“Carcinoma a cellule renali: approccio morfologico e molecolare”

Approvato dal Gruppo di Studio sulla Patologia Molecolare

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Dipartimento Rete Oncologica Piemonte e Valle d'Aosta 2019

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20 giugno 2019

A cura di

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Condiviso dal Gruppo di Studio di Patologia Molecolare

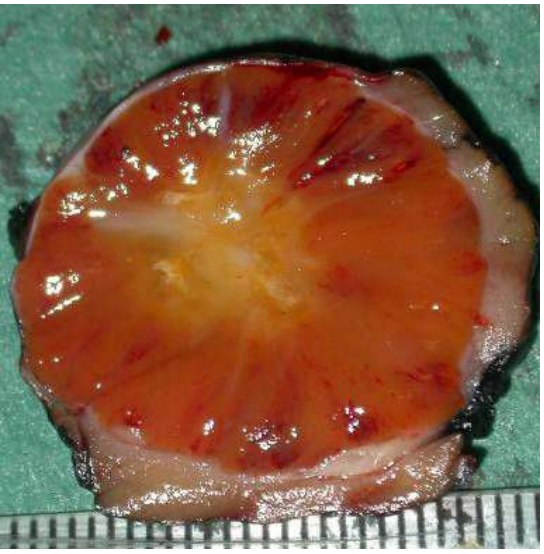
Conflict of Interest declaration

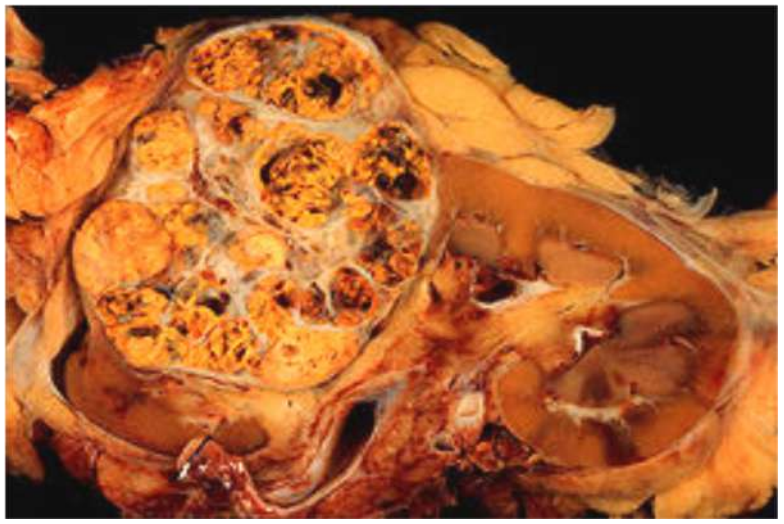
ERB is declaring his participation under fee in
Educational events,
Scientific events and
Advisory boards for

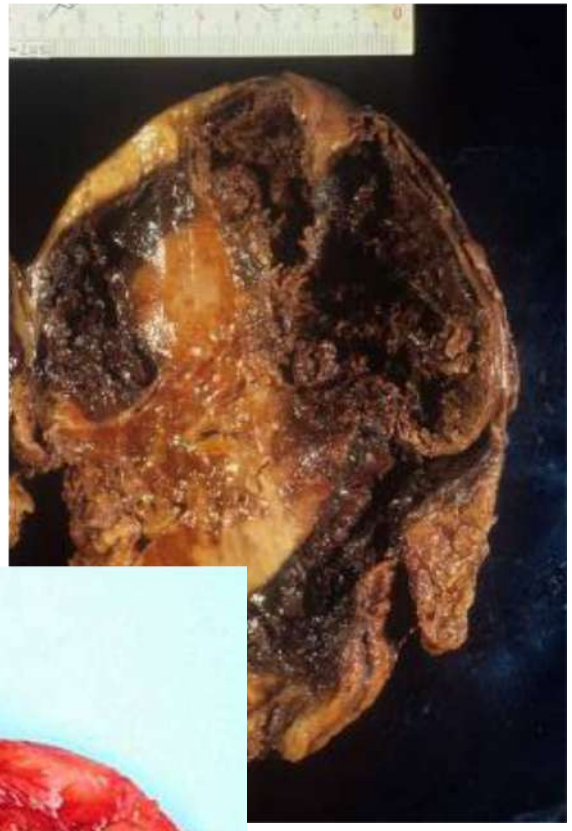
Myriad Generic Inc., Salt Lake City, UT

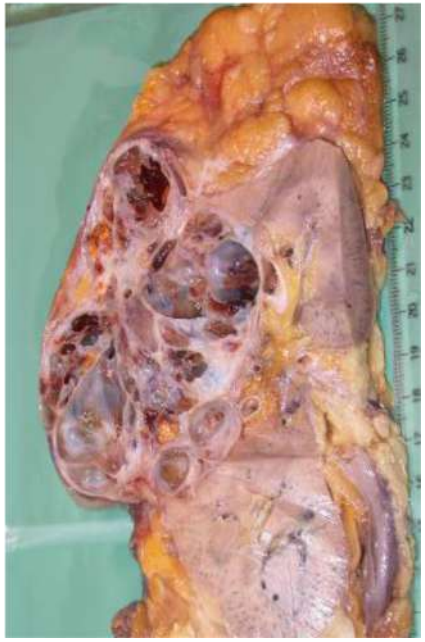
- **I tumori parenchimali del rene costituiscono un gruppo alquanto eterogeneo che comprende istotipi diversi con caratteristiche macroscopiche, istomorfologiche, immunofenotipiche e molecolari differenti. Questi aspetti si associano spesso a differenze cliniche e prognostiche talora anche rilevanti.**

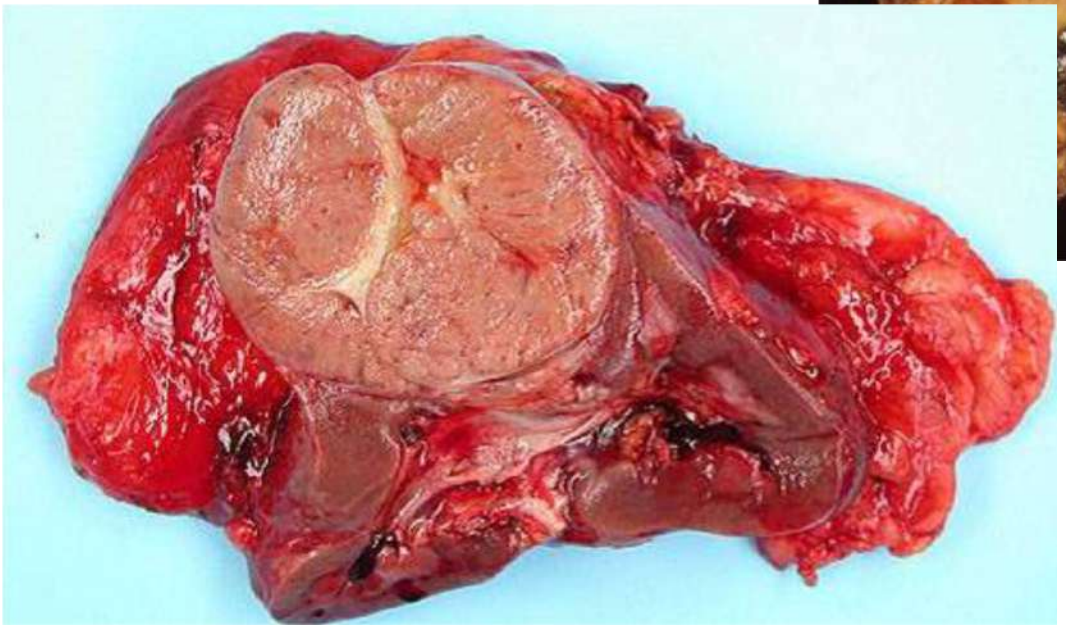
Renal Cell Carcinoma is a heterogeneous group of malignancies arising from the epithelium of the renal tubules

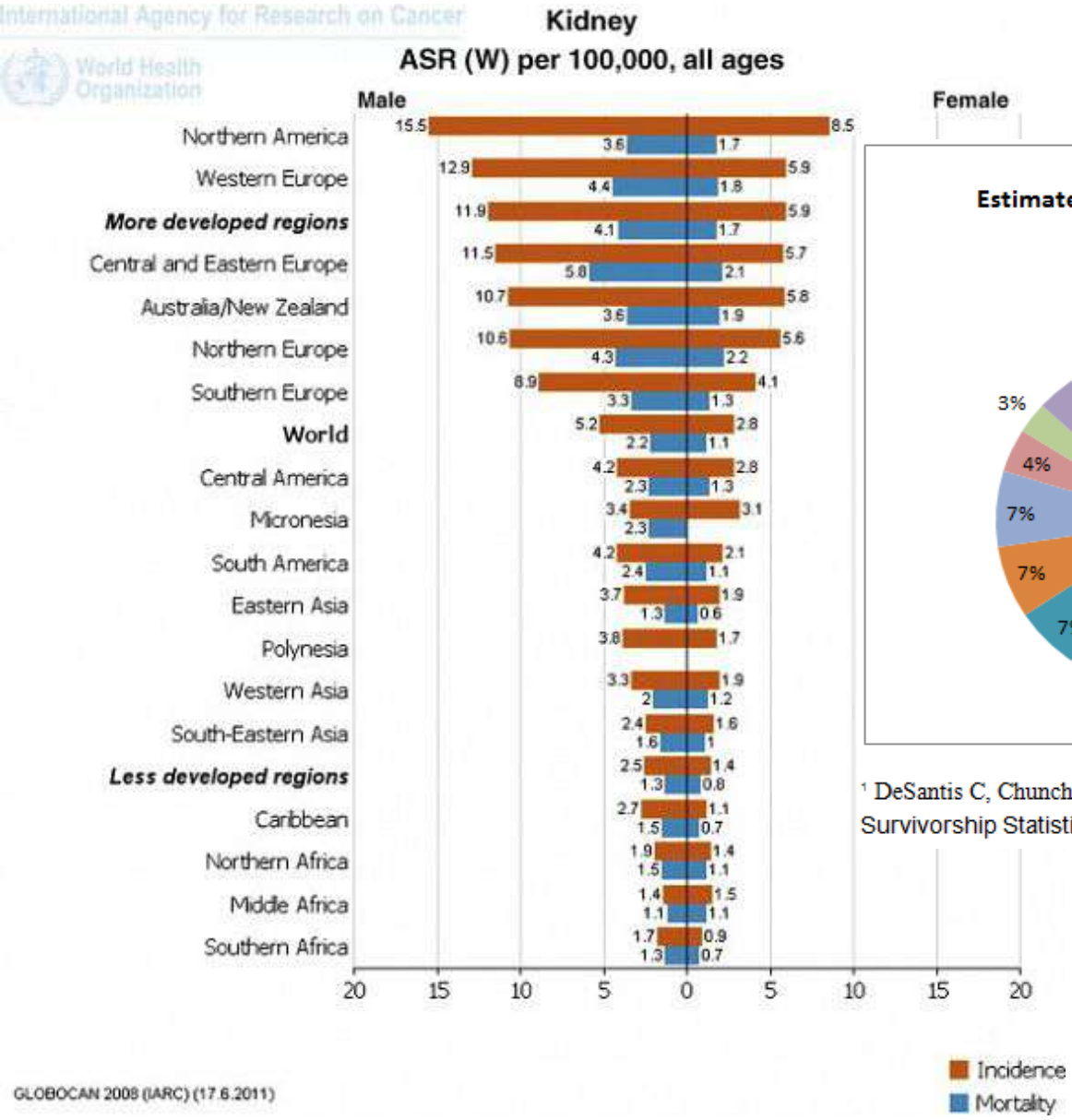


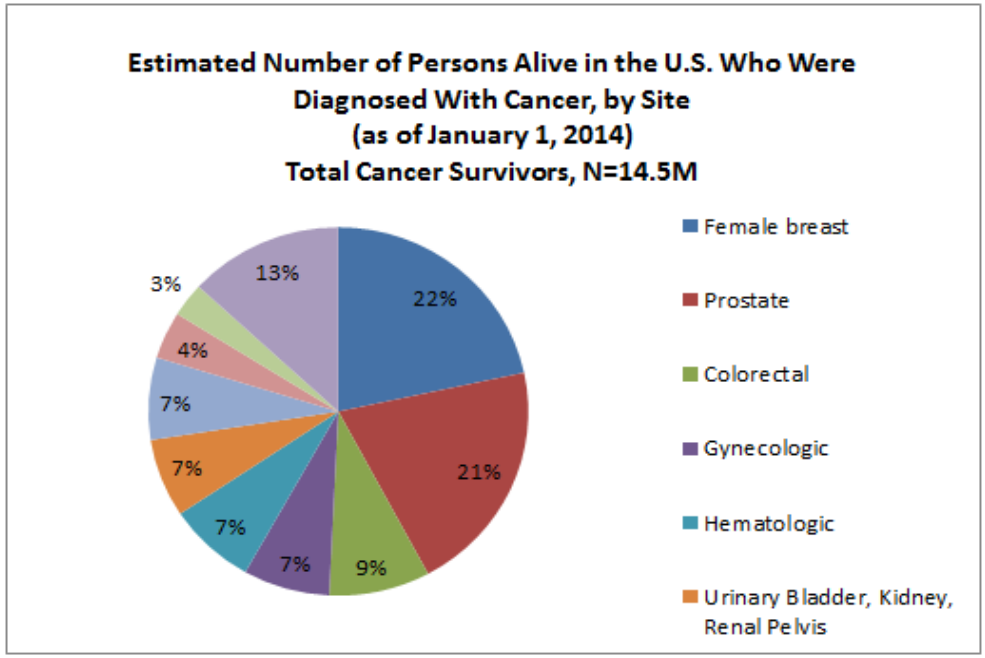












[1] DeSantis C, Chunchieh L, Mariotto AB, et al. (2014). Cancer Treatment and Survivorship Statistics, 2014. CA: A Cancer Journal for Clinicians. In press.

Si tratta di tumori non particolarmente frequenti. Tutavia il miglioramento della diagnostica radiologica evidenzia oggi numerosi casi in fase precoce e il buon risultato di terapie anche di nuova generazione ha aumentato la prevalenza di questi casi.

I tumori del rene (parenchima + via escretrice) sono circa il 7% del totale neoplasie e circa metà quelle che originano dal parenchima renale

La corretta classificazione di questi tumori è essenziale per un inquadramento clinico idoneo a condurre ad un adeguato approccio terapeutico

Il sistema classificativo è in costante evoluzione perché nuove metodiche soprattutto molecolari hanno consentito di recente una tipizzazione molto più fine e precisa

La prima osservazione suggestiva del tumore insorto nel rene è stata fatta da Daniel Sennert (Practicae Medicinae, 1613)

Il primo caso inequivocabile di RCC fu pubblicato da Miril nel 1810

La prima classificazione fu fatta da Koening nel 1926 [SCHIRROUS, STEATOMATOUS, FUNGOID e MEDULLARY]

Paul Grawitz 1883: HYPERNEPRHOMA

Foot and Humphreys introdussero il termine Carcinoma a Cellule Renali nel 1951

</> 3 cm adenoma vs carcinoma (fino al 1997 classificazione di Heidelberg)

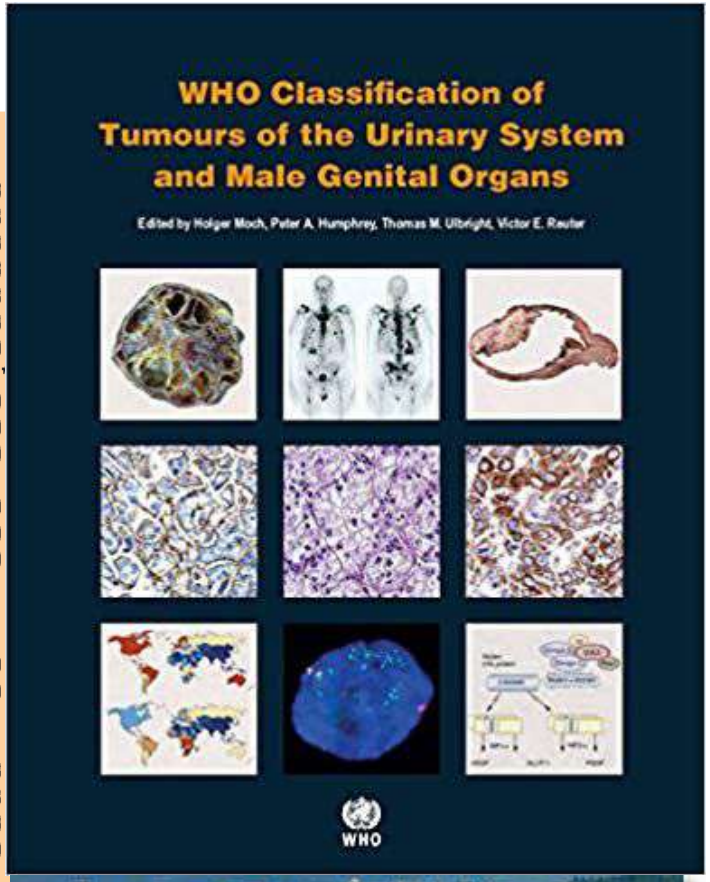
Il cambiamento fondamentale è stato la classificazione di Heidelberg proposta da Gyula Kovacs che ha dimostrato cambiamenti molecolari specifici in ogni singolo istotipo.

