1995. He then completed a forensic pathology fellowship at the University of Maryland in Baltimore and practiced in forensic pathology for two years in Toronto. He then decided to go back into full-time surgical pathology practice and moved back to Nova Scotia in 1998 to work at QEII Health Sciences Centre in Halifax. There he practiced head and neck pathology and cytopathology and as a full professor of pathology at Dalhousie University Medical School, with a cross appointment in the Division of Otolaryngology.

Dr. Bullock is also a member of the National Pathology Standards Committee of the Canadian Partnership Against Cancer. So without any further ado, I'd like to pass the microphone over to Martin to give today's talk on the Thyroid Electronic Cancer Checklist. Martin.

Dr. Martin Bullock:

Thank you very much. Today, we are going to talk about latest version of the CAP cancer protocol for thyroid cancer.

Disclosure Information
Martin Bullock

- I have no financial relationships to disclose

- and -

- I will not discuss off label use and/or investigational use in my presentation

2

First of all, I would just like to disclose that I have no financial relationships to disclose and I will not be discussing any off-label use or investigational use of my presentation.

Objectives

- Review the latest version of the CAP "Protocol for the Examination of Specimens From Patients With Carcinomas of the Thyroid Gland" (August 2014)
- Discuss changes to protocol from prior version (June 2012)
- Discuss practical application of the "Cancer Case Summary" components

3

The objectives of today's talk are to review the latest version of the CAP "Protocol for the Examination of Specimens from Patients with Carcinomas in the Thyroid Gland". This was released in August of 2014, and I am going to discuss some of the changes to the protocol from its prior iteration in June of 2012, and I am going to discuss some practical applications for recording the Cancer Case Summary components.

CAP Thyroid Gland Protocol Revision History
Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.
Version: Thyroid 3.1.0.0

Summary of Changes
The following changes have been made since the June 2012 release:
This is a major revision to the protocol. Extensive changes have been made throughout the document.*

**versus minimal change from Nov 2011 to June 2012*

4

This version of the protocol came out in August of 2014, and all the protocols are available on the CAP website. This is a major revision of the protocol and extensive changes have been made from the prior version which was in 2012. Prior to that, there have not been much change in recent years, so there was very minimal change from 2011 to 2012. This protocol, however, does have some fairly considerable changes that we will try and emphasize.

Authors

- Only 4 of 9 were also authors of prior version
- Primary and senior author have changed:
  - Drs. Seethala and Nikiforov, U Pittsburgh
  - 6 pathologists
  - Endocrine surgeon
  - H&N surgeon
  - Endocriniologist

5

Part of the reason may have been that there was some change in authorship. Of the nine authors, less than half of them were on the prior version of the checklist, so they may have had some new ideas. The primary and senior authors have changed, and that is Drs. Seethala and Nikiforov, both of whom are at the University of Pittsburgh. On the protocol panel was also an endocrine surgeon, a head and neck surgeon and an endocrinologist.

Significant Changes from 2012

1. Detailed pathological descriptions of both dominant and second tumors have been removed.
2. Lymph-vascular invasion has been divided into separate lymphatic invasion and angioinvasion components
3. Requirements to provide architecture and cytomorphology of PTC have been removed.
4. Histologic grade has been removed entirely (previously optional element)

Simplified case summary; much additional info can be added at pathologist's discretion

6

To begin, I will highlight some of the significant changes from 2012, just so that you know what to expect.

First of all, the detailed pathological descriptions of both a dominant and a second tumour have been removed. So really now, the protocol detailed information is given just for the most clinically significant tumour. Another major change is that lymph-vascular invasion has been divided into separate lymphatic invasion and angioinvasion components, which is very relevant for thyroid pathology. The requirement to provide information about the architecture and the cytomorphology of papillary thyroid carcinoma have been removed. And the histologic grade, which was previously an optional element, has been removed entirely. I think what results is a simplified, or more straightforward, case summary. And of course, pathologists are able to add a whole bunch of additional information about thyroid cancers at their own discretion. I certainly try and do that when I can.

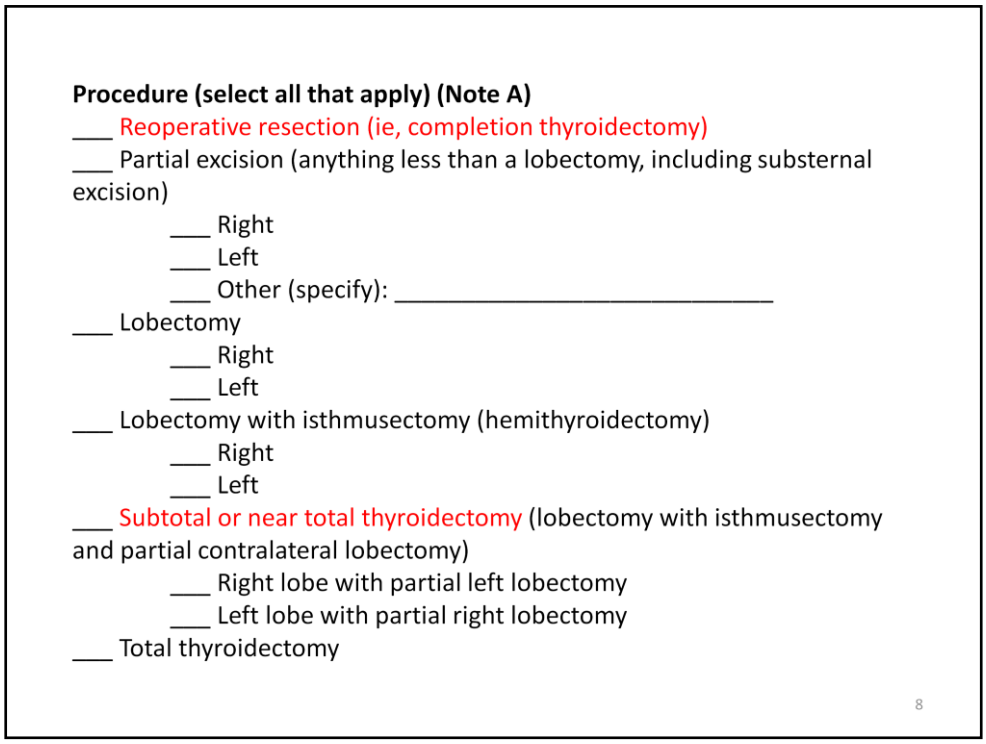
A few caveats…

- + Data elements preceded by this symbol are not required.
  - may be clinically important but not yet validated or regularly used in patient management.
- The manner in which the elements are reported is at the discretion of the pathologist/institution.
- Applies to carcinomas only (not lymphomas, sarcomas or metastases)

7

Here are a few caveats about the protocol before we go into it in detail. As you probably know, the data elements that are preceded by a little 'plus' mark are not required. These are elements that may be clinically important, but have not been validated yet or not necessarily used regularly in patient management.

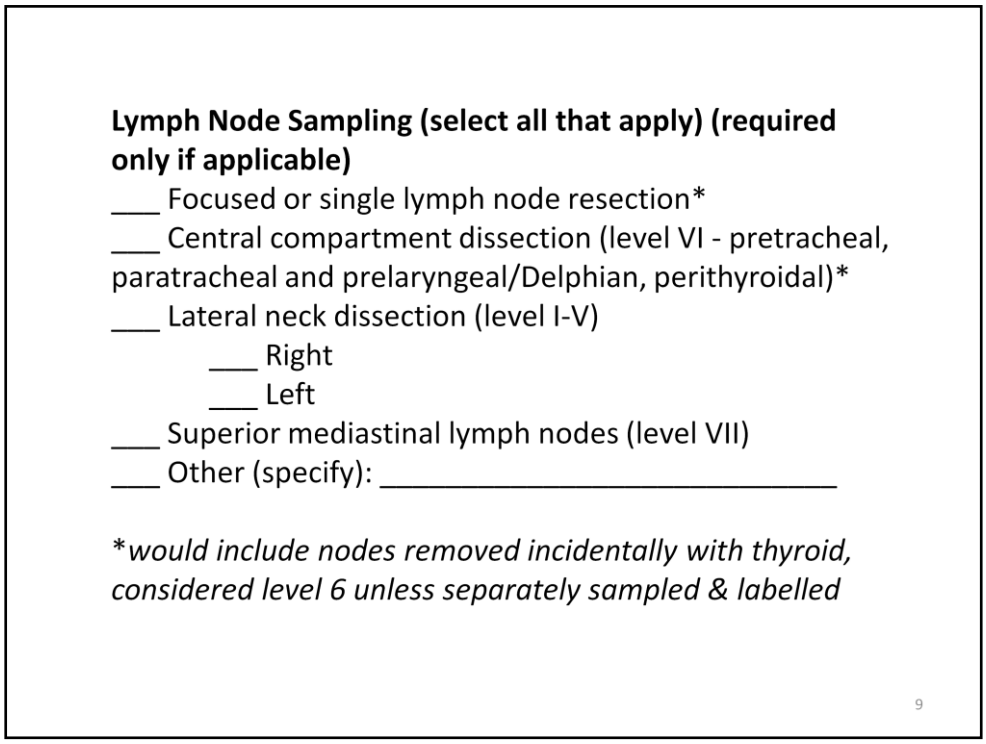
The College of American Pathologists states in its website that the manner in which the elements are reported is at the discretion of the pathologist or the institution. Ideally, they should be reported in a synoptic manner. The definition of what constitutes synoptic reporting, as per the College of American Pathologists, is clearly laid out on their website, if anybody is interested. This protocol applies only to carcinomas, not to lymphomas, sarcomas or metastases to the thyroid.



The first element is the procedure. The terminology here has changed somewhat from the prior version. The elements relating to the extent of the lymph node dissection have been removed from this component and have been given a separate section.

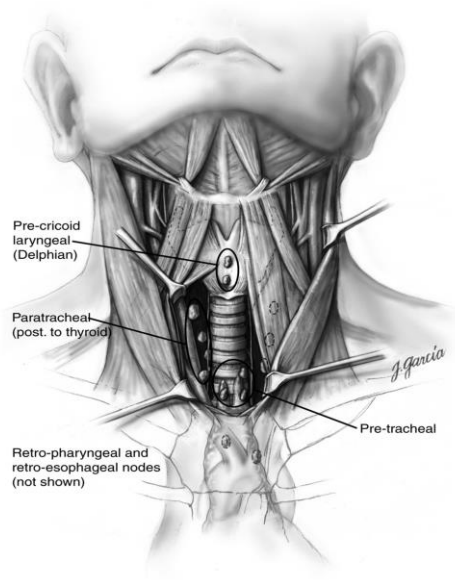
The components called reoperative resection, and subtotal or near total thyroidectomy are new components. Reopertative resection refers to completion thyroidectomy. It has been given a separate heading in this version of the protocol. And that is quite common in patients who have a lobectomy or a hemithyroidectomy for thyroid cancer to end up with a total thyroidectomy as a completion thyroidectomy.

Then, there's a partial excision, rarely seen in my experience. We do sometimes see rather large biopsies in patients who have anaplastic thyroid carcinoma. Sometimes, if, for instance there is a superior mediastinal mass, we may get a partial excision of the thyroid or a hyperplastic nodule for instance, which may have cancer in it, potentially. The most common types of specimens that we see however are lobectomies, hemithyroidectomies, which include the isthmus and total thyroidectomies. I don't see subtotal thyroidectomies, and I don't think that's standard procedure for thyroid cancer surgery these days.



The lymph node sampling would include just the focused or single lymph node resection and we do see that commonly. Either that lymph nodes are removed as part of a lobectomy, unintentionally, or they're received as a single specimen, perhaps a biopsy of a Delphian lymph node. Those would be typically level VI lymph nodes, unless they are separately sampled and labelled.

Most commonly, we see a central compartment neck dissection, and I will show you exactly what that means in a second. But that is synonymous with level VI, and it includes pretracheal, paratracheal, prelaryngeal and perithyroidal lymph nodes. You may or may not get a lateral neck dissection, which would include levels I through V. You would state the laterality. Superior mediastinal lymph nodes are categorized as level VII and those would be N1b nodes in the TNM staging, which I will talk about in a few minutes.



Boundaries of level VI:
- Hyoid bone
- Suprasternal notch
- Common carotids
- Prevertebral fascia

Often removed "en bloc" with portion of thymus, difficult to exclude inclusion of superior mediastinal nodes (VII)

Detailed anterior view of the central neck compartment

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With respect to level VI – level VI refers to lymph nodes that are found between the hyoid bone and the suprasternal notch inferiorly and medial to the common carotid arteries. So all those nodes would be level VI.

Typically they are removed "en bloc", sometimes with a portion of thymus. It is difficult in these circumstances to exclude the inclusion of some superior mediastinal nodes, level VII. In fact, I emailed one of our head and neck surgeons today and asked him, "Do you ever include some superior mediastinal nodes in your level VI neck dissections?"

He said, "All the time." So, that can create a little bit of difficulty with respect to the staging. Ideally, those should be submitted in separately for proper staging.

Indications for central neck dissection (ATA management guidelines)

- Therapeutic central-compartment (level VI) neck dissection for patients with clinically (or by imaging) involved central or lateral neck lymph nodes should accompany total thyroidectomy, to provide clearance of disease from the central neck.
- Prophylactic CCND (ipsilateral or bilateral) may be performed in patients with PTC with clinically uninvolved central neck nodes, especially for advanced primary tumors (T3 or T4)
- Routine level 6 ND for PTC? Controversial.
  - Advocated by some of our H&N surgeons
  - Little morbidity in proper hands vs. re-operation
  - Microscopic level VI nodal involvement is common (at QE2 about 20% of nodes < 1 cm)
  - Lowers risk of local recurrence

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To briefly review the indications for central neck dissection – typically, certainly for patients who have clinically, or by imaging, involved central or lateral neck lymph nodes, the level VI neck dissection will be performed. It can be performed prophylactically in patients with advanced primary tumours, so T3, so that would be tumours that are more than 4 cm or showing at least minimal extrathyroidal extension.

Is there a role for routine level VI neck dissection in papillary thyroid carcinoma? It is somewhat controversial. It is advocated and routinely practiced by most of our head and neck surgeons. The argument is that, in fact, the morbidity in the proper hands is quite low, and lower than it would be if one had to go back and re-excise level VI following the initial surgery. In fact, microscopic level VI nodal involvement is quite common. We did a study several years ago and found that about 20% of nodes less than 1 cm, in patients who had papillary thyroid carcinoma, did contain metastatic disease. Those would be nodes that would be considered not clinically involved by ultrasound for instance. There is some evidence that routine level VI dissection lowers the risk of local recurrence, but this is a somewhat controversial topic.

+ Received:
+ ___ Fresh
+ ___ In formalin
+ ___ Other

+ Specimen Integrity
+ ___ Intact
+ ___ Divided (thyroidectomy performed as lobectomy and completion thyroidectomy)
+ ___ Fragmented

Note: Integrity previously considered "required"

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The next two slides are elements that most of us would record in our gross description of a thyroid specimen, not necessarily in a synoptic format, but it would be there in the specimen. These are optional elements – so, it would be the state in which the specimen is received, the integrity of the specimen. This could include a divided specimen, for instance, so a thyroidectomy that's performed as a lobectomy with a completion, or specimens that are fragmented which are quite uncommon.

+ Specimen Size
+ Right lobe: ___ x ___ x ___ cm
+ Left lobe: ___ x ___ x ___ cm
+ Isthmus ± pyramidal lobe: ___ x ___ x ___ cm
+ Additional dimensions (ie, overall or aggregate): ___ x ___ x ___ cm

Note: Specimen size previously considered "required"

+ Specimen Weight(s)
+ Overall or aggregate weight (specify): ___ g
+ Individual specimen or fragment weights (specify): ___ g
+ ___ Not available

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The specimen size – with the size of the individual lobes and isthmus. Specimen size was previously considered a required element, but is now considered optional. Although we would record it in our gross description somewhere, I would expect. The specimen weight is also an optional element in the cancer case summary.

Case summary applies to dominant excised tumor, which means:

- Most aggressive tumor, imparts the highest stage & dictates management
- Often but not necessarily the largest (e.g. in the case of ETE)
- Additional tumors with significant features (e.g. tall cell morphology) or of different type (e.g. PTC and MTC): use second synoptic report
- Additional foci with relevant features not affecting management: use “additional pathological findings”

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The cancer case summary applies to the dominant excised tumour, and that means the most aggressive tumour that imparts the highest stage and would dictate management. Usually, that would be the largest tumour. Although not necessarily, if one tumour, for instance, was showing extrathyroidal extension but was not the largest by measurement. So, it may not be the dominant excised tumour.

There are choices about what to do if you find other tumours within the thyroid. If there are additional tumours which have significant features – so perhaps one that has a tall cell morphology when the dominant excised tumour was classical type, or tumours of a different type, such as a papillary thyroid carcinoma and a medullary thyroid carcinoma – you can use a second synoptic report. Or, if there are additional foci of tumour with relevant features, but that you suspect those wouldn’t affect the management, you can use the “additional pathological findings” component of the report.

Tumor Focality (Note B)
___ Unifocal
___ Multifocal *

**designated by suffix "m" after T stage (number and size range? "additional pathological findings")*

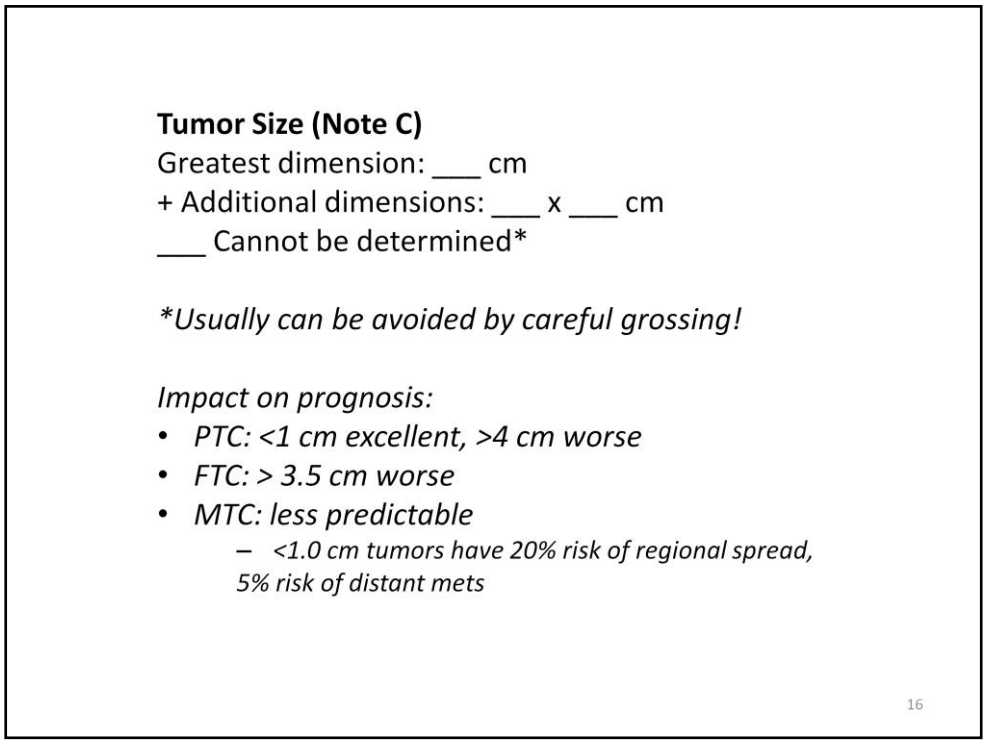
Tumor Laterality (select all that apply) (Note B) *
___ Right lobe
___ Left lobe
___ Isthmus
___ Pyramidal lobe
___ Other (specify): _____

**I assume the dominant tumor*

15

The next component is tumour focality – unifocal or multifocal. And in the pT staging, if a tumour is multifocal, you would put that suffix "m" in brackets after the T stage.

