文 献 汇 报

Clinicopathologic and Molecular Features of Metastatic Follicular Thyroid Carcinoma in Patients Presenting With a Thyroid Nodule Versus a Distant Metastasis

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Backgrounds

- **Follicular thyroid carcinoma (FTC) is the second most common malignancy.**
- **Although most FTCs behave indolently, metastasis occurs in 1.2% to 13% of cases.**
- **End-organ metastases are particularly characteristic of FTC, especially in comparison to papillary thyroid carcinoma.**

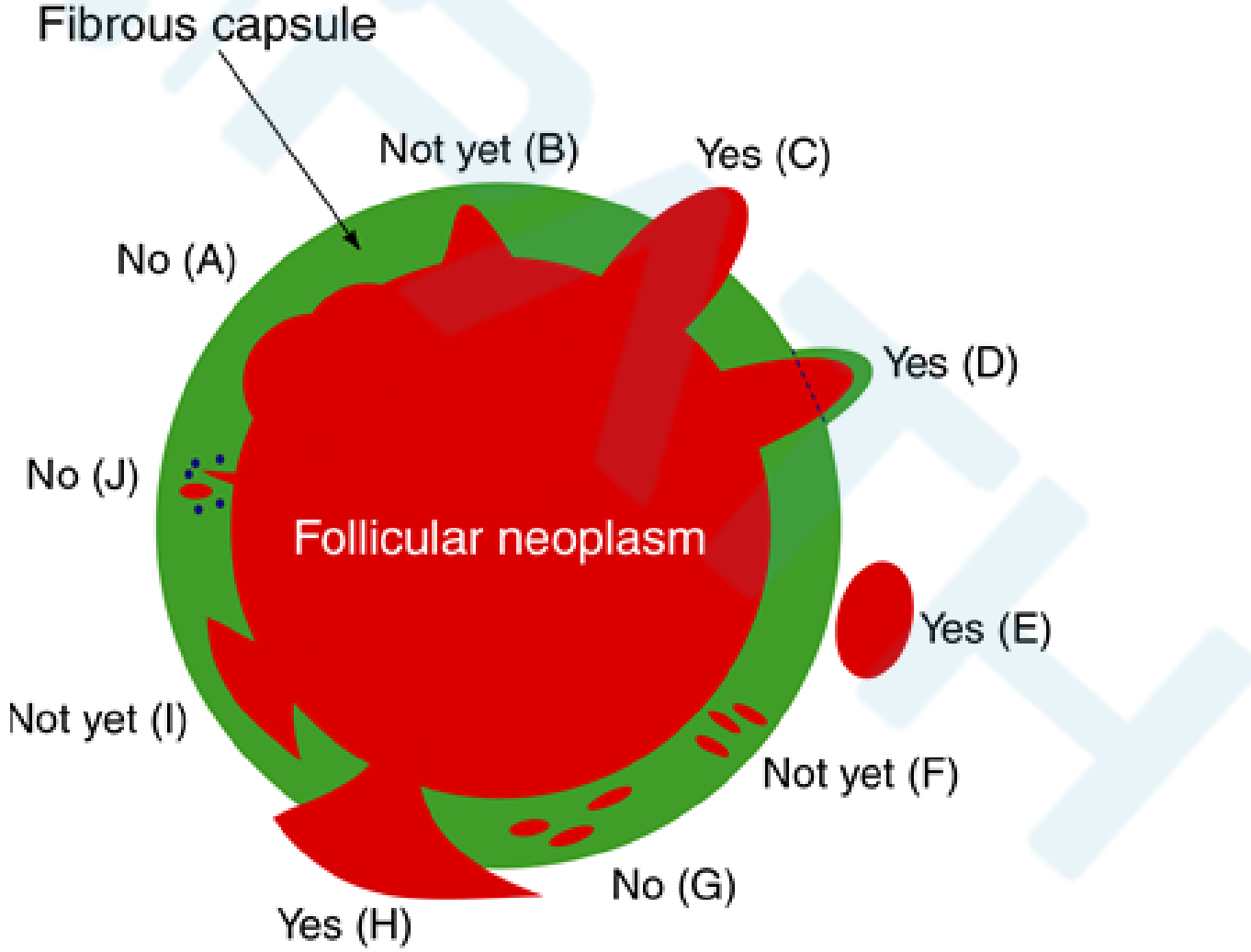
Backgrounds

- **A diagnosis of FTC can be rendered when a follicular-patterned neoplasm of follicular epithelial cells lacking PTC-like nuclei demonstrates unequivocal invasion through the surrounding capsule, into adjacent thyroid parenchyma, or into vasculature.**

- **There are no current immunohistochemical or molecular assays which reliably distinguish a benign follicular adenoma from FTC.**

Backgrounds

- **The true capsular invasion requires tumor extending into and through the capsule, to at least beyond the outer contour of the nodule.**

