Medullary thyroid carcinoma

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WHO 2022

- Medullary thyroid carcinoma (MTC) is a malignant tumour derived from the calcitonin producing parafollicular C cells of the thyroid gland.

Epidemiology

- Rare disease: 2% of thyroid malignancies; 8% of thyroid cancer-related deaths.
- Sex: Slight female predominance

- Sporadic in 75% of cases, hereditary in 25%

- Age at presentation: Sporadic: mean45-55 yrs
  Hereditary: usually 10-30 yrs

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Hereditary medullary thyroid carcinoma (MTC)

- MEN 2A (1 in 2 millions): MTC, pheochromocytoma and/or parathyroid proliferations

- MEN 2B (1 in 38 millions): Aggressive MTC, pheochromocytoma, oral and intestinal ganglioneuromas, and a Marfanoid body habitus

- Isolated MTC: (formerly familial MTC)

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Hereditary medullary thyroid carcinoma (MTC)

- MEN2A with cutaneous lichen amyloidosis

- MEN2A with Hirschsprung's disease

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RET mutations and associated risk of aggressive medullary thyroid carcinoma (MTC), pheochromocytoma (PHEO) and hyperparathyroidism (HPT)

Very strong mutation

Weak mutation

Aggressive MTC risk	RET mutation (protein change)	PHEO risk	HPT risk
HIGHEST	Met918Thr	High	Low
HIGH	Ala883Phe	High	Low
	Cys634Ser/Arg/Gly/Tyr/Trp/Phe/Leu	High	High
MODERATE	Leu790Phe	Low	Low
	Ser891Ala	Low	Intermediate
	Val804Met/Leu	Low	Intermediate
	Asp631Tyr	High	Intermediate
	Cys630Arg/Tyr/Phe	Intermediate	Intermediate
	Cys620Phe/Arg/Ser/Gly/Tyr/Trp	Intermediate	Intermediate
	Cys618Phe/Arg/Ser/Gly/Tyr/Trp	Intermediate	Intermediate
	Cys611Phe/Gly/Ser/Tyr/Trp	Intermediate	Intermediate
	Cys609Phe/Gly/Arg/Ser/Tyr	Intermediate	Intermediate

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Clinical presentation

- Sporadic: Palpable thyroid mass. Nodal metastasis (50-70%). Distant metastasis (10-15%). Flushing, diarrhea, and/or weight loss.

- Hereditary: Most pts detected by genetic screening. Associated disease (pheochromocytoma or hyperparathyroidism.

  Flushing, diarrhea, and/or weight loss

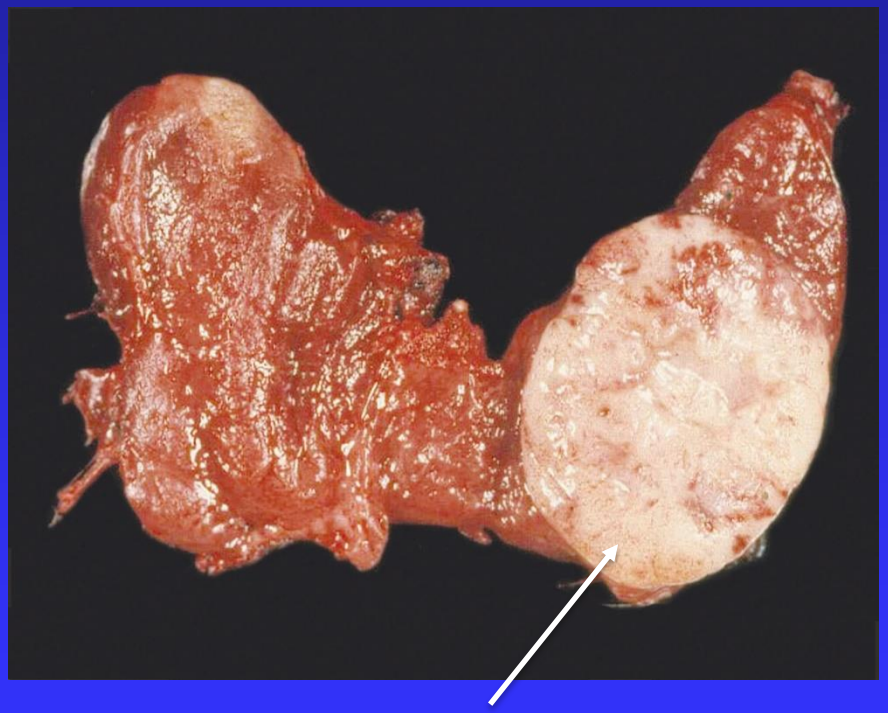
MACROSCOPIC

- Unilateral (sporadic), multicentric and bilateral (hereditary).

