A nodule amongst polyps

Matt Ettleson, M.D.*

Endorama

January 16, 2020

M170

*I have no conflicts of interest to disclose.

AT THE FOREFRONT
UChicago Medicine

Learning Objectives

- Brief review of colorectal cancer syndromes
- Explore early literature of the association between familial adenomatous polyposis (FAP) and thyroid cancer
- Recognize the histopathological features of papillary thyroid cancer associated with FAP
- Evaluate the current recommendations for screening for thyroid cancer in patients with FAP

A 37 year old African-American woman with an extensive personal and family history of gastrointestinal polyposis presents to the GI cancer risk clinic.

Initial evaluation in UCMC system

Nov, 2016

The patient reports a personal and family history of polyps. She underwent total colectomy at age 25. She had two additional desmoid tumors removed in her late 20s and early 30s. She recently underwent endoscopy which demonstrated multiple polyps in the duodenum, several > 1cm.

Her father had his colon removed many years ago and is alive at 74. She had a sister who died at 33 years old from colon cancer. Her paternal grandfather died of rectal cancer in his mid-30s. A paternal aunt was diagnosed with pancreatic cancer in her 50s. She has two other siblings who are healthy (no polyps). She is not aware of any genetic testing done in any family member. She is on no regular medications.

Clinic Evaluation

Vitals

Temp: 37.4
Pulse: 76
BP: 107/67
Weight: 75.8 kg
Height: 165.1 cm

Physical Exam

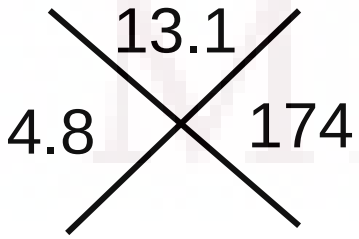
General: awake, alert, appears comfortable in clinic
HEENT: extraocular motion intact. Pupils equal, round and reactive to light. Oropharynx is clear. Sclerae are nonicteric.
Neck: There is no lymphadenopathy; the thyroid is non-palpable. Extra teeth noted.
Cardiac: RRR, normal S1/S2. No murmur.
Pulmonary: clear to auscultation bilaterally.
Abdomen: soft, non-tender. No obvious masses. Surgical scars noted.
Skin: no cysts noted.
MSK: normal gait and station. No edema.
Neuro: DTRs 2+ throughout.

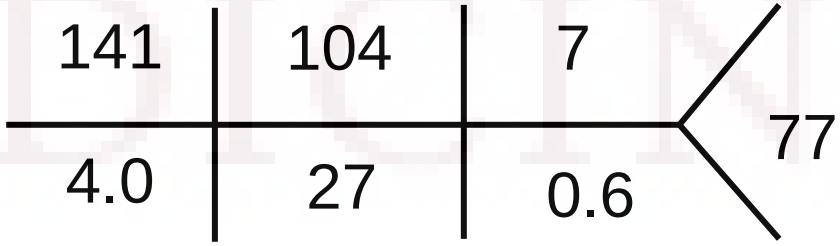
Available lab work and imaging

EGD
Flex Sig

Normal esophagus. Normal stomach. Normal ampulla. 25 mm adenoma at 3rd part of the duodenum. Three 10 mm adenomas at 2nd part of the duodenum and at 3rd part of the duodenum. Multiple smaller adenomas throughout the examined duodenum.

Patent functional end-to-end ileo-anal anastomosis, characterized by healthy appearing mucosa. Multiple 5 mm, non-bleeding polyps from 0 to 10 cm proximal to the anus. One clear adenoma at the anal verge the rest could be hyperplastic.





calcium 9.2

**Most recent available labs from 2011.

Hereditary colorectal cancer syndromes

Hereditary Non-Polyposis Colorectal Cancer (HNPCC, Lynch syndrome)

The most common hereditary CRC syndrome; associated with germline mutations in mismatch repair genes (*MLH1, MSH2, MSH6, PMS2, EPCAM/TACSTD1*).

Classic Familial Adenomatous Polyposis (FAP)

Associated with germline mutations in the *APC* tumor suppressor gene; without colectomy, lifetime risk of CRC is >90%.

Attenuated Familial Adenomatous Polyposis (AFAP)

Greater than 20 but less than 100 colonic polyps; can be associated with APC or MUTYH mutations, but often no genetic basis is identified. Extracolonic neoplasms are rare.

MUTYH-associated Polyposis (MAP)

Autosomal recessive inheritance; average age of onset in the mid-50s.

**Peutz-Jeghers syndrome, Cowden syndrome, juvenile polyposis*

J Clin Oncol. 2015 Jan 10; 33(2): 20-217.

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J Clin Oncol. 2015 Jan 10; 33(2): 20-217.

Clinic Evaluation (14 months after initial visit)