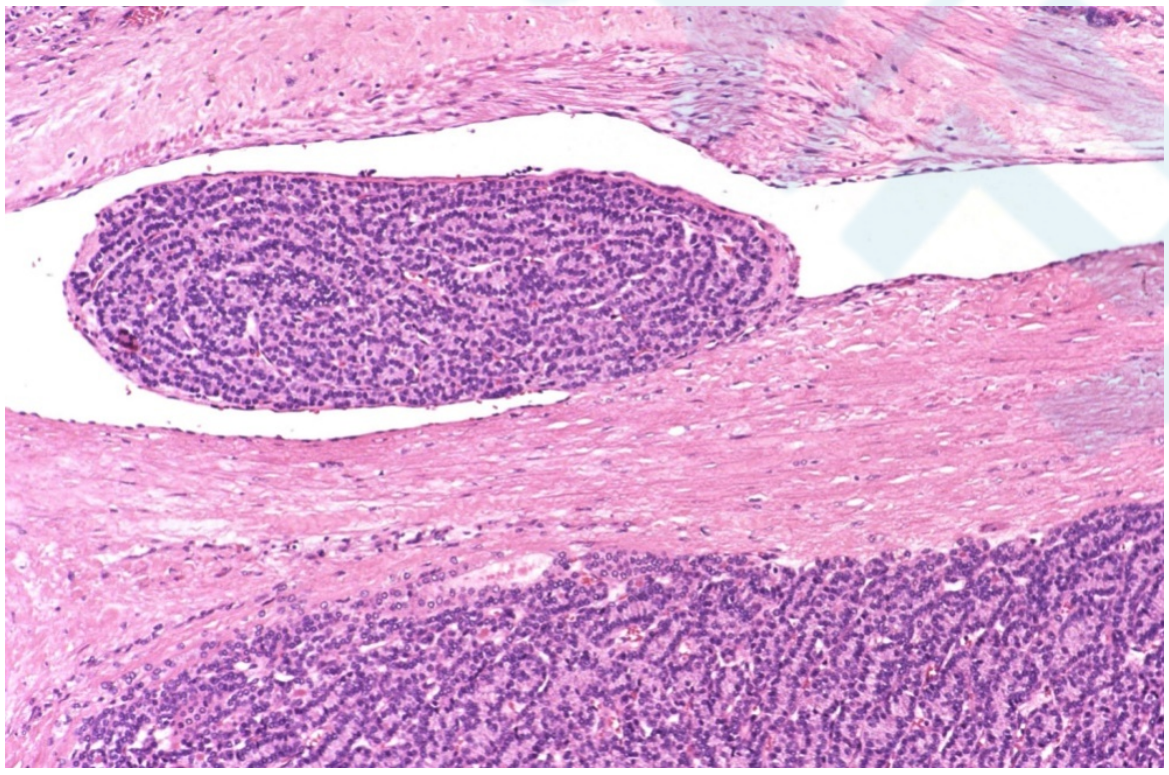


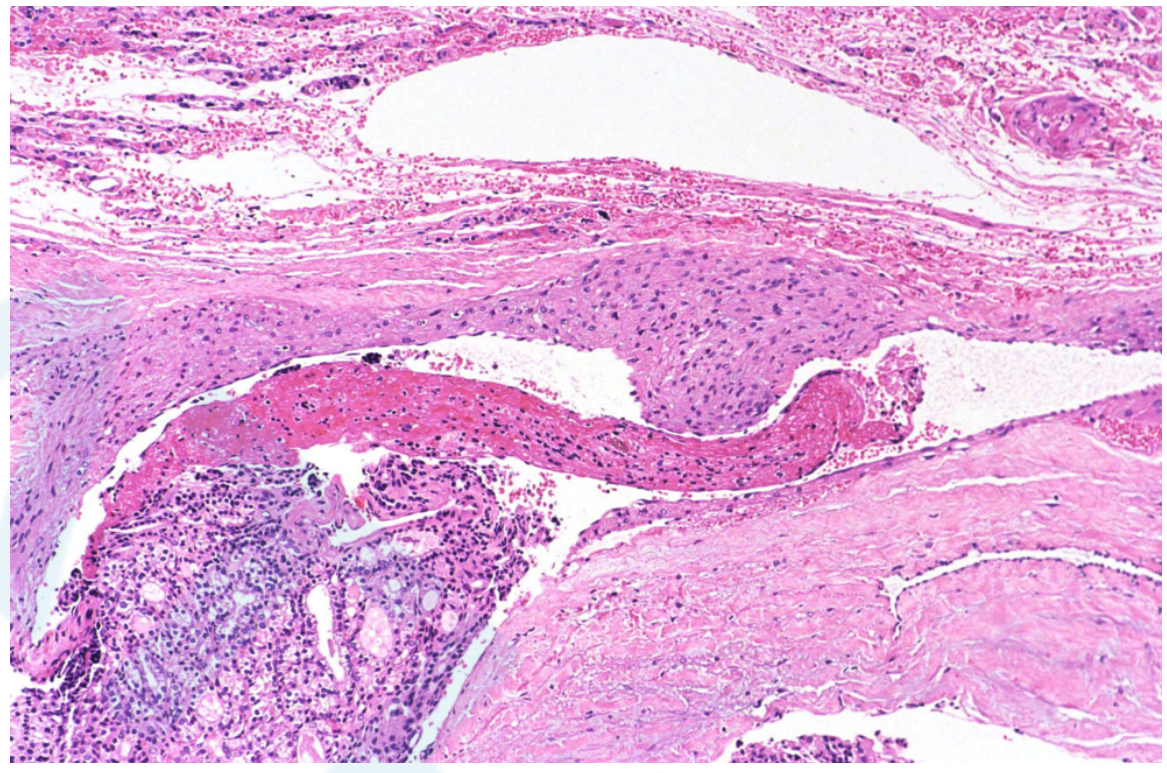
图片引用自陈国璋教授幻灯

Backgrounds

◆**The true vascular invasion requires tumor cells to protrude into the lumen of a large caliber vessel beyond the outer edge of the nodule, with evidence of thrombosis or with endothelium covering the tumor cells.**

Backgrounds





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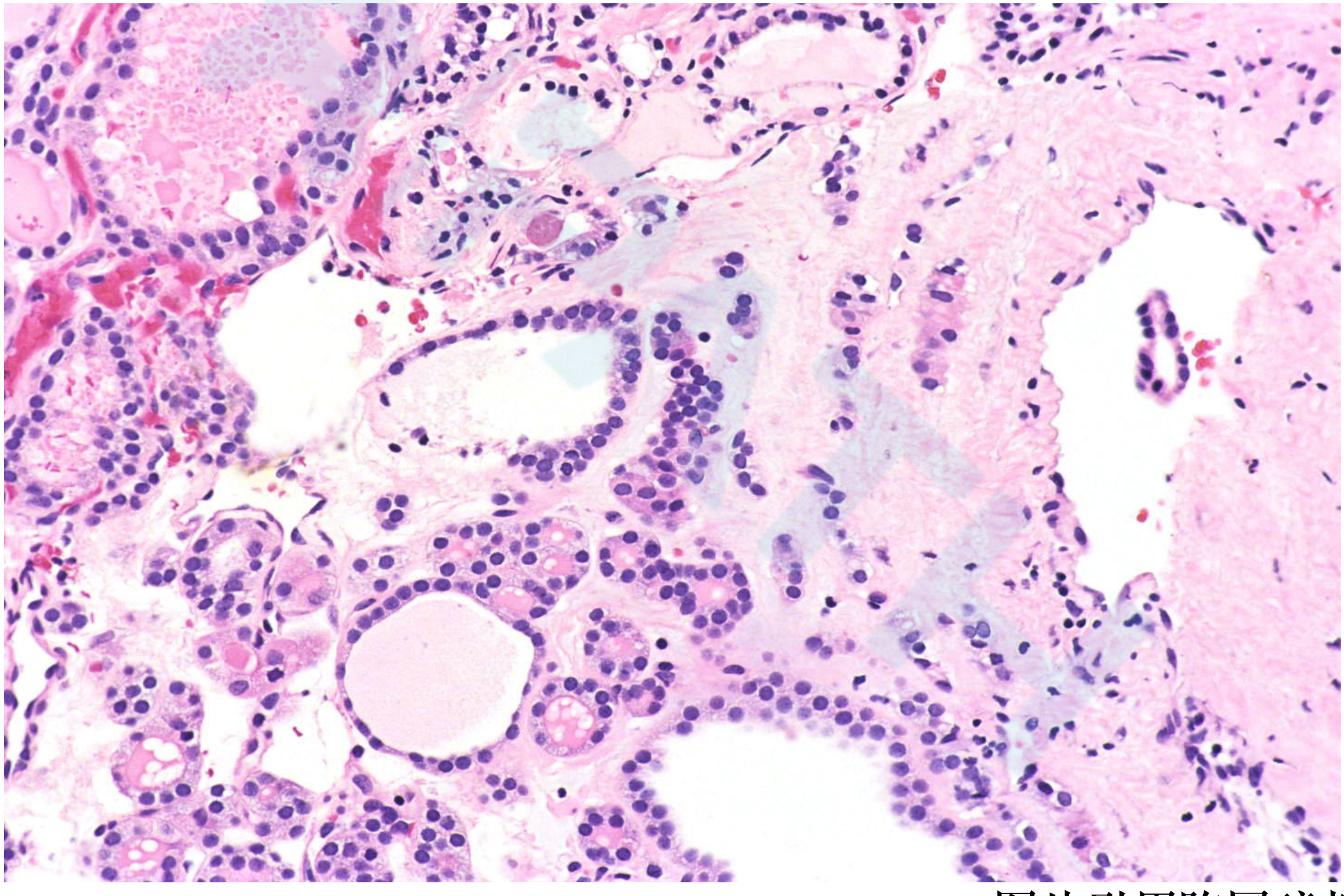