- Usually well defined but not encapsulated

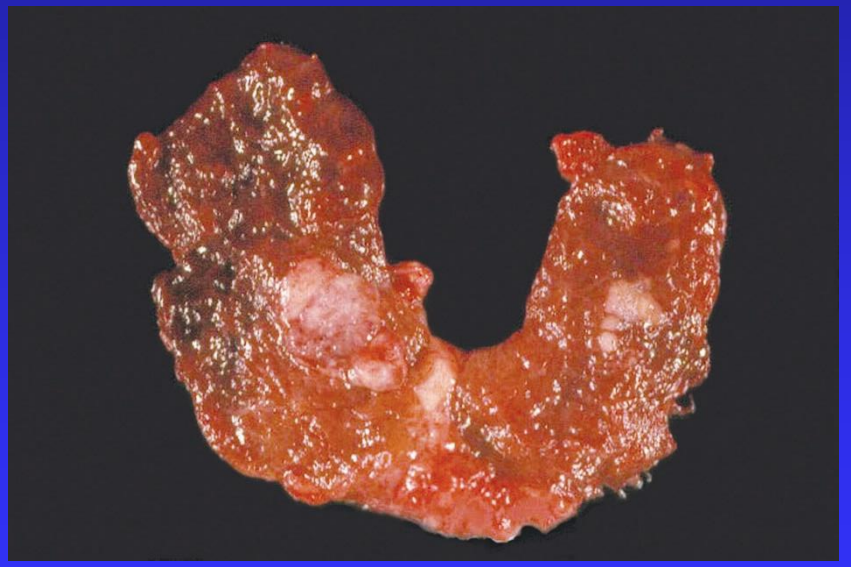
Macroscopy

Sporadic unilateral



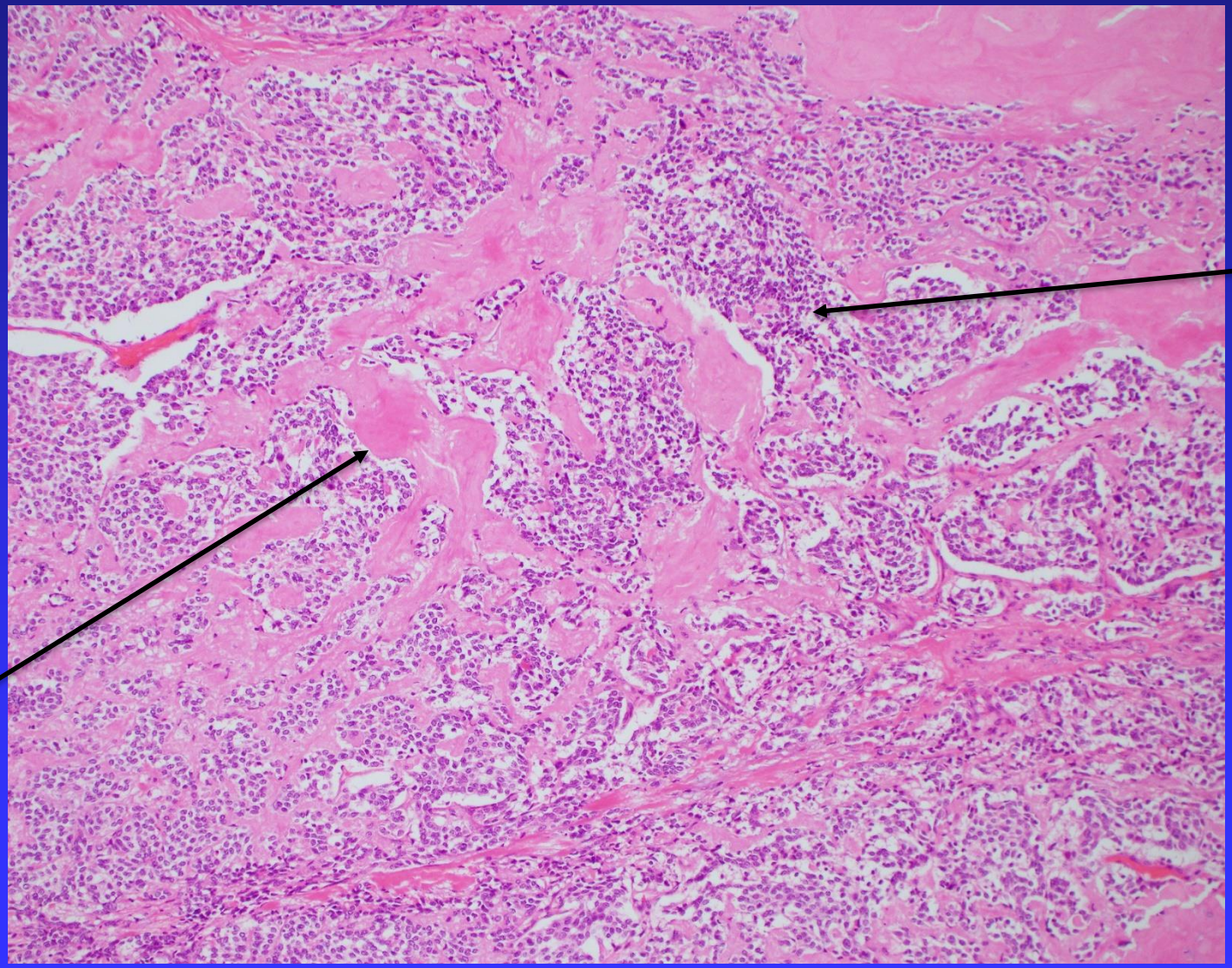
Well defined but not encapsulated

MEN2A bilateral



AFIP fascicle 4th series

Medullary classic



Solid nests

Fibrous septae with stromal amyloid

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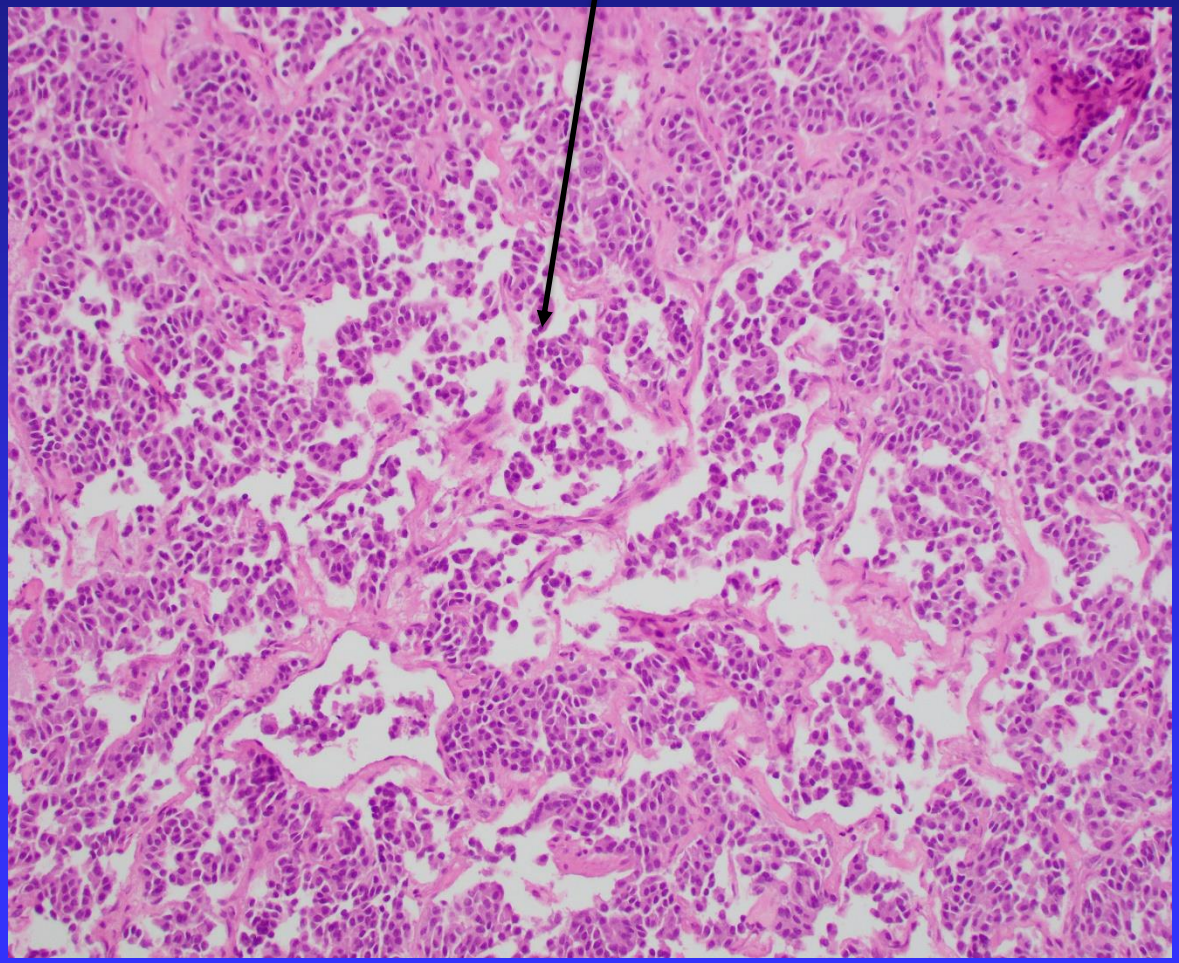
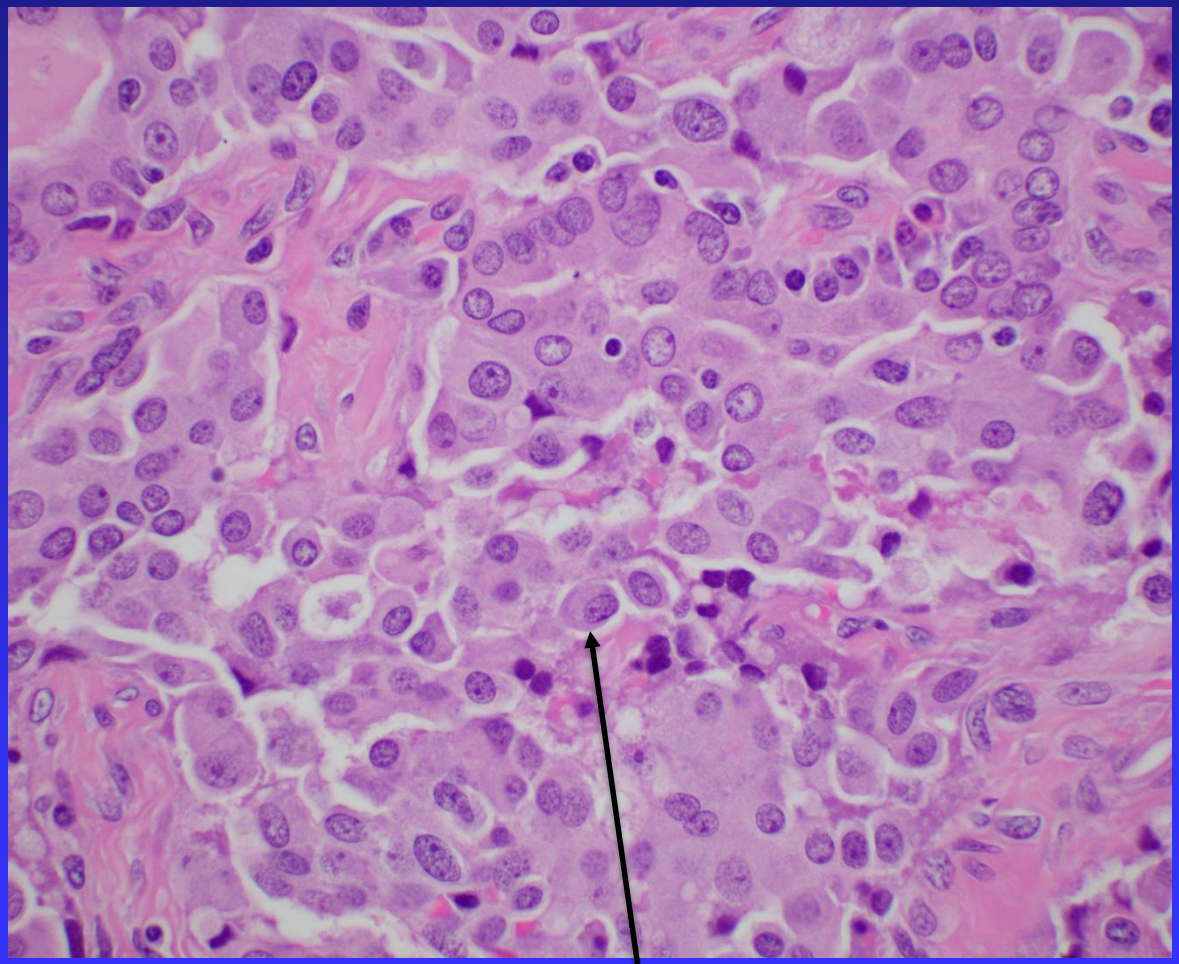
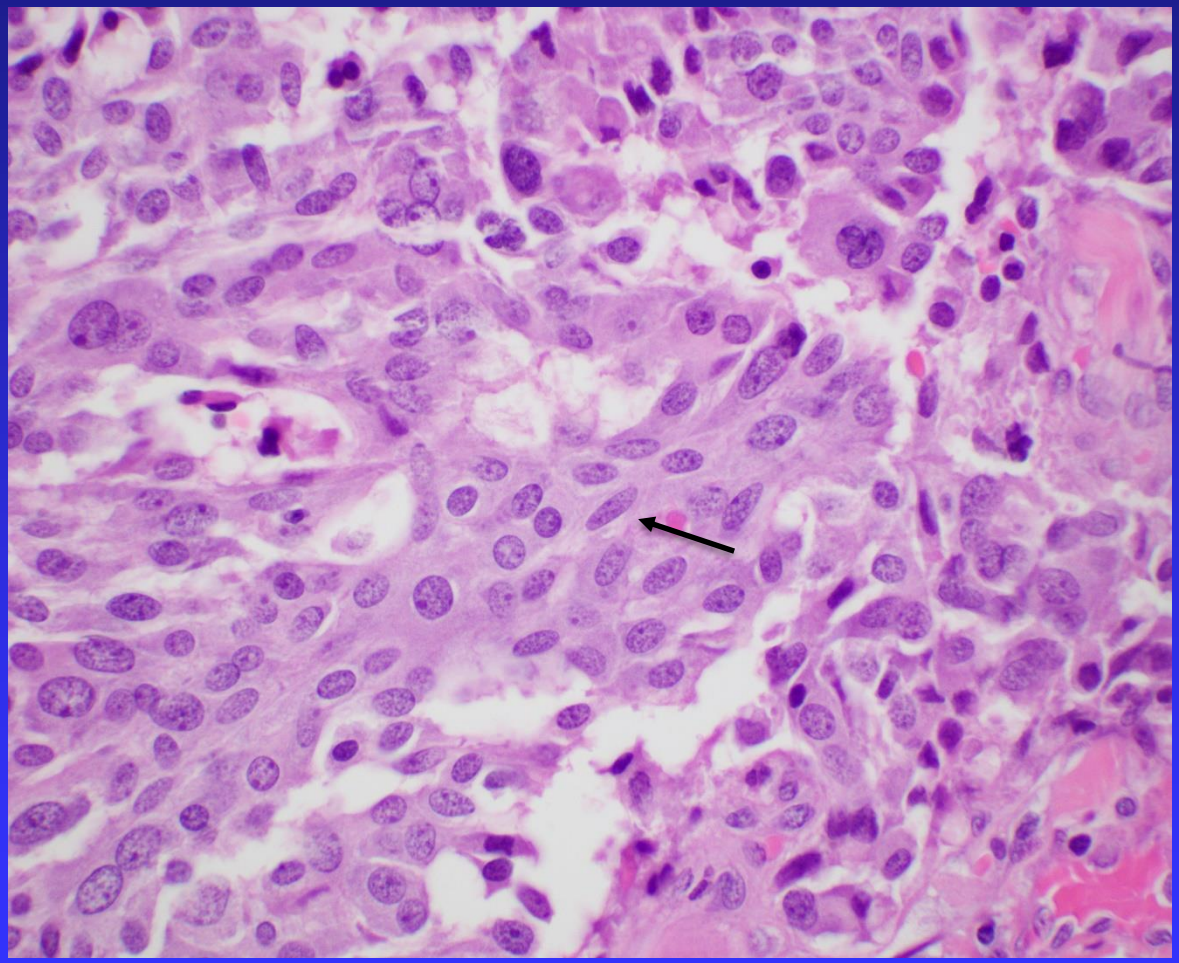
Discohesive cells