Kovacs G, et al: The Heidelberg classification of renal cell tumours
J Pathol. 1997 Oct;183(2):131-3.

WHO classification of tumours of the kidney

Renal cell tumours	
Clear cell renal cell carcinoma	8310/3
Multilocular cystic renal neoplasm of low malignant potential	8316/1*
Papillary renal cell carcinoma	8260/3
Hereditary leiomyomatosis and renal cell carcinoma–associated renal cell carcinoma	8311/3*
Chromophobe renal cell carcinoma	8317/3
Collecting duct carcinoma	8319/3
Renal medullary carcinoma	8510/3*
MiT family translocation renal cell carcinomas	8311/3*
Succinate dehydrogenase–deficient renal carcinoma	8311/3
Mucinous tubular and spindle cell carcinoma	8480/3*
Tubulocystic renal cell carcinoma	8316/3*
Acquired cystic disease–associated renal cell carcinoma	8316/3
Clear cell papillary renal cell carcinoma	8323/1
Renal cell carcinoma, unclassified	8312/3
Papillary adenoma	8260/0
Oncocytoma	8290/0
Metanephric tumours	
Metanephric adenoma	8325/0
Metanephric adenofibroma	9013/0
Metanephric stromal tumour	8935/1
Nephroblastic and cystic tumours occurring mainly in children	
Nephrogenic rests	
Nephroblastoma	8960/3
Cystic partially differentiated nephroblastoma	8959/1
Paediatric cystic nephroma	8959/0
Mesenchymal tumours	
Mesenchymal tumours occurring mainly in children	
Clear cell sarcoma	8964/3
Rhabdoid tumour	8963/3
Congenital mesoblastic nephroma	8960/1
Ossifying renal tumour of infancy	8967/0
Mesenchymal tumours occurring mainly in adults	
Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Rhabdomyosarcoma	8900/3
Osteosarcoma	9180/3
Synovial sarcoma	9040/3
Ewing sarcoma	9364/3
Angiomyolipoma	8860/0
Epithelioid angiomyolipoma	8860/1'
Leiomyoma	8890/0
Haemangioma	9120/0
Lymphangioma	9170/0
Haemangioblastoma	9161/1
Juxtaglomerular cell tumour	8361/0
Renomedullary interstitial cell tumour	8966/0
Schwannoma	9560/0
Solitary fibrous tumour	8815/1
Mixed epithelial and stromal tumour family	
Cystic nephroma	8959/0
Mixed epithelial and stromal tumour	8959/0
Neuroendocrine tumours	
Well-differentiated neuroendocrine tumour	8240/3
Large cell neuroendocrine carcinoma	8013/3
Small cell neuroendocrine carcinoma	8041/3
Phaeochromocytoma	8700/0
Miscellaneous tumours	
Renal haematopoietic neoplasms	
Germ cell tumours	
Metastatic tumours	

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [917A]. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. The classification is modified from the previous WHO classification [756A], taking into account changes in our understanding of these lesions.
*New code approved by the IARC/WHO Committee for ICD-O.



Rochester MN 1997-8

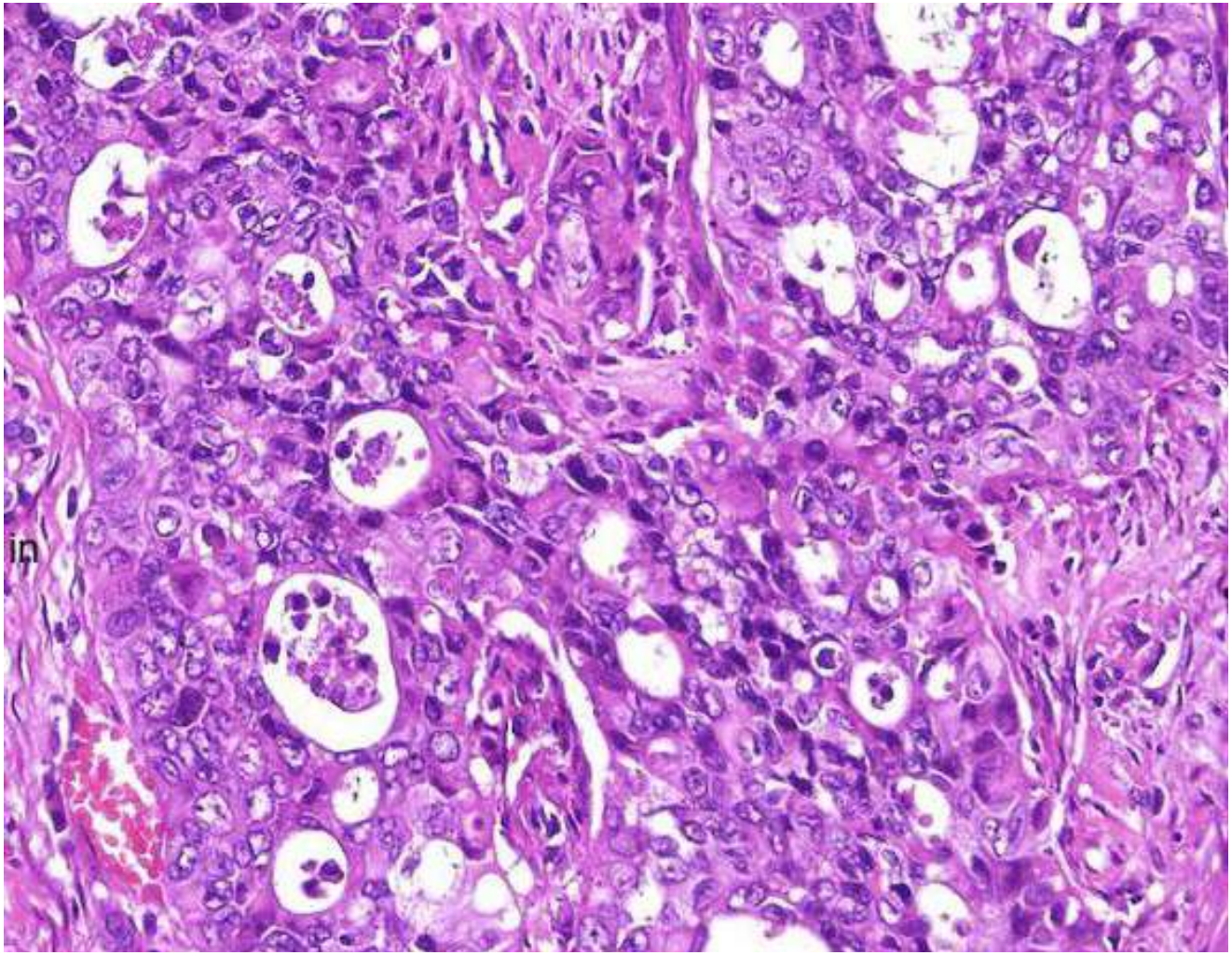
Oggi la necessità è quella di fornire ai clinici una migliore caratterizzazione anatomo patologica al fine di

fare una diagnosi istologica precisa

dare una valutazione prognostica

valutare le pathway molecolari coinvolte in modo di prevedere la sensibilità a farmaci mirati e eventualmente scoprire nuove molecole

Di Stefano RF, Tucci M, Bollito E et al, **Metastatic Renal Medullary Carcinoma Treated With Immune Checkpoint Inhibitor: Case Report and Literature Review.** *Clin Genitourin Cancer. 2018 Dec;16(6)*



La comparsa di nuovi farmaci ne impone una valutazione di efficacia nei diversi casi: solo con una tipizzazione precisa dell'istotipo è possibile ottenere valutazioni attendibili e successivamente utilizzabili nella pratica clinica

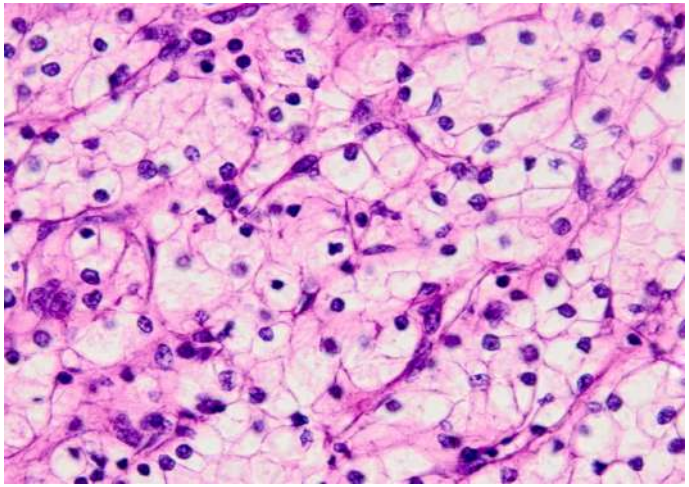
Una caratterizzazione accurata dell'istotipo è la sola via con cui potremo realmente capire in quali casi utilizzare le diverse terapie

Il caso proposto prima come esempio è lesione di elevata aggressività e ad oggi non ci sono protocolli predefiniti di terapia per questo tumore visto che non erano stati ottenuti sinora risultati accettabili con farmaci di uso più consolidati: al contrario si è ottenuta un'ottima risposta con l'utilizzo di inibitori di checkpoint

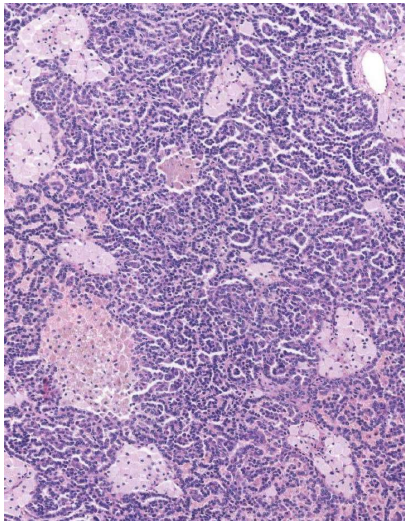
La diagnosi differenziale tra queste forme si avvale di morfologia, immunoistochimica e metodiche FISH.
La necessità di disporre di tessuto fresco ha relegato la citogenetica classica ad un ruolo marginale.

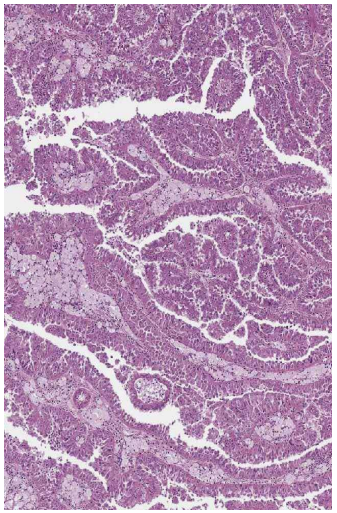
KIDNEY: istotipi usuali e frequenti

(Courtesy Prof Martignoni G. Verona)

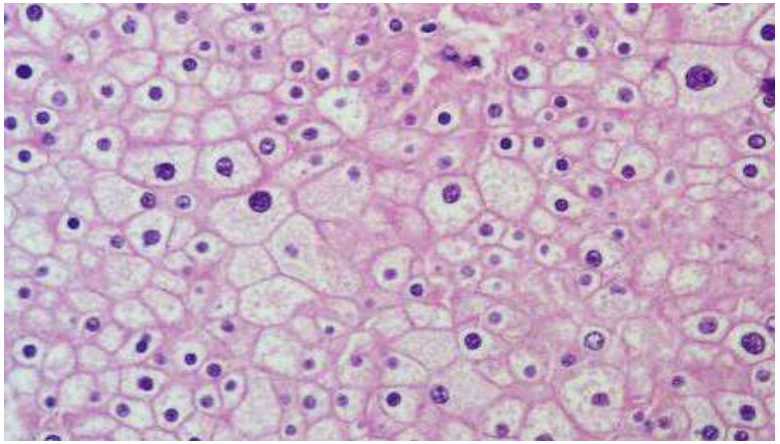


clear cell

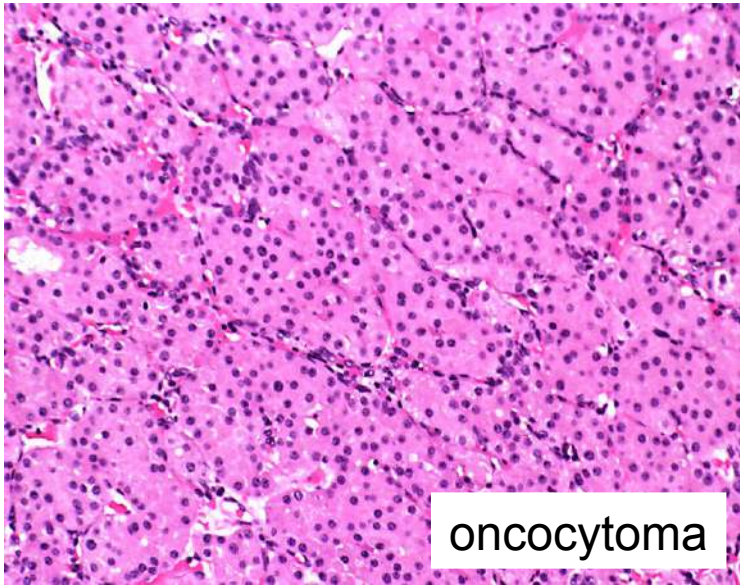




papillary



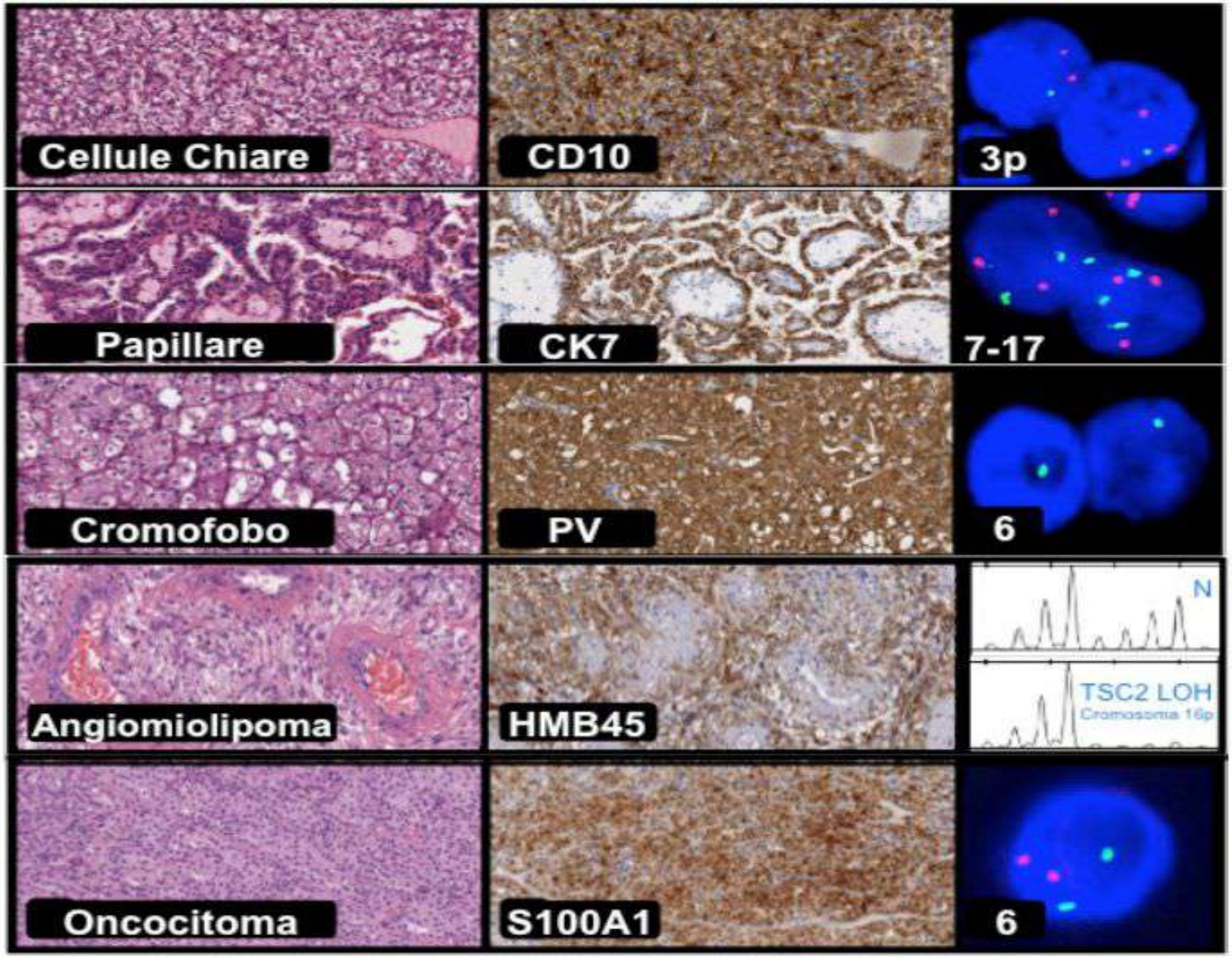
chromophobe



Da qui in avanti verranno presentati i singoli istotipi con le loro caratteristiche essenziali soprattutto molecolari. Un aspetto importante da tenere in considerazione è che l'intero sistema classificativo dei tumori parenchimali del rene è in costante – e ora piuttosto rapida e tumultuosa– evoluzione