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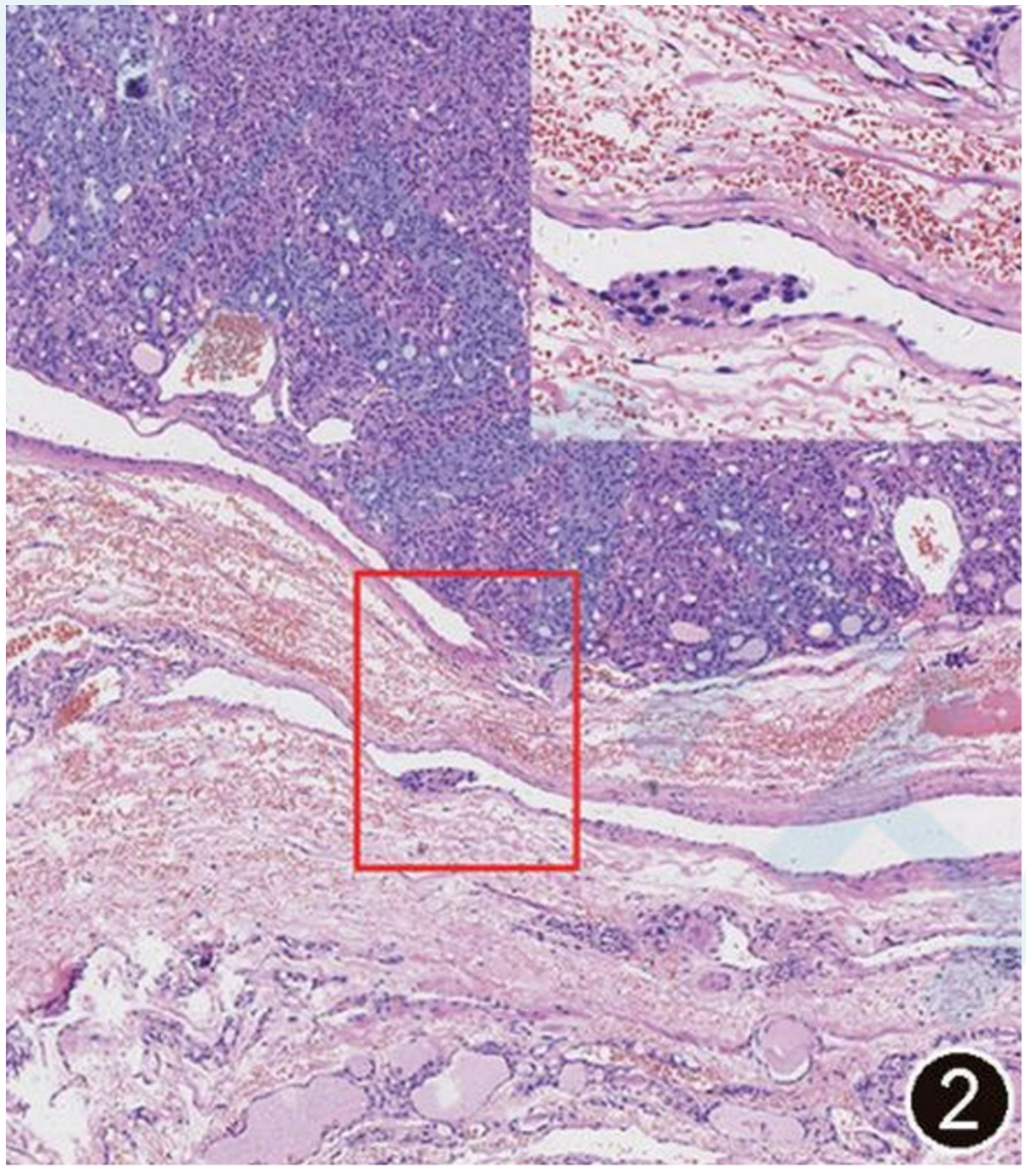

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Backgrounds

Follicular neoplasm: features warranting more careful search for invasion

- Thick fibrous capsule
- High cellularity: predominantly solid, trabecular or microfollicular
- Diffuse nuclear atypia
- Readily identifiable mitotic figures
- Hurthle cell neoplasm
- Perpendicularly aligned follicles in capsule

But these features are by themselves insufficient for rendering a diagnosis of follicular carcinoma

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Backgrounds

- **The minimally invasive carcinomas have full thickness capsular invasion is identified without greater involvement of the thyroid parenchyma and without vascular invasion.**

- **The encapsulated angioinvasive carcinomas have angioinvasion with or without capsular invasion.**

- **Widely invasive carcinomas have extensive intrathyroidal and extrathyroidal invasion.**

Backgrounds

- **RAS gene family Mutations are present in 30% to 50% of FTC, and are exclusive of PAX8-PPARgamma fusions, RET rearrangements, and BRAF V600E mutations.**

- **TERT promoter mutations have been identified in ~15% of FTCs and are associated with an increased risk of recurrence, metastasis, and poorly differentiated.**

- **TERT promoter mutations are often found in association with RAS mutations, which portends a worsened prognosis than RAS mutation alone.**

Backgrounds

- **Patients with metastatic FTC may either present with a primary thyroid nodule (PT) that subsequently metastasizes after thyroidectomy, or with distant metastatic (DM) thyroidcarcinoma and then undergo thyroidectomy.**

- **The aim of this study is to compare the histologic, clinical, and molecular features of patients who present with a PT versus a DM.**

MATERIALS AND METHODS

36 patients from 2000 to 2017

2 groups：distant metastatic (DM) and primary thyroid nodule (PT)

MATERIALS AND METHODS

- **The each case were reviewed for: the presence and quantity of capsular and vascular (angio) invasion, extrathyroidal extension (ETE), solid growth, mitotic count in areas of solid growth, presence of necrosis, and presence of stromal change (fibrosis, hyalinization, and calcification).**

- **Both primary and/or metastatic lesions were tested using the targeted hybrid capture 1213 gene UCM OncoPlus panel.**

Clinical Features

TABLE 1. Clinicopathologic Features of Metastatic Follicular Thyroid Carcinomas in Patients Presenting With Distant Metastasis Versus Primary Thyroid Nodule

	Presenting With Distant Metastases (n = 15)	Presenting With Primary Thyroid Nodule (n = 21)
Mean age at presentation (y)	69.8* (59-87) (median: 67)	55.4* (30-76) (median: 54.2)
Sex	5 male**, 10 female	10 male**, 11 female
Location of initial metastasis (n [%])		
Bone	11 (73)***	8 (38)***
Lung	3 (20)****	12 (57)****
Multiple	1 (7) (lung and adrenal)	1 (5) (lung, liver, and bone)
Surgical intervention (n [%])		
Initial total thyroidectomy	13 (87)	12 (57)
Hemithyroidectomy followed by completion thyroidectomy	1 (6)	6 (29)
Hemithyroidectomy	0	2 (10)
Unknown/Other	1 (6)	1 (5)
Lymph node dissection (n [%])		
Performed with thyroidectomy	3 (20)	2 (10)
Performed at follow-up procedure	0	8 (38)
Not performed	11 (73)	10 (48)
Unknown	1 (7)	1 (5)

