

# **Metanephric Adenoma–Epithelial Wilms Tumor Overlap Lesions**

## **An Analysis of BRAF Status**

汇报人：张微晨

# 关键词1：后肾腺瘤（Metanephric adenoma, MA）

## 概述：

MA于1979年被Bove等首次报道，1992年由Brisigotti等命名，2016年WHO将MA归入后肾肿瘤大类，包括MA、后肾腺纤维瘤（MAF）和后肾间质瘤（MST），生物学行为均为良性。

## 临床表现：

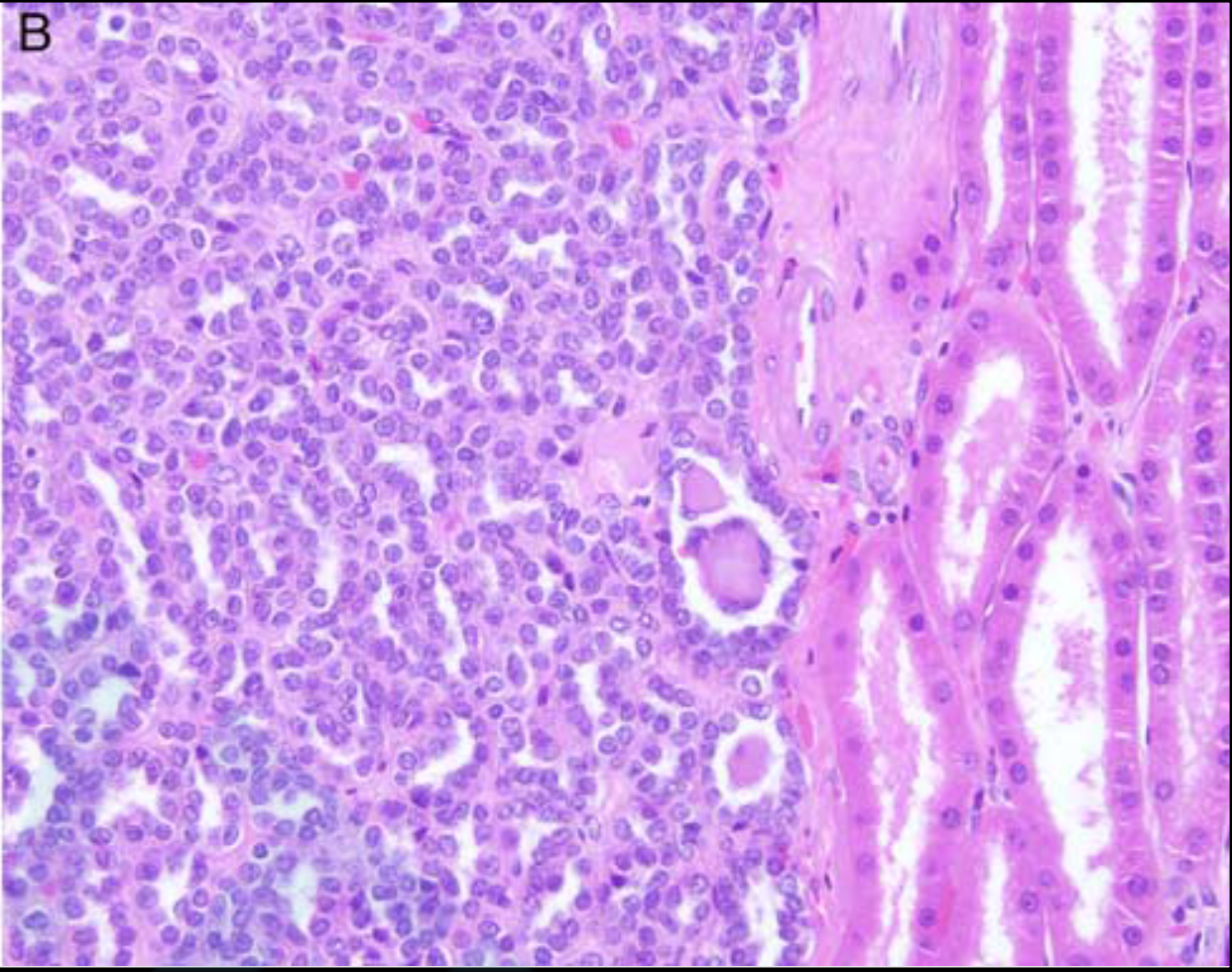
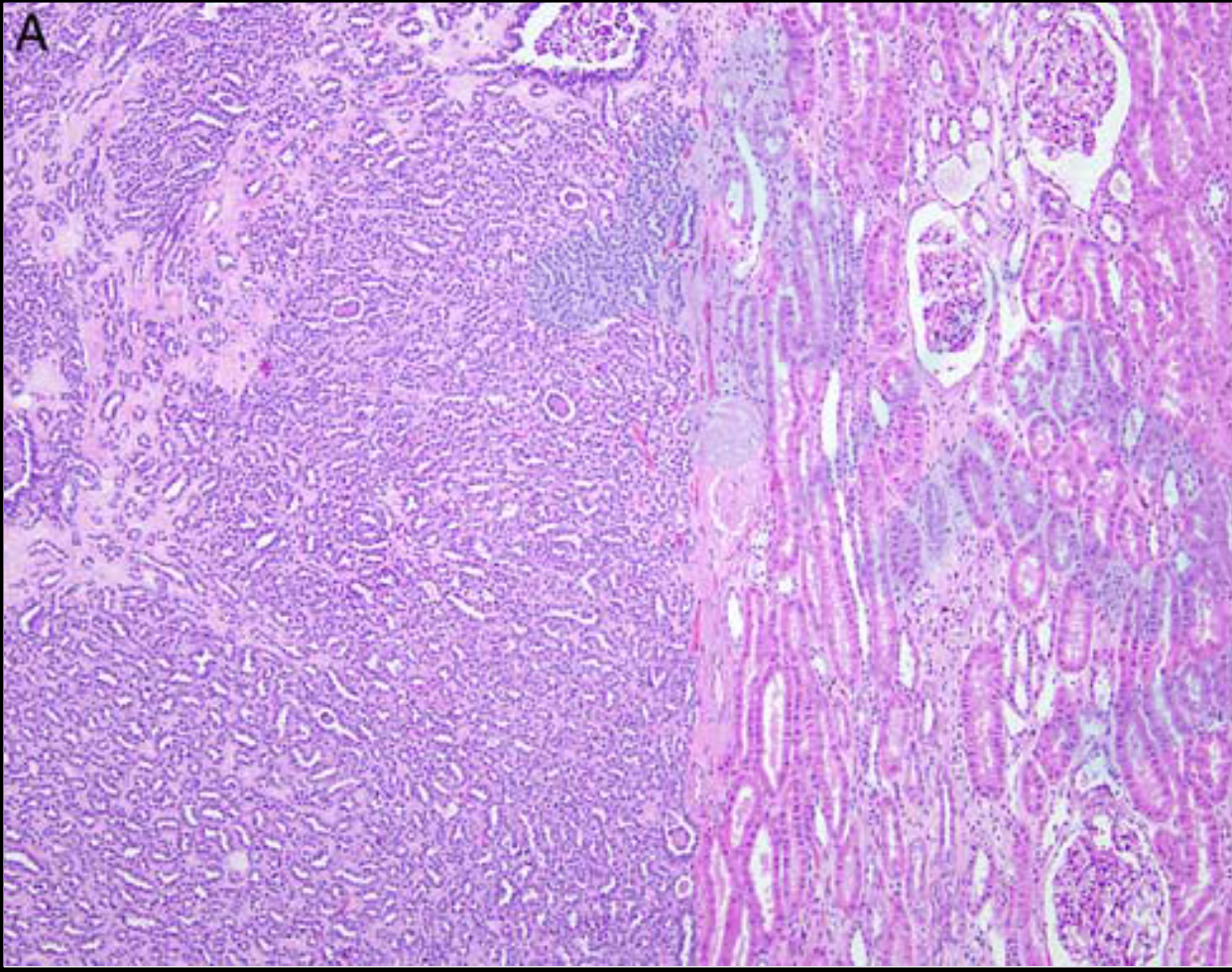
MA可发生于任何年龄，多在50-60岁之间，女性多见，临床表现缺乏特异性，半数以上的患者体检偶然发现，少数患者有腰腹部疼痛，无痛性肉眼血尿等。有报道约12%的患者可见红细胞增多症，原因与MA细胞可产生并分泌EPO及其他多种细胞因子有关。

# 组织病理学

## 大体：

多位于皮质，大小不一，多灶性发病少见，典型者肿瘤边界清楚，有/无包膜。切面可呈灰、褐、黄色，质软或坚韧，可有囊变、出血、钙化和纤维瘢痕。





肿瘤细胞呈分支状，或鹿角样小管样结构，呈腺泡状、条索状及肾小球样排列。

瘤细胞圆形，卵圆形，胞浆稀少，细胞核呈小圆形，细胞大小较一致，无明显异型性，核分裂象罕见。

# 免疫组化 & 分子遗传学

## 免疫组化：

一般WT-1、CD57、Vimentin多呈阳性，而EMA、AMACR和CK7多呈阴性。  
钙黏蛋白17（CDH17）阳性。

## 分子遗传学：

研究发现大部分MA患者存在BRAF V600E基因突变，而其余非MA的其他肾癌患者中BRAF V600E基因突变却非常罕见。另外，在V600E阴性的患者中发现存在新的BRAF基因突变，包括V600D错义突变及混合V600D和K601L的错义突变。

## 关键词2：肾母细胞瘤（Wilms tumor, WT）

### 概述：

肾母细胞瘤是婴幼儿泌尿系统最常见的恶性肿瘤，在恶性实体肿瘤中，仅次于神经母细胞瘤。外科医生Max Wilms于1899年较为详细系统的描述其特点，故称Wilms瘤。

