Thyroid Cancer in Patients with Familial Adenomatous Polyposis

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14th September 2023

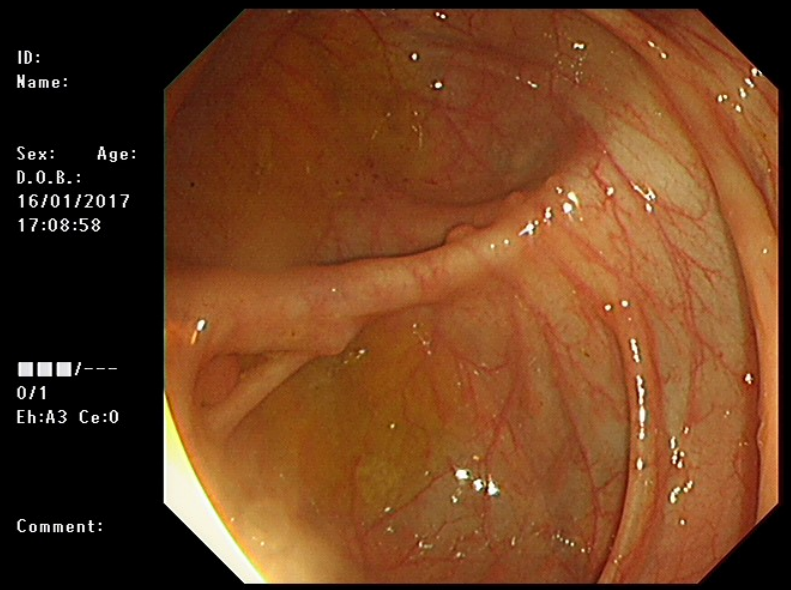
Case presentation

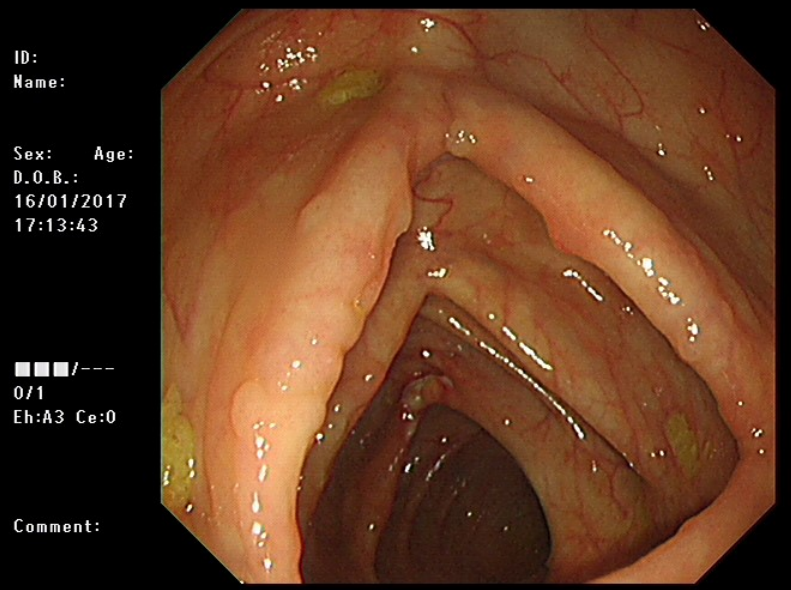
Ms Hui

20-year-old

Mother had proctocolectomy done for colonic polyposis

2 maternal uncles and 1 maternal aunt died of colon cancer





13-year-old

Started colonoscopy surveillance

19-year-old

Hereditary GI cancer registry confirmed germline mutation in the APC gene

20-year-old

Colonoscopy: hundreds of small polyps along entire colon (TA LGD)

21-year-old

Laparoscopic total colectomy + IRA

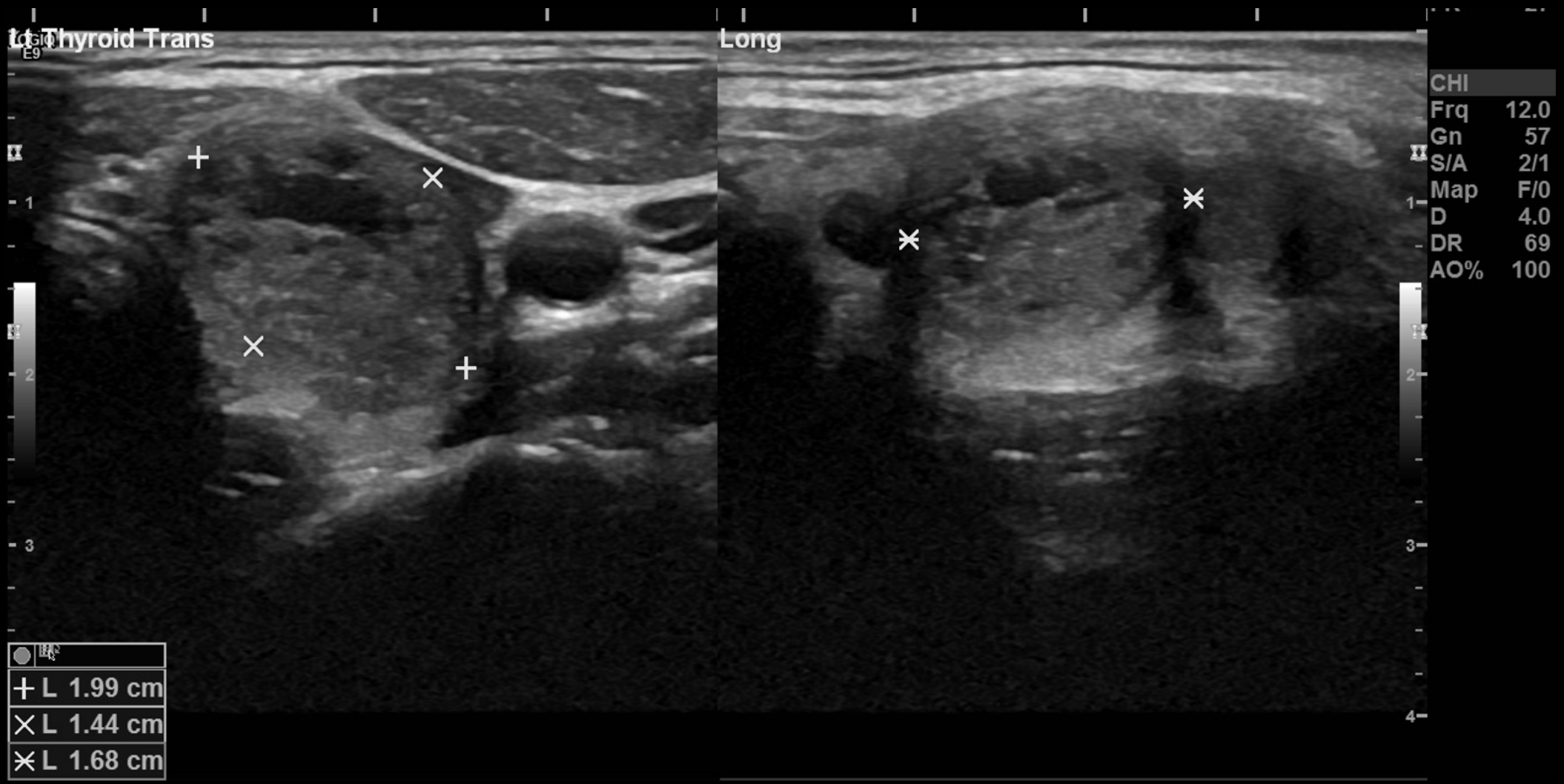
(numerous TA)