*$P = 0.001$.
**$P = 0.09$.
***$P = 0.03$.
****$P = 0.034$

Clinical Features

Additional therapies (n [%])		
RAI only	7 (47)	5 (24)
Chemotherapy only	0	3 (14)
RAI and chemotherapy	4 (27)	8 (38)
RAI and EBRT	0	1 (5)
EBRT and chemotherapy	1 (7)	0
RAI, EBRT, and chemotherapy	1 (7)	2 (10)
None	2 (14)	1 (5)
Unknown	0	1 (5)
Outcomes (n [%])		
Died of disease	5 (33)	7 (33)
Alive with diffuse metastatic disease	3 (20)	5 (23)
Alive with minimal† or no disease	7 (46)	7 (33)
Unknown	1	2
Mean size of primary carcinoma (cm)	2.5# (SD: 1.6) Range: 0.7-4.6 Median: 2.6	4.0# (SD: 2.64) Range: 1.8-10 Median: 3.5
Invasion (n/N [%])	10/12 (83)	6/6 (100)
Capsular invasion only	5	2
Capsular and vascular invasion	5	4
No invasion	2	0
Unknown	3	15
Extrathyroidal extension (n/N [%])	1/13 (8)#	3/7 (43)#
Solid growth (n/N [%])	7/12 (58)	4/6 (67)
Mitoses in areas of solid growth (range)	1-14/10 hpf	3-7/10 hpf
Tumor necrosis (n/N [%])	2/12 (17)	1/6 (17)
Poorly differentiated areas (n/N [%])	3/12 (25)	2/6 (33)
Intralesional fibrosis (n/N [%])	6/12 (50)##	0/6 (0)##
Oncocytic features (n/N [%])	1/12 (8)***	4/7 (57)***

*$P = 0.0001$.
**$P = 0.09$.
***$P = 0.03$.
****$P = 0.034$.
#$P = 0.1$.
##$P = 0.002$.

Pathologic Features in 15 Patients With DM

- In the 10 cases with capsular invasion, 4 had extensive invasion, 1 had 5 foci of invasion, 1 had 2 foci of invasion, 1 had “rare” foci per report, and 3 had invasion “present” per report without quantification.

- In the 5 cases with vascular invasion, 2 had 3 foci, 1 had 4 foci, 1 had 2 foci, and 1 had 5 foci.

- The presence or absence of ETE was able to be assessed in 13 cases. A single case demonstrated ETE.

Pathologic Features in 15 Patients With DM

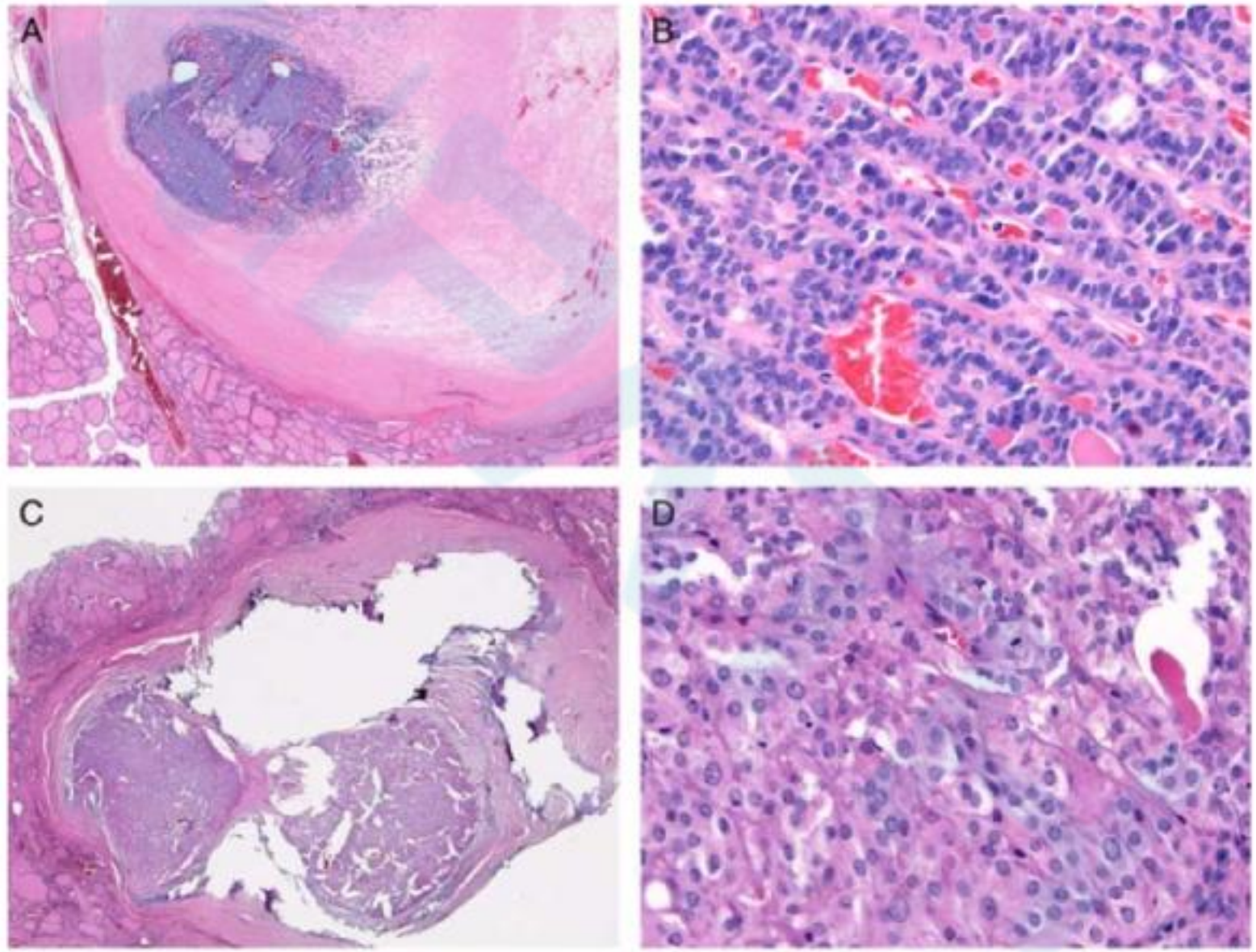
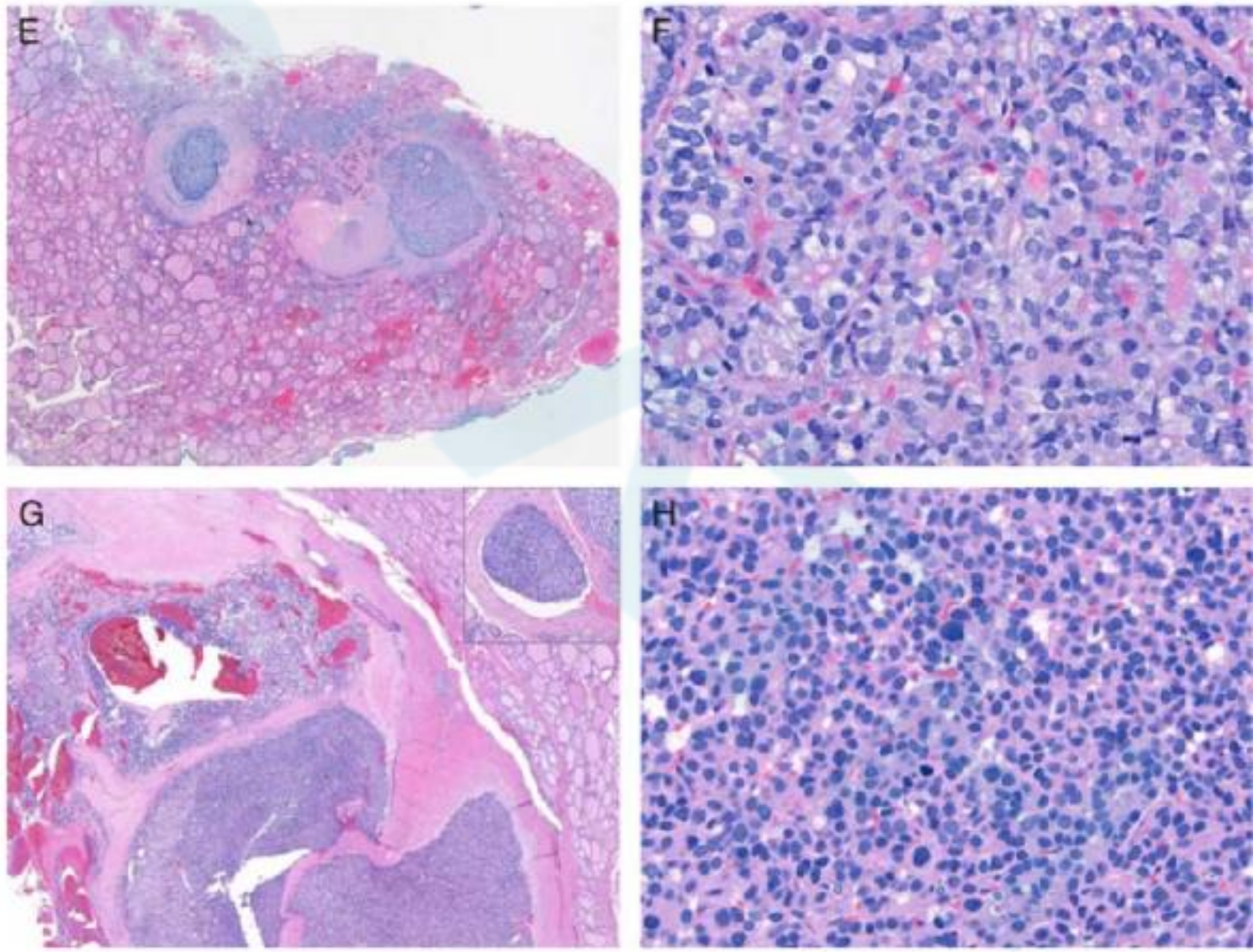