### 流行病学：

发病年龄集中在出生后最初5年内，多见于2-4岁，男女发病率相近，生存率较高。

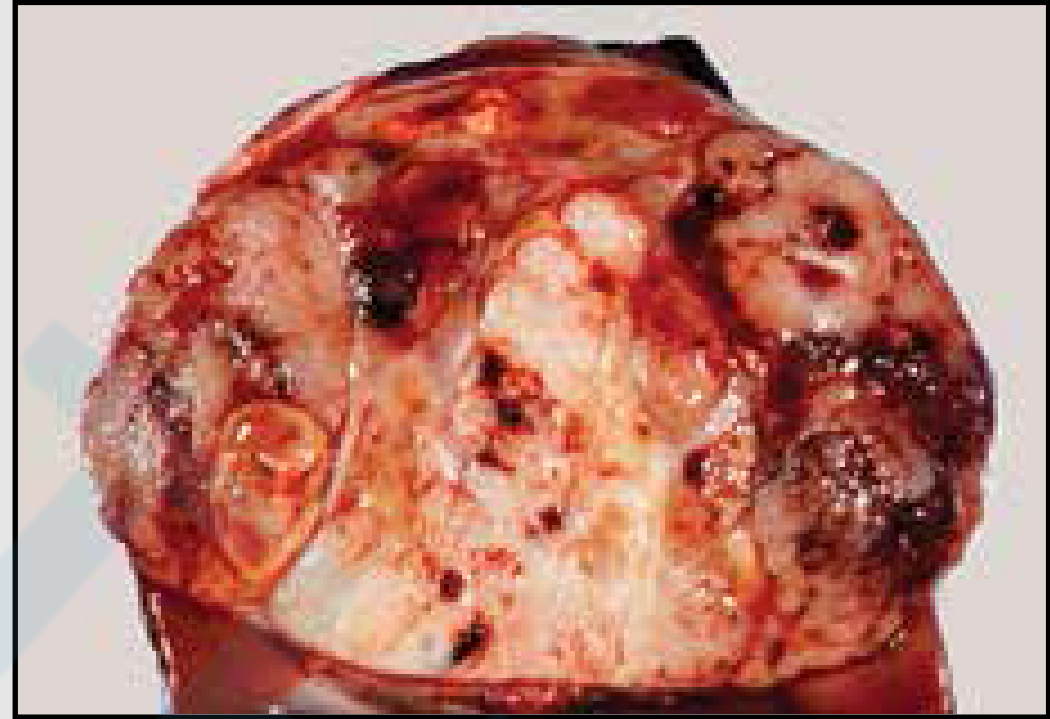
### 临床表现：

腹部包块最常见，腰痛或腹痛、血尿、消瘦及不规则发热等，偶有患者出现高血压及红细胞增多症，少数患儿伴有畸形。

# 组织病理学

大体：

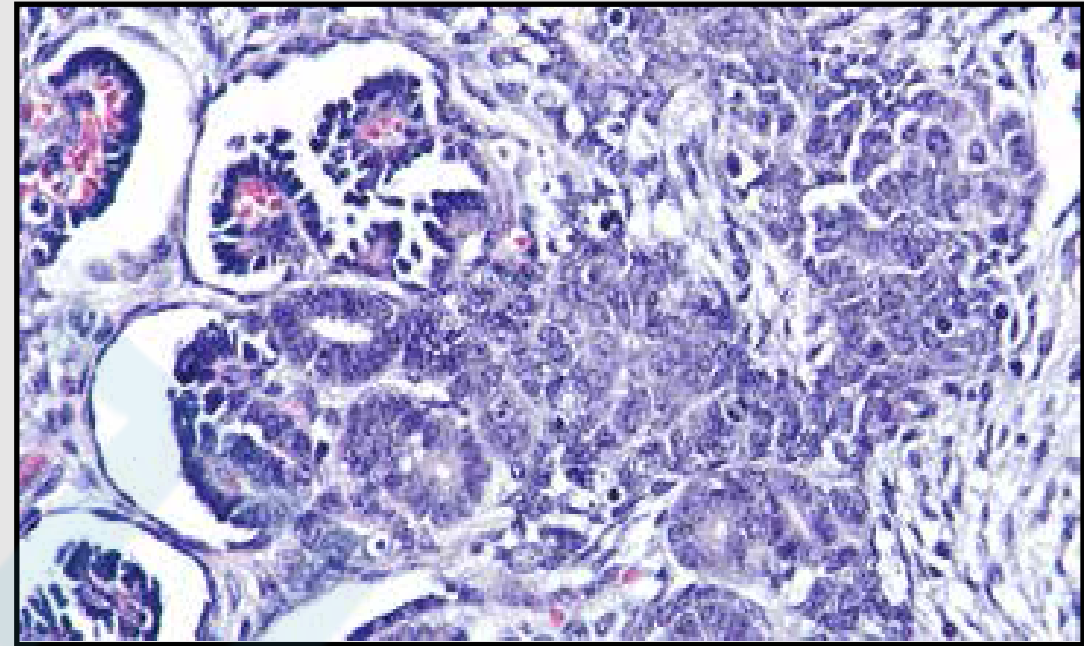
多表现为单个实性肿物，多结节状，体积较大，边界清楚，可有假包膜形成，肿瘤质软，切面呈鱼肉状，灰白或灰红色，可有灶性出血，坏死或囊性变。



# 组织病理学

镜下：

肿瘤具有特征性的三相组织学形态：未分化的胚基细胞、不同分化程度的上皮和间质，非肾脏成分如骨骼肌和软骨。肿瘤细胞异型性明显，核分裂象多见。



# 免疫组化 & 分子遗传学

免疫组化：

大约80%的病例WT1阳性。

分子遗传学：

在WT中检测到WT1（11p13）、WT2（11p15）、WTX（Xq11.1）、CTNNB1（3p22.1）和TP53等基因突变。

# 美国肾母细胞瘤研究组 (National Wilms' tumor study, NWTs)



## 上皮型WT (e-WT)

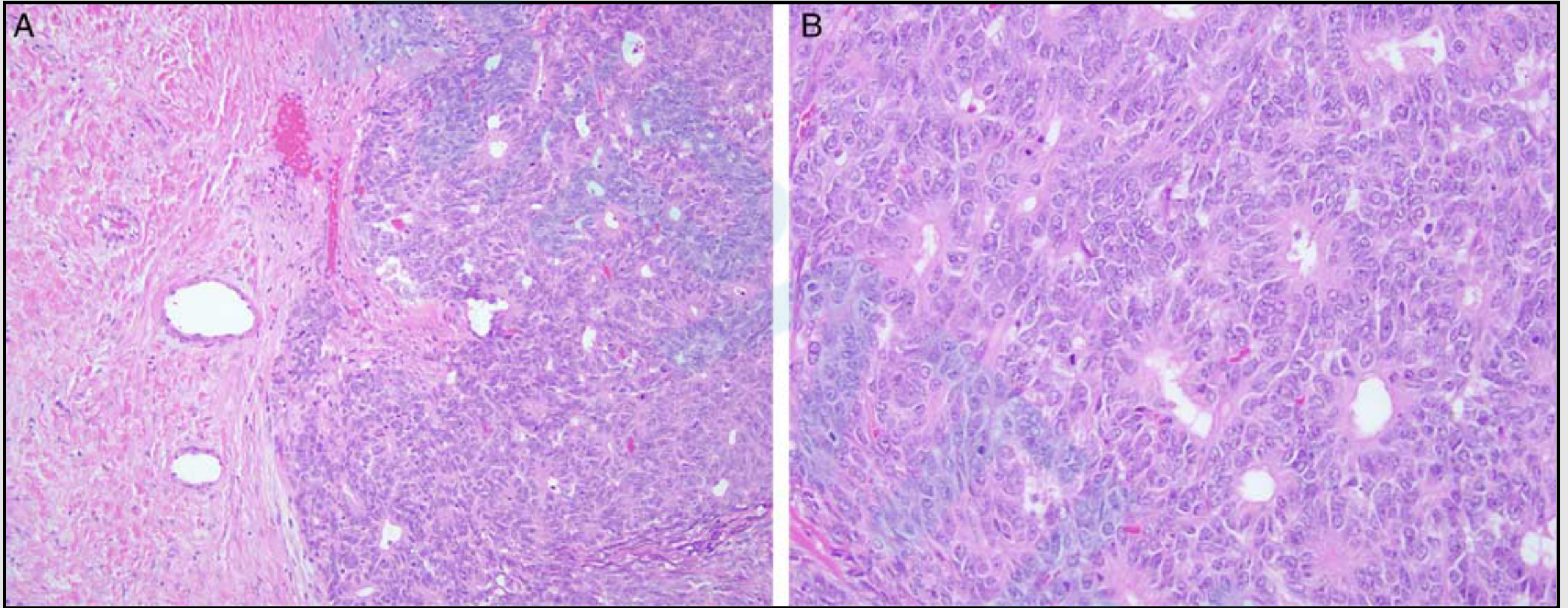
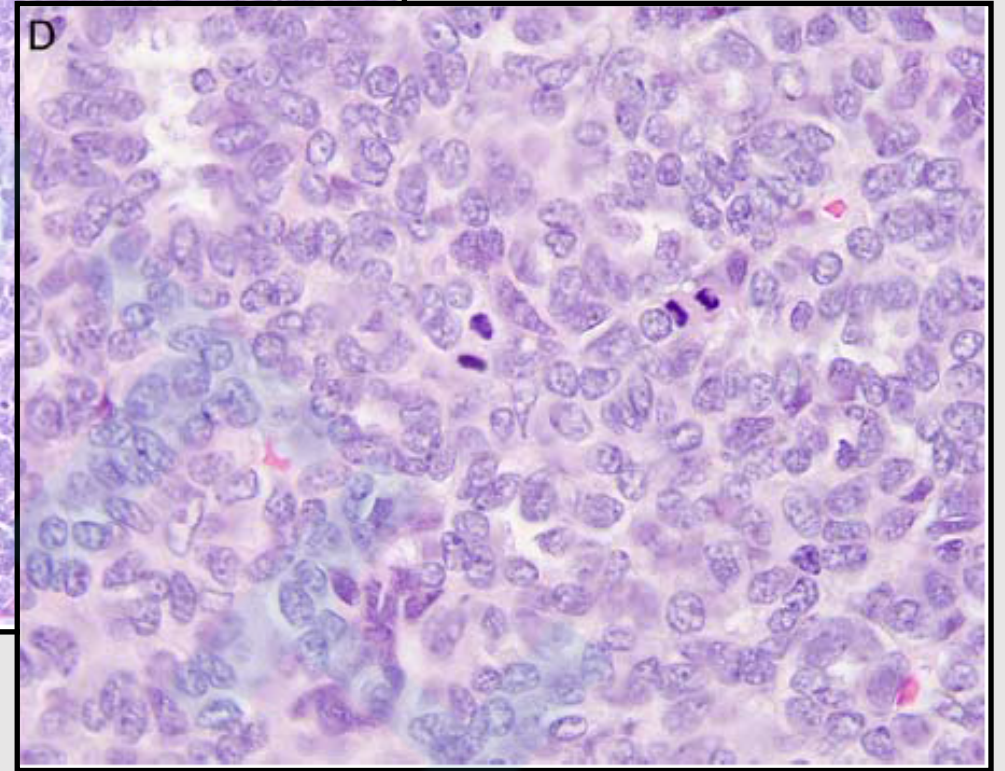
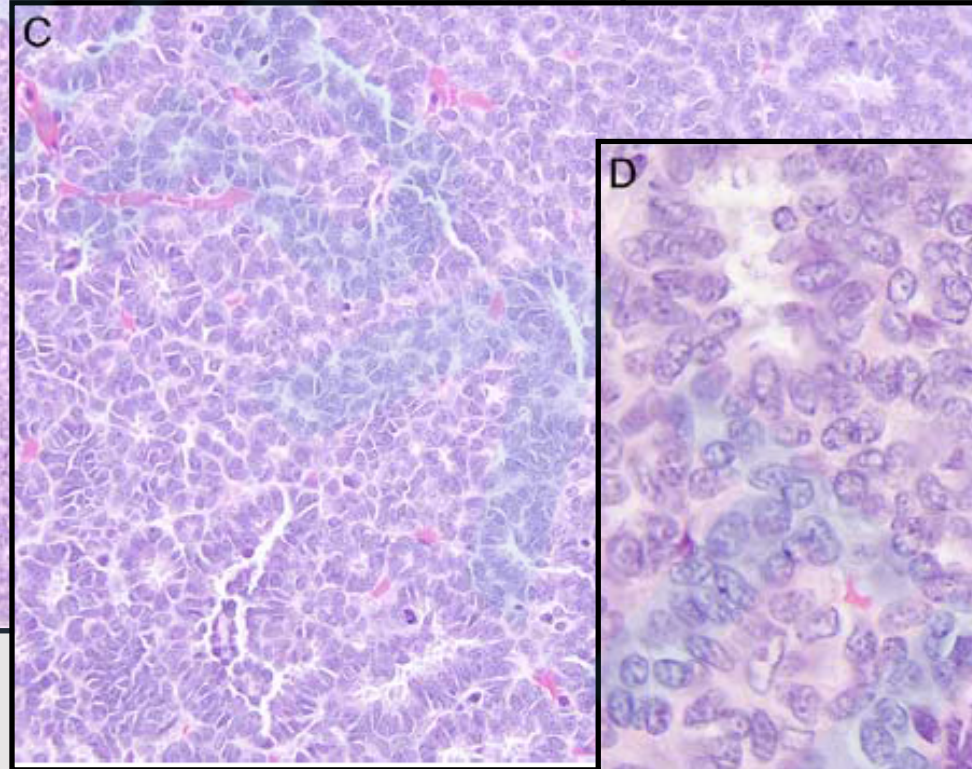
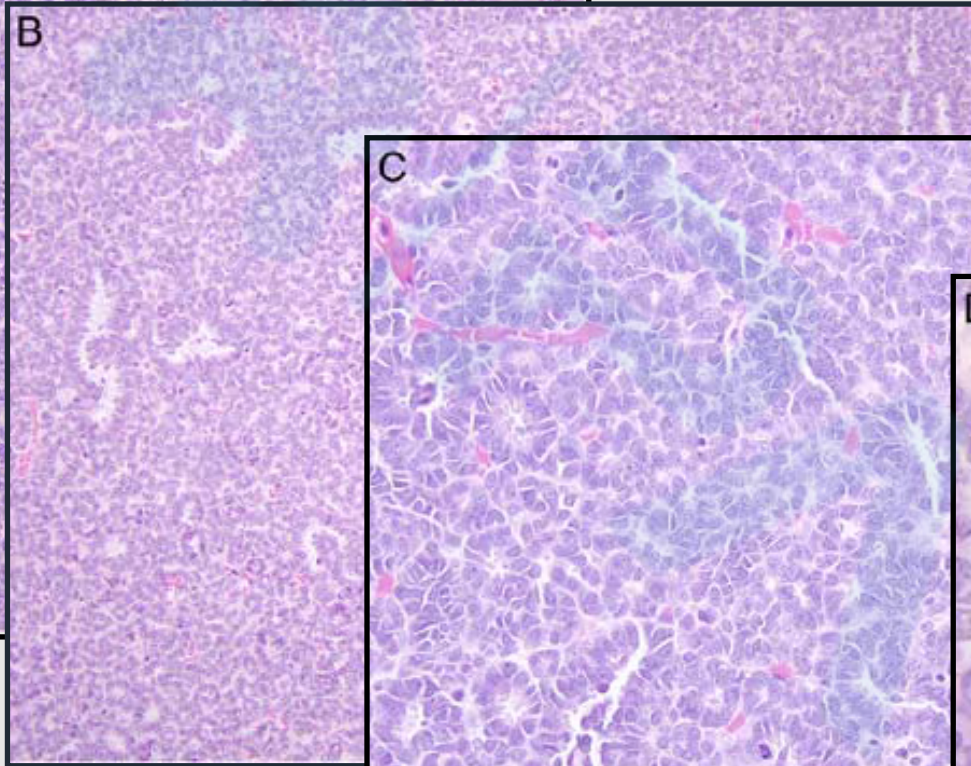
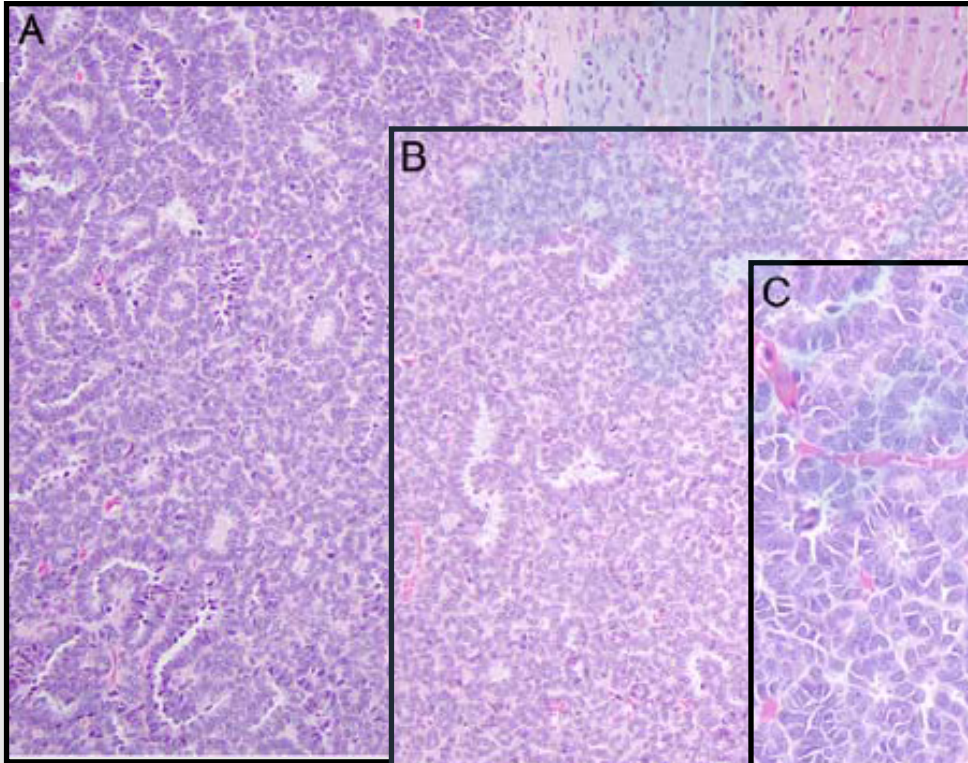