March, 2019

Vitals

Temp: 37.1
Pulse: 84
BP: 149/80
Weight: 79.2 kg
Height: 165.1 cm

Physical Exam

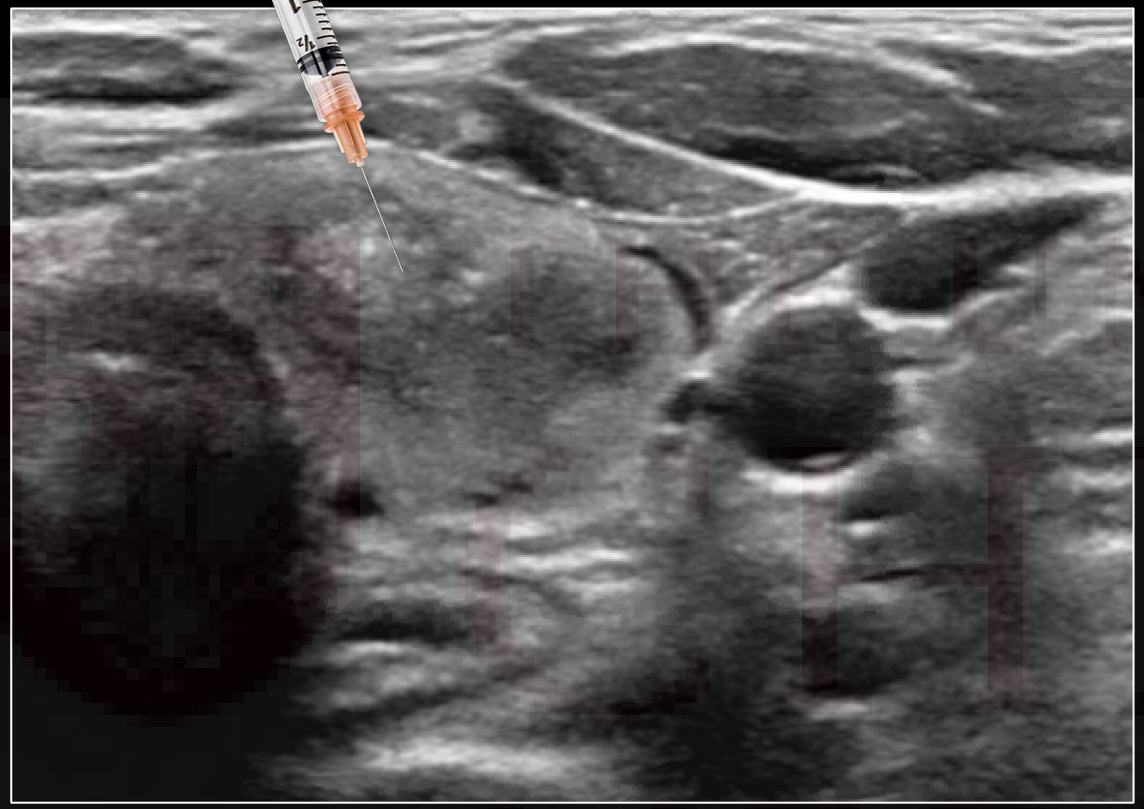
General: awake, alert, appears comfortable in clinic
HEENT: extraocular motion intact.
Neck: **Enlarged thyroid with no discrete nodule palpated.** Extra teeth noted.
Cardiac: RRR, normal S1/S2. No murmur.
Pulmonary: clear to auscultation bilaterally.
Abdomen: soft, non-tender. No obvious masses. Surgical scars noted.
Skin: no cysts noted.
MSK: normal gait and station. No edema.
Neuro: DTRs 2+ throughout.

Plan: EGD, pouchoscopy, **thyroid ultrasound** (and endocrine consult)

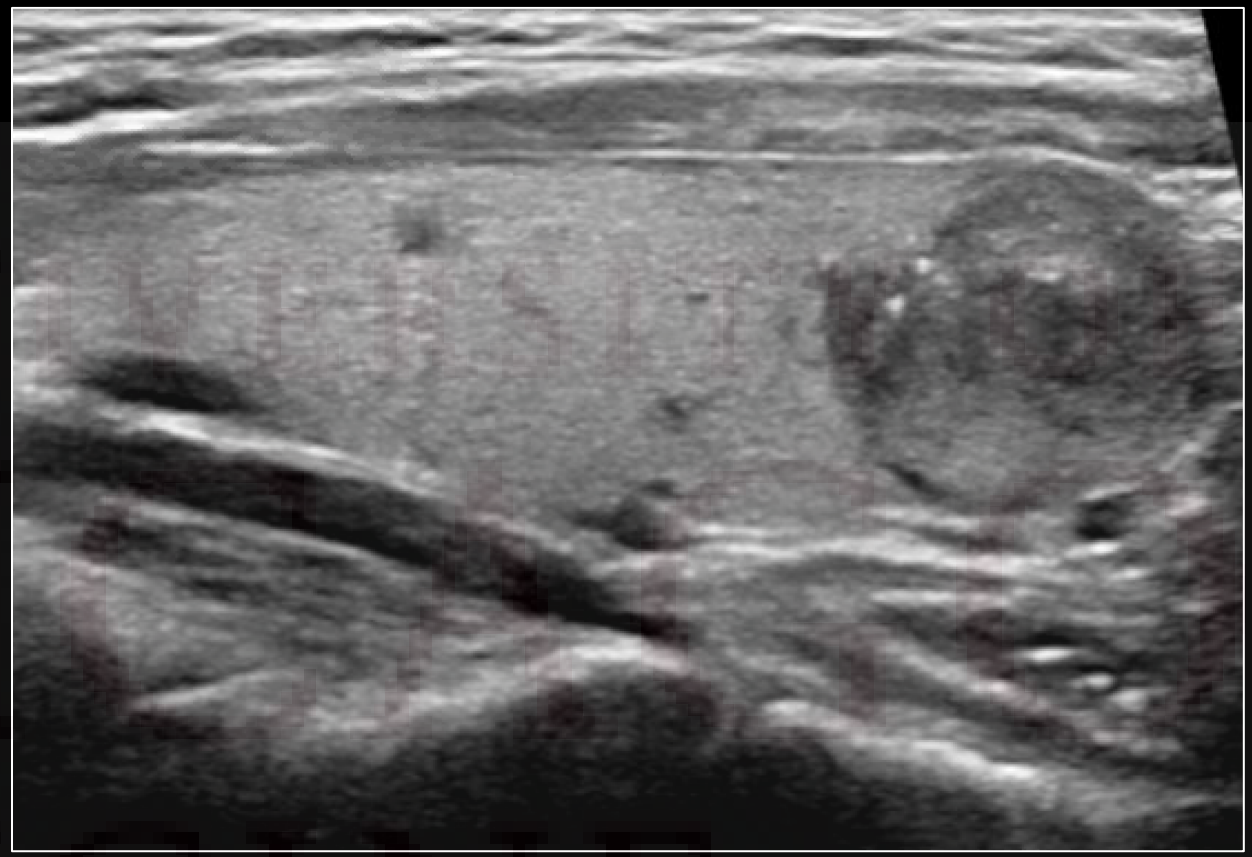
Lab Evaluation

TSH 2010: 0.83

TSH: 0.83
TSI: <1.0
TPO: <0.4



trans L lobe



long L lobe

Left inferior pole hypoechoic lesion with internal calcifications and irregular margins is intermediate to highly suspicious for malignancy. FNA is recommended.

FNA results (first attempt)

Specimen(s) Received
Needle Aspiration - Left Inferior Thyroid Nodule

Diagnosis
Needle Aspiration - Left Inferior Thyroid Nodule:

- Follicular lesion of undetermined significance

Specimen Adequacy/Quality Indicators
Satisfactory for evaluation.

FNA results (second attempt)

Calcitonin: <5

Thyroglobulin: ?

Diagnosis
Needle Aspiration - Left Inferior Thyroid Nodule:

Suspicious for malignancy (see note)

Note: The smears are hypercellular and consist of lesional cells dispersed singly and arranged in crowded overlapping groups. There are structures resembling follicles with the cells surrounding dense extracellular material. The nuclei show irregular membranes and discernible nucleoli; nuclear molding and chromatin strings are seen. The cytoplasm is overall scant; however, some cells display more abundant dense cytoplasm with squamoid appearance.