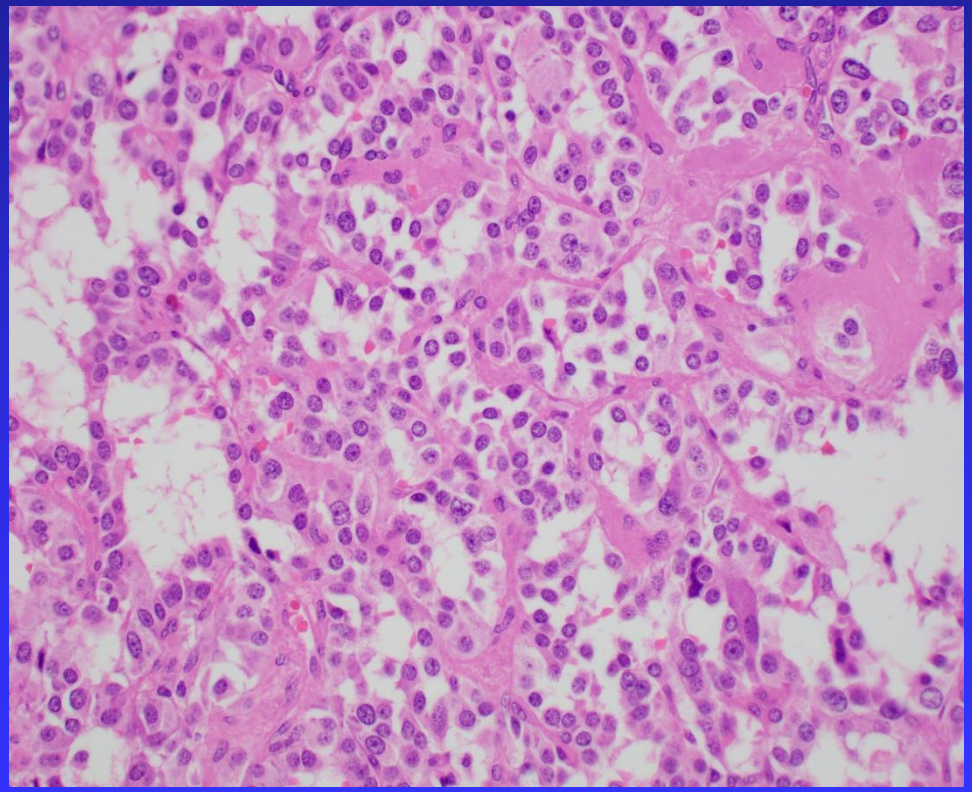
Epithelioid cells



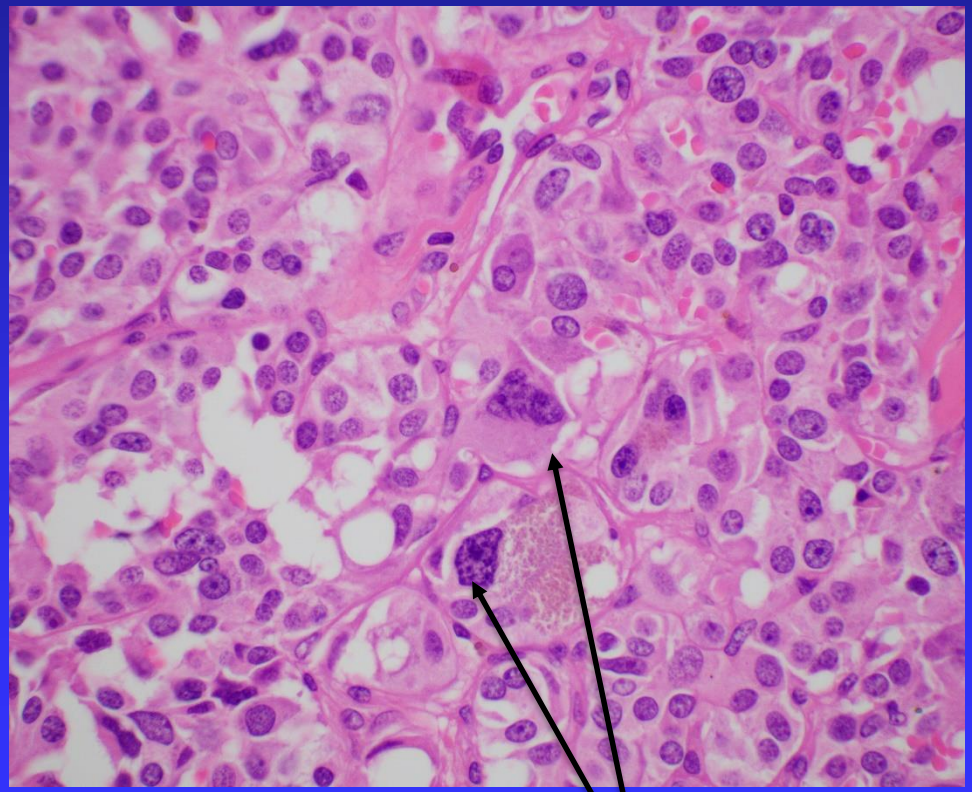
Spindle cells



Usually mild atypia and no mitosis

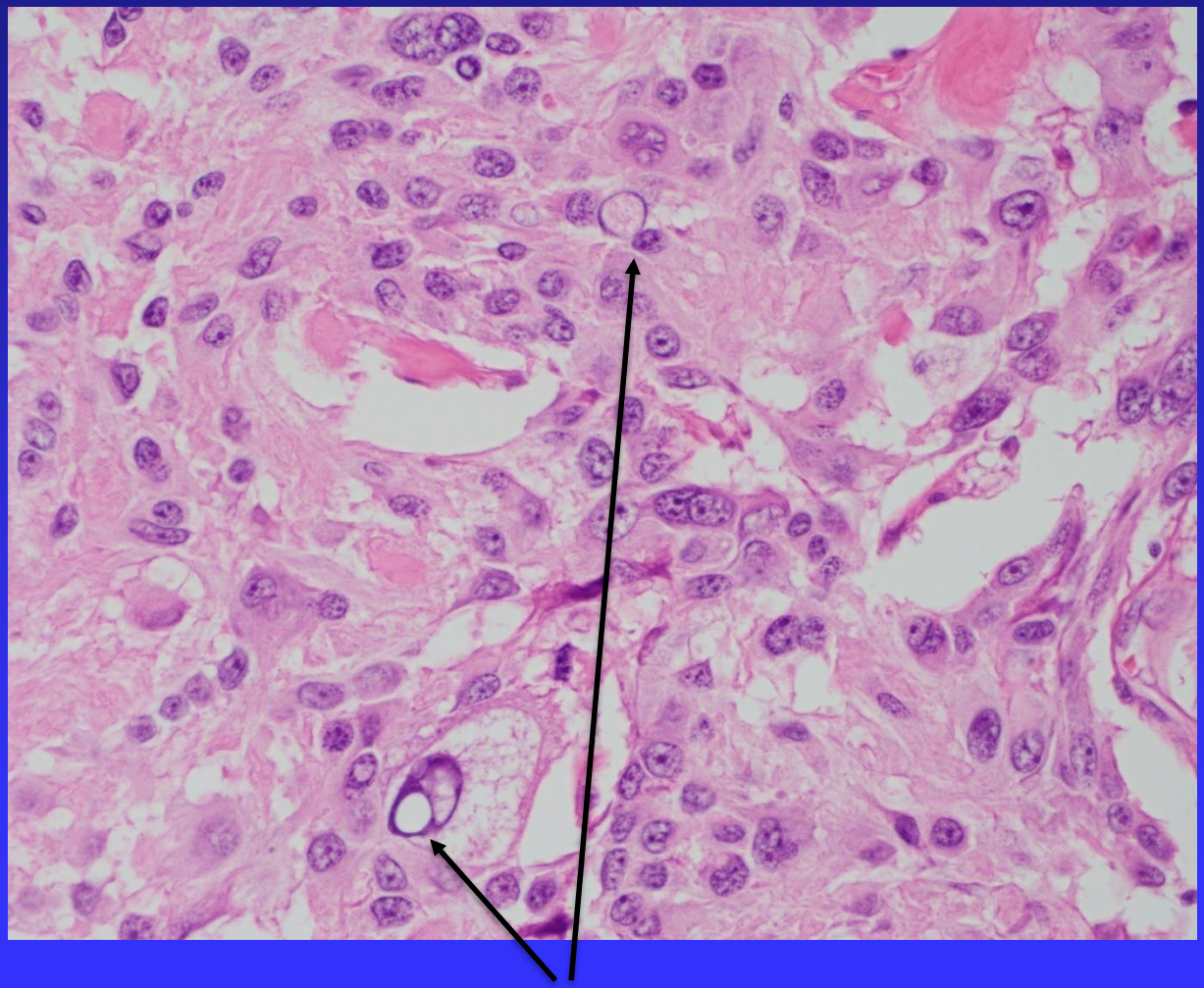


Marked atypia of no prognostic significance



Marked nuclear atypia

Marked nuclear atypia and pseudonuclear inclusions



Pseudonuclear inclusions

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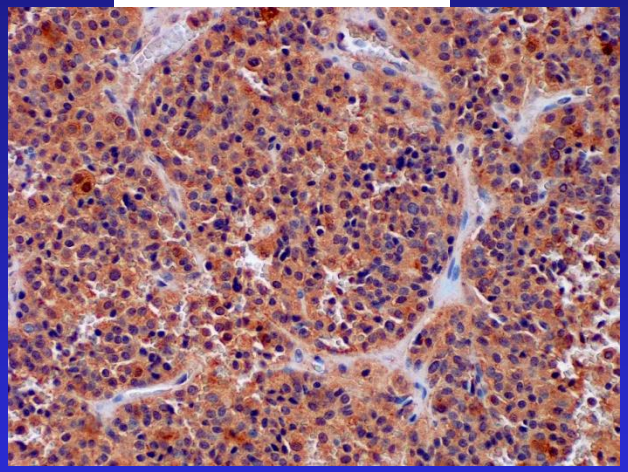
IMMUNOPROFILE

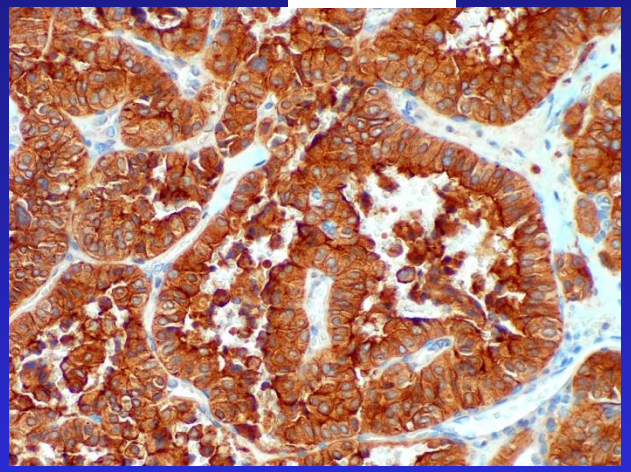
- Calcitonin: + (95% of cases)
- Chromogranin +, synaptophysin +, INSM-1 +
- CEA: +
- TTF-1: + (usually patchy)
- Monoclonal PAX8: negative
- Thyroglobulin: negative

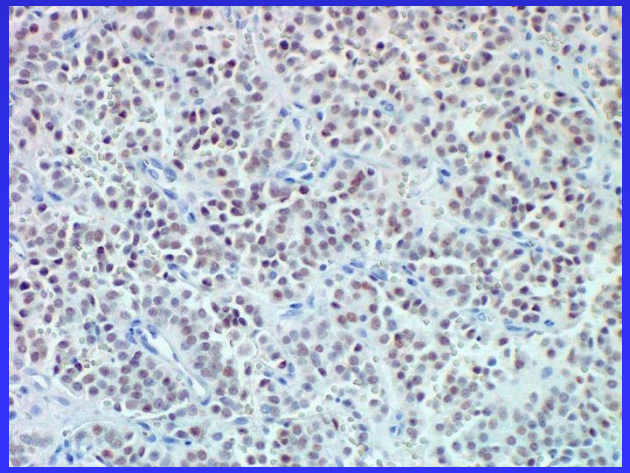
IMMUNOSTAINS

Calcitonin

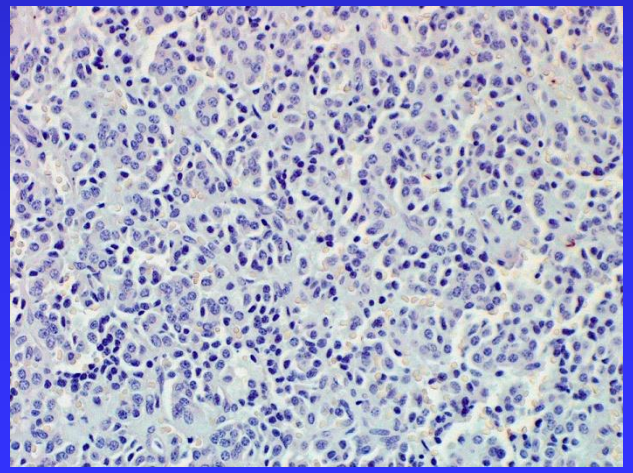


CEA





TTF-1 usually patchy

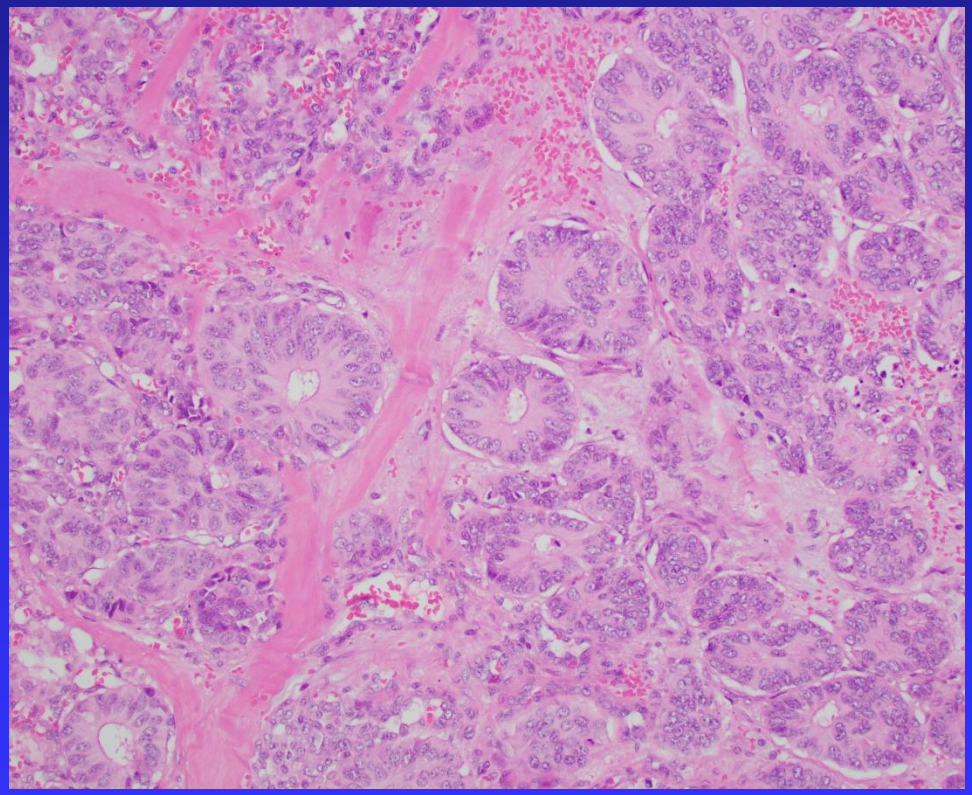


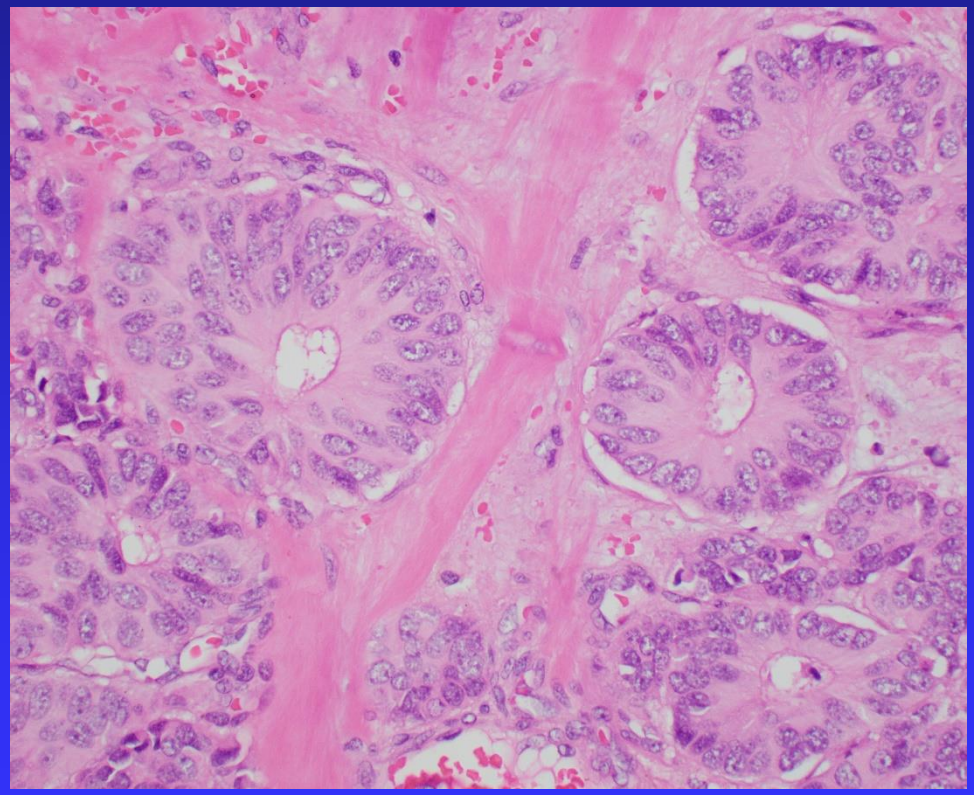
TGB

DIFFERENTIAL DIAGNOSIS
Medullary classic

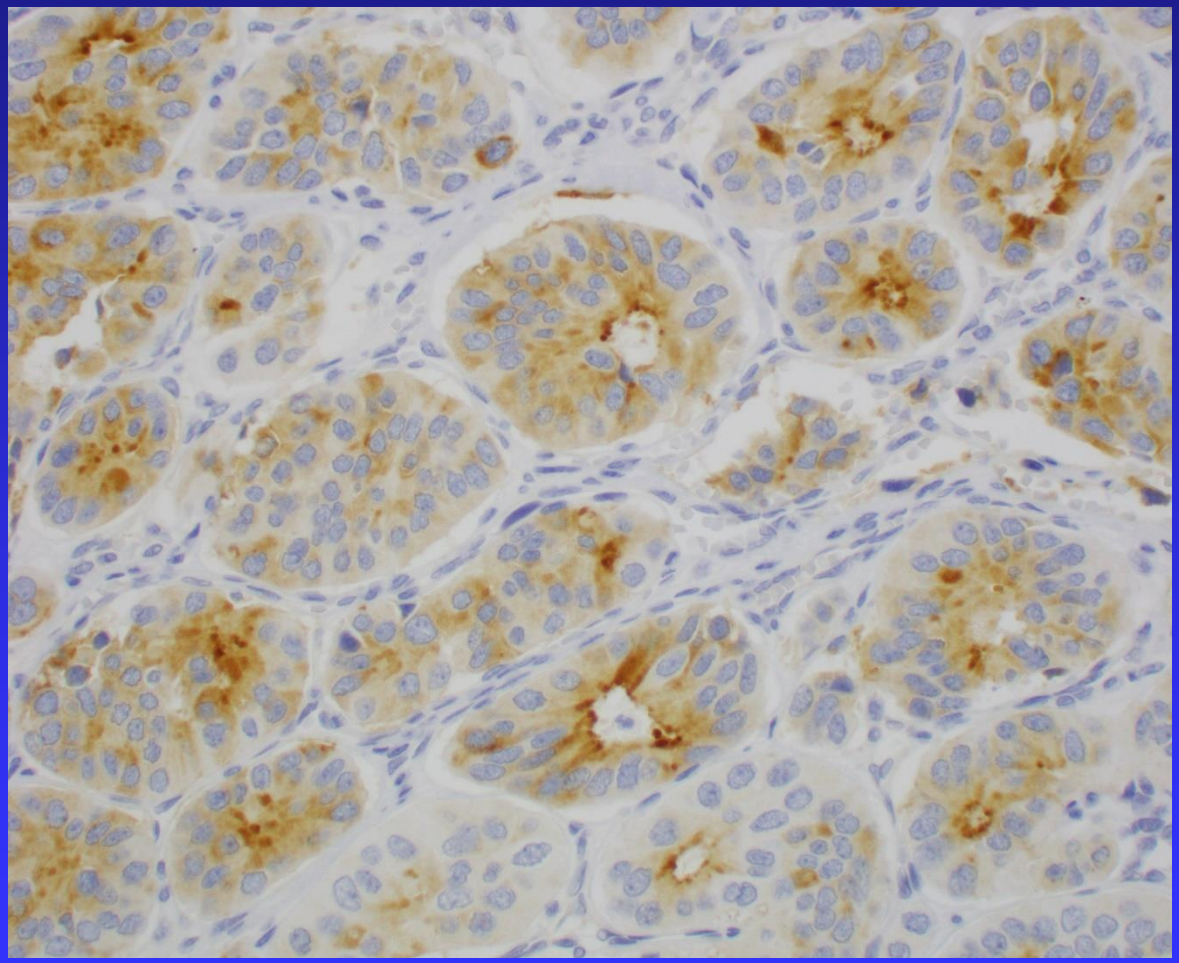
Entity in differential diagnosis	Overlapping feature with medullary classic	Differential features from medullary classic
Solid variant of papillary carcinoma	Solid nests	-Immunoprofile (TGB+, Calcitonin neg) -Papillary carcinoma nuclei
Poorly differentiated thyroid carcinoma	Solid nests	-Immunoprofile (TGB+, Calcitonin neg)
Hyalinizing trabecular tumor	Solid/trabecular growth Hyalinization mimicking amyloid	-Immunoprofile (TGB+, Calcitonin neg) -Papillary carcinoma nuclei
Solid cell nests	Solid growth Rare calcitonin + cells	-P63 +, TTF-1 neg -Stellate shape