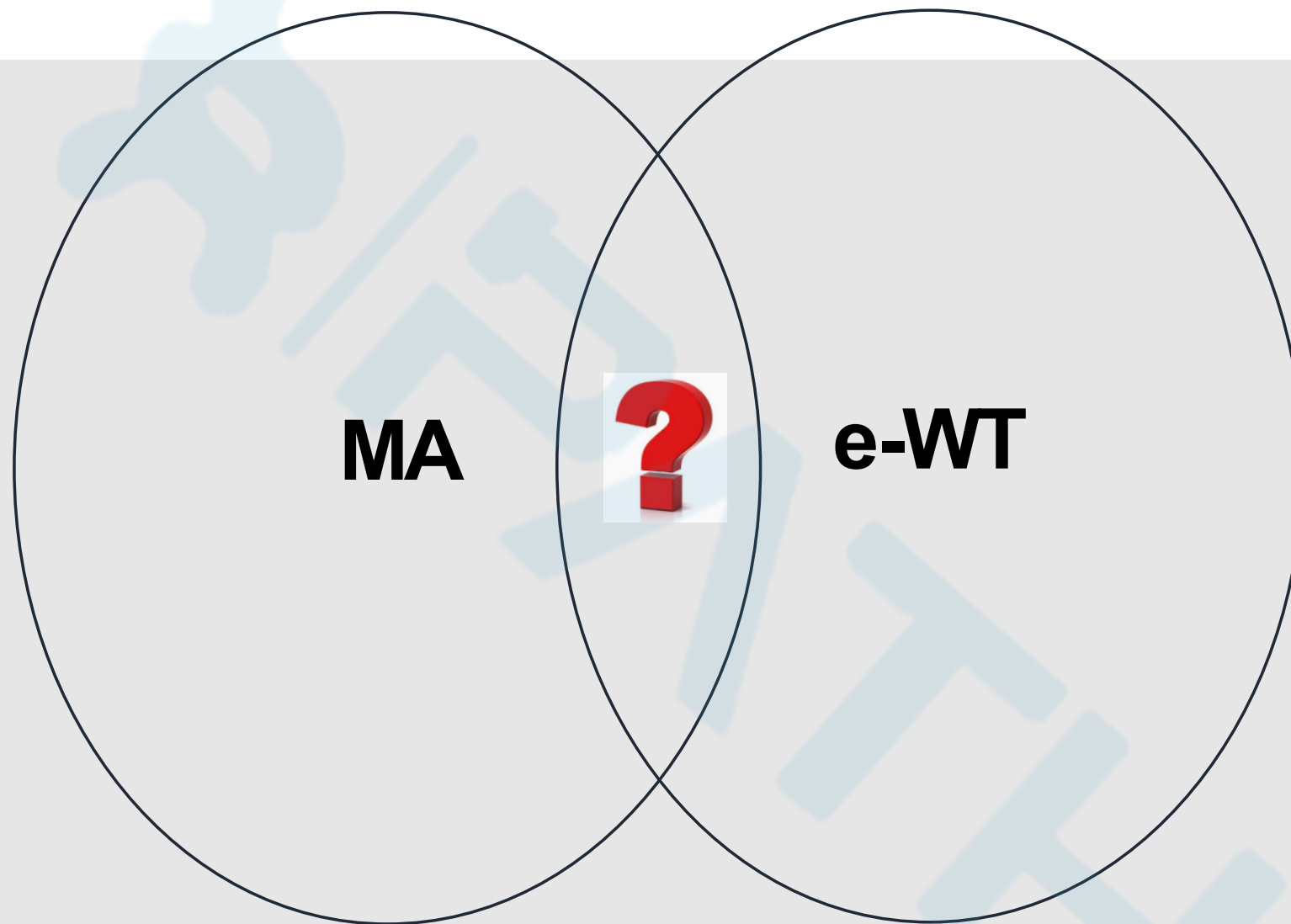
FIGURE 2. Typical epithelial-predominant Wilms tumor that was BRAF V600E mutation-negative (WT control case 1). This was an encapsulated neoplasm (A) composed predominantly of tubules formed by primitive cells with columnar-shaped nuclei and frequent mitoses, characteristic of epithelial Wilms tumor (B).

# 成人WT诊断标准

- (1) 肾脏原发性肿瘤；
- (2) 具有原始母细胞样梭形或圆形细胞成分；
- (3) 病理发现不成熟胚胎样肾小球，肾小管样结构；
- (4) 无肾癌组织；
- (5) 年龄大于15岁。

Adult wilms' tumor: A report of prolonged survival and review of the literature. J Urol 1980; 124: 1-5





# 材料 & 方法

## 4组病例：

- (1) 8例MA（**对照组**）。
- (2) 7例上皮型WT（**对照组**）。
- (3) 2例核分裂多见的MA（**实验组**）。
- (4) 9例与MA相似的e-WT（**实验组**）。

方法： (1) IHC: Braf V600E, Ki-67

(2) 二代测序: Braf V600E

对照组：

| TABLE 1. Cases in This Study                       |              |           |                   |               |                            |          |             |                       |                       |
|----------------------------------------------------|--------------|-----------|-------------------|---------------|----------------------------|----------|-------------|-----------------------|-----------------------|
| Case                                               | Age (y)/ Sex | Size (cm) | IHC               | BRAF Mutation | Comment                    | BRAF IHC | Ki-67 Index | Mitotic Count Hotspot | Mitotic Count Overall |
| Metanephric adenoma (control cases)                |              |           |                   |               |                            |          |             |                       |                       |
| 1                                                  | 60/F         | 2.5       | WT-1+, EMA-       | Positive      |                            | Positive | 0.1         | 0                     | 0                     |
| 2                                                  | 62/F         | 2.5       | WT-1+, EMA-       | Positive      |                            | Positive | 0.1         | 0                     | 0                     |
| 3                                                  | 57/M         | 2.9       | ND                | Positive      |                            | Positive | 0.2         | 0                     | 0                     |
| 4                                                  | 10/M         | 1.3       | ND                | Negative      |                            | Negative | 4.7         | 0                     | 0                     |
| 5                                                  | 42/F         | 3.2       | WT-1+, CD57+      | Positive      |                            | Positive | 2.4         | 2                     | 2                     |
| 6                                                  | 59/M         | 3.4       | WT-1+, CD57+      | Positive      |                            | Positive | NA          | 0                     | 0                     |
| 7                                                  | 43/F         | 1.9       | WT-1-             | Negative      | Focal synaptophysin+       | Negative | NA          | 1                     | 1                     |
| 8                                                  | 48/F         | 3.1       | WT-1+, focal CK7+ | Positive      |                            | Positive | 2.6         | 1                     | 2                     |
| Epithelial-predominant Wilms tumor (control cases) |              |           |                   |               |                            |          |             |                       |                       |
| 1                                                  | 13/M         | 13        |                   | Negative      | Stage 3 (lymph node)       | Negative | 3.1         | 11                    | 8                     |
| 2                                                  | 6/F          | 6         |                   | Negative      | Stage 2                    | Negative | 11.3        | 30                    | 19                    |
| 3                                                  | 6/F          | 9         |                   | Negative      | Stage 2, diffuse anaplasia | Negative | 4.0         | 24                    | 27                    |
| 4                                                  | 14/F         | 7         |                   | Negative      | Stage 2 posttherapy        | Negative | 0.8         | 6                     | 5                     |
| 5                                                  | 19/F         | 7.8       | WT-1+             | Negative      | Stage 1, ILNR              | NA       | NA          | 4                     | 4                     |
| 6                                                  | 2/M          | 10.5      |                   | Negative      | Stage 2                    | NA       | NA          | 54                    | 38                    |
| 7                                                  | 1/F          | 7.5       |                   | Negative      | Stage 1                    | NA       | NA          | 32                    | 42                    |