Occorre quindi che chi vuole avvicinarsi a questo argomento, una volta acquisita una base di conoscenze iniziali allo stato attuale (alle quali è destinata questa breve presentazione), le aggiorni di volta in volta con dati di letteratura e loro eventuale acquisizione in statements o aggiormenti classificativi WHO

Courtesy Prof Martignoni G. Verona)



Renal tumors with clear cytoplasm:

Clear cell RCC
Clear cell-papillary RCC
Chromophobe RCC
Translocation associated RCC (tX;1); t(6;11)
TCEB1 mutated RCC
Papillary RCC (usually focal)
Oncocytoma (areas of scarring)
Unclassified RCC
"Xantogranulomatous pyelonephritis" Epithelioid angiomyolipoma

Virtually all renal tumours may have clear cell areas

Tumour with clear cell cytoplasm are not clear cell renal carcinoma

Virtually all renal tumors may have clear cell areas

Clear cell RCC

Clear cell-papillary RCC

Chromophobe RCC

Translocation associated RCC (tX;1); t(6;11)

TCEB1 mutated RCC

Papillary RCC (usually focal)

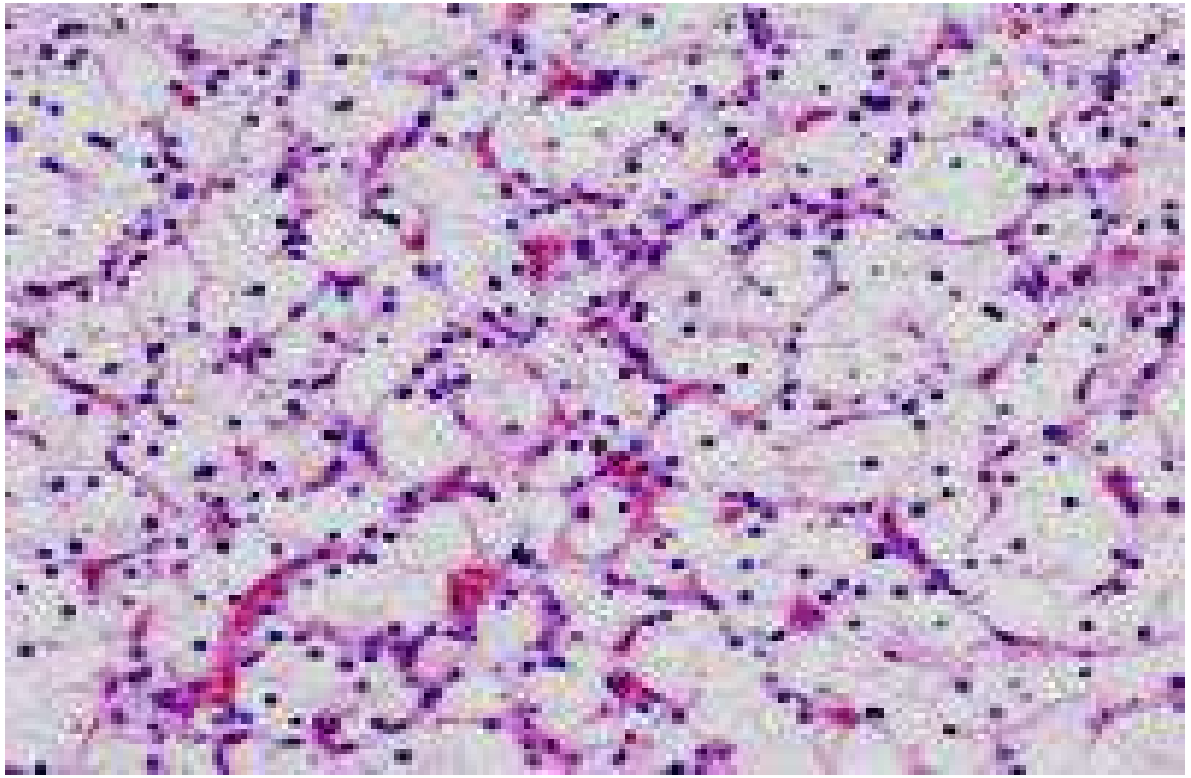
Oncocytoma (areas of scarring)

Unclassified RCC

"Xantogranulomatous pyelonephritis"

Epithelioid angiomyolipoma

Clear cell renal cell carcinoma



CD10, CD13, CA-IX: +
VIMENTIN: sometimes +
CK7: usually negative

..... Nel gruppo

Renal tumors with clear cytoplasm

Low nucleolar grade : clear cell papillary RCC

High nucleolar grade : MIT family RCC

Human Pathology (2014) 45, 59–64

ELSEVIER

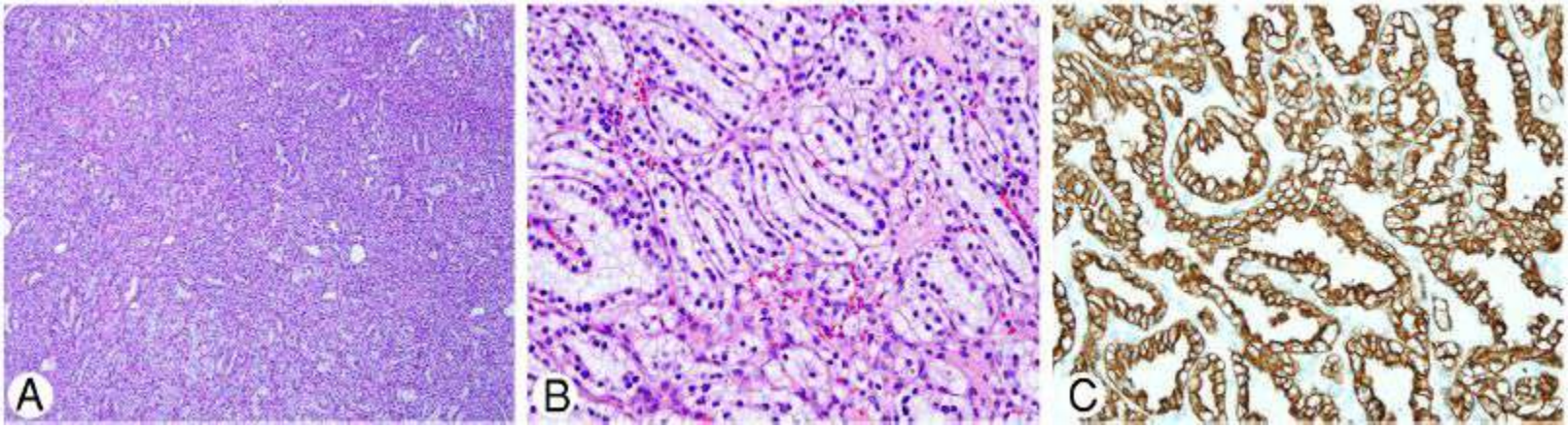
Human
PATHOLOGY

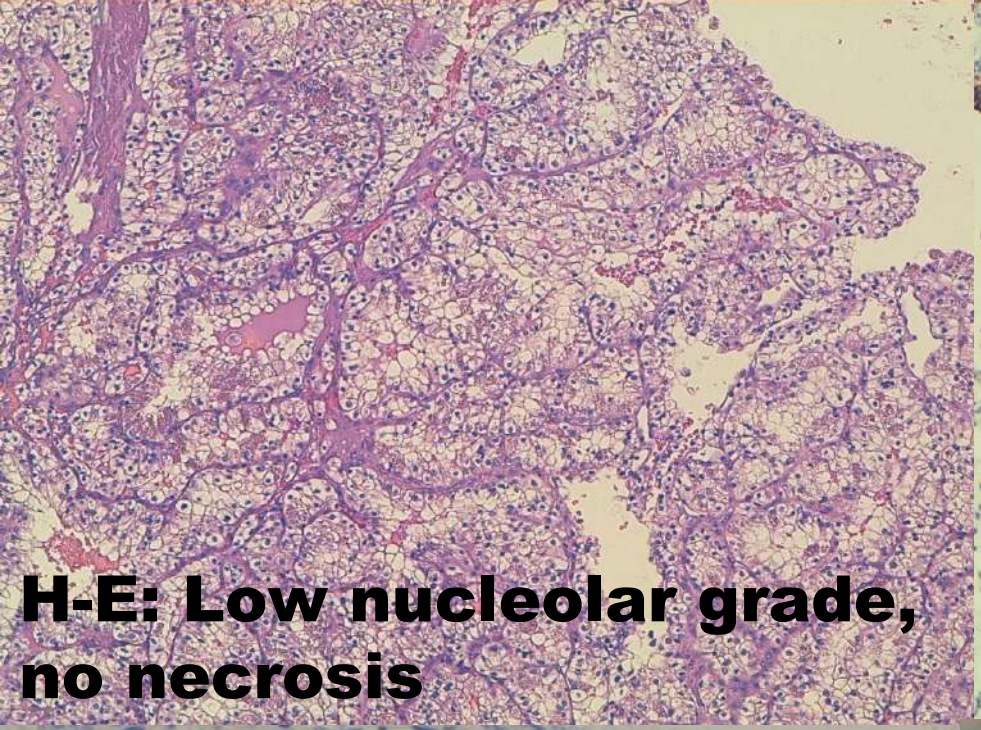
www.elsevier.com/locate/humpath

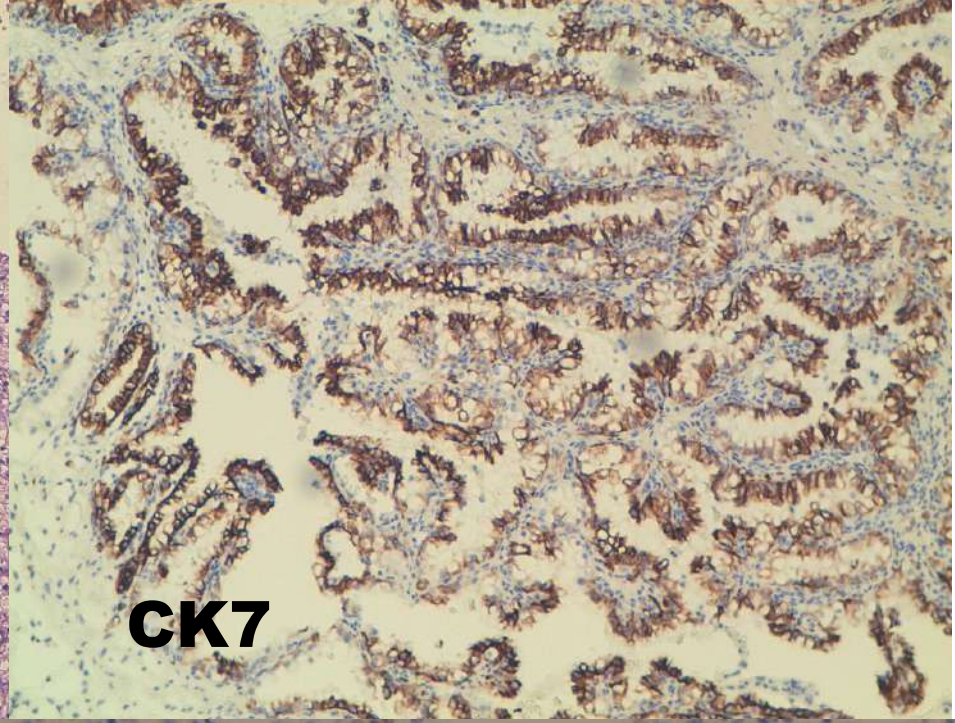
Original contribution

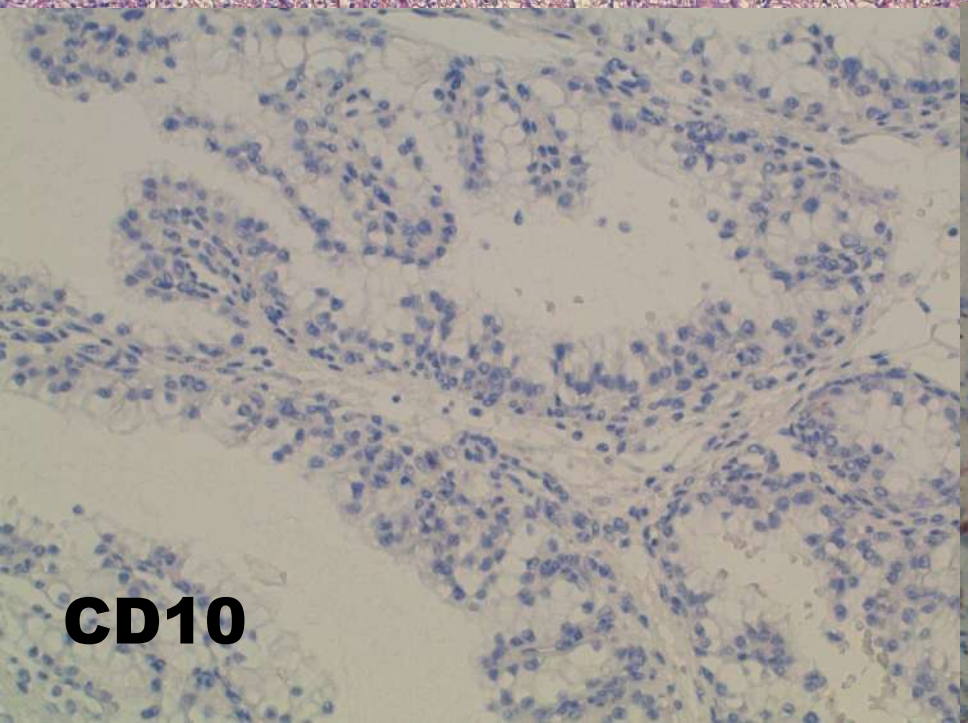
Clear cell papillary renal cell carcinoma is the fourth most common histologic type of renal cell carcinoma in 290 consecutive nephrectomies for renal cell carcinoma☆

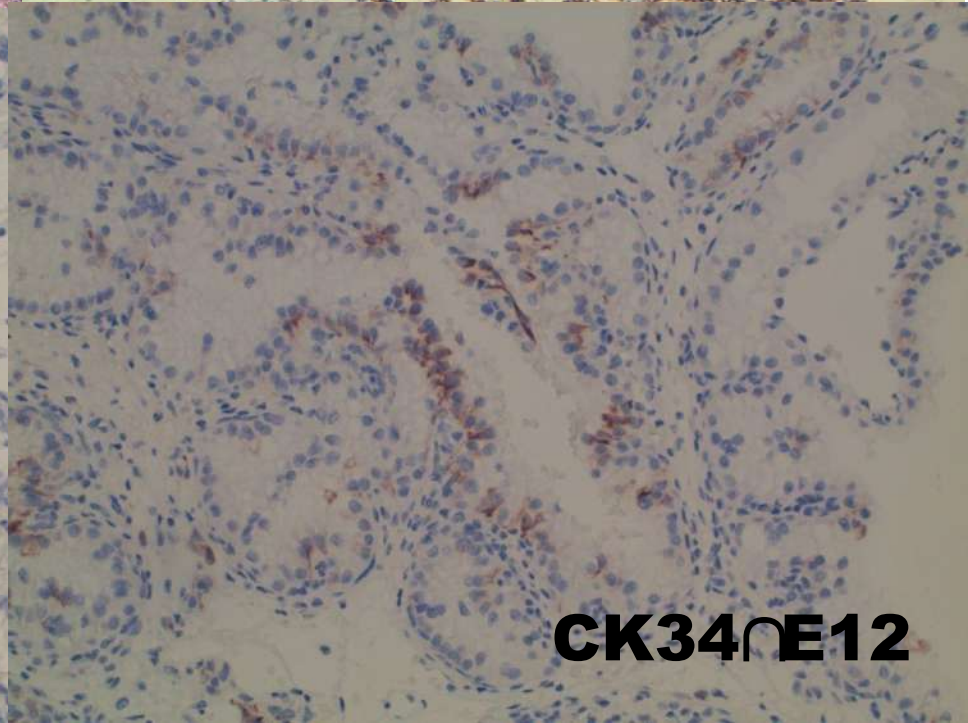
Haijun Zhou MD, PhD[a,b], Shaojiang Zheng MD, PhD[c], Luan D. Truong MD[a,b], Jae Y. Ro MD, PhD[a,b], Alberto G. Ayala MD[a,b], Steven S. Shen MD, PhD[a,b,*]