The cytomorphological features suggest an epithelial thyroid malignancy. Nevertheless, the findings are not characteristic/specific to allow a definitive cytologic diagnosis of a single entity. The differential diagnosis is of a medullary thyroid carcinoma (with groups of C-cells surrounding amyloid or colloid) or a follicular neoplasm as well as a cribriform morular variant of papillary thyroid carcinoma (particularly given patient's history of Familial Adenomatous Polyposis). The final classification is deferred to an anticipated surgical specimen.

The case is reviewed with Drs. Antic and Reeves who concur with the diagnosis and interpretation. The findings are discussed with Dr. Sarne on 5/23/2019. The prior FNA specimen (NC19-56, 04/24/19) is reviewed in conjunction with the current material.

Specimen Adequacy/Quality Indicators
Satisfactory for evaluation

Total thyroidectomy

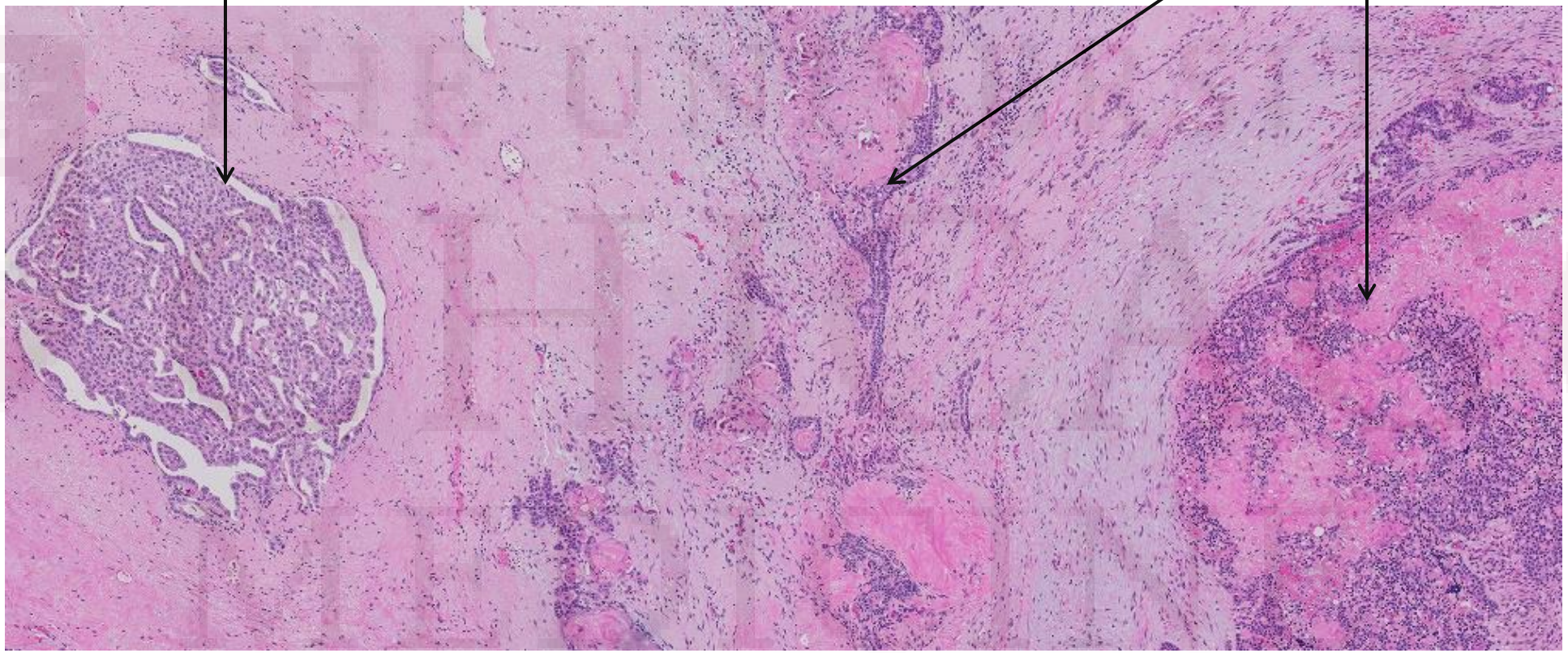
Operative report

Neck ultrasound in the operating room confirmed a 2 cm hypoechoic nodule in the inferior L lobe. No evidence of central or lateral lymphadenopathy.

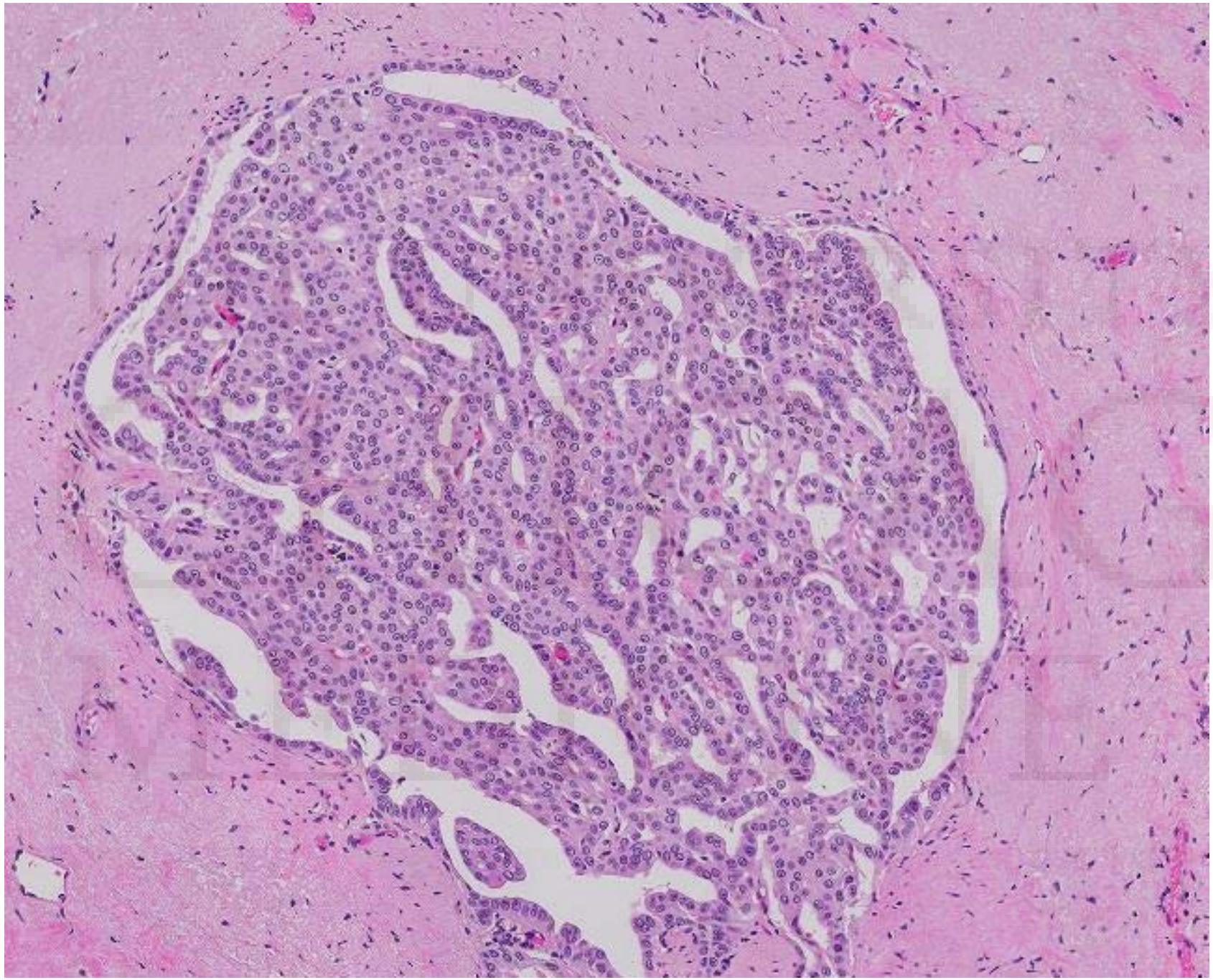
The procedure was largely unremarkable. There was no comment of any obvious thyroid abnormality or any notable surrounding lymph nodes. The R superior parathyroid gland was isolated and auto-transplanted in the surrounding neck musculature.