Medullary carcinoma, follicular pattern

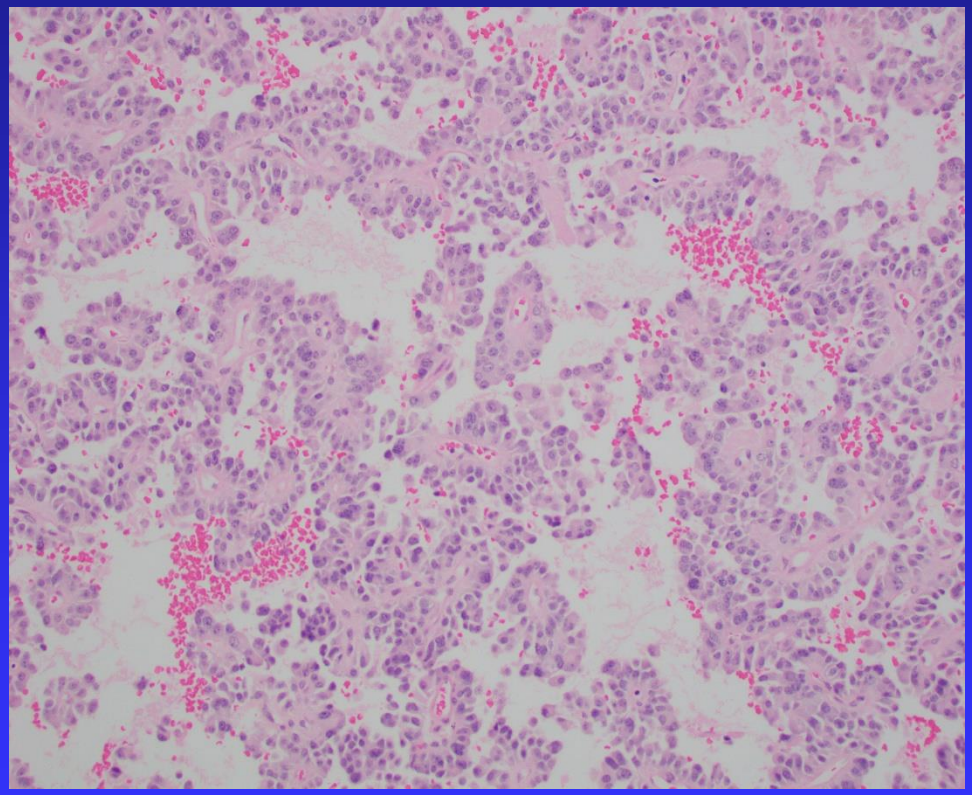


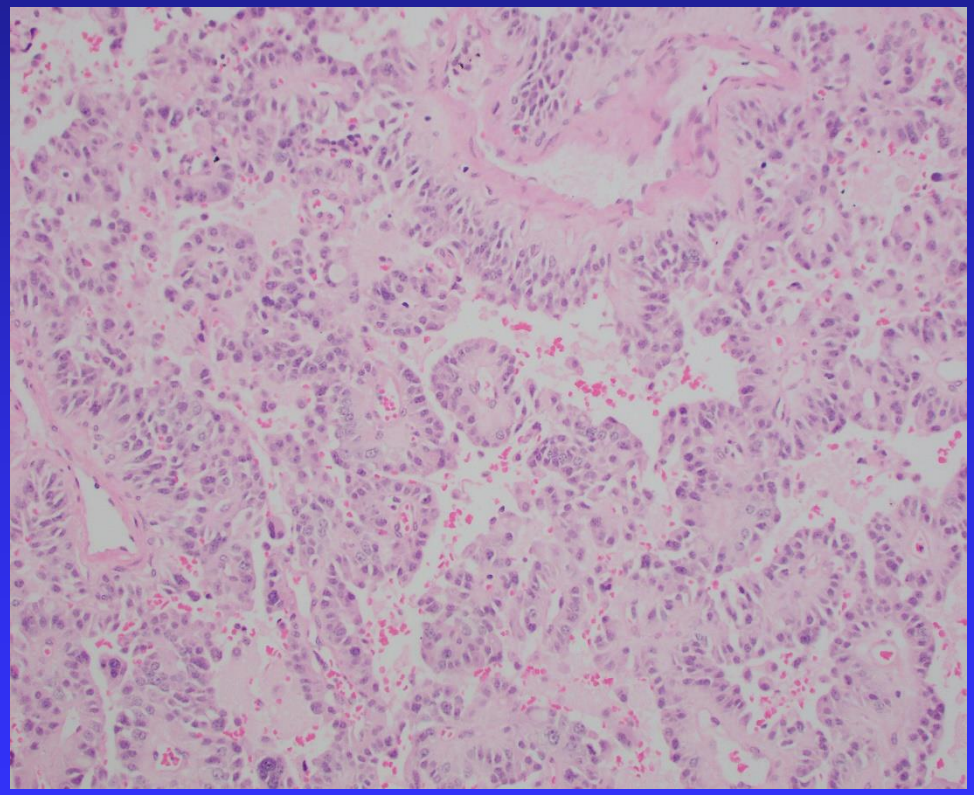


Medullary carcinoma, follicular pattern (Calcitonin)



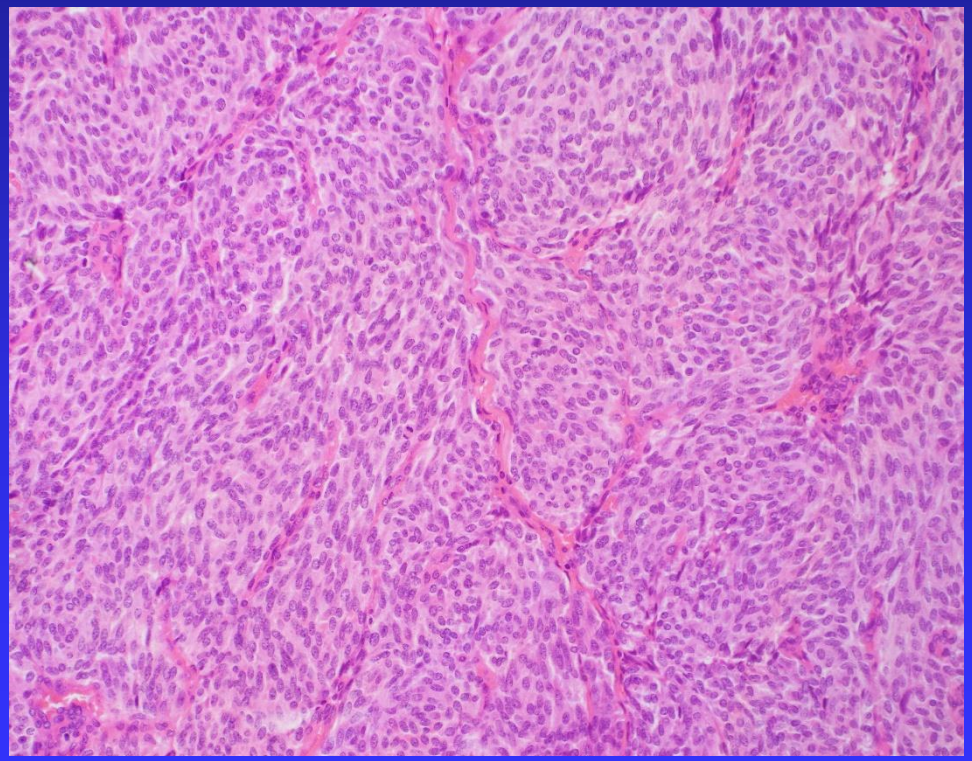
Medullary carcinoma, papillary pattern



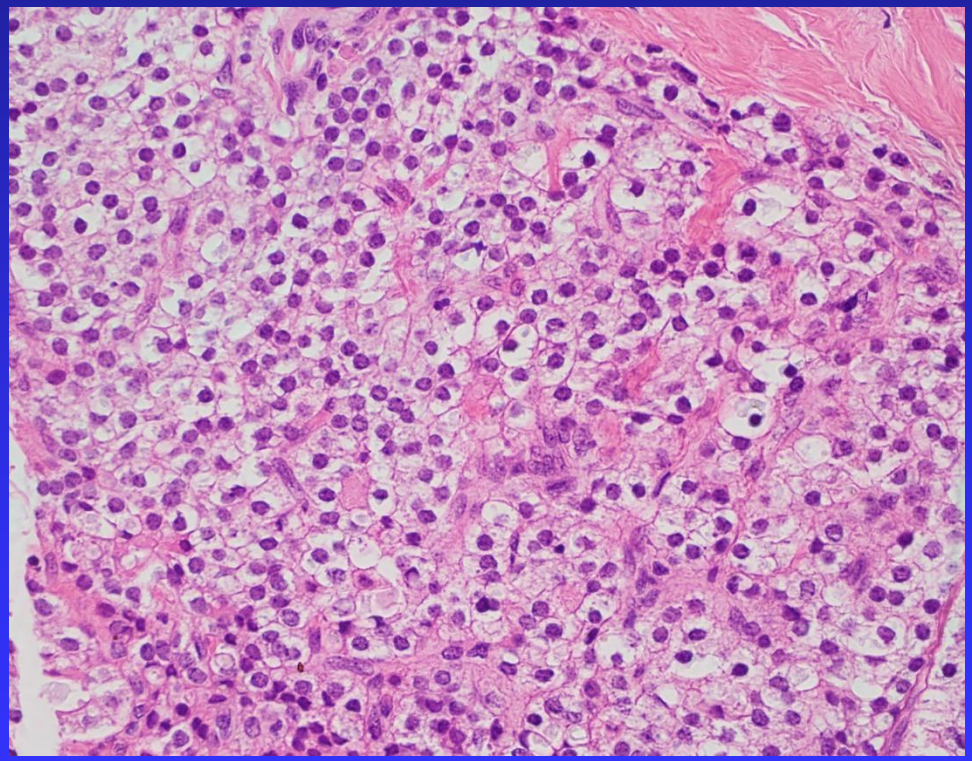


Medullary carcinoma patterns

Spindle cell pattern



Clear cell pattern



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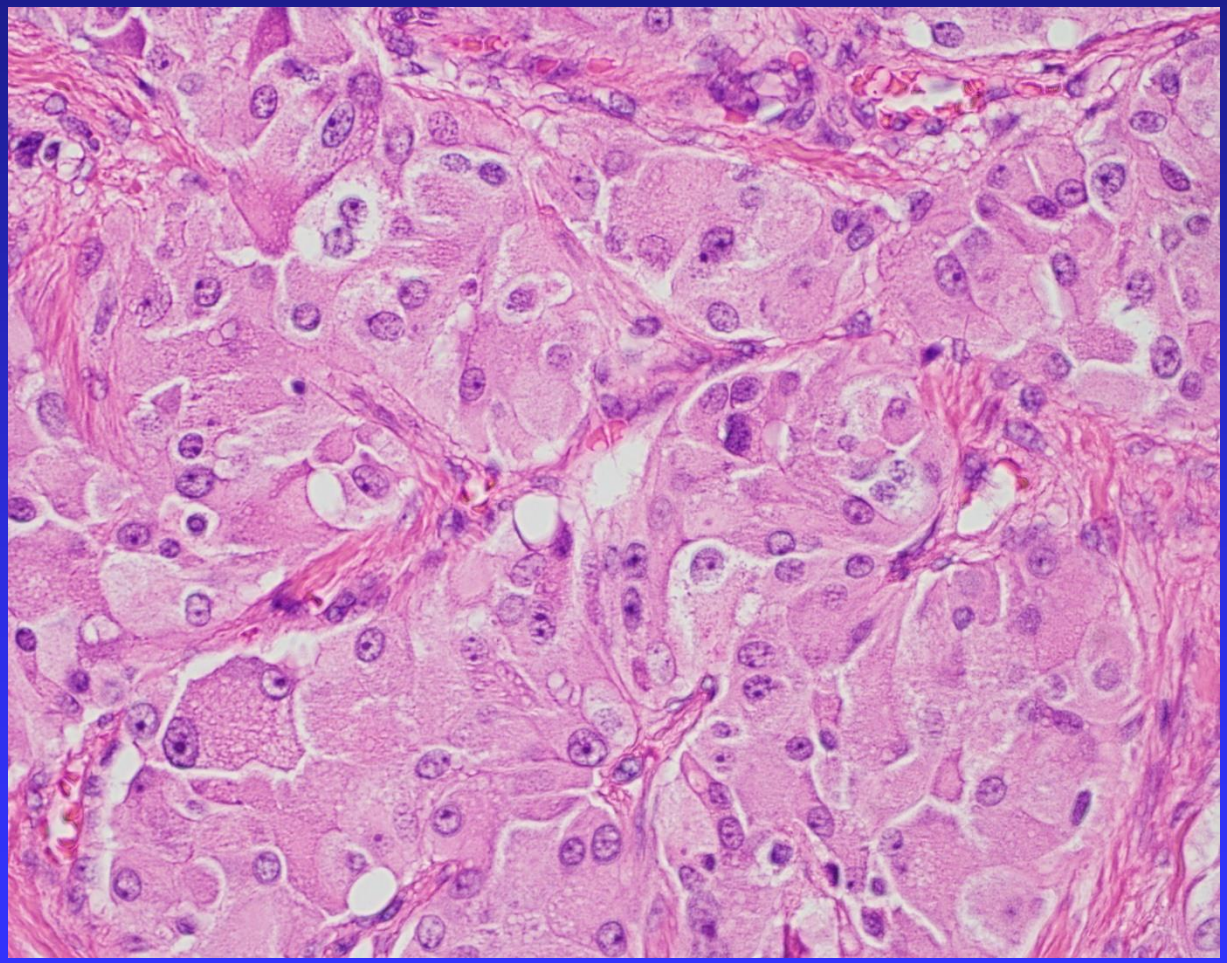
Medullary carcinoma, oncocytic pattern