H-E: Low nucleolar grade,
no necrosis

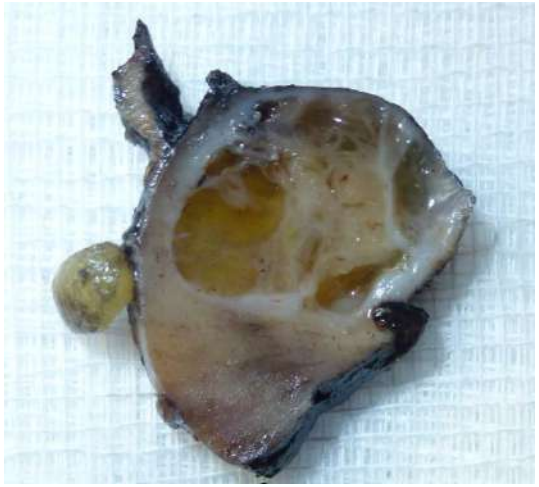

CK7


CD10


CK34∩E12

Clear cell papillary RCC

Number of cases: 160 (frequency: 3%)
cases in end stage renal disease: 51
cases not in end stage renal disease: 31



Mean age: 57
cases in end stage renal disease: 55
cases not in end stage renal disease: 59

M/F: 1.4/1
multifocality: 18 cases (5 cases in end stage renal disease)

Tumor dimension: 2,5 cm
cases in end stage renal disease: 2,5 cm
cases not in end stage renal disease: 3,4 cm

Grading: G1-G2

Pathologic stage: pT1(3 cases pT1b)

Follow-up (1-85 month)
No evidence of recurrences

Tickoo et al. Am J Surg Pathol.2006;30:141
Gobbo et al. Am J Surg Pathol.2008;32:1239
Nouh et al. BJUI 2009;105: 620
Aydin et al Am J Surg Pathol 2010;34:1608
Rohan et al. Mod Pathol 2011;24(9):1207-20
Adam et al. Histopatholgy 2011; 58(7): 1064-71
Park et al Kor J Surg Pathol 2012;46(6):541-7
Williamson et al. Mod Pathol 2013; 26:697-708

Do Clear Cell Papillary Renal Cell Carcinomas Have Malignant Potential?

Mairo L. Diolombi, MD, Liang Cheng, MD,†‡ Pedram Argani, MD,* and Jonathan I. Epstein, MD*§‖*

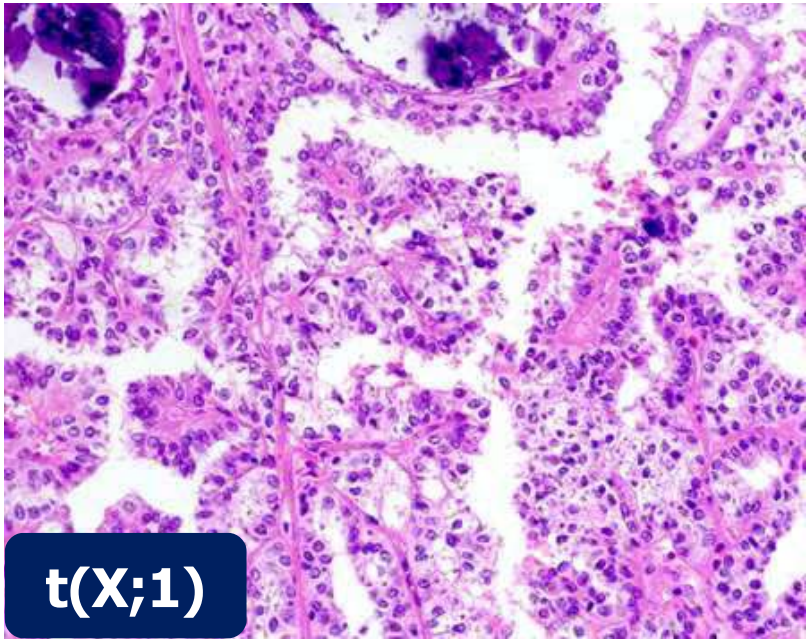
(*Am J Surg Pathol* 2015;39:1621–1634)

The Tumor Entity Denominated "*clear cell-papillary renal cell carcinoma*" According to the WHO 2016 new Classification, have the Clinical Characters of a Renal Cell Adenoma as does Harbor a Benign Outcome

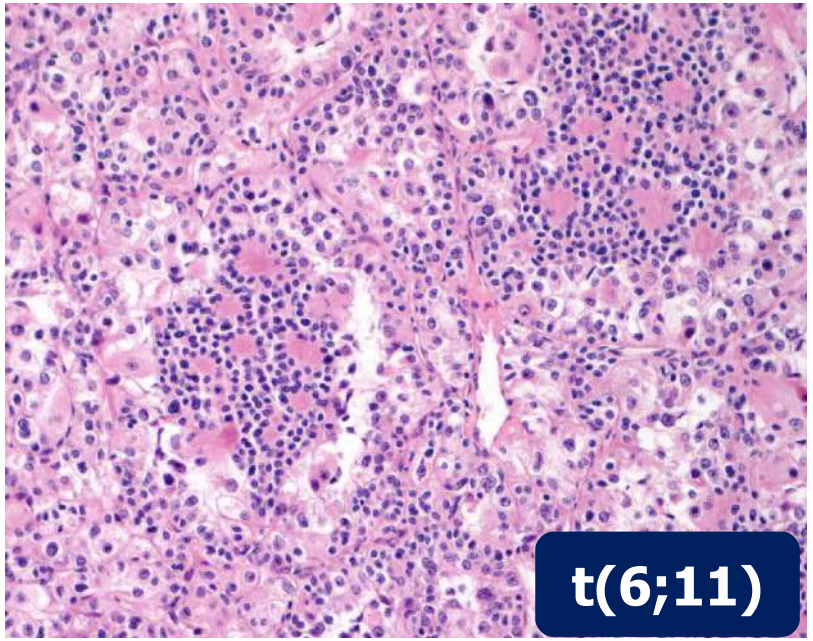
Francesco Massari[1] · Chiara Ciccarese[2] · Ondrej Hes[3] · Michal Michal[3] · Anna Caliò[4] · Michelangelo Fiorentino[5] · Francesca Giunchi[5] · Alessandro D'Amuri[6] · Francesca Sanguedolce[7] · Roberto Sabbatini[8] · Annalisa Guida[8] · Andrea Ardizzoni[1] · Camillo Porta[9] · Roberto Iacovelli[2] · Giampaolo Tortora[2] · Luca Cima[4] · Cinzia Ortega[10] · Alberto Lapini[11] · Guido Martignoni[4,12] · Matteo Brunelli[4]

Pathol. Oncol. Res.
10 July 2017

MiT FAMILY translocation renal cell carcinomas

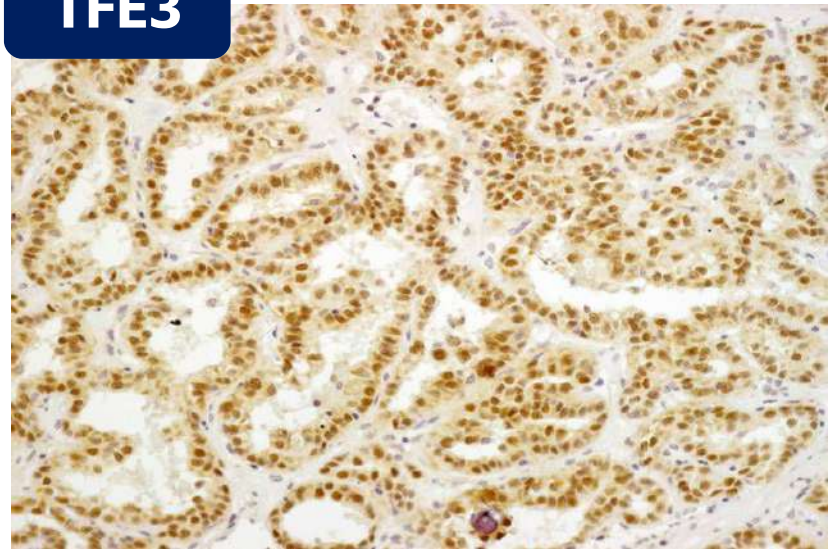


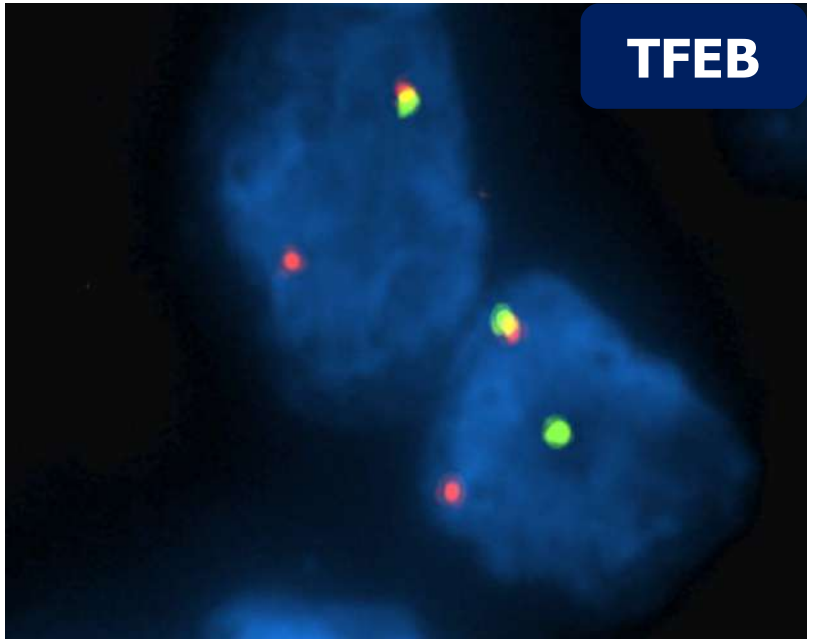
t(X;1)



t(6;11)

TFE3





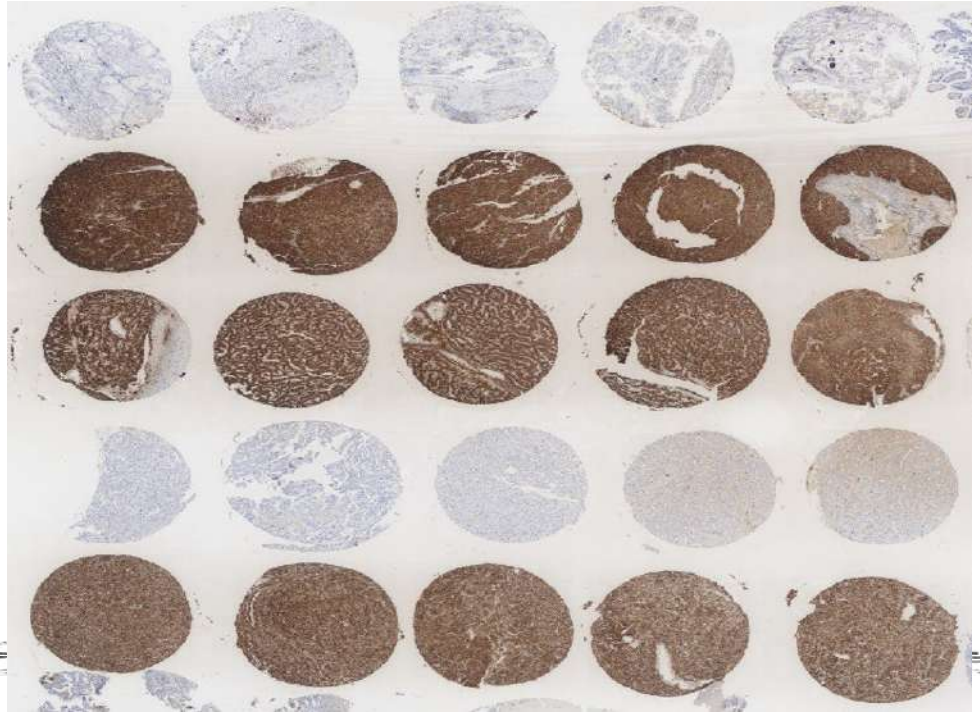
TFEB

(*Am J Surg Pathol* 2017;41:655–662)

RBM10-TFE3 Renal Cell Carcinoma

A Potential Diagnostic Pitfall Due to Cryptic Intrachromosomal Xp11.2 Inversion Resulting in False-negative TFE3 FISH

Pedram Argani, MD,† Lei Zhang, MD,‡ Victor E. Reuter, MD,‡ Satish K. Tickoo, MD,‡ and Cristina R. Antonescu, MD‡*



Xp11 renal cell translocation carcinomas

1	68/F/R	pT1bNXMX stage I (5 cm primary)	Molecularly confirmed *ASPL-TFE3* type 1 fusion. t(X;17)(p11;q25)
2	23/F/R	pT1aNXMX stage I (2.8 cm primary)	Cytogenetically confirmed t(X;1)(p11;p34) (*PSF-TFE3* fusion)
3	28/F/R	pT3aNXMX stage III (21 cm primary)	NED 4 mo: cystic and extensively necrotic neoplasm
4	27/F/R	pT1bNXMX stage I (5.5 cm primary)	Biphasic small cell/large cell mimicking t(6;11) renal carcinoma
5	34/F/L	pT1N1M1 stage IV (6.5 cm primary, 3/4 lymph nodes positive, lung metastasis)	Probable *ASPL-TFE3* RCC
6	38/M/L	pT3bN2MX stage IV (8.3 cm primary)	DOD 3 mo; probable *ASPL-TFE3* RCC
7	29/M/?	Stage IV (spinal metastasis)	DOD 10 mo; probable *ASPL-TFE3* RCC
8	20/F/?	Stage IV (supraclavicular lymph node metastasis)	Probable *ASPL-TFE3* RCC
9	47/F/R	pT1bNxMx stage I (5 cm primary)	NA
10	78/M/L	pT3bN2MX stage IV (10 cm primary, 11/15 positive lymph nodes)	Probable *ASPL-TFE3* RCC
11	26/F/R	pT3aNXMX stage III (6 cm primary)	NA
12	37/F/?	pT1aNXMX stage I (2.8 cm primary, partial nephrectomy)	Probable *ASPL-TFE3* RCC
13	28/F/R	pT1bN2MX stage IV (5.8 cm primary, 3/8 positive lymph nodes)	NA
14	58/F/R	pT1bN2MX stage IV (4.8 cm primary, 3/6 positive lymph nodes)	Probable *ASPL-TFE3* RCC
15	63/F/R	pT1NXMX stage I (3.3 cm primary)	Favor *ASPL-TFE3* RCC. Calcified on plain film, thought to be lithiasis until contrast CT was performed; patient underwent ESWL
16	34/M/R	pT3N2MX stage IV (8.8 cm primary)	Developed epidural metastasis at 6 y; probable *ASPL-TFE3* RCC
17	22/F/R	pT1aNXMX stage I (2.1 cm primary, partial nephrectomy)	NED 6 mo
18	33/M/R	pT1bN0M1 stage IV (6.1 cm primary, spinal metastasis)	Developed liver metastasis at 1 y, alive with disease (spinal metastases); probable *ASPL-TFE3* RCC
19	25/M/L	pT2NXMX stage II (9 cm)	Hematuria
20	44/F/L	pT3bN2MX stage IV (7.5 cm primary)	NA
21	29/F/R	pT1bNXMX stage I (6 cm primary)	NA
22	27/F/R	pT2NXMX stage II (7 cm primary)	NA
23	26/F/L	pT2N0MX stage II (7.5 cm primary)	NED 3 y
24	22/F/?	pT1bN2MX stage IV (6 cm primary, 7 lymph nodes positive)	Probable *ASPL-TFE3* RCC protruded into renal pelvis, causing xanthogranulomatous pyelonephritis.
25	32/F/L	pT3aN2MX stage IV (3.5 cm primary, 3 lymph nodes positive)	Cytogenetically confirmed t(X;3)(p11;q23), morphologically similar to *ASPL-TFE3* RCC
26	77/F/L	pT1bNXMX stage I (5 cm primary)	Cystic lesion, present for 13 y by imaging, spindle cell areas
27	38/M/?	pT3N2M1 Stage IV (13 cm primary)	Metastasis to esophagus 1 y after diagnosis
28	30/F/?	pT2N1M1 stage IV (9 cm primary; adrenal, retroperitoneal, mediastinal, cervical nodal	Poor response to interleukin therapy and radiation therapy