Tumour laterality – I am assuming here that what we are talking about is the dominant tumour, so you would just select the site or all sites that would apply to that tumour.



Tumour size – I typically include the greatest dimension, additional dimensions are optional, but I'm not sure that they add any clinically relevant information, so I typically just include the greatest dimension.

Cannot be determined – I think that when the tumour size cannot be determined – that can usually be avoided by carefully grossing the specimen. If the tumour size isn't given in the gross description, then I would typically try to reconstruct the size form the slides, and you may be able to say, "this tumour is at least *x* cm" or give a range of centimetres, just depending on how the specimen was received.

Tumour size has an impact on prognosis. Typically for papillary thyroid carcinoma, tumours that are considered microcarcinomas, which are less than 1 cm in greatest dimension, usually have an excellent prognosis. There are certain features that may indicate that they will behave in a more aggressive fashion. For instance, if they're at the edge of the gland, if there's sclerosis, if they have tall cell morphology or BRAF mutations.

Papillary thyroid carcinomas that are more than 4 cm behave in a more aggressive fashion. That is why they are upstaged. Follicular thyroid carcinomas, larger follicular thyroid carcinomas, tend to behave in a worse fashion. In my experience, it's quite

uncommon to see small follicular thyroid cancers, but they do happen from time to time.

Medullary thyroid carcinoma is much less predictable and, in fact, even small tumours, microtumours, have a significant risk of regional spread to lymph nodes and a 5% risk of distant metastases.

Histologic Type (select all that apply) (Notes D and E)

___ Papillary carcinoma

Common significant variants (Note F) (required only if applicable):

___ Classic (usual, conventional)

___ Follicular variant, encapsulated/well demarcated

Tumor capsular invasion:

___ Yes

___ No

___ Follicular variant, infiltrative

___ Tall cell variant

___ Cribriform-morular variant

___ Diffuse sclerosing variant

___ Other variant (specify) (Note F): _____

NB: 1) Although other PTC variants recognized by WHO, only those listed are considered clinically, biologically relevant
2) Presence of encapsulation/circumscription is only considered relevant for FVPTC

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Histologic type – I divided this over two slides.

Just with respect to papillary carcinoma, that has been simplified from the prior version of the protocol. What they have included are the common significant variants, which they consider to be classical – which is usual or conventional type, and follicular variants – which is now specifically divided into two subtypes – the encapsulated/well demarcated subtype and the infiltrative type, which is probably best considered two separate variants.

Then with respect to the encapsulated or well demarcated variant, whether or not there is tumour capsular invasion. And then, they have also identified as being significant variants – the tall cell variant, the cribriform-morular variant, the diffuse sclerosing variant, which I'll talk about all three of those in a few minutes. And then of course, there are other variants of papillary thyroid carcinoma recognized by the WHO, and I would suggest that if you recognize them, you designate them specifically as such.

Encapsulated FVPTC

- More common than unencapsulated (By how much? Depends on criteria used)
- Behaviour and molecular pathology is more akin to follicular tumors (FA/FTC) than classical PTC or unencapsulated FVPTC (Ghossein, MSKCC)
  - Rarely metastasize in the absence of AI
  - Metastasize to distant sites >> lymph nodes
  - Lower rate of multifocality than classical PTC
    - *But not uncommon to find PMC associated with EFVPTC*

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The encapsulated follicular variants of papillary thyroid carcinoma is a rather controversial entity. They are more common in my experience and I think the literature bears that out, but they're more common than unencapsulated follicular variants. By how much? I think it depends on the criteria that are used. If you include all microcarcinomas, then certainly many microcarcinomas are unencapsulated and have a follicular pattern. Then of course, with respect to larger tumours, the number of encapsulated follicular variants of papillary carcinomas is very dependent on the strictness of the criteria that the pathologist uses to diagnose them.

But it is probably in the order of 3 to 1, perhaps 4 to 1, just depending on the study that you read. It has been found that the behaviour and the molecular pathology of encapsulated follicular variants of papillary carcinoma is more akin to other follicular pattern tumours, follicular adenoma, and follicular thyroid carcinoma, than to classical papillary thyroid carcinoma. And so, they tend to only rarely metastasize in the absence of angioinvasion.

When they do metastasize, they tend to metastasize to distant sites rather than lymph nodes, and they tend to have a lower rate of multifocality than classical papillary thyroid carcinoma. But in my experience, it is not uncommon to find papillary microcarcinomas associated with the encapsulated variants. I have not added it up, but it may be that it is not a whole lot different than finding incidental papillary carcinomas,

which we tend to find quite commonly in patients who have hyperplastic nodules or follicular adenomas.

Common Genetic Alterations in Thyroid Cancer

	BRAF	RET/PTC	RAS*	PAX8/PPARγ
Follicular adenoma	No (rare K601)	No	30%	10%
Follicular carcinoma	No	No	40-50%	30%
Papillary carcinoma	45%	15%	15% (FVPTC)	5% (FVPTC)

NTRK1 translocations in 2-5% of PTC; mutations mutually exclusive
*HRAS, NRAS, KRAS

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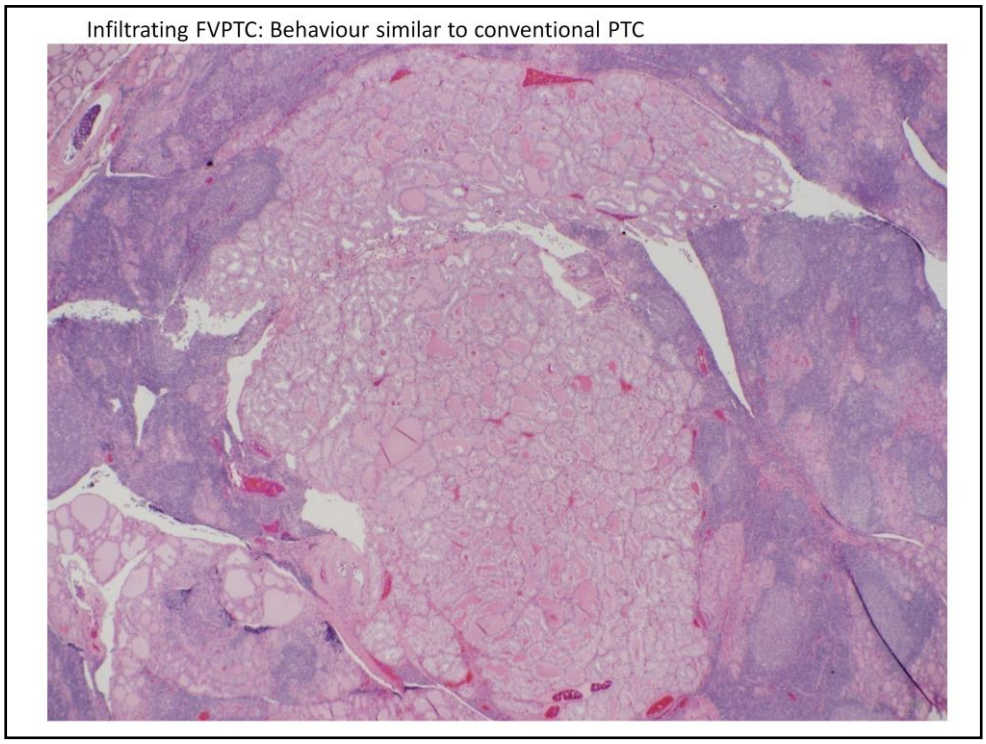
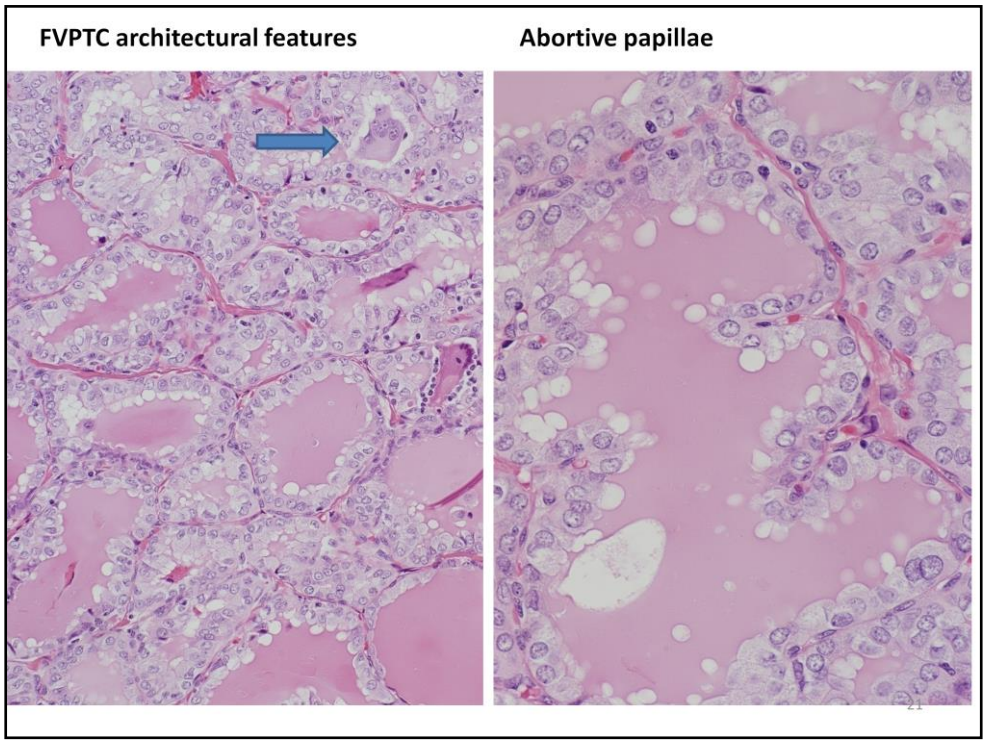
This slide summarizes the common genetic alterations in thyroid cancer. When we look at the major types of genetic abnormalities – BRAF mutations, RET/PTC translocations, mutations in RAS, and PAX8/PPARγ rearrangements – papillary thyroid carcinoma tends to show, as well as NTRK1 translocations, most commonly BRAF mutations, RET/PTC translocations, and RAS mutations. Whereas follicular adenoma and follicular carcinoma, when they show mutations – follicular carcinoma in particular – has a high rate of RAS mutations and PAX8/PPARγ rearrangements.

Interestingly, it is the follicular variant of papillary thyroid carcinoma that tends to share with those follicular tumours the RAS mutations and sometimes PAX8/PPARγ mutations. This, again, suggests that, at least on a molecular basis, those tumours are more akin to their follicular patterned cousins than to conventional papillary thyroid carcinoma.

Not all those studies that have shown RAS and PAX8/PPARγ mutations, have divided the tumours into the encapsulated and unencapsulated variants of the follicular variant. But I think some of them have and have shown that it is really the encapsulated ones that share these RAS and Pax8/PPARγ mutations with follicular patterned tumours.



This is an example of a follicular variant papillary carcinoma. This is the unencapsulated infiltrated version. Even though it is fairly well circumscribed in some areas, we do have tumour follicles that are infiltrating that surrounding inflamed thyroid with chronic lymphocytic thyroiditis. I don't see any papillae here from low power.



At higher power you tend to see, in addition to the obvious nuclear features of papillary carcinoma, the crowding, the overlap, the enlargement of the nuclei and irregularity, as well as nuclear clearing.

You tend to see architectural features, which include the irregularity and elongation of the follicles, dense colloid, sometimes multinucleated giant cells within the colloid, and sometimes you will find these little abortive papillae – those small papillae or papillary-like projections of tumour cells into the follicular lumen.

This is in my experience very common and quite typical for the unencapsulated follicular variant, but may be a bit more difficult to find in the capsulated variant. Again, there are pathologists who argue on both sides of this issue with respect to how many of these architectural features are necessary in addition to the nuclear features of papillary carcinoma in order to diagnose it. So, that's a controversial issue that I won't go into anymore in this talk.

Tall cell variant (<10%)

- Aggressive variant:
  - Higher frequency of BRAF mutations (80%)
  - Typically older patients, large tumors, extrathyroidal extension +/- distant mets
  - More likely to be refractory to radioactive iodine
  - Worse prognosis than classical, even when matched for age & stage
- Features:
  - Cells 3x taller than wide, distinct borders
  - Eosinophilic, granular cytoplasm (mitochondria)
  - More than 50% qualifies as tall cell
  - Mention any true tall cell component, may indicate BRAF mutated tumor

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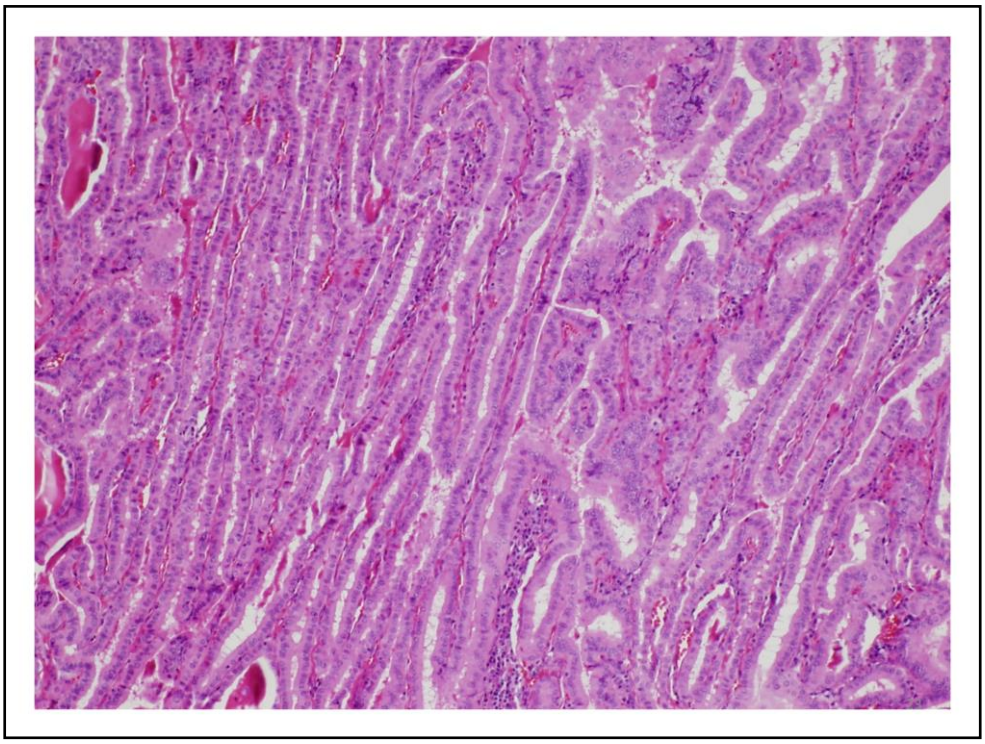
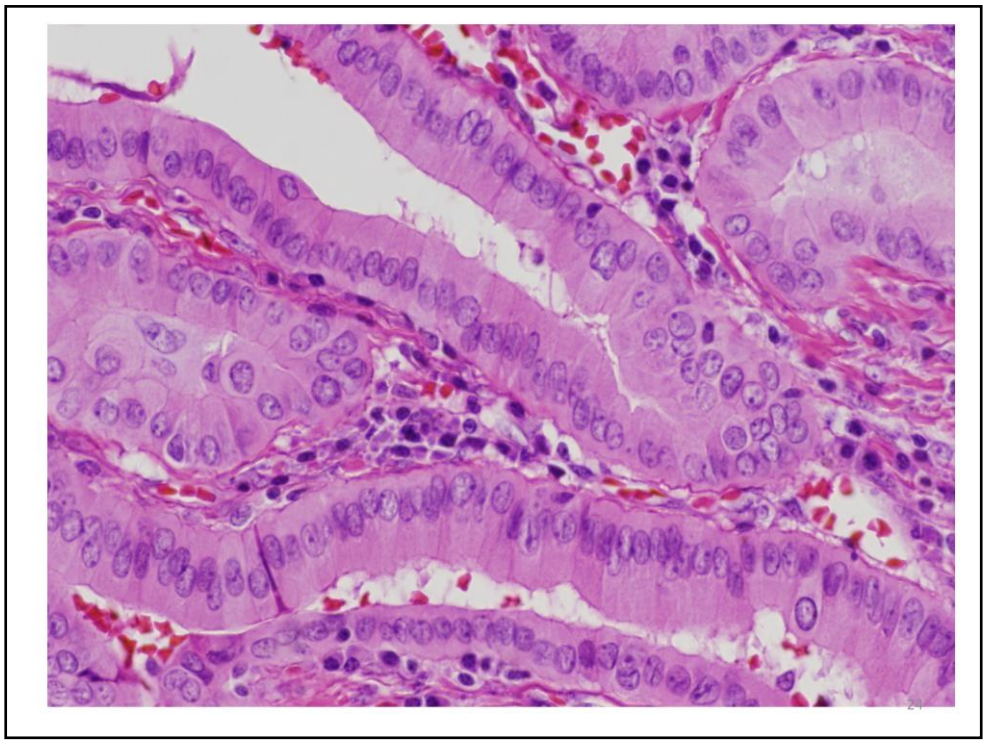
The tall cell variant is relatively uncommon, less than 10%, but certainly I think you see tall cells in many papillary thyroid carcinomas, at least as a minor component. It's an aggressive variant. It has a very high frequency of BRAF mutations. Patients are typically older, they have large tumours with extrathyroidal extensions, and these tumours tend to behave in an aggressive manner. They have a worse prognosis than classical papillary thyroid carcinoma, even when the patients are matched for age and stage, and they can sometimes be refractory to radioactive iodine therapy.

The features, when carefully applied, the cells should be three times taller than they are wide. They tend to have quite distinct lateral borders where they're adjacent cells, and they have an eosinophilic granular cytoplasm, which is due to the presence of mitochondria. Although, they are not in such abundance that the cells have that voluminous cytoplasm that you see in true oncocytes. So, the definition is of more than 50% of the tumour would qualify as a tall cell.

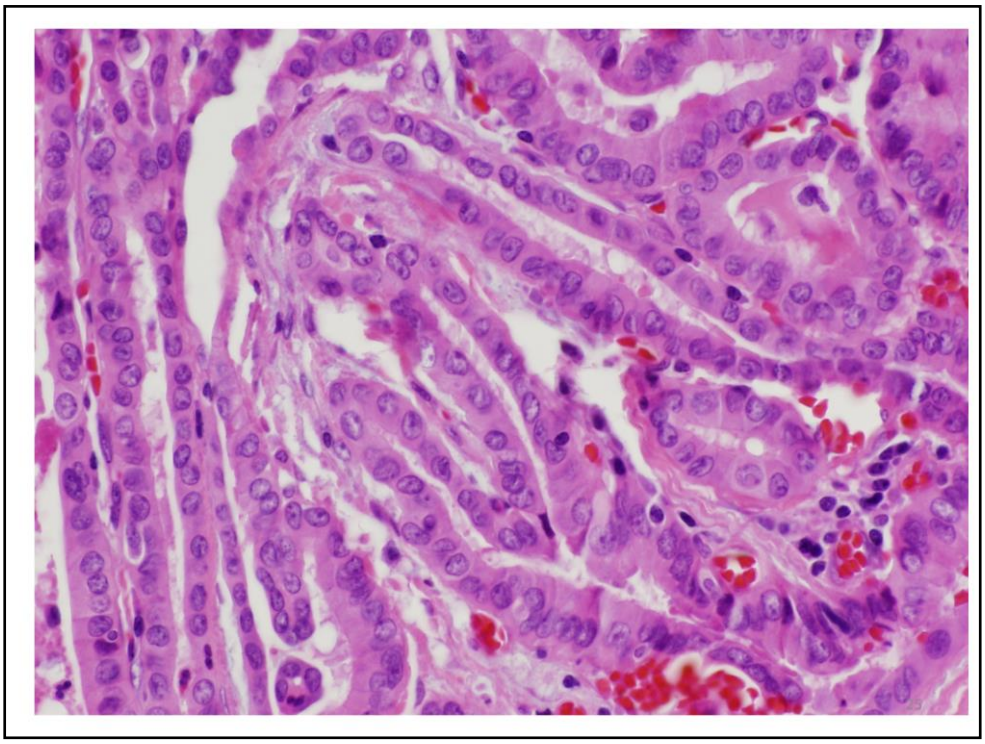
I have read 30% in some references, but as far as I know the WHO definition is 50%, I believe. I think it is important to mention any true tall cell component because that may indicate a BRAF mutated tumour, even if it is called classical type.