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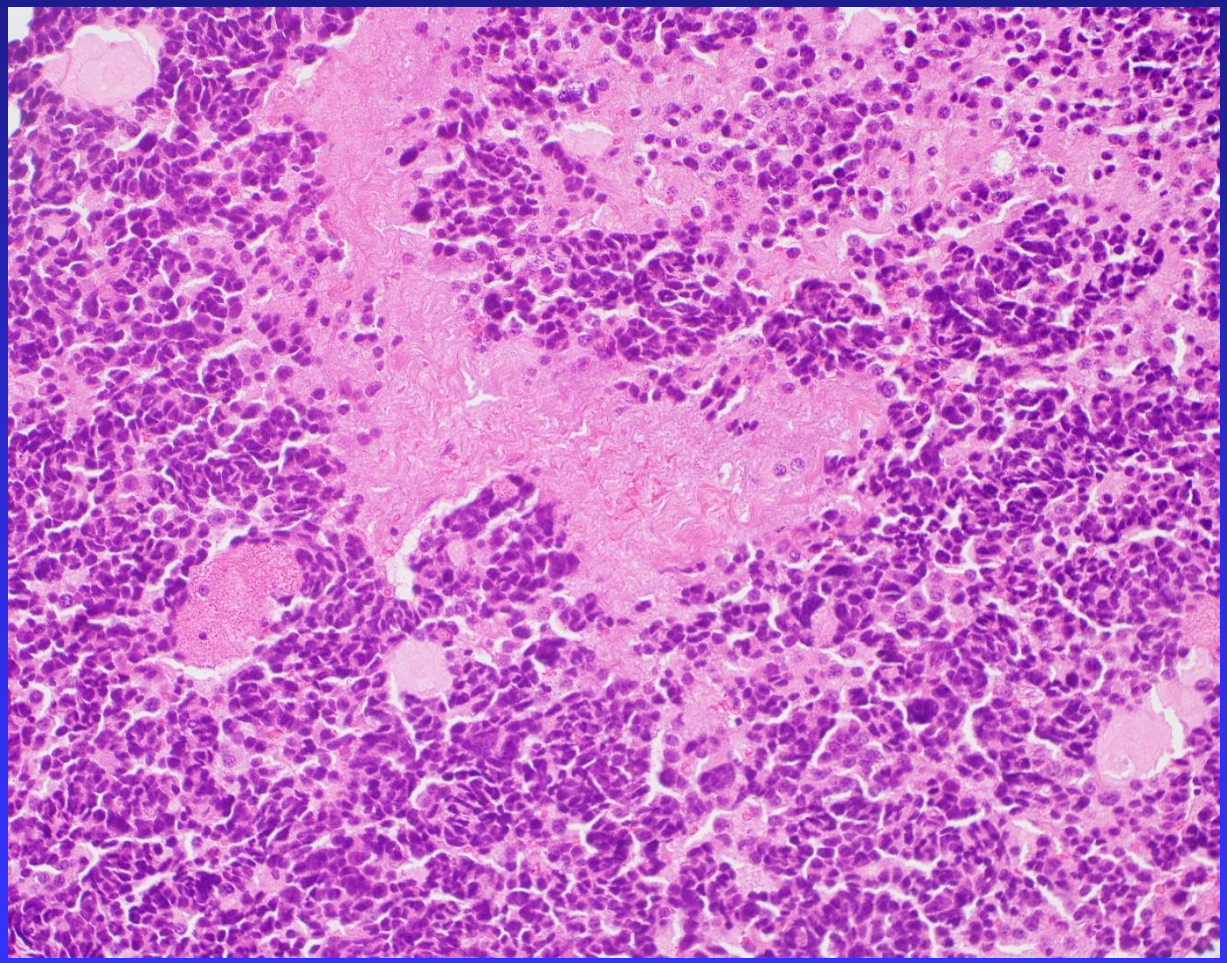
Medullary carcinoma, “small cell” pattern



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DIFFERENTIAL DIAGNOSIS
Medullary patterns

Medullary specific pattern	Entity in differential diagnosis	Overlapping feature with medullary pattern	Differential features from medullary pattern
-Follicular	Follicular variant of papillary carcinoma	Follicles	-Immunoprofile (TGB+, Calcitonin neg)
-Papillary	Papillary thyroid carcinoma (PTC), classic	Papillae	-Immunoprofile (TGB+, Calcitonin neg)
-Spindle cell	Papillary carcinoma with spindle cell metaplasia -Anaplastic ca	Spindle cells	-Immunoprofile (TGB+, Calcitonin neg)
-Clear cell	-PTC with clear cells -Renal cell ca	Clear cells	-Immunoprofile (TGB+, Calcitonin neg)

DIFFERENTIAL DIAGNOSIS
Medullary patterns

Medullary specific pattern	Entity in differential diagnosis	Overlapping feature with medullary pattern	Differential features from medullary pattern
-Oncocytic	Oncocytic (Hurthle cell) carcinoma	Oncocytes	-Immunoprofile (TGB+, Calcitonin neg)
-Small cell	-Metastatic neuroendocrine ca	-Immunoprofile -small cell	-presence of multiple nodules, interstitial interfollicular pattern of growth, extensive vascular invasion extra-thyroid primary
	-Ewing Family tumors	-Small cells	-*EWSR1::FLI1*

Molecular profile of sporadic medullary carcinoma

- RET mutation in 50% of cases (RET 918 comprises 80% of RET mutations)
- RAS mutation in 20-35% (H-RAS most common)
- Rare RET and ALK fusions

Medullary thyroid carcinoma grading

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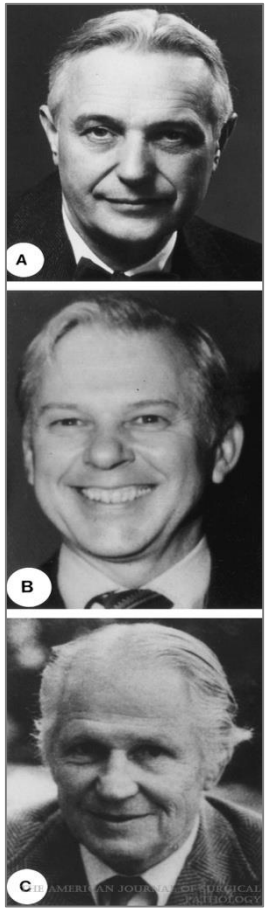
Definite histologic description of medullary thyroid carcinoma (1959)

JB. Hazard

WA. Hawk

GC. Crile



MEDULLARY (SOLID) CARCINOMA OF THE THYROID—A CLINICOPATHOLOGIC ENTITY*

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Prognostic factors of medullary thyroid carcinoma

- Clinical and molecular characteristics (age, sex, TNM stage, serum CEA/calcitonin, type of RET mutation, sporadic versus hereditary disease, distant metastasis, nodal metastatic burden, response to initial therapy, and extent of thyroidectomy.)
- **But no grading system**
- Pulmonary and pancreatic neuroendocrine neoplasms have well accepted and validated histologic grading systems

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MODERN PATHOLOGY

Article | Published: 20 April 2020

Grading of medullary thyroid carcinoma on the basis of tumor necrosis and high mitotic rate is an independent predictor of poor outcome

Bayan Alzumaili, Bin Xu, Philip M. Spanheimer, R. Michael Tuttle, Eric Sherman, Nora Katabi, Snjezana Dogan, Ian Ganly, Brian R. Untch ✉ & Ronald A. Ghossein ✉

Modern Pathology **33**, 1690–1701 (2020) | Cite this article

A Proposed Grading Scheme for Medullary Thyroid Carcinoma Based on Proliferative Activity (Ki-67 and Mitotic Count) and Coagulative Necrosis

Fuchs, Talia L. MD[*,+,++]; Nassour, Anthony J. MBBS[S]; Glover, Anthony PhD, FRACS[++,S]; Sywak, Mark S. MMedSci FRACS[++,S]; Sidhu, Stan B. PhD, FRACS[++,S]; Delbridge, Leigh W. MD, FRACS[++,S]; Clifton-Bligh, Roderick J. PhD, FRACP[++,//]; Gild, Matti L. PhD, FRACP[++,//]; Tsang, Venessa PhD, FRACP[++,//]; Robinson, Bruce G. MD, FRACP[++,//]; Clarkson, Adele BSc[*,+]; Sheen, Amy BSc[*,+]; Sioson, Loretta BSc[*,+]; Chou, Angela PhD, FRCPA[*,+,++]; Gill, Anthony J. MD, FRCPA[*,+,++]

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Keywords: medullary thyroid carcinoma, Ki-67 proliferative index, mitotic count, coagulative necrosis, grading system

Memorial Sloan Kettering Cancer Center (MSKCC) system – a two-tiered approach

Low grade: Mitotic index <5 per 2 mm² and no tumor necrosis

High grade:Mitotic index ≥ 5 per 2 mm² and/or tumor necrosis

Sydney system – a three-tiered approach

Mitotic Count/2 mm²	Ki-67 Proliferative Index (%)	Coagulative Necrosis	Grade
<3	<3	Absent	Low
<3	<3	Present	**Intermediate**
3-20	3-20	Absent	**Intermediate**
3-20	3-20	Present	High
>20	>20	Present or absent	High

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Correlation between clinicopathologic variables and outcomes (univariate analysis) (Memorial data 144 pts)

Significant histologic parameters:
-Mitosis/necrosis
-pleomorphic nuclei
-Encapsulation
-vascular invasion
-Extrathyroid extension
-margin
-node size

Characteristics (values p values)	DSS	LRFS	DMFS
Age	0.742	0.227	0.641
Sex	0.008	0.050	0.018
Tumor size	0.001	0.042	0.013
Mitotic index (cut off 2 and10/10 HPFs) [a]	0.025	0.029	<0.001
Mitotic index (cut off 5/10 HPFs) [b]	<0.001	0.004	0.001
Atypical mitosis	0.431	0.441	0.435
Tumor necrosis	<0.001	<0.001	<0.001
Nuclear pleomorphism	<0.001	0.049	0.072
Amyloid	0.611	0.972	0.538
Fibrosis	0.501	0.060	0.269
Infiltration	0.201	0.033	0.331
Encapsulation	0.614	0.010	0.704
Lymphovascular invasion (LVI)	0.041	0.090	0.408
Extent of VI	0.526	0.609	0.009
Extrathyroidal VI	0.145	0.287	0.188
Extrathyroidal extension	0.013	0.165	<0.001
Margin	0.013	0.623	0.051
Separate focus of MTC	0.679	0.539	0.689
Nodal status (N0 vs. N1)	0.060	0.005	0.011
Number of metastatic LN (<5 vs. ≥5)	0.324	0.959	0.859
Size of largest nodal metastasis	0.022	0.003	0.012
Extranodal extension	0.215	0.642	0.096
Post-operative serum calcitonin (all cases)	0.001	0.001	0.004
Post- operative serum calcitonin (excluding those with DM at presentation)	0.003	<0.001	0.004
Post- operative serum CEA	0.216	0.392	0.188
DM at presentation	0.046	0.504	NA
Familial MTC	0.492	0.724	0.844

Non-significant histologic parameters:
-Fibrosis
-Amyloid
-Extra-nodal extension

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Multivariate analysis (Memorial data)

Except for mitosis and necrosis, no histologic parameters are significant

DSS	P values	Hazard ratio	95% CI
Sex	0.350	0.193	0.006-6.077
Tumor size	0.649	1.618	0.204-12.819
Mitotic index (<5 vs. ≥5/10 HPFs)	0.021	71.606	1.886-2718.969
Tumor necrosis	0.007	16.381	2.163-124.044
Nuclear pleomorphism	0.208	5.536	0.387-79.271
Lymphovascular invasion	0.453	1.998	0.328-12.183
Extrathyroidal extension	0.575	1.877	0.208-16.945
Margin	0.536	0.402	0.022-7.204
Post-op calcitonin level (all cases)	0.114	2.491	0.803-7.732
DM at presentation	0.562	0.455	0.032-6.527
LRFS			
Sex	0.745	0.847	0.311-2.306
Tumor size	0.987	0.994	0.502-1.969
Mitotic index (<5 vs. ≥5/10 HPFs)	0.122	3.764	0.702-20.183
Tumor necrosis	0.001	4.672	1.892-11.535
Nuclear pleomorphism	0.144	2.476	0.733-8.367
Infiltration	0.977	714036.100	0-indefinite
Encapsulation	0.193	0.581	0.256-1.317
Nodal status	0.272	1.901	0.605-5.975
Post-op calcitonin (all cases)	0.105	1.351	0.939-1.944
DMFS			
Sex	0.694	0.711	0.130-3.885
Tumor size	0.553	1.359	0.493-3.749
Mitotic index (<5 vs. ≥5/10 HPFs)	0.254	4.124	0.361-47.158
Tumor necrosis	0.001	8.119	2.242-29.401
Extrathyroidal extension	0.810	0.826	0.173-3.946
Nodal status	0.176	4.649	0.503-42.964
Post-op calcitonin (all cases)	0.199	1.596	0.782-3.253