Glomeruloid/cribriform architecture

Squamous differentiation



Anna Trzcinska, M.D.



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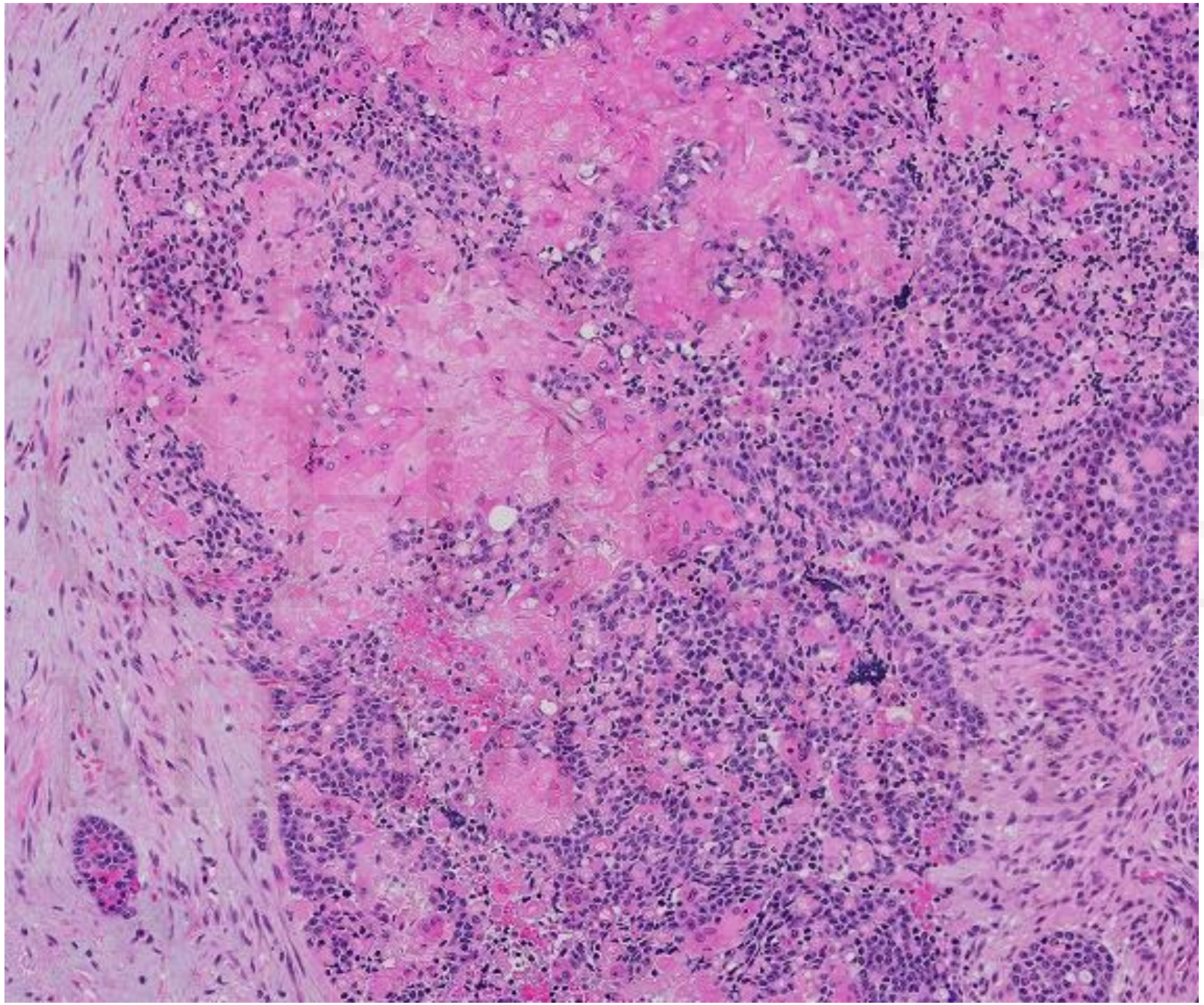

Anna Trzcinska, M.D.