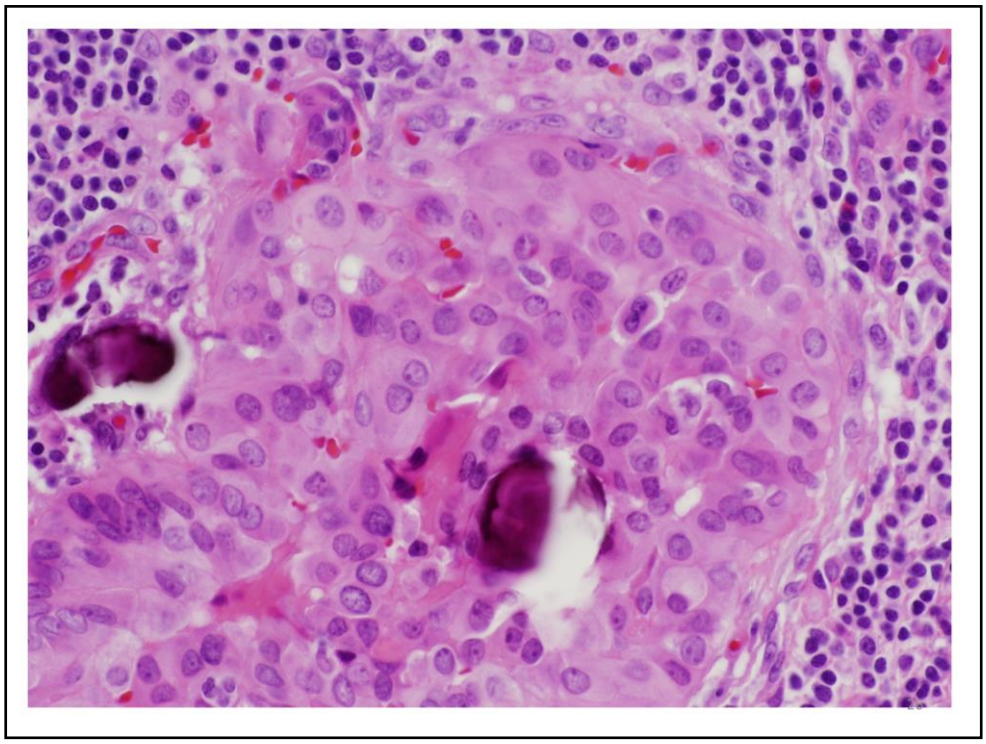
These tumours are quite characteristic from low power, and you can often recognize them because they look very pink. The cells are very pink, and they do show discrete papillae, but quite frequently, they'll also have these very elongated, zipper-like follicles, and the cells kind of line up parallel to one another.



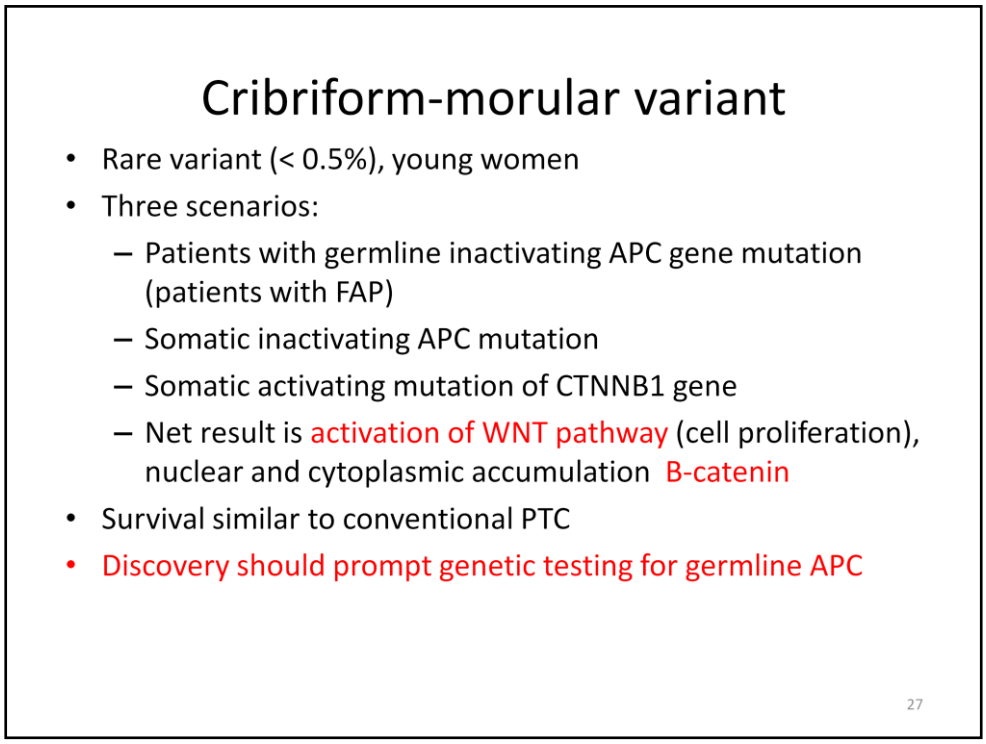
When you look at them at high power, they do look quite eosinophilic, granular, and you can see that there are quite distinct cell borders. I don't think this example emphasizes the quite marked nuclear features that they show for papillary thyroid carcinoma. They often have quite obvious intranuclear peudoinclusions and quite obvious grooves, even more so than you can see here.



But these tumours are often mixed with other patterns, so you may see areas where the cells look a little bit pink, where the cells are somewhat cuboidal. They may be two times taller than they are wide, but this pattern is mixed with the more typical tall cells.



And then, you can also often time see areas where the cells have a little bit more voluminous cytoplasm and look more just like run of the mill oncocytes. Those three types of cells, I find, are often mixed in in these tall cell tumours.



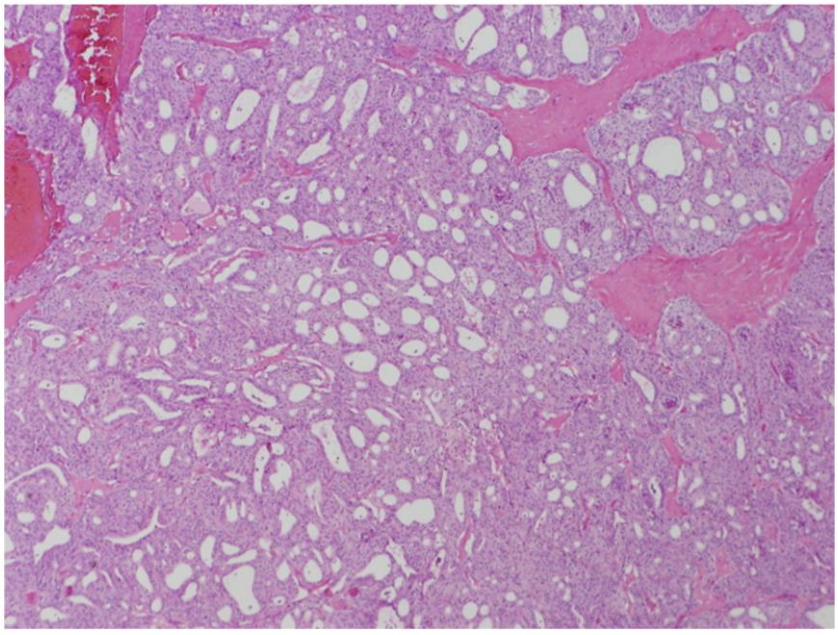
The cribriform-morular variant is a very rare variant of papillary thyroid carcinoma and it's important because of the mutations which may arise in it. This is a rare variant found commonly in young women, and there's basically three typical scenarios, or three scenarios, that you might find.

One is patients who have FAP – who have a germline inactivating mutation of the APC gene. Sometimes these tumours, though, can also have a somatic inactivating APC mutation in patients who don't have FAP, or they may have a somatic activating mutation of the CTNNB1 gene – and that's the gene that encodes for the protein β-catenin.

But the net result of all these mutations is that there's activation of the WNT pathway, which results in cell proliferation, and the nuclear and cytoplasmic accumulation of β-catenin – which is usually found in minimal amounts in cells and in thyroid cells – would typically be just found in the membrane. But you get nuclear and cytoplasmic accumulation of β-catenin.

The overall survival is similar to conventional papillary thyroid carcinoma. Although, I suspect these patients, especially if they have FAP or if they have FAP, would be at a high risk for colon cancer as well. But if you discover one of these, this should prompt

genetic testing for a germline APC mutation and that is why they are considered so clinically relevant. I will show you a few pictures.



2.8 cm thyroid tumor, 34 year old female

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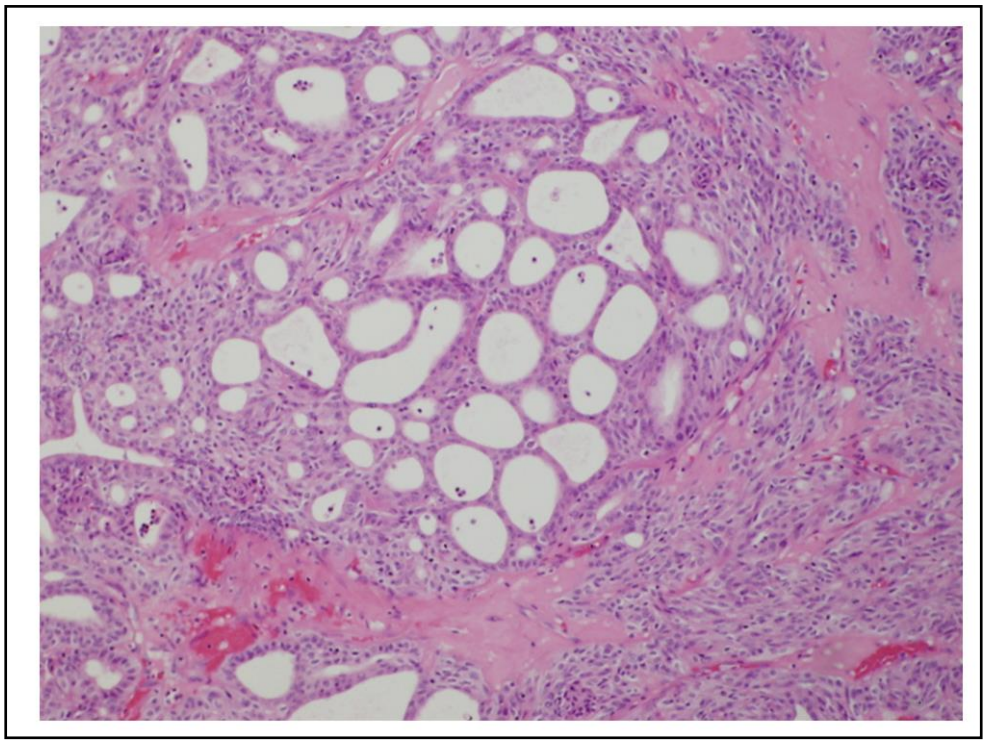
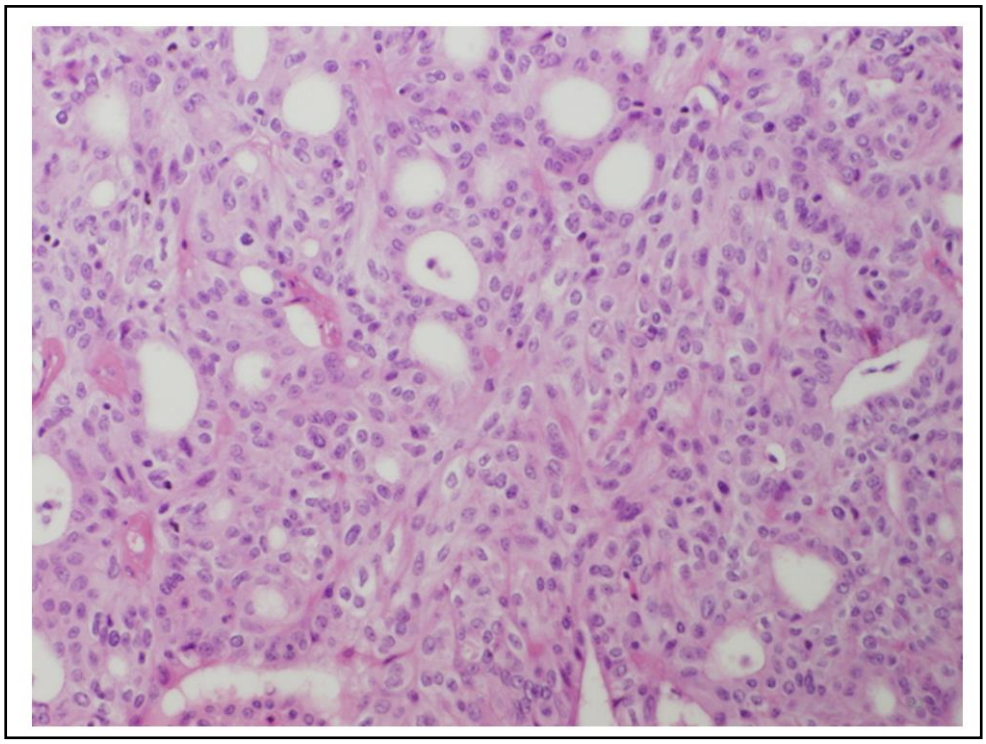
This was a patient who was a 34 year old woman. She had a 2.8 cm thyroid tumour. This is quite an old case. It definitely has a cribriform pattern, and you might say, “Well, why isn’t that just a follicular pattern?”

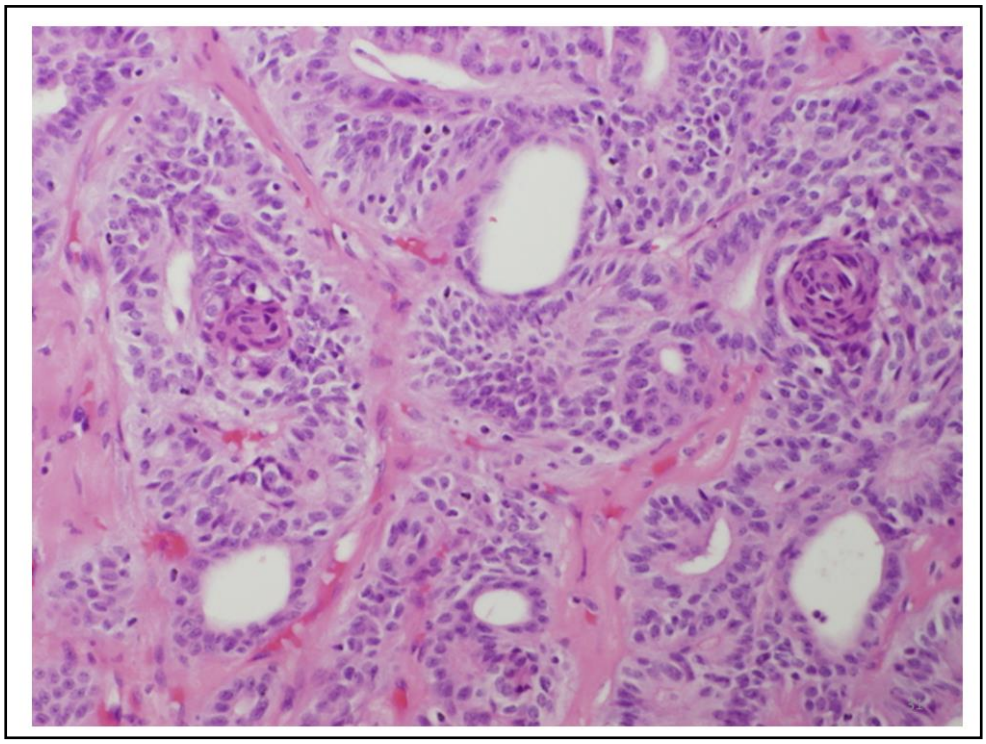
Well, the fact is, the follicles that are being formed are separated from one another by the presence of other cells. So, it does look like a cribriform pattern, like, for instance you might see in an adenoid cystic carcinoma. The other thing about it is that there’s no colloid, or very little colloid. The follicles tend to be quite empty looking.



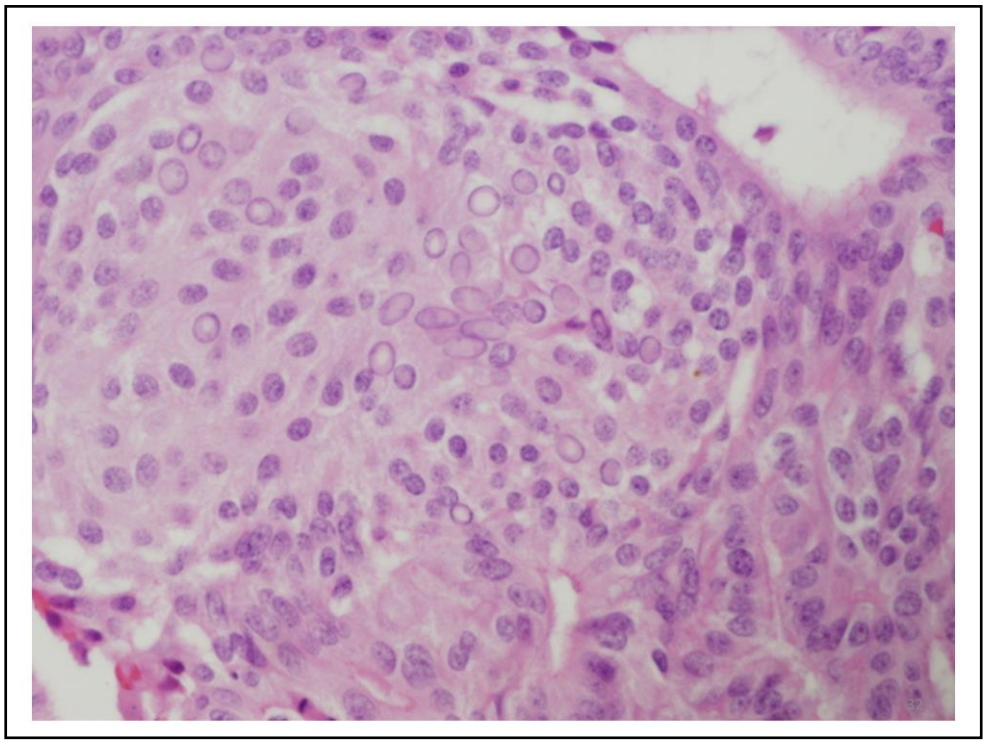
You can look at it again here. You can see there's two cell types. There's these cells around the follicles, as well as the cells in between, that look rather spindly.