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Univariate and multivariate analysis (Sydney data 76 pts)

- Significant histologic parameters:

  -Mitosis and necrosis

- Non-significant histologic parameters:

  -Fibrosis

  -Amyloid

  -Nuclear grade

  -Spindle cell

  -Prominent nucleoli

  -Vascular invasion

Am J Surg Pathol October 2020

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Background for medullary thyroid carcinoma grading

- Brigham and women's hospital (Barletta):

-Validation of MSKCC and Sydney grading in a genotyped cohort of sporadic medullary thyroid carcinoma (*Histopathology* March 2021)

Key Objective:

- Development of a universal grading system

  -Consensus cut-offs for all indices

  - Large cohort from multiple international centers

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Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

International Medullary Thyroid Carcinoma Grading System: A Validated Grading System for Medullary Thyroid Carcinoma

Bin Xu, MD, PhD[1]; Talia L. Fuchs, MD[2,3]; Sara Ahmadi, MD[4]; Mohammed Alghamdi, MD[1]; Bayan Alzumaili, MD[1]; Mohamed-Amine Bani, MD[5]; Eric Baudin, MD[6]; Angela Chou, MD[2,3]; Antonio De Leo, MD[7]; James A. Fagin, MD[8]; Ian Ganly, MD, PhD[9]; Anthony Glover, MD[3,10]; Dana Hartl, MD[11]; Christina Kanaan, MD[5]; Pierre Khneisser, MD[5]; Fedaa Najdawi, MD[12]; Aradhya Nigam, MD[9]; Alex Papachristos, MD[3,10]; Andrea Repaci, MD[13]; Philip M. Spanheimer, MD[9]; Erica Solaroli, MD[14]; Brian R. Untch, MD[9]; Justine A. Barletta, MD[12]; Giovanni Tallini, MD[7]; Abir Al Ghuzlan, MD[5]; Anthony J. Gill, MD[2,3]; and Ronald A. Ghossein, MD[1]

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Study cohort

- **327 patients with resected medullary thyroid carcinoma**
  - Royal North Shore Hospital, Sydney, Australia: n=79; (A.Gill)
  - Institut Gustave Roussy, Villejuif, France: n=70; (A. Ghuzlan)
  - Memorial Sloan Kettering Cancer Center, New York, NY, USA: n=69; (Xu B, Untch B, Ghossein R)
  - University of Bologna Medical Center, Bologna, Italy: n=65; (G. Tallini)
  - Brigham and Women's Hospital, Boston, MA, USA: n=44 (J. Barletta)

Parameters collected

- Mitotic count: per 2 mm^2 at hotspot
- Ki67 proliferation index: 500-2000 cells counted per tumor, at hotspot
- Tumor necrosis

- Other clinicopathologic parameters: sex, age, tumor size, post-operative serum CEA, post-operative serum calcitonin, AJCC 8^{th} edition prognostic groups, status of *RET* germline mutation, vascular invasion, microscopic extrathyroidal extension, and resection margin status.

- Outcome: Overall survival (OS), Disease specific survival (DSS), Locoregional free survival (LRFS), Distant metastasis free survival (DMFS)

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Material and Methods:

- Retrospective cohort of **327 patient's** with Medullary carcinoma **from five centers across the United States, Europe, and Australia**
- **All slides were reviewed by expert thyroid pathologists at participating sites who were blinded to the patients' outcome**
- The mitotic count and Ki67 proliferative index were evaluated using the same methods proposed for gastrointestinal neuroendocrine tumors (GINET)
- Necrosis (present or absent) regardless of its extent

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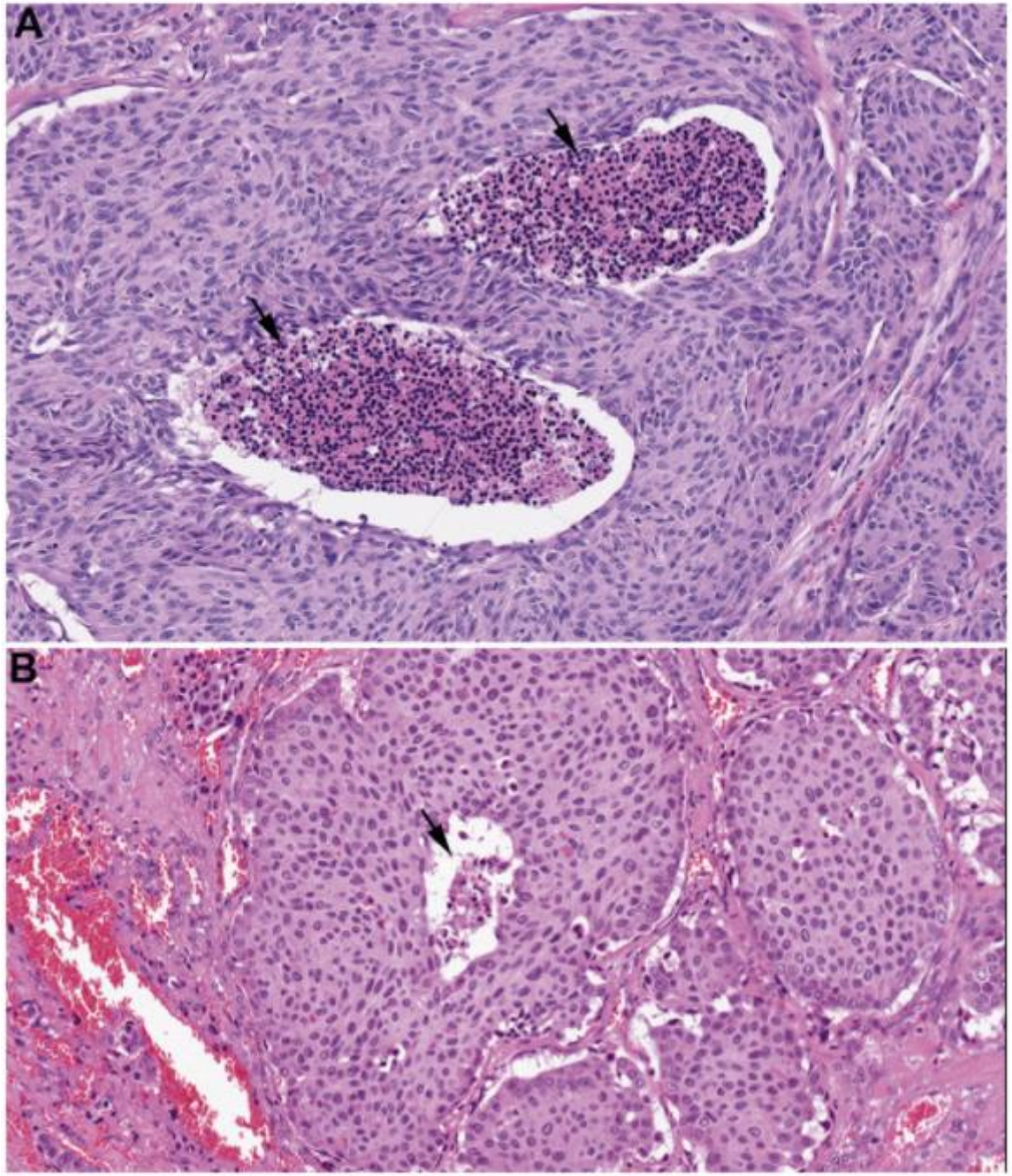
Tumor necrosis:



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Determination of a Consensus Grading Scheme:

- Both the MSKCC and Sydney grading schemes and eight other potential grading schemes were investigated using various cutoffs for
  - Mitotic index
  - Ki67
  - Tumor necrosis
- Consensus conference was held, and a single system was agreed upon

International Medullary Thyroid Carcinoma Grading System (IMTCGS)

International Medullary Thyroid Carcinoma Grading System (IMTCGS)

- A medullary thyroid carcinoma is considered high-grade when it had at least one of the following three criteria:

1. Mitotic index ≥ 5 per 2 mm^2
2. Ki67 proliferative index ≥ 5%
3. Tumor necrosis

Mitosis and Ki-67 should be reported as a continuous variable prognosis worsens as the proliferative activity of a tumor increases

INTERNATIONAL MEDULLARY THYROID CARCINOMA GRADING SYSTEM

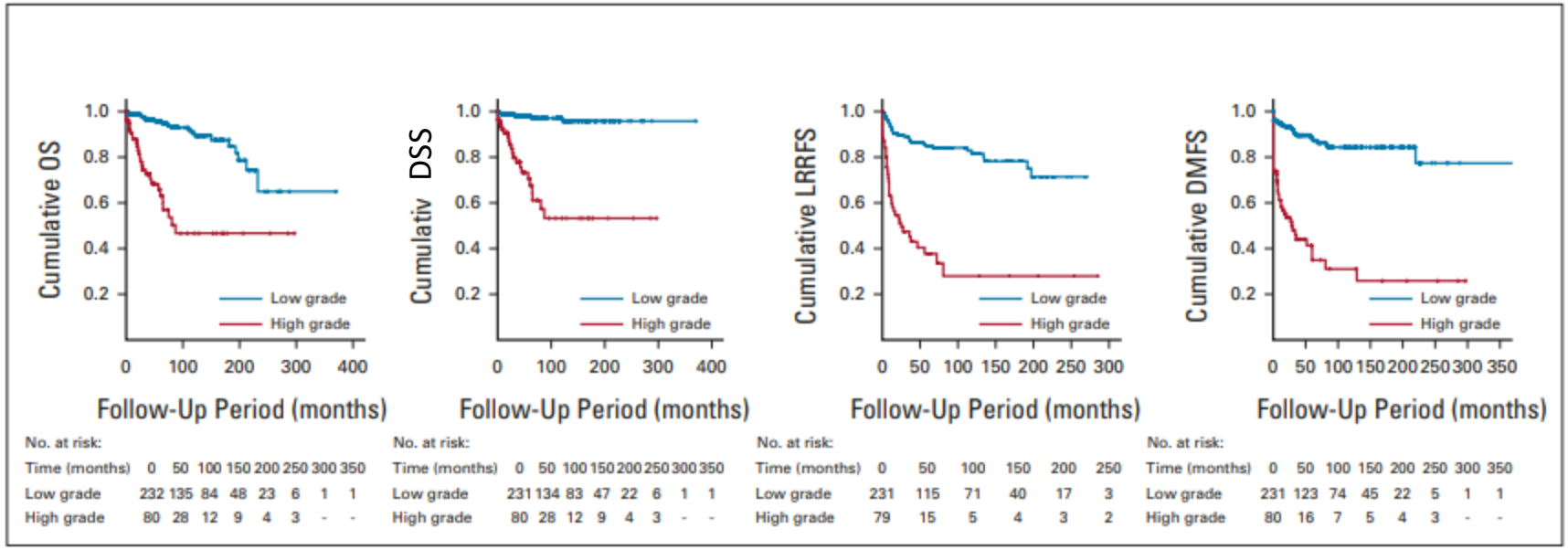

FIG 2. Kaplan-Meier curves for survival according to the international medullary thyroid carcinoma grading system. DMFS, distant metastasis-free survival; DSS, disease-specific survival; LRRFS, locoregional recurrence-free survival; OS, overall survival.

TABLE 3. Three-Year, Five-Year, and Ten-Year Survival According to the International Medullary Thyroid Carcinoma Grading System

Survival	All	LG	HG
OS			
3-year	90 (87 to 94)	96 (94 to 99)	73 (62 to 84)
5-year	88 (84 to 92)	96 (93 to 99)	66 (54 to 78)
10-year	80 (74 to 86)	91 (85 to 96)	47 (31 to 63)
DSS			
3-year	93 (90 to 96)	98 (96 to 100)	78 (67 to 88)
5-year	91 (88 to 95)	98 (96 to 100)	71 (58 to 83)
10-year	87 (82 to 92)	97 (94 to 100)	53 (37 to 70)
DMFS			
3-year	78 (73 to 83)	90 (86 to 94)	44 (32 to 56)
5-year	76 (71 to 82)	88 (84 to 93)	41 (28 to 53)
10-year	71 (65 to 77)	84 (78 to 90)	31 (17 to 44)
LRRFS			
3-year	79 (74 to 84)	89 (84 to 93)	47 (35 to 60)
5-year	74 (68 to 79)	85 (80 to 90)	37 (24 to 50)
10-year	69 (63 to 76)	82 (75 to 88)	28 (13 to 43)

NOTE. Values are expressed as cumulative survival % (95% CI).

Abbreviations: DMFS, distant metastasis-free survival; DSS, disease-specific survival; HG, high grade; LG, low grade; LRRFS, locoregional recurrence-free survival; OS, overall survival.

10 year distant Metastasis free survival:
-Low grade: 84%
-High grade: 31%

10 year disease specific survival:
-Low grade: 97%
-High grade: 53%

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Subgroup analyses

Prognostic significance of consensus grading for each participating site was maintained

	Univ of Bologna	Brigham& women (Boston)	Inst.Gustave Roussy (Paris)	Memorial Hospital (NY, NY)	Royal N.S. (Sydney)
Overall survival	**0.011**	**<0.001**	**0.015**	**<0.001**	**<0.001**
Disease specific survival	**0.011**	**<0.001**	**0.032**	**<0.001**	**<0.001**
Locoregional recurrence free survival	0.074	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Distant metastasis free survival	**<0.001**	**<0.001**	**<0.001**	**0.001**	**<0.001**

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CONSENSUS GRADING SYSTEM INDEPENDENT PREDICTOR OF OUTCOME

TABLE 4. Multivariate Survival Analysis Using Cox Proportional Hazards Model to Identify Prognostic Factors in Medullary Thyroid Carcinoma

	OS			DSS			DMFS			LRRFS		
Parameter	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**
IMTCGS	**< .001**	10.847	2.903 to 40.531	**.017**	8.491	1.461 to 49.327	**.045**	2.267	1.018 to 5.049	**.042**	1.938	1.044 to 3.876
Sex	.981	0.981	0.338 to 2.880	.684	1.304	0.363 to 4.685	.363	1.389	0.684 to 2.819	.274	1.467	0.738 to 2.915
Tumor size	.950	1.008	0.777 to 1.308	.998	1.000	0.729 to 1.372	.991	1.001	0.857 to 1.168	.067	1.141	0.991 to 1.314
Postoperative CEA	.054	1.000	1.000 to 1.000	**.013**	1.000	1.000 to 1.000	.030	1.000	1.000 to 1.000	.480	1.000	1.000 to 1.000
AJCC eighth prognostic grouping	**.008**	3.384	1.367 to 8.374	.923	61.047	0 to 1E+38	**< .001**	2.712	1.596 to 4.606	**.004**	1.819	1.215 to 2.725
Vascular invasion	.081	0.290	0.072 to 1.163	.565	0.575	0.087 to 3.797	.511	1.397	0.515 to 3.788	**.014**	3.690	1.303 to 10.452
Microscopic extrathyroidal extension	.848	1.149	0.278 to 4.749	.647	0.695	0.146 to 3.309	.524	0.756	0.319 to 1.790	.425	1.399	0.613 to 3.191
Margin status	.579	1.331	0.485 to 3.649	.651	1.324	0.392 to 4.472	**.027**	2.287	1.099 to 4.762	.973	0.988	0.478 to 2.041
Age	**.014**	1.051	1.010 to 1.093	**.036**	1.057	1.004 to 1.112						
External beam radiotherapy	.989	1.008	0.331 to 3.070				.116	1.794	0.866 to 3.713	.288	1.505	0.708 to 3.202
Postoperative calcitonin				.118	1.000	1.000 to 1.000	**.049**	1.000	1.000 to 1.000			
RET germline mutation				.960	0.000	0 to 1.3E+177						

NOTE. Age, tumor size, postoperative CEA, and calcitonin are treated as continuous variables. Bold *P* values are significant *P* values.