METASTASIS up to 50%

t(6;11) renal cell translocation carcinomas

Table 4. Aggressive t(6;11) renal cell carcinomas

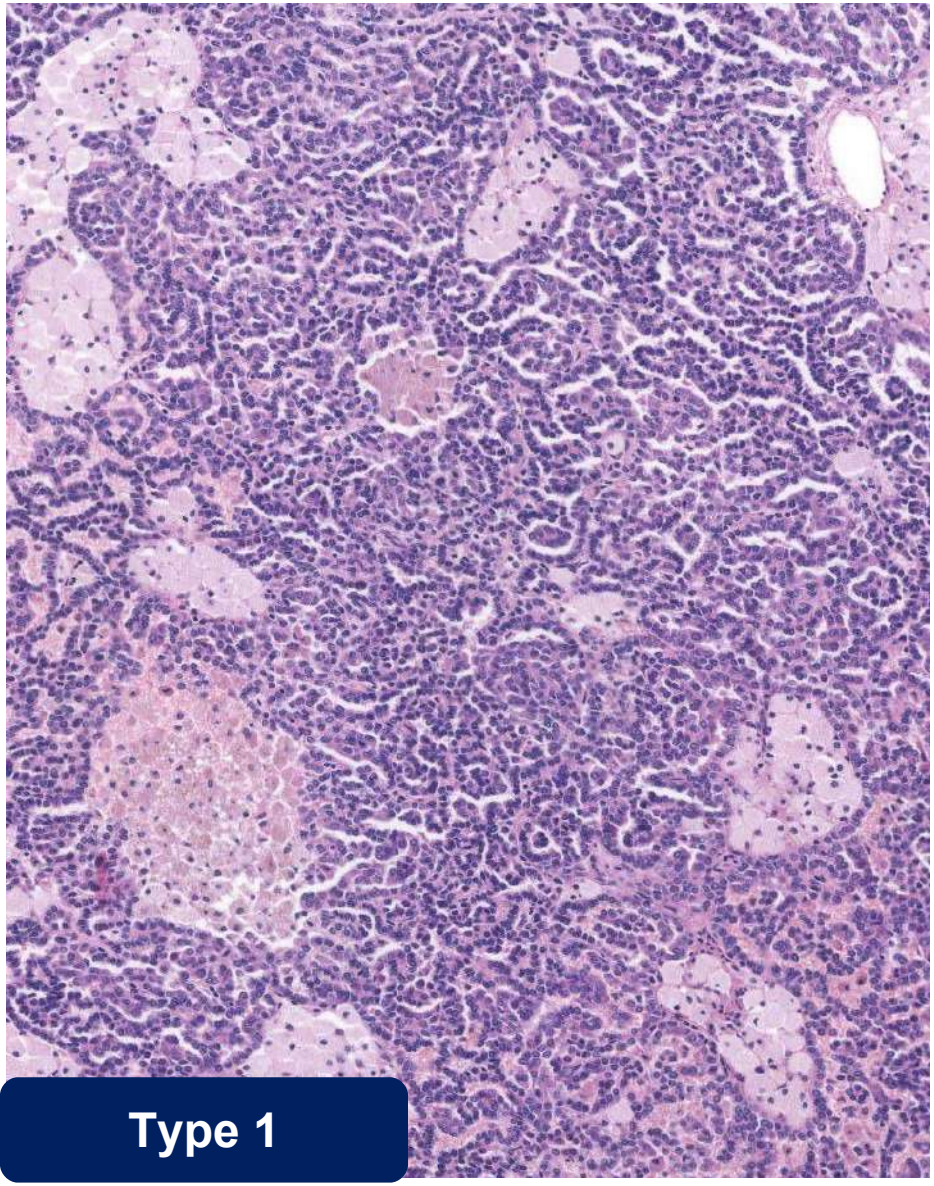
Case	References	Age	Gender	Size (cm)	Karyotype/FISH	Follow up	Notes
1	Camparo et al., 2008	36	M	20	NA	dead after 3 months	multiple metastasis
2	Ishihara et al., 2011	45	M	7	NA	7 months alive	lung and vertebral metastasis
3	Argani et al., 2012	42	M	27	break apart probe	NA	liver metastasis
4	Argani et al., 2012	60	M	14	break apart probe	NA	liver metastasis + IVC thrombus
5	Inamura et al., 2012	37	M	NA	t(6;11)(p21.1;q12 13)	dead after 120 months	lung metastasis
6	Peckova et al., 2014	77	F	12	RT-PCR + break apart	dead after 2,5 months	adrenal gland and lung metastasis
7	Smith et al., 2014	34	M	3	break apart probe	96 months alive	rib metastasis
8	Lilleby et al., 2015	42	M	NA	break apart probe	97 months alive	vertebral and rib metastasis
9	Argani et al., 2016	61	F	19	break apart probe	18 months alive	vaginal metastasis
10	Present series	42	F	10	break apart probe	dead after 46 months	lung metastasis
11	Present series	33	M	8	break apart probe	48 months alive	perinephric nodules

M: male, F: female, NA: not available, IVC: inferior vena cava

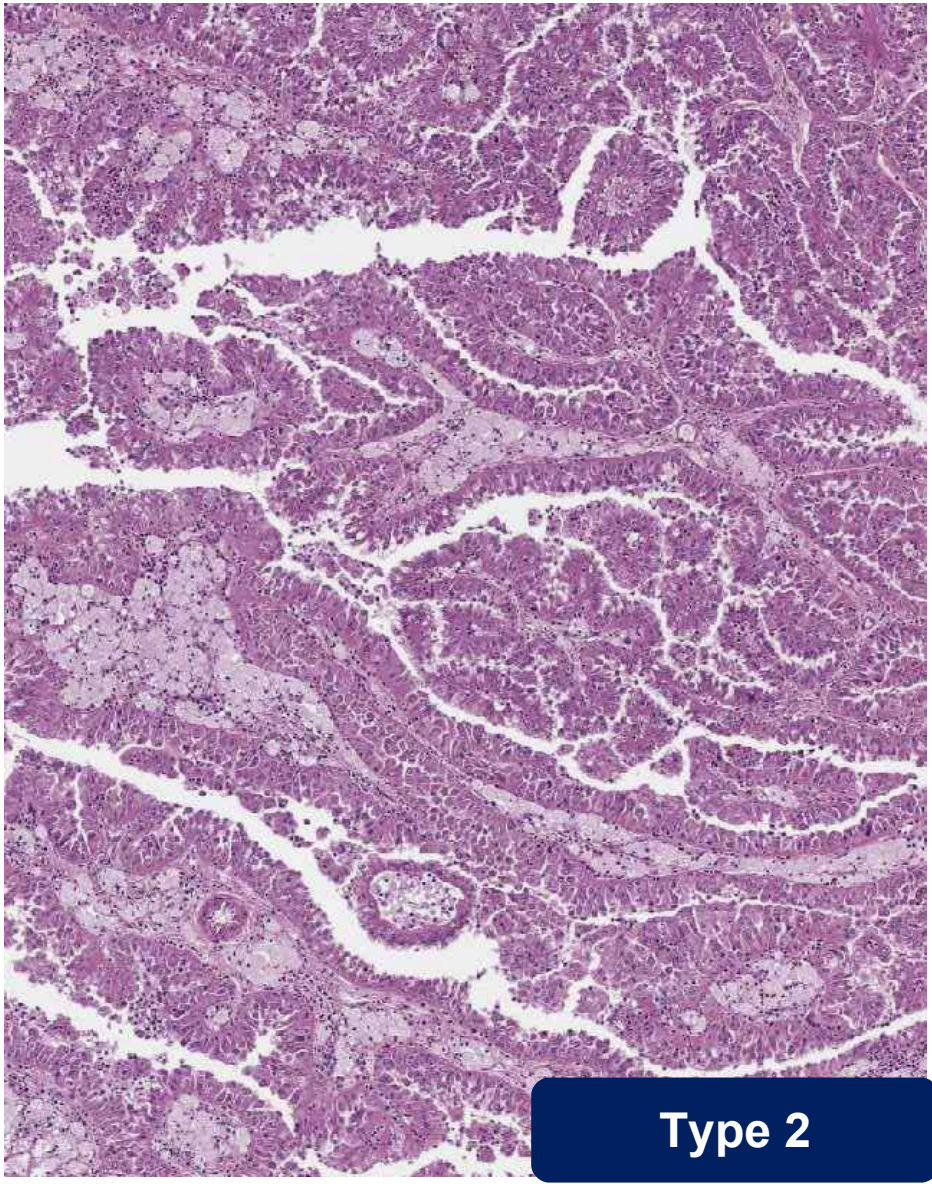
METASTASIS up to 17%

Caliò et al, Mod Pathol 2017

Papillary Renal Cell Carcinoma



Type 1



Type 2

Papillary renal cell carcinoma

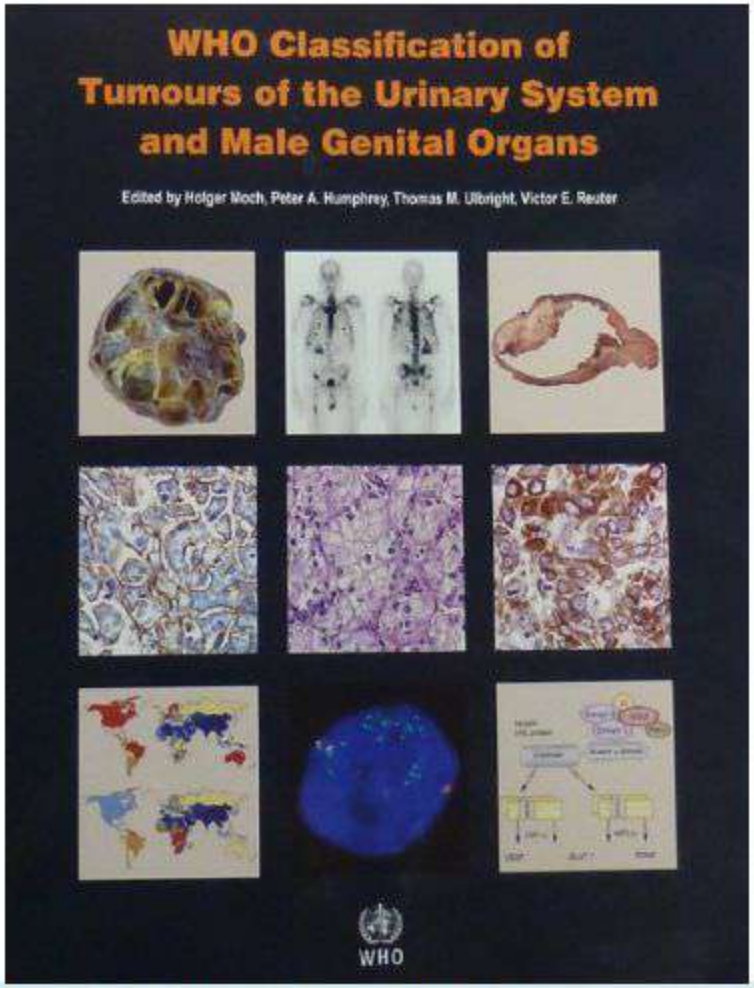
Delahunt B.
Algaba F.
Eble J.
Cheville J.
Amin M.B
Argani P.
Martignoni G.
Moch H.
Srigley J.R.
Tan P.H.
Tickoo S.K.

Definition:

- **Well circumscribed tumor**
- **Papillary/tubulopapillary architecture**

Recommendation:

- **Type 1 carcinoma**
  - **Papillae with single layer of cells & containing scant cytoplasm**
- **Type 2 carcinoma**
  - **Papillae with nuclear pseudostratification, often eosinophilic, often high-grade**
  - **Increasing experience and molecular studies suggest that type 2 tumors may not constitute a single well-defined entity, but the type 2 designation remains a useful morphological descriptor**
- **Oncocytic papillary carcinoma**
  - **Single layer, eosinophilic cytoplasm and oncocytoma-like nuclei, still to be defined**
- **WHO/ISUP grading recommended**



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma

The Cancer Genome Atlas Research Network*

- MET mutation in Type 1 Tumors (80% MET alterations)
- CDKN2A Mutation in Type 2 Tumors
- SETD2, BAP1 and PBRM1 Mutation in Type 2 Tumors (3 clear cell RCC 5%)
- CpG Island Methylator phenotype (CIMP) (5/60 9% FH tumors) in Type 2 Tumors
- Translocation RCC in Type 2 Tumors (7/60 11%)

Renal tumors with papillary architecture

Low nucleolar grade : papillary adenoma

High nucleolar grade : Hereditary leiomyomatosis RCC syndrome associated RCC

Renal tumors with oncocytic cytoplasm

Oncocytoma

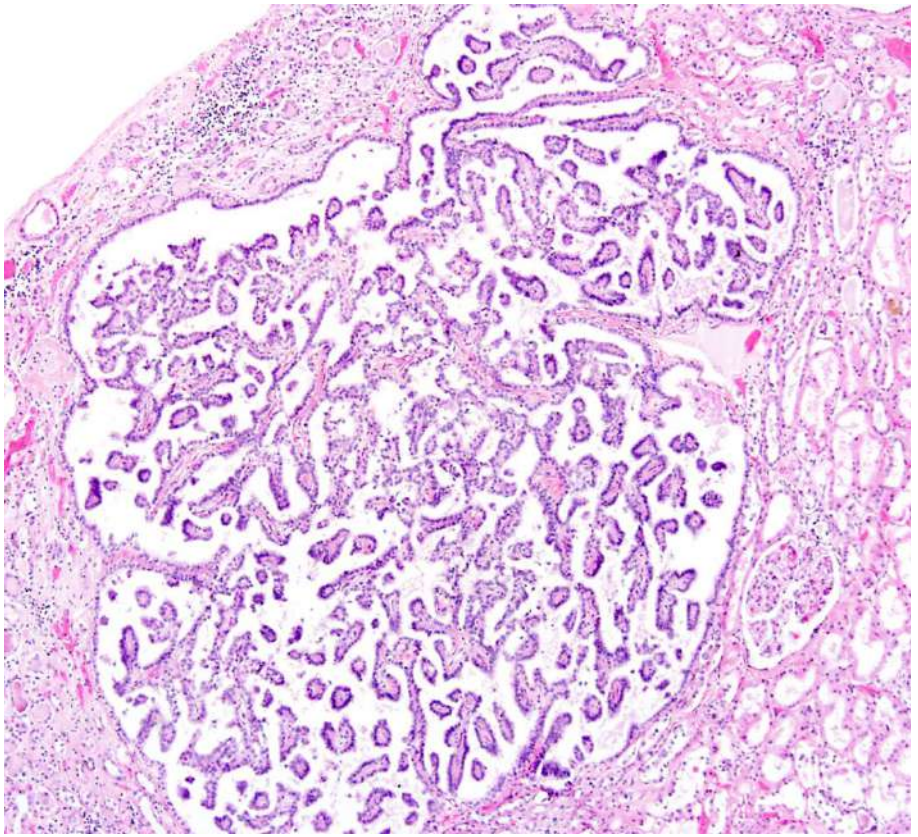
Chromophobe carcinoma (oncocytic variant)