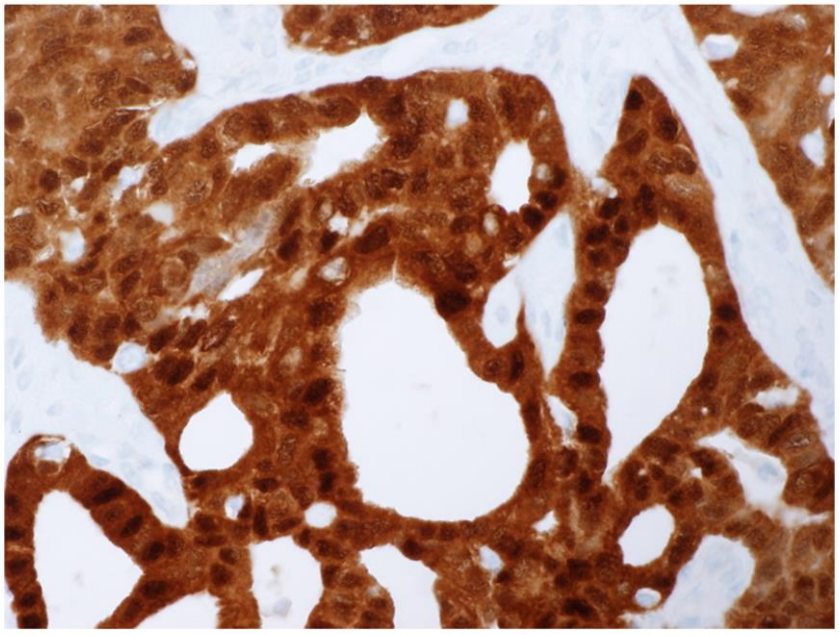
At higher power, you do see the cells forming the follicles, which are often rather tall. And then, the cells in between them that have this sort of tail eosinophilic cytoplasm and a rather spindled sort of nature. Those are the morular cells.



In this particular case, you can actually see cells that looked rather more squamoid, forming what looks a little bit like squamous eddies , although I couldn't see and intercellular bridges. Again, you see these rather tall cells lining the follicles.



The other interesting finding that you sometimes see is that you get the nuclei in the morular cells that have this, almost, an exaggerated kind of ground-glass type clearing, not quite like what you see in typical papillary carcinoma. In fact, these tumours do not often show absolutely classical features of papillary carcinoma. They have these unusual cleared, glassy looking nuclei. They tend to stain weakly for thyroglobulin, but they should stain for TTF1.



Beta catenin (cytoplasmic & nuclear, vs. membranous) 33

This is a big β-catenin stain on this tumour and you can see the very strong nuclear, as well as cytoplasmic staining.

Diffuse sclerosing variant

- 2% of PTC; children, young adults; F>M
- Commonly RET/PTC rearrangement
- Pathology
  - Diffuse enlargement with involvement one or both lobes
  - May be no grossly discrete mass
  - 80% LN involvement, often bilateral
  - High rate of distant mets (15%), usually lung
  - Clinically aggressive, overall 10 yr: 93%

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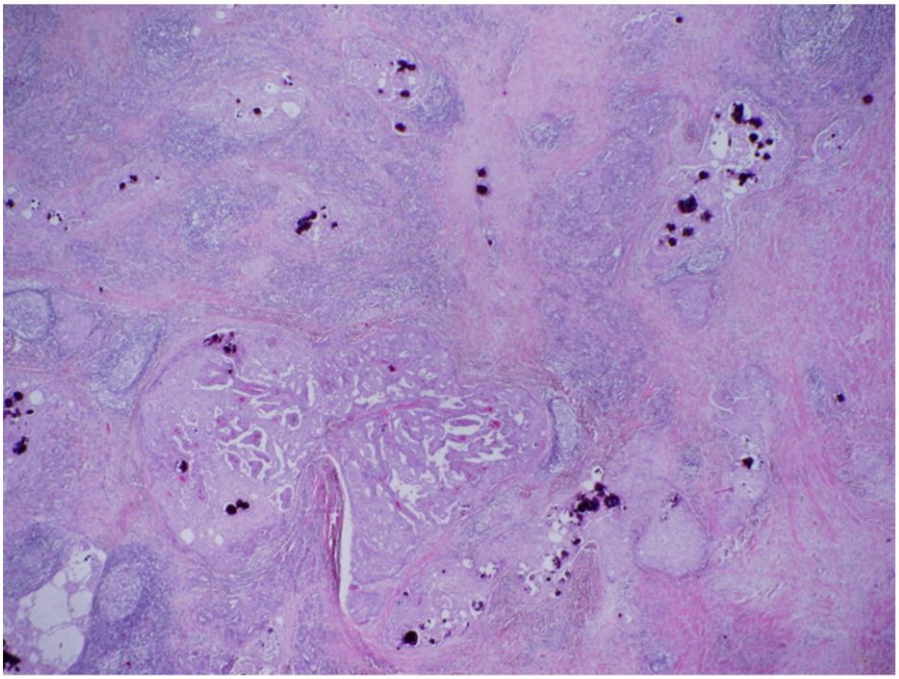
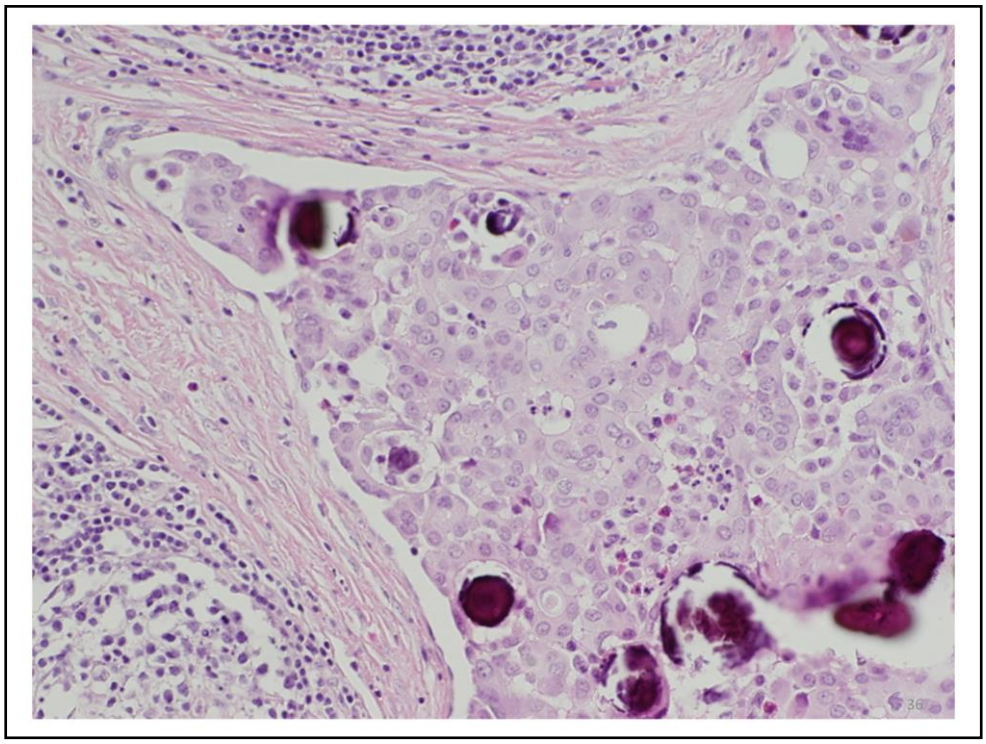
The diffuse sclerosing variant, again it's uncommon – 2% overall. Tends to occur in younger people, children, young adults, women more than men, commonly associated with a RET/PTC rearrangement. Pathologically, there typically is diffuse enlargement of the entire gland, and on grossing there may actually be no discrete mass. Although, sometimes you will find a discrete mass, as well as abnormality throughout the rest of the gland. I think patients very commonly have lymph node involvement. It is often bilateral, and it tends to show a fairly high rate of distant metastases, usually to the lung. They tend to be clinically aggressive, although the overall survival is 93%, which really does not count for an aggressive papillary thyroid carcinoma.

28 year old female, diffusely enlarged thyroid, 93 g specimen

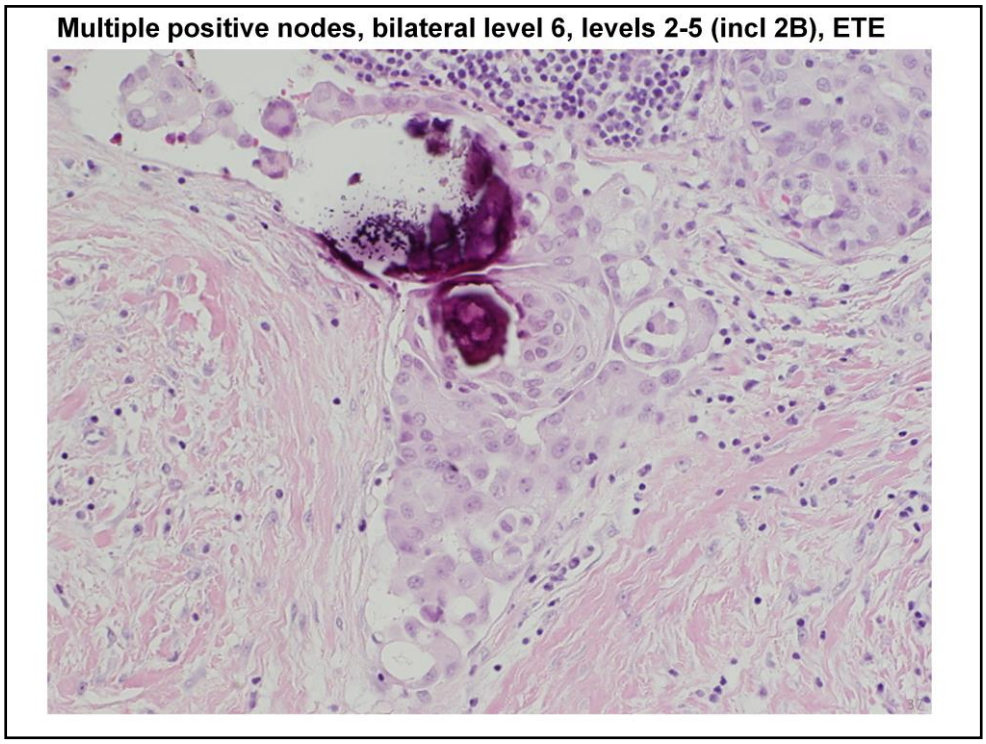


This is an example. This was a 28 year old woman, and her thyroid specimen weighed 93 g. It did include a right lateral neck dissection, but it still was a very enlarged heavy thyroid.

I is kind of a lousy picture, but just from low power, you can see this extensive fibrosis. The chronic inflammation is usually associated with chronic lymphocytic thyroiditis. You can see numerous psammoma bodies scattered throughout the whole gland and sometimes, you can even see from low power where the psammoma bodies have caused tearing of the tissue section as the section is made. There are multiple foci of tumour, and the more you look, the more you find with these tumours. Often, you will find individual psammoma bodies within lymphatic spaces within the fibrous background.

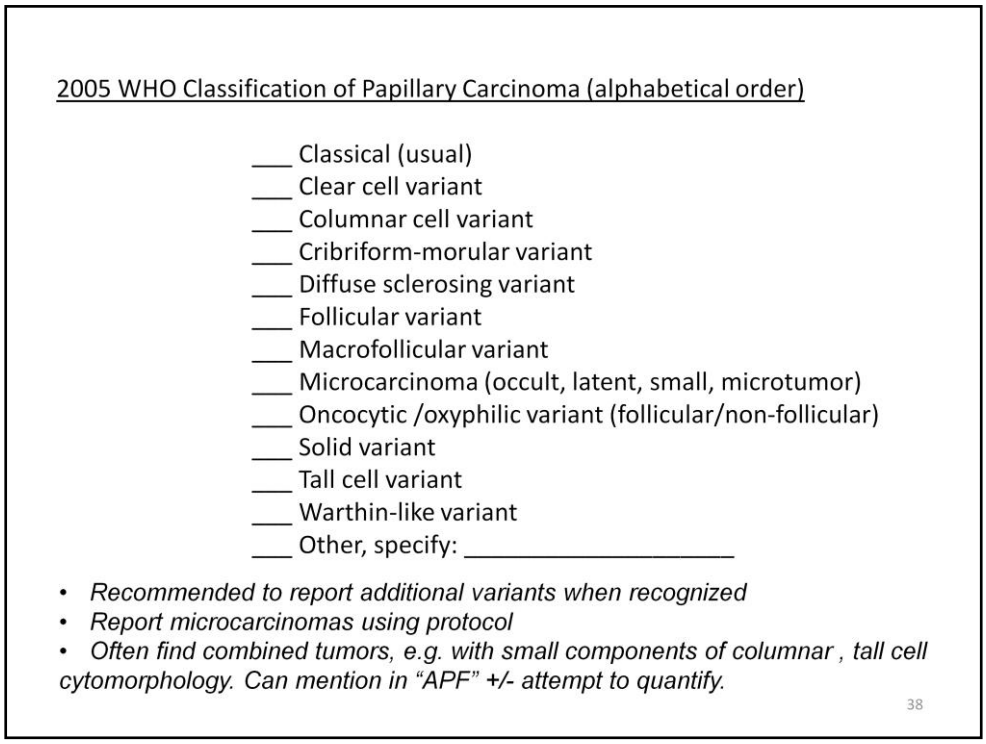


Here it is at somewhat higher power. I think you'd probably buy that this is actually within a lymphatic space.



Sometimes the tumour cells will undergo squamous metaplasia. These cells in here, in the middle, I think are squamoid and probably, frankly, squamous. I think I can see the odd intercellular bridge. But they do tend to show squamous differentiation.

This woman actually had bilateral level VI lymph node positivity. She had positivity throughout levels II through V in her lateral neck, as well as extrathyroidal extension. But a couple of years now after surgery, she's still going strong and shows no evidence of recurrence.



The complete WHO classification of the variants of papillary thyroid carcinoma is listed here.

I would recommend reporting these additional variants when they are recognized. The recommendation is to report microcarcinomas – that is tumours that are incidentally found and less than 1 cm, using the CAP protocol. Often, you can find combined tumours – so classical tumours typically with a small component of a columnar pattern or tall cell cytomorphology. I think that is important to mention within the additional pathological findings and I would make some attempt to quantify that.

Histologic Type (select all that apply) (Notes D and E)

___ Follicular carcinoma (Note G)
Variant (required only if applicable):
___ Oncocytic (Hürthle cell)*
___ Other variant (specify): _____
**Extent of tumor invasion:
___ Minimally invasive
___ Widely invasive *Something in between??*

___ Poorly differentiated thyroid carcinoma (Note H)
___ Undifferentiated (anaplastic) carcinoma (Note H)
___ Focal or minor component without extrathyroidal extension
___ Major component
___ Medullary carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined ***

**No longer considered a distinct entity (i.e Hurthle cell carcinoma)*
*** Refers to capsular invasion only, angioinvasion is a different issue!*
****Usually FTC vs. PTC*

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Next, we go on to the other histologic types.

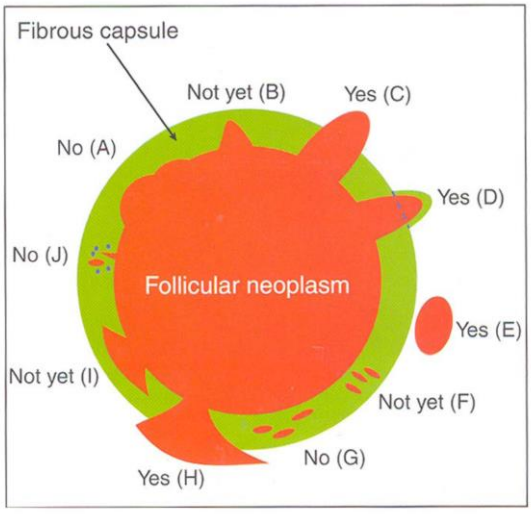
Follicular carcinoma and its commonest variant, which is the oncocytic or Hürthle cell variant. You should note that Hürthle cell carcinoma, so to speak, is no longer considered by most people a distinct entity. It's rather either considered to be a variant of follicular carcinoma or papillary thyroid carcinoma. The extent of tumour invasion for follicular carcinomas – they can either be minimally invasive or widely invasive.

The definition of a minimally invasive tumour is one that shows microscopic invasion through the capsule, which is not grossly visible. A widely invasive carcinoma would be a tumour that shows gross invasion through the capsule, and in many of these cases, they really are much more widely invasive, so the capsule is either not present, or there are multiple areas of invasion through the capsule. They may show extrathyroidal extension. They often show angioinvasion. Some people have proposed that there should be something in between – so, a category of a grossly visual capsular invasion, but not extensive infiltration of the thyroid. But the tumour invasion refers to capsular invasion only. Angioinvasion is a separate category and it really is a different issue.

Then we have poorly differentiated thyroid cancer, undifferentiated thyroid cancer, medullary carcinoma, and "carcinoma other types", and "carcinoma type cannot be

determined". In my experience, when I've used it, which is rarely, it's usually cases where you're having some difficulty distinguishing between a follicular thyroid carcinoma and an encapsulated papillary thyroid carcinoma, on the basis of nuclear features.

From Fletcher CDM, ed. *Diagnostic Histopathology of Tumours*. 3rd ed. Edinburgh: Churchill Livingstone Elsevier; 2007. Modified with permission © Elsevier.



Some might accept F, G, I as capsule invasion (not me!); levels & more in should follow. Some would question "E" (how distinct is tumor?)

40

This is a diagram showing the proposed diagnosis for capsular invasion. Again, this is somewhat controversial, but there are diagnostic features of capsular invasion. So, if the green part is the capsule, the orange part is the tumour.

If the tumour extends completely through the capsule into the adjacent thyroid parenchyma, then yes, that would be capsular invasion. If the tumour does the same, but still has a fibrous pseudo-capsule around the periphery, then that would still be considered capsular invasion.

Capsular invasion might be in this anvil-shaped or triangular sort of pattern. That would count. Anything that is not completely through the capsule would not strictly speaking be capsular invasion in the eyes of many pathologists, although, there are pathologists who certainly would accept extensive infiltration into the capsule, but not entirely through the capsule. I personally like to see tumour invasion completely through the capsule into the adjacent parenchyma. You have to be careful when you're dealing with the periphery of the gland, where you don't actually see thyroid parenchyma around the outside. I think it is sometimes possible to overcall capsular invasion in that circumstance, where you do not have parenchyma surrounding the tumour.

Some would question this (E) portion. Most would, and myself included, would like to

see a connection between the tumour and the tumour that is outside the capsule. I think it depends on the circumstance, but ideally, you would want to do deeper levels and additional sections to prove that connection. If it is an extremely distinct architectural and cytomorphologic pattern, I think, in some cases, you would, or could, assume that it is the same tumour. You have to be very, very careful in that circumstance, however.

Poorly differentiated thyroid carcinoma

- WHO: "Follicular cell neoplasms that show limited evidence of structural follicular differentiation and occupy both morphologically and behaviourally an intermediate position between differentiated and undifferentiated carcinomas"

- Diagnostic criteria historically controversial, variable
- Arise "de novo" or from pre-existing PTC or FTC , usually latter
- Maintain TTF1 and Tg expression unlike anaplastic Ca. (may be muted), Ki67 20-30%
- p53 and RAS mutations common
- Often widely invasive, angioinvasive, but may also be a component of well-differentiated tumor
- As little as 10% PDTC may confer a more aggressive behaviour

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Poorly differentiated thyroid carcinoma – these are tumours defined by the WHO as tumours that show limited evidence of structural follicular differentiation. They occupy an intermediate position between differentiated and undifferentiated carcinomas. The diagnostic criteria are somewhat controversial, but I will provide you with some criteria that are fairly discrete and that you can use.