Pathology report

Procedure: Total thyroidectomy
Lymph Node Sampling: Not performed
Fresh Specimen Weight: 25.2 gm
Tumor Site: Unifocal, Left lobe
Tumor Size: 2.9 cm; Location: Left lower lobe
Histologic Type: Papillary thyroid carcinoma, cribriform morular variant with extensive squamous differentiation
Angioinvasion: Not identified
Lymphatic Invasion: Not identified
Perineural Invasion: Not identified
Extrathyroidal Extension: Not identified
Margins: Uninvolved by carcinoma by 0.1 cm
Regional Lymph Nodes: Not examined

AJCC 8th Edition Pathologic TNM Staging: pT2, NX
Primary Tumor: pT2: Tumor more than 2 cm, but not more than 4 cm, limited to thyroid/fibroadipose tissue
Regional Lymph Nodes: pNX: Cannot be assessed

Pathology report

Comment

A minority of the carcinoma demonstrates classic cribriform morphology compatible with cribriform-morular variant of papillary thyroid carcinoma. However, the majority shows primitive squamous differentiation composed of small-to-medium, round-to-oval monotonous cells with abrupt keratinization and keratin pearls. Appropriately controlled immunostains show both components to be positive for beta catenin (cytoplasmic and nuclear expression). The cribriform-morular component is positive for TTF-1; the squamous component is negative. Conversely, the squamous component is positive for p40; the cribriform component is negative. Both components are negative for PAX8, Chromogranin, Synaptophysin, Calcitonin, BRAF VE1, and NUT (performed at Mayo, see addendum). Stroma is negative for Congo Red. The clinical significance of extensive primitive squamous differentiation in thyroid carcinoma is not certain. However, reports of cribriform morular variant with aberrant differentiation have occasionally been shown to have aggressive behavior (1).

Familial adenomatous polyposis associated thyroid carcinoma: a distinct type of follicular cell neoplasm

H.R.HARACH, G.T.WILLIAMS* & E.D.WILLIAMS
*Department of Histopathology, Addenbrooke's Hospital, University of Cambridge, Cambridge and *Department of Pathology, University of Wales College of Medicine, Cardiff, UK*

Thyroglobulin immunohistochemistry identifies **follicular cell origin**.

Some features shared with PTC: **grooved nuclei** and **papillary architecture.**

Some features distinct from PTC: **cribriform pattern** and solid areas with **spindle cell component**.

In some cases, thyroid cancer was diagnosed **prior to recognition of FAP**, prompting these pathological features to signal **screening of the patient and family.**

The authors advocate for **total thyroidectomy** due to **multicentricity**.

Histopathology 1994, 25, 549-561.

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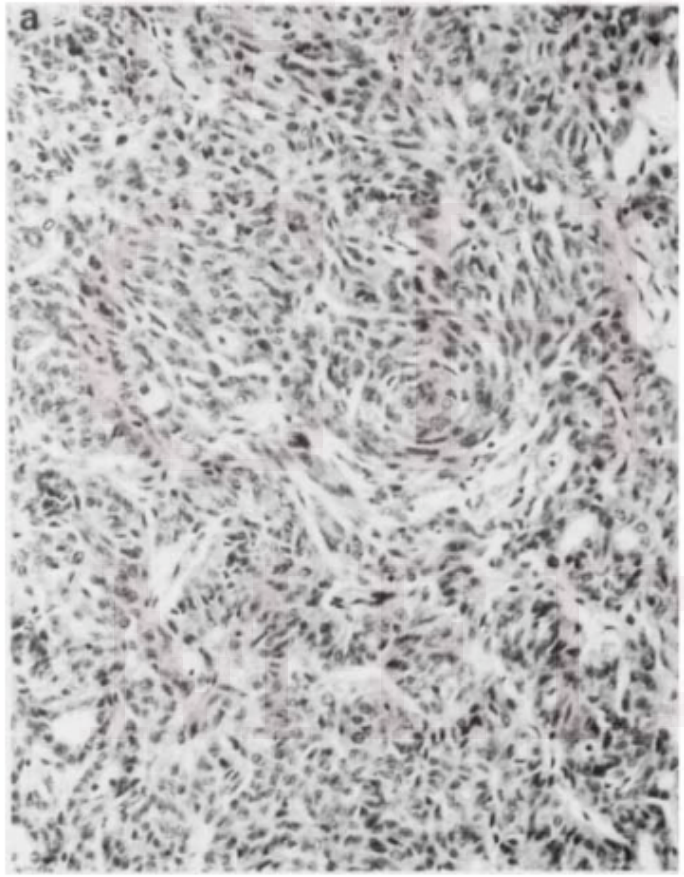
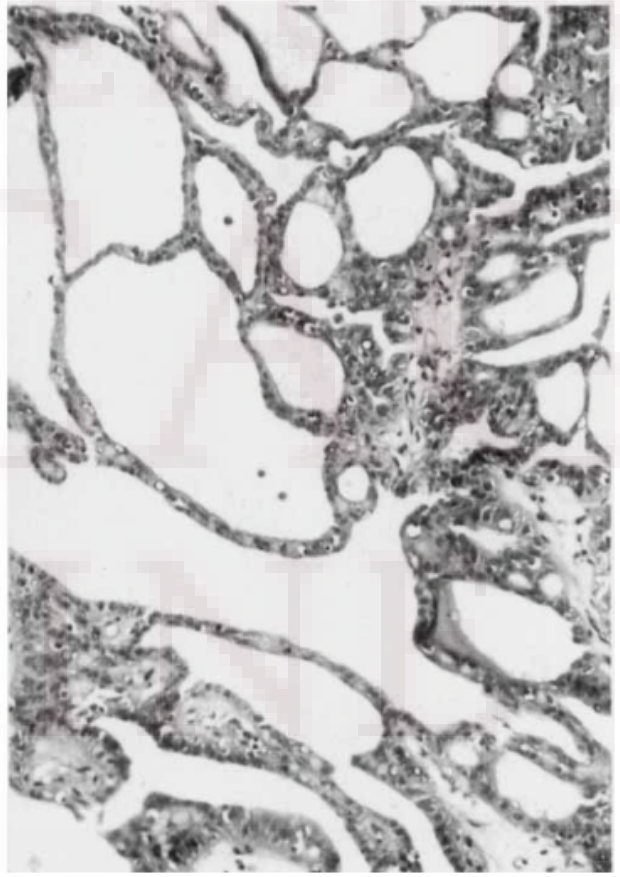
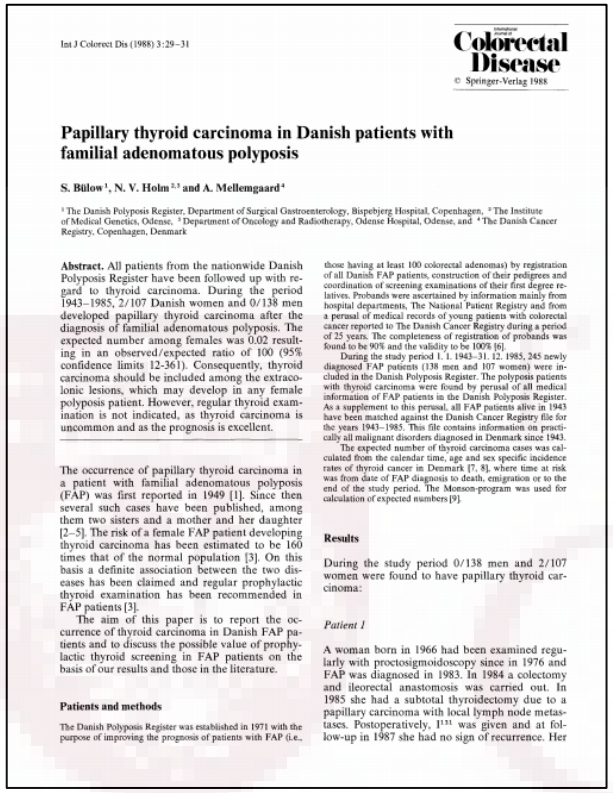
Samples from two tumor foci from the thyroid of a patient with FAP.