FIGURE 1. Histologic features of regression in 4 patients presenting with metastatic follicular thyroid carcinoma. This 1.4 cm carcinoma was well-circumscribed and had abundant intralesional fibrosis and no evidence of capsular or vascular invasion (A). On higher power, trabecular growth is present, but without increased mitoses or necrosis (B). Pathogenic mutations were not identified. This 0.7 cm carcinoma also had abundant fibrosis and calcification (resulting in tissue dropout) but no capsular or vascular invasion (C). Trabecular growth and scattered mitoses (< 3/10 hpf) were present (D), along with a pathogenic *BRCA2* mutation.

Pathologic Features in 15 Patients With DM



. This 0.4 cm carcinoma had a small sclerotic center surrounded by infiltrative nests and nodules (E) of bland-appearing follicular cells (F) without vascular invasion or solid growth. *NRAS* Q61R and *TERT* mutations were present. This 1.8 cm carcinoma was intersected by thick, focally calcified fibrous bands (G). It had capsular and angioinvasion (G, inset), as well as solid growth with pleomorphic nuclei and abundant mitoses (> 10/10 hpf) (H) and a *TERT* mutation.

Pathologic Features in 21 Patients With PT

- In the 6 cases with capsular invasion, 1 had 2 foci, 1 had 1 focus, 1 had “multiple” foci per report, and 3 had invasion “present” per report without quantification.
- In the 4 cases with vascular invasion, 1 had 7 foci, 1 had 6 foci, and 2 had invasion “present” per report without quantification.
- The presence or absence of ETE was able to be assessed in 7 cases. Three cases (43%) demonstrated ETE.

High-risk Histologic Features in PTC

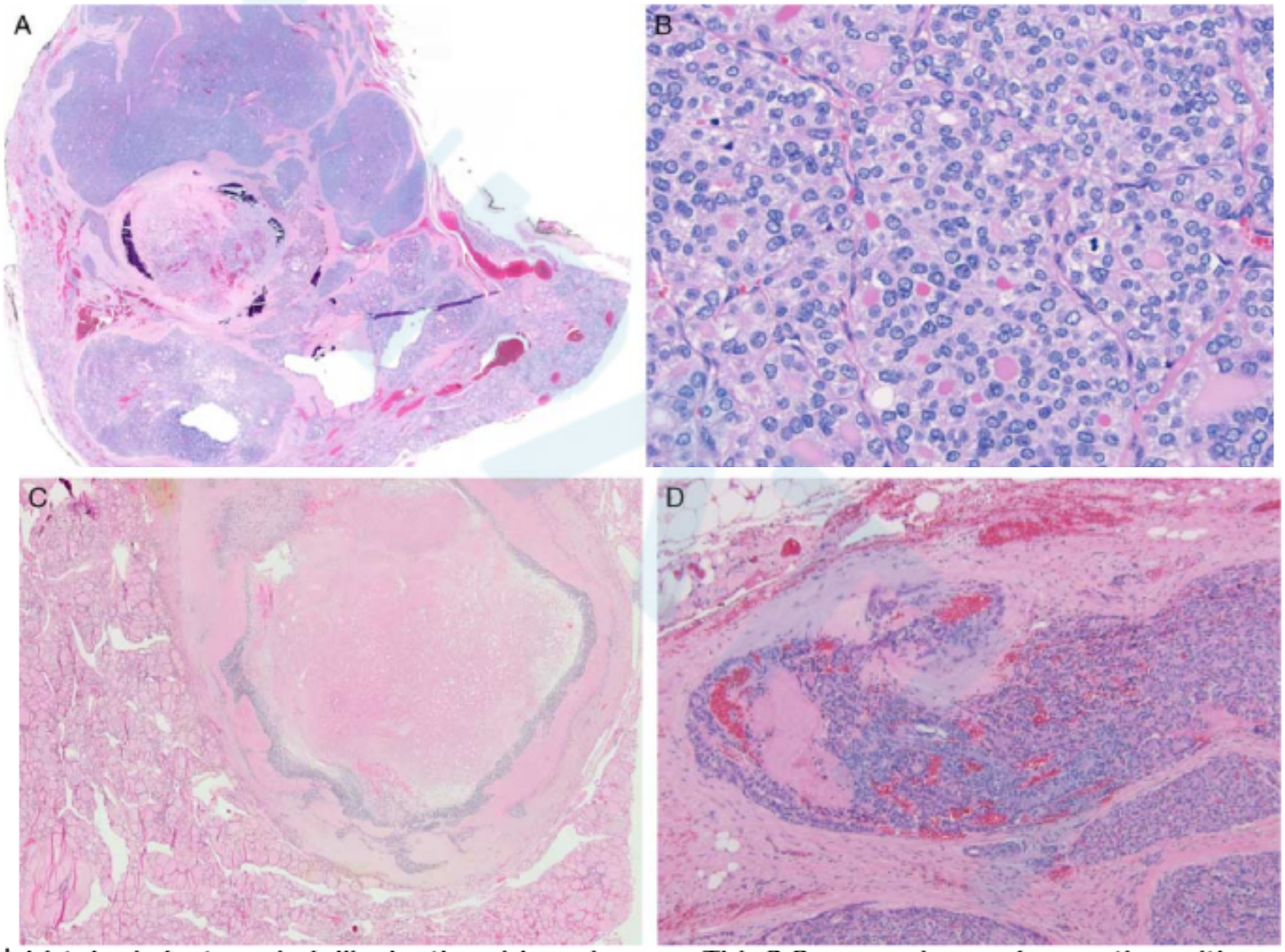


FIGURE 2. High-risk histologic features in follicular thyroid carcinomas. This 2.9 cm carcinoma (presenting with a metastasis) had a small, calcified, sclerotic nodule in the center, surrounded by extensive intrathyroidal invasion (A). Solid growth with increased mitoses (>10/10 hpf) (B) was present, as well as *NRAS* Q61K and *TERT* mutations. Extensive necrosis was present in this 1.1 cm carcinoma (presenting with a metastasis) (C). *NRAS* Q61R mutation was identified. Angioinvasion with associated thrombosis (D) is exemplified by this 4.8 cm carcinoma presenting with a primary thyroid nodule. *NRAS* Q61K mutation was identified.