# 实验组：

## Unusual metanephric adenoma with increased mitotic activity (consult cases)

|   |      |     |                 |          |                                |          |     |   |    |
|---|------|-----|-----------------|----------|--------------------------------|----------|-----|---|----|
| 1 | 24/F | 2.8 |                 | Positive |                                | NA       | 3.4 | 6 | 10 |
| 2 | 19/M | 3.5 | WT-1+,<br>CD57+ | Positive | Called WT on<br>frozen section | Positive | 3.2 | 3 | 12 |

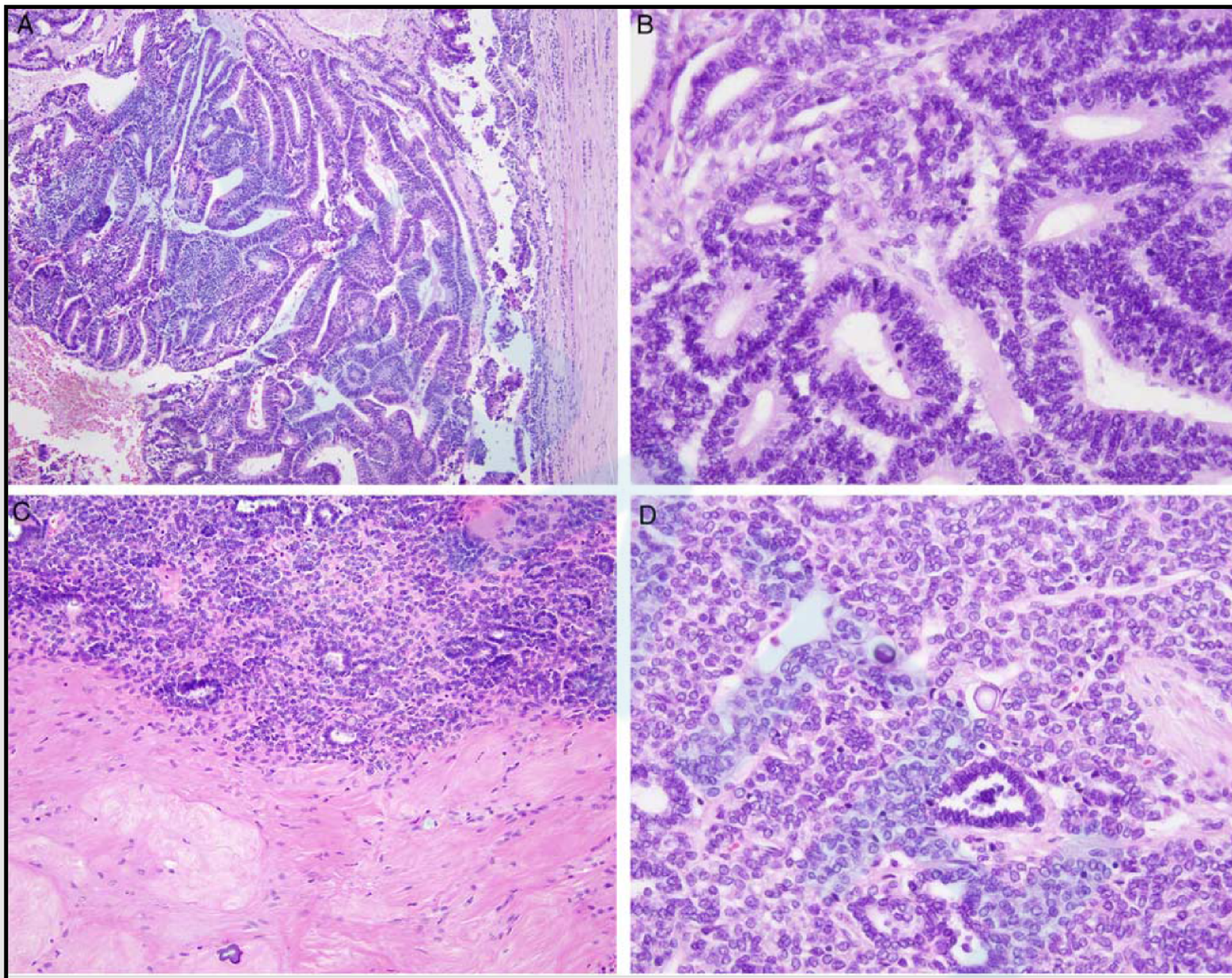
## Epithelial Wilms tumor mimicking metanephric adenoma (all but one consult cases)

|   |      |     |                 |                                  |                                                         |                                         |                                                           |                                                        |                                                       |
|---|------|-----|-----------------|----------------------------------|---------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------------|
| 1 | 54/M | 11  | WT-1+           | Positive<br>(both<br>components) | Discrete MA-like<br>and WT-like<br>components           | MA-like and<br>WT-like both<br>positive | MA-like 3.6;<br>WT-like 26.7                              | MA-like 2;<br>WT-like 40                               | MA-like 0;<br>WT-like 45                              |
| 2 | 3/M  | NA  | WT-1+           | Negative                         |                                                         | Negative                                | 32.2                                                      | 6                                                      | 9                                                     |
| 3 | 28/F | 6   | WT-1+,<br>CD57+ | Negative                         |                                                         | Negative                                | 10.1                                                      | 3                                                      | 5                                                     |
| 4 | 29/F | 5.5 | WT-1+           | Negative                         |                                                         | Negative                                | 9.8                                                       | 17                                                     | 9                                                     |
| 5 | 3/F  | 6   | WT-1+,<br>CD57+ | Positive                         | Posttherapy                                             | Positive                                | 10.3                                                      | 1                                                      | 1                                                     |
| 6 | 53/M | 4.2 | WT-1+,<br>EMA+  | Negative                         | Stage 2<br>(perinephric fat)                            | Negative                                | Core bx (MA-like)<br>0; Resection<br>(WT-like) 8.4<br>7.5 | Core bx (MA-like)<br>0; Resection<br>(WT-like) 16<br>6 | Core bx (MA-like)<br>0; Resection<br>(WT-like) 6<br>6 |
| 7 | 46/M | 5   | WT-1+           | Negative                         | Stage 2<br>(perinephric fat)                            | NA                                      |                                                           |                                                        |                                                       |
| 8 | 6/M  | 6.5 | WT-1+           | Positive                         | Lung metastases<br>after 1 y                            | MA-like and<br>WT-like<br>both positive | MA-like 0.1;<br>WT-like 9.2                               | MA-like 1;<br>WT-like 29                               | MA-like 1;<br>WT-like 34                              |
| 9 | 57/F | 3   | WT-1+;<br>EMA-  | Positive                         | Stage 2<br>(extensive sinus<br>soft tissue<br>invasion) | MA-like and<br>WT-like<br>both positive | MA-like 0.6;<br>WT-like 36.6                              | MA-like 0;<br>WT-like 19                               | MA-like 0;<br>WT-like 35                              |

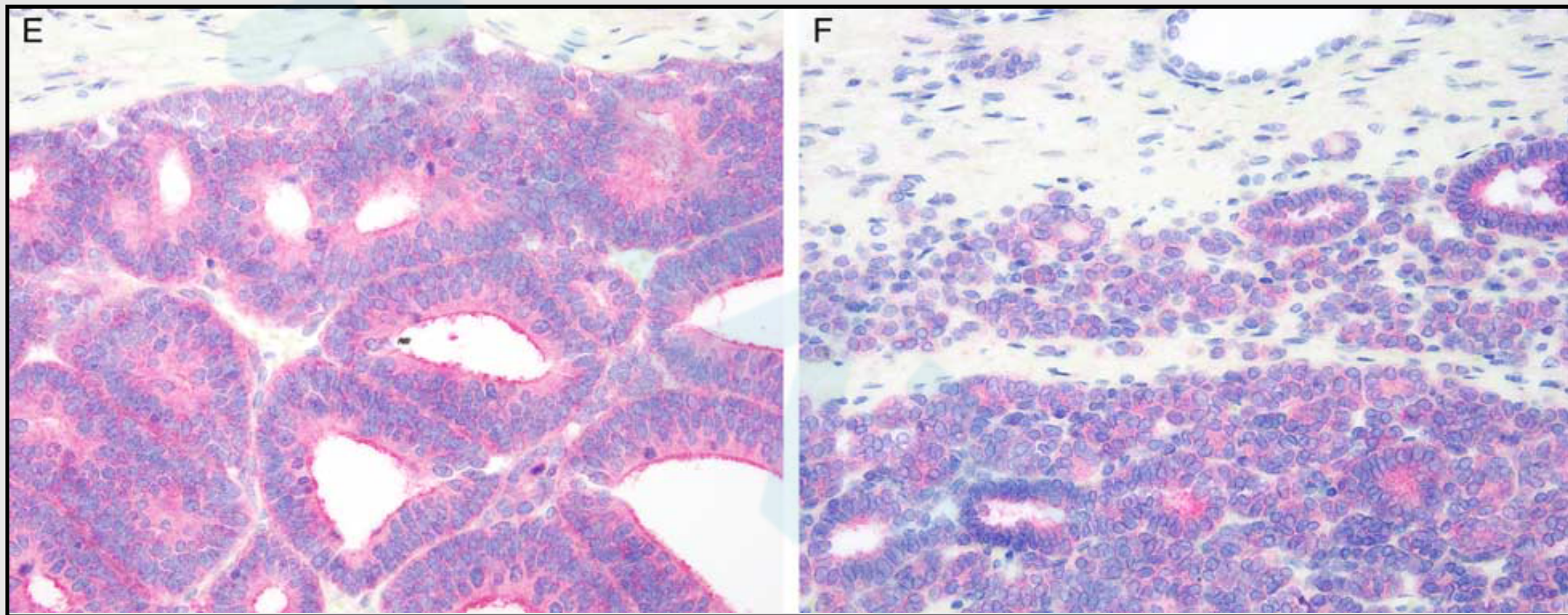
bx indicates biopsy; F, female; ILNR, intralobar nephrogenic rest; M, male; NA, not available (inadequate material for testing).