Solid component with spindle cells in a whirling pattern.



Large follicles in a cribriform pattern with papillary projections.



Int J Colorect Dis (1988) 3:29–31

Colorectal Disease

© Springer-Verlag 1988

Papillary thyroid carcinoma in Danish patients with familial adenomatous polyposis

S. Bülow [1], N. V. Holm [2,3] and A. Mellemgaard [4]

[1] The Danish Polyposis Register, Department of Surgical Gastroenterology, Bispebjerg Hospital, Copenhagen, [2] The Institute of Medical Genetics, Odense, [3] Department of Oncology and Radiotherapy, Odense Hospital, Odense, and [4] The Danish Cancer Registry, Copenhagen, Denmark

Abstract. All patients from the nationwide Danish Polyposis Register have been followed up with regard to thyroid carcinoma. During the period 1943–1985, 2/107 Danish women and 0/138 men developed papillary thyroid carcinoma after the diagnosis of familial adenomatous polyposis. The expected number among females was 0.02 resulting in an observed/expected ratio of 100 (95% confidence limits 12-361). Consequently, thyroid carcinoma should be included among the extracolonic lesions, which may develop in any female polyposis patient. However, regular thyroid examination is not indicated, as thyroid carcinoma is uncommon and as the prognosis is excellent.

The occurrence of papillary thyroid carcinoma in a patient with familial adenomatous polyposis (FAP) was first reported in 1949 [1]. Since then several such cases have been published, among them two sisters and a mother and her daughter [2–5]. The risk of a female FAP patient developing thyroid carcinoma has been estimated to be 160 times that of the normal population [3]. On this basis a definite association between the two diseases has been claimed and regular prophylactic thyroid examination has been recommended in FAP patients [3].

The aim of this paper is to report the occurrence of thyroid carcinoma in Danish FAP patients and to discuss the possible value of prophylactic thyroid screening in FAP patients on the basis of our results and those in the literature.

Patients and methods

The Danish Polyposis Register was established in 1971 with the purpose of improving the prognosis of patients with FAP (i.e., those having at least 100 colorectal adenomas) by registration of all Danish FAP patients, construction of their pedigrees and coordination of screening examinations of their first degree relatives. Probands were ascertained by information mainly from hospital departments, The National Patient Registry and from a perusal of medical records of young patients with colorectal cancer reported to The Danish Cancer Registry during a period of 25 years. The completeness of registration of probands was found to be 90% and the validity to be 100% [6].

During the study period 1. 1. 1943–31. 12. 1985, 245 newly diagnosed FAP patients (138 men and 107 women) were included in the Danish Polyposis Register. The polyposis patients with thyroid carcinoma were found by perusal of all medical information of FAP patients in the Danish Polyposis Register. As a supplement to this perusal, all FAP patients alive in 1943 have been matched against the Danish Cancer Registry file for the years 1943–1985. This file contains information on practically all malignant disorders diagnosed in Denmark since 1943.

The expected number of thyroid carcinoma cases was calculated from the calendar time, age and sex specific incidence rates of thyroid cancer in Denmark [7, 8], where time at risk was from date of FAP diagnosis to death, emigration or to the end of the study period. The Monson-program was used for calculation of expected numbers [9].

Results

During the study period 0/138 men and 2/107 women were found to have papillary thyroid carcinoma:

Patient 1

A woman born in 1966 had been examined regularly with proctosigmoidoscopy since in 1976 and FAP was diagnosed in 1983. In 1984 a colectomy and ileorectal anastomosis was carried out. In 1985 she had a subtotal thyroidectomy due to a papillary carcinoma with local lymph node metastases. Postoperatively, I^{131} was given and at follow-up in 1987 she had no sign of recurrence. Her

Papillary thyroid carcinoma in Danish patients with familial adenomatous polyposis.

During the period of study from January 1943 to December 1985, 138 men and 107 women were identified with FAP.

Using the Danish Cancer Registry file, no men with FAP were found to have papillary thyroid cancer. Two women were found the have PTC.

"In our opinion, cases of FAP and thyroid cancer therefore represent more than mere coincidence. Some sort of relationship between the two disease appears probable and, consequently, thyroid carcinoma should be included among the several extracolonic manifestations which may occur in any FAP patient."

Int J Colorect Dis (1988) 3:29-31.

Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis

***The Johns Hopkins Registry**

TABLE I *Patients with familial adenomatous polyposis from The Johns Hopkins Registry who developed extraintestinal cancer*

Age at diagnosis of cancer (y)	*Race*	*Sex*	*Location of cancer*
29	W	M	Thyroid
27	W	F	Thyroid
27	W	F	Thyroid
29*	W	F	Thyroid
18	B	F	Thyroid
52	W	F	Pancreas
47	W	M	Pancreas
32	W	M	Pancreas
78	W	M	Pancreas
60	W	F	Lung
45	W	M	Lung
57	W	F	Breast
50	W	F	Breast

*Patient at risk for FAP. All others were affected with FAP.

