Ospedale
"Sacro Cuore - Don Calabria"

Incontri
di aggiornamento
del Dipartimento
Oncologico

Responsabile Scientifico:
Dott.ssa Stefania Gori

19 settembre - 6 novembre
4 dicembre
2014

SEDE
CENTRO FORMAZIONE
Ospedale "Sacro Cuore - Don Calabria"
Via Don Angelo Sempreboni, 5 - 37024 Negrar (Verona)

ONCOLOGIA E RENE

6 novembre 2014

CARCINOMA DEL RENE: ASPETTI ANATOMO-PATOLOGICI

Guido Martignoni
Dipartimento di Patologia e Diagnostica
Università di Verona

ISUP Consensus Conference on Adult Renal Tumors Vancouver, 18 march 2012

Working Group I – Tumour Classification
Group Chair John Srigley**, Co-Chair** Pete Argani, **Rapporteur** Ming Zhou, **Other Members:** John Eble, Jonathan Epstein, Ondrej Hes, Rodolfo Montironi, Satish Tickoo

Working Group II – Histological Prognostic Factors
Group Chair Brett Delahunt**, Co-chair** Guido Martignoni, **Rapporteur** Jesse McKenney, **Other Members:** Ferran Algaba, John Cheville, Lars Egevad, Peter Humphrey, Cristina Magi-Galluzzi

Working Group III – Staging and Specimen Handling
Group Chair David Grignon**, Co-chair** Steve Bonsib, **Rapporteur** Kiril Trpkov, **Other Members:** Mahul Amin, Athanase Billis, Antonio Lopez-Beltran, Hema Samaratunga, Pheroze Tamboli

Working Group IV – Biomarkers (Diagnosis, Prognosis, Prediction)
Group Chair Holger Moch**, Co-chair** Liang Cheng, **Rapporteur** Steven Shen, **Other Members:** Victor Reuter(corresponding), Nathalie Leclerq-Roux, Maria Merino, George Netto, Puay Hoon Tan

The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia

John R. Srigley, MD, Brett Delahunt, MD,† John N. Eble, MD,‡ Lars Egevad, MD, PhD,§ Jonathan I. Epstein, MD,‖ David Grignon, MD,‡ Ondrej Hes, MD, PhD,¶ Holger Moch, MD,# Rodolfo Montironi, MD,** Satish K. Tickoo, MD,†† Ming Zhou, MD, PhD,‡‡ Pedram Argani, MD,§§ and The ISUP Renal Tumor Panel*

- Renal cell tumors
  - Papillary adenoma
  - Oncocytoma
  - Clear cell renal cell carcinoma
    - Multilocular cystic clear cell renal cell neoplasm of low malignant potential*
  - Papillary renal cell carcinoma†
  - Chromophobe renal cell carcinoma
    - Hybrid oncocytic chromophobe tumor*
  - Carcinoma of the collecting ducts of Bellini
  - Renal medullary carcinoma
  - MiT family translocation renal cell carcinoma*
    - Xp11 translocation renal cell carcinoma
    - t(6;11) renal cell carcinoma*
  - Carcinoma associated with neuroblastoma
  - Mucinous tubular and spindle cell carcinoma
  - Tubulocystic renal cell carcinoma*
  - Acquired cystic disease associated renal cell carcinoma*
  - Clear cell (tubulo) papillary renal cell carcinoma*
  - Hereditary leiomyomatosis renal cell carcinoma syndrome-associated renal cell carcinoma*
  - Renal cell carcinoma, unclassified
- Metanephric tumors
  - Metanephric adenoma
  - Metanephric adenofibroma
  - Metanephric stromal tumor
- Nephroblastic tumors
  - Nephrogenic rests
  - Nephroblastoma
    - Cystic partially differentiated nephroblastoma
- Mesenchymal tumors
  - Occurring mainly in children
    - Clear cell sarcoma
    - Rhabdoid tumor
    - Congenital mesoblastic nephroma
    - Ossifying renal tumor of infants
  - Occurring mainly in adults
    - Leiomyosarcoma (including renal vein)
    - Angiosarcoma
    - Rhabdomyosarcoma
    - Malignant fibrous histiocytoma
    - Hemangiopericytoma
    - Osteosarcoma
    - Synovial sarcoma*
    - Angiomyolipoma
      - Epithelioid angiomyolipoma*
    - Leiomyoma
    - Hemangioma
    - Lymphangioma
    - Juxtaglomerular cell tumor
    - Renomedullary interstitial cell tumor
    - Schwannoma
    - Solitary fibrous tumor
- Mixed mesenchymal and epithelial tumors
  - Cystic nephroma/mixed epithelial stromal tumor
- Neuroendocrine tumors
  - Carcinoid (low-grade neuroendocrine tumor)
  - Neuroendocrine carcinoma (high-grade neuroendocrine tumor)
  - Primitive neuroectodermal tumor
  - Neuroblastoma
  - Pheochromocytoma
- Hematopoietic and lymphoid tumors
  - Lymphoma
  - Leukemia
  - Plasmacytoma
- Germ cell tumors
  - Teratoma
  - Choriocarcinoma
- Metastatic tumors
- Other tumors

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*Additions and changes in terminology or position in classification.

†The majority of consensus attendees subtype papillary carcinoma (type 1, type 2 or not otherwise specified).

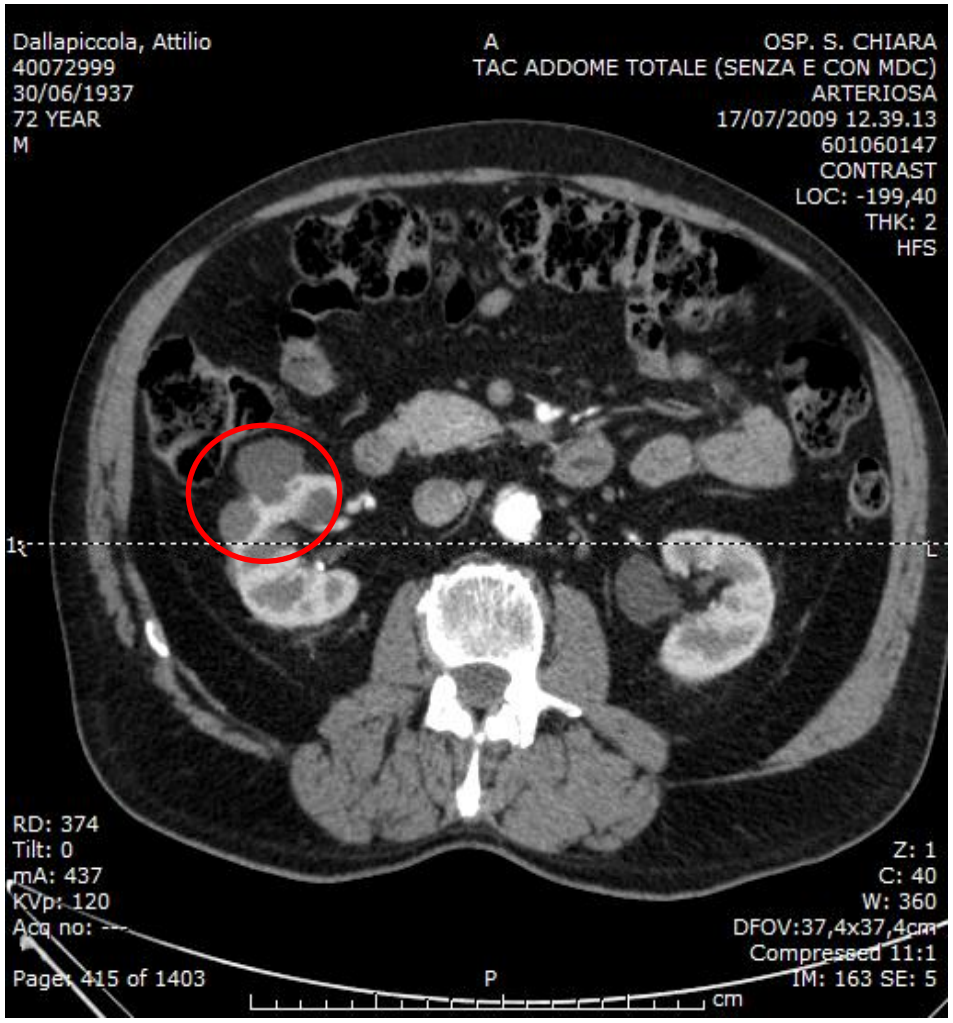
NUOVI TUMORI EPITELIALI

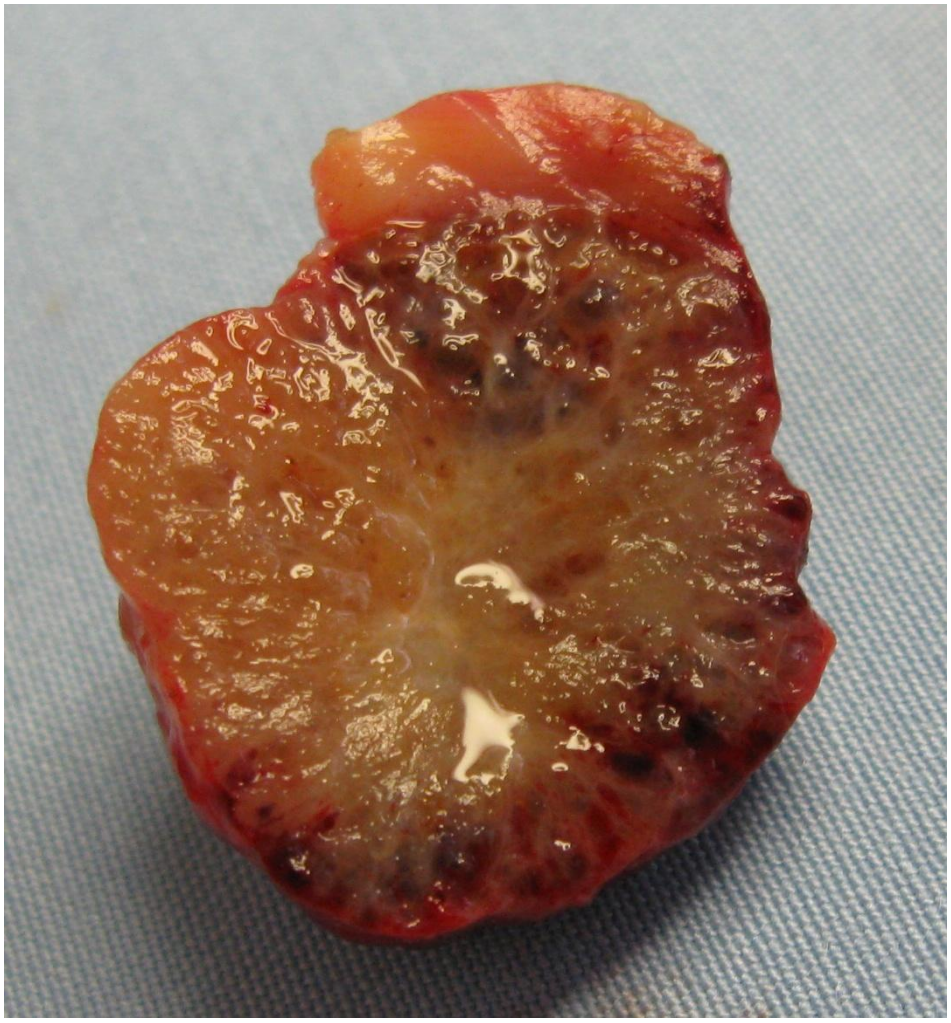
- **TUBULOCYSTIC RENAL CELL CARCINOMA (RCC)**
- **ACQUIRED CYSTIC DISEASE (ACD)-ASSOCIATED RCC**
- **CLEAR CELL (TUBULO)PAPILLARY RCC**
- **MiT FAMILY TRANSLOCATION RENAL CELL CARCINOMA including t(6;11) RCC**
- **HEREDITARY LEIOMYOMATOSIS RCC SYNDROME ASSOCIATED RCC**

ENTITA' EMERGENTI / PROVVISORIE

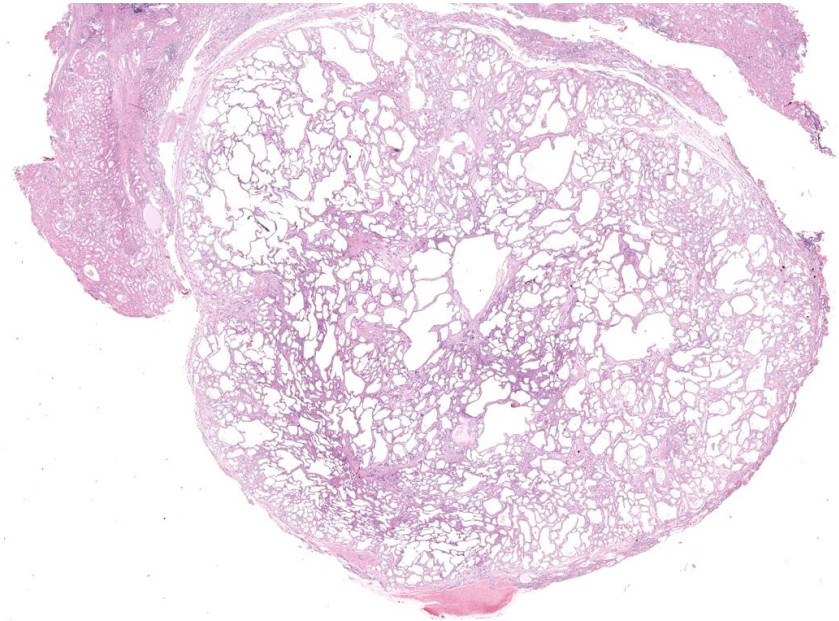
- **THYROID-LIKE FOLLICULAR CARCINOMA**
- **SUCCINIC DEHYDROGENASE DEFICIENCY ASSOCIATED RCC**
- **ALK – TRANSLOCATION RCC**

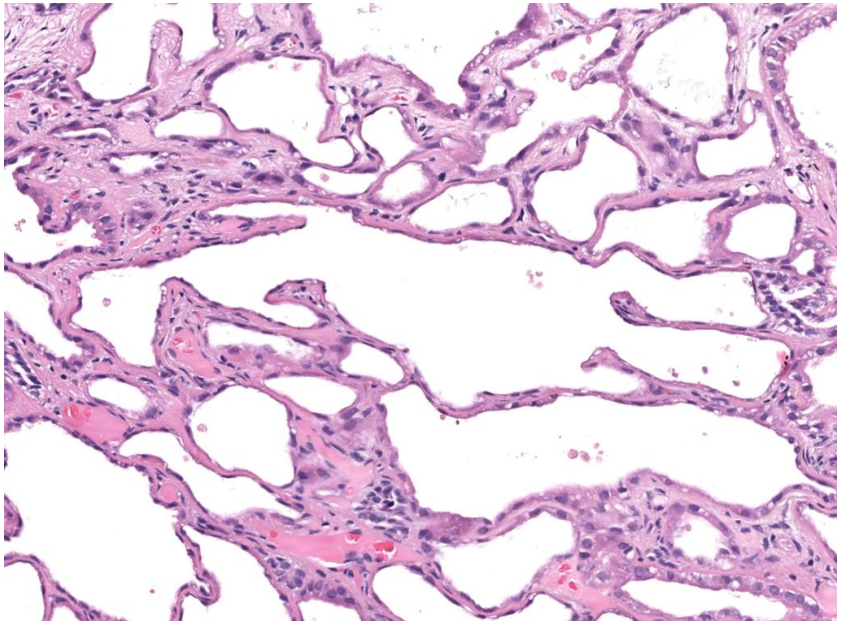
Tubulocystic carcinoma

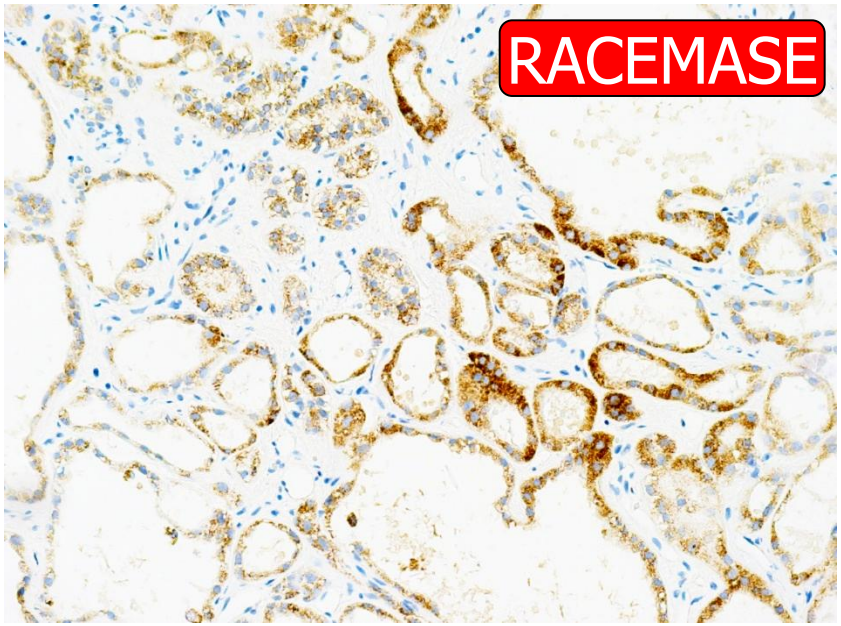


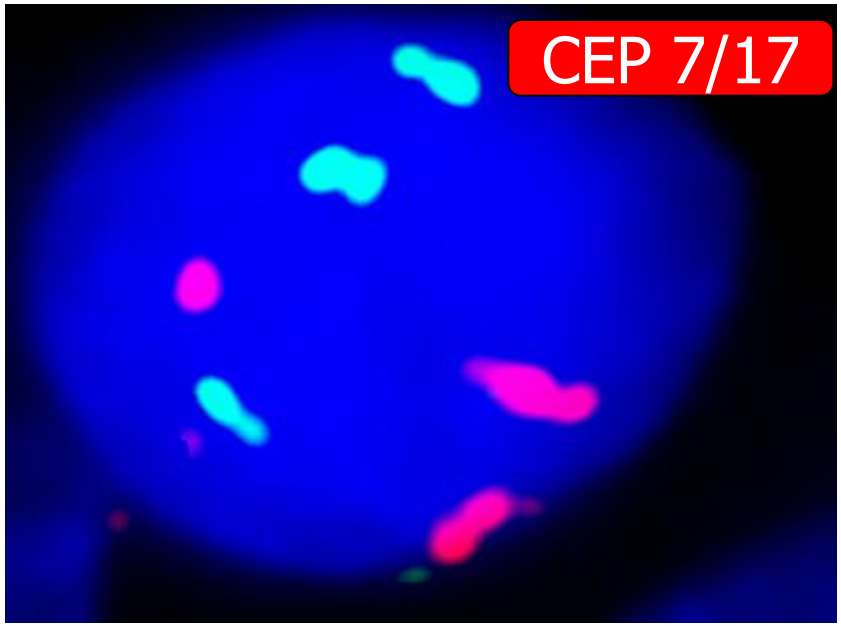


Tubulocystic carcinoma









Tubulocystic carcinoma

Number of cases: 66

Mean age: 58 years (30-94)

M/F: 6/1

Multifocality: 4 cases out of 20

Tumor diameter: 0,1-17 cm

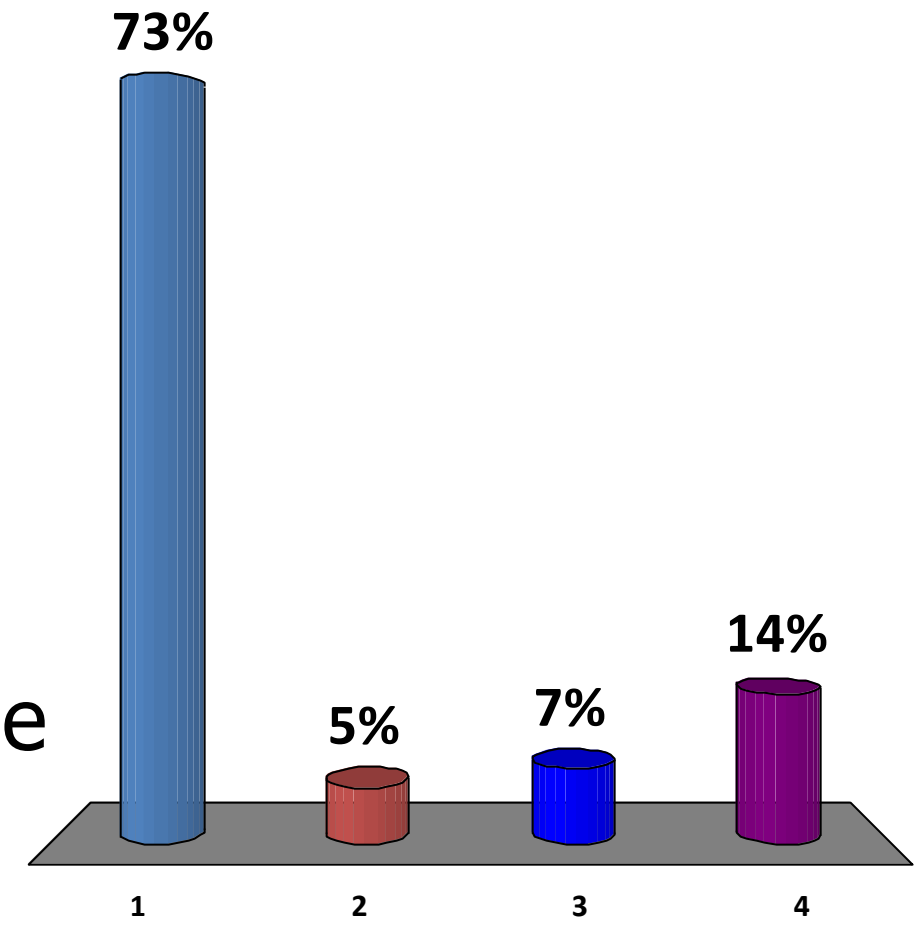
Grading: G3

Pathological stage: T1a (rare T1b, T2, one T3 and one T2N2)

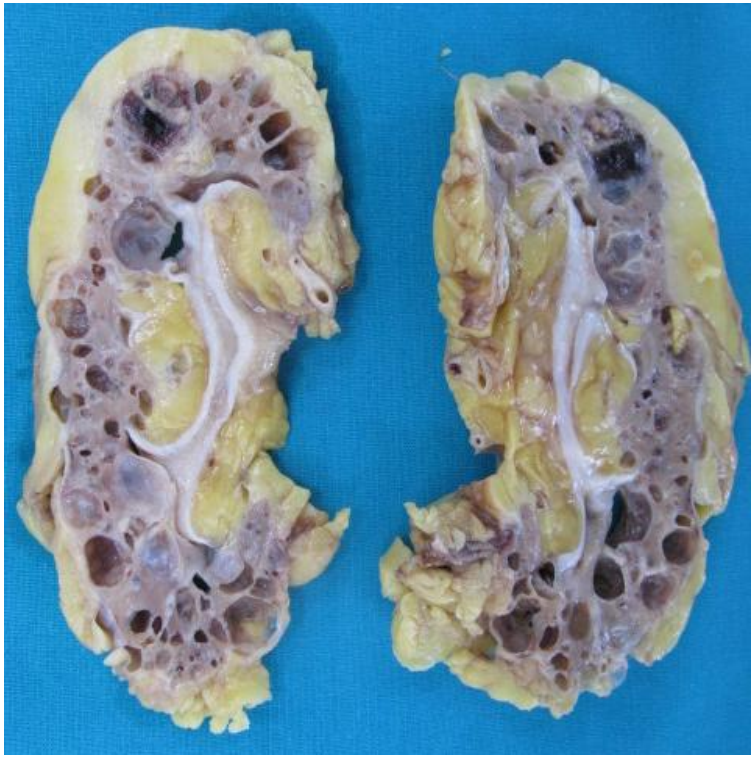
Azoulay et al. Virchows Arch 2007;451:905
Amin et al. Am J Surg Pathol.2009;33:384
Zhou et al. Am J Surg Pathol.2009;33:1840
Hora et al. World J Urol 2011;29:349.