Referred to thyroid clinic in 10/2021

- Thyroid nodules detected on routine USG in mainland China
- Asymptomatic
- PE: 2 cm left thyroid nodule, no palpable cervical LN, euthyroid
- TFT normal

USG thyroid 4/ 2022:

- Multiple hypoechoic nodules in both thyroid lobes
- Some nodules contain coarse calcifications
- A dominant nodule contains some cystic component, measured about 2 x 1.4x 1.7 cm in left upper pole
- No abnormal cervical lymph node


Thyroid Trans
Long
CHI
Frq 12.0
Gn 57
S/A 2/1
Map F/0
D 4.0
DR 69
AO% 100
L 1.99 cm
L 1.44 cm
L 1.68 cm

USG guided FNAC to left dominant thyroid nodule:

Patho:

- **Cytologic atypia of undetermined significance with nuclear groovings and papillary pattern.**
- **Suggested excision for assessment**

Total thyroidectomy 5/2022

(frozen section of left thyroid lobe confirmed multifocal PTC, total thyroidectomy done)

Patho:

Left thyroid:

- **multifocal papillary carcinoma (Total 9 foci)**
- largest one 22mm.
- No extrathyroidal extension. No LVI.
- Cribriform-morular variant

Right thyroid:

- **2 papillary carcinoma**
- largest one 7mm.

RAI given 10/2022

Post-WBS 11/2022

- no evidence of distant metastasis of differentiated thyroid cancer

FAP

- Autosomal-dominant colorectal cancer syndrome
- Germline mutation in the adenomatous polyposis coli (APC) gene on chromosome 5q21
- APC is a tumor suppressor gene, first identified in 1987
- Spontaneous mutation rate varies from 10 – 30%

- Characterised by hundreds of adenomatous colorectal polyps
- Progression to colorectal cancer at an average age of 35 to 40.

- Incidence around 1 in 10 000 individuals.
- Account for 1% of all colorectal cancer
- Extracolonic manifestations: thyroid cancer, UGI polyps, congenital hypertrophy of the retinal pigment epithelium, desmoid tumors, and other extracolonic malignancies.

Thyroid cancer in FAP

- First reported by Crial et al in 1949.
- Lifetime risk traditionally reported as **2%**
- The age at diagnosis is earlier than that for colon cancer, with an average age of 25-33 years.
- Female to male ratio 8: 1
- The risk of young women under the age of 35 with FAP could be up to 160 times that of normal individuals according to St Mark's Hospital Polyposis Registry

Table 1. Extracolonic Cancer Risks in FAP

Malignancy	Relative Risk	Absolute Lifetime Risk (%)
Desmoid	852.0	15.0
Duodenum	330.8	3.0–5.0
Thyroid	7.6	2.0
Brain	7.0	2.0
Ampullary	123.7	1.7
Pancreas	4.5	1.7
Hepatoblastoma	847.0	1.6
Gastric	–	0.6*

Note. Adapted from Giardiello *et al*. (78), Jagelman *et al*. (76), Sturt *et al*. (57), Lynch *et al*. (58), Bülow *et al*. (27).
*The Leeds Castle Polyposis Group.

1. Polymnia Galiatsatos et al. Familial Adenomatous Polyposis. American Journal of Gastroenterology 2006; 101: 385- 398.

Increase in prevalence of TC in FAP patients

- Higher prevalence in reports published from 2002 onwards
- In the three latest articles, published since 2010, the prevalence of thyroid cancer ranged from 4 to 12%

Table 4 Characteristics of the studies included in the analysis

	Study	Year	Location	Years included	Patients with FAP (n)	Rate of thyroid cancer (%)	Number of Patients with thyroid cancer(F:M)
1	Plail et al. [11]	1987	UK	1925–1987	998	0.7	7:0
2	Bülow et al. [19]	1988	Denmark	1943–1985	245	0.8	2:0
3	Giardiello et al. [12]	1993	US	1969–1987	1391	0.4	4:1
4	Iwama et al. [13]	1993	Japan	–1990	1050	1.1	9:2
5	Bülow et al. [14]	1997	UK	1959–1995	3727	1.2	44:1
6	Perrier et al. [20]	1998	US	1949–1995	2754	0.5	11:1
7	van der Linde et al. [21]	1998	Netherlands	1985–1995	601	0.7	4:0
8	Ho et al. [28]	2002	Hong Kong	1995–2001	70	5.7	4:0
9	Truta et al. [15]	2003	North America	1980–2003	1194	1.3	16:0
10	Herraiz et al. [22]	2007	US	1994–2007	51	11.8	6:0
11	Jarrar et al.[a] [23]	2011	US	2008–2009	192	2.6	8:2
12	Steinhagen et al.[a] [24]	2012	US	2001–2010	66	6.1	4:0
13	Steinhagen et al.[a] [25]	2014	US	2010–2012	50	4.0	2:0
14	Present research	2014	Japan	2010–2012	303	6.4	16:2

2. Haruki Sada et al. Prevalence of and risk factors for thyroid carcinoma in patients with familial adenomatous polyposis: results of a multicentre study in Japan and a systematic review. Surgery Today 2019; 49: 72-81.