They may arise *de novo* or from a pre-existing well differentiated thyroid cancer. In my experience, this is more usually the case. Unlike anaplastic carcinoma, they do maintain thyroglobulin expression and TTF1 expression although it may be muted, especially the thyroglobulin. They have a fairly high proliferative index. These tumours can be widely invasive or angioinvasive, but in other circumstances, they are a component of a well differentiated tumour that may actually be found entirely within that tumour. It should be reported as little as 10% of poorly differentiated thyroid carcinoma component, can confer a more aggressive behaviour.

Poorly differentiated thyroid carcinoma

- Turin Criteria (AJSP 2007): attempt to reach uniform diagnostic criteria
  - European, Japanese, American pathologists
  - Case review followed by consensus conference
  - Started with carcinomas with solid, trabecular, insular architecture (no oncocytic tumors)
  - Further evaluated:
    - Nuclear features
    - Mitotic activity
    - Necrosis

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The criteria that were developed, were developed in 2007 at a meeting of thyroid pathologists in Turin. Basically they started with carcinomas that didn't show follicular architectures, they showed solid trabecular or insular architecture. They did not include oncocytic tumours. Then, they further evaluated the nuclear features, the mitotic activities and the presence of necrosis.

Poorly differentiated thyroid carcinoma

1. Growth pattern: solid, trabecular, insular (usually mixed), and…
2. Absence of usual PTC-like nuclei, and…
3. Presence of at least one of:
   1. Convoluted nuclei (small, hyperchromatic, irregular/raisinoid)
   2. MF >/= 3 per 10 hpf
   3. Necrosis

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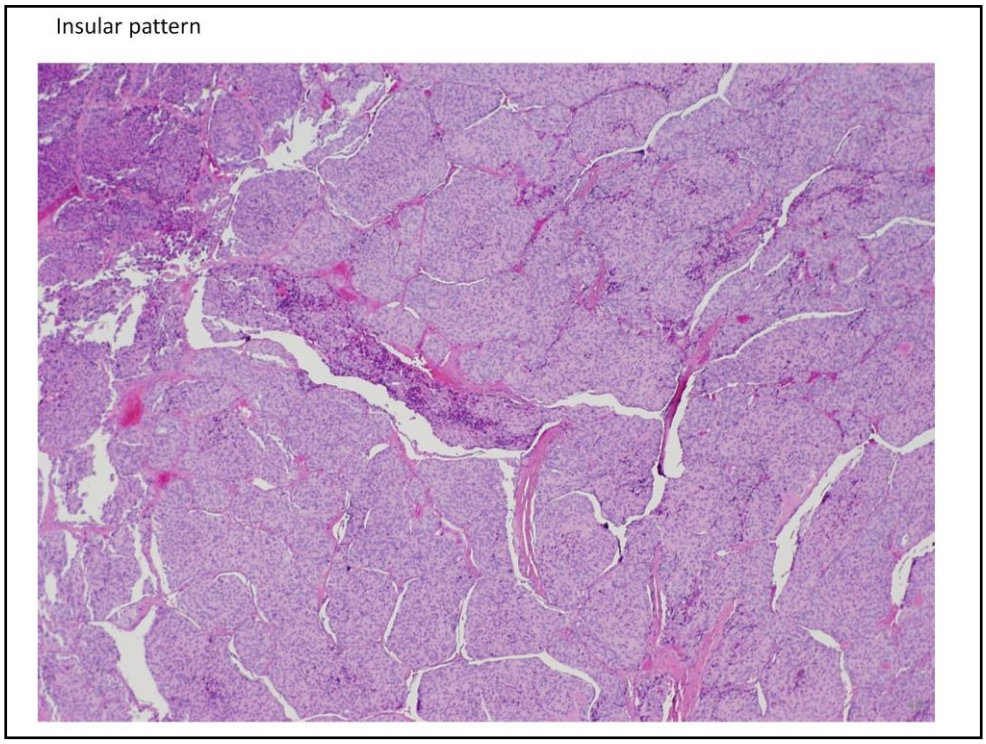
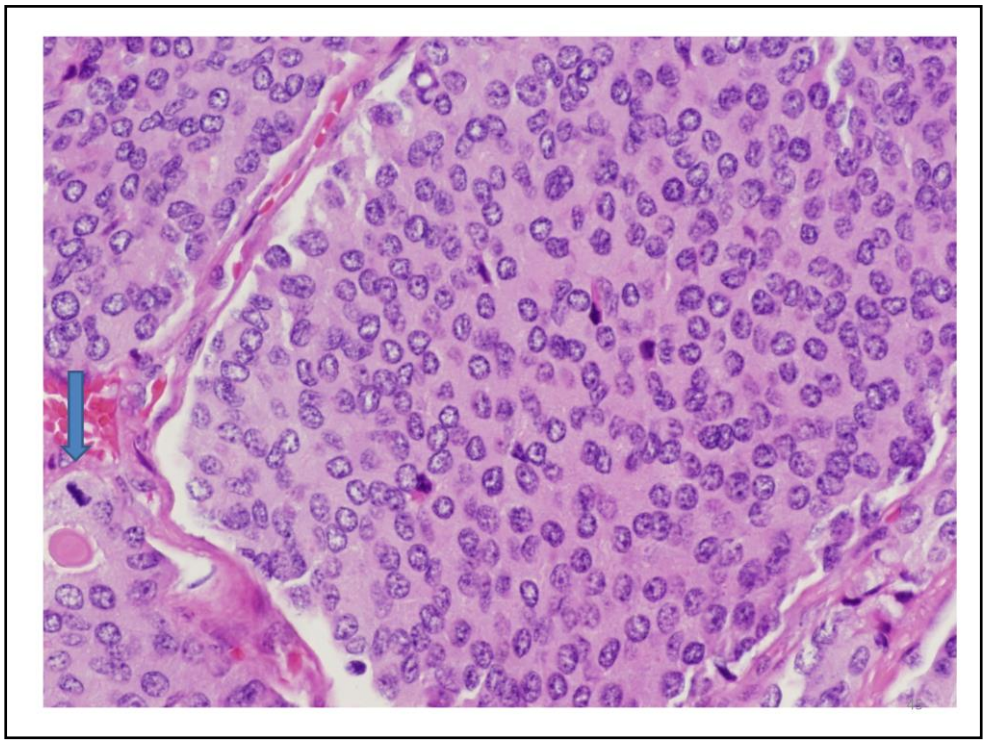
The criteria are as follows: A gross pattern that is solid, trabecular or insular, often mixed, with the absence of usual PTC-like nuclei. Presence of at least one of: convoluted nuclei – which are small hyperchromatic and rather irregular or raisionoid; the presence of more than, or equal to, three mitotic figures for 10 hpf; or the presence of necrosis.

Originally it was proposed and batted around that perhaps these convoluted nuclei were a reflection of tumours that arose within papillary thyroid carcinomas, but it confers no real distinction to those tumours. They behave in a similar fashion to ones that don't have convoluted nuclei.

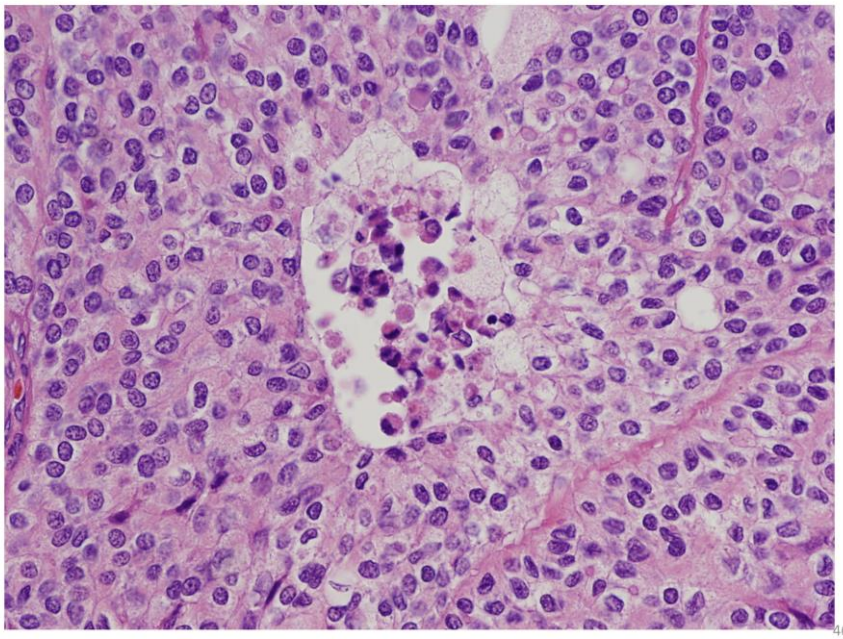


This is an example of an insular carcinoma, and the tumour is really very monomorphic looking from low power. The follicles is forming islands, or insulae, and sometimes the insulae will have these little clefts around them resulting in a clear space.



At higher power the cells are actually quite monomorphous, they are a bit wrinkled. I don't know if I would consider them raisonoid, but they tend to be quite monomorphous. You can see a mitotic figure over at the left hand side, as indicated by the arrow.

Necrosis – punctate or comedo



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Then, in other parts of the tumour, you see these little punctate areas.

PDTC – diagnostic issues

- PTC is always diagnosed if nuclear features are typical (but comment on necrosis, mitotic activity as correlated with poor prognosis). Solid variant PTC has better prognosis than PDTC.
- How much PD component is necessary for the diagnosis? Majority (WHO 2004)? I would report any, give approximate percentage.
- What about oncocytic or clear cell tumors?
- Versus anaplastic? APC has marked nuclear atypia, extensive necrosis, high mitotic rate

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Diagnostic issues with respect to poorly differentiated thyroid cancer – one would always diagnose papillary thyroid carcinoma if the nuclear features are typical. But comment on the presence of necrosis and mitotic activity because it has been correlated with a poor prognosis in papillary thyroid carcinoma. Nevertheless, the solid variant of papillary thyroid carcinoma does have a better prognosis than poorly differentiated thyroid carcinoma.

How much of a poorly differentiated component is necessary to make the diagnosis outright? The WHO looks as majority, but I think it's important to report any component of poorly differentiated thyroid cancer.

What about oncocytic or clear cell tumours? I think they exist, but the definition is somewhat less defined.

And versus anaplastic? Anaplastic thyroid carcinoma – the cells are much less monomorphous. They show marked nuclear atypia. They tend to have extensive areas of coagulative necrosis and a high mitotic rate – higher than what we see in poorly differentiated cancer.

Margins (Note I)

___ Cannot be assessed

___ Margins uninvolved by carcinoma

+ Distance of invasive carcinoma to closest margin: ___ mm

___ Margin(s) involved by carcinoma

+ Site(s) of involvement: _____

- *External surface of specimen (may be surface of gland) or isthmic margin*
- *Tumors often extend to surface of gland but are excised (ink on external surface)*
- *Margin positivity common with ETE*
- *"meticulous studies on the effect of positive margins….are lacking"*

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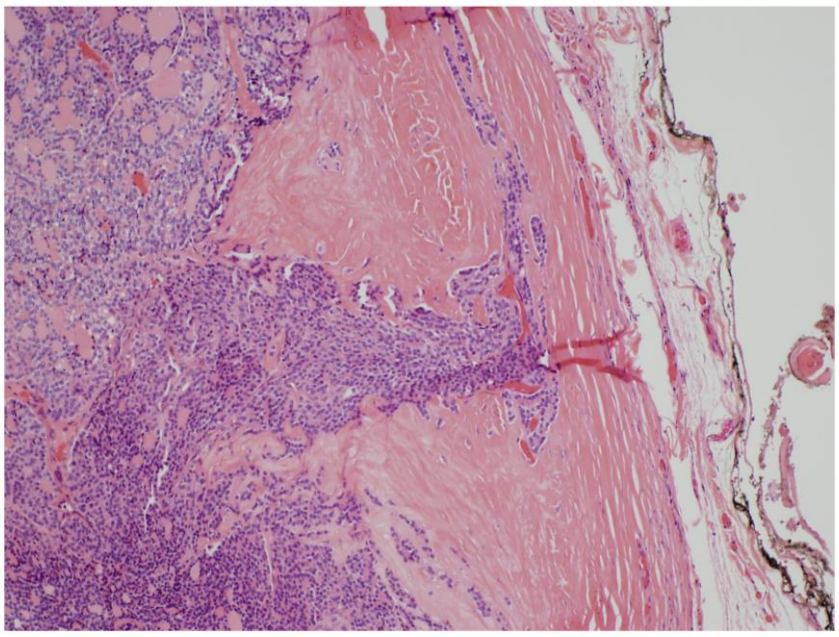
The next component is margin status. And that's divided into cannot be assessed, uninvolved, or involved. The distance of the carcinoma to the closest margin is optional. Site involvement is optional. So this really, with respect to thyroids, refers to the external surface of the specimen which we would typically ink, and that may actually be the surface of the gland, or it applies to the isthmic margin, which is the true surgical margin divided by the surgeon.

And tumours will often extend to the surface of the gland, but they are excised, inked on the external surface of the tumour either within capsule, or the capsule, or just some compressed fibro adipose tissue. However, true margin positivity is common when you have extrathyroidal extension.



The protocol states that, although we expect there will be some comments about margin status, meticulous studies on the effect of positive margins are lacking.

Here is what I was talking about just a minute ago. These tumours, this tumour in particular, extends to the surface of the gland. You've got a little bit of connective tissue with ink on the outer surface. So this tissue will be completely excised. I think the distance from the margins in this case would probably not be of great relevance.

Angioinvasion (vascular invasion) (select all that apply) (Note J)

___ Cannot be determined
___ Not identified
___ Present
+ Extent:
+ ___ Focal (less than 4 vessels)
+ ___ Extensive (4 or more vessels)

- *Distinction from lymphatic invasion drawn in this version*
- *FTC primarily AI, PTC primarily LI (LI>>AI)*
- *AI a better predictor of aggressive behaviour (distant mets)*
- *Impact of extent of AI on behaviour is controversial and contradictory*

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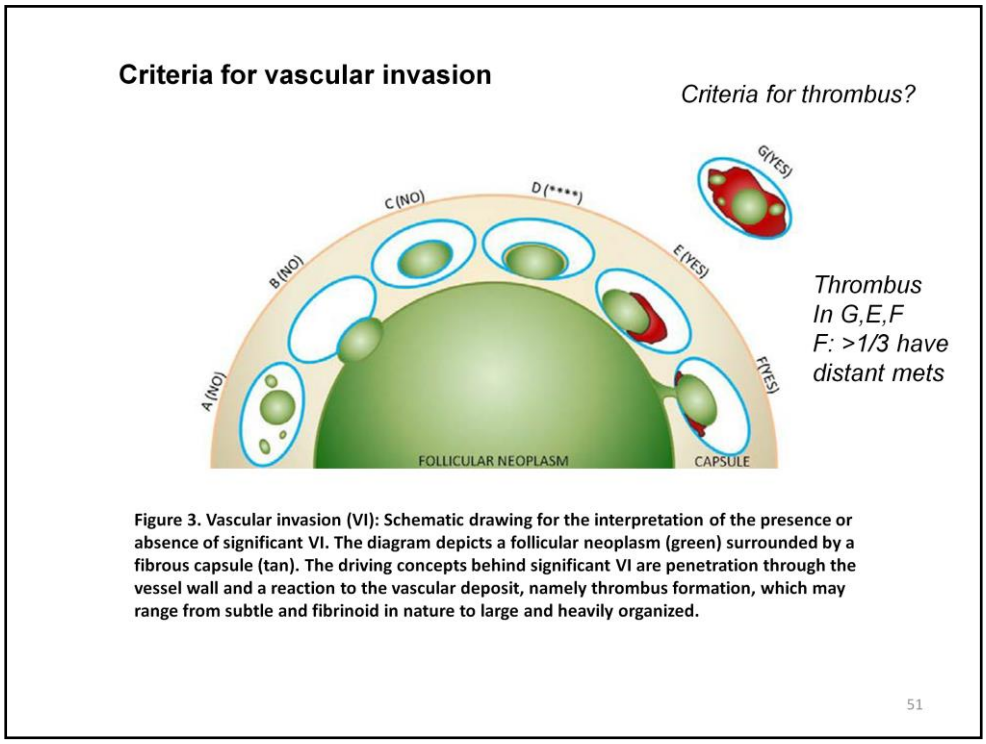
Angioinvasion is another controversial topic.

Angioinvasion is separated from lymphatic invasion in the thyroid protocol. So, the categories are cannot be determined, not identified, or present, and then it's an optional element to add the extent of invasion, whether that's focal, less than four vessels, or extensive. As you probably know, follicular thyroid carcinoma primarily metastasizes via angioinvasion whereas papillary thyroid carcinoma primarily shows lymphatic invasion. Although you do see angioinvasion in papillary thyroid carcinomas.

Angioinvasion is a better predictor of aggressive behaviour in distant metastases. The extent of angioinvasion on behaviour – that is somewhat more controversial.

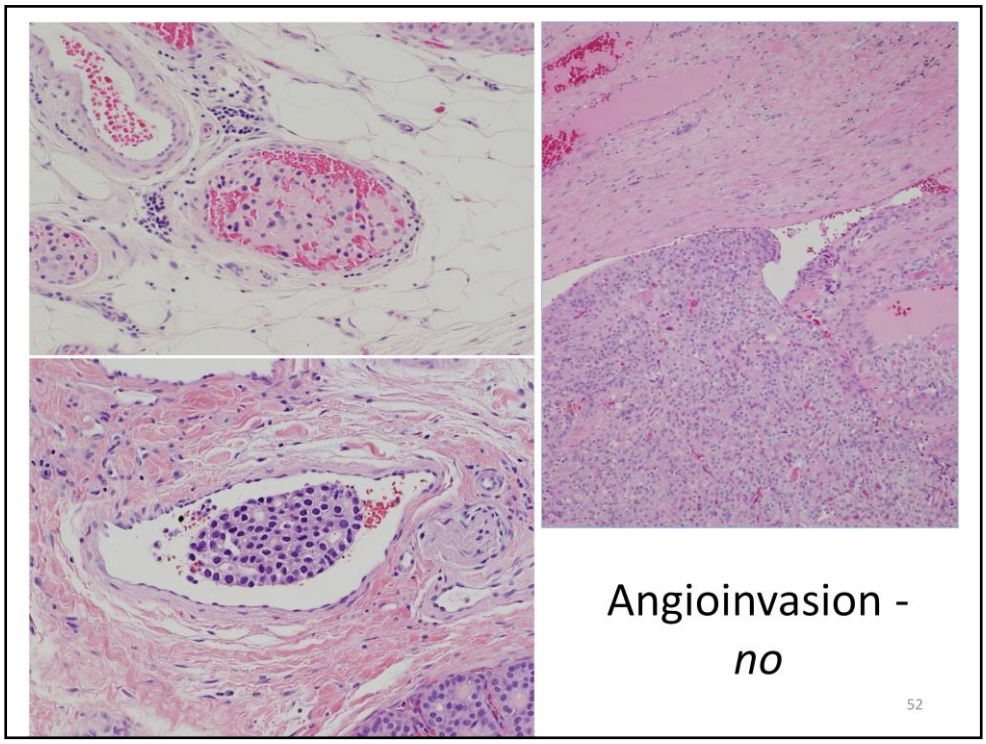


This is a diagram included in the protocol which discusses the criteria for vascular invasion. I think what it comes down to is that in order to unequivocally diagnose angioinvasion, which as you know has to be within the capsule or outside the capsule, one has to see tumour with the associated thrombus.