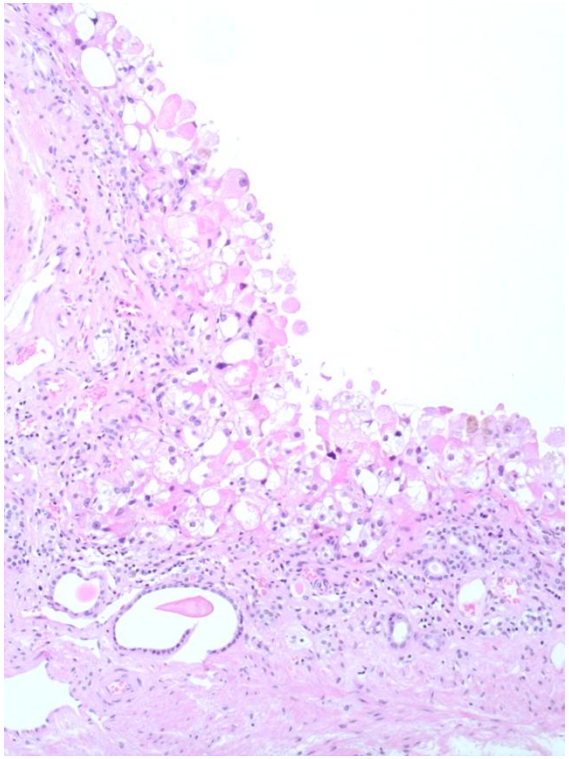
Should Tubulocystic-RCC be recognized as an entity at this time?

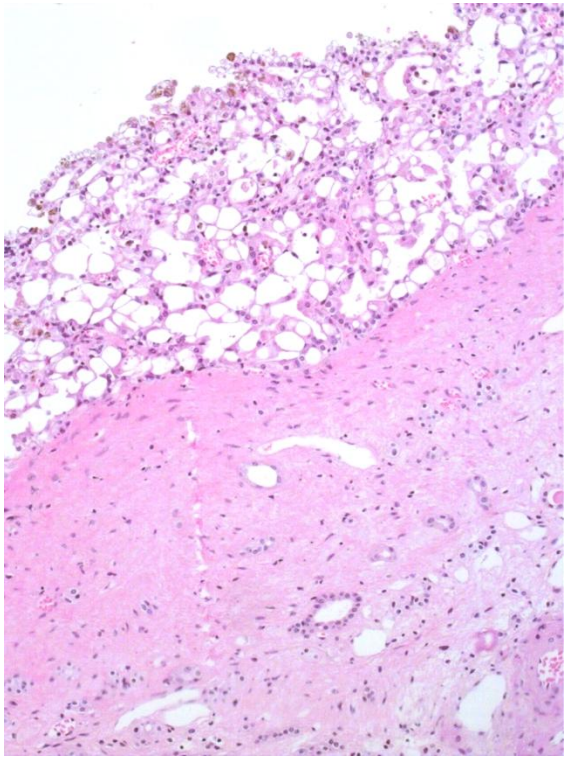
1. Yes
2. No
3. Uncertain even with personal experience/ knowledge
4. Not enough personal experience/knowledge

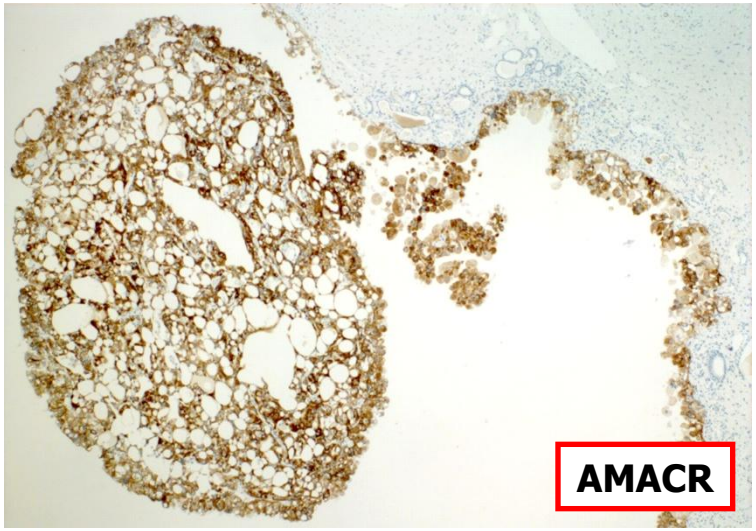


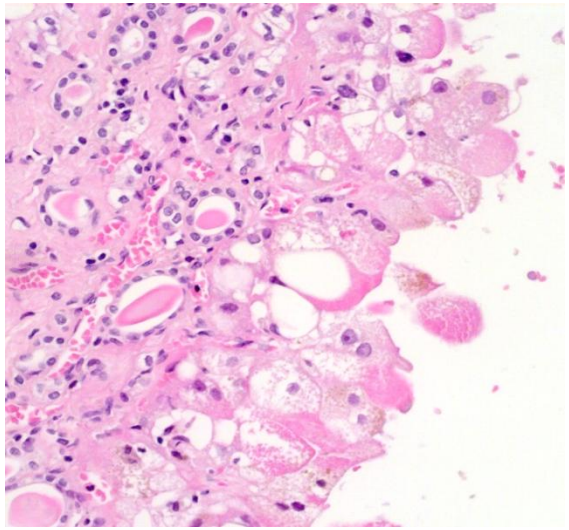
Acquired Cystic Disease (ACD)

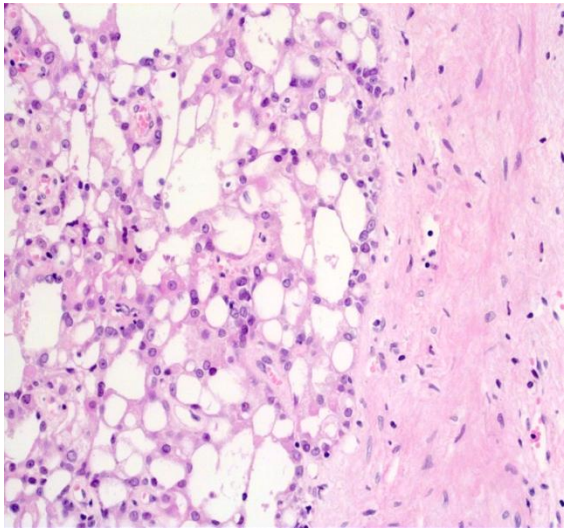






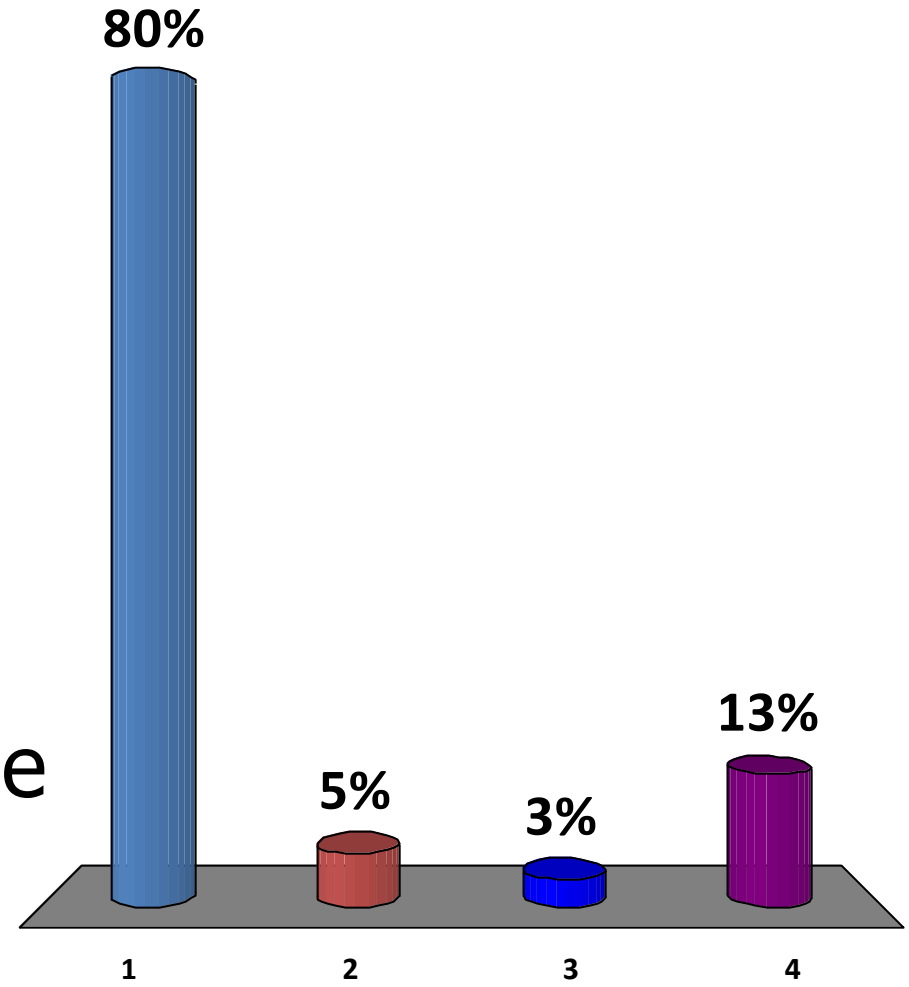




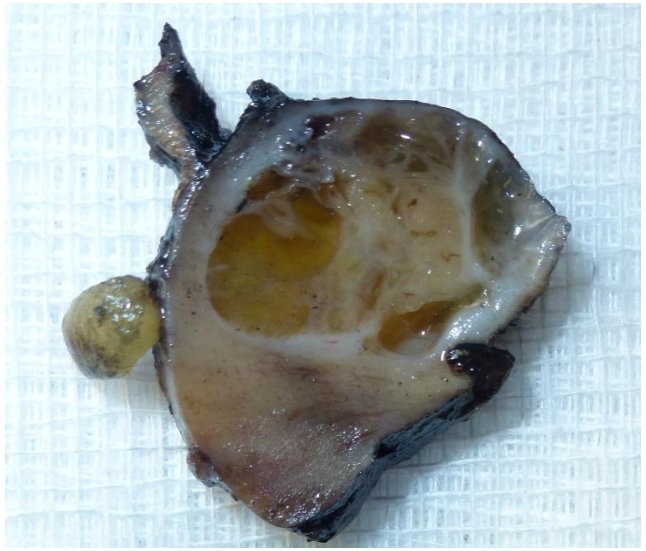


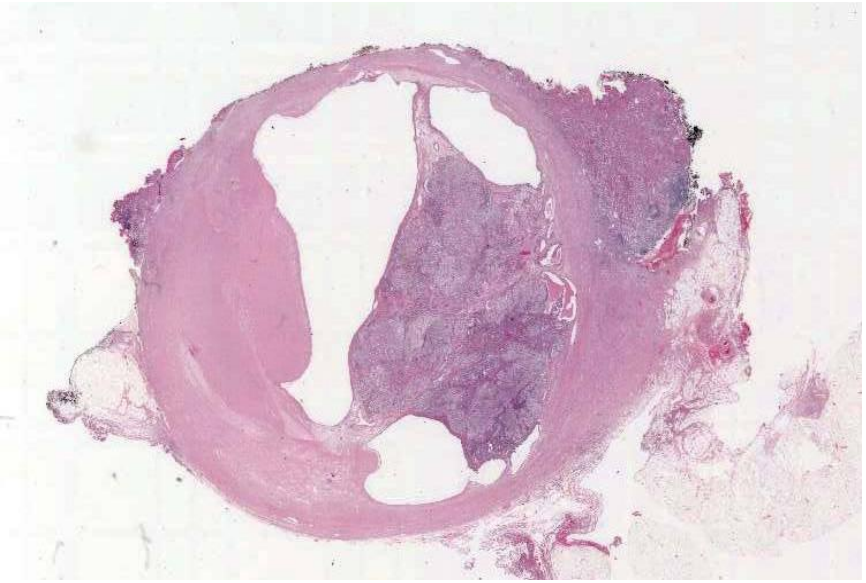
Should Acquired Cystic Disease (ACD)-associated RCC be Recognized as an Entity at this time?

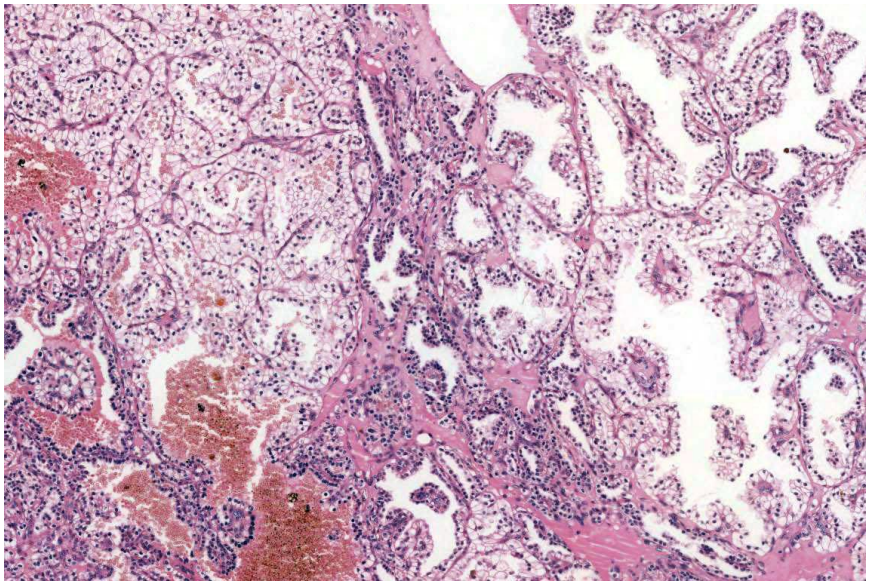
1. Yes
2. No
3. Uncertain even with personal experience/ knowledge
4. Not enough personal experience/knowledge