TABLE II *Risk analysis of extrainterestinal cancers in patients with familial adenomatous polyposis (The Johns Hopkins Polyposis Registry) as compared with the general population of the United States (SEER data)*

Site, ICD 9th revision	*Patient number (person years)*	*Number of carcinomas*	*Relative risk (O/E)*	*95% confidence limits*	*Rate per 100 000 (person years)*
Thyroid 193·0	1391 (18 682·6)	5	7·6	2·5 to 17·7	26·8
Pancreas 157·0–0·9	1391 (18 682·6)	4	4·5	1·2 to 11·4	21·4
Lung 162·0–0·9	1391 (18 682·6)	2	0·4	0·4 to 1·4	10·7
Breast 174·0–0·9	711 (9698·1)	2	0·4	0·04 to 1·3	20·6

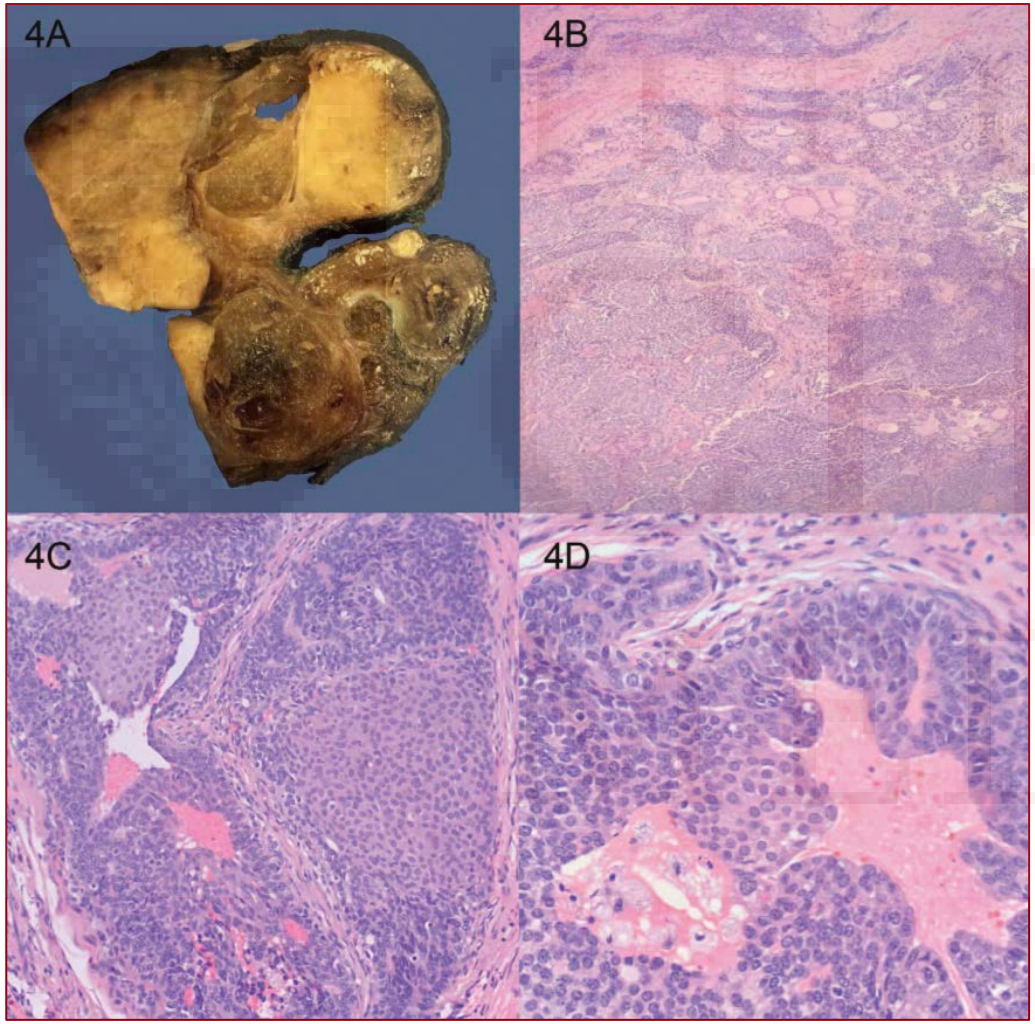
O/E = Observed/expected.

Gut 1993; 34: 1394-1396.

Familial Adenomatous Polyposis Syndrome

An Update and Review of Extraintestinal Manifestations

Peyman Dinarvand, MD; Elizabeth P. Davaro, MD; James V. Doan, DO; Mary E. Ising, BS; Neil R. Evans, MD; Nancy J. Phillips, MD; Jinping Lai, MD, PhD; Miguel A. Guzman, MD



The reported lifetime risk of development of thyroid cancer in FAP ~2% (some say closer to 10-12%).

10% of cases present with metastatic disease, like classic PTC.

Often stain strongly for B-catenin, while calcitonin and thyroglobulin staining are negative.

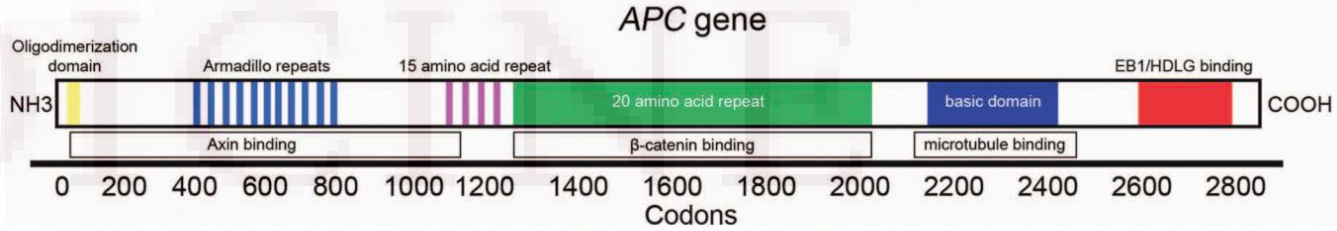


Figure 3. *A, Supernumerary teeth (arrows). B, Structure of the protein coded by adenomatous polyposis coli gene (APC). Abbreviations: EB1, end-binding protein 1; HDLG, homologue of* Drosophila *discs large.*

Arch Pathol Lab Med; (143) Nov 2019.

How should we risk-stratify FAP patients with CMV-PTC?

Recommendations for screening patients with FAP for thyroid cancer?

ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes

Sapna Syngal, MD, MPH, FACG[1,2,3], Randall E. Brand, MD, FACG[4], James M. Church, MD, FACG[5,6,7], Francis M. Giardiello, MD[8], Heather L. Hampel, MS, CGC[9] and Randall W. Burt, MD, FACG[10]

11. Annual thyroid screening by ultrasound should be recommended to individuals affected with FAP, MAP, and attenuated polyposis (conditional recommendation, low quality of evidence).