What constitutes as thrombus can vary in different people's minds from subtle fibrin accumulation to an actual organizing, vascularized thrombus. Nevertheless, to be absolutely sure, you have to see thrombus. That could include the example here, (G), where you have tumour within a vessel surrounded by thombus; (E), where you have tumour attached to the wall with associated thrombus; or (F), where you have the tumour actually invading through the vessel wall, attached to the wall and the thrombus. (F) has been determined and studied by Dr. Asa. In Toronto, the (F) category is a very strong predictor of aggressive behaviour, and more than a third of the patients will have distant metastases.

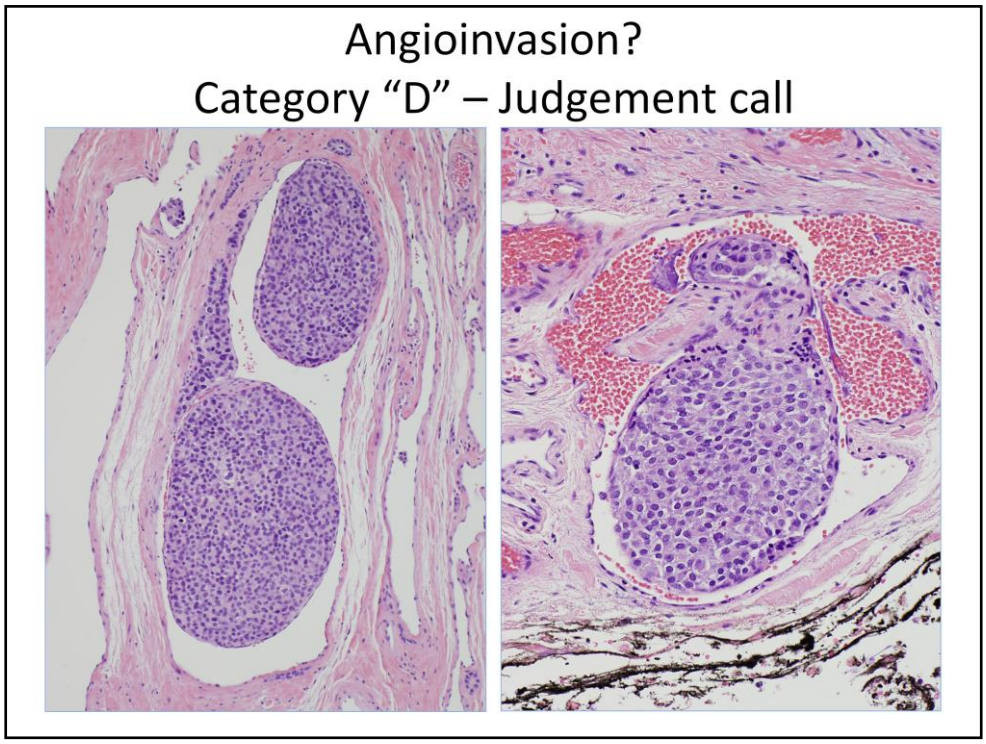
Categories that would not be considered in this diagram of angioinvasion would include: isolated islands of tumours within a vessel probably just getting there by artifactual displacement; Category (B), where you have tumour that has endothelialized surface that's bulging into a vessel; or tumour actually within a vessel that is endothelialized – that's the blue rim around the green tumour portion. Those would not be considered diagnostic angioinvasion. Category (D), where you have the tumour

attached to a wall with endothelialization is a little bit more controversial. I will get on to that in a minute.



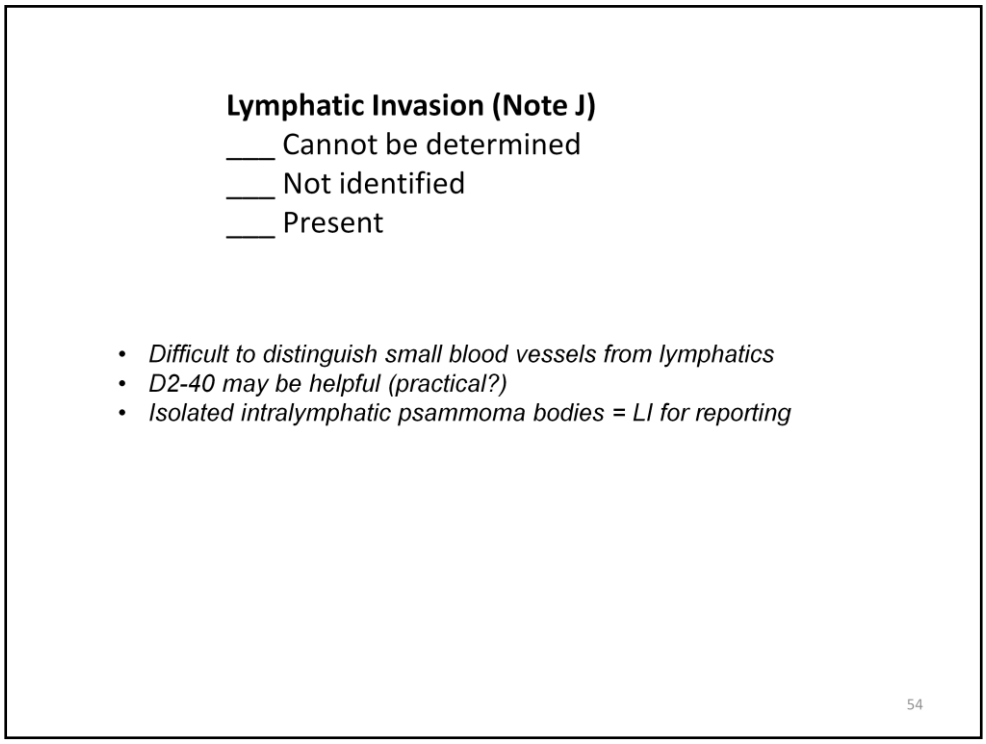
Here are some examples of things that I would not consider angioinvasion.

Tumour cells in the upper left-hand side, tumour cells isolated in the vessel, are probably just there by artifactual displacement . On the lower left hand side where you have an island of tumour cells, it doesn't look endothelialized, it's just floating in the vessel, that would not be angioinvasion. Tumour that's protruding into the vessel here like a little tongue, I would not consider that angioinvasion.



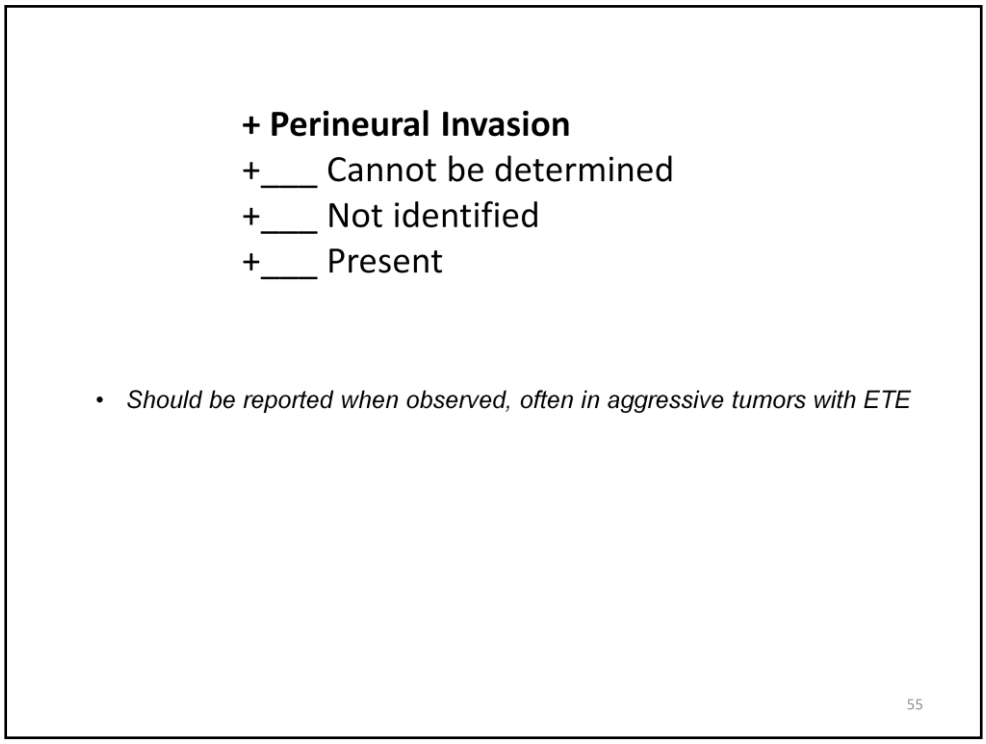
On the other hand, if this were the Category (D), which in the protocol is left to the discretion of the pathologist, you have tumour islands that are attached to the wall and endothelialized surrounded by red blood cells. Again, that would be up to the discretion of the pathologist.

I would probably call this angioinvasion, but obviously, there would be some discrepancy about that.

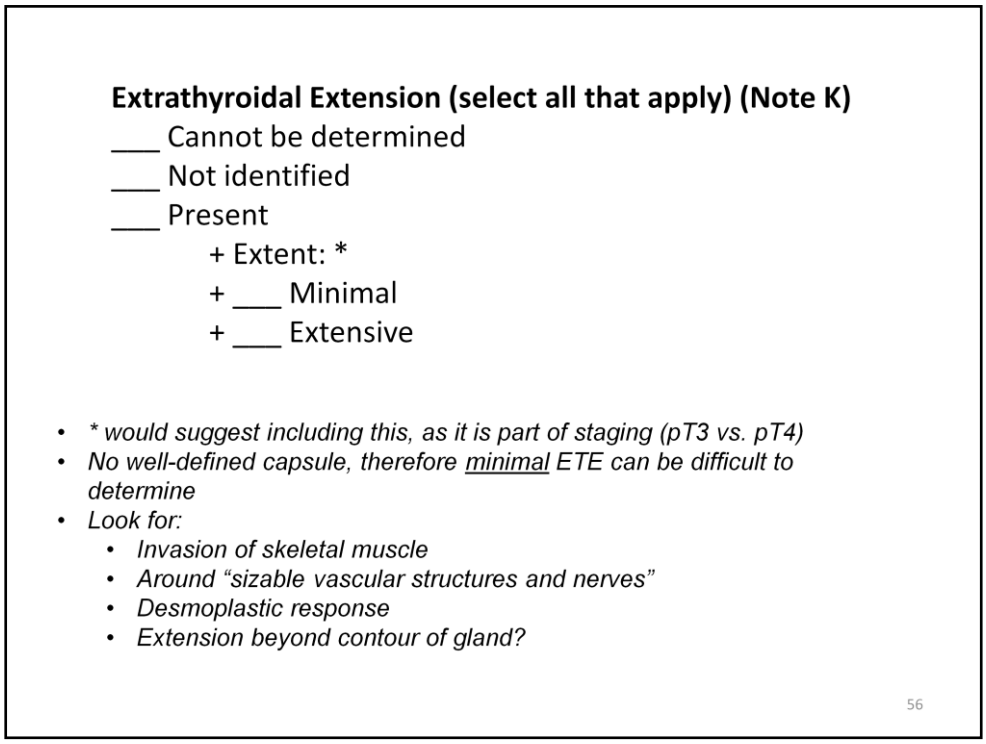


The next category is lymphatic invasion. Cannot be determined, not present, or present. I find it difficult to diagnose small vessel invasion in thyroid cancers and so trying to distinguish between small blood vessels and lymphatics, I think is an even more difficult proposition. They discuss in the protocol potentially using D2-40 to identify endothelial cells of the lymphatic channel. I don't know if that's necessarily always practical, but it can be used.

Isolated intralymphatic psammoma bodies, that should be considered lymphatic invasion for reporting purposes. An example would be for instance if the diffuse sclerosing variant of papillary thyroid carcinoma where you do have extensive, typically extensive, lymphatic invasion. Often times what you'll see, is just isolated psammoma bodies, which are really just islands of necrotic tumour cells that have undergone calcification.



Perineural invasion is an optional component. I would report it when I observe it. It's often found in tumours with extrathyroidal extension.

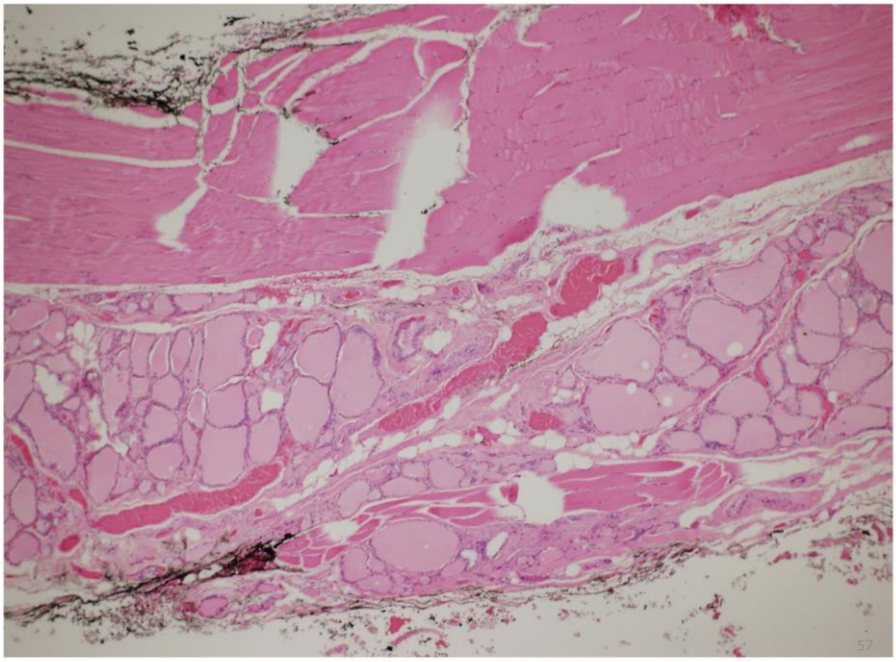


Now getting on to extrathyroid extension. This is a required component of the protocol. It's divided into three categories: cannot be determined, not identified, or present. And then under "present", the extent of extrathyroidal extension, in my opinion is relevant to determine whether this is minimal or extensive, because it is part of the staging system (pT3 versus pT4).

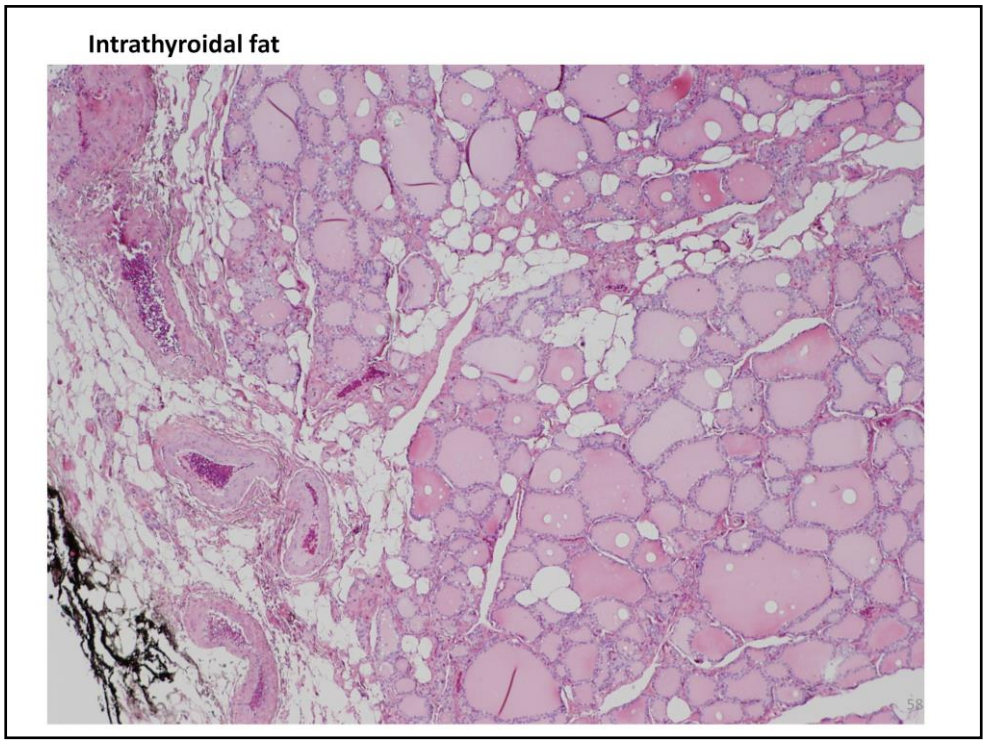
The thyroid doesn't have a defined capsule, so therefore minimal extrathyroidal extension would be difficult to determine and make up your mind about. But there are certain features that one should look for. Obviously, invasion of skeletal muscle is evidence of extrathyroidal extension. Invasion of fat however, can be controversial because fat can actually sometimes be found within the thyroid in small quantities.

Invasion around "sizable vascular structures of nerves" I think, is a good and reliable criterion, but again, there's no definition given to the "sizable". Also look for a desmoplastic response around the periphery of the tumour, especially if you're looking for a tumour that extends beyond the contour of the gland I just mentioned. So if you do see a tumour that's extending beyond the contour of the gland with a desmoplasmic response, they often are useful evidence for extrathyroid extention.