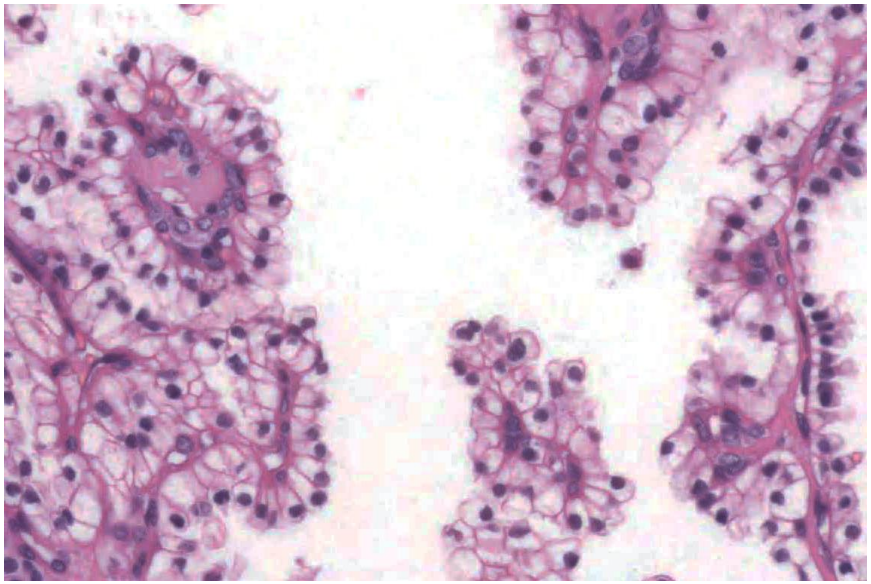


Clear cell (tubulo)papillary RCC

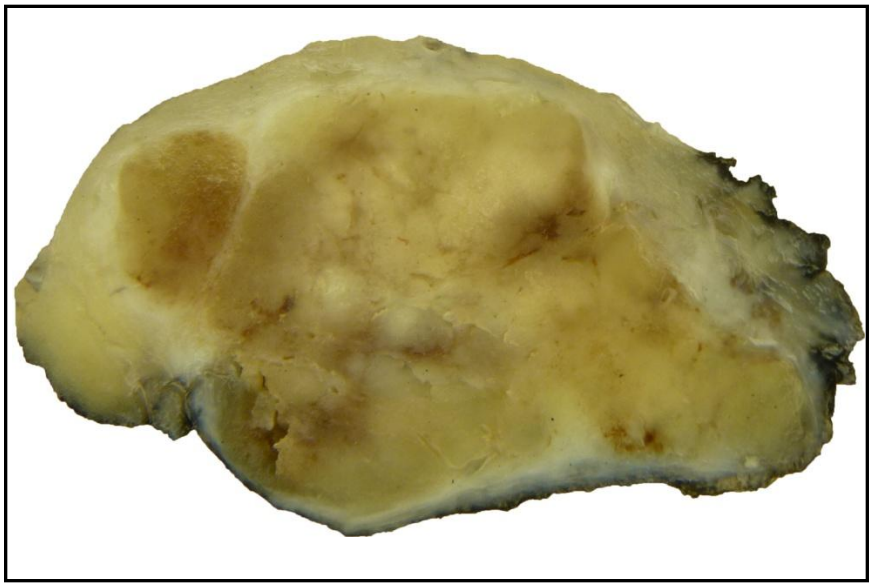


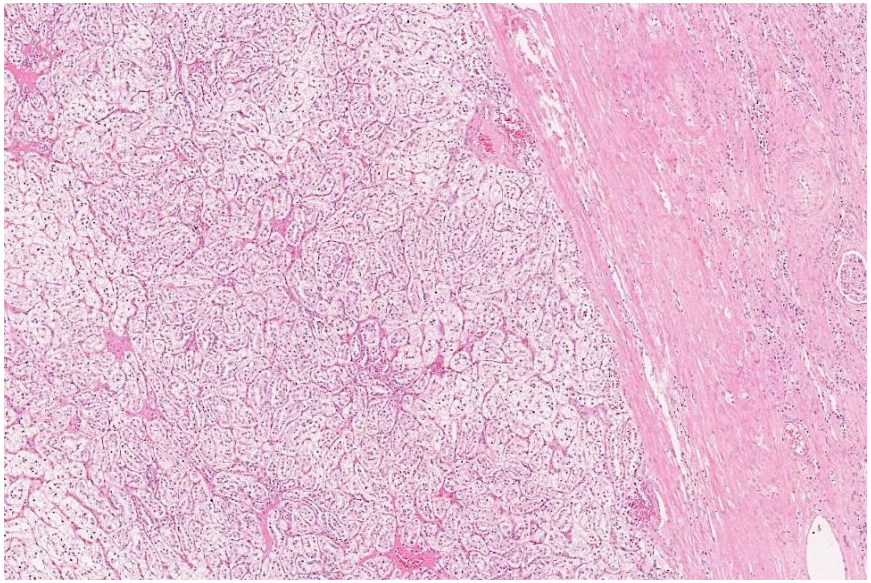


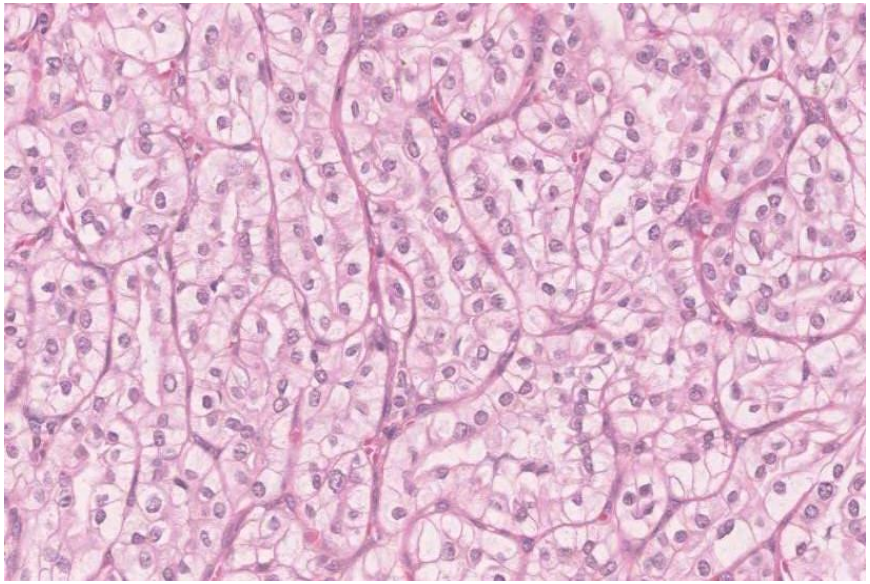


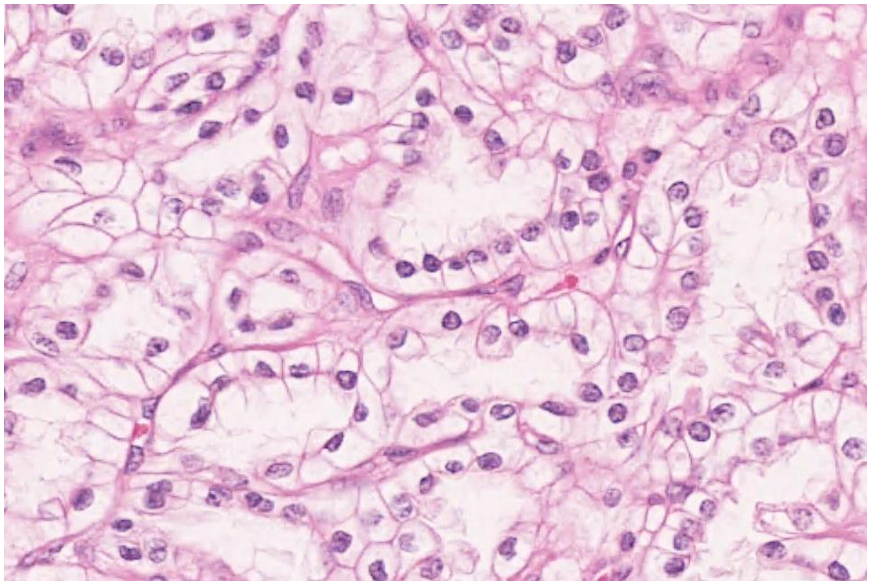


Clear cell (tubulo)papillary RCC

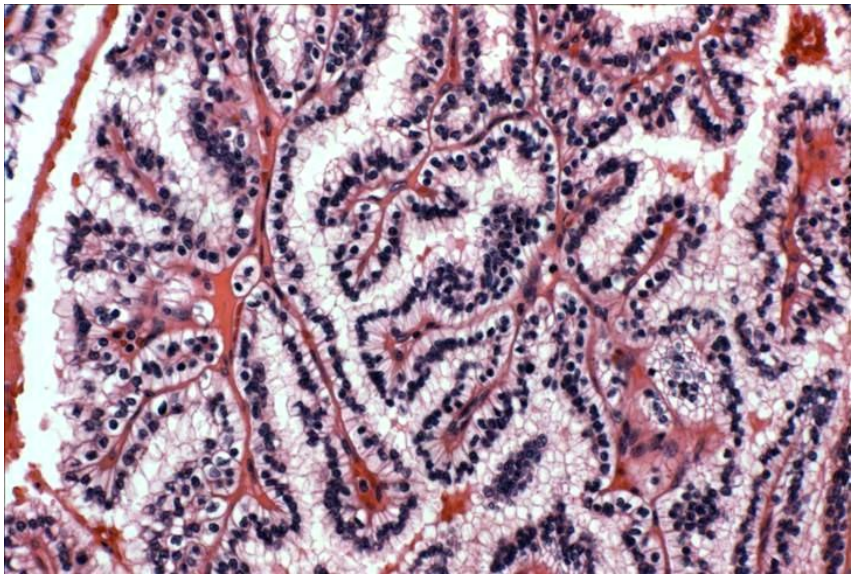


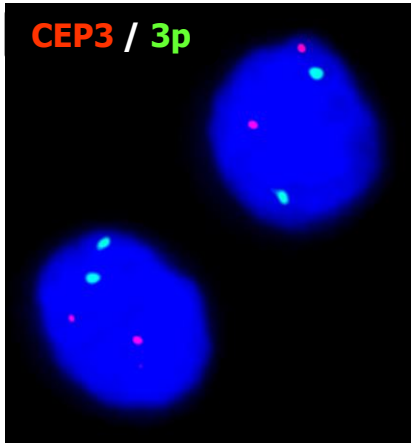


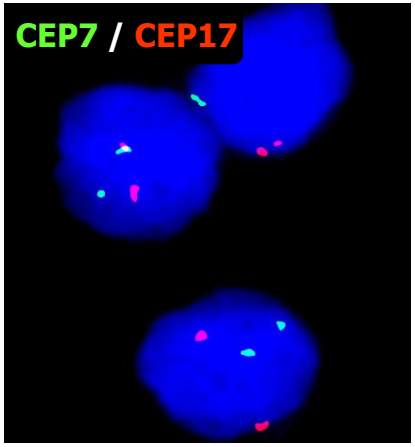


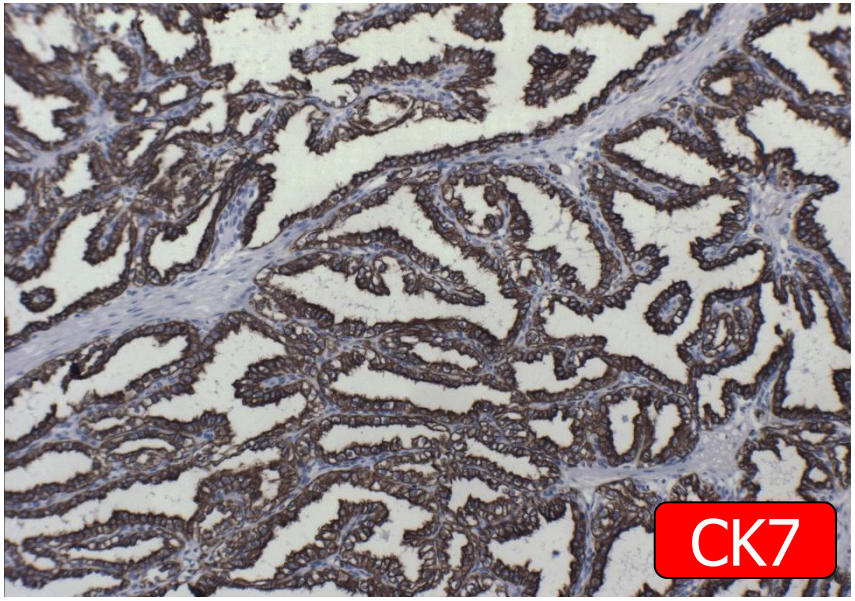


Clear cell (tubulo)papillary RCC









FISH				ICH		
7	17	Y	3p	CD10	AMACR	CK7
normal				neg	neg	+

Gobbo et al. Am J Surg Pathol.2008;32:1239

Clear cell (tubulo)papillary RCC

NUMERO DI CASI: 160 (FREQUENZA: ≈ 3%)
CASI IN MALATTIA RENALE TERMINALE: 63

ETÀ MEDIA: 57 anni
CASI IN MALATTIA RENALE TERMINALE: 55 anni
CASI NON IN MALATTIA RENALE TERMINALE: 59 anni

M/F: 1.4/1

MULTIFOCALITÀ: 18 CASI

DIMENSIONE MEDIA TUMORI: ≈ 2.5 cm

GRADO
TUTTI TUMORI G1-G2

STADIO PATOLOGICO: pT1
QUASI TUTTI TUMORI pT1a

FOLLOW-UP (1-108 MESI)
TUTTI CASI SENZA EVIDENZA
DI RECIDIVA DI MALATTIA

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 2012. Epub 2012/12/15

Clear-cell papillary renal cell carcinoma: molecular and immunohistochemical analysis with emphasis on the *von Hippel–Lindau* gene and hypoxia-inducible factor pathway-related proteins

Stephen M Rohan[1], Yonghong Xiao[1], Yupu Liang[2], Maria E Dudas[1], Hikmat A Al-Ahmadie[1], Samson W Fine[1], Anuradha Gopalan[1], Victor E Reuter[1], Marc K Rosenblum[1], Paul Russo[3] and Satish K Tickoo[1]

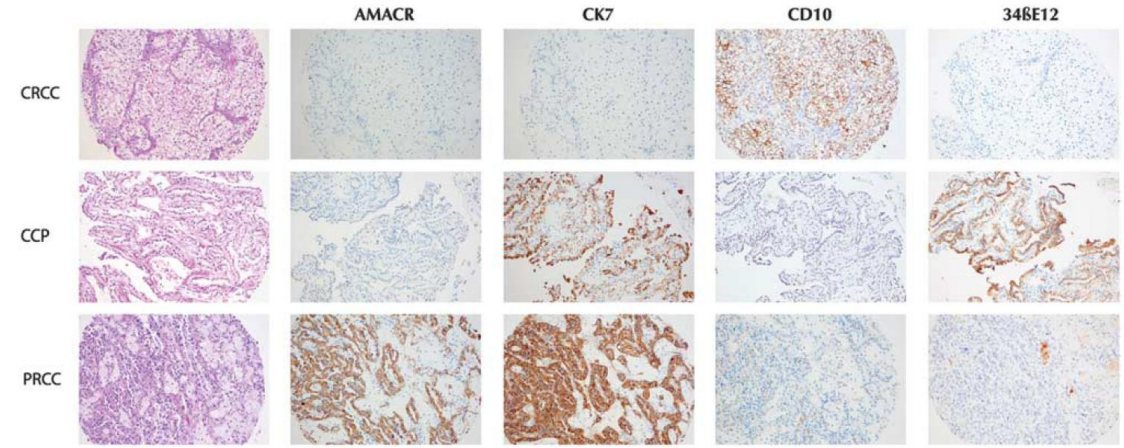
MODERN PATHOLOGY (2011) 24, 1207–1220

Case no.	VHL *mutation*	*3p25 loss*	VHL *mRNA*[a]	*HIF-1α*	*GLUT-1*
CCP1	–	–	Increased	90%, 3+	90%, 3+
CCP2	–	–	Decreased	70%, 3+	80%, 2+
CCP3	–	–	Increased	80%, 3+	80%, 3+
CCP4	–	–	Increased	70%, 3+	90%, 3+
CCP5	–	–	Increased	90%, 3+	90%, 3+
CCP8	–	–	Increased	95%, 3+	90%, 3+
CCP9	–	–	Decreased	90%, 3+	90%, 3+
CRCC2	–	+	Decreased	90% 3+	50%, 2+
CRCC3	+	+	Unchanged	80%, 3+	70%, 3+
CRCC6	–	+	Decreased	95%, 3+	50%, 3+
CRCC7	+	+	Decreased	90%, 3+	95%, 3+
CRCC10	+	+	Unchanged	70%, 2+	90%,3+

Clear-cell papillary renal cell carcinoma: molecular and immunohistochemical analysis with emphasis on the *von Hippel–Lindau* gene and hypoxia-inducible factor pathway-related proteins

Stephen M Rohan[1], Yonghong Xiao[1], Yupu Liang[2], Maria E Dudas[1], Hikmat A Al-Ahmadie[1], Samson W Fine[1], Anuradha Gopalan[1], Victor E Reuter[1], Marc K Rosenblum[1], Paul Russo[3] and Satish K Tickoo[1]

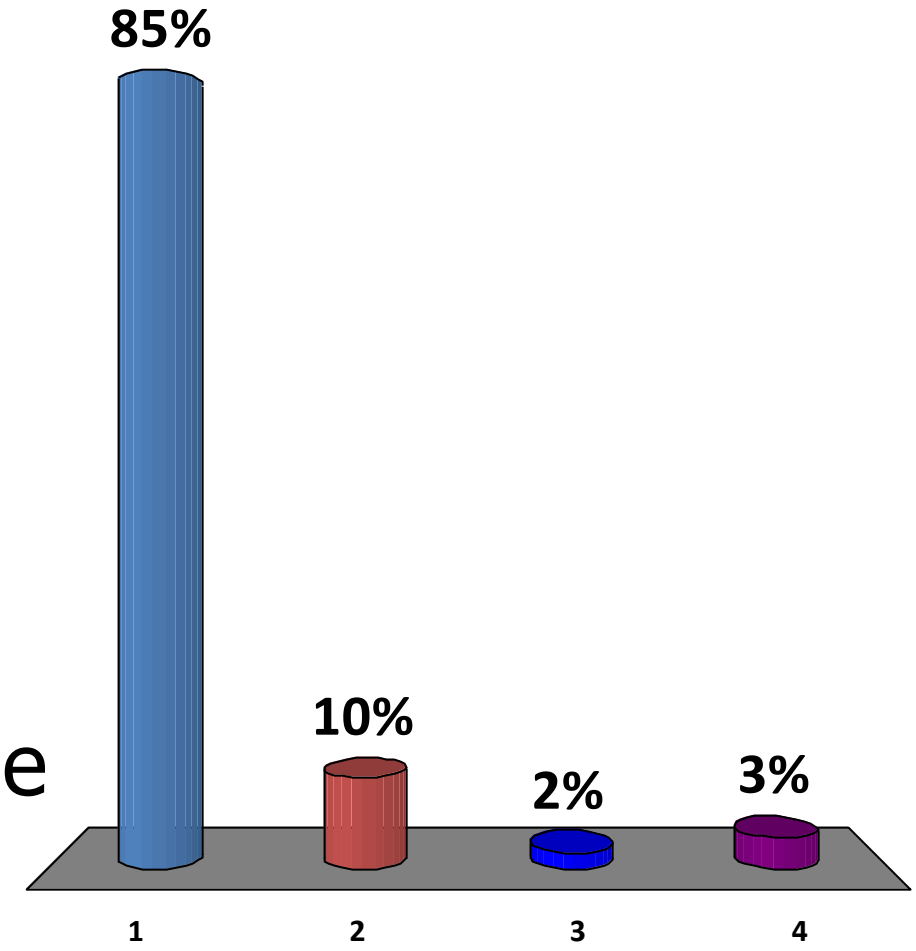
Modern Pathology (2011) 24, 1207–1220



In our opinion, based on the characteristic morphological features, clear-cell papillary RCC is easily separable from papillary RCCs with clear-cell changes and clear-cell RCC with focal papillary architecture.[3,7,8] In only rare instances, the support of immunohistochemical staining may be an absolute requirement for making this distinction.[31]

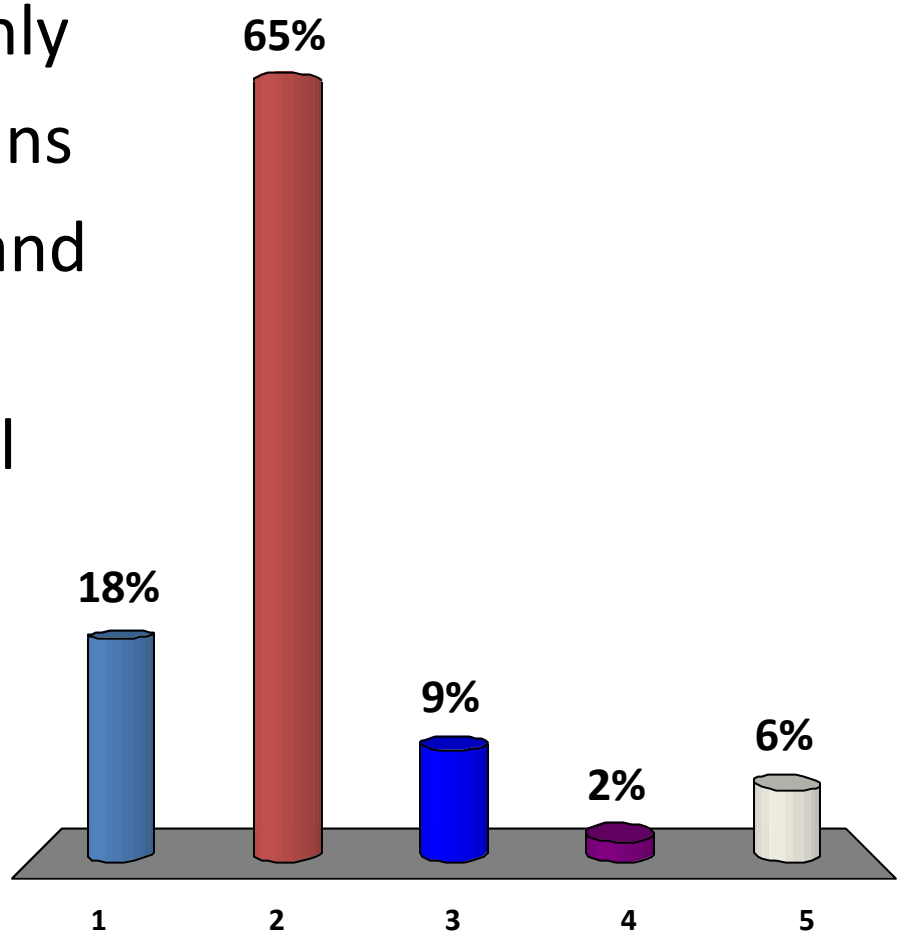
Should Clear Cell Papillary Renal Cell Carcinoma be Recognized as an Entity at this time?

1. Yes
2. No
3. Uncertain even with personal experience/ knowledge
4. Not enough personal experience/knowledge



What is required to make a diagnosis of CCPRCC/CCTPRCC?