Increasing trend

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Familial Adenomatous Polyposis

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Discussion

FAP: CANCER RISKS

Site	Estimated Average Age of Presentation	Cumulative Risk for Diagnosis Through Age 80 y[a]	Cumulative Risk for Diagnosis Through Lifetime for General Population[f]	References
Colon cancer (without colectomy)	39 years (median)	Approaches 100%	4.1%	Reference: 1
Colon cancer (post-colectomy)	Rectal (s/p IRA): 46–48 years Pouch and ATZ/rectal cuff (s/p IPAA): Not available	Rectal (s/p IRA): 10%–30%[b] Pouch and ATZ/rectal cuff (s/p IPAA): <1%–3%	4.1%	References: 2–10
Duodenal or periampullary cancer	50–52 years	<1%–10%	—[g]	References: 11–19
Gastric cancer	52–57 years	0.1%–7.1%[c]	0.8%	References: 19–27
Small bowel cancer (distal to duodenum)	43 years	<1%	0.3%	Reference: 19
Intra-abdominal desmoid tumors	31–33 years	10%–24%[d] Mutations in the 3' end of the *APC* gene have a higher risk[e]	—[g]	References: 28–33
Thyroid cancer (predominantly papillary thyroid carcinoma)	26–44 years	1.2%–12%	1.2%	References: 34–43
Hepatoblastoma	18–33 months	0.4%–2.5%	—[g]	References: 44–48
CNS cancer (predominantly medulloblastoma)	18 years	1%	0.6%	References: 49–50

Local data

- In HK, the Hereditary Gastrointestinal Cancer Registry was established in 1995 with the aim of achieving secondary colorectal cancer prevention for high-risk families.

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ORIGINAL ARTICLE

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ST Yuen 袁兆燦

Phenotype and management of patients with familial adenomatous polyposis in Hong Kong: perspective of the Hereditary Gastrointestinal Cancer Registry

香港的遺傳腺瘤狀息肉病患者的表型與處理：遺傳性腸胃癌資料庫的前瞻

Objectives. To report on the phenotypic spectrum and clinical management of Chinese patients suffering from the rare autosomal dominant colorectal cancer syndrome of familial adenomatous polyposis.

Design. Analysis of prospectively collected data from the database of a regional registry.

Setting. The Hereditary Gastrointestinal Cancer Registry, Hong Kong.

Participants. One hundred and eight patients with proven familial adenomatous polyposis from 36 local Chinese families with the condition recruited to the Registry from 1995 to 2001.

Local data: Thyroid Cancer 5.7%

Key words:
Adenoma;
Familial adenomatous polyposis;
Phenotype;
Registries

關鍵詞：
腺瘤；
遺傳腺瘤狀息肉病；
表型；
資料庫

Hong Kong Med J 2002;8:342-7

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Results. Fifty patients suffered from colorectal cancer with a mortality rate of 78.0%. The strategy of presymptomatic diagnosis by screening and appropriate prophylactic surgery reduced the incidence of colorectal cancer. Affected individuals were prone to develop potentially serious extracolonic lesions including thyroid cancer (5.7%), desmoid tumour (15.7%), gastroduodenal adenomas (7.1%), duodenal microadenoma (17.1%), and pouch polyposis (17.4%).
Conclusions. Screening and prophylactic surgery are effective ways to prevent colorectal cancer for patients with familial adenomatous polyposis. Lifelong regular surveillance is necessary to detect and manage extracolonic lesions. A dedicated registry is essential to coordinate clinical management and to compile data for furthering knowledge of this rare but complex syndrome.

目的：報告患有罕見的常染色體顯性遺傳腺瘤狀息肉病的華人患者，其表型範圍和臨床處理。
設計：於地區資料庫預期搜集的資料分析。
安排：香港遺傳性腸胃癌資料庫。
參與者：由1995年到2001年，資料庫內36個本地華人家庭中的108名被證實患有遺傳腺瘤狀息肉病的患者。
療法：對有可能患病的家庭成員進行篩查、預兆診斷的預防性手術、及對個別患者進行結腸外損害的監察。
主要結果測量：結直腸癌率，手術治療類型，結腸外損害的範圍，以及徵狀的治理。
結果：50名病人患上結直腸癌，死亡率為78.0%。通過篩查進行預兆診斷和適當的預防性手術，減少了結直腸癌的發生。受影響的患者有較大機會患上具潛在嚴重性的結腸外損害，包括甲狀腺癌(5.7%)、硬纖維瘤(15.7%)、胃十二指腸腺瘤(7.1%)、十二指腸微腺瘤(17.1%)、及袋狀息肉病(17.4%)。
結論：對於遺傳腺瘤狀息肉病患者，篩查和預防性手術可有效預防結直腸癌的發生。此外，終生定期監察可以發現和醫治結腸外的損害。專門的資料庫對於協調臨床治療和綜合資料的工作，並進一步了解這種罕見而複雜的綜合病症是必需的。

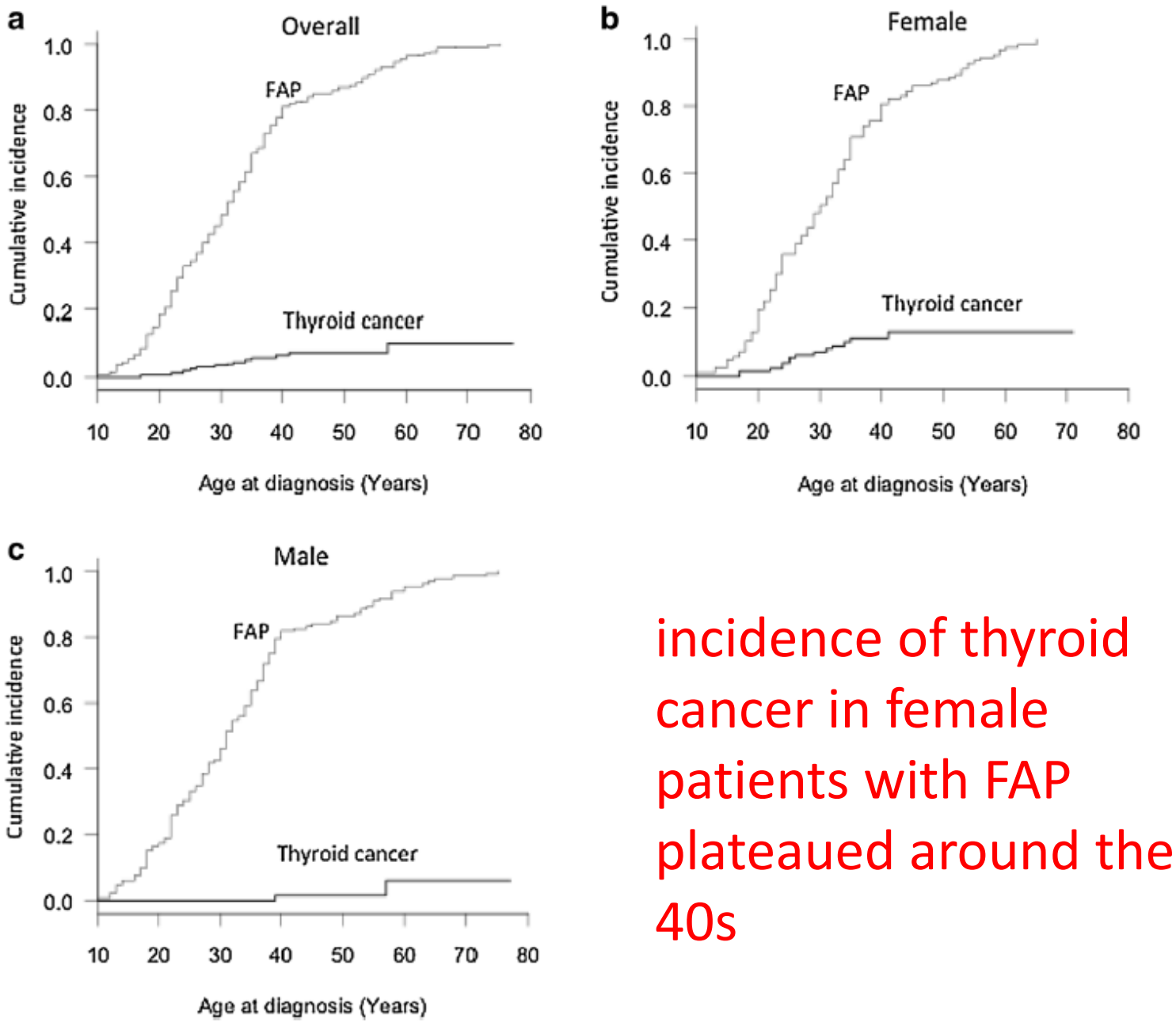
How to explain the increase in prevalence?