# 病例1

(实验组e-WT)

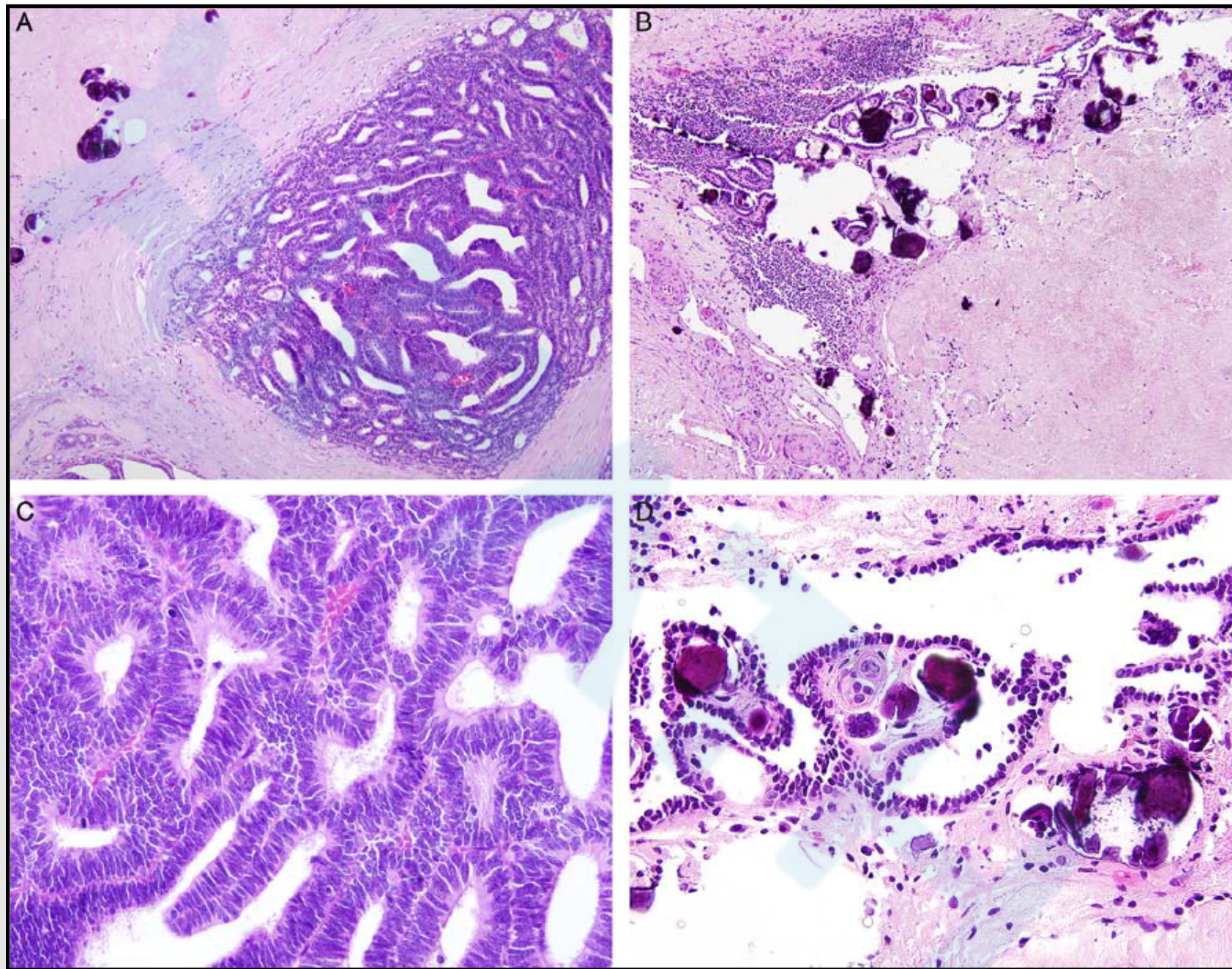


## 病例1 BRAF染色

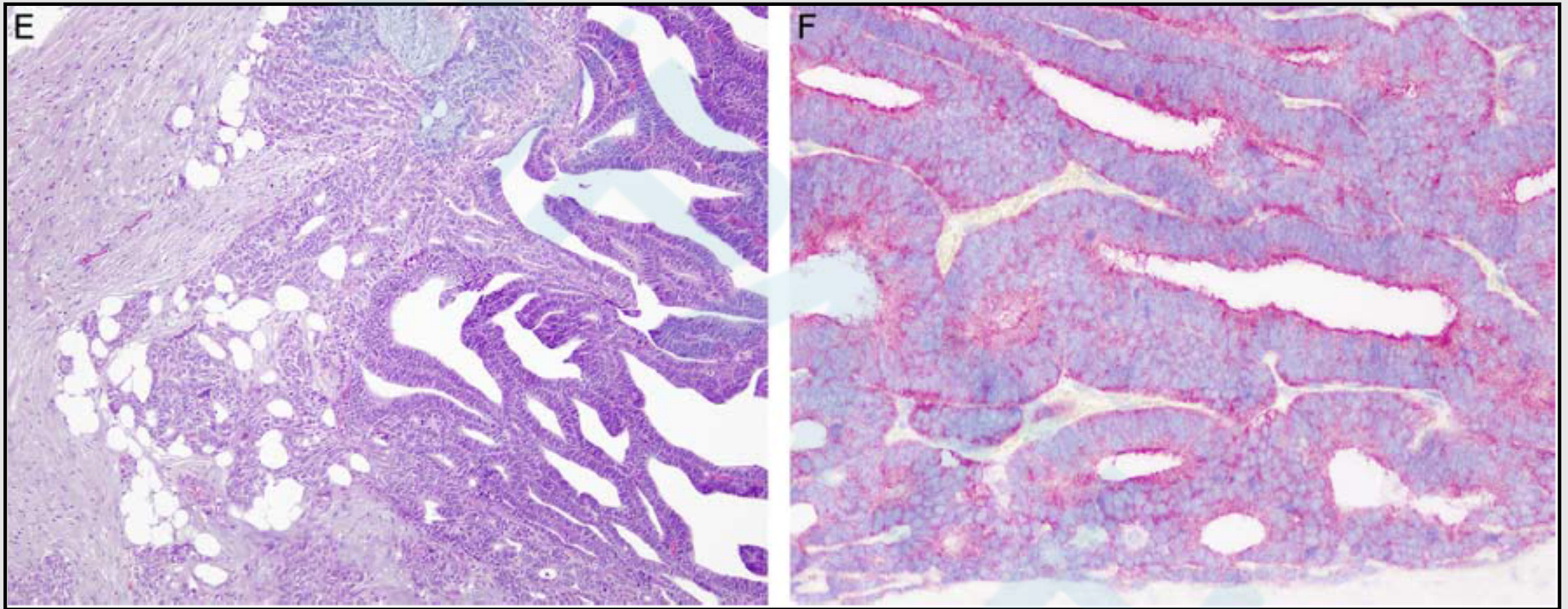


## 病例2

(实验组e-WT)