1. Characteristic morphology only
2. Morphology and immunostains
3. Morphology, immunostains and genetics
4. Uncertain even with personal experience/knowledge
5. Not enough personal experience/knowledge

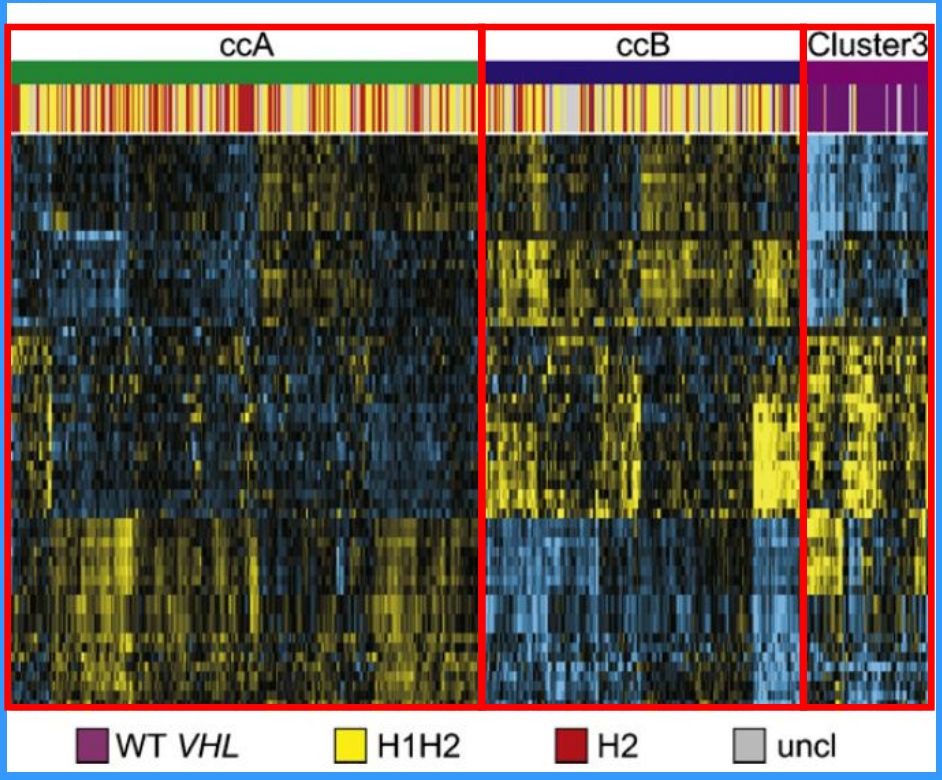


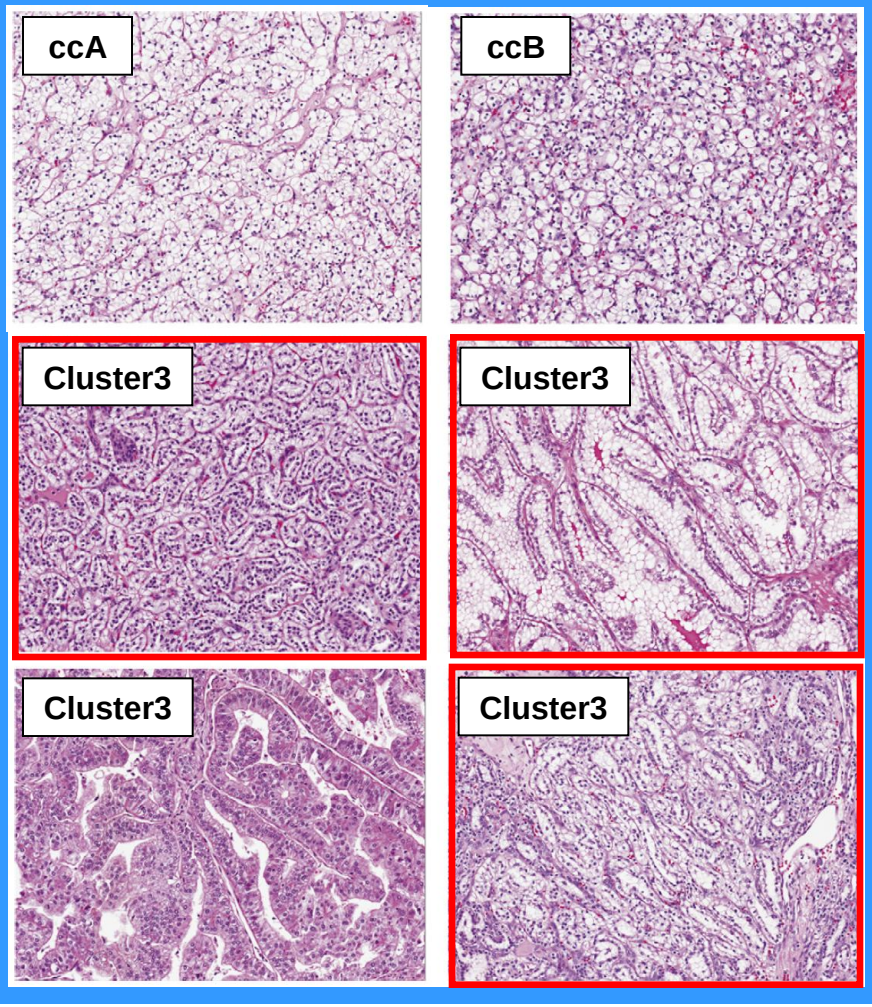
EUROPEAN UROLOGY 61 (2012) 258–268

Meta-analysis of Clear Cell Renal Cell Carcinoma Gene Expression Defines a Variant Subgroup and Identifies Gender Influences on Tumor Biology

A. Rose Brannon[a,b,1], *Scott M. Haake*[a,c,1], *Kathryn E. Hacker*[a,b], *Raj S. Pruthi*[a,d], *Eric M. Wallen*[a,d], *Matthew E. Nielsen*[a,d], *W. Kimryn Rathmell*[a,b,c,*]

GENE EXPRESSION PROFILE





Clear cell papillary renal cell carcinoma: micro-RNA expression profiling and comparison with clear cell renal cell carcinoma and papillary renal cell carcinoma ☆

Enrico Munari MD[a,1], Luigi Marchionni MD, PhD[b,1], Apurva Chitre BS[b], Masamichi Hayashi MD[c], Guido Martignoni MD[d,e], Matteo Brunelli MD, PhD[d], Stefano Gobbo MD[d,e], Pedram Argani MD[a], Mohamad Allaf MD[f], Mohammad O. Hoque PhD[c,*], George J. Netto MD[a,b,f,*]

Table 3 Selected differentially expressed miRNAs in CCPRCC, CCRCC, and PRCC

miRNA	CCPRCC	CCRCC	PRCC	Selected validated targets[a]
miR-210	Up	Up	NS	*EFNA, MNT, VMP1*
miR-155	Up	Up	NS	*AGTR1, BACH1, LDOC1*
miR106b	Up	Up	NS	*E2F1, VEGFA, CDKN1A*
miR-15a	Up	Up	NS	*BCL2, VEGFA, PDCD4*
miR-18a	Up	Up	NS	*BIM, CTGF, ESR1*
miR-130a	Up	NS	NS	–
miR135b	Up	NS	NS	*APC*
miR-101	Up	NS	NS	–
miR-10b	NS	Down	Down	*HOXD10, KLF4, SFRS1*
miR-141	NS	Down	-	*CLOCK, SERBP1, ELMO2*
miR-200a	NS	Down	Down	*ZEB1, ZEB2, ELMO2*
miR-200b	NS	Down	Down	*ZEB1, ZEB2, ELMO2*
miR-200c	NS	Down	Down	*ZEB1, ERRFI1, JAG1*
miR-26a	NS	Down	Down	*SMAD1, PLAG1, TGFBR2*
miR-218	NS	Down	Down	*LAMB3, COL1A1, ECOP*
miR-187	NS	Down	Down	–
miR-138	Down	Down	Down	*RHOC, KRT, ROCK2*
miR-422a	Down	NS	Down	–
miR-648	Down	NS	NS	–
miR-215	Down	NS	NS	*DHFR, TYMS, DTL, WNK1*
miR-663	Down	NS	NS	–
miR-204	Down	Down	NS	*ARPC1B, MMP3, MMP9*
miR-135a	Down	Down	NS	*APC, FLAP, JAK2*

Abbreviations: CCPRCC, clear cell papillary renal cell carcinoma; CCRCC, clear cell renal cell carcinoma; PRCC, papillary renal cell carcinoma; *, experimentally proven gene targets listed in miRWalk and miRecords; NS, not significantly different compared with matched normal.

[a] Experimentally proven gene targets listed in miRWalk and miRecords.

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,*]

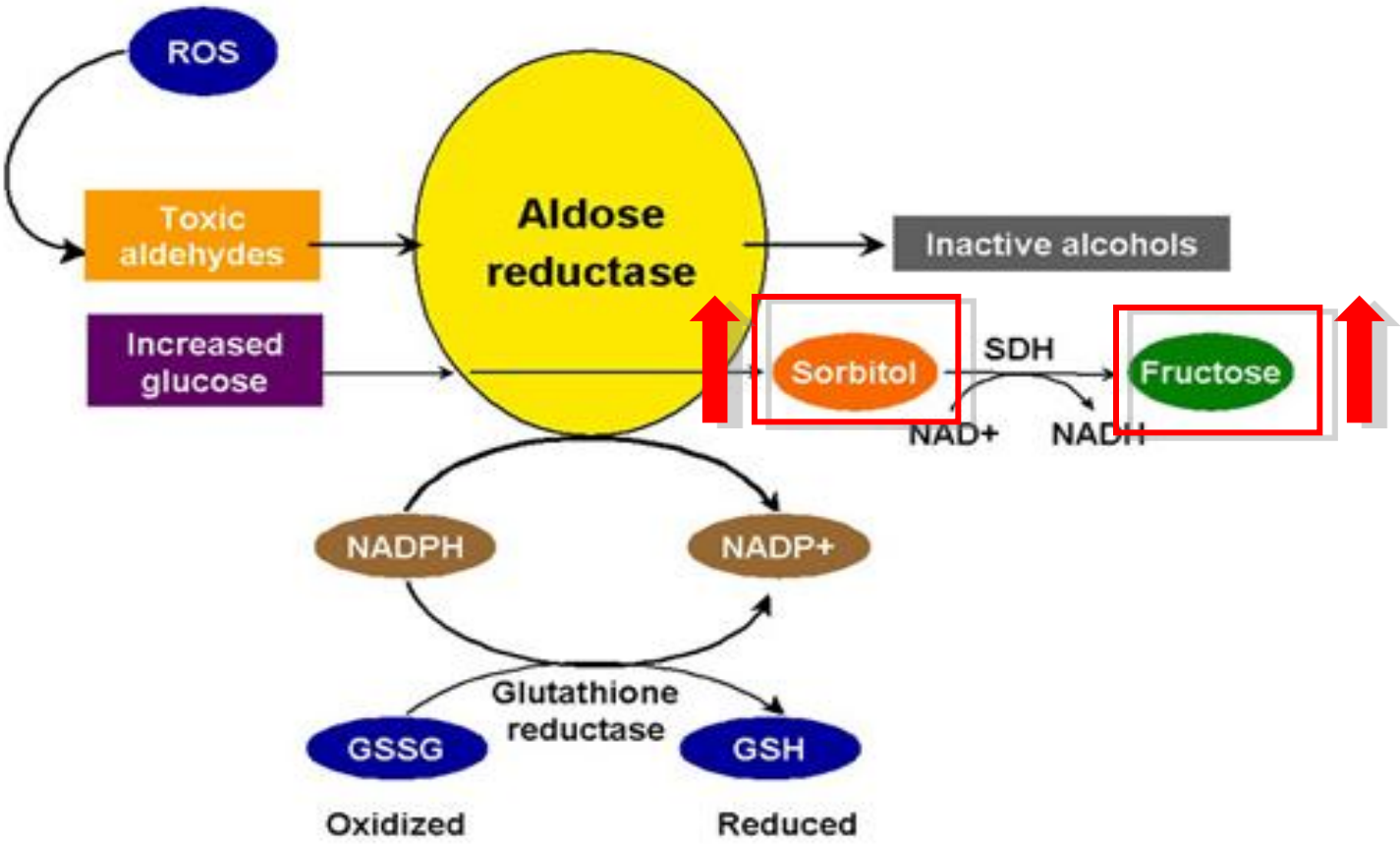
Table 1 Clinicopathologic characteristics of the 12 CCP-RCC patients

Case no.	Sex	Age (y)	Clinical presentation	Tumor size (cm)	Stage	Follow-up (mo)	Disease progression	Operation	Comments
1	M	66	No symptom	0.8	T1a	6	No	RN	Coexist with papillary RCC, Type 1
2	M	62	Right flank pain	2	T1a	9	No	PN	Initial Dx with CC-RCC
3	F	74	No symptom	4.5	T1b	10	No	RN	Coexist with CC-RCC
4	F	68	No symptom	2.5	T1a	11	No	PN	
5	M	69	No symptom	1.6	T1a	15	No	PN	
6	F	36	Abdominal pain	2	T1a	17	No	PN	
7	F	58	No symptom	2.7	T1a	22	No	PN	
8	F	63	ESRD	1.3	T1a	22	No	RN	
9	F	81	ESRD	6	T1b	24	No	RN	Initial Dx with CC-RCC
10	M	18	VHL	3	T1a	27	No	PN	Coexist with multiple CC-RCC
11	M	58	ESRD	2.5	T1a	30	No	RN	
12	M	45	ESRD	1.2	T1a	35	No	RN	

Abbreviations: M, male; F, female; ESRD, end-stage renal disease; VHL, von Hippel-Landau syndrome; RN, radical nephrectomy; PN, partial nephrectomy; Dx, diagnosis.

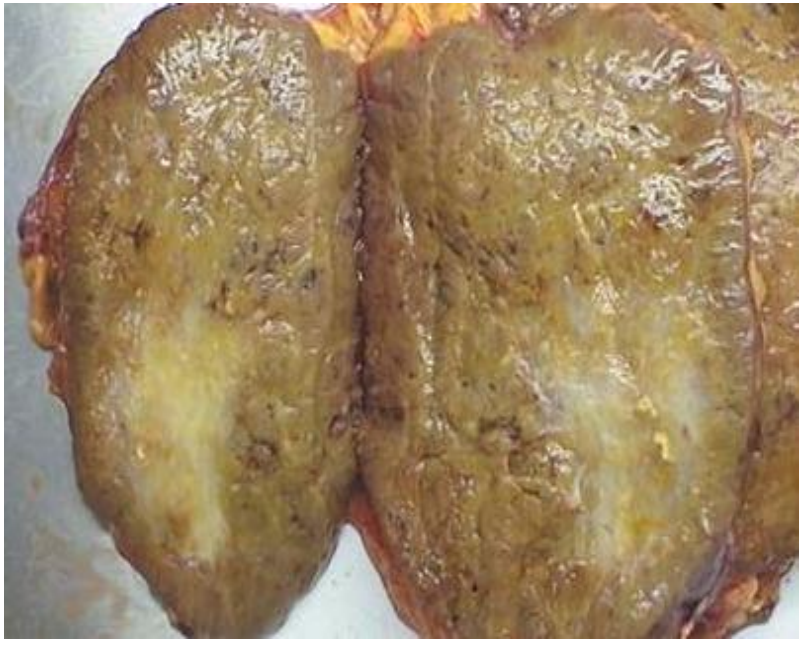
Sorbitol as a Novel Mechanism of Hypoxia-Inducible Factor (HIF) Pathway Activation in Clear Cell Papillary Renal Cell Carcinoma (CCPRCC).

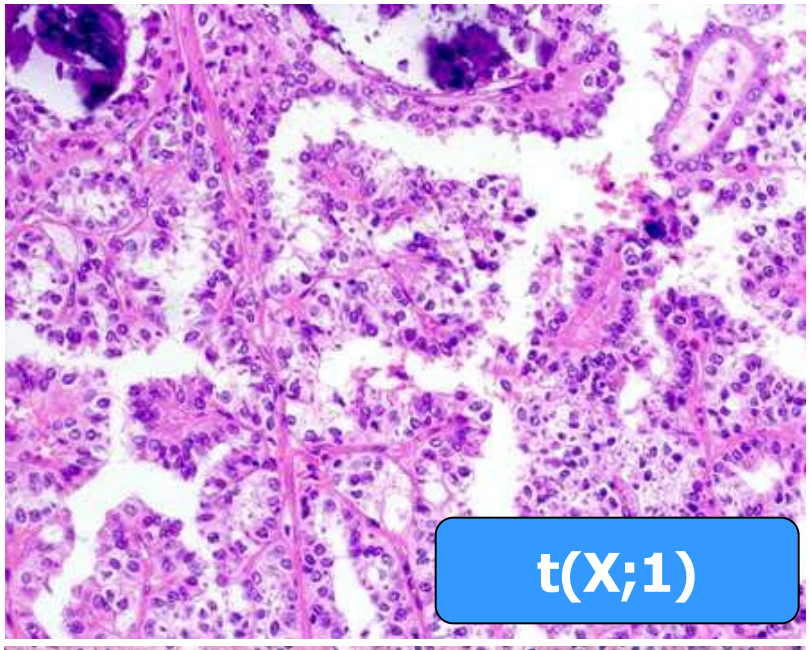
SK Tickoo et al. USCAP 2014

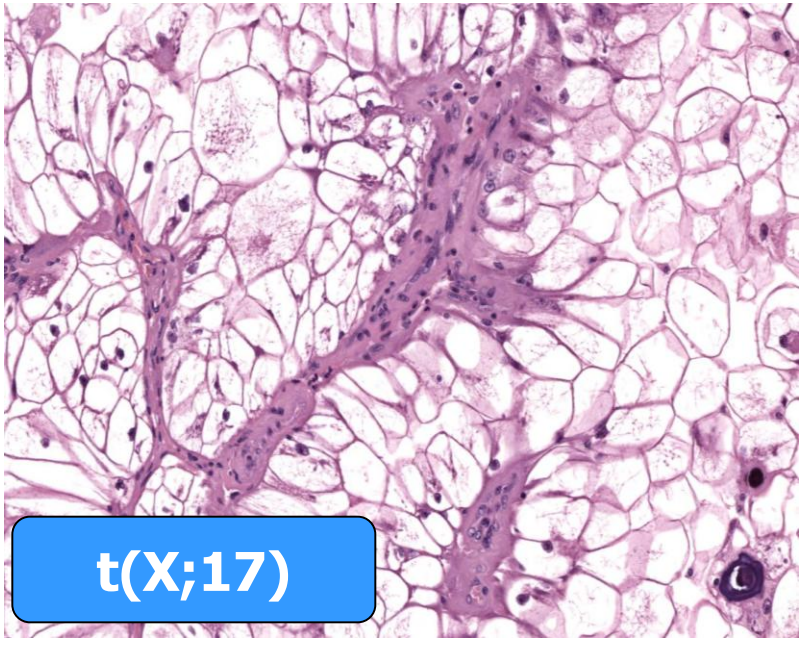


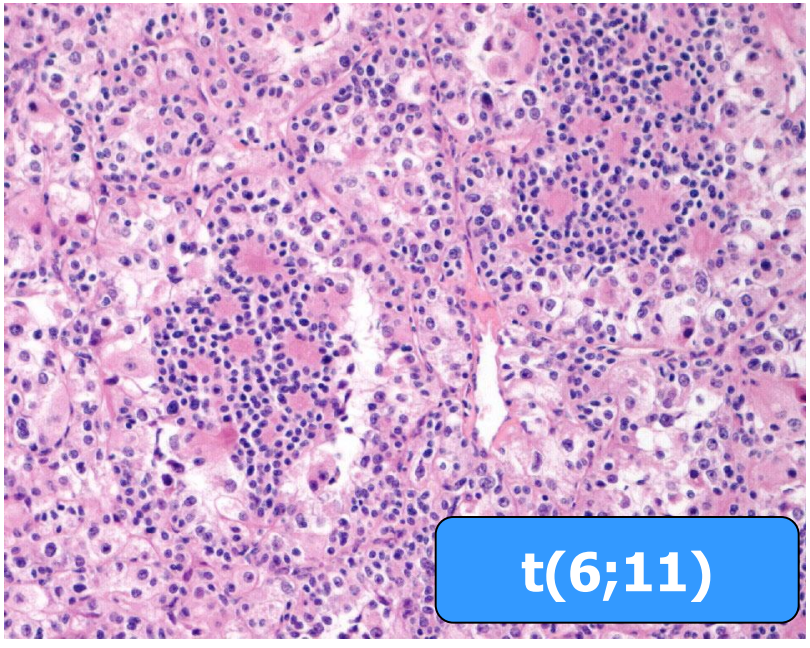
in 9/11 (82%) CCPRCCs

MiTF/TFE family renal translocation carcinomas

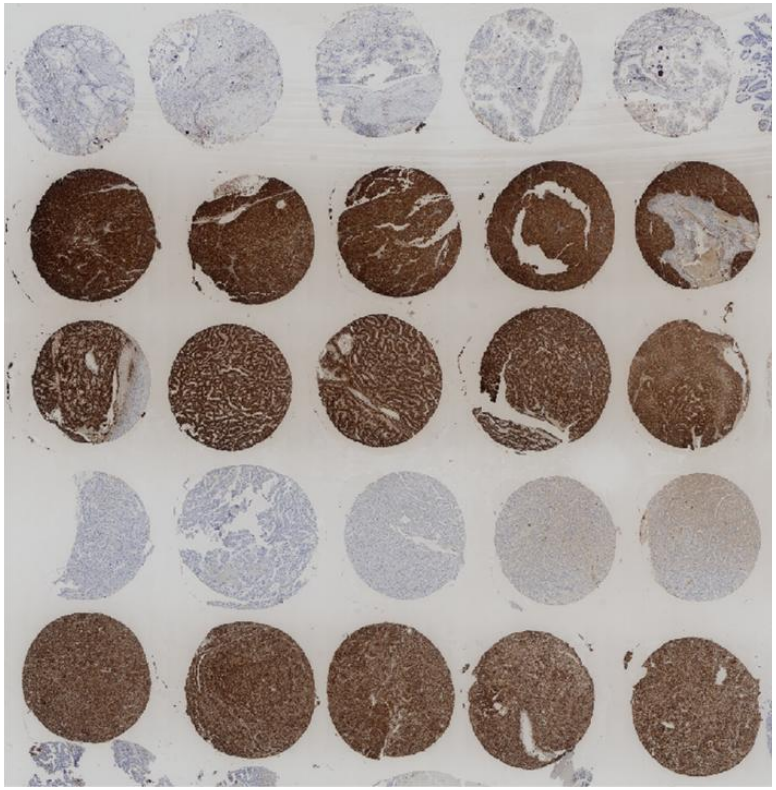








Cathepsin K immunoreactivity distinguishes MiTF/TFE family renal translocation carcinomas from other renal carcinomas



Case #	Genetic	Cathepsin K
1	t(X;1)(p11;q21)	90%
2	t(X;1)(p11;q21)	100%
3	t(X;1)(p11;q21)	80%
4	t(X;1)(p11;q21)	90%
5	t(X;1)(p11;q21)	70%
6	t(X;1)(p11;p34)	Neg
7	t(X;1)(p11;p34)	80%
8	t(X;1)(p11;p34)	Neg
9	t(X;17)(p11;q25)	Neg
10	t(X;3)(p11;q23)	Neg
11	t(6;11)(p21;q12)	100%
12	t(6;11)(p21;q12)	90%
13	t(6;11)(p21;q12)	80%
14	t(6;11)(p21;q12)	100%
15	t(6;11)(p21;q12)	100%
16	t(6;11)(p21;q12)	90%
17	t(6;11)(p21;q12)	90%

Martignoni G, Pea M, Gobbo S, Brunelli M, Bonetti F, Segala D, Pan CC, Netto G, Doglioni C, Hes O, Argani P, Chilosi M

Modern Pathology 2009

Dual-color, Break-apart FISH Assay on Paraffin-embedded Tissues as an Adjunct to Diagnosis of Xp11 Translocation Renal Cell Carcinoma and Alveolar Soft Part Sarcoma

Minghao Zhong, MD, PhD, Patricia De Angelo, MS,† Lisa Osborne, MS,†*
Megan Keane-Tarchichi, MD, Michael Goldfischer, MD,‡ Lisa Edelmann, PhD,§*
Youfeng Yang, MS,‖ W. Marston Linehan, MD,‖ Maria J. Merino, MD,¶
Seena Aisner, MD, and Meera Hameed, MD**