1. Advances in imaging modalities, including the widespread use of US
2. Thyroid cancer screening program
3. Improved life expectancy of FAP patients
4. The increase in prevalence of thyroid cancer in the general population

Sex difference

According to database of Polyposis Registry of Japan:

- The incidence of thyroid cancer in the general was 2.8 and 0.7% in women and men (female ratio 4:1)
- Among the FAP patients was 11.4 and 1.4%, respectively (female-to-male ratio being 8:1)



incidence of thyroid cancer in female patients with FAP plateaued around the 40s

Fig. 1 The cumulative prevalence of familial adenomatous polyposis (FAP) and FAP-associated thyroid cancer. The cumulative prevalence of thyroid cancer in women with FAP peaks and plateaus at around 40 years of age. Overall (**a**), female patients (**b**), male patients (**c**)

Haruki Sada et al. Prevalence of and risk factors for thyroid carcinoma in patients with familial adenomatous polyposis: results of a multicentre study in Japan and a systematic review. Surgery Today 2019; 49: 72-81

Higher risk of desmoids tumor in FAP patients with TC

TABLE 3. The Association Between Extracolonic Manifestations of FAP and Thyroid Cancer

	FAP with Normal Screening	*P**	FAP with Benign Nodules	*P**	FAP with Thyroid Cancer
All extracolonic manifestations†	89/113 (79%)	0.4*	66/72 (92%)	NS*	5/5 (100%)
CHRPE‡	15/113 (13%)	0.15*	11/72 (15%)	0.20*	2/5 (40%)
Desmoids	25/113 (22%)	0.01*	14/72 (19%)	0.01*	4/5 (80%)

*Compared to FAP patients with thyroid cancer.

† Data in the table are represented as the number of individuals with extracolonic FAP features per each FAP subgroup. The other extracolonic manifestations examined included Congenital Hypertrophy of the Retinal Pigment Epithelium, gastric and duodenal polyps and carcinomas, desmoids, benign skin tumors/lipomas and osteomas.

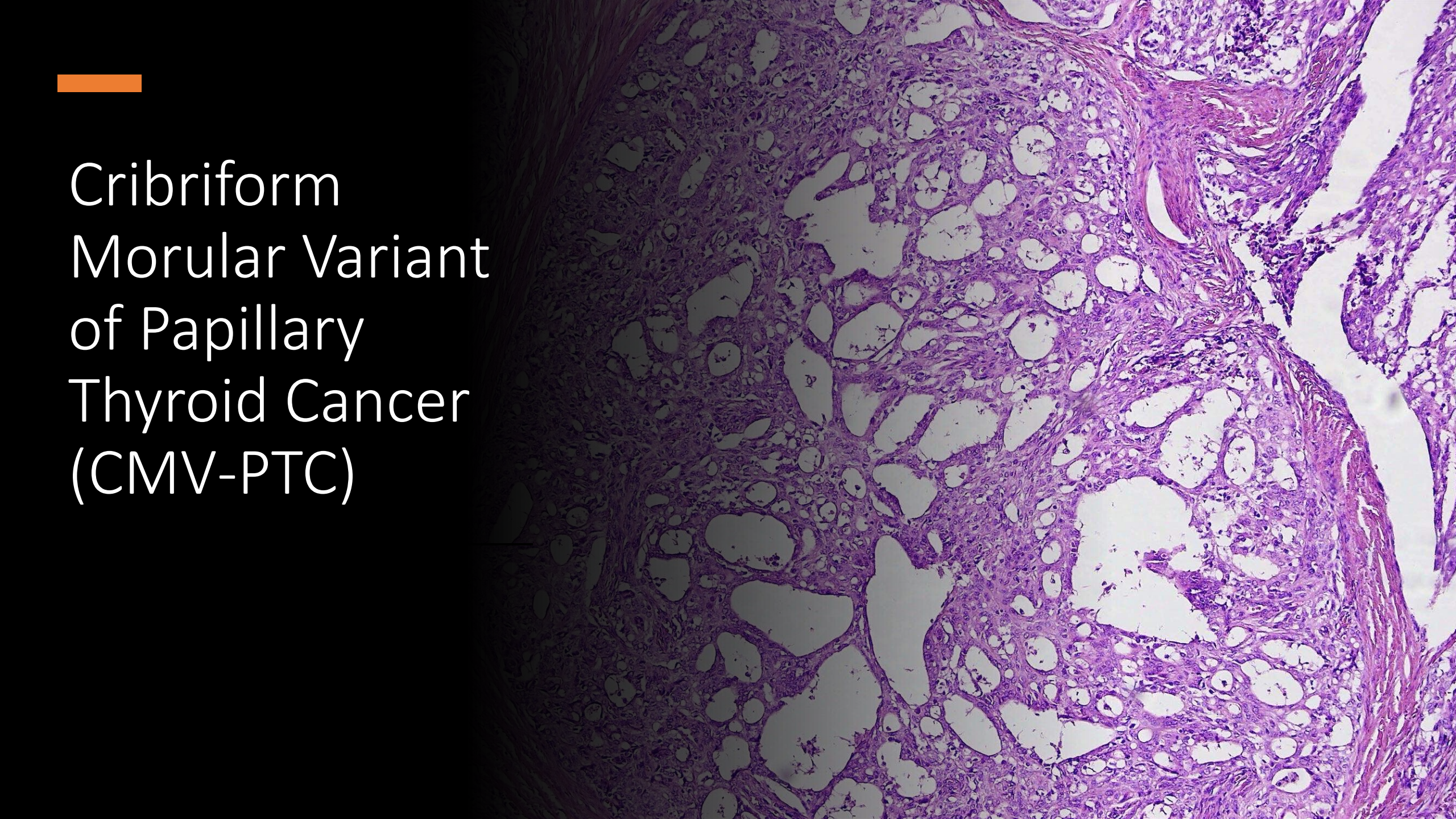
‡ Congenital Hypertrophy of the Retinal Pigment Epithelium.