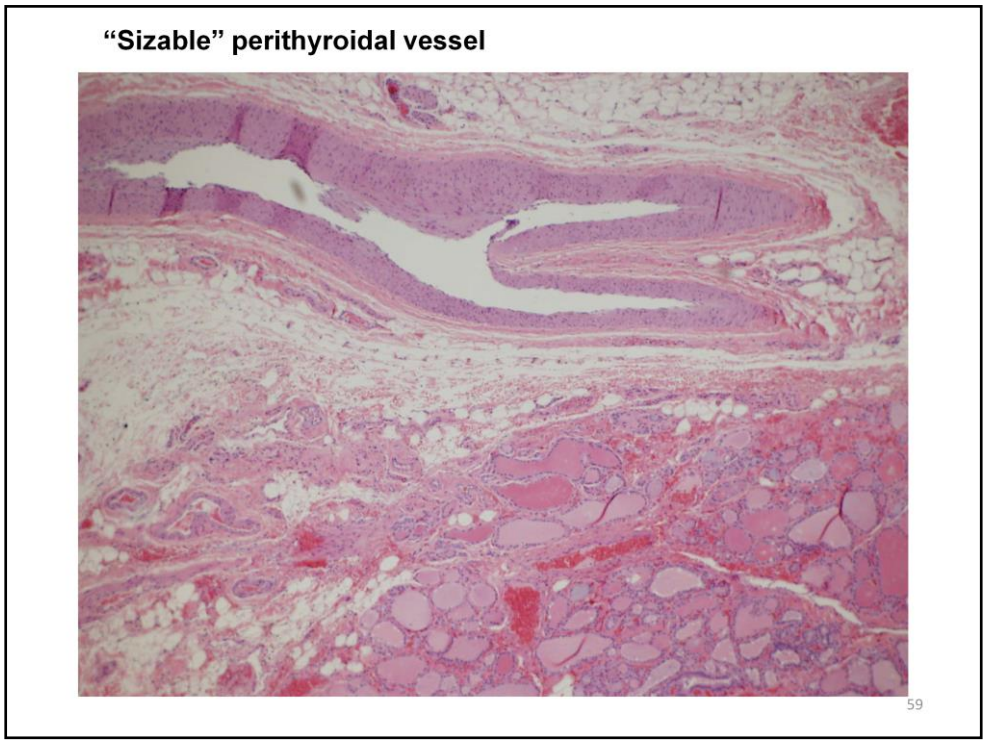
Skeletal muscle and adipose tissue at isthmus



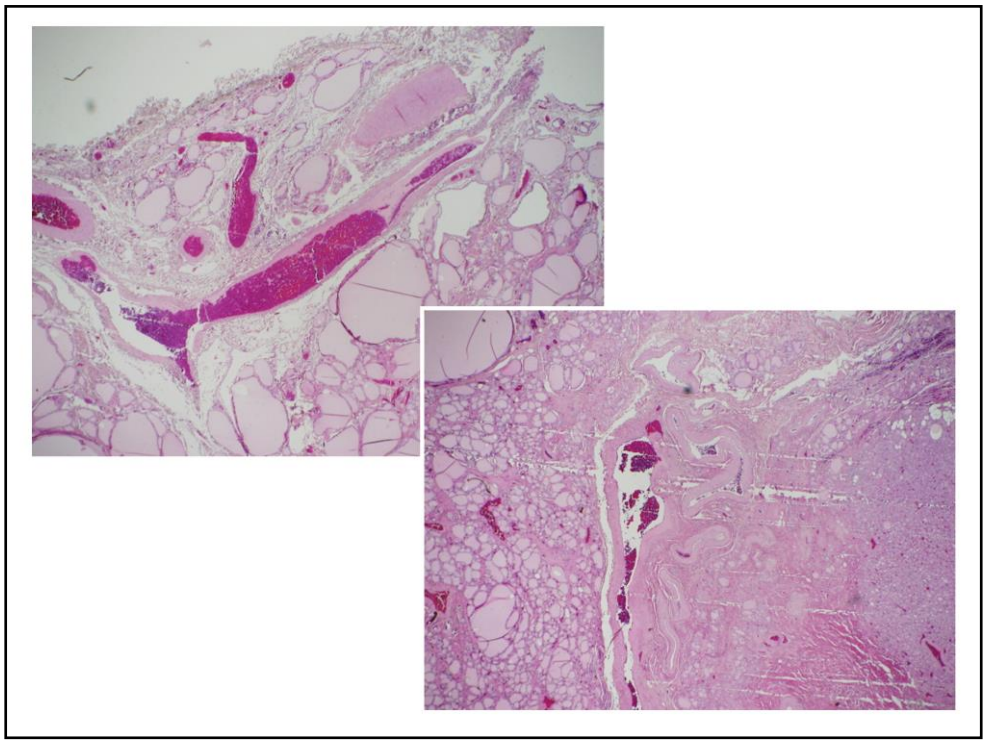
Thyroid tumours are often difficult to interpret.



Here's an example of adipose tissue found within the thyroid tissue. Purely the presence of papillary thyroid carcinoma in continuity with fat. I don't think you should use that as an unequivocal criterion for extrathyroidal extension.



This, I would consider a sizable perithyroidal vessel. You'll often see them draped around the outside of the thyroid and if one were to find tumour around that, I think that's reasonable evidence for extrathyroidal extension. However, again, you see these often.



These two thyroids both of which have, what I would consider as sizable vessels, sort of plunging down into the thyroid itself. So you have to be careful and I think it's a judgment call, and my inclination would be to be conservative about the interpretation.

Primary Tumor (pT)

___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pT1: Tumor size 2 cm or less, limited to thyroid
___ pT1a: Tumor 1 cm or less in greatest dimension limited to the thyroid
___ pT1b: Tumor more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid
___ pT2: Tumor more than 2 cm, but not more than 4 cm, limited to thyroid
___ pT3: Tumor more than 4 cm limited to thyroid or any tumor with minimal extrathyroid extension (eg, extension to sternothyroid muscle or perithyroidal soft tissues)
___ pT4a: Moderately advanced disease. Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve
___ pT4b: Very advanced disease. Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels

Note: There is no category of carcinoma in situ (pTis) relative to carcinomas of thyroid gland.

Undifferentiated (Anaplastic) Carcinoma

___ pT4a: Intrathyroidal undifferentiated (anaplastic) carcinoma
___ pT4b: Undifferentiated carcinoma (anaplastic) with gross extrathyroid extension

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Finally, we'll get onto the actual staging system itself.

This is the key tumour category. And as you can see, pT1 is 2 cm or less, divided into microtumours – and tumours that are between 1 cm and 2 cm. pT2 is between 2 and 4 cm or less. pT3 are more than 4 cm with minimal extrathyroid extension. pT4a and pT4b tumours are considered moderately advanced or very advanced, and those are tumours that show extensive extrathyroidal extension.

All anaplastic carcinomas are considered pT4, whether they are intrathyroidal or extrathyroidal.

Regional Lymph Nodes (pN)[#] (Notes M and N)

___ pNX: Regional lymph nodes cannot be assessed

___ pN0: No regional lymph node metastasis

___ pN1a: Metastasis to level VI (pretracheal, paratracheal and prelaryngeal/Delphian, perithyroidal) lymph nodes

___ pN1b: Metastasis to unilateral, bilateral or contralateral cervical (levels I, II, III, IV, V) or retropharyngeal or superior mediastinal lymph nodes (level VII)

Specify: Number examined: ___
Number involved: ___
Size (greatest dimension) of the largest metastatic focus in the lymph node: ____ (required only if applicable)

___ Lymph nodes with "psammoma bodies only"[##]

[#] *Superior mediastinal lymph nodes are considered regional lymph nodes (level VII). Midline nodes are considered ipsilateral nodes.*

[##] *As there are currently no guidelines for pN staging with psammoma bodies only, these cases are best classified as pNX.*

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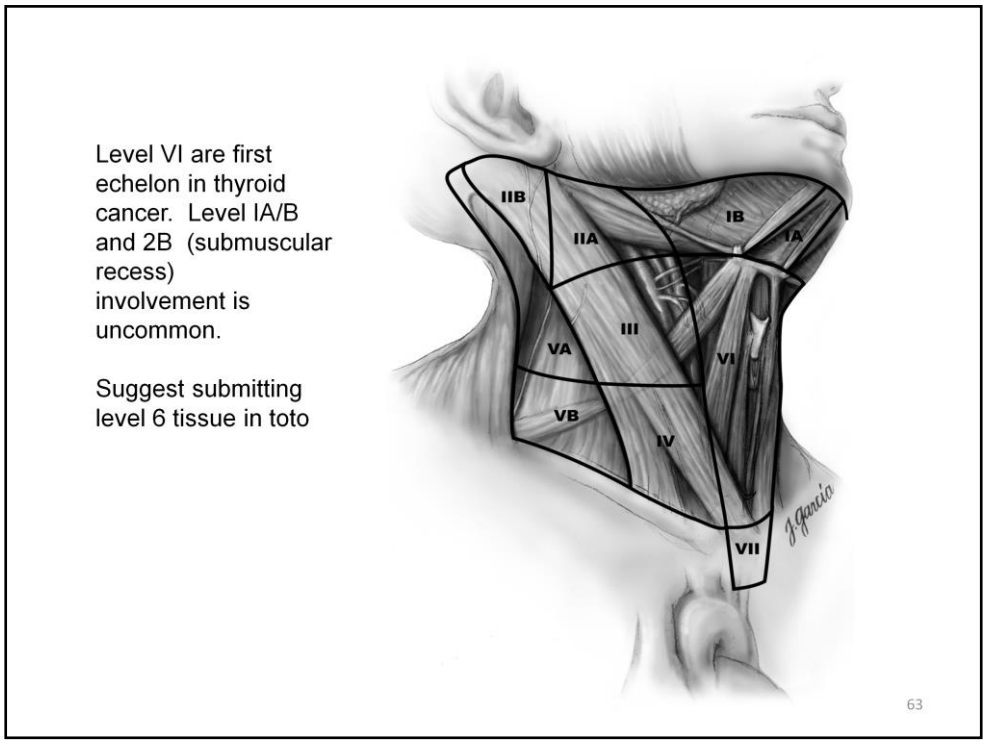
Regional lymph nodes are divided into lymph nodes positivity level VI, which is considered pT1a, and other lymph nodes, which is considered pT1b. And that would include the lateral lymph nodes in levels I through V, as well as retropharyngeal lymph nodes or superior mediastinal lymph nodes. So those are lymph nodes that are found below the suprasternal notch – would be level VII, and therefore pT1b. If one were able to definitively know that those were lymph nodes that were being sampled. You have to specify the number you've examined, the numbers that are involved, and the size of the largest metastatic focus.

Lymph nodes with "psammoma bodies only", that's an interesting topic because on occasion, you will have lymph nodes where you can just see a psammoma body in the subcapsular sinus. It's recommended in the protocol that you call those PNX, in that they have showed a capacity for lymphatic spread. But there is no evidence of actual tumour cells.



Just to briefly show the categories of the next section – Level VI as I said, is the first echelon in thyroid cancer. In my experience, it's very uncommon to have levels 1A or 1B – the submandibular node dissections – uncommon to see them involved. Level 2B, which is submuscular recess, again, very uncommon that that's involved, although that woman that I showed you with the diffuse sclerosing variant did have level 2B nodes that were positive.

I always put through Level VI *in toto*. I ask the pathology assistants to pick out any obvious nodes, and submit those separately, and then submit the remaining fat. You never know what you're going to find in them. You find little bits of thymic tissue. You find all kinds of odd inclusions of seromucinous (?) glands and sometimes thyroid tissue. They're interesting, if nothing else.

Notes on LN involvement

- In PTC:
  - Large nodal deposits and ENE confer increased risk of recurrence +/- death
  - Adverse prognostic factor in older patients
  - Micrometastases (< 2mm) does not confer increased risk of LRR
  - Psammoma bodies only? Mention in report, classify as pNX (indicates capacity for lymphatic spread)

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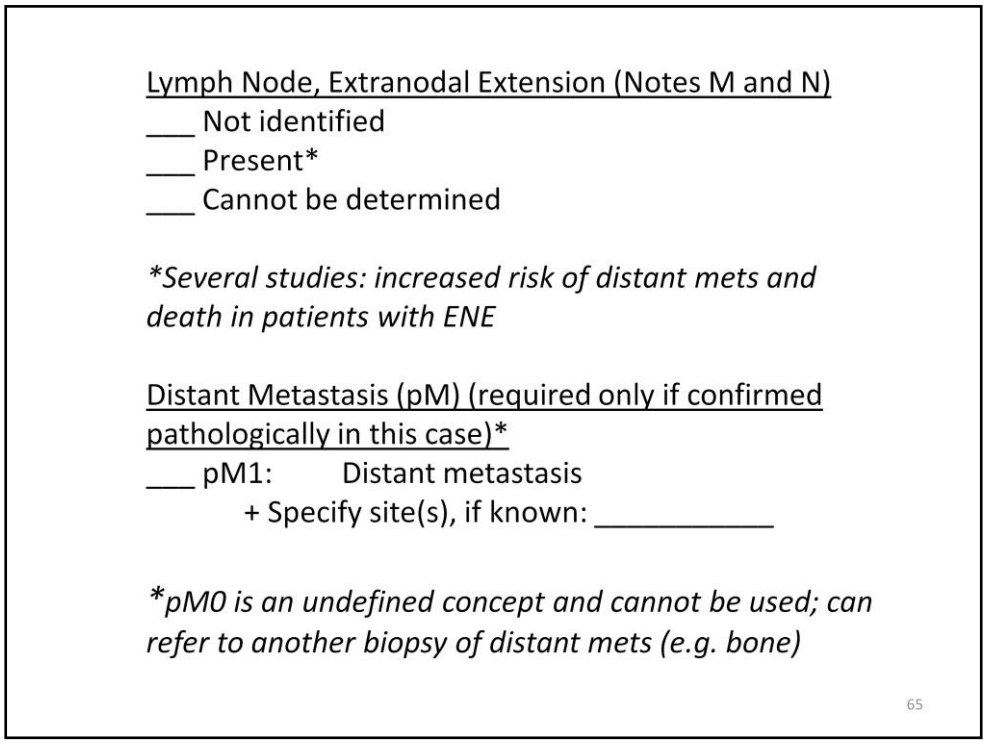
Just a few notes on lymph node involvement. With respect to papillary thyroid carcinoma – large nodal deposits and extranodal extension do confer an increased risk of recurrence and/or death. It's an adverse prognostic factor in older patients. But the parts of micrometastases that is defined by those of less than 2mm greatest dimensions does not confer increased risk of local regional recurrence.

For psammoma bodies only – they recommend to classify those as pNX.



Extranodal extension, if it involves lymph nodes, should be mentioned, as several studies have shown an increased risk of distant metastasis and death in patients with extranodal extension.

The pM category – pM0 is an undefined concept and cannot be used, so really all we can categorize, if we do state an M category, is pM1. And in order for pathologists to do that, you have to have a specimen with a metastatic tumour in it, so that might be bone, or lung, or something else.

Stage Groupings

Papillary or Follicular Carcinoma

Under 45 Years of Age	
Stage I	Any T Any N M0
Stage II	Any T Any N M1
45 Years or Older	
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
	T1 N1a M0
	T2 N1a M0
	T3 N1a M0
Stage IVA	T4a N0 M0
	T4a N1a M0
	T1 N1b M0
	T2 N1b M0
	T3 N1b M0
	T4a N1b M0
Stage IVB	T4b Any N M0
Stage IVC	Any T Any N M1

Large tumors, minimal ETE or any +ve central neck nodes = Stage 3

Moderately or severely advanced local disease or lateral (cervical nodes) or distant mets = Stage 4

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Stage groupings – papillary thyroid and follicular carcinoma are somewhat unique and have interesting staging systems in that patients under 45 years of age are only considered stage I or II, the distinction being the presence or absence of distant metastases.

For patients who are older than 45, you reach Stage III if you have a large tumour or a tumour with minimal extrathyroidal extension, so a T3 tumour, or if you have any positive central neck nodes, that equals Stage III.

Stage IV, is for either a primary tumour that is moderately or severely advanced, or if you have involved lateral lymph nodes, or if you have distant metastases.

Medullary Carcinoma (All Age Groups)

Stage I	T1 N0 M0
Stage II	T2 N0 M0
	T3 N0 M0
Stage III	T1 N1a M0
	T2 N1a M0
	T3 N1a M0
Stage IVA	T4a N0 M0
	T4a N1a M0
	T1 N1b M0
	T2 N1b M0
	T3 N1b M0
	T4a N1b M0
Stage IVB	T4b Any N M0
Stage IVC	Any T Any N M1

Same as PTC/FTC for those > 45 yrs

Undifferentiated (Anaplastic) Carcinoma

All anaplastic carcinomas are considered Stage IV

Stage IVA	T4a Any N M0
Stage IVB	T4b Any N M0
Stage IVC	Any T Any N M1

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For medullary thyroid carcinoma, it's the same staging as for papillary carcinoma or follicular carcinoma for patients who are older than 45. Undifferentiated carcinomas are all considered Stage IV, the distinction being the degree of extrathyroidal extension and the presence or absence of distant metastases.

+ Additional Pathologic Findings (select all that apply)

+ ___ Adenoma
+ ___ Adenomatoid nodule(s) or nodular follicular disease (eg, nodular hyperplasia, goitrous thyroid)
+ ___ Diffuse hyperplasia (Graves disease)
+ ___ Thyroiditis (specify type):_____
+ ___ Parathyroid gland(s):
    + ___ Not present
    + ___ Present (specify number and location):_____
        + ___ Within normal limits
        + ___ Hypercellular
        + ___ Other (specify): _____
+ ___ C-cell hyperplasia *
+ ___ None identified
+ ___ Other (specify): _____

- **Crucial not optional in cases of MTC, typically indicates inherited MTC and need for genetic testing for germline RET mutation*
- *I always comment on number and site of parathyroid glands*

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Additional pathological findings are as listed here. I tend to include additional pathological findings rather liberally. I always include the number of parathyroid glands that are present, and the sites that they were found. Sometimes these patients will have transient or maybe even permanent hypocalcaemia following the surgery, and I think it's useful for the surgeons to know whether or not they remove parathyroid glands. Sometimes you even find adenomas in parathyroid glands or parathyroid hyperplasia.

C-cell hyperplasia, is not, in my opinion, an optional category for patients who have medullary thyroid carcinoma – that typically indicates inherited MTC, and indicates need for genetic testing. In fact, probably anybody with medullary thyroid carcinoma should have genetic testing for germline RET mutation.

+ Ancillary Studies (Note Q)
+ Specify type (eg, histochemistry, immunohistochemistry, DNA analysis): _____
+ Specify results: _____

+ Clinical History (select all that apply)
+ ___ Radiation exposure:
    + ___ Yes (specify type): _____
    + ___ No
    + ___ Unknown
+ ___ Family history
+ ___ Other (specify): _____

+ Comment(s) **(always useful in my opinion!)**

- *Inclusion of ancillary test results may vary depending on test: e.g. beta catenin in CM variant PTC virtually diagnostic; I usually include ancillary studies somewhere in report*

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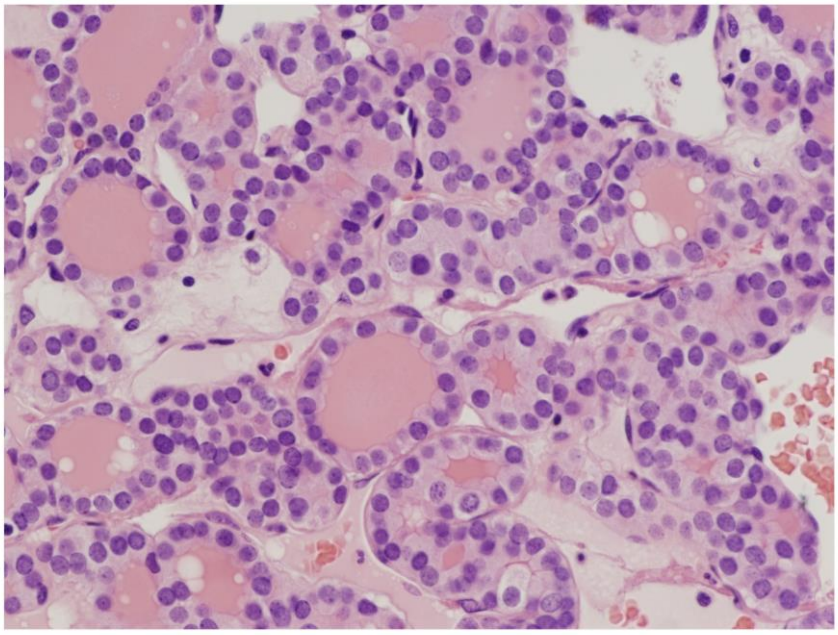
Other optional components are ancillary studies, and clinical history, and comments. I love comments, so I frequently include them.