Am J Surg Pathol • Volume 34, Number 6, June 2010

Validation of a *TFE3* Break-apart FISH Assay for Xp11.2 Translocation Renal Cell Carcinomas

Juan-Miguel Mosquera, MD, MSc,† Paola Dal Cin, PhD,*†*
Kirsten D. Mertz, MD,† Sven Perner, MD, PhD,*†‡ Ian J. Davis, MD, PhD,†§‖*
David E. Fisher, MD, PhD,†§‖ Mark A. Rubin, MD,† and Michelle S. Hirsch, MD, PhD*†*

Diagn Mol Pathol • Volume 20, Number 3, September 2011

Usefulness of a break-apart FISH assay in the diagnosis of Xp11.2 translocation renal cell carcinoma

Soo Hee Kim · Yoomi Choi · Hae Yeon Jeong · Kyoungbun Lee · Ji Youn Chae · Kyung Chul Moon

Virchows Arch (2011) 459:299–306

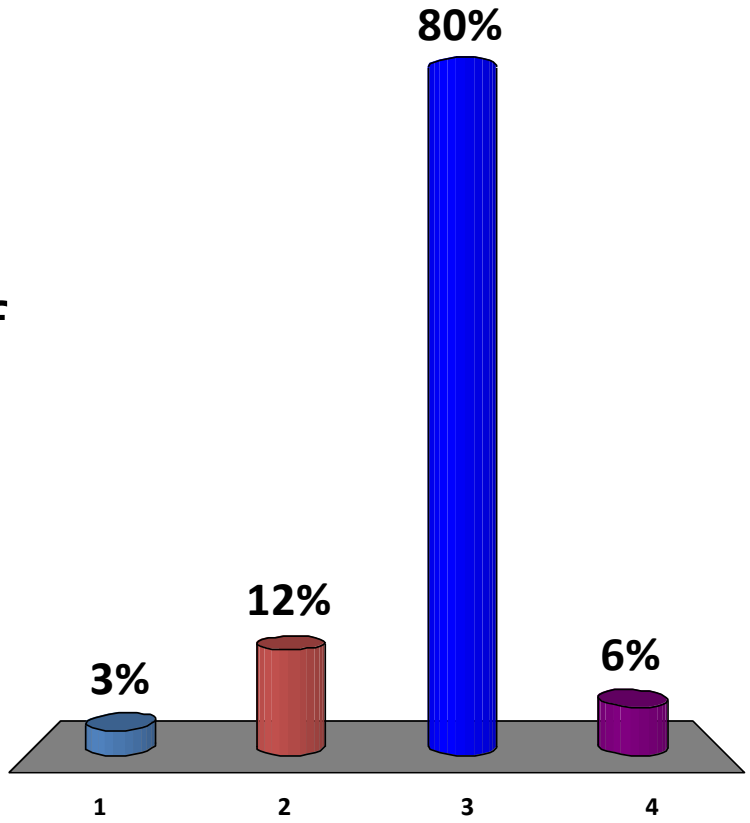
TFE3 Rearrangements in Adult Renal Cell Carcinoma: Clinical and Pathologic Features With Outcome in a Large Series of Consecutively Treated Patients

William R. Sukov, MD, Jennelle C. Hodge, PhD,* Christine M. Lohse, MS,†*
*Bradley C. Leibovich, MD,‡ R. Houston Thompson, MD,‡ Kathryn E. Pearce, BS,**
Anne E. Wiktor, BS, and John C. Cheville, MD**

Am J Surg Pathol • Volume 36, Number 5, May 2012

When should TFE3 and TFEB analysis (IHC and/or FISH) be requested to identify translocation RCC cases?

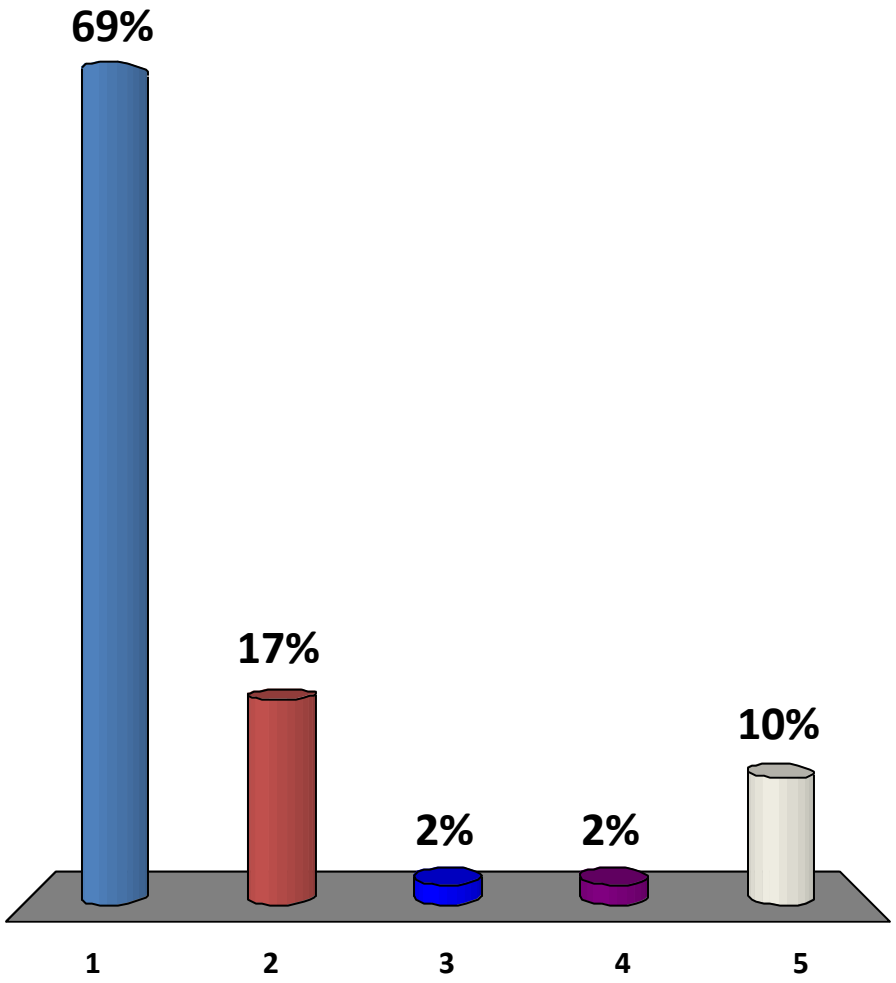
1. When RCC is diagnosed in a patient under 30 years of age
2. When the morphology is suggestive of translocation RCC in a patient older than 30 year of age
3. Both A and B
4. I do not request for TFE3 or TFEB immunostaining



ISUP Consensus Conference, Vancouver 18 march 2012

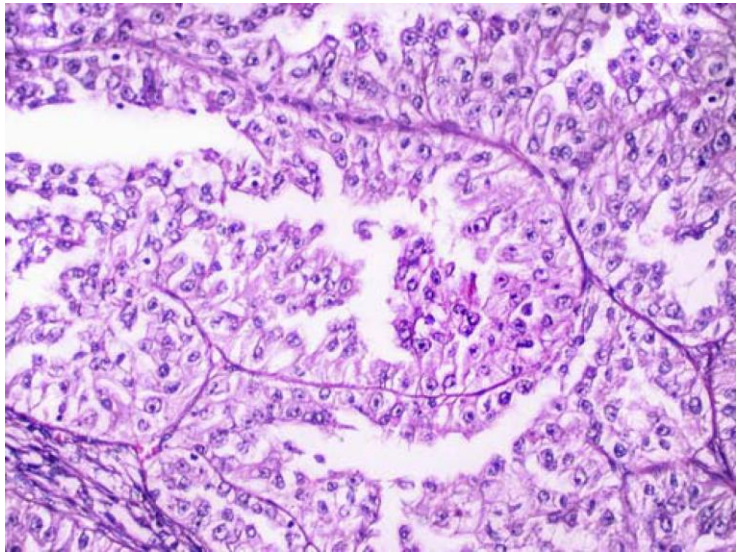
Should t(6;11) RCC be Recognized as an Entity at this time?

1. Yes, include it with Xp11 RCC under MiT Family Translocation RCC
2. Yes, make it its own category
3. No
4. Uncertain even with personal experience/knowledge
5. Not enough personal experience/knowledge



Hereditary leiomyomatosis RCC syndrome associated RCC

- **In 2004 WHO classification viewed as hereditary counterpart of type II PRCC;**
- **HL RCC syndrome aumosomal dominant and associated with germline mutation in the fumarate hydratase gene located at 1q42;**



- **Cutaneous and uterine leiomyomas;**
- **Prominent eosinophilic nucleulus with a clear halo, similar to the cytology of a cytomegalovirus inclusion;**
- **Frequently papillary architecture;**
- **Aggressive behaviour.**

Merino MJ et al Am J Surg Pathol 2007;31; 1578

Grubb RL et al J Urol 2007; 177: 2074

ISUP Consensus Conference on Adult Renal Tumors Vancouver, 18 march 2012

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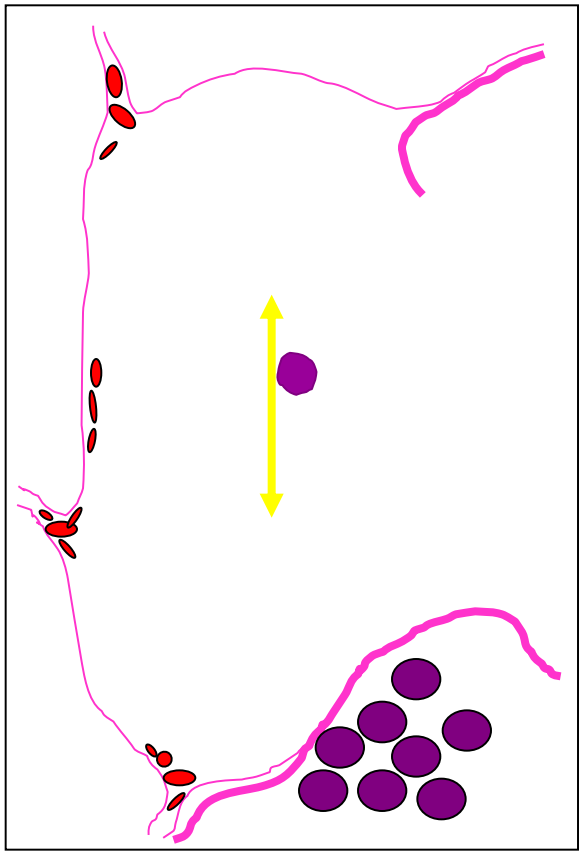
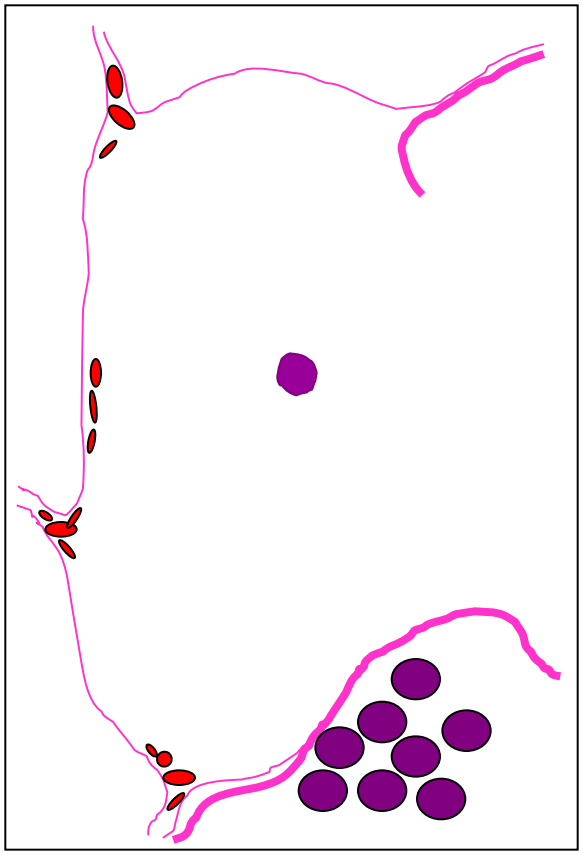
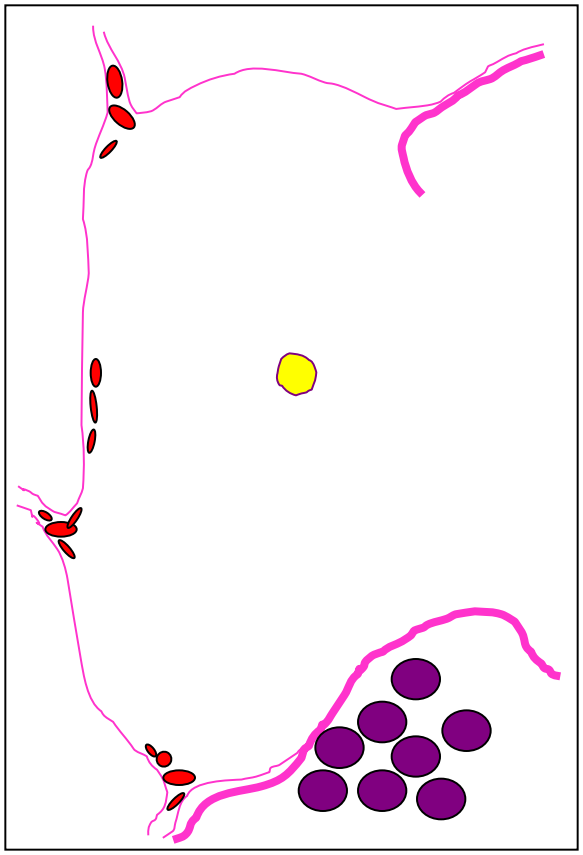
Fuhrman Nuclear Grading



Diameter



Shape



Nucleoli

	Positive	Responses
• What system do you use for grading RCC?		206*
Fuhrman	96%	
World Health Organization	7%	
Broder	0.5%	
Japanese	2%	
Nucleolar	11%	
Other	2%	
• Do you provide a grade for:		204*
Clear cell RCC	100%	
Multilocular cystic RCC	67%	
Papillary adenoma	5%	
Papillary RCC	85%	
Chromophobe RCC	57%	
Oncocytoma	1%	
Collecting duct carcinoma	41%	
Renal medullary carcinoma	31%	
Translocation carcinoma	50%	
Mucinous tubular spindle cell carcinoma	37%	
Tubulocystic carcinoma	37%	
End stage renal disease associated carcinoma	52%	
Unclassified carcinoma	66%	
• How do you assess Fuhrman grade?		204
Most frequent (1^0) pattern	2%	
Highest grade	83%	
Combined most frequent and highest grade	13%	
Provide % of each grade present	2%	
• What is the minimum area of tumor assessed for grading purposes?		194
1 low power field (x10 objective)	37%	
1 high power field (x 40 objective)	41%	
5 high power fields	10%	
Other	12%	
• For Fuhrman grading do you evaluate?		205*
Nucleolar prominence	99%	
Nuclear shape	57%	
Nuclear pleomorphism	79%	
• In case of discordance, which parameter do you put most emphasis on?		205
Nucleolar prominence	68%	
Nuclear shape	2%	
Nuclear pleomorphism	28%	
None	2%	

ORIGINAL ARTICLE

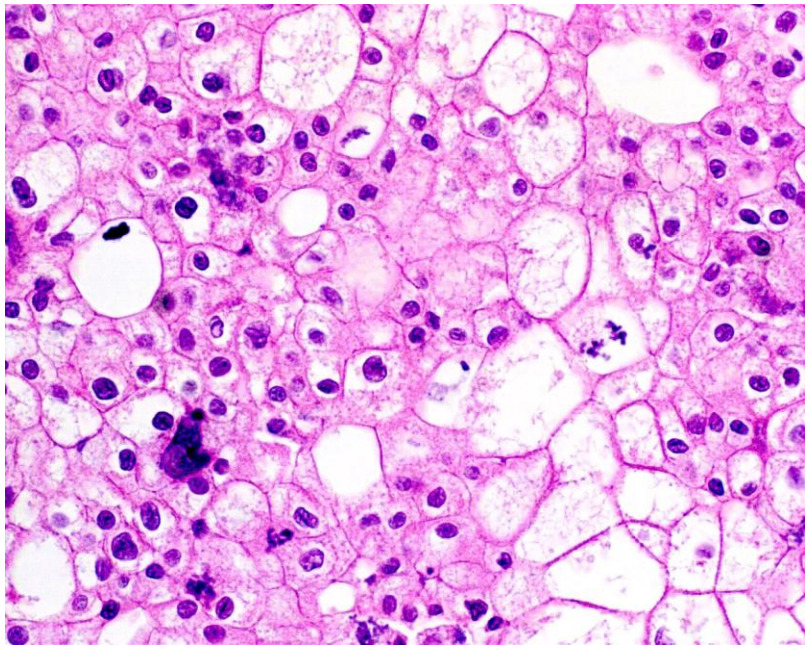
Grading of Clear Cell Renal Cell Carcinoma Should be Based on Nucleolar Prominence

Brett Delahunt, MD, FRCPA, FRCPath,† Dianne Sika-Paotonu, MBiomedSc,†*
Peter B. Bethwaite, PhD, FRCPA, Thomas William Jordan, PhD,*† Cristina Magi-Galluzzi, MD,‡*
Ming Zhou, MD,‡ Hemamali Samaratunga, FRCPA,§ and John R. Srigley, MD, FRCPC‖

(*Am J Surg Pathol* 2011;35:1134–1139)

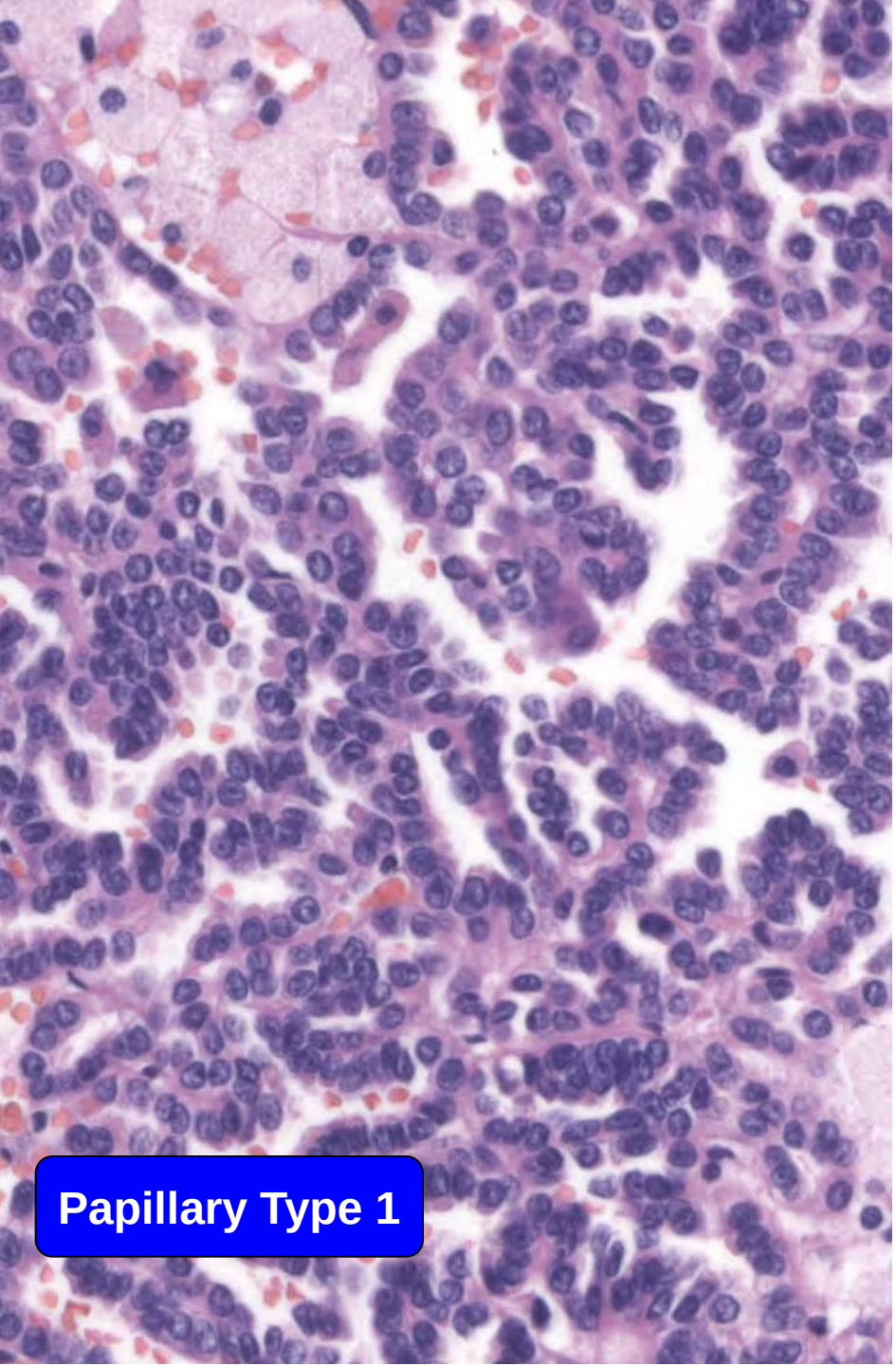
Table 1. Ranges of Nuclear Major Axis for Cases Stratified According to Whole Case and Focal Nucleolar Grade