Abbreviations: AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HR, hazard ratio; IMTCGS, International Medullary Thyroid Carcinoma Grading System; LRRFS, locoregional recurrence-free survival; OS, overall survival.

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Validation of the IMTG system

- Consensus grading independent predictor of DFS in an Independent cohort of 101 MTC including 68 sporadic cases.

Vissio E,..., Papotti M.
Endocr Pathol 2022

- Consensus grading independent prognostic factor in a cohort of 87 cases

Lubin DJ,..., Viswanathan K.
Mod Pathol 2023

- Consensus grading reproducible between academic pathologists

Williams JF,..., Barletta J.
Endocr Pathol 2022

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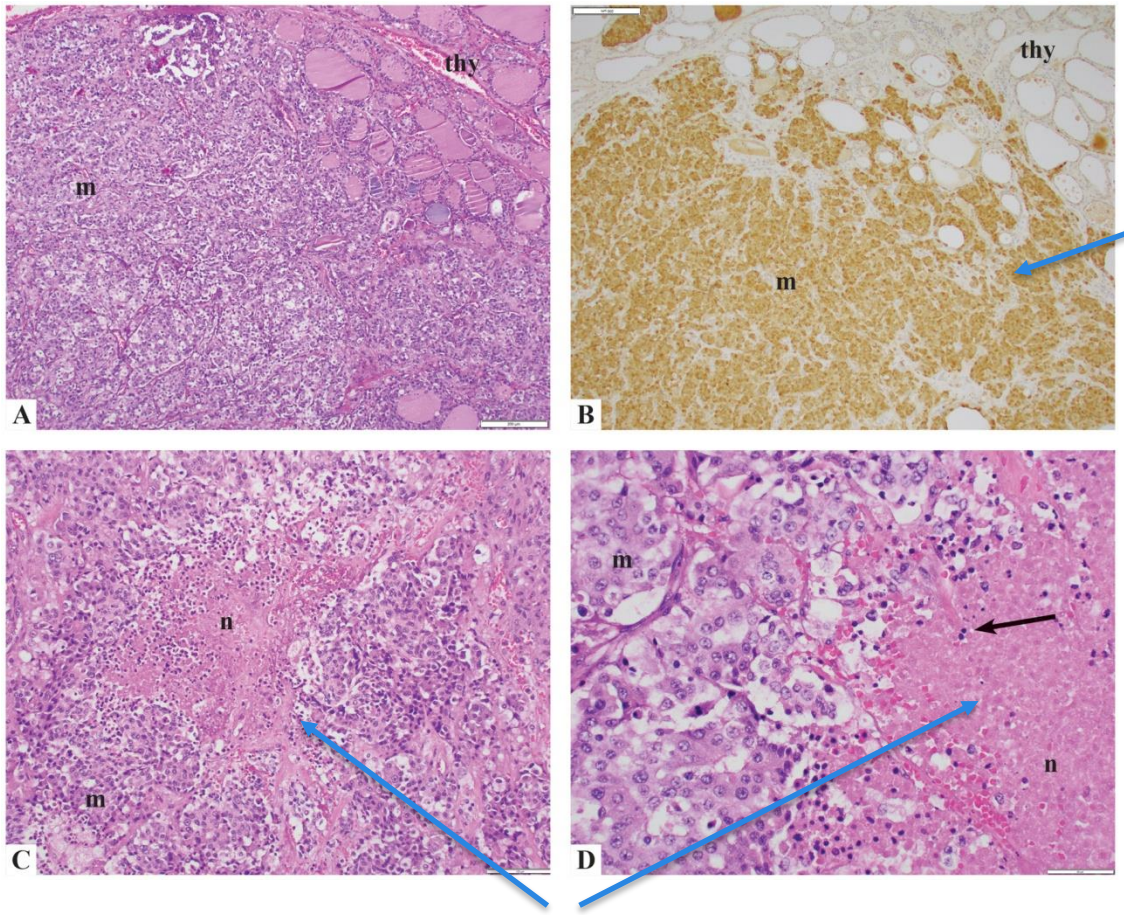
66 year old male Mo at presentation
Dead of disease 2 years and 3 month after thyroidectomy.



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BIG QUESTION

- **MUTATION AND GRADE IN MEDULLARY THYROID CARCINOMA**

Association of the Genomic Profile of Medullary Thyroid Carcinoma with Tumor Characteristics and Clinical Outcomes in an International Multicenter Study

Bin Xu MD, PhD[1*], Kartik Viswanathan MD[2*], Mahsa S. Ahadi MD[3,4,5], Sara Ahmadi MD [6], Bayan Alzumaili MD [1], Mohamed-Amine Bani MD [7], Eric Baudin MD [8], David Blake Behrman MD [2], Marzia Capelletti MD [9], Nicole G Chau MD [9], Federico Chiarucci MD [10], Angela Chou MD [3,4,5], Roderick Clifton-Bligh MD [3,4,5], Sara Coluccelli MD [10], Dario de Biase MD [11], Antonio De Leo MD [10], Snjezana Dogan MD [1], James A. Fagin MD [12], Talia L. Fuchs MD [3,4,5], Anthony Robert Glover MD [3], Julien Hadoux MD [8], Ludovic Lacroix MD [7], Livia Lamartina MD [8], Daniel J. Lubin MD [2], Catherine Luxford PhD [3,4,5], Kelly Magliocca DDS, MPH[2], Thais Maloberti MD [10], Abhinita S. Mohanty MSc [1], Fedaa Najdawi MD [9], Aradhya Nigam MD [13], Alexander James Papachristos MD [3,4,5], Andrea Repaci MD [14], Bruce Robinson MD [3,4,5], Jean-Yves Scoazec MD [7], Qiuying Shi MD [2], Stan Sidhu MD [3,4,5], Erica Solaroli MD [15], Mark Sywak MD [3,4,5], R. Michael Tuttle MD [12], Brian Untch MD [13], Justine A. Barletta MD [9], Abir Al Ghuzlan MD [7], Anthony J. Gill MD [3,4,5], Ronald Ghossein MD [1*], Giovanni Tallini MD [10*], Ian Ganly MD, PhD [13*]

Thyroid (In Press)

RET somatic mutation was associated with adverse clinicopathologic features

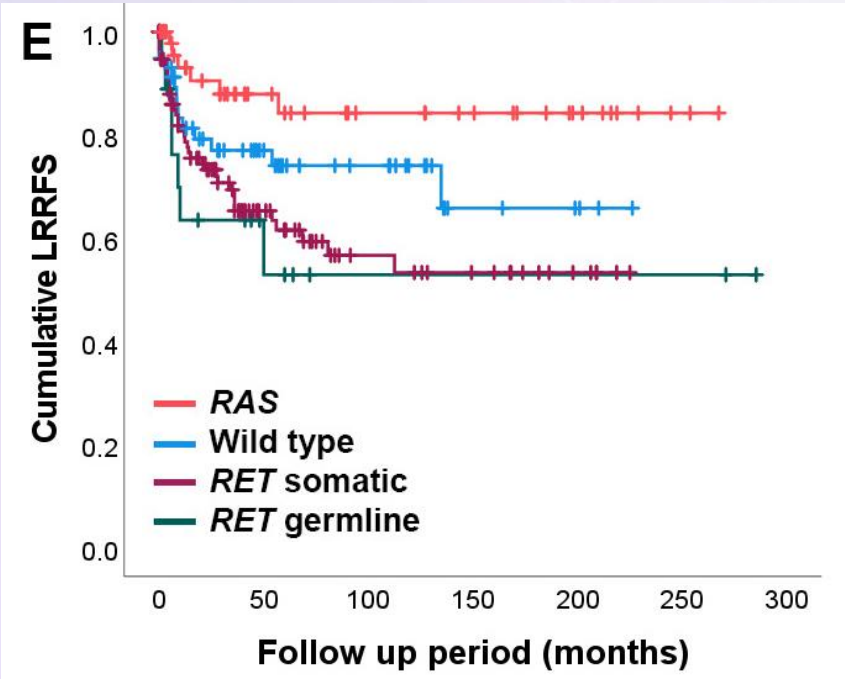
	RET somatic mutations	*RET/RAS* wild type (WT)	P values
Tumor size (cm, median, range)	2.1 (0.4-8.0)	1.9 (0.3-6.0)	0.036
AJCC prognostic group 4	77 (56.6%)	15 (24.6%)	<0.001
Vascular invasion	76 (55.9%)	20 (32.8%)	0.005
IMTCGS high grade	48 (35.3%)	11 (18.0%)	0.027

- *RET* germline mutations were only associated with younger age at MTC diagnosis.
- *RAS* somatic mutations did not alter clinicopathologic parameters.

Mutations and survival

- No impact of RET, RET p.M918T, and RAS mutations on overall and disease specific survival (OS and DSS)

RET germline or somatic mutations were associated with decreased distant metastasis free survival (DMFS) on univariate analysis



Univariate log rank test	P values
RET somatic vs. *RET* germline	0.745
RET somatic vs. *RET/RAS* WT	0.010
RET germline vs. *RET/RAS* WT	0.045
RAS mutated vs. *RET/RAS* WT	0.081
RET M918T somatic vs. other *RET* somatic	0.375

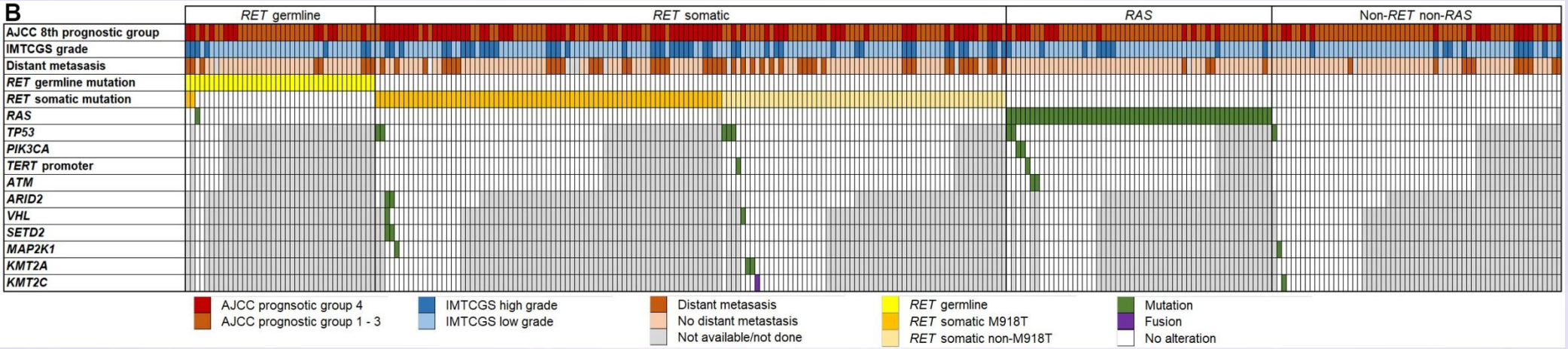
RET or *RAS* mutations did not impact overall survival (OS), disease specific survival (DSS), and locoregional recurrence free survival (LRRFS).

RET or *RAS* mutation was **NOT** an independent prognostic factor for DMFS

	P values	Hazard ratio (95% confidence interval)
RET or RAS mutations		
RET and RAS wild type	Reference	
RET germline mutations	0.154	1.945 (0.779-4.856)
RET somatic mutations	0.217	1.525 (0.780-2.979)
RAS somatic mutation	0.147	0.428 (0.136-1.349)
IMTCGS high grade	0.006	2.031 (1.230-3.353)
AJCC stage group 4	<0.001	1.478 (1.221-1.789)

IMTCGS high grade and AJCC stage group 4 remained as independent adverse prognostic factors for DMFS.