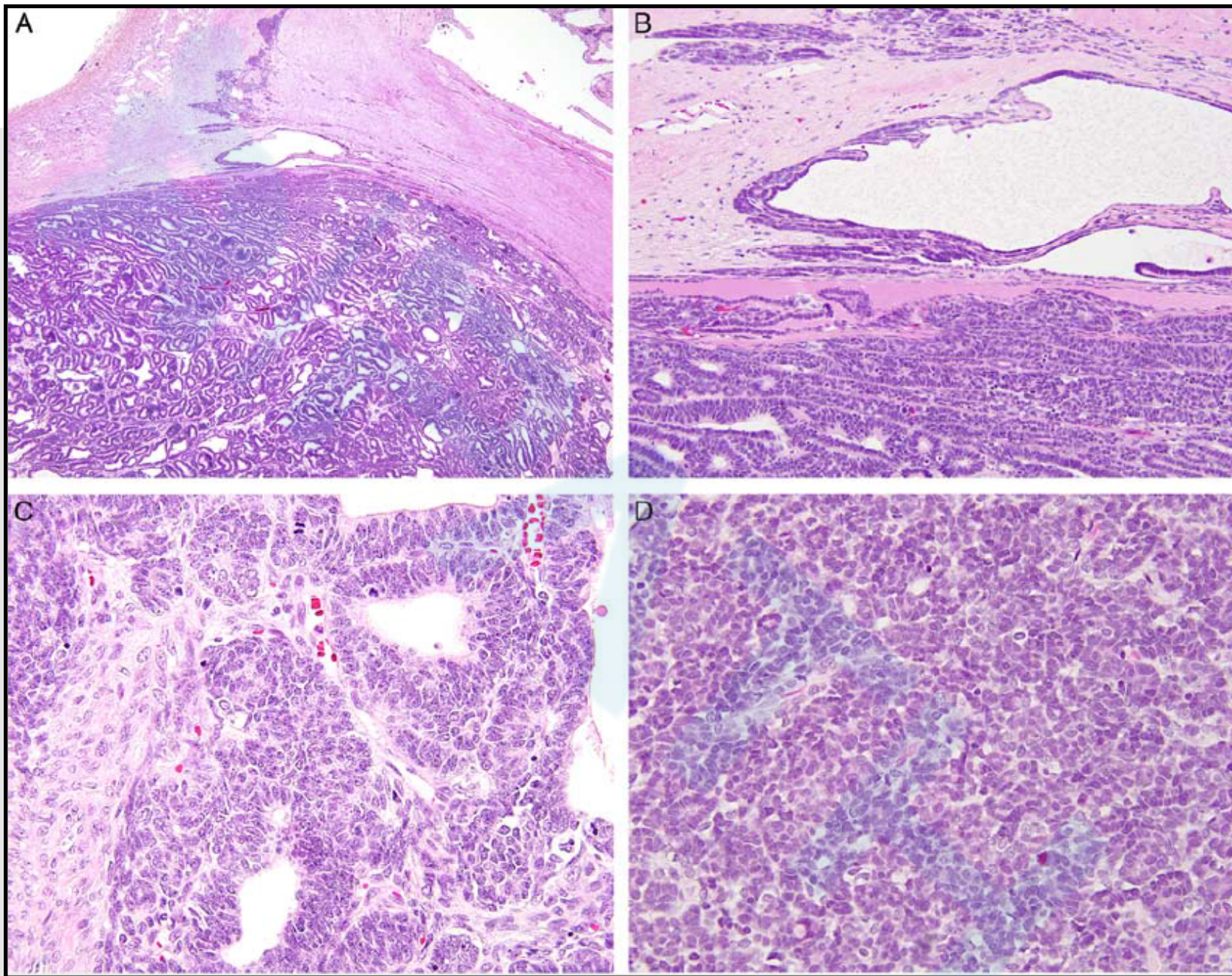


## 病例2

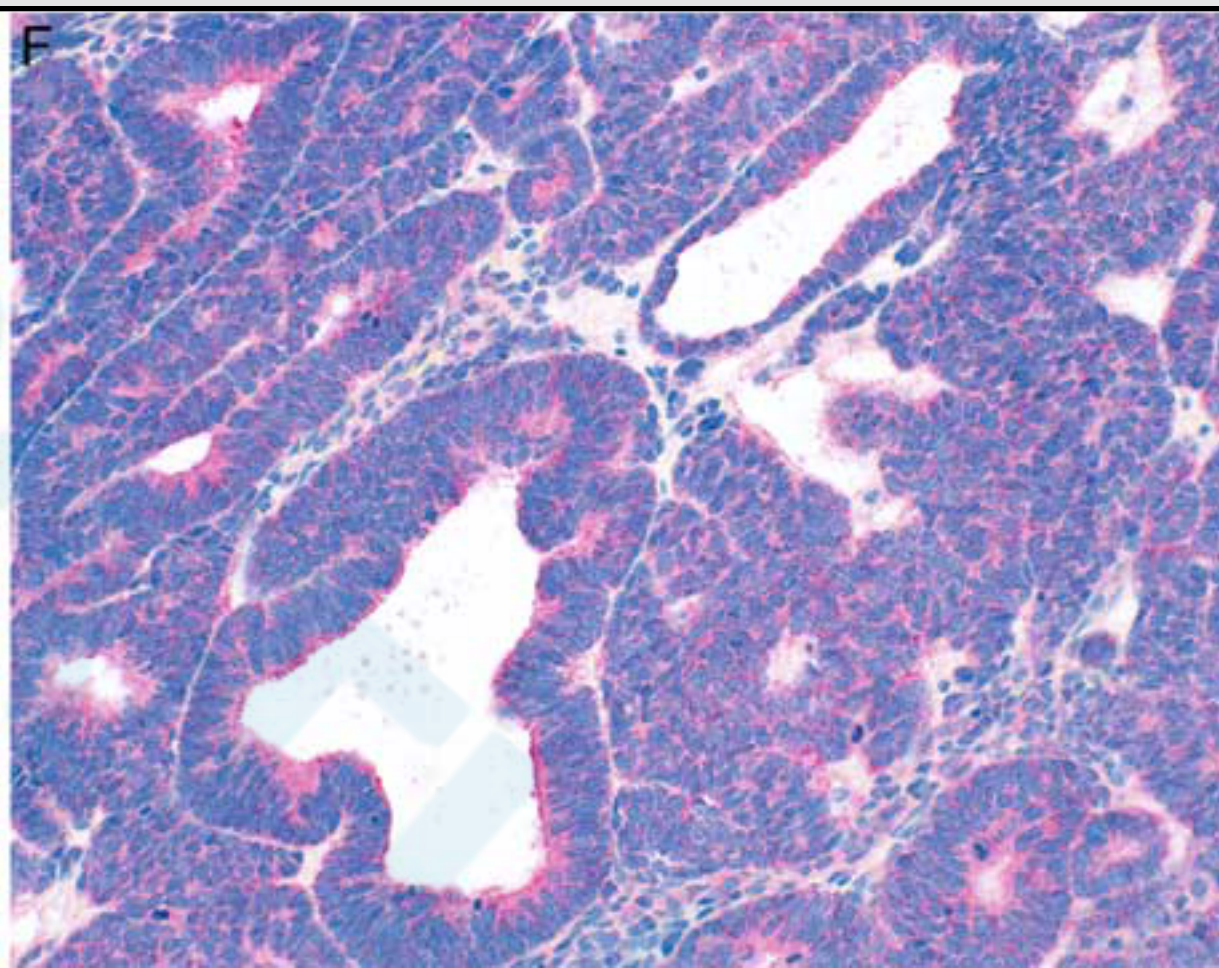
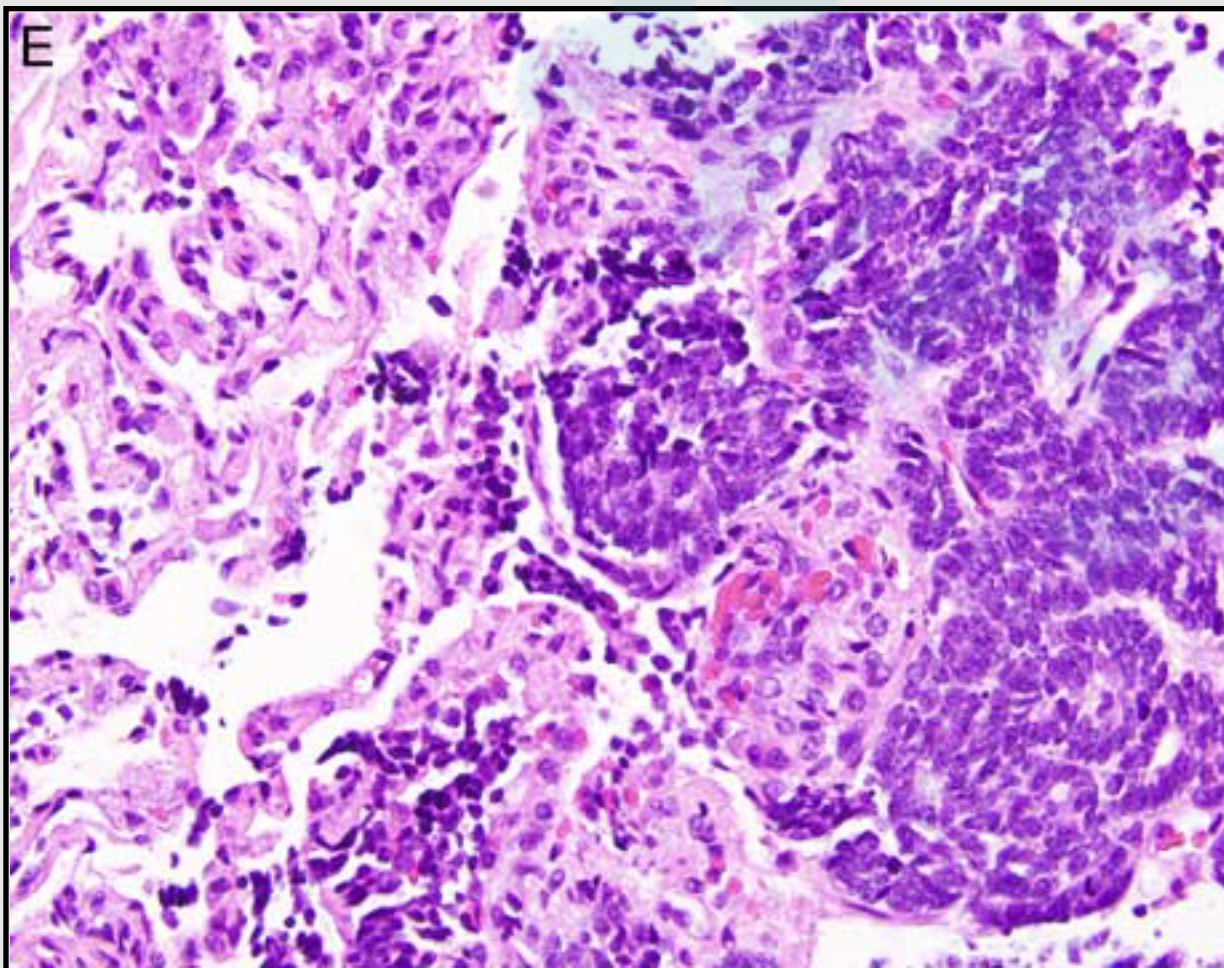


# 病例3

(实验组e-WT)

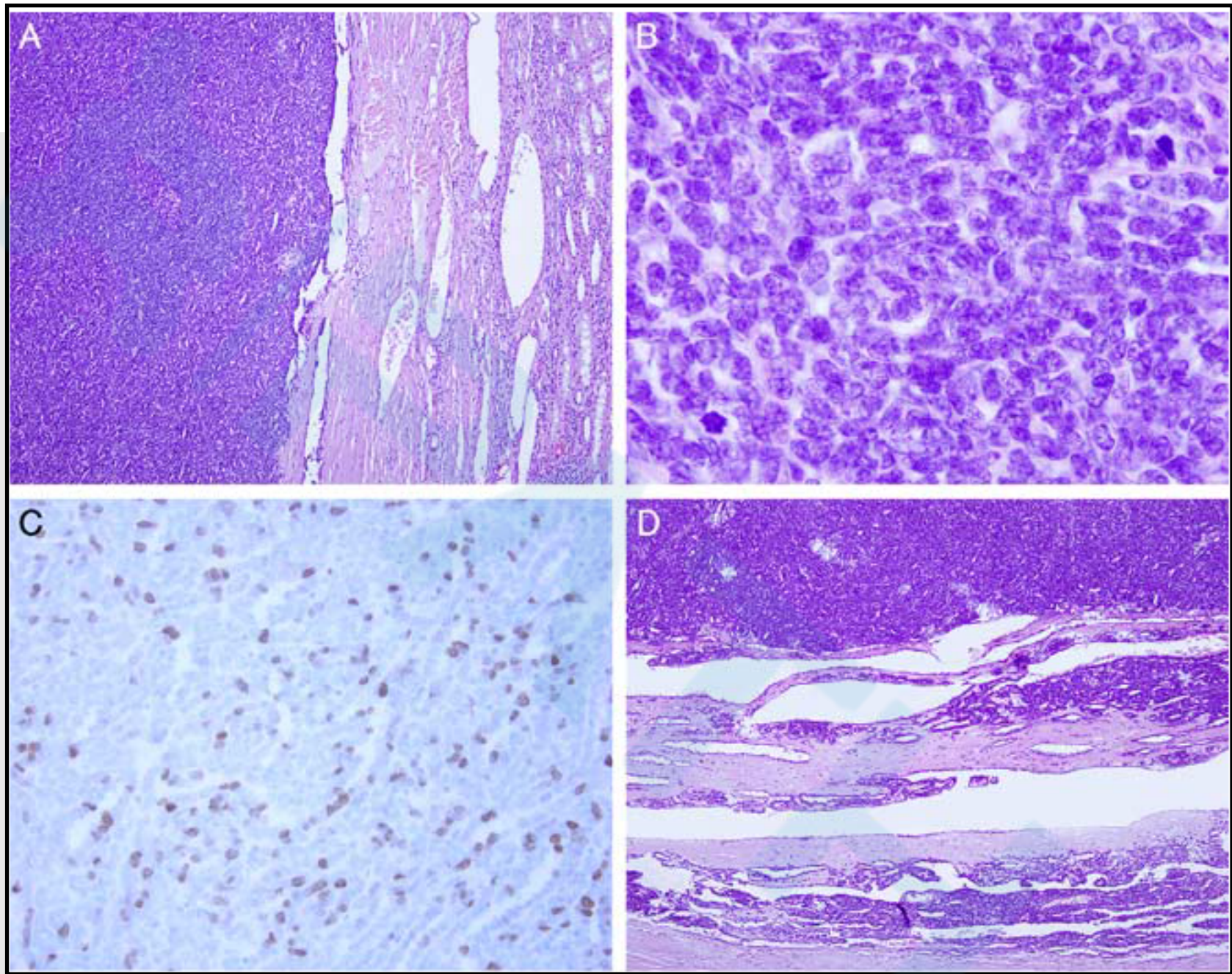


### 病例3

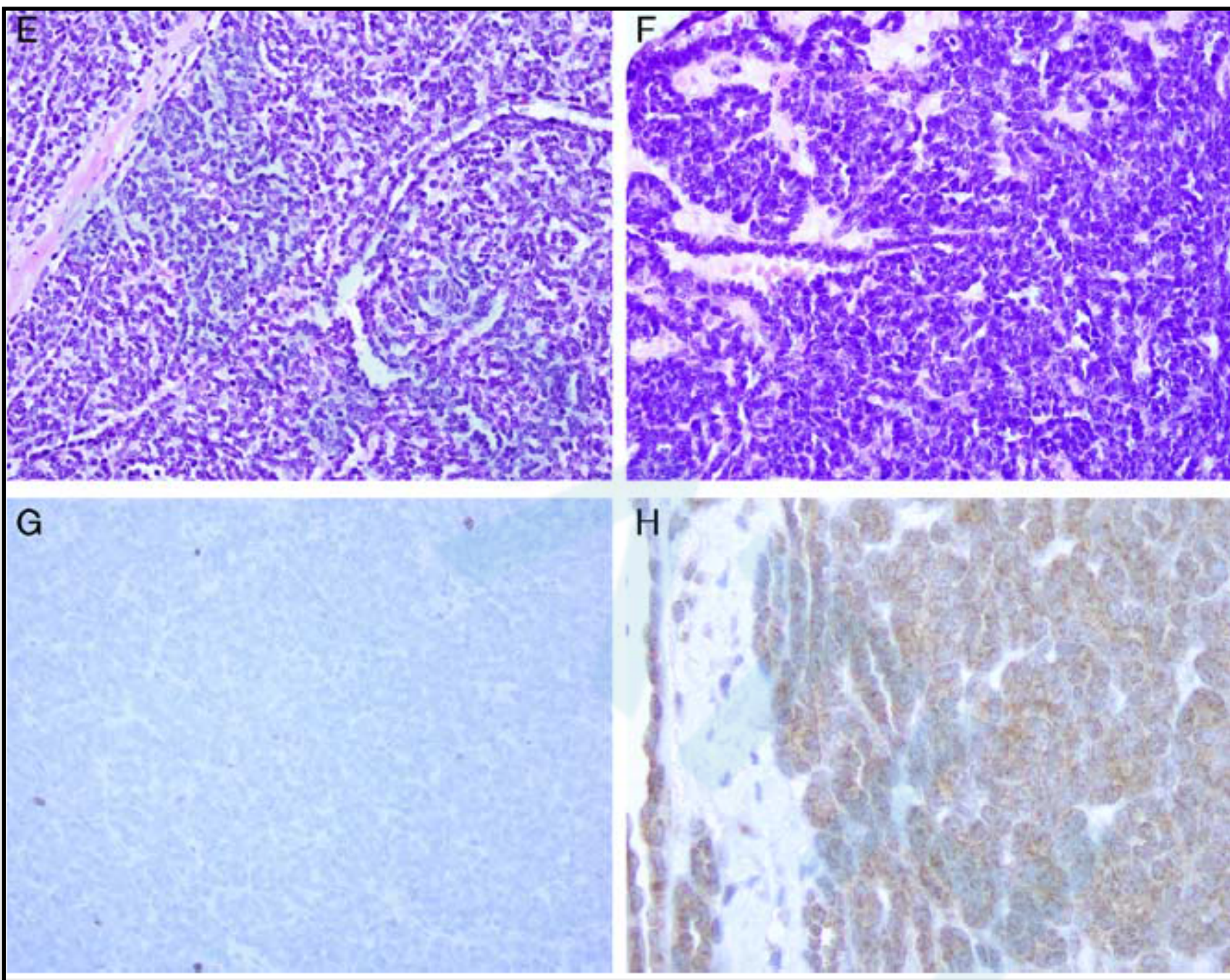


## 病例4

(实验组e-WT)