Pathological fracture of femur –histopathology prior to TT



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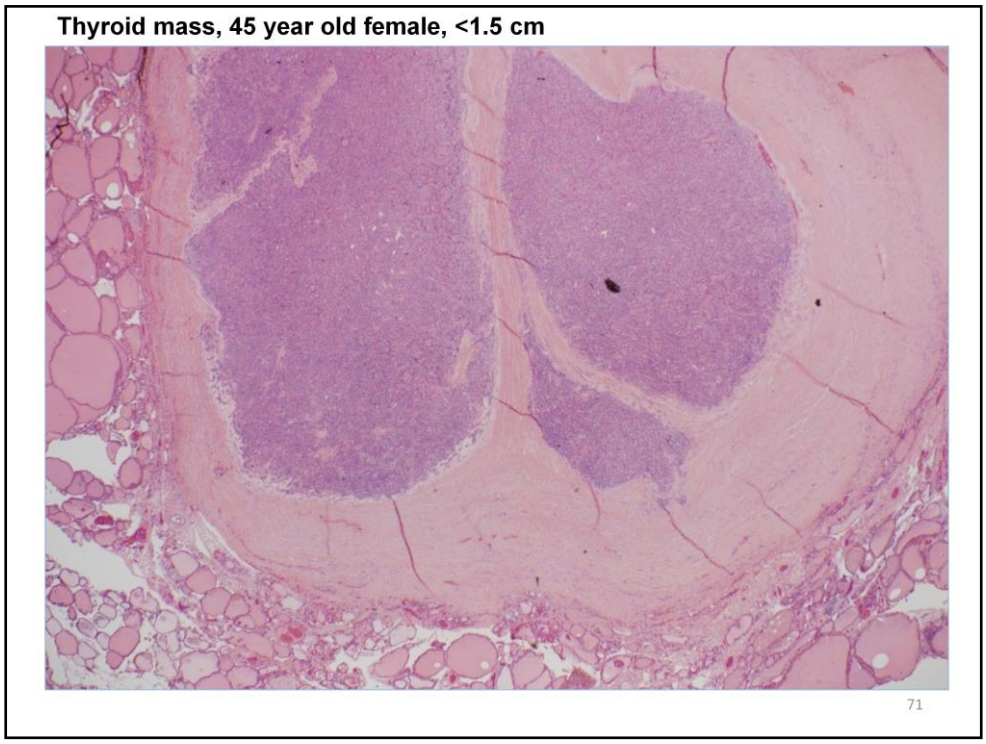
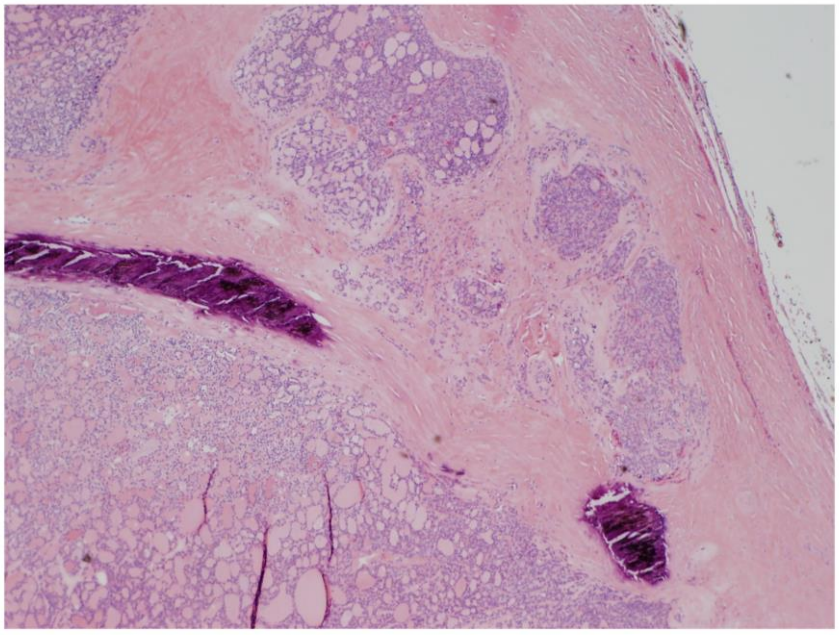
I thought as I'm finishing, I would throw in one interesting case to illustrate the pitfalls of thyroid pathology and how careful we must be when assessing these tumours.

This is a case of a 45 year old woman who was diagnosed with a pathological fracture of her femur, and you can see that it shows a thyroid cancer, and it doesn't seem to show any nuclear features of papillary carcinoma.

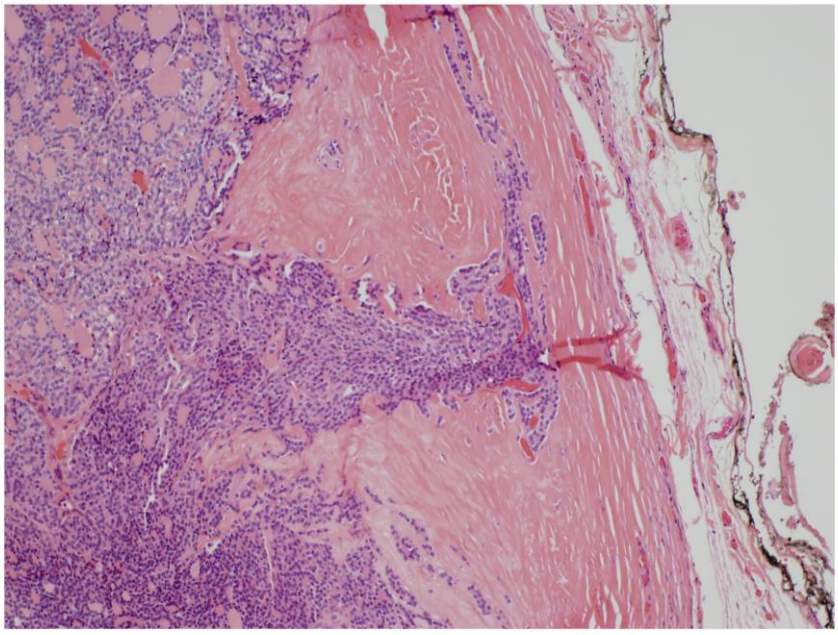


This is a thyroid tumour of an older patient that I found as I was going through the files for follicular carcinoma. And it was a completely encapsulated tumour. In fact, there was no complete capsular perforation identified, and there was no angioinvasion identified.

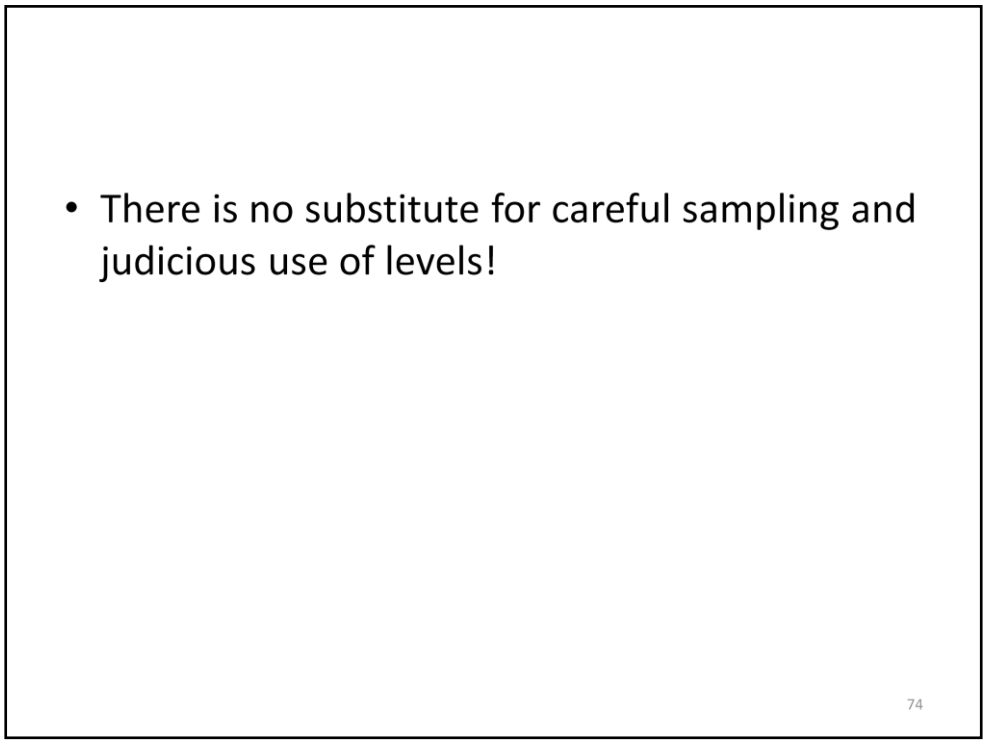
But this kind of tumour really worries me. From low power, you have an extremely thick capsule and an extremely cellular tumour with microfollicular pattern, and I think that even from low power, that's a very worrisome pattern. And it indicates that we need to really aggressively sample this specimen.



So this here, you can see tumour capsule - calcification of the capsule, but nothing going through.



Here, you have one of these anvil-shaped, invaginations. I suspect, is because of certain cases like this, why pathologists would actually diagnose follicular thyroid carcinoma without complete capsule perforation. But I think somewhere in this case, there must have been some angioinvasion.



I think when it comes to thyroid pathology, the rules should be that there's little substitute for careful sampling and judicious use of levels.

Summary of cancer case elements…

Required

- Procedure
- Lymph node sampling
- Focality
- Laterality
- Tumor size
- Histologic type & variant
- Margin status
- Angioinvasion
- Lymphatic invasion
- Extrathyroidal extension
- pTNM

Optional

- How received
- Specimen integrity
- Specimen size
- Specimen weight
- Perineural invasion
- Additional pathological findings
- Ancillary studies
- Clinical history
- Comments

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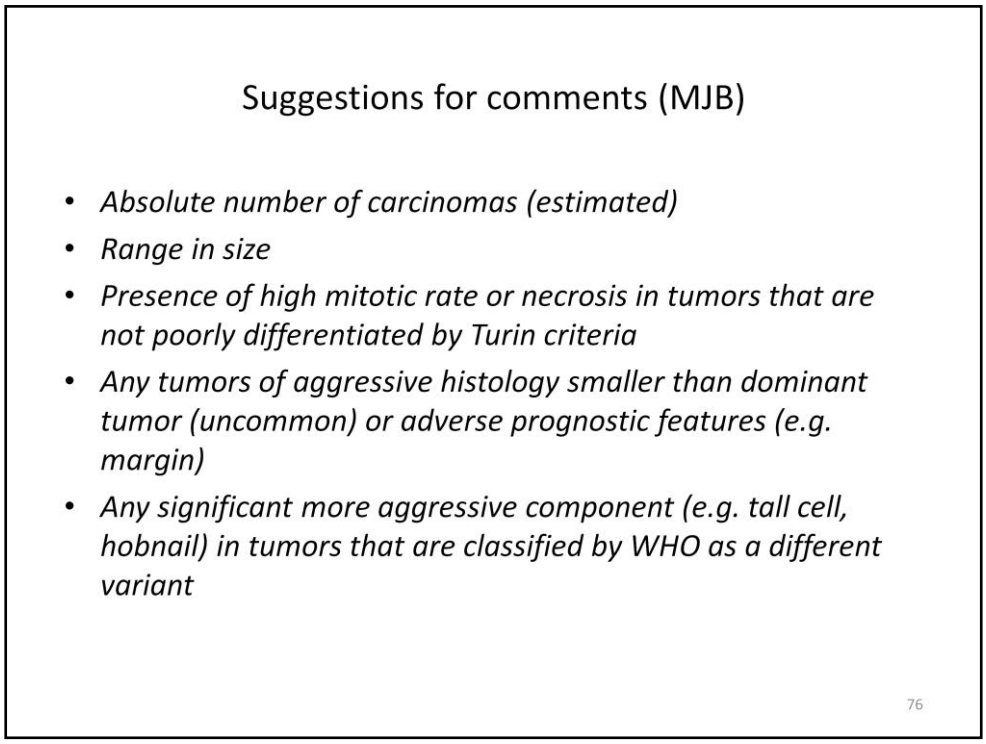
To summarize this cancer case summary:

The required elements are the procedure, the extensive lymph node sampling, tumour focality, tumour laterality, tumour size, histologic type and variant, margin status, angioinvasion, lymphatic invasion - a separate component - extra thyroidal extension, and the pTNM staging.

The optional include those gross elements that we would all typically include in our gross description, perineurial invasion, additional pathological findings, ancillary studies, clinical history, and comments.



Suggestions for comments - I just do this routinely in my cases:

- An absolute number of carcinomas estimated – sometimes, they're innumerable, and you can't give even an estimate;
- A range in size – if you have tumours that are not poorly differentiated;
- If they show mitotic activity – high mitotic rate or necrosis - it's important to mention;
- Any tumours that show aggressive histology that are smaller than the dominant tumour, which is usually uncommon, but does occur. Or those that have adverse prognostic features, so a smaller tumour for instance that is present at the margin, I would comment on that; and
- Any significant more aggressive component, like tall cell pattern, or hobnail pattern, or columnar pattern, in tumours that would be classified by WHO as a classical variant for instance - I would mention.

This is orphan Annie. Orphan Annie and her dog, who is called Sandy, both have orphan Annie eyes, meaning that they don't have any pupils or irises. I think it's quite a good name. But you could call them, in fact, Sandy nuclei, and that might even be a better, more accurate description for what they actually look like.

That's the end for me, and happy to answer any questions.

CCO staff: Thank you Dr. Bullock, we do actually have some questions that have already come in. So I'll just get started. What I'll do is just read them in the order that they have come in. The first comes from Dr. Bishara at Grand River Hospital, and the question is, "How do you interpret isolated psammoma body in a lymph node from patients with PTC?"

Dr. Bullock: Isolated psammoma bodies should be categorized as pNX. That's the recommendation of the CAP protocol. It's because, even though there are not viable tumour cells present, psammoma bodies are collections of necrotic tumour cells that have calcified, and so it does indicate that there is a potential for lymphatic spread and lymph node involvement.

CCO staff: The next question also comes from Dr. Bishara, and the question is, “Do you issue a synoptic report for a completion thyroidectomy with additional foci of cancer, even if there is a previous synoptic report for the first resection?”

Dr. Bullock: That’s a good question, and I don’t have a specific answer for it. But I would say that the most appropriate answer would be, yes. If you find additional foci of tumour, but that you would refer to the previous report. So if I were to find additional foci of cancer, I would report it in a synoptic fashion, but I would add a comment to the effect that the dominant tumour was found in the previously excised lobe and the stage of this tumour is *x,y,z*. I’ve asked myself that question, and I don’t know that I know the answer that CAP would give.

CCO staff: Thank you. The next comes from Amir from Brampton Civic Hospital, and the question is, “Some believe that encapsulated follicular lesions with papillary carcinoma nuclear features are papillary carcinoma, only if there’s desmoplasia, capsular, or tissue invasion. What are your thoughts on this?”

Dr. Bullock: No, I believe that encapsulated papillary thyroid carcinomas do exist, and they do not necessarily need to show capsular or vascular invasion in order to be called cancers, because in many cases to my mind, they show unequivocal nuclear and/or architectural features of papillary thyroid carcinoma. I think, however, that encapsulated follicular variant of papillary thyroid carcinomas that do not exhibit invasion will in the vast majority of circumstances behave in a non-aggressive manner. And there is some evidence developing that these patients may be better treated with lobectomy for instance, because they tend to have lesser incidences of multifocality than papillary carcinomas. That they can be treated with lobectomy adequately.

CCO staff: Great, the next question, we’re going back to Grand River Hospital. Dr. Bishara asks, “Have you ever seen psammoma bodies in benign thyroid, and how do you interpret benign cytology with psammoma bodies?”

Dr. Bullock: I think you have to draw distinction between what some people call pseudo-psammoma bodies, which are laminated calcifications that look very similar to psammoma bodies, well identical actually. But they’re found within follicles. So those are pseudo-psammoma bodies, and you do see those in some adenomas for instance, especially oncocydic ones. But true psammoma bodies are more often found in classical papillary carcinoma, where you get infarction and calcification on the tips of the papillae. And ultra-structurally, they contain necrotic tumour cells. I think that very rarely you see what could be considered a psammoma body that is not an intrafollicular

calcification of the colloid, that is a true psammoma body in benign tumours. But I think it's extremely rare, and I would be very, very cautious about that.

CCO staff: The next two question comes from the University of Alberta Hospital. The first part of the question asks, "BRAF – how often do you personally, or other pathologists from your group, order this test for your thyroid cancer reporting?"

Dr. Bullock: Not routinely. On occasion. We've talked about it. Although, it may in some circumstances alter the treatment, in speaking with our radiation oncologist and endocrinologist who treat patients with thyroid cancer, they're not pushing for it. And since we have no money, we haven't introduced it. I think it would be nice, in an ideal world, to do it more routinely and especially now as we have immunostains for BRAF, it may be more straightforward. But I think if you're going to do molecular testing on thyroid cancers, you need to do, or you need to have access to a comprehensive molecular testing panel. And just isolated BRAF testing, I'm not sure that that would be terribly clinically helpful.

CCO staff: Okay, you did touch on this a bit then. The second part of that question is, "How often do your clinicians use this result to change patient management?"

Dr. Bullock: They don't use it very often because we don't do it very often. I think in an ideal world, it would be nice to have access to a more comprehensive panel of molecular testing, and I think it would be relevant, especially in the classification of these tumours, and potentially the treatment. But unfortunately, in our institution, the circumstances don't allow routine BRAF testing on thyroid tumours.

CCO staff: The next question asks, "How often do level your non-visible remaining fat tissue and find more sub-centimeter sub-millimeter nodes? Can this be seen as a measure of quality of the level VI dissection by the surgeon, or how thorough is the lab at finding them?"

Dr. Bullock: So, as I said, I don't typically do levels on the Level VI nodes. As I said, when we get to the Level VI neck dissections, I ask the pathology assistants to dissect out any visible lymph nodes that they can find, and submit those. And then submit the remaining tissue. And I don't typically ask for levels. Unless I see something that I'm not happy about.

CCO staff: The next question comes in again from University of Alberta Hospital, which

asks, “PLIC - papillary lesion of indolent course - are you familiar with this term? Have you used it or advocated it?”

Dr. Bullock: Papillary lesions of indolent course? No. I guess that probably means papillary micro-tumours. So, small, I’m assuming that’s what that means, but I don’t know for sure. Small micro-carcinomas. No, I report tumours as papillary carcinomas when I see the nuclear features of papillary carcinoma. Very rarely there are tumours of papillary morphology that are not papillary carcinoma, in which case I’ll report them as whatever I consider them to be.

CCO staff: Great, thank you. This question is from Dr. Brooks from Cambridge Memorial Hospital, who asks, “If one node has metastatic cancer and the second node has only psammoma body, how many positive nodes are there?”

Dr. Bullock: One. I guess that would follow from calling nodes with psammoma body as pNX. I think in that circumstance, I would call it one. But probably if you did levels, you might find some viable tumour cells. I don’t think practically speaking it would make a difference. It wouldn’t change the stage.

CCO staff: Okay, given time, we have to put a close to the Question/Answer section. Thank you Dr. Bullock, and I’ll hand it back to Dr. Srigley to close us out.

Dr. Srigley: On behalf Cancer Care Ontario’s partnership and the Canadian Association of Pathologists, I want to thank Dr. Bullock for a truly comprehensive, informative, and very clear presentation today. Martin, you’ll be pleased to know that there was more than 90 lines open today, and I’m sure that it amounts to several hundred pathologists.

This is the third session of our 2015 series of CAP checklist presentation that we would welcome your comments and suggestions for ways to ensure that these sessions are informative and relevant to your practice. Please include your feedback and suggestions as part of the completed online evaluations. Once the WebEx recordings of this presentation becomes available, they’ll be made widely available via links through Cancer Care Ontario, the Canadian Partnership Against Cancer, and the Canadian Association of Pathologists. Access to this recording will be available for review at your convenience and is not restricted. As a reminder, both the live and recorded presentations are eligible for CME credits. Please see the session notice for more details and information. Please note that the CME certificates for each CAP checklist education session will only be issued for one month from the presentation date. The sessions will remain electronically available for an indeterminate period of time, but the CME

certificates will only be issued for one month. Please refer to the session notice for the exact deadline date. Now our next session is going to be on February 25th, and we're pleased to have Blake Gilks talk to us about the endometrium, ovarian, peritoneum and fallopian tube protocols. Look forward to seeing you then.