Other molecular alterations in MTC



TP53: 8/191, 4%

PIK3CA: 2/191 1%

VHL: 2/191, 1%

TERT promoter mutation: 2/191 1%

ATM: 2/87, 2.3%

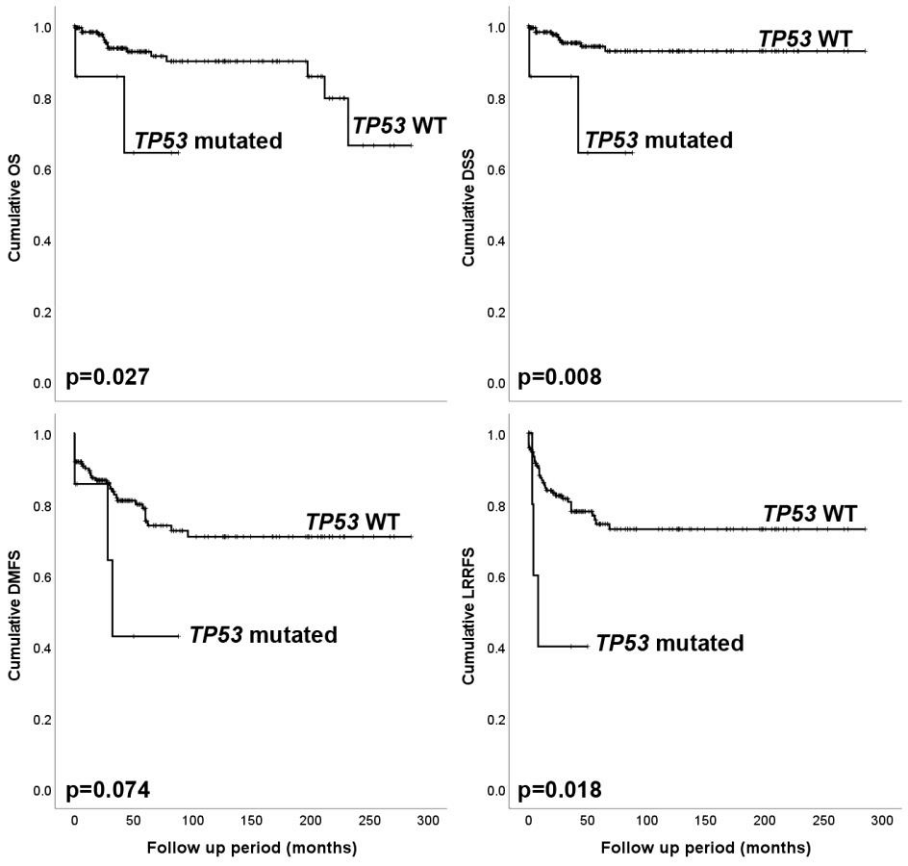
ARID2: 2/70, 2.9%

SETD2: 2/70, 2.9%

KMT2A: 2/70, 2.9%

KMT2C: 2/70, 2.9%

TP53 was associated with decreased overall, disease-specific and locoregional recurrence free survival



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Potential benefits of grading medullary thyroid carcinoma

- Stratification of patients for early lateral neck dissection, close follow up, low thresholds for cross-sectional imaging, and careful work-up for distant metastasis.

- Datapoint for clinical trial: (High grade may benefit more from adjuvant therapy)

CONCLUSIONS

- Medullary thyroid carcinoma often underdiagnosis because rare
- Every case should be immunostained. (High price for a mistake)
- Grading should be performed

- THE END

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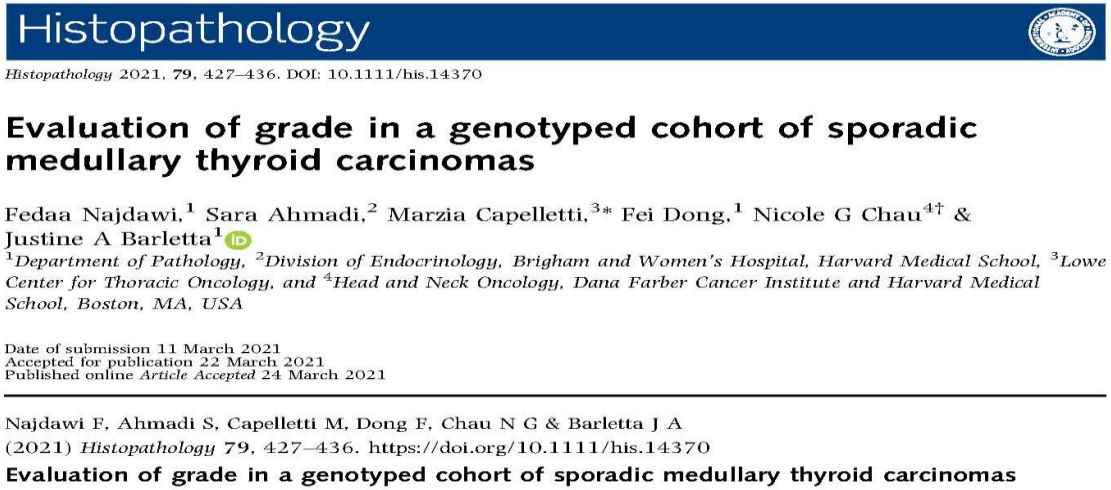
Remaining question

- Mutation and grade in sporadic tumors
- One paper shows no correlation between grade and sporadic mutation



Histopathology

Histopathology 2021, **79**, 427–436. DOI: 10.1111/his.14370

Evaluation of grade in a genotyped cohort of sporadic medullary thyroid carcinomas

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Evaluation of grade in a genotyped cohort of sporadic medullary thyroid carcinomas

- An

WHO classification of tumours of the thyroid gland (2017)

Follicular adenoma	8330/0
Hyalinizing trabecular tumour	8336/1*
Other encapsulated follicular-patterned thyroid tumours	
Follicular tumour of uncertain malignant potential	8335/1*
Well-differentiated tumour of uncertain malignant potential	8348/1*
Noninvasive follicular thyroid neoplasm with papillary-like nuclear features	8349/1*
Papillary thyroid carcinoma (PTC)	
Papillary carcinoma	8260/3
Follicular variant of PTC	8340/3
Encapsulated variant of PTC	8343/3
Papillary microcarcinoma	8341/3
Columnar cell variant of PTC	8344/3
Oncocytic variant of PTC	8342/3
Follicular thyroid carcinoma (FTC), NOS	8330/3
FTC, minimally invasive	8335/3
FTC, encapsulated angioinvasive	8339/3
FTC, widely invasive	8330/3
Hürthle (oncocytic) cell tumours	
Hürthle cell adenoma	8290/0
Hürthle cell carcinoma	8290/3
Poorly differentiated thyroid carcinoma	8337/3
Anaplastic thyroid carcinoma	8020/3
Squamous cell carcinoma	8070/3
Medullary thyroid carcinoma	8345/3
Mixed medullary and follicular thyroid carcinoma	8346/3
Mucoepidermoid carcinoma	8430/3
Sclerosing mucoepidermoid carcinoma with eosinophilia	8430/3
Mucinous carcinoma	8480/3
Ectopic thymoma	8580/3
Spindle epithelial tumour with thymus-like differentiation	8588/3
Intrathyroid thymic carcinoma	8589/3
Paraganglioma and mesenchymal/stromal tumours	
Paraganglioma	8693/3
Peripheral nerve sheath tumours (PNSTs)	
Schwannoma	9560/0
Malignant PNST	9540/3
Benign vascular tumours	
Haemangioma	9120/0
Cavernous haemangioma	9121/0
Lymphangioma	9170/0
Angiosarcoma	9120/3
Smooth muscle tumours	
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Solitary fibrous tumour	8815/1
Hematolymphoid tumours	
Langerhans cell histiocytosis	9751/3
Rosai-Dorfman disease	
Follicular dendritic cell sarcoma	9758/3
Primary thyroid lymphoma	
Germ cell tumours	
Benign teratoma	9080/0
Immature teratoma	9080/1
Malignant teratoma	9080/3
Secondary tumours	

The first four digits indicate the specific histological term; the fifth digit after th
behavior code, including /0 for benign tumours, /1 for unspecified, borderline,
behavior, /2 for carcinoma in situ and grade III intraepithelial neoplasia, and /
tumours

* These new codes were approved by the IARC/WHO Committee for ICD-O

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WHO Classification of Thyroid Neoplasms, 5th ed

Developmental Abnormalities

1. Thyroglossal duct cyst
2. Other congenital thyroid abnormalities

Follicular Derived Neoplasms

1. Benign Tumors
   a. Thyroid follicular nodular disease*
   b. Follicular adenoma
   c. Follicular adenoma with papillary architecture*
   d. Oncocytic adenoma of the thyroid*
2. Low Risk Neoplasms
   a. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
   b. Thyroid tumors of uncertain malignant potential
   c. Hyalinizing trabecular tumor
3. Malignant Neoplasms
   a. Follicular thyroid carcinoma
   b. Invasive encapsulated follicular variant papillary carcinoma*
   c. Papillary thyroid carcinoma
   d. Oncocytic carcinoma of the thyroid*
   e. Follicular-derived carcinomas, high-grade*
      i. Differentiated high-grade thyroid carcinoma
      ii. Poorly differentiated thyroid carcinoma
   f. Anaplastic follicular cell derived thyroid carcinoma

Thyroid C-cell Derived Carcinoma

1. Medullary thyroid carcinoma

Mixed Medullary and Follicular-cell Derived Carcinomas

Salivary Gland-type Carcinomas of the Thyroid*

1. Mucoepidermoid carcinoma of the thyroid
2. Secretory carcinoma of salivary gland type

Thyroid tumors of uncertain histogenesis*

1. Sclerosing mucoepidermoid carcinoma with eosinophilia
2. Cribriform morular thyroid carcinoma

Thymic Tumors Within the Thyroid

1. Thymoma family
2. Spindle epithelial tumour with thymus-like elements
3. Thymic carcinoma family

Embryonal Thyroid Neoplasms

1. Thyroblastoma

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Squamous cell carcinoma of thyroid

- Separate entity from anaplastic carcinoma in WHO 2017

- Now a form of anaplastic carcinoma (WHO 2022)

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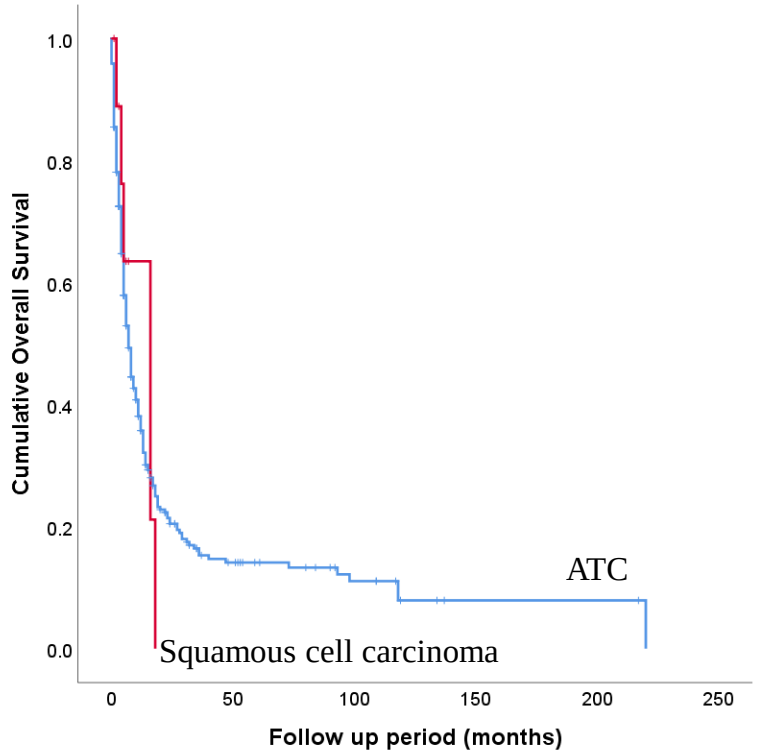
Thyroid squamous cell carcinoma: a form of Anaplastic carcinoma in WHO 2022



- Defined as a separate entity in WHO 2017:
  - Comprised entirely of tumor cells with squamous differentiation
  - No evidence of other type of thyroid carcinoma
- **Similar molecular profile as other ATC**
  - *BRAF* V600E 60%
- **Similar outcome as other ATCs**
  - Median overall survival 14 months (vs. 10 months)

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WHO 2022

- Cribriform morular variant of papillary carcinoma
- Renamed as cribriform morular thyroid carcinoma.

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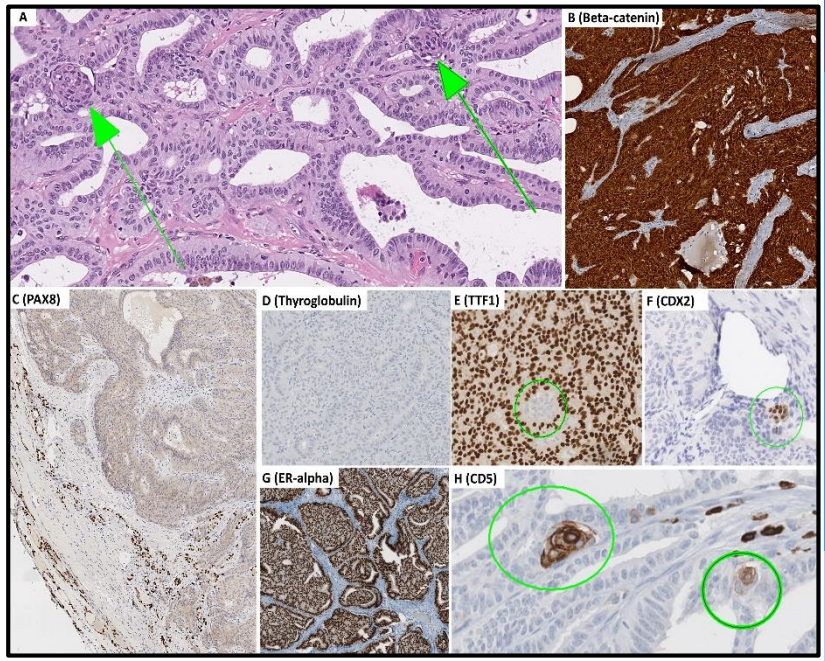
WHO 2022
Cribriform Morular Thyroid Carcinoma

- Previously termed as "Cribriform Morular Variant of Papillary Thyroid Carcinoma"
- Do not display *BRAFV600E* mutation
- Rarely have *RAS* or *PIK3CA* mutations
- Frequent genetic alterations - **Wnt/beta-catenin pathway**.
- APC mutations being the most common
  - Both the familial and sporadic setting
- Mutations in other genes involved in the Wnt/Beta-catenin pathway - *CTNNB1*
- TTF1 expression only in the cribriform elements
- **Absence/focal weak PAX8 and thyroglobulin expression**
- **Radioactive iodine may not be needed**



Boyraz B, Sadow PM, Asa SL, Dias-Santagata D, Nosé V, Mete O. *Endo Pathol* 2021