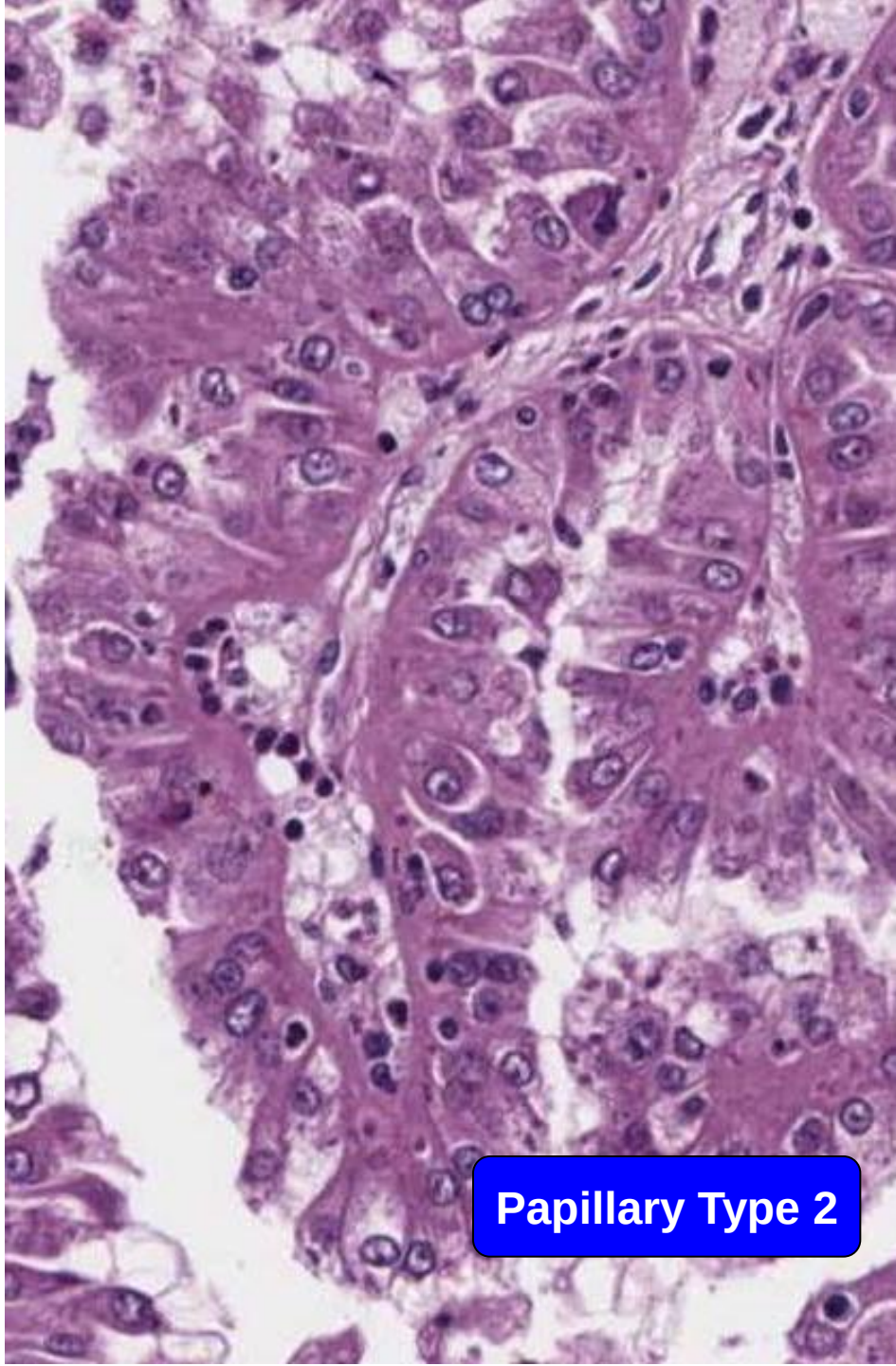
Grade	Whole case nucleolar grade		Focal nucleolar grade	
	Range	Mean	Range	Mean
1	6.49 – 11.42μM	8.04μM	7.20 – 9.63μM	8.57μM
2	6.98 – 13.21μM	8.61μM	6.68 – 11.24μM	8.05μM
3	8.50 – 9.52μM	8.91μM	8.07 – 13.21μM	9.39μM



Fuhrman Grading is not Appropriate for Chromophobe Renal Cell Carcinoma

Delahunt B, Sika-Paotonu D, Bethwaite PB, McCredie MR, Martignoni G, Eble JN, Jordan TW Am J Surg Pathol 2007; 31: 957-60.

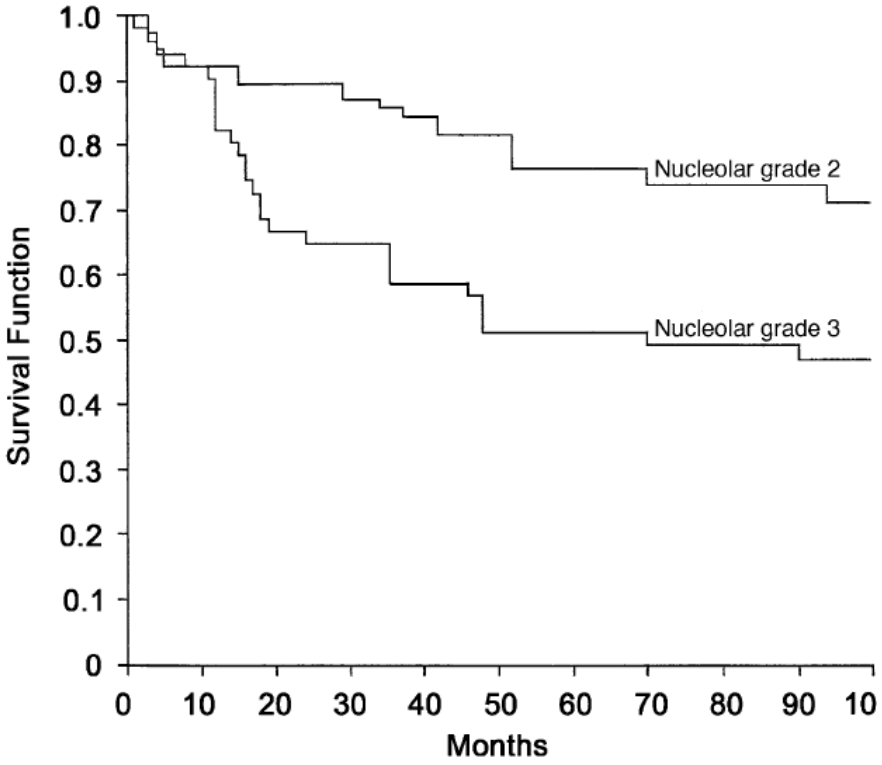

Papillary Type 1


Papillary Type 2

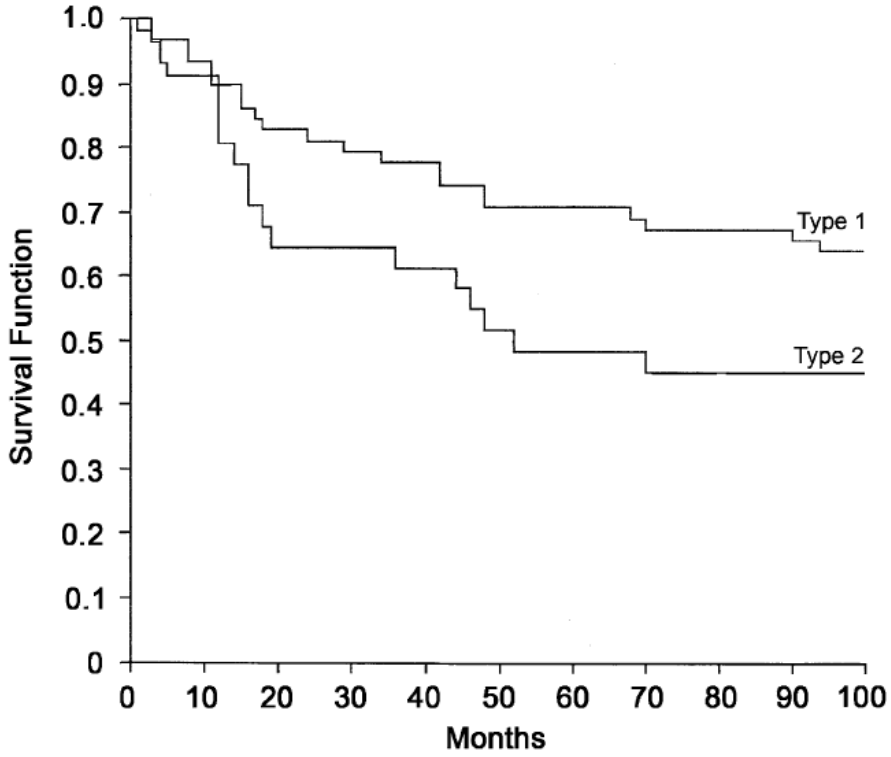
Nucleolar Grade But Not Fuhrman Grade is Applicable to Papillary Renal Cell Carcinoma

Dianne Sika-Paotonu, BSc, Peter B. Bethwaite, PhD, FRCPA,**
Margaret R. E. McCredie, PhD,† T. William Jordan, PhD, and Brett Delahunt, MD, FRCPA**

SURVIVAL / NUCLEOLAR GRADING



SURVIVAL / HISTOTYPE



Am J Surg Pathol 2006;30:1091

ISUP Consensus Conference on Adult Renal Tumors Vancouver, 18 march 2012

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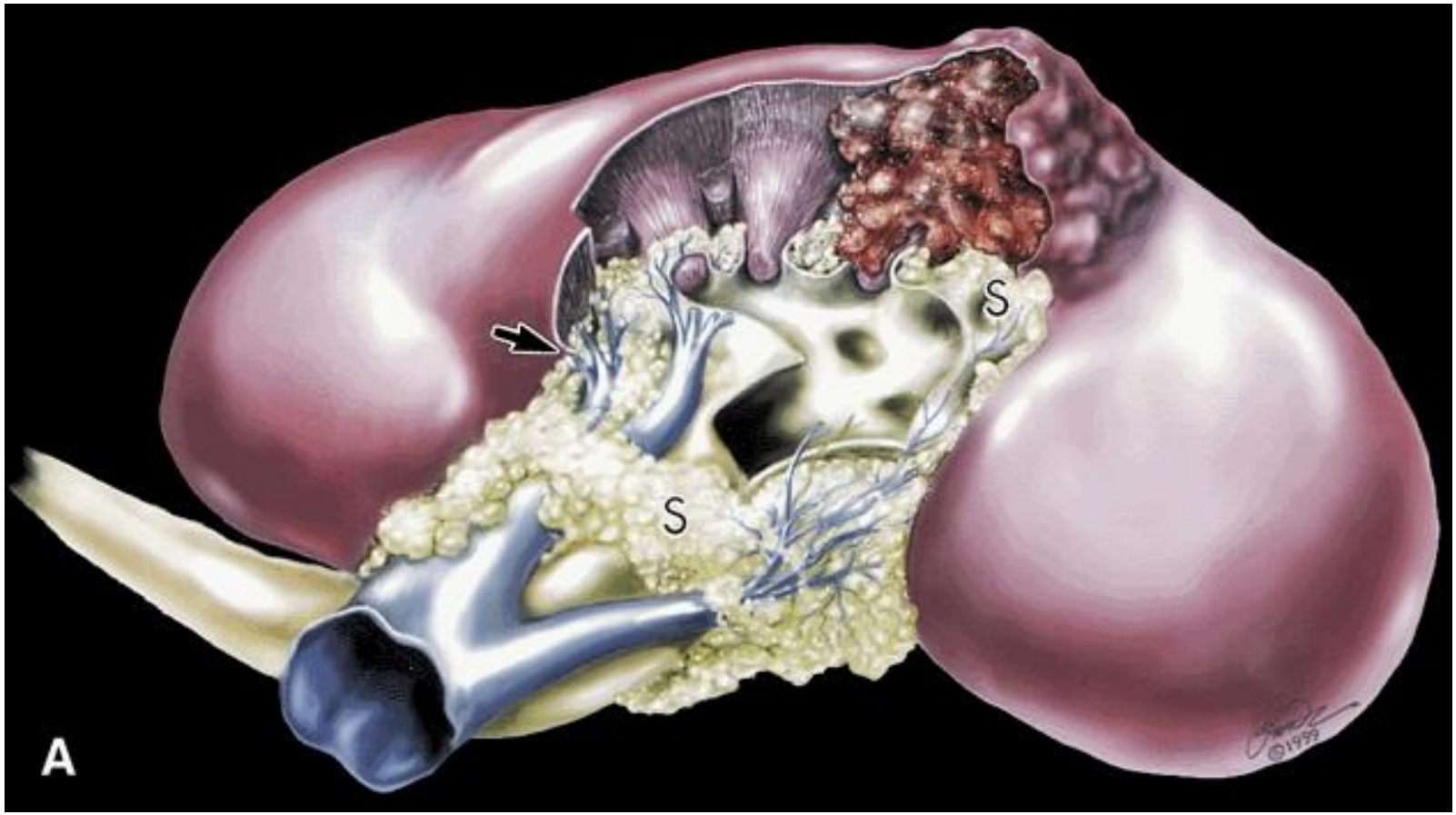
Renal sinus involvement in RCC



Bonsib SM et al. Am J Surg Pathol 2000; 24: 451-458

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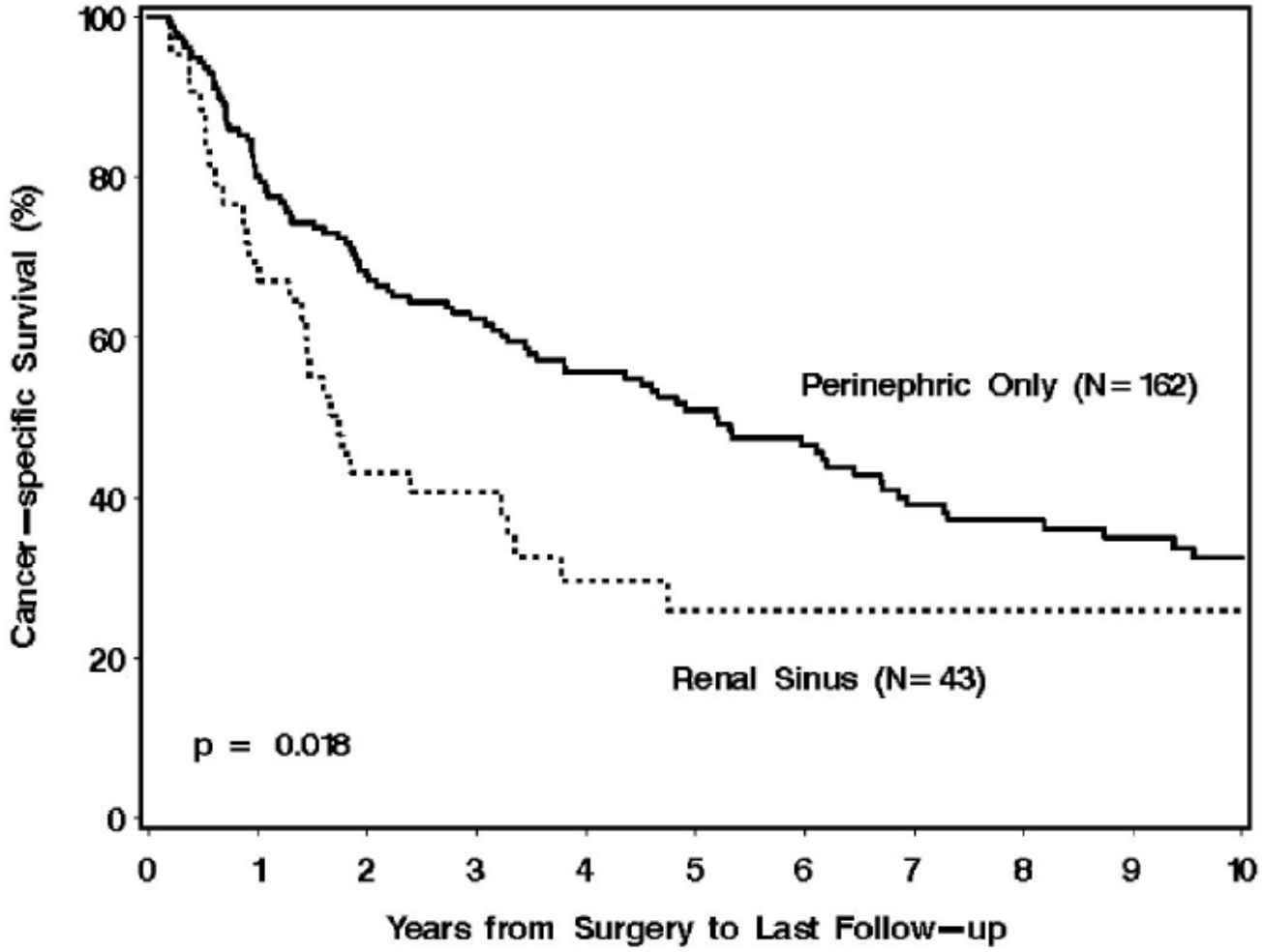

Thompson RH et al. J Urol 2005; 174: 1218-1221

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TABLE 1. Summary of Online Survey and Conference Results on Biomarkers in RCC

	% of Responses
Questions with consensus online responses	
• Immunohistochemistry is occasionally/ sometimes used for histologic subtyping	86.9
• Immunohistochemistry is used before diagnosing unclassified RCC	80.5
• Biomarkers and cytogenetics are currently not used for prognostication	94, 98
• VHL mutations/LOH analyses are not performed in diagnostic practice	83.1
• Predictive markers are not required by clinical colleagues	83.8
• FISH is the most commonly used molecular platform	66.2
• CAIX does not need to be identified in tumor tissue	66.1
Questions with consensus conference responses	
• TFE3 and TFEB analysis (immunohistochemistry and/or FISH) should be requested when RCC is diagnosed in a patient under 30 years of age, and/or when the morphologic appearances are suggestive	79.6
• Pax 2 and/or Pax 8 are the most useful markers in confirming a renal primary	70.9

Tan et al. *Am J Surg Pathol* 2013;37:1518-1531

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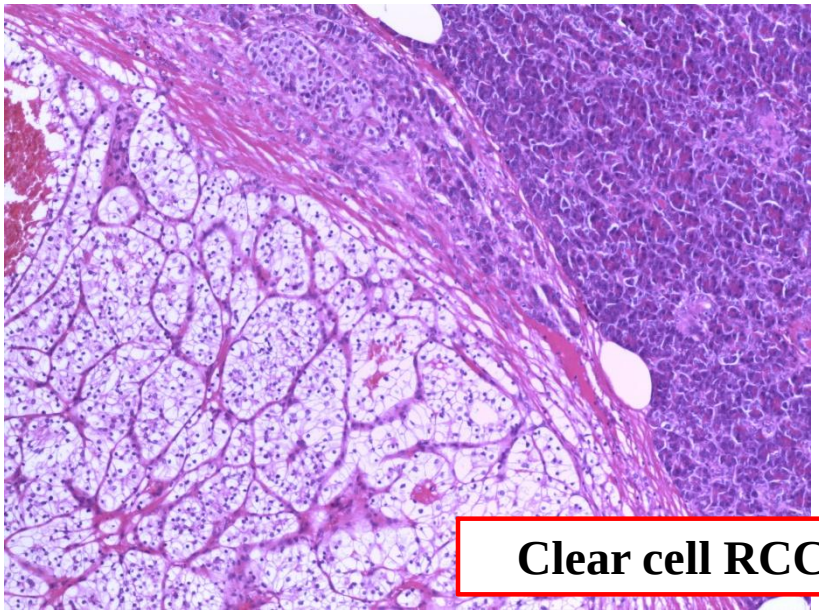
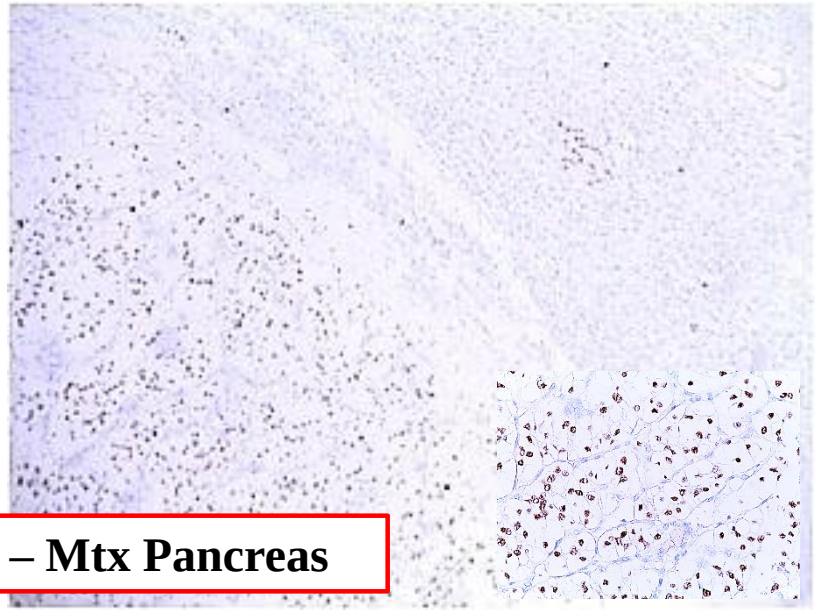
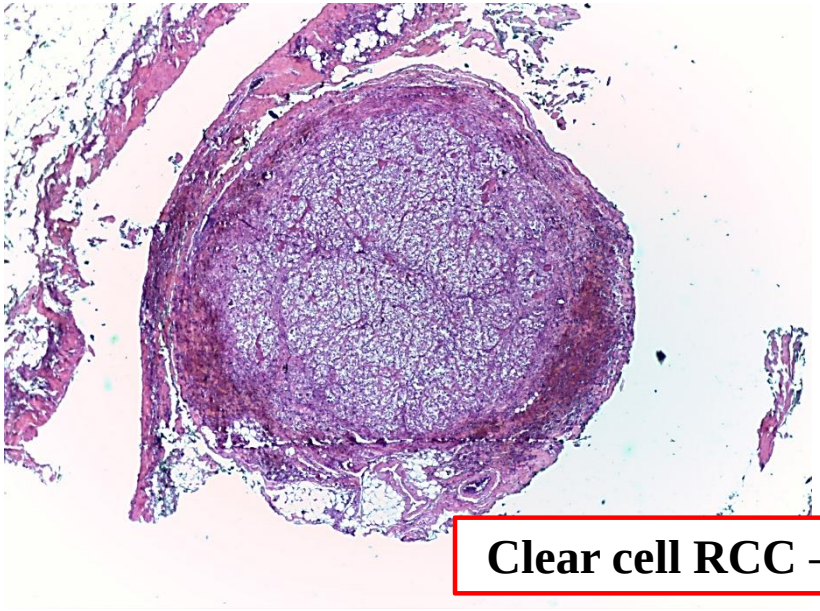
Tan et al. *Am J Surg Pathol* 2013;37:1518-1531