5. Awad M Jarrar et al. Screening for Thyroid Cancer in Patients With Familial Adenomatous Polyposis. Annals of Surgery 2011; 253: 515-521

Multifocality

- Reported to be multifocal in 44% to 64% of cases
- Comparable to classical PTC

Cribriform Morular Variant of Papillary Thyroid Cancer (CMV-PTC)

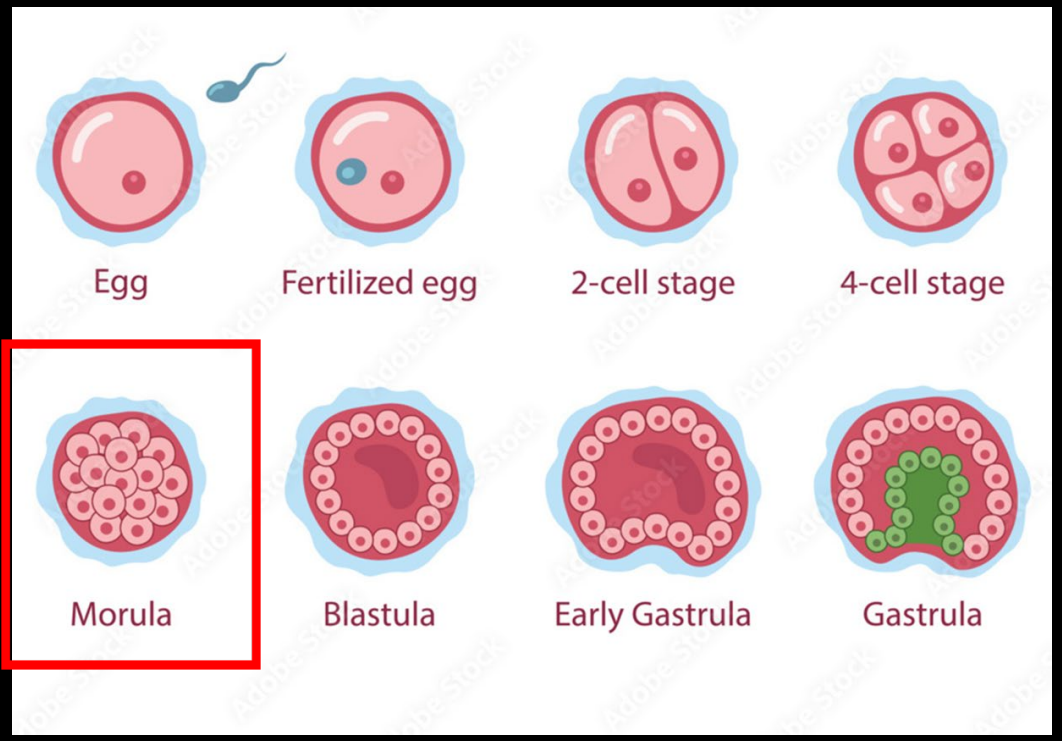


Cribriform Morular Variant -PTC

- A rare subtype of PTC
- Contributes to 0.16% of all PTCs
- 39% associated with FAP
- 92% of TC in FAP
- 10% developing metastatic disease (comparable to classical PTC)
- Long term prognosis Is good with 5-year survival rate > 90%

Cribriform Morular Variant -PTC

- FNAC typically showed classical PTC features
- Can be mistaken for poorly differentiated thyroid carcinoma
- Positive IHC staining for b-catenin
- BRAF mutations often negative (unlike classical PTC)
- Histologically: cribriform and morular features