Pathogenic Mutations in Metastatic FTC

TABLE 2. Pathogenic Mutations in Metastatic Follicular Thyroid Carcinomas From Patients Presenting With Distant Metastasis Versus a Primary Thyroid Nodule

Presenting With Distant Metastases (n = 13)		**Presenting With Primary Thyroid Nodule (n = 7)**	
8 *RAS* (62%) 5 *TERT* (38%) Including 4 combined *RAS* and *TERT* (31%)		3 *RAS* (43%) ($P = 0.64$) 4 *TERT* (57%) ($P = 0.64$) Including 2 combined *RAS* and *TERT* (29%) ($P = 1.0$)	
Primary lesion	Metastatic lesion	Primary lesion	Metastatic lesion
NRAS p.Q61R *TERT* promoter	*NRAS* p.Q61R *TERT* promoter	Not tested	*NRAS* p.Q61R *TERT* promoter
NRAS p.Q61K *TERT* promoter	*NRAS* p.Q61K *TERT* promoter	Not tested	*HRAS* p.Q61K *TERT* promoter
NRAS p.Q61R *TERT* promoter	Not tested	*NRAS* p.Q61K	Not tested
Not tested	*HRAS* p.Q61K *TERT* promoter	*TERT* promoter *PTEN* p.R130Q	*TERT* promoter *PTEN* p.R130Q *RET* p.A883F
HRAS p.Q61R *NRAS* p.Q61R	*HRAS* p.Q61R *NRAS* p.Q61R	Not tested Not tested	*TERT* promoter *PTEN* p.E299* *NF1* p.Q209*
NRAS p.Q61R *NRAS* p.Q61K *TERT* promoter *BRCA2* p.S1982Rfs*22	Not tested *NRAS* p.Q61K *TERT* promoter Not tested	*NF1* p.Y2285Tfs*5	Not tested
No pathogenic mutations	No pathogenic mutations		
No pathogenic mutations	Not tested		
No pathogenic mutations	Not tested		

All *TERT* promoter mutations were c.-124C > T.

Graphical representation of molecular and histologic findings in select cases

Clinical Presentation	Patient #	Molecular Features: *NRAS*	*HRAS*	*TERT* promoter	*RET*	*PTEN*	*BRCA2*	*NF1*	No Pathogenic Mutation Identified	Histologic Features: Capsular Invasion Only	Capsular and Vascular Invasion	No Invasion	Extrathyroidal Extension	Solid Growth	Increased Mitoses in Solid Areas	Tumor Necrosis	Intralesional Fibrosis	Oncocytic Features
Distant Metastasis	1	*		*														
	2	±		±														
	3	#		#														
	4		&	&						Not available for Review								
	5		^															
	6	*																
	7	#																
	8	±																
	9			*														
	10						#											
	11								*									
	12								#									
	13								#									
Primary Thyroid Nodule	16	&		&														
	17		&	&														
	18	#																
	19			*	@	*												
	20			&														
	21					&		&										
	22							#										

Key

- p.Q61R
- p.Q61K
- c.-124C>T
- p.R130Q
- p.E299*
- p.Q209*
- p.Y2285Tfs*5
- p. A883F
- p.S1982Rfs*22
- Present

* = present in both primary and metastasis

= present in primary only (metastasis not tested)

& = present in metastasis only (primary not tested)

@ = not present in primary but present in metastasis

Conclusions

- **Patients who presented with DM were on average 15 years older than those who presented with PT.**
- **Initial isolated bone metastasis occurred significantly more often in patients who presented with DM compared with PT (73% vs. 38), and initial isolated lung metastasis occurred significantly more often in patients who presented with PT compared with DM (57% vs. 20%).**
- **50% (n = 6) of patients presenting with DM demonstrated a histologic feature not seen in those with PT, namely, extensive intralesional fibrosis.**
- **Oncocytic features were more common in those with PT.**

Conclusions

No significant differences were identified:

- **Outcomes**
- **Extent of capsular or vascular**
- **ETE**
- **High-risk histologic features (solid growth, increased mitotic activity, necrosis)**
- **Type of pathogenic mutations.**

Conclusions

- **FTC afflicts females 2 to 2.5 times more often than males.**
- **However, in our study, males (n =15, 42%) and females (n = 21, 58%)were similarly affected by metastatic FTC.**
- **This finding may suggest that FTCs in males metastasize more frequently than those in females.**

Conclusions

- **Pathogenic mutations were present in 85% of tested cases (55% with a RAS mutation) and were in keeping with the reported relative frequencies of mutations in FTC.**
- **TERT promoter mutations were common (45% of tested cases) in both DM and PT patients, supporting the use of TERT as an indicator of possible aggressive behavior.**
- **In patients with paired samples, most (87.5%) had identical mutations within both the primary carcinoma and the metastasis.**

谢谢…

Backgrounds

- **The poorly differentiated carcinoma can be rendered.**

1. **capsular and vascular invasion**
2. **solid, trabecular, or insular growth patterns**
3. **tumor necrosis(unrelated to prior biopsy)**
4. **increased mitotic activity($\geqslant$ 3/10hpf)**

Backgrounds

- **The true capsular invasion requires tumor extending into and through the capsule, to at least beyond the outer contour of the nodule.**

- **The true vascular invasion requires tumor cells to protrude into the lumen of a large caliber vessel beyond the outer edge of the nodule, with evidence of thrombosis or with endothelium covering the tumor cells.**