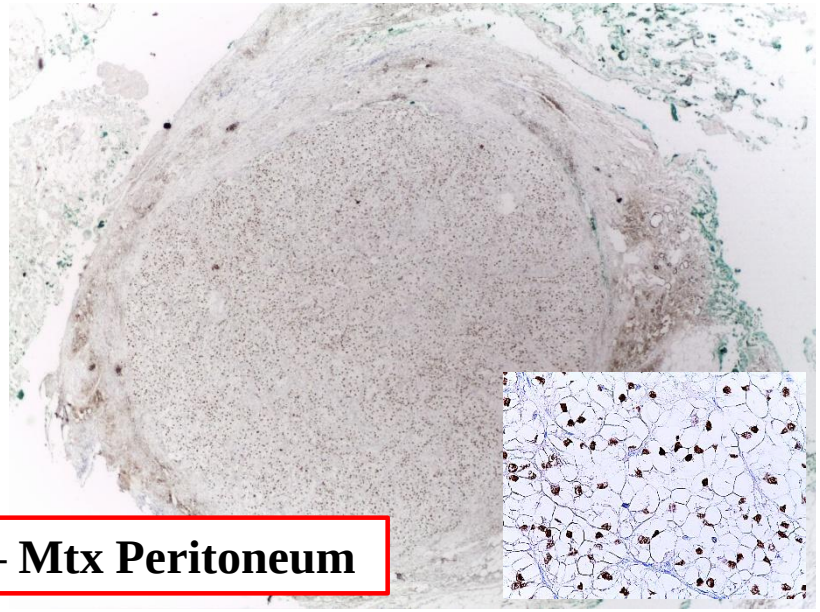
•PAX8





Clear cell RCC – Mtx Pancreas





Clear cell RCC – Mtx Peritoneum

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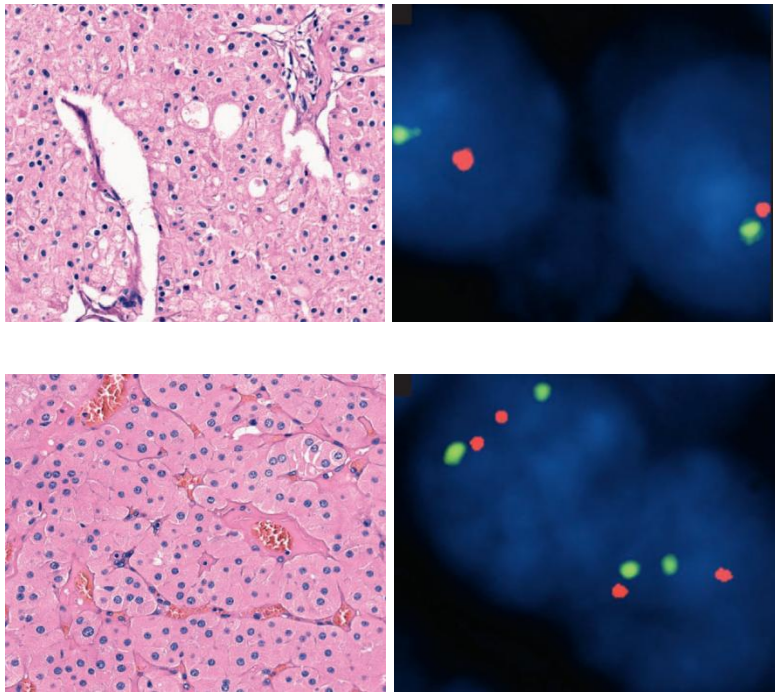
Tan et al. *Am J Surg Pathol* 2013;37:1518-1531

Diagnostic Usefulness of Fluorescent Cytogenetics in Differentiating Chromophobe Renal Cell Carcinoma From Renal Oncocytoma

A Validation Study Combining Metaphase and Interphase Analyses

Matteo Brunelli, MD, PhD,[1] Brett Delahunt, MD,[2] Stefano Gobbo, MD,[1] Regina Tardanico, MD,[3] Albino Eccher, MD,[1] Samantha Bersani, BSc,[1] Paolo Cossu-Rocca, MD,[4] Claudia Parolini, BSc,[1] Piera Balzarini, BSc,[3] Fabio Menestrina, MD,[1] Liang Cheng, MD,[5] John Nelson Eble, MD,[5] and Guido Martignoni, MD[1]

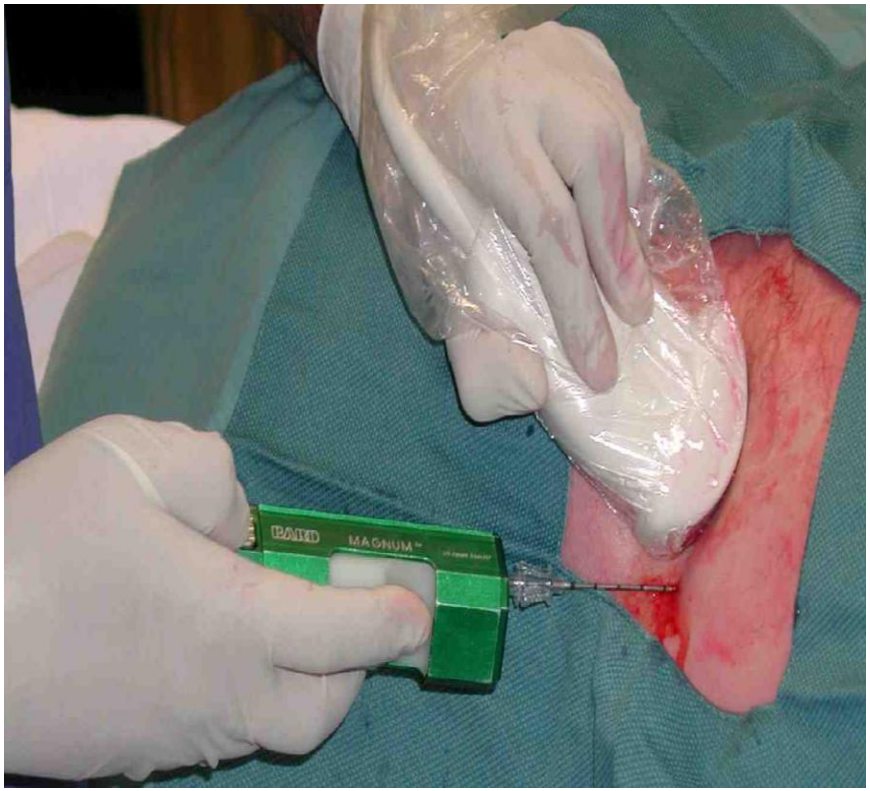


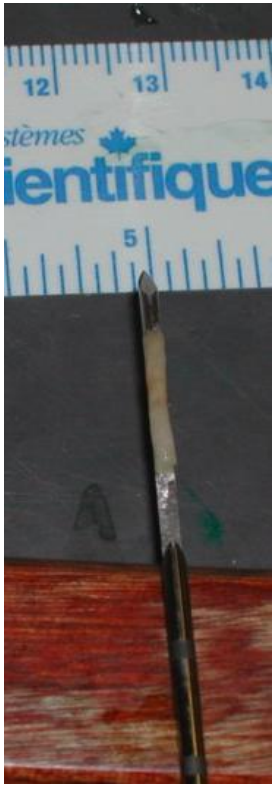
Chromophobe RCC and Renal Oncocytoma: Combining Results From Interphase FISH and Metaphase Karyotyping Analyses

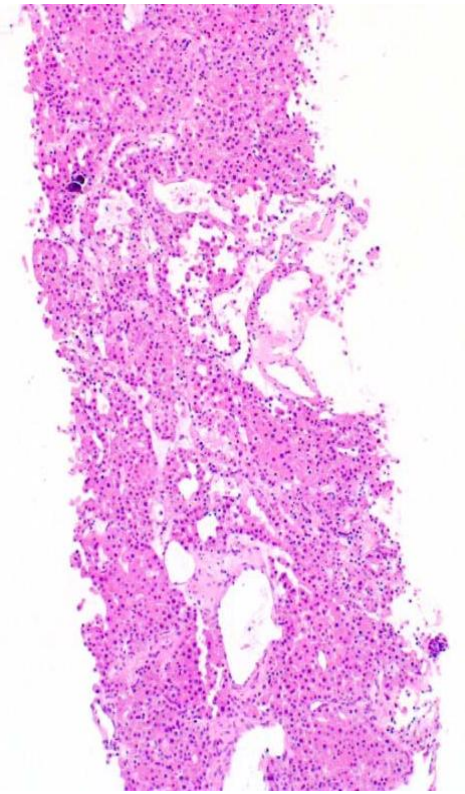
	FISH/Chromosome					
	1	2	6	10	17	Karyotyping
RCC						
1	Loss	Loss	Loss	Loss	Loss	37,X,–X,–1,–2,–6,–7,–12,–15,–21,–22[2]
2	Loss	Loss	Loss	Loss	Loss	38,X,–Y,–3,–8,–9,–10,–11,–13,–22[2]
3	Loss	No loss	No loss	No loss	Loss	38-40,X,–X,–1,–2,–4,–5,–6,–7,–10,–17,–22[2]
4	Loss	No loss	Loss	Loss	Loss	No growth
5	Loss	Loss	Loss	Loss	Loss	No growth
6	No loss	No loss	No loss	Loss	Loss	No growth
7	No loss	No loss	Loss	Loss	No loss	No growth
8	No loss	No loss	No loss	Loss	Loss	73<4n>,XX,YY,–1–1,–2,–3,–6,–9,–10,–11,–12,–14,–15,–16,–17, –18,–19,–20,–21,–22,–22[1]
9	No loss	Loss	Loss	Loss	Loss	78-90<4n>
10	No loss	Gains	No loss	No loss	Gains	78-90<4n>,XX,–Y,–Y[5]/46,XY[10]
11	Loss	Loss	Loss	Loss	Loss	46,XX[2]
Renal oncocytoma						
12	No loss	No loss	No loss	No loss	No loss	46,XX,t(6;15)(p21;q21),t(6;9)(p12;p24)[2]
13	No loss	No loss	No loss	No loss	No loss	46,XY[2]
14	No loss	No loss	No loss	No loss	No loss	46,XX,del(9)(q21q22)(20)[2]
15	No loss	No loss	No loss	No loss	No loss	47,XX,+7[20]
16	No loss	No loss	No loss	No loss	No loss	46,XY[20]
17	No loss	Loss	No loss	No loss	No loss	38,X,–Y,–1,–3,–4,–5,–11,–11,–14,–16,+add(17)(q25),–21[1]/46,XY[5]
18	No loss	Loss	No loss	Loss	No loss	46,XY[20]
19	No loss	No loss	No loss	Loss	No loss	46,XX,der(12)t(12;?)(q12;?)[20]
20	No loss	No loss	No loss	No loss	No loss	46,XY[2]
21	Loss	No loss	No loss	No loss	No loss	46,XY,t(3;?19)(p11;?p13),der(11)t(3;11)(p14;p15)[2]
22	Loss	No loss	No loss	No loss	No loss	X,–Y,+inv(7)(p22;q11),+12,+17,+20[2]/46,XY,del(12)(q14q21)[2]
23	Loss	No loss	No loss	No loss	No loss	46,XY[2]

Am J Clin Pathol 2010;133:116-126

Core biopsies nei tumori renali







Rationale for Percutaneous Biopsy and Histologic Characterisation of Renal Tumours

Alessandro Volpe[a,*], *Antonio Finelli*[b], *Inderbir S. Gill*[c], *Michael A.S. Jewett*[b], *Guido Martignoni*[d], *Thomas J. Polascik*[e], *Mesut Remzi*[f], *Robert G. Uzzo*[g]

Table 2 – Outcomes of needle core biopsies of renal masses in recent series

	No. of tumours biopsied	Mean tumour size, cm	No. of pathologically confirmed tumours	Image guidance	Needle size, gauge	No. of biopsies taken	Diagnostic biopsies, %	Accuracy for malignancy, %	Accuracy for RCC subtyping, %	Accuracy for grading, %	Impact on management, %
Neuzillet et al. [8]	88	2.8	62	CT	18	≥2	91	92	92	69.8	47.8
Shannon et al. [9]	235	2.9	108	CT/US	18	1–4	78	100	98	NR	NR
Schmidbauer et al. [10]	78	4.0	78	CT	18	2–3	97	Sensitivity 93.5 Specificity 100	91	76	24.3*
Lebret et al. [11]	119	3.3	64	CT/US	18	1–4	79	86	86	46/74**	30.4
Maturen et al. [12]	152	4.1	106	CT/US	18	2–4	96	Sensitivity 97.7 Specificity 100	NR	NR	60.5
Volpe et al. [13]	100	2.4	20	CT/US	18	≥2	84	100	100	66.7/75**	43
Wang et al. [14]	110	2.7	36	CT/US	18	≥2	90.9	100	96.6	NR	NR
Veltri et al. [15]	103	3.4	40	US	18	1–2	100	NR	93.2	NR	68.9
Leveridge et al. [16]	345	2.5	74	CT/US	18	≥2	80.6	99.7	88	63.5	NR

RCC = renal cell carcinoma; CT = computed tomography; US = ultrasound; NR = not reported.

* Retrospective evaluation.

** Four-tiered Fuhrman classification/two-tiered simplified Fuhrman classification (Fuhrman I–II = low grade; Fuhrman III–IV = high grade).

CONCLUSIONI

- Classificazione sec. ISUP
- Grading sec. ISUP
- TNM 2010
- Immunoistochimica e FISH

"The Verona Group" 2000

"The Verona Group" 2014

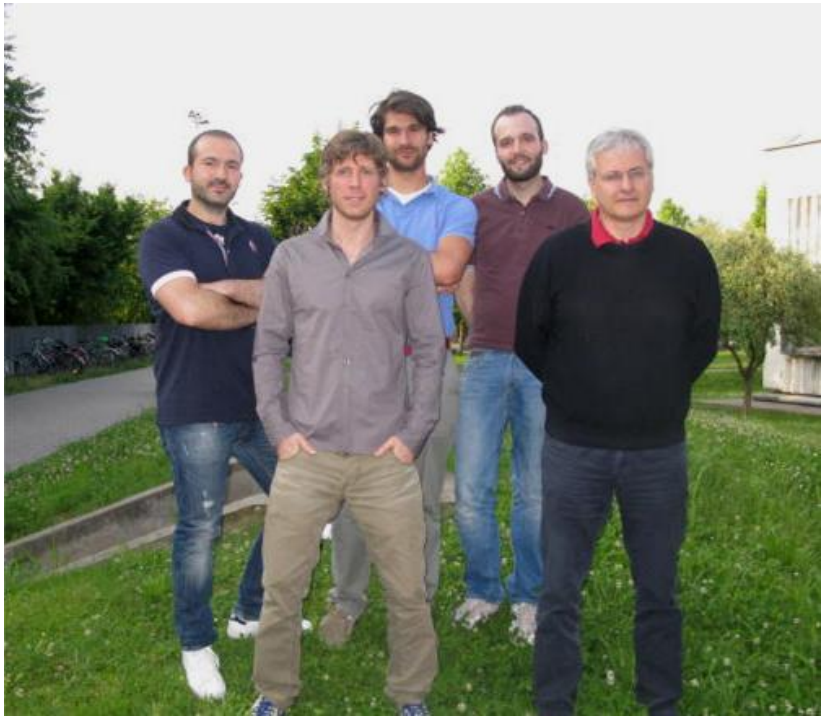


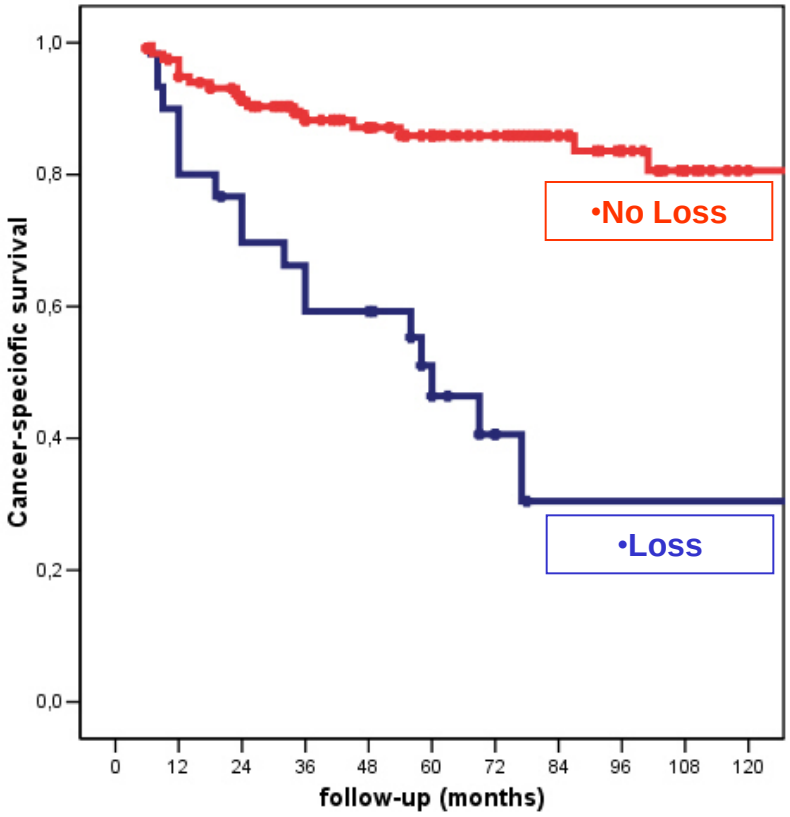
TABLE 1. Summary of Online Survey and Conference Results on Biomarkers in RCC

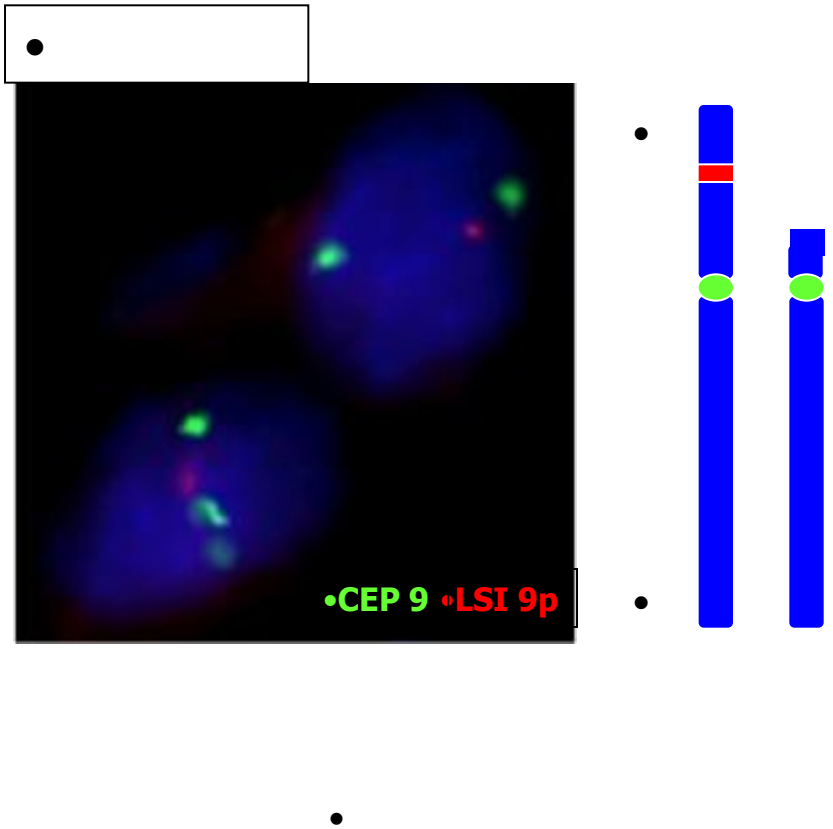
	% of Responses
Questions with consensus online responses	
• Immunohistochemistry is occasionally/ sometimes used for histologic subtyping	86.9
• Immunohistochemistry is used before diagnosing unclassified RCC	80.5
• Biomarkers and cytogenetics are currently not used for prognostication	94, 98
• VHL mutations/LOH analyses are not performed in diagnostic practice	83.1
• Predictive markers are not required by clinical colleagues	83.8
• FISH is the most commonly used molecular platform	66.2
• CAIX does not need to be identified in tumor tissue	66.1
Questions with consensus conference responses	
• TFE3 and TFEB analysis (immunohistochemistry and/or FISH) should be requested when RCC is diagnosed in a patient under 30 years of age, and/or when the morphologic appearances are suggestive	79.6
• Pax 2 and/or Pax 8 are the most useful markers in confirming a renal primary	70.9