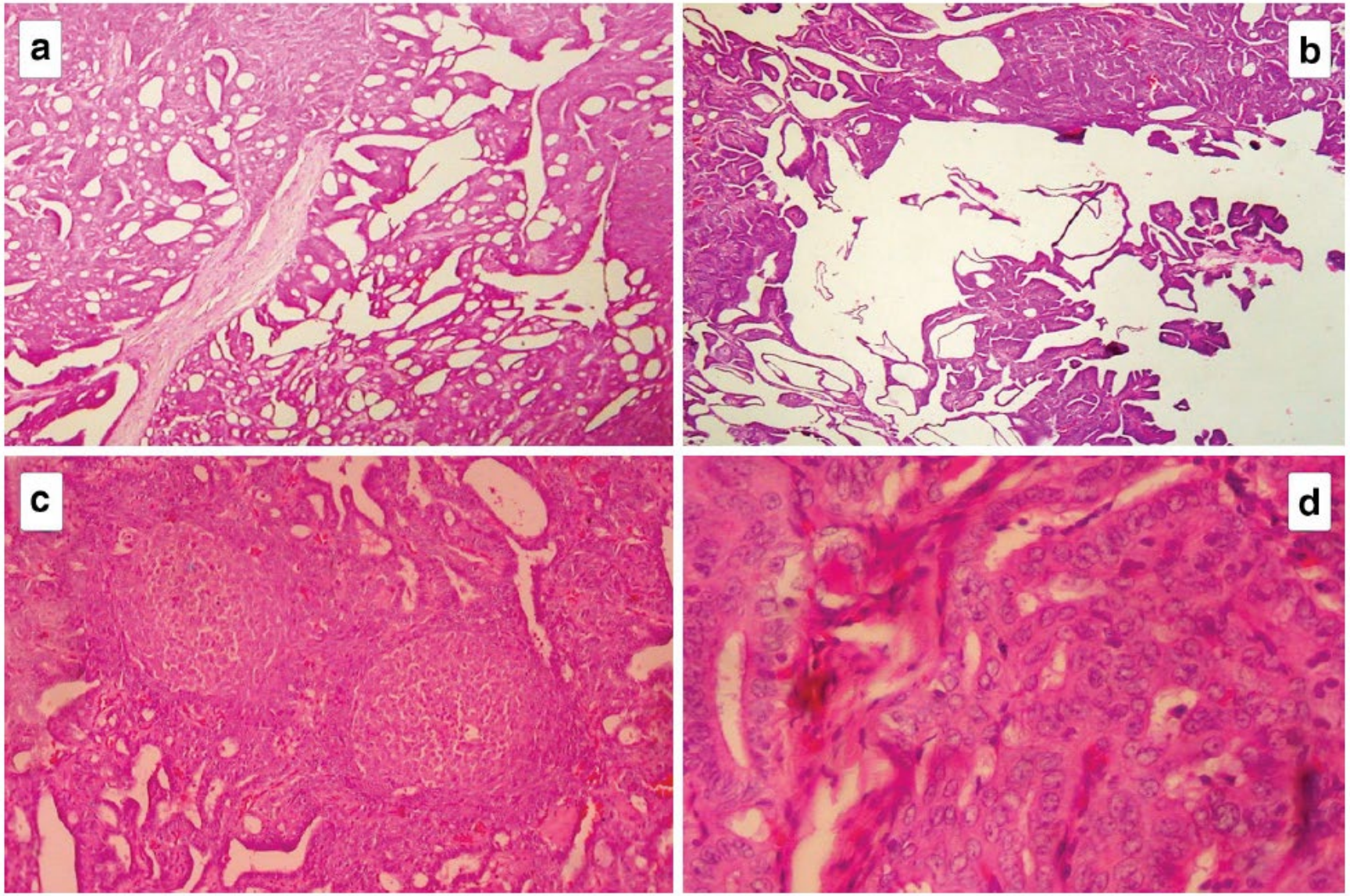


Fig. 2 Microscopic appearance of Cribriform morular variant of papillary thyroid carcinoma, showing all under mentioned features in the same tumour. **a** Cribriform growth pattern. **b** Papillary growth pattern. **c** Characteristic whorls of cell nests forming morules. **d** Cytological details—rounded cells with clear nuclei

6. Nishantha Liyanpathirana et al. A distinct variant of papillary thyroid carcinoma indicating familial adenomatous polyposis (FAP): a case report and brief review. BMC Res Notes 2015; 8: 795.

2015 ATA Guidelines

[B15] What are the basic principles of histopathologic evaluation of thyroidectomy samples?

RECOMMENDATION 46

(C) Histopathologic variants associated with familial syndromes (cribriform-morular variant of papillary carcinoma often associated with FAP, follicular or papillary carcinoma associated with PTEN-hamartoma tumor syndrome) **should be identified during histopathologic examination and reported.**

(Weak recommendation, Low-quality evidence)

First Presentation as CMV- PTC

- Recognition of the association of CMV-PTC with FAP presents an opportunity for early diagnosis of FAP
- Most studies recommended screening of FAP for patients diagnosed with CMC- PTC
- 39% CMV-PTC associated with FAP

Screening

Old studies recommended not to screen

TABLE 5. Summary of the Largest Published Series Investigating Thyroid Cancer in FAP Patients and Recommended Screening for Thyroid Disease

	Study Name (Reference)	Number of Patients	Disease	Type of Screening Recommended
1987	Plail et al[5]	998		Neck palpation
1988	Bulow et al[10]	245	FAP*	Recommend not to screen
1997	Bulow et al[4]	3727	FAP	Recommend not to screen
	Bell et al[11]	37	FAP and thyroid cancer	US†
	Giardiello et al[13]	1391	FAP	US for patients older than 30 years
	Cetta et al[18]	112	FAP and thyroid cancer	US for patients with CHRPE‡
	Herraiz et al[6]	51	FAP	US†
	Perrier et al[19]	14	FAP and thyroid cancer	Not addressed in study
	Dotto et al[16]	8	FAP and thyroid cancer	Not addressed in study

*Familial Adenomatous Polyposis.
†Ultrasound.
‡Congenital Hypertrophy of the Retinal Pigmented Epithelium.

5. Awad M Jarrar et al. Screening for Thyroid Cancer in Patients With Familial Adenomatous Polyposis. Annals of Surgery 2011; 253: 515-521.

A trend towards USG screening based on more recent studies

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5. Awad M Jarrar et al. Screening for Thyroid Cancer in Patients With Familial Adenomatous Polyposis. Annals of Surgery 2011; 253: 515-521.

Screening

2015 American College of Gastroenterology Guidelines

- Annual thyroid screening by ultrasound
  (conditional recommendation, low quality of evidence).
- Starting from late teenage years

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- Ultrasound starting from late teenage years.
- If normal, consider repeating ultrasound every 2–5 y
- If abnormal, consider referral to a thyroid specialist.
- Shorter intervals may be considered for individuals with a family history of thyroid cancer.

Rationale for USG screening

- 38% patients had thyroid nodules
- Increase in prevalence of TC in FAP patients
- Longer life expectancy of FAP patients
- Slow growing treatable disease
- Readily available
- Low cost
- Non-invasive nature

Why screening should be started at late teenage years?

- The youngest FAP patient with benign thyroid nodule reported was 17 years old
- Majority of reported patients with both FAP and TC were 20-30 years old.
- Some studies suggest screening at the age of 16