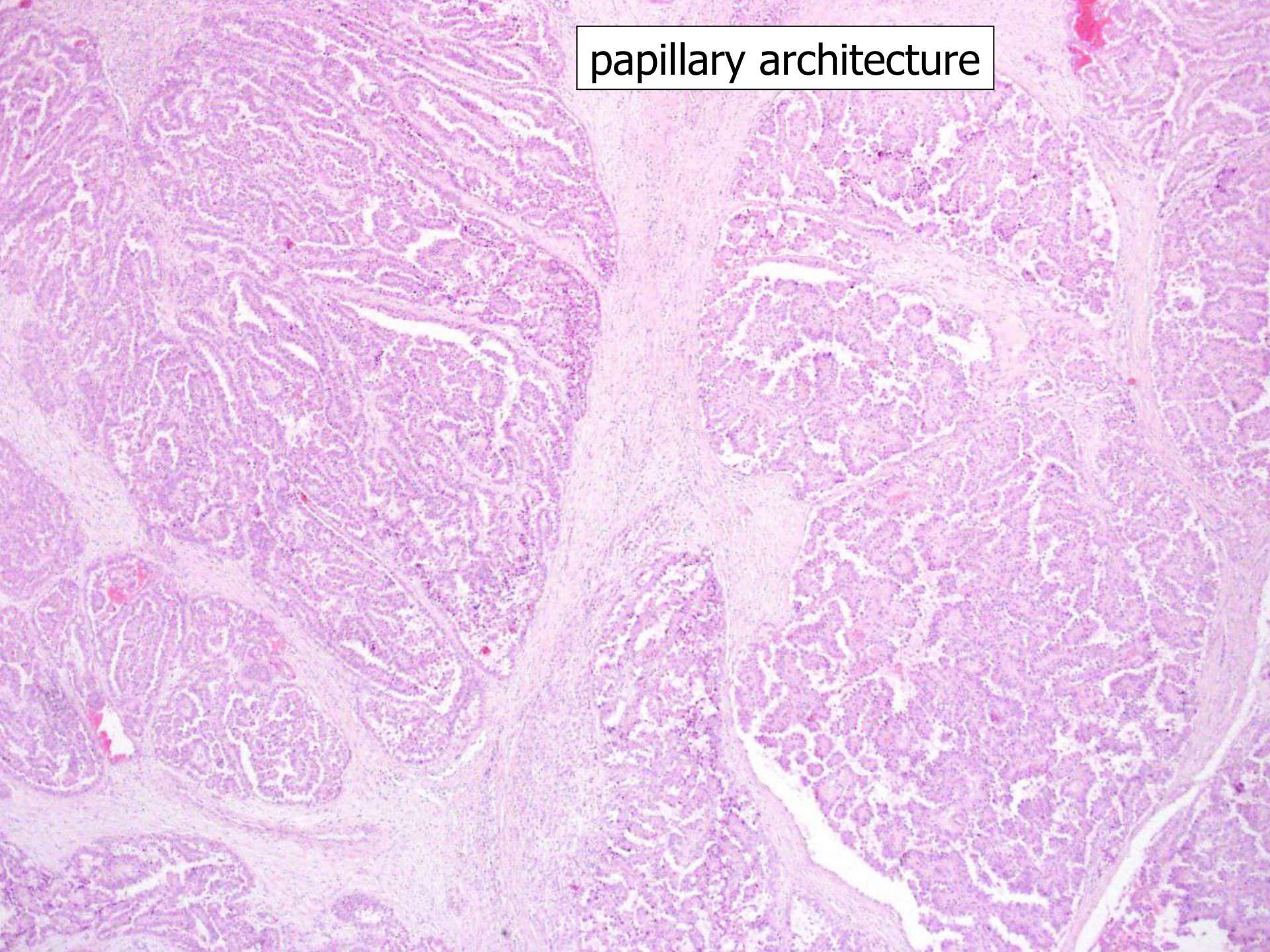
Succinate dehydrogenase deficient RCC

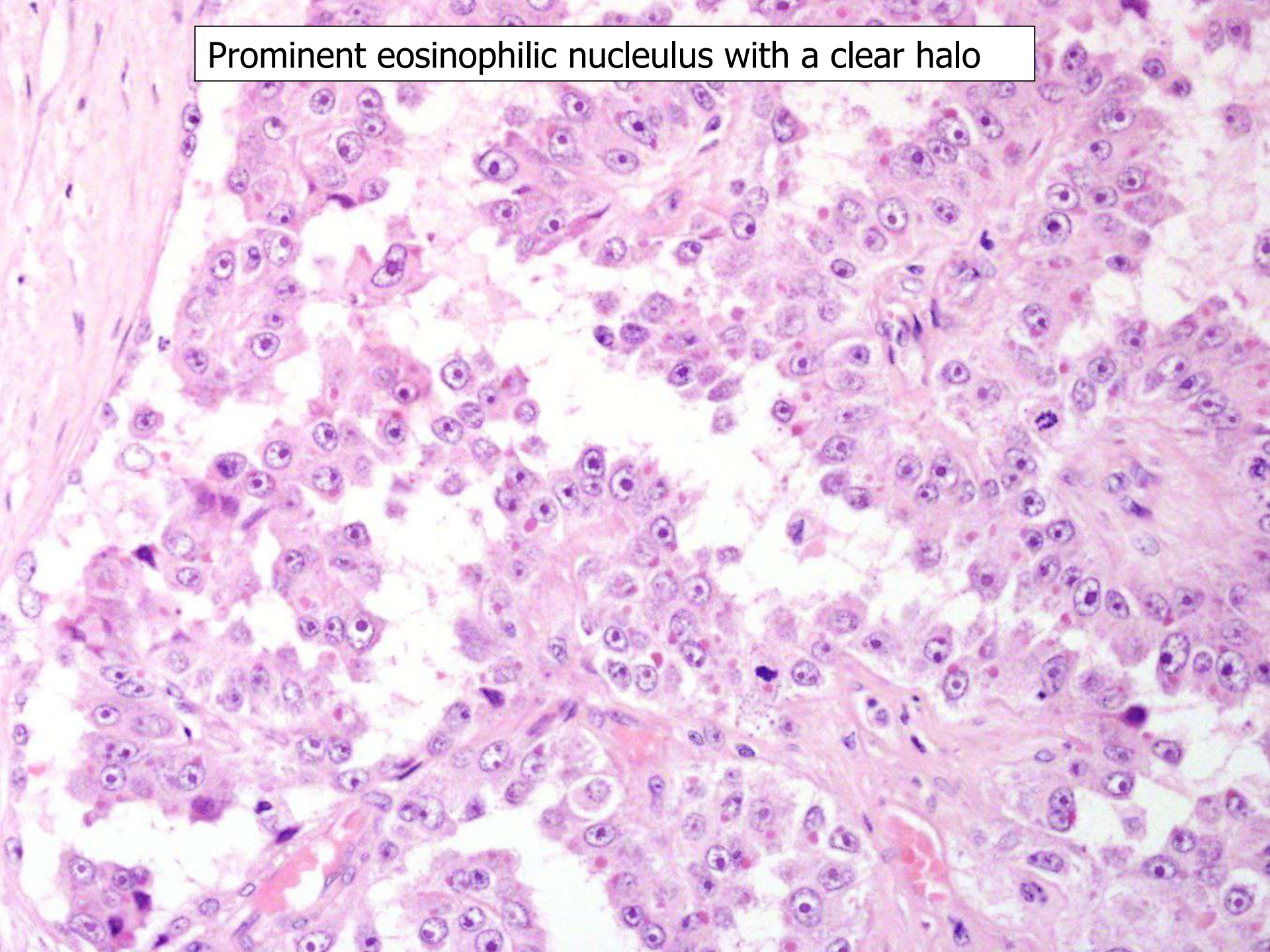
Papillary Adenoma

Def nition:

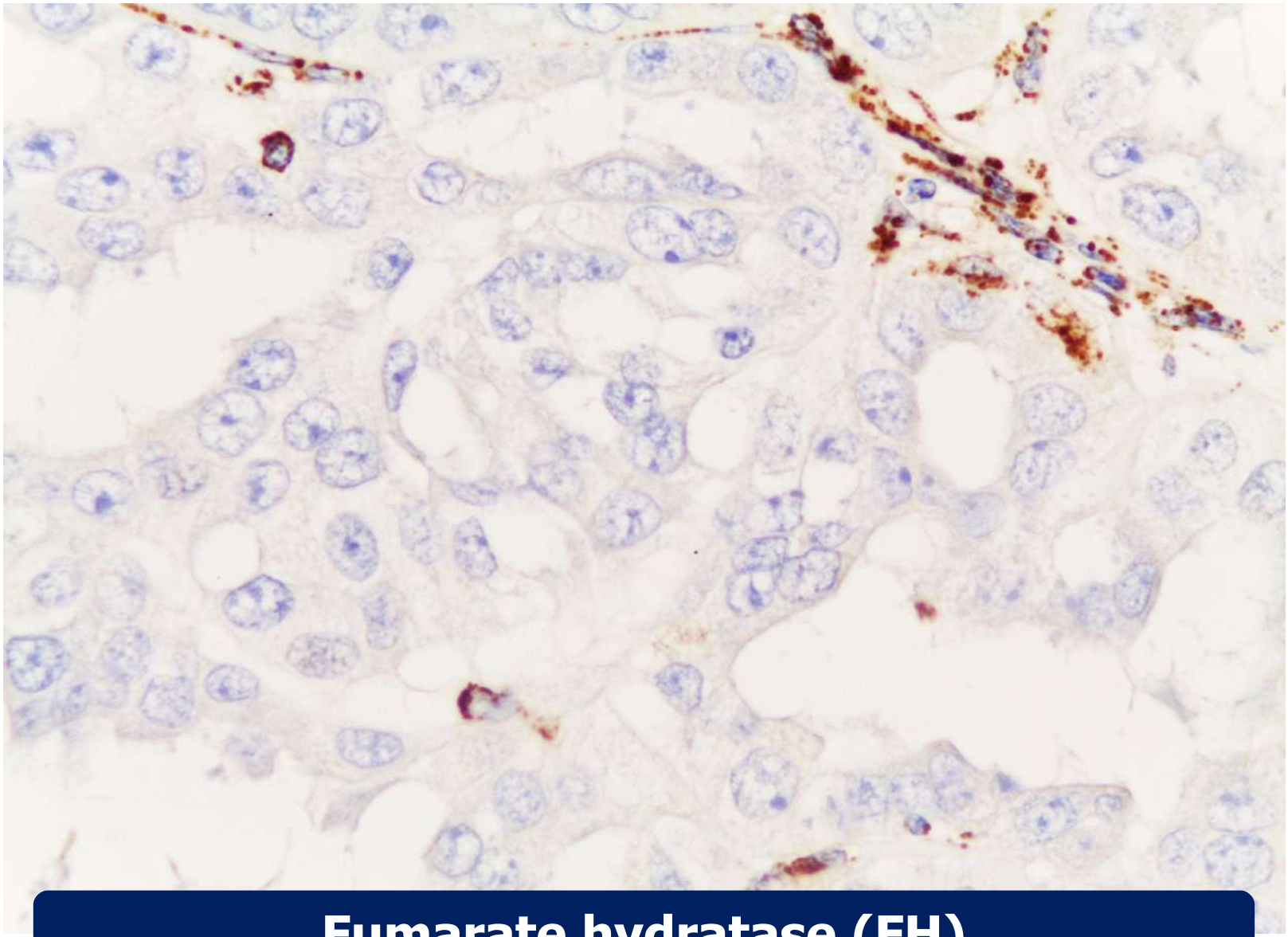
- **Unencapsulated**
- **Tubulopapillary**
- **<15 mm in diameter**




papillary architecture


Prominent eosinophilic nucleulus with a clear halo

Hereditary leiomyomatosis RCC syndrome associated RCC



Fumarate hydratase (FH)

Hereditary leiomyomatosis RCC syndrome associated RCC

Clinical and Genetic aspects:

Multiple cutaneous and uterine leiomyomas - well described since 1950s (Reeds syndrome)
Autosomal dominant form (mutation in the **fumarate hydratase** gene)
20% of families develop HLRCC (36-39 yrs)
Uterine leiomyomas (90%) early age and requiring hysterectomy
Small subset develop leiomyosarcomas
Adrenal cortical hyperplasia reported

Clinical Impact

Clinical characteristics of 9 genetically confirmed HLRCC patients with renal tumors

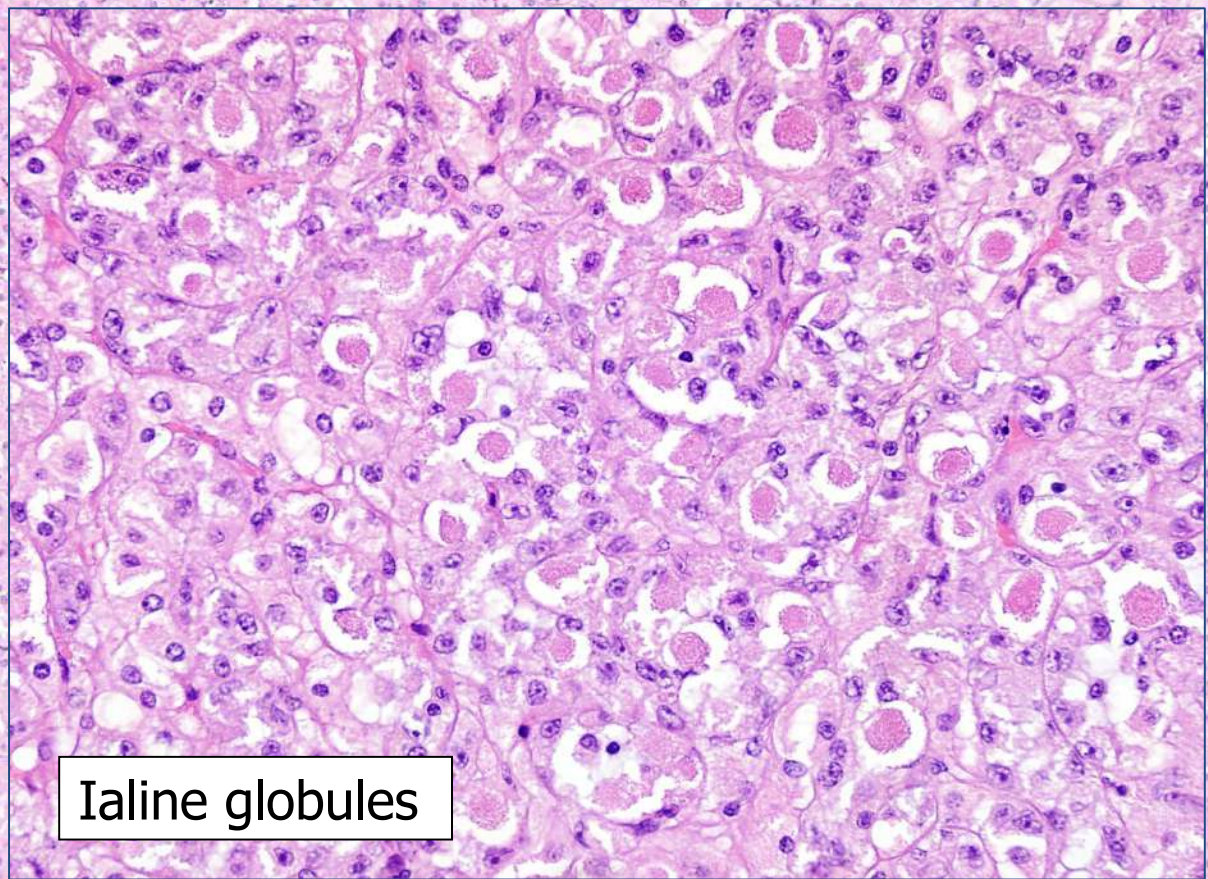
Pt	Sex	Age	Symptoms	Leiomyoma	Family Hx at Presentation	Kidney Mass	Size (cm)	pT	Metastasis	Follow-Up (Month)
1	F	37	Flank pain	Uterine at 32	None	L /solitary	4.9	pT3a	RPLNs	DOD (44)
2	M	38	Flank pain, hematuria	None	None	R/solitary	12.5	pT3a	RPLNs, adrenal, liver, lung, bone	DOD (28)
3	F	32	Abdominal discomfort	Uterine (imaging only)	N/A (adopted)	R/ solitary	9.2	pT3a	RPLNs, lung, liver	DOD (23)
4	M	24	Flank pain	None	Mother ovarian ca	L /solitary	5	pT3a	RPLNs, lung	AWD (10)
5	M	61	Flank pain, hematuria	None	Father RCC, mother breast ca, daughter fibroid	L /two masses	15; 3	pT3a	RPLNs, adrenal, liver	DOD (8)
6	M	42	Flank pain, hematuria	None	None	L /solitary	6.5	pT3a	RPLNs, adrenal, liver	DOD (8)
7	M	34	Incidental renal mass	None	Father non-small cell lung ca	L /solitary	12.2	pT3a	RPLNs	AWD (10)
8	F	30	Flank pain	None	None	R /solitary	6.7	pT3a	RPLNs, adrenal	AWD (12)
9	F	25	Flank pain	Yes (but not identified initially)	Mother RCC	R/solitary	11.5	pT3a	RPLNs	NED (6)

RPLNs: retroperitoneal lymph nodes; DOD: death of disease; AWD: alive with disease; RCC: renal cell carcinoma; ca:cancer