可疑包膜浸润为肿瘤细胞浸润包膜但未穿透 (有或无蘑菇样

新版中将广基范围内肿瘤细胞顶起纤维结缔组织被膜 (穹顶样) 时，同样定义为可疑包膜浸润。

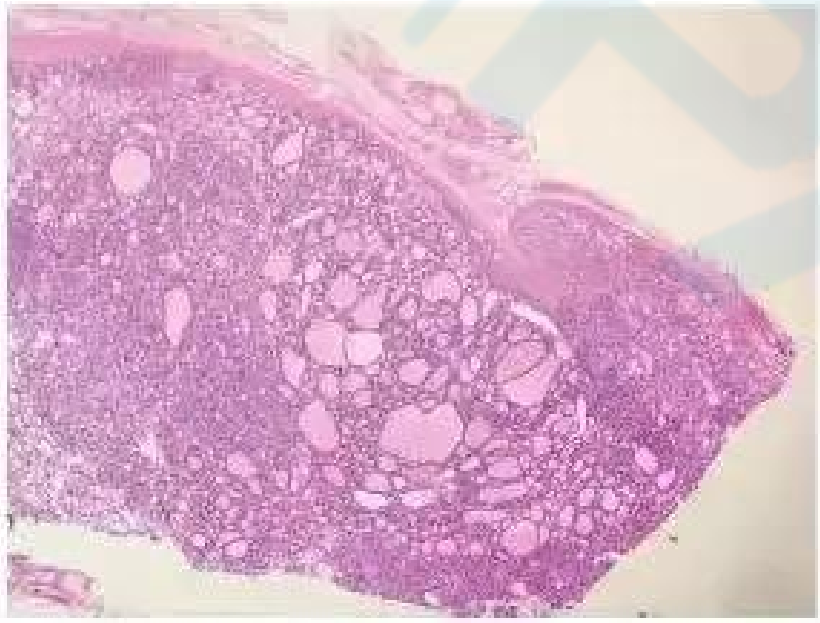
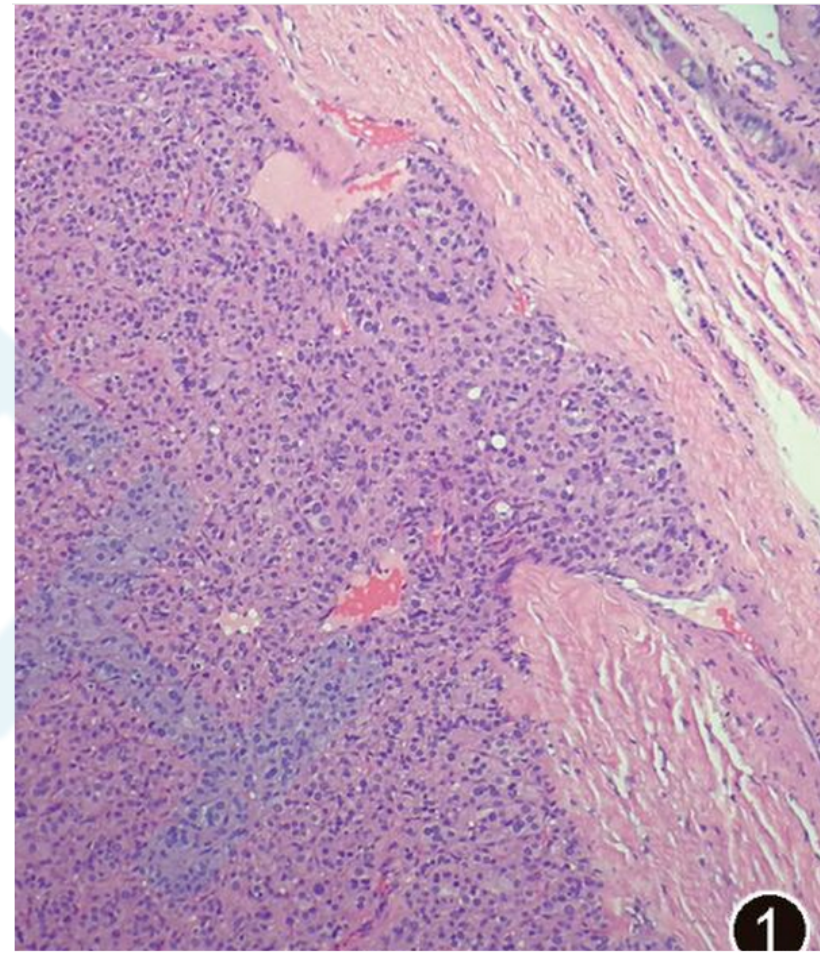


图 1　恶性潜能未定的肿瘤：可疑被膜浸润。只有单侧肿瘤细胞呈蘑菇样突出纤维结缔组织包膜(HE 染色)

Fig. 1　Tumor of uncertain malignant potential because of questionable capsular invasion. Only half of the "mushroom" plunges into the fibrous capsule (hematoxylin and eosin stain)