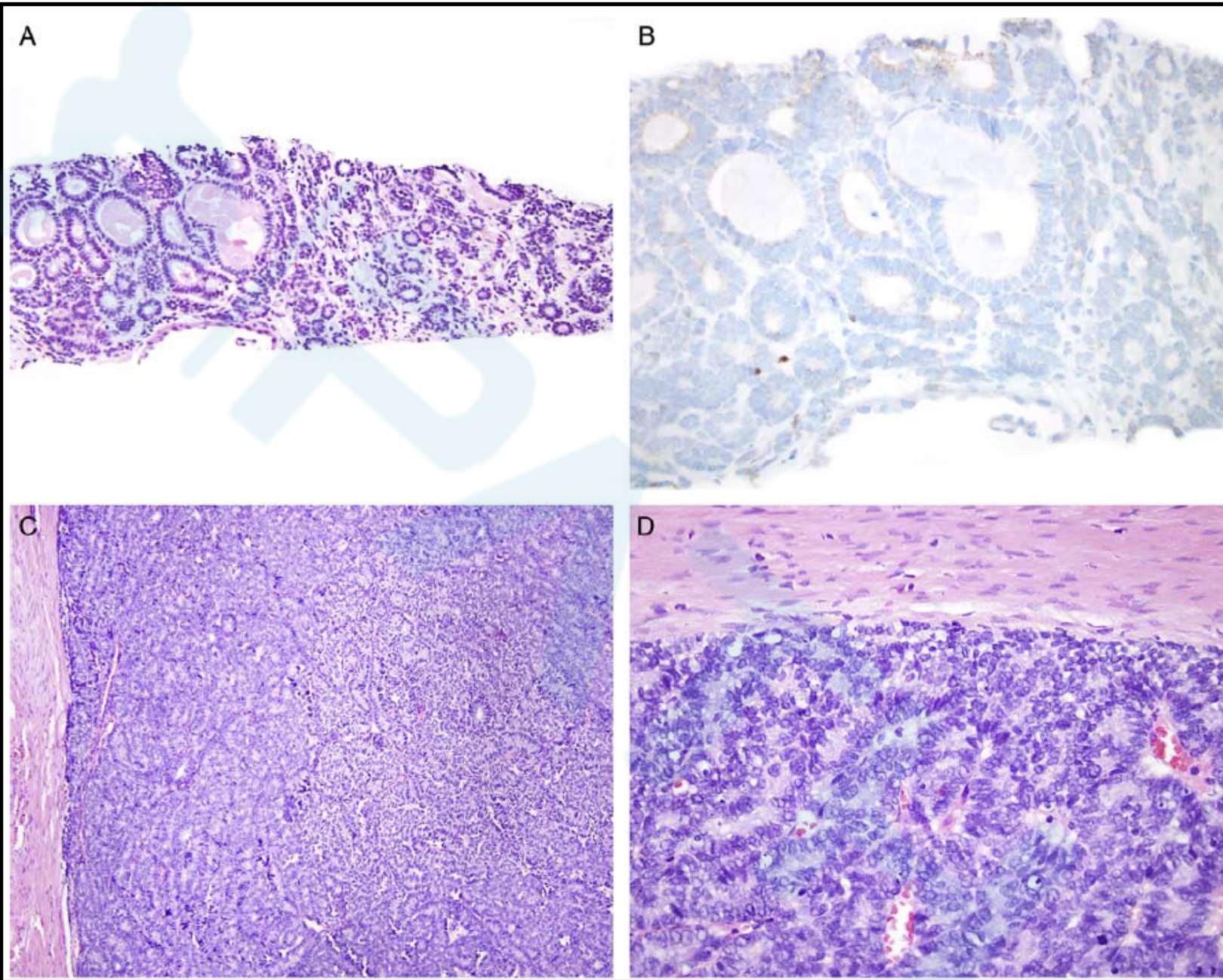


## 病例4

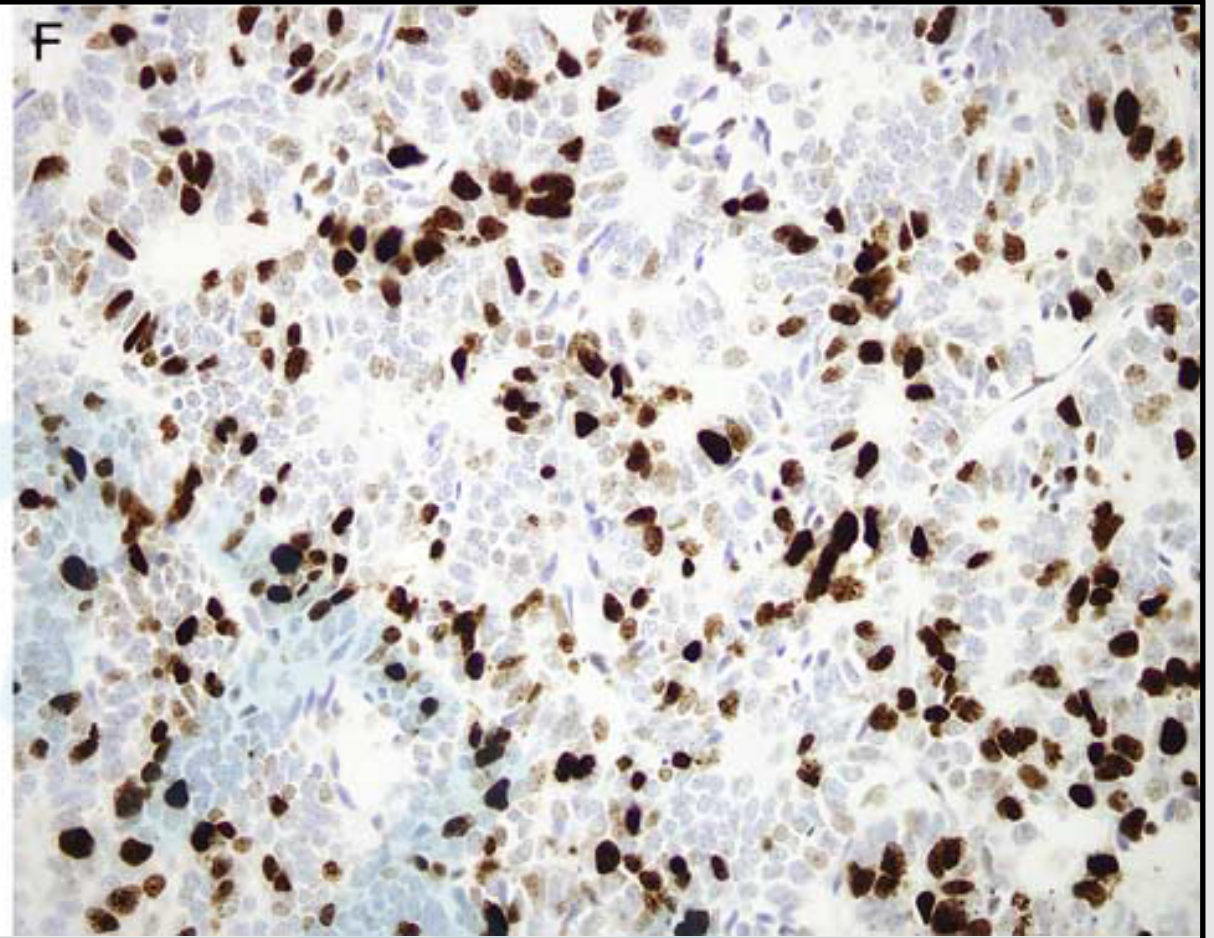
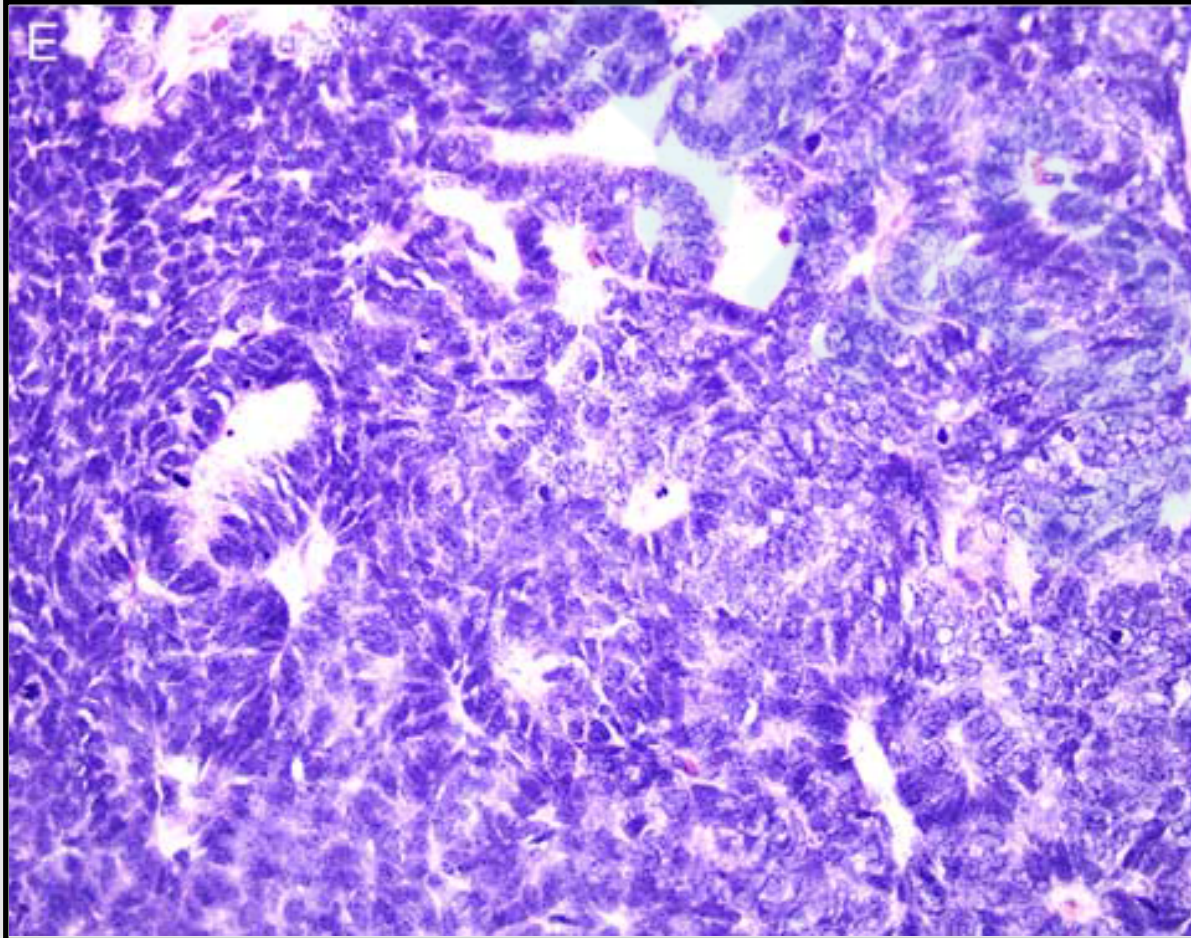