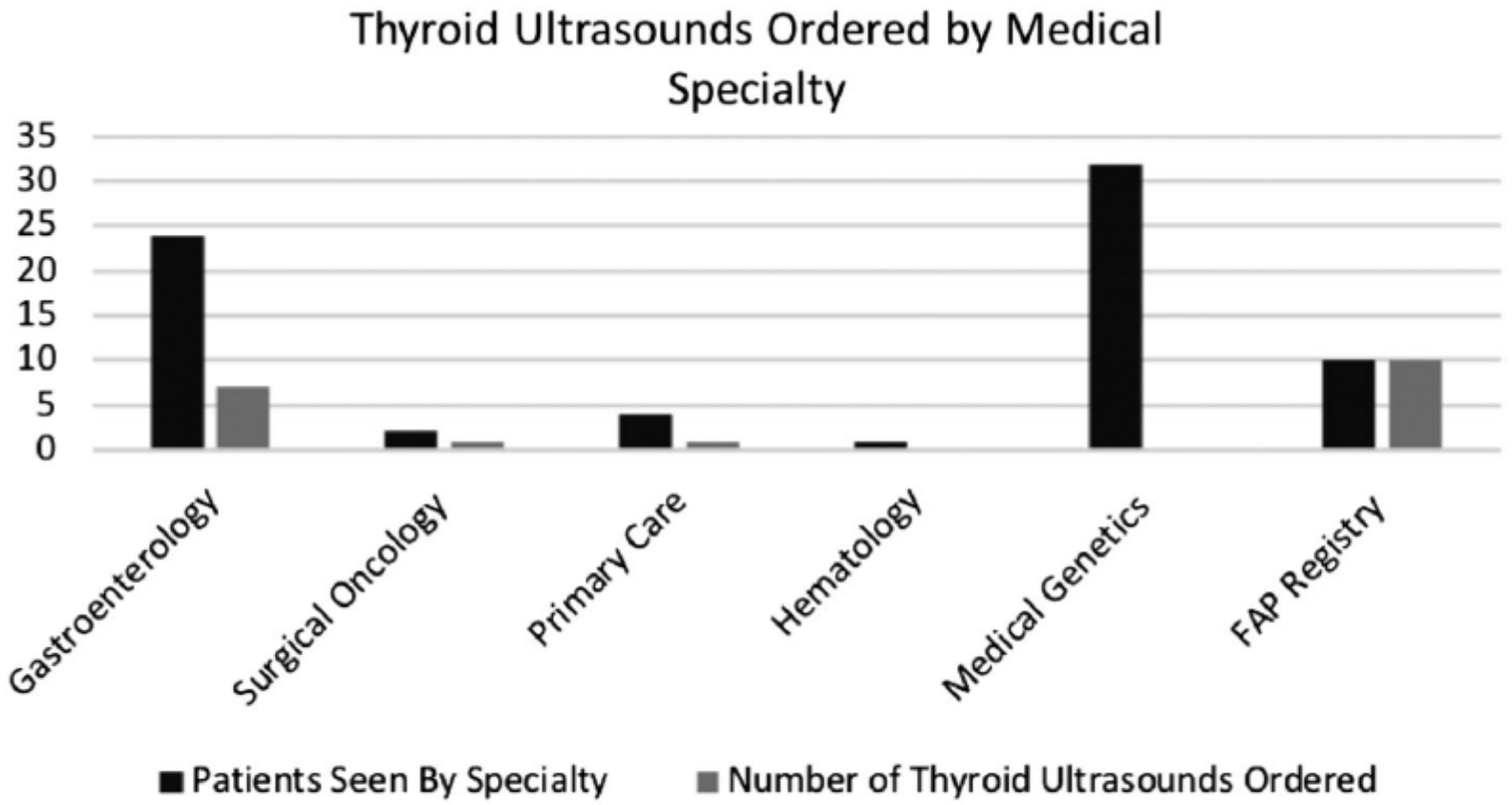


Fig. 2. How often a screening thyroid ultrasound (TUS) was ordered when a familial adenomatous polyposis (FAP) patient was seen by a particular medical specialty. If a patient learned of TUS during the interview portion of the study and then underwent TUS, they are not included in these data.

13. Celeste Nagy et al. Barriers to Thyroid Cancer Screening With Ultrasound in Patients With Familial Adenomatous Polyposis. The Laryngoscope. 2019; 129: 2436-2441.

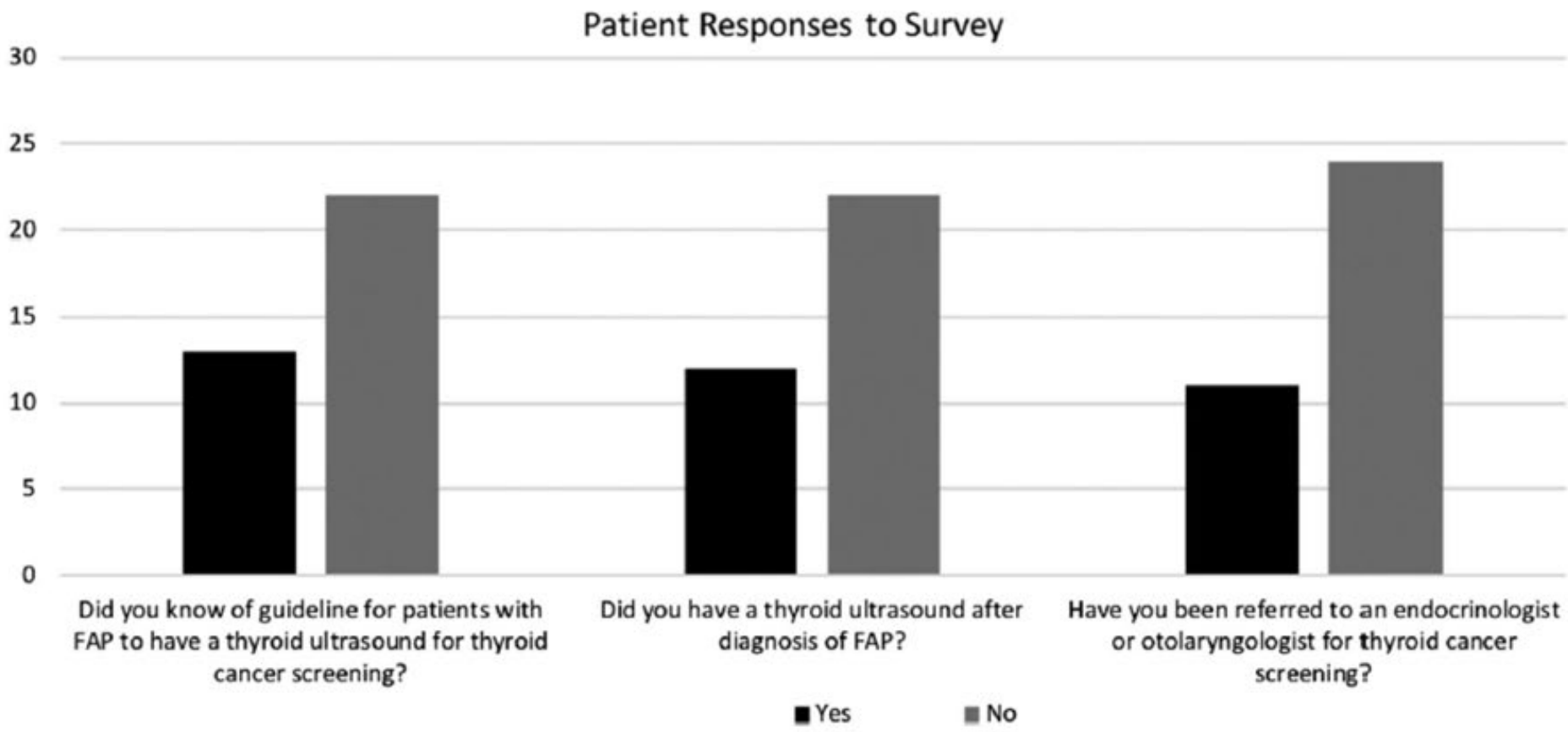
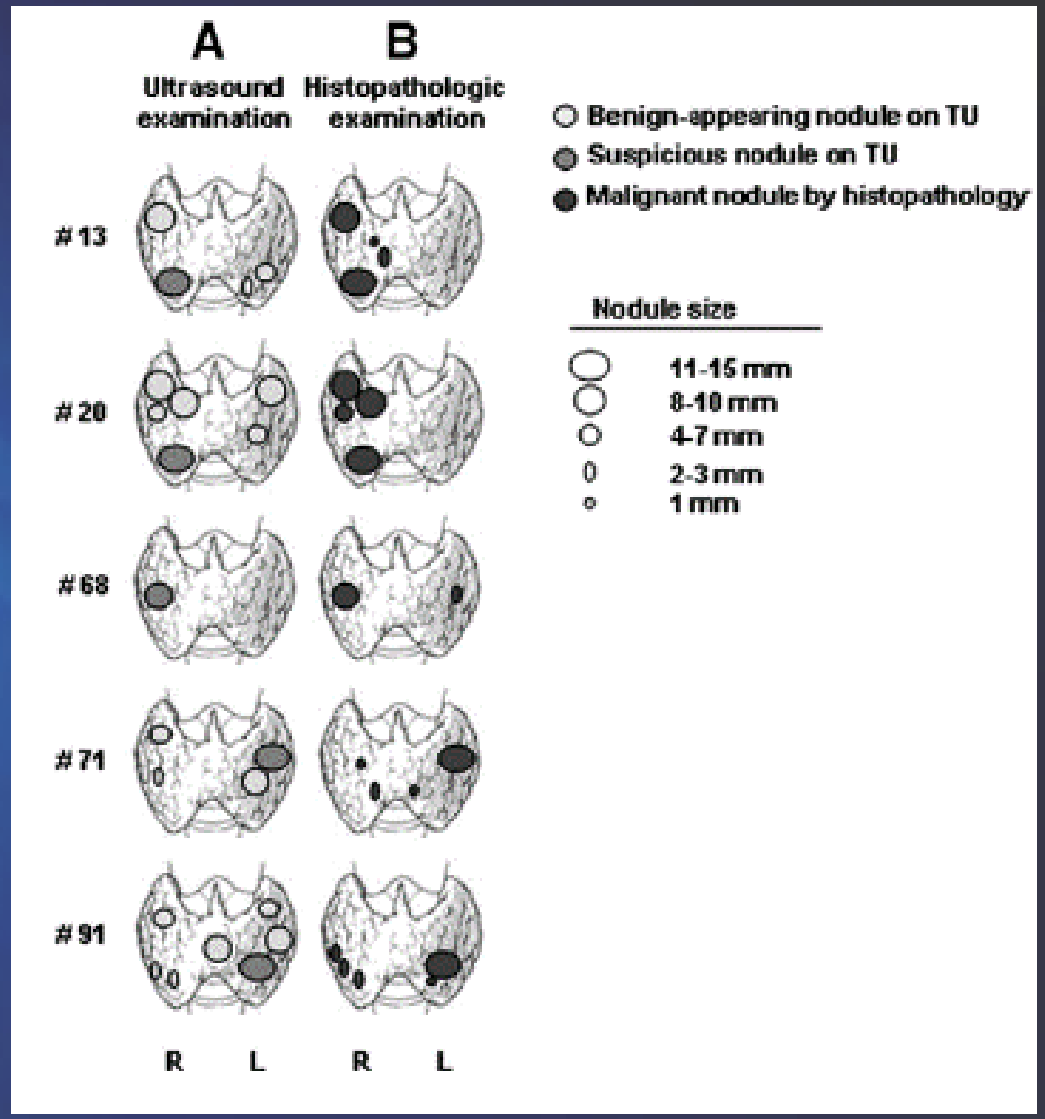