当血管间隙内肿瘤细胞巢缺乏内皮细胞被覆和相关血栓、纤维结缔组织内肿瘤细胞巢与血管接触，定义为可疑脉管浸润。

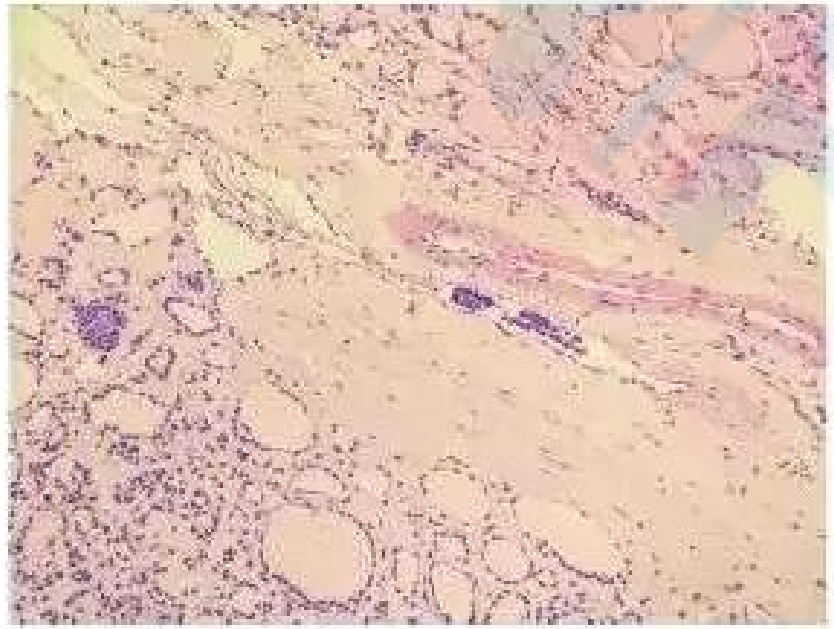
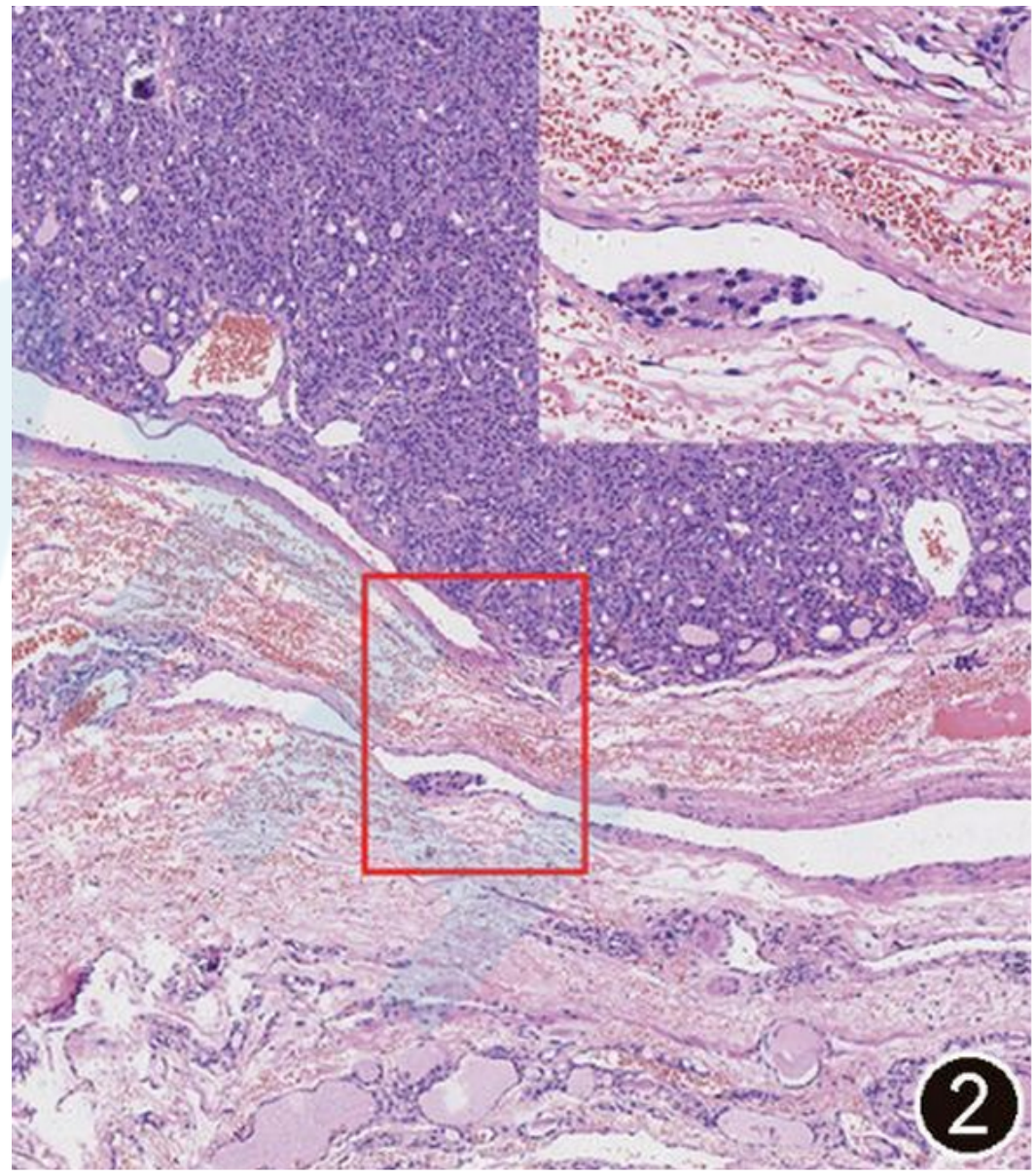
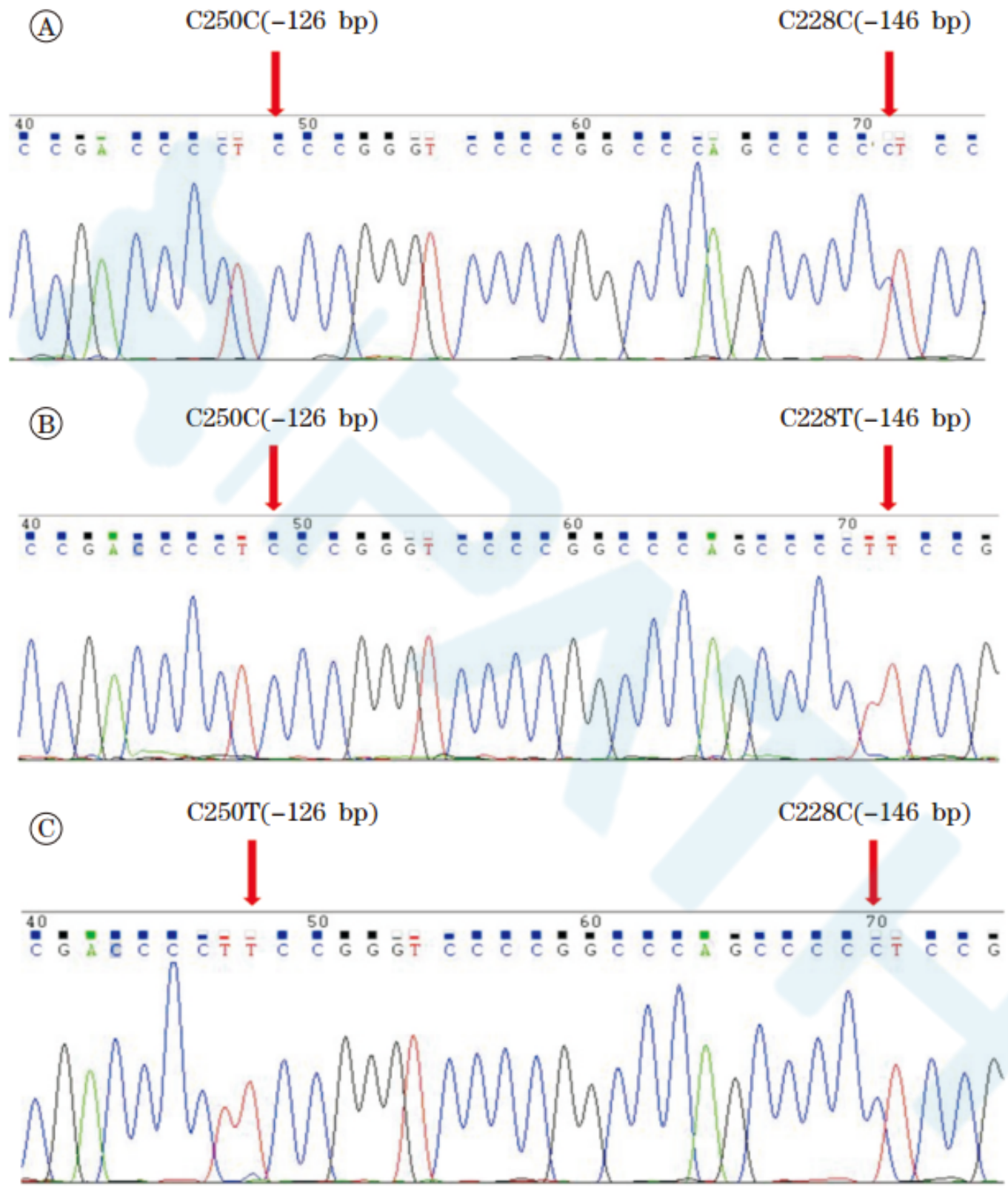


图 2　恶性潜能未定的肿瘤：可疑血管浸润。纤维结缔组织包膜中血管内可见成团肿瘤细胞，但缺乏血管内皮被覆及纤维素性血栓（HE 染色）

Fig. 2　Tumor of uncertain malignant potential because of questionable vascular invasion. Foci of tumor cells were observed in the vessel inside the fibrous capsule, which lack the vascular endothelium and fibrous thrombus (hematoxylin and eosin stain)





A：TERT启动子区野生型序列，箭头示启动子区−126和−146 bp位点，野生型序列中两个位点均为C碱基；B：TERT启动子区−146 bp位点突变型，箭头示该位点原C碱基突变为T碱基；C：TERT启动子区−126 bp位点突变型，箭头示该位点原C碱基突变为T碱基.

TERT启动子区突变后会形成一段特殊的DNA碱基序列，5′-CCCCTTCCGGG-3′，该序列含有ETS转录因子结合位点，该位点大量募集ETS家族转录因子与之结合，随后引起TERT表达的上调[5, 14]。TERT作为端粒酶的一个重要组成部分，是影响端粒酶活性的关键分子。因此，TERT启动子区突变可能通过上调TERT的表达，进而激活端粒酶，维持端粒的长度和结构，从而保护了染色体结构和功能，延迟了细胞的衰老凋亡，实现肿瘤细胞的永生化。这可能也是TERT启动子区突变影响胶质瘤患者预后的重要分子机制之一。

ＲＥＴ重排是乳头状甲状腺癌基因改变最常见的类型之一，在散发性乳头状甲状腺癌中重排率为２０％～４０％，与放射暴露有关。目前已经发现１５种不同的ＲＥＴ重排，其中融合基因ＣＣＤＣ６拟ＲＥＴ和ＮＣＯＡ４拟ＲＥＴ最常见。ＲＥＴ癌基因对正常甲状腺细胞株有转变作用，使其不依赖促甲状腺激素信号途径生长，特别是ＣＣＤＣ拟ＲＥＴ３型能够显著促进细胞增殖。这表明ＲＥＴ基因的突变与肿瘤发生启动有关。总体来说ＲＥＴ重排甲状腺癌预后相对较好