## 病例5

(实验组e-WT)



## 病例5



# BRAF检测结果

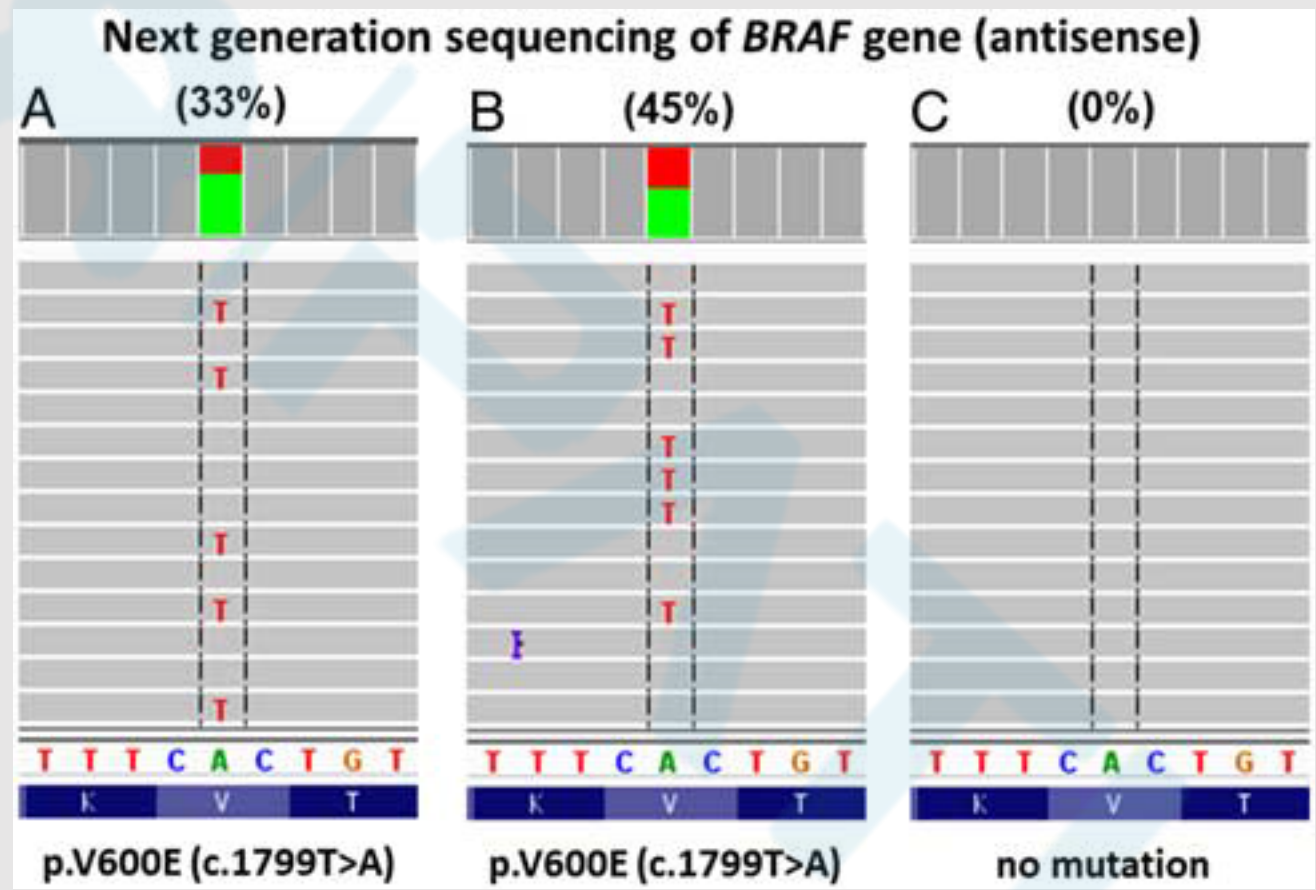


FIGURE 9. Representative next-generation sequencing results. BRAF V600E was detected in both the metanephric adenomalike (A) and Wilms tumor-like (B) areas of epithelial Wilms tumor mimicking metanephric adenoma case 1, but not the negative control (lymphoblastoid cell line) (C). Percentage in the parenthesis indicates variant allele frequency.

# BRAF检测结果

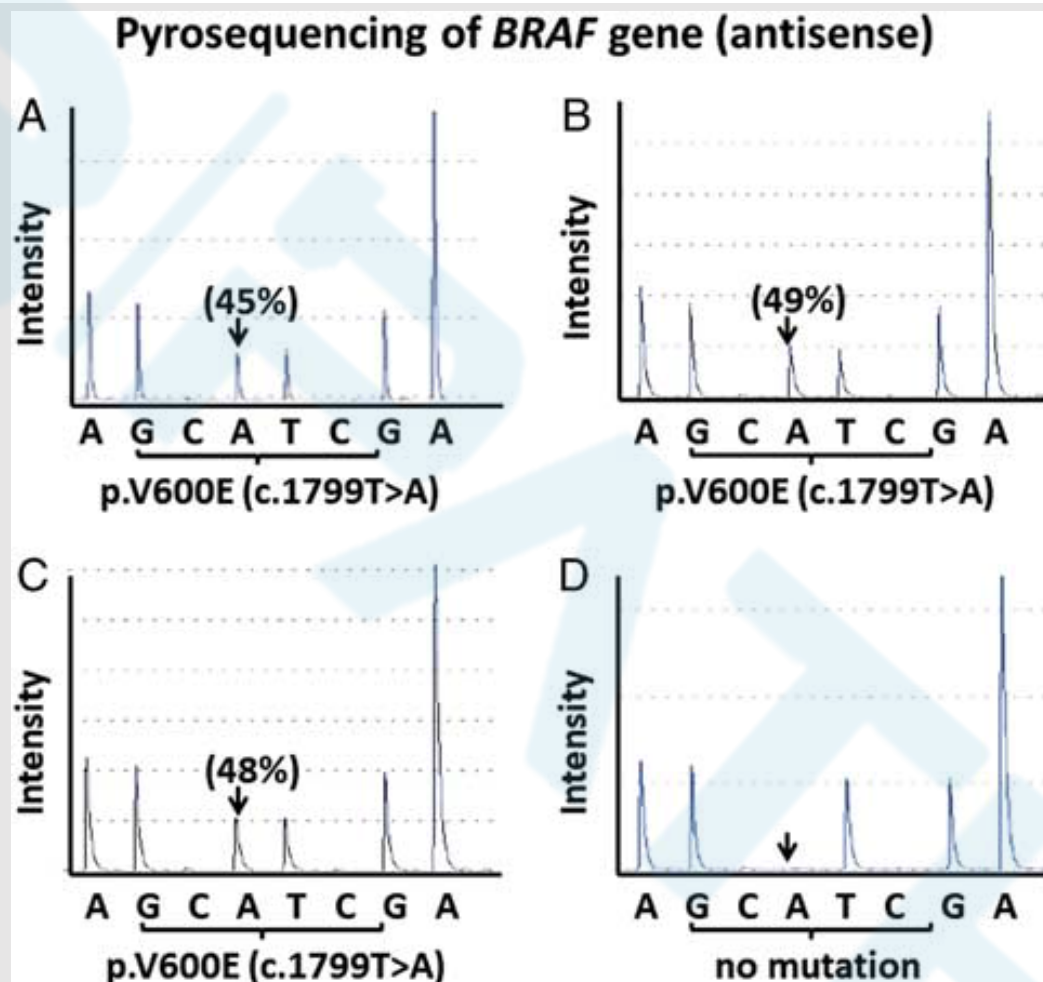


FIGURE 10. Representative pyrosequencing results. BRAF V600E was detected in epithelial Wilms tumor mimicking metanephric adenoma case 5 (A), unusual metanephric adenoma with increased mitoses case 1 (B), and metanephric adenoma control case 2 (C), but not in epithelial Wilms tumor mimicking metanephric adenoma case 6 (D). Percentage in the parenthesis indicates variant allele frequency.

Unusual metanephric adenoma with increased mitotic activity (consult cases)

|   |      |     |                 |          |                                |          |     |   |    |
|---|------|-----|-----------------|----------|--------------------------------|----------|-----|---|----|
| 1 | 24/F | 2.8 |                 | Positive |                                | NA       | 3.4 | 6 | 10 |
| 2 | 19/M | 3.5 | WT-1+,<br>CD57+ | Positive | Called WT on<br>frozen section | Positive | 3.2 | 3 | 12 |

Epithelial Wilms tumor mimicking metanephric adenoma (all but one consult cases)

|   |      |     |                 |                                  |                                                         |                                         |                                                           |                                                        |                                                       |
|---|------|-----|-----------------|----------------------------------|---------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------------|
| 1 | 54/M | 11  | WT-1+           | Positive<br>(both<br>components) | Discrete MA-like<br>and WT-like<br>components           | MA-like and<br>WT-like both<br>positive | MA-like 3.6;<br>WT-like 26.7                              | MA-like 2;<br>WT-like 40                               | MA-like 0;<br>WT-like 45                              |
| 2 | 3/M  | NA  | WT-1+           | Negative                         |                                                         | Negative                                | 32.2                                                      | 6                                                      | 9                                                     |
| 3 | 28/F | 6   | WT-1+,<br>CD57+ | Negative                         |                                                         | Negative                                | 10.1                                                      | 3                                                      | 5                                                     |
| 4 | 29/F | 5.5 | WT-1+           | Negative                         |                                                         | Negative                                | 9.8                                                       | 17                                                     | 9                                                     |
| 5 | 3/F  | 6   | WT-1+,<br>CD57+ | Positive                         | Posttherapy                                             | Positive                                | 10.3                                                      | 1                                                      | 1                                                     |
| 6 | 53/M | 4.2 | WT-1+,<br>EMA+  | Negative                         | Stage 2<br>(perinephric fat)                            | Negative                                | Core bx (MA-like)<br>0; Resection<br>(WT-like) 8.4<br>7.5 | Core bx (MA-like)<br>0; Resection<br>(WT-like) 16<br>6 | Core bx (MA-like)<br>0; Resection<br>(WT-like) 6<br>6 |
| 7 | 46/M | 5   | WT-1+           | Negative                         | Stage 2<br>(perinephric fat)                            | NA                                      |                                                           |                                                        |                                                       |
| 8 | 6/M  | 6.5 | WT-1+           | Positive                         | Lung metastases<br>after 1 y                            | MA-like and<br>WT-like<br>both positive | MA-like 0.1;<br>WT-like 9.2                               | MA-like 1;<br>WT-like 29                               | MA-like 1;<br>WT-like 34                              |
| 9 | 57/F | 3   | WT-1+;<br>EMA-  | Positive                         | Stage 2<br>(extensive sinus<br>soft tissue<br>invasion) | MA-like and<br>WT-like<br>both positive | MA-like 0.6;<br>WT-like 36.6                              | MA-like 0;<br>WT-like 19                               | MA-like 0;<br>WT-like 35                              |

bx indicates biopsy; F, female; ILNR, intralobar nephrogenic rest; M, male; NA, not available (inadequate material for testing).

# 总结

(1) 共研究了11例形态学上有重叠的病例（2例核分裂象多见的MA，9例与MA相似的e-WT），其中2例核分裂象多见的MA BRAFV600E突变阳性，4/9例似MA的e-WT BRAFV600E突变阳性。

(2) BRAFV600E免疫组化染色结果与测序结果一致。

# 讨论

- (1) BRAF突变并不仅局限于典型的MA，非典型的MA（核分裂象多见）同样检测到BRAF突变。
- (2) 典型的e-WT BRAF突变阴性，当e-WT部分形态改变与MA重叠时则有可能出现BRAF突变阳性，机理尚不明确，需进一步研究确定。
- (3) BRAFV600E免疫组化染色结果与测序结果一致。
- (4) 本文的局限性则在于只检测了BRAFV600E，未检测BRAF其他位点，可能会造成疏漏。

谢谢