Characteristics of Benign and Malignant Thyroid Disease in Familial Adenomatous Polyposis Patients and Recommendations for Disease Surveillance

TABLE 2. TNM STAGING COMPARISON OF SCREENING-DETECTED COMPARED WITH NON-SCREENING DETECTED THYROID CANCER CASES

	SD cases	*NSD cases*
Mean primary tumor size ($p=0.04$)	1.1 cm	2.4 cm
Lymph node positivity	1/15 cases	5/13 cases
Metastases	0/15 cases	1/15 cases
Complications	0/15 cases	3/15 cases

SD, screening detected; NSD, non-screening detected.

Am J Gastroenterol. 2015 Feb; 110(2):223-262.

Thyroid. 2015 Mar:25(3):325-332.

Hereditary Colorectal Cancer Syndromes: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the Familial Risk–Colorectal Cancer: European Society for Medical Oncology Clinical Practice Guidelines

Elena M. Stoffel, Pamela B. Mangu, Stephen B. Gruber, Stanley R. Hamilton, Matthew F. Kalady, Michelle Wan Yee Lau, Karen H. Lu, Nancy Roach, and Paul J. Limburg

- *Thyroid cancer:* Annual cervical ultrasonography ***may be considered*** starting at age 25 to 30 years.

THYROID CANCER

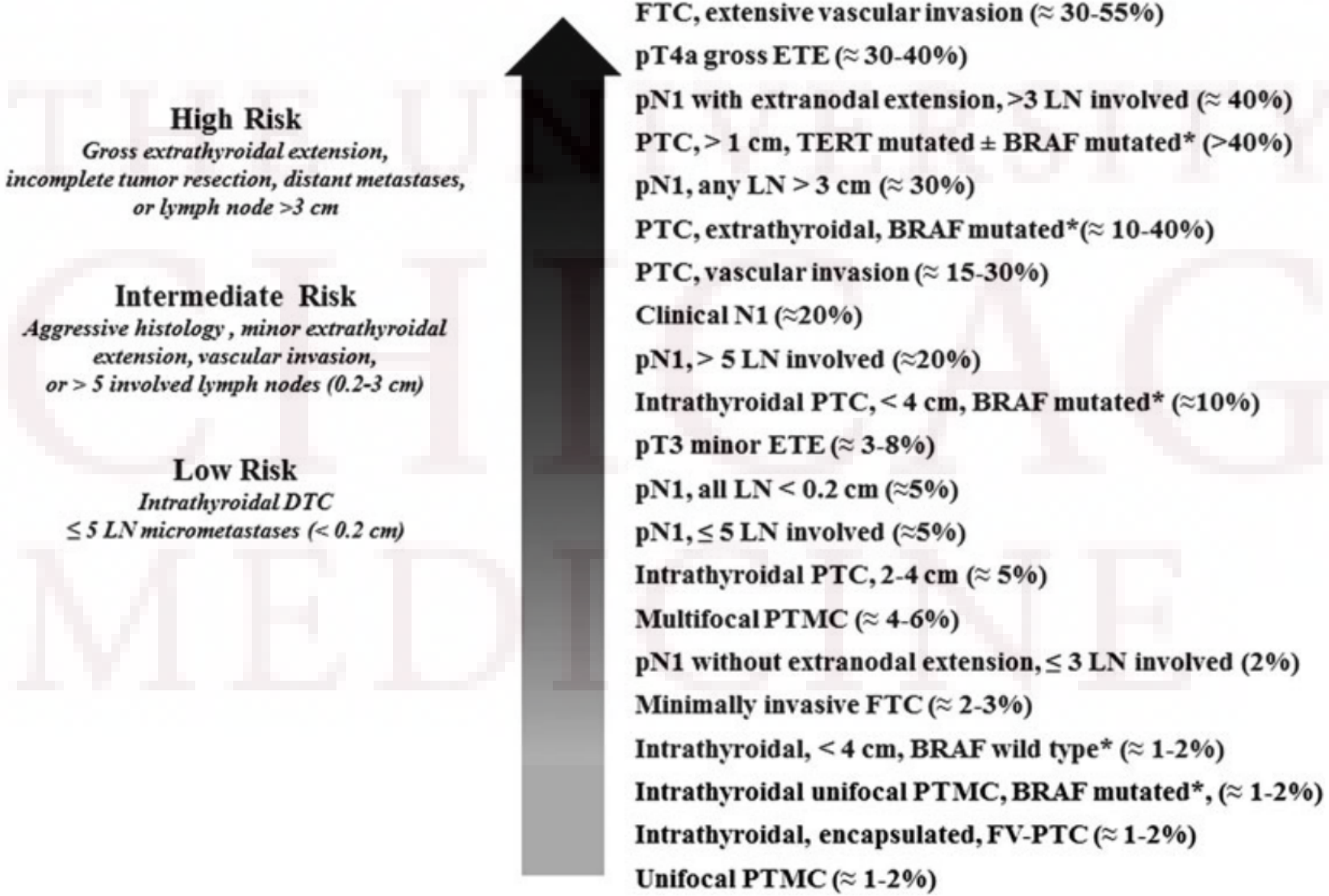
We perform an annual thyroid ultrasound in patients with familial adenomatous polyposis (FAP) starting in the late teens [1]. Physical examination alone is insufficient to detect malignancy. In a study of 192 FAP patients screened for thyroid cancer, none of the five patients diagnosed with thyroid cancer was diagnosed through clinical history and neck examination [21]. In a prospective screening program that included 205 patients with FAP, approximately one half of patients had at least one thyroid nodule and approximately one third required fine-needle aspiration biopsy [22].

J Clin Oncol. 2015 Jan 10; 33(2): 20-217.

Uptodate.com "FAP: screening and management of patients and families"

Risk of Structural Disease Recurrence

(In patients without structurally identifiable disease after initial therapy)



Thyroid 26.1 (2016): 1-133.

Table 11. ATA 2009 Risk Stratification System with Proposed Modifications

ATA low risk	Papillary thyroid cancer (with all of the following): • No local or distant metastases; • All macroscopic tumor has been resected • No tumor invasion of loco-regional tissues or structures • The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) • If ^{131}I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan • No vascular invasion • Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in largest dimension)[a] Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer[a] Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion[a] Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including *BRAF*^{V600E} mutated (if known)[a]
ATA intermediate risk	Microscopic invasion of tumor into the perithyroidal soft tissues RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Papillary thyroid cancer with vascular invasion Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension[a] Multifocal papillary microcarcinoma with ETE and *BRAF*^{V600E} mutated (if known)[a]
ATA high risk	Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE) Incomplete tumor resection Distant metastases Postoperative serum thyroglobulin suggestive of distant metastases Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension[a] Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)[a]

[a]Proposed modifications, not present in the original 2009 initial risk stratification system. See sections [B19]–[B23] and Recommendation 48B.