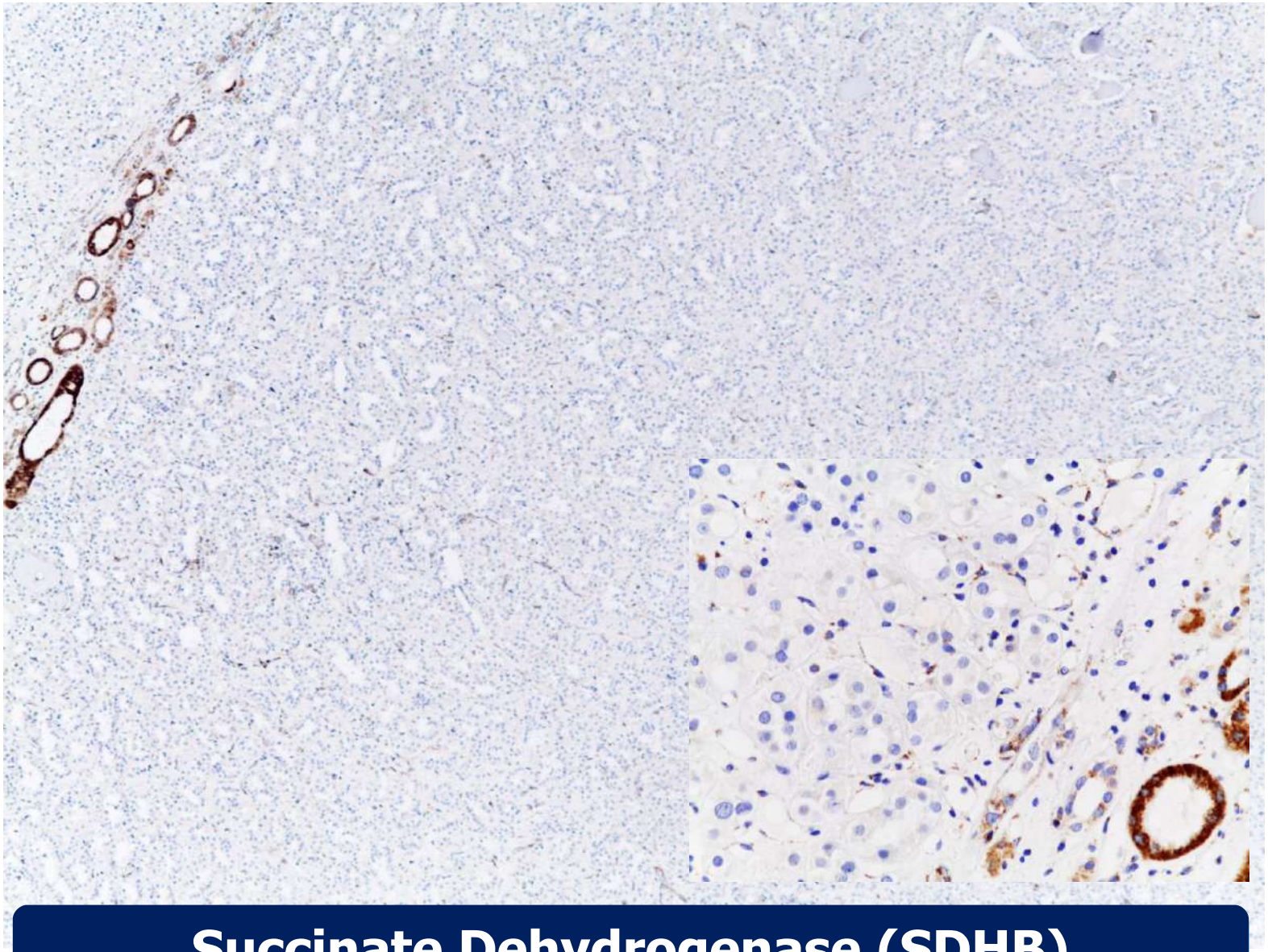
Most patients affected by Hereditary Leiomiomatosis RCC died of disease

Succinate dehydrogenase (SDH) – deficient RCC

Oncocytoma-like pattern



Succinate dehydrogenase (SDH) – deficient RCC



Succinate Dehydrogenase (SDHB)

Succinate dehyrogenase (SDH) – deficient RCC

Reported in association with germline mutation of SDHB

The pheocromocytoma/paraganglioma syndrome type 4

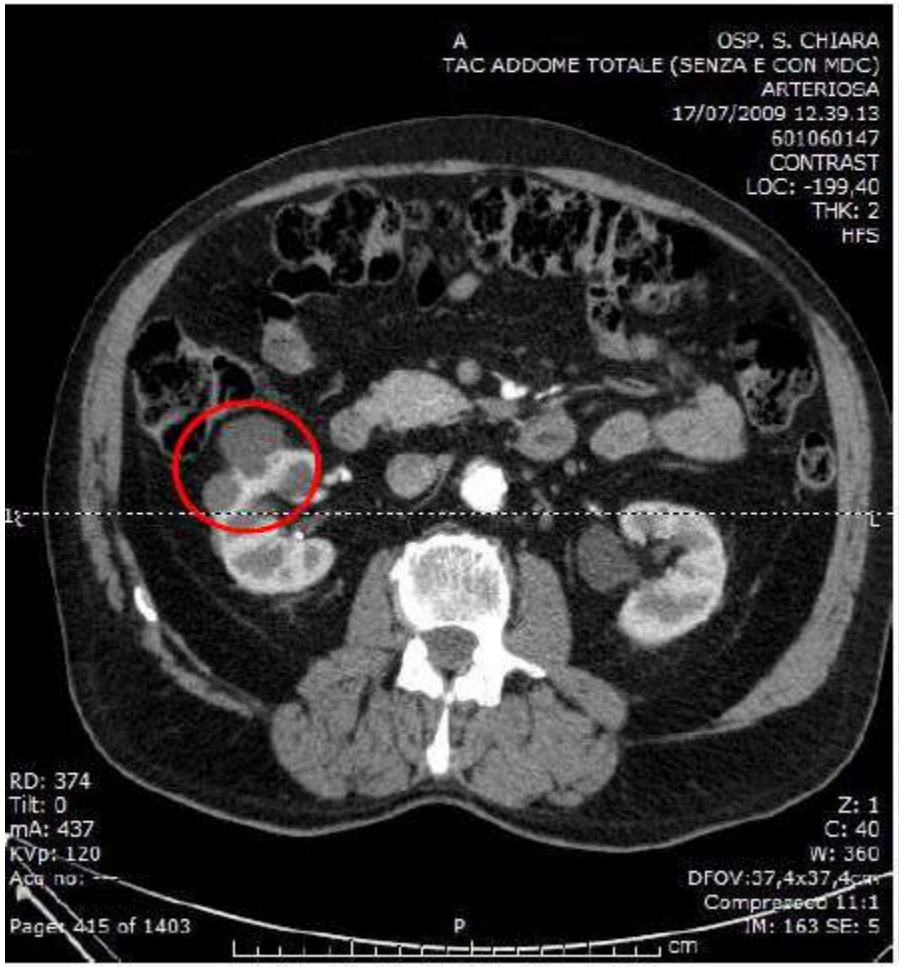
Predilection to pheocromocytoma / paraganglioma so called type 2 GI tumours

14% lifetime risk of renal neoplasia
Bilateral – multifocal 25%

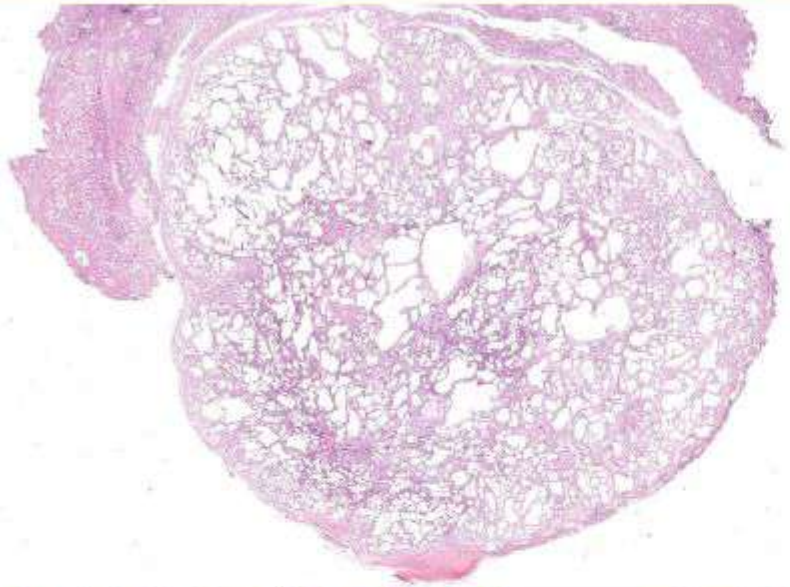
Most affected young adults / male predominance

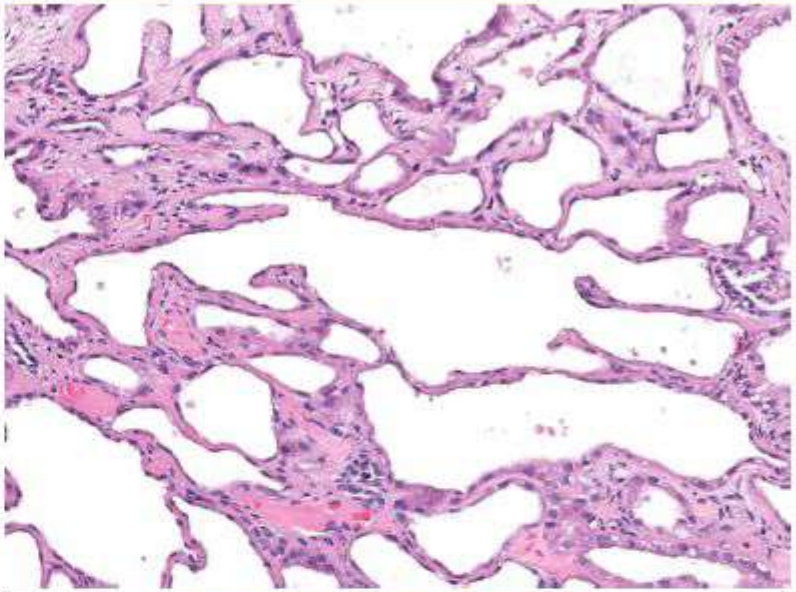
Indolent course on limited follow-up

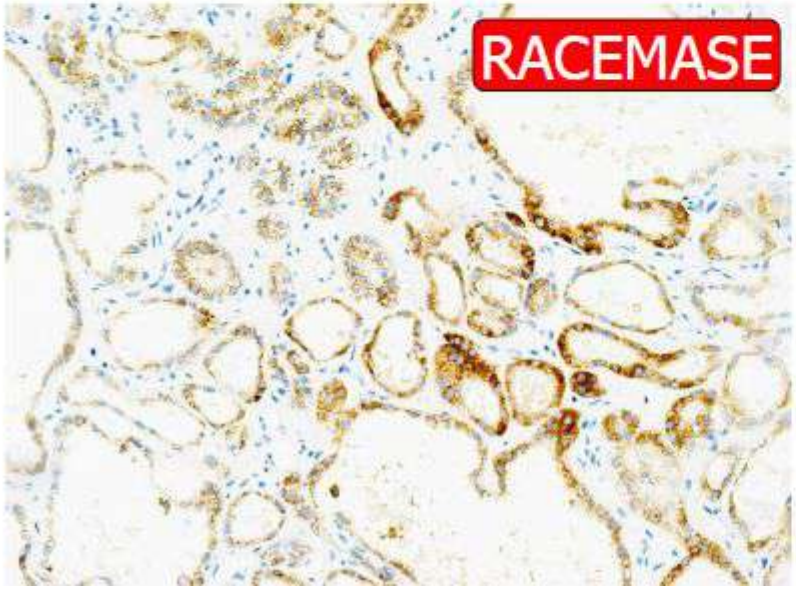
Tubulocystic carcinoma

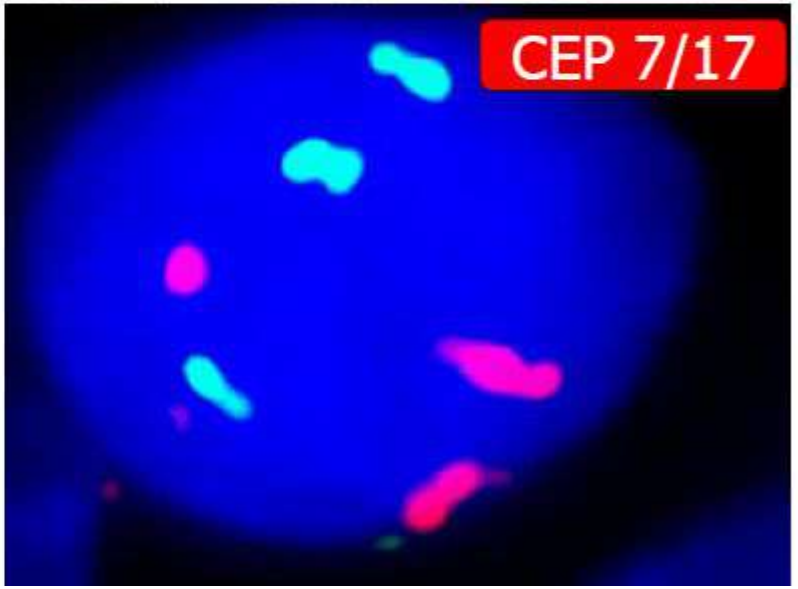


Tubulocystic carcinoma









Tubulocystic carcinoma

"Low grade Collecting Duct Carcinoma:

Initial Reports Pierre Masson –1955 – "Bellininien epithelioma"

- Low grade, cystic, central kidney
- Hobnail cells
- George Farrow & Beckwith – 1994 –AFIP 3 Series Fascicle
- Designated as "renal cell carcinoma, collecting duct type"
- McLennan Farrow et al. – 1997 – J Urol
- 8 examples of "low-grade collecting duct RCCs"
- 5 subsequently recognized as MTSC

Tubulocystic Carcinoma of the Kidney With Poorly Differentiated Foci

A Frequent Morphologic Pattern of Fumarate Hydratase-deficient Renal Cell Carcinoma

Steven C. Smith, MD, PhD, Kiril Trpkov, MD,† Ying-Bei Chen, MD, PhD,‡ Rohit Mehra, MD,§ Deepika Sirohi, MD,‖ Chisato Ohe, MD,‖ Andi K. Cani, MS,§ Daniel H. Hovelson, MS,§ Kei Omata, MD,§ Jonathan B. McHugh, MD,§ Wolfram Jochum, MD,¶ Maurizio Colecchia, MD,# Mitual Amin, MD,** Mukul K. Divatia, MD,‖ Ondřej Hes, MD, PhD,†† Santosh Menon, MD,‡‡ Isabela Werneck da Cunha, MD, PhD,§§ Sergio Tripodi, MD, PhD,‖‖ Fadi Brimo, MD,¶¶ Anthony J. Gill, MD,##*** Adeboye O. Osunkoya, MD,††† Cristina Magi-Galluzzi, MD, PhD,‡‡‡ Mathilde Sibony, MD,§§§ Sean R. Williamson, MD,‖‖‖ Gabriella Nesi, MD, PhD,¶¶¶ Maria M. Picken, MD,### Fiona Maclean, MBBS,**** Abbas Agaimy, MD,†††† Liang Cheng, MD,‡‡‡‡ Jonathan I. Epstein, MD,§§§§ Victor E. Reuter, MD,‡ Satish K. Tickoo, MD,‡ Scott A. Tomlins, MD, PhD,§,‖‖‖‖ and Mahul B. Amin, MD‖*