Fig. 1. Summary of patient responses to survey questions about their knowledge of thyroid cancer screening in patients with familial adenomatous polyposis (FAP).

13. Celeste Nagy et al. Barriers to Thyroid Cancer Screening With Ultrasound in Patients With Familial Adenomatous Polyposis. The Laryngoscope. 2019; 129: 2436-2441.

Problems with USG screening

- Poor correlation between histopathologic and ultrasonographic findings
- Duration and frequency of USG?
- Cost-effectiveness ?
- No evidence to demonstrate a reduced morbidity or mortality



7. Maite Herraiz et al. Prevalence of Thyroid Cancer in Familial Adenomatous Polyposis Syndrome and the Role of Screening Ultrasound Examinations. Clinical Gastroenterology and Hepatology 2007; 5:367-373.

When to perform FNAC?

Follow ATA guidelines for suspicious nodules?

→ Be aware that FAP patients have a higher risk of developing TC

→ Consider a lower threshold for bx of concerning nodules

Management

- ATA guidelines for PTC

Summary

- Increase in prevalence of FAP-associated thyroid cancer
- Specific histopathology and epidemiology for FAP-associated thyroid cancer
- Emerging evidence in support of screening of thyroid cancer in FAP patients
- Low awareness of thyroid cancer screening amongst clinicians and patients
- clinical coordinator or registry may help patients navigate all the subspecialties involved to arrange follow-up and imaging to prevent the pitfall to care.

	General Population	FAP patients
Lifetime Risk of PTC	1%	4-12%
Female to Male Ratio	3: 1	8:1
Age of Diagnosis	50	30
Histology	Majority – Classical PTC	Majority – CMV-PTC
Multifocality	Similar	Similar
Overall 5yr survival	>90%	>90%
Correlation between HP and US features	Good	Poor

References

1. Polymnia Galiatsatos et al. Familial Adenomatous Polyposis. American Journal of Gastroenterology 2006; 101: 385- 398.
2. Haruki Sada et al. Prevalence of and risk factors for thyroid carcinoma in patients with familial adenomatous polyposis: results of a multicentre study in Japan and a systematic review. Surgery Today 2019; 49: 72-81.
3. Shinya Uchino et al. Age – and Gender-Specific Risk of Thyroid Cancer in Patients with Familial adenomatous Polyposis. J clin Endocrinol Metab. 2016;,101(12): 4611-2617.
4. JWC Ho et al. Phenotype and management of patients with familial adenomatous polyposis in Hong Kong: perspective of the Hereditary Gastrointestinal Cancer Registry. Hong Kong Med J 2002; 8:342-7.
5. Awad M Jarrar et al. Screening for Thyroid Cancer in Patients With Familial Adenomatous Polyposis. Annals of Surgery 2011; 253: 515-521.
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8. Kensuke Kumamoto et al. Germline and somatic mutations of the APC gene in papillary thyroid carcinoma associated with familial adenomatous polyposis: Analysis of three cases and a review of the literature. Oncology Letters 2015; 10: 2239- 2243.

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Thank You