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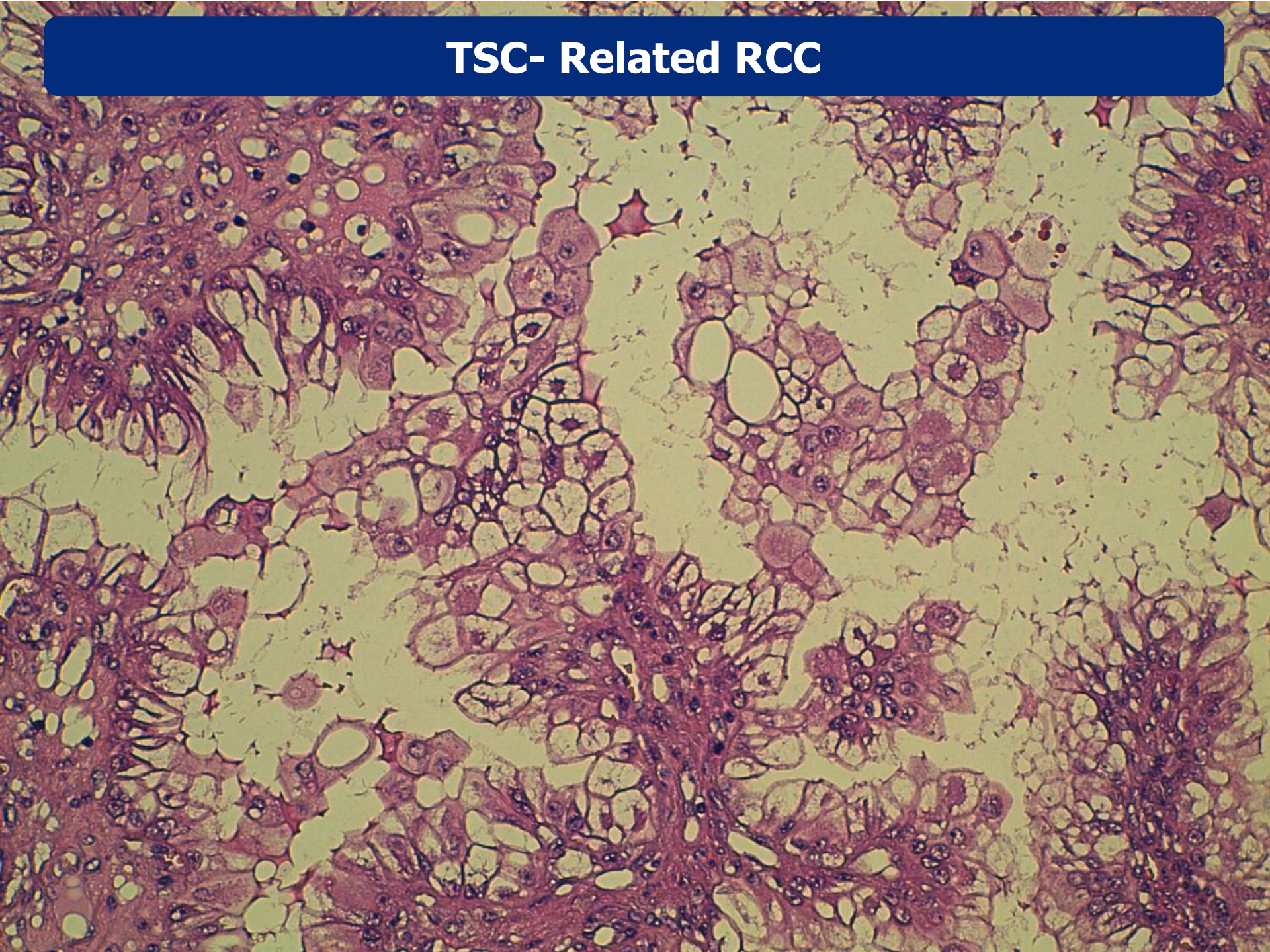
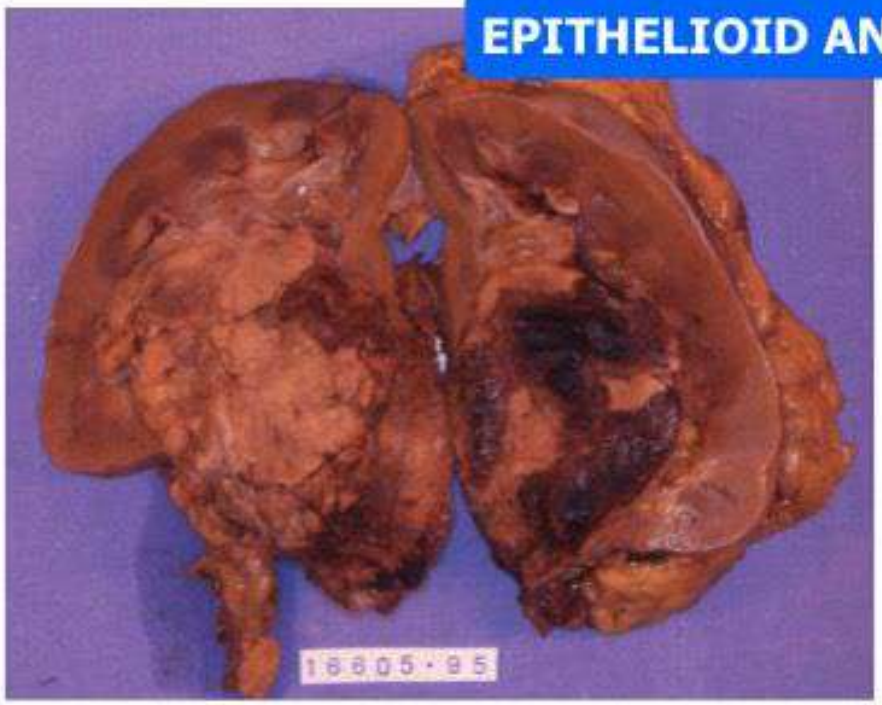
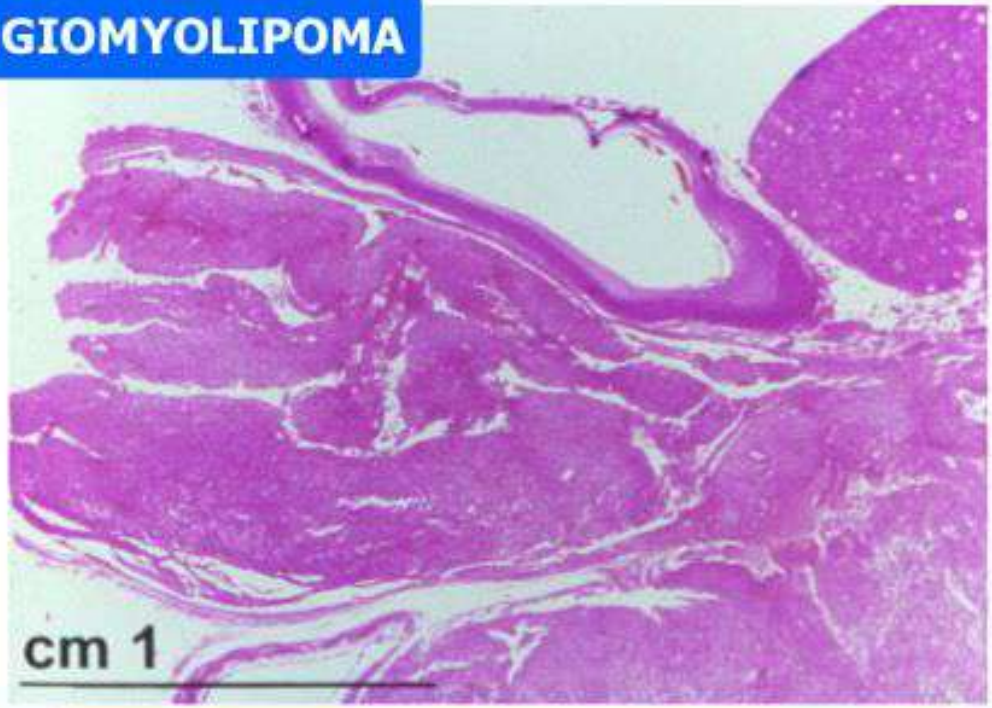
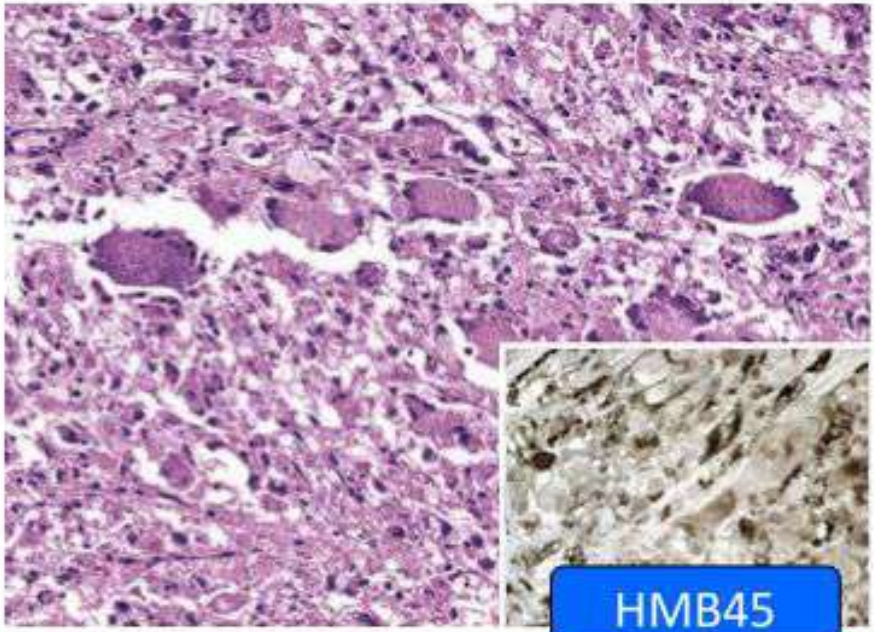
TSC- Related RCC



EPITHELIOID ANGIOMYOLIPOMA







Martignoni G, Pea M, Bonetti F et al.
Carcinomalike monotypic epithelioid angiomyolipoma in patients without evidence of tuberous sclerosis: a clinicopathologic and genetic study.
Am J Surg Pathol. 1998;22:663

Pea M, Bonetti F, Martignoni G et al.
Apparent renal cell carcinoma in tuberous sclerosis are heterogeneus: the identification of malignant angiomyolipoma
Am J Surg Pathol. 1998 Feb;22(2):180-7

	Reference*	Age (years)	Gender	AML†	First diagnosis‡	Follow-up	Second diagnosis§
Case 1	32	31	F	No	Oncocytoma	NA	Oncocytoma
Case 2	38	18	F	No	Carcinoma	NA	EpAML
Case 3	20	24	F	Yes	Carcinoma	DOD 12 mo	EpAML
Case 4	34	29	M	Yes	Carcinoma	DOD 18 mo	EpAML
Case 5	19	30	M	Yes	Oncocytoma	Dead, cachexia	uncl

DOD, dead of disease; EpAML, epithelioid angiomyolipoma; uncl, unclassified tumor; NA, not available.
* Reference of the original article.
† Associated angiomyolipoma in the same kidney.
‡ Diagnosis originally reported.
§ Diagnosis after revision performed in this study.

Pea M, Bonetti F, Martignoni G, Henske EP, Manfrin E, Colato C, Bernstein J. **Apparent renal cell carcinomas in tuberous sclerosis are heterogeneous: the identification of malignant epithelioid angiomyolipoma.**

Am J Surg Pathol. 1998;22:180.

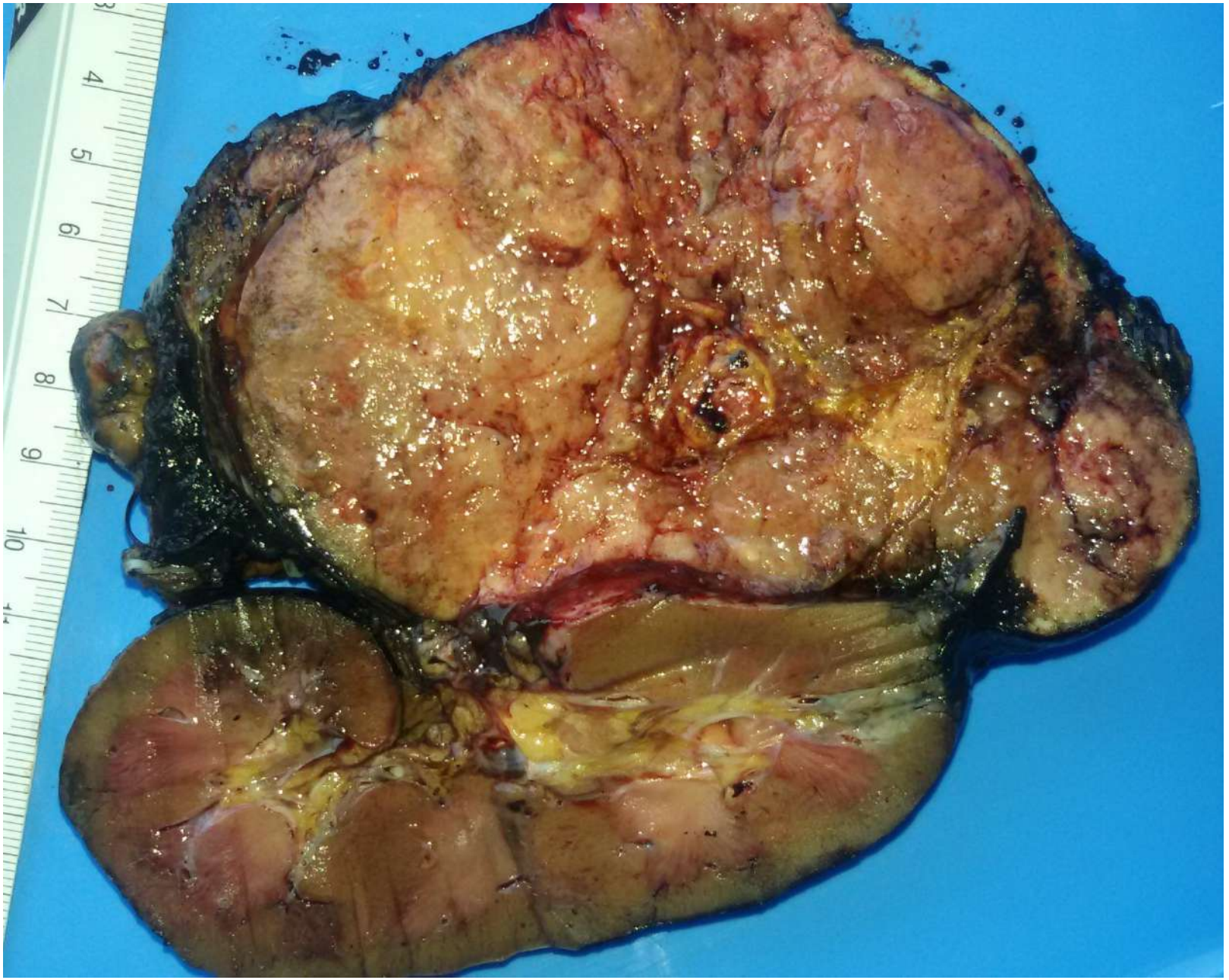
Antibody	Case 1	Case 2	Case 3	Case 4	Case 5
CAM 5.2	Pos 100%	Neg	Neg	Neg	Pos 10%
AE1 and AE3	Pos 100%	Neg	Neg	Neg	Neg
CK7	ND	Neg	Neg	Neg	Neg
CK 20	ND	Neg	Neg	Neg	Neg
K 903	ND	Neg	Neg	Neg	Neg
BerEp4	ND	Neg	Neg	Neg	Neg
EMA	Pos 100%	Pos 20%	Pos 30%	Neg	Neg
HMB-45	Neg	Pos 40%	Pos 80%	Pos 80%	Pos 10%
S-100	Neg	Neg	Neg	Neg	Neg
Vimentin	Neg	Pos 2%	Neg	Neg	Neg
Desmin	Neg	Neg	Neg	Neg	Neg
Muscle-specific actin (HHF35)	Neg	Pos 2%	Neg	Neg	Neg
Smooth muscle actin	Neg	Neg	Neg	Neg	Neg
CD68	Neg	Pos 40%	Pos 30%	Pos 60%	Neg

Neg, negative; ND, not done; Pos %, percentage of positive cells.

Clinico-pathological parameters related to the progression

1	Tuberous sclerosis or multiple angiomyolipomas	p=0,042
2	Necrosis	p=0,012
3	Size more than 7 cm	p=0,021
4	Extrarenal extension and/or renal vein involvement	p=0,023
5	Carcinoma-like pattern	p=0,025

Pure Epithelioid PEComas (So-Called Epithelioid Angiomyolipoma) of the kidney: A Clinopathologic Study of 41 Cases: Detailed Assessment of Morphology and Risk Stratification.
Nese N, Martignoni G, Fletcher CD, Gupta R, Pan CC, Kim H, Ro JY, Hwang IS, Sato K, Bonetti F, Pea M, Amin MB, Hes O, Svec A, Kida M, Vankalakunti M, Berel D, Rogatko A, Gown AM, Amin MB.
Am J Surg Pathol. 2011 Feb;35(2):161-176.



Seminoma 30-60%, Mixed 30% Teratoma 5% Embryonal 10% Yolk sac 1% Chorio <1%

Conclusions

La diagnosi istologica dei tumori renali è "MULTIMODALE" e richiede morfologia, immunoistochimica e talvolta anche studio molecolare

L'attuale orientamento è una precisa caratterizzazione allo scopo di fornire un inquadramento terapeutico corretto e una valutazione prognostica affidabile

Si tratta di un nuovo modo di sviluppare nuovi farmaci in base all'istotipo corretto

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George J. Netto, MD, Birmingham AL