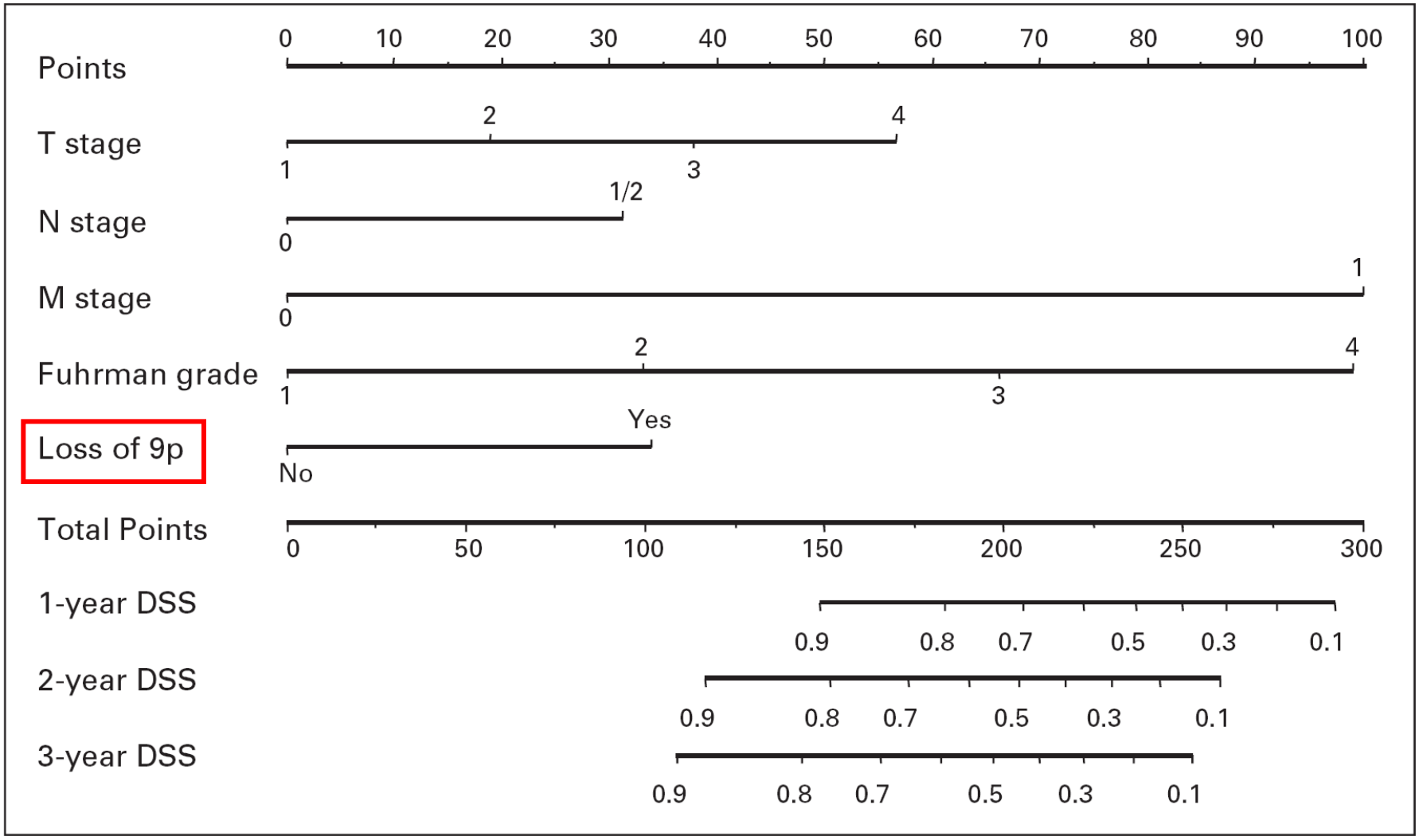
Tan et al. *Am J Surg Pathol* 2013;37:1518-1531

Loss of chromosome 9p is an independent prognostic factor in patients with clear cell renal cell carcinoma

Matteo Brunelli[1], Albino Eccher[1], Stefano Gobbo[1], Vincenzo Ficarra[2], Giacomo Novara[2], Paolo Cossu-Rocca[3], Franco Bonetti[1], Fabio Menestrina[1], Liang Cheng[4], John N Eble[4] and Guido Martignoni[1]







•Cytogenetic profile predicts prognosis of patients with clear cell renal cell carcinoma
•Klatte T, Rao PN et al. J Clin Oncol 2009;10;27:746

TABLE 1. Summary of Online Survey and Conference Results on Biomarkers in RCC

	% of Responses
Questions with consensus online responses	
• Immunohistochemistry is occasionally/ sometimes used for histologic subtyping	86.9
• Immunohistochemistry is used before diagnosing unclassified RCC	80.5
• Biomarkers and cytogenetics are currently not used for prognostication	94, 98
• VHL mutations/LOH analyses are not performed in diagnostic practice	83.1
• Predictive markers are not required by clinical colleagues	83.8
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• TFE3 and TFEB analysis (immunohistochemistry and/or FISH) should be requested when RCC is diagnosed in a patient under 30 years of age, and/or when the morphologic appearances are suggestive	79.6
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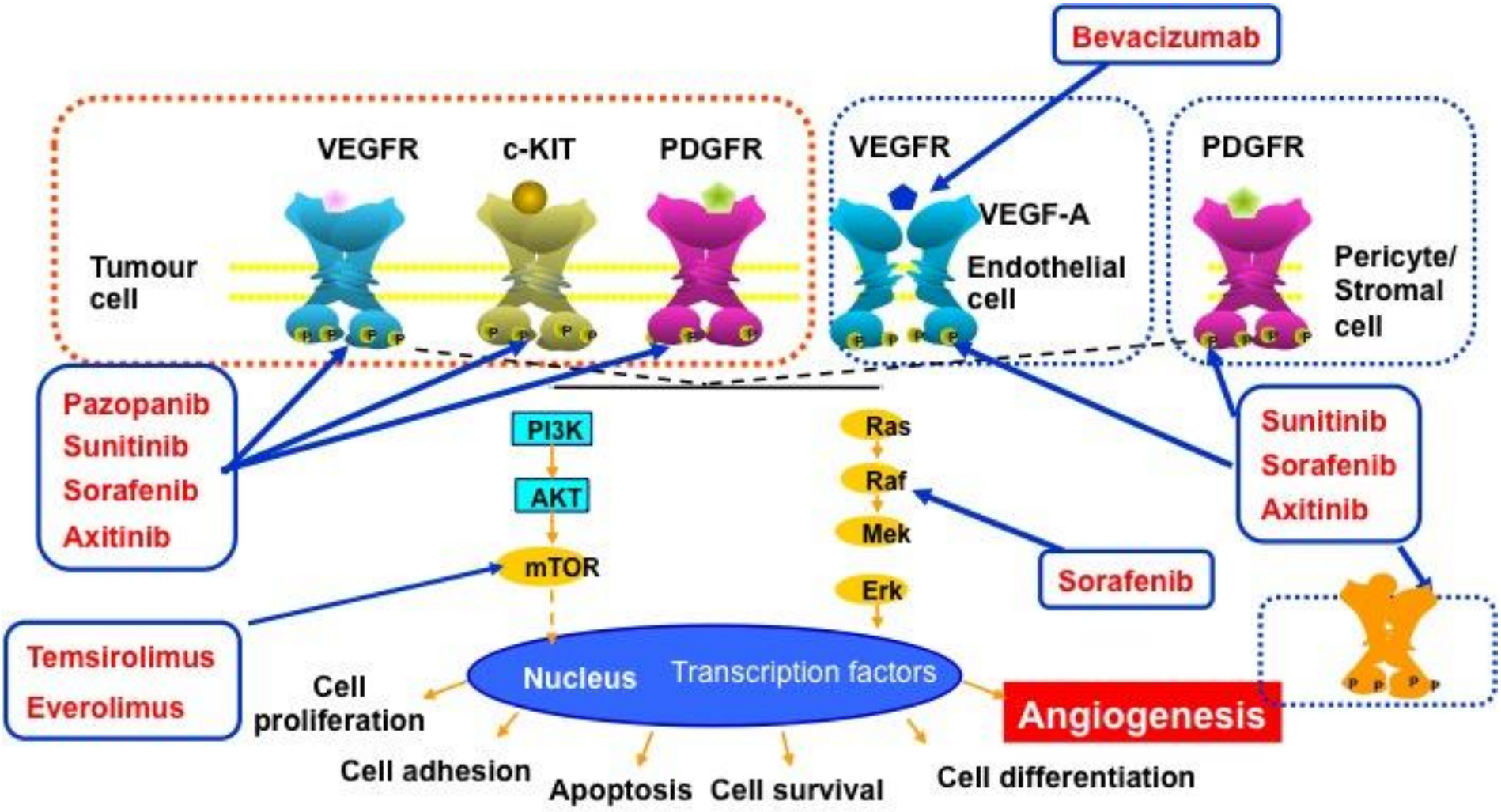
•Targeted therapy - Angiogenesis



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RUOLO DEL PATOLOGO

PASSATO

PRESENTE

FUTURO

STRATEGIE TERAPEUTICHE:

TERAPIA CHIRURGICA

NEFRECTOMIA RADICALE

"OPEN" vs "LAPARO"

NEFRECTOMIA PARZIALE

"OPEN" vs "LAPARO"

ABLAZIONE CON RADIOFREQUENZA

CRIOABLAZIONE

WAIT AND SEE

TERAPIA MEDICA

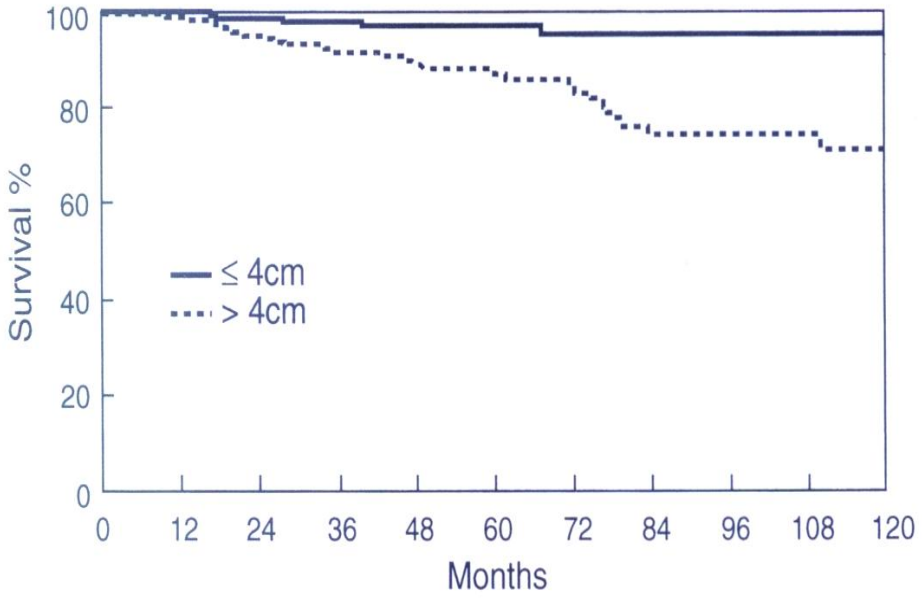
IMMUNOTERAPIA

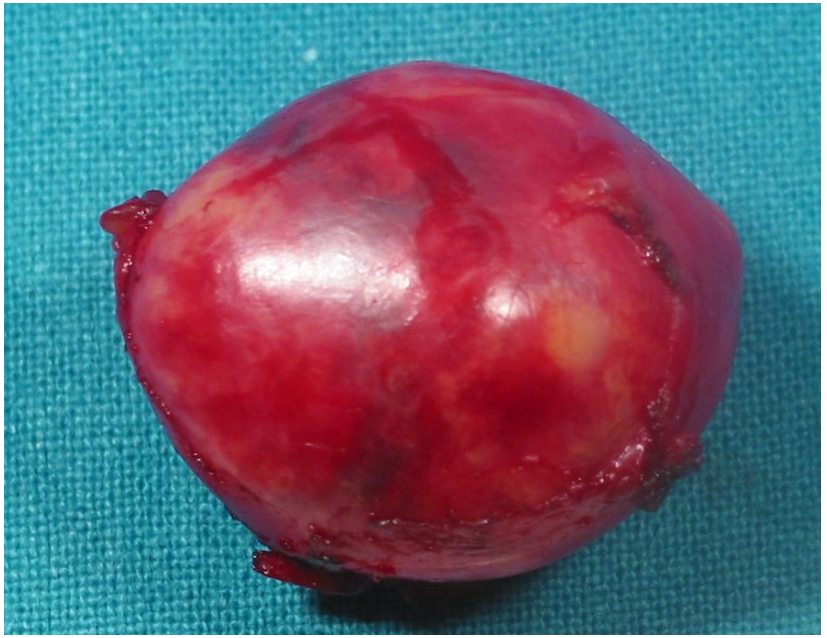
CHEMIOTERAPIA

"TARGETED THERAPIES"

- SORAFENIB
- TEMSIROLIMUS
- SUNITINIB
- altre…

DEFINIZIONE





Hafez KS et al. J. Urol. 1999; 162: 1930-1933

Benign Lesions After Partial Nephrectomy for Presumed Renal Cell Carcinoma in Masses 4 cm or Less: Prevalence and Predictors in Korean Patients

Benign lesions	81 (21.5%)
Angiomyolipoma	35 (9.3%)
Oncocytoma	11 (2.9%)
Cyst	26 (6.9%)
Others	9 (2.4%)
Renal cell carcinoma	295 (78.5%)
Conventional	238 (63.3%)
Chromophobe	14 (3.7%)
Papillary	26 (6.9%)
Cystic	17 (4.5%)

- 376 pazienti
- Nefrectomia parziale
- Tumori ø ≤ 4 cm

Jeon et al. Urology 2010; 76: 574-9

BIOPSIE

- Guida
- Aghi
- FNAB versus biopsia
- Sicurezza
- Impianti lungo il tramite
- Sanguinamento
  - Accuratezza diagnostica - sensibilità
  - Accuratezza diagnostica - specificità
- Falsi negativi
- Accuratezza nell'assegnazione del grading
- Biopsia delle masse cistiche complesse

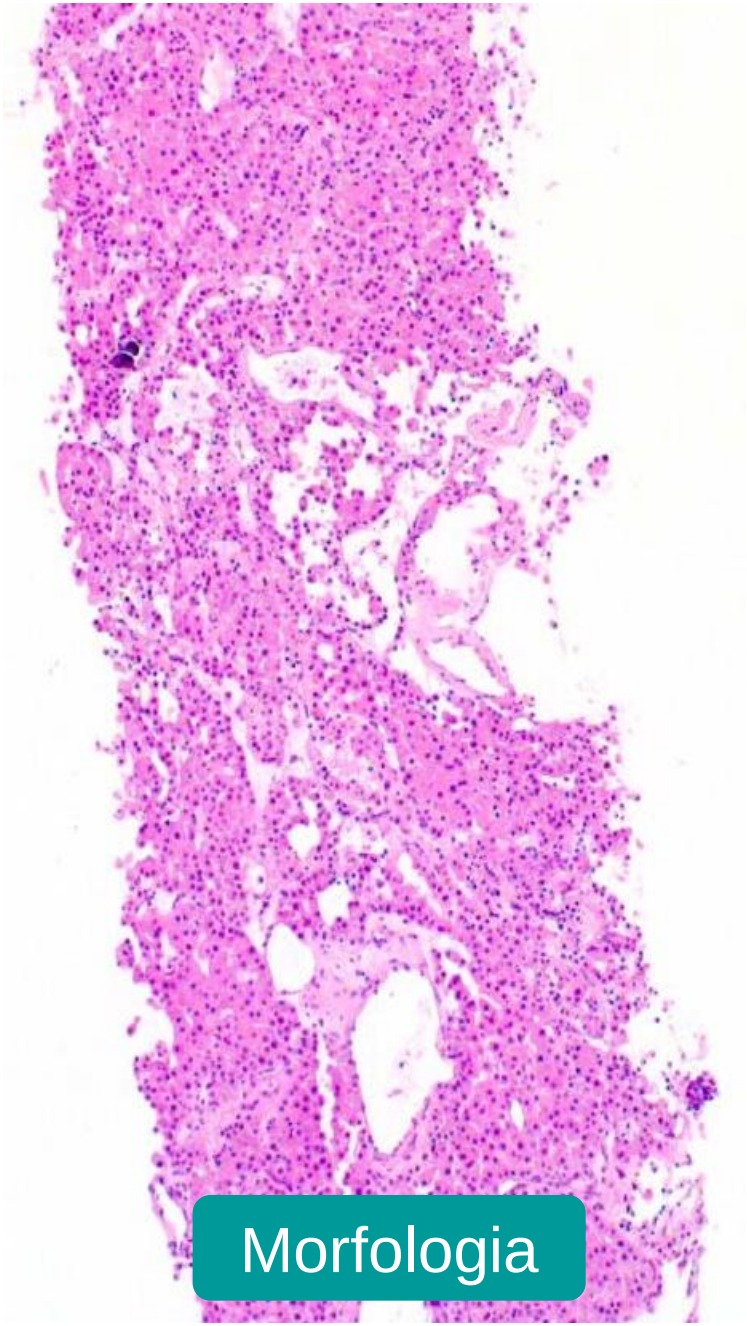
Variabili	Pazienti (n=56)
Età mediana (anni)	
sesso (%) Maschile Femminile	
Dimensione mediana clinica (cm)	
Presentazione (%) Incidentale Sintomatica	
Trattamento chirurgico (%) Nefrectomia parziale Nefrectomia radicale	
Dimensione mediana patologica (cm)	
Diagnosi finale (%) Tumore benigno Tumore maligno	
pT (TNM, 2002) - pT1a - pT1b - pT2 - pT3a - pT3b	
Coinvolgimento linfonodale (%) - pN0/pNx - pN+	45 (95.7%) 2 (4.3%)
Metastasi a distanza (%) Assenti Presenti	43 (91.5%) 4 (8.5%)

Istotipo assegnato su biopsia

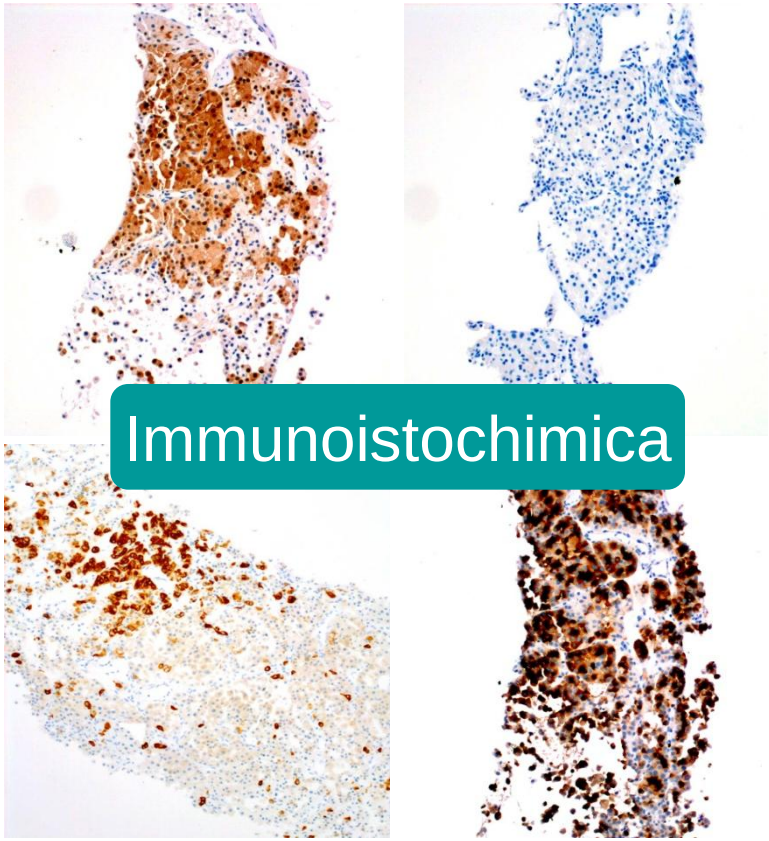
Istotipo assegnato alla diagnosi finale su pezzo operatorio	Tumori benigni	Cellule chiare	Papillare	Cromofobo	Inclassificabile	Totale
Tumori benigni	6 (100%)	0	0	1 (25%)	1 (25%)	8
Cellule chiare	0	34 (100%)	0	0	0	34
Papillare	0	0	4 (100%)	0	2 (50%)	6
Cromofobo	0	0	0	3 (75%)	0	3
Inclassificabile	0	0	0	0	1 (25%)	1

- **56 pazienti**
- **22 (46,8%) pT1a**
- **45 (95,7%) pN0/pNx**
- **43 (91,5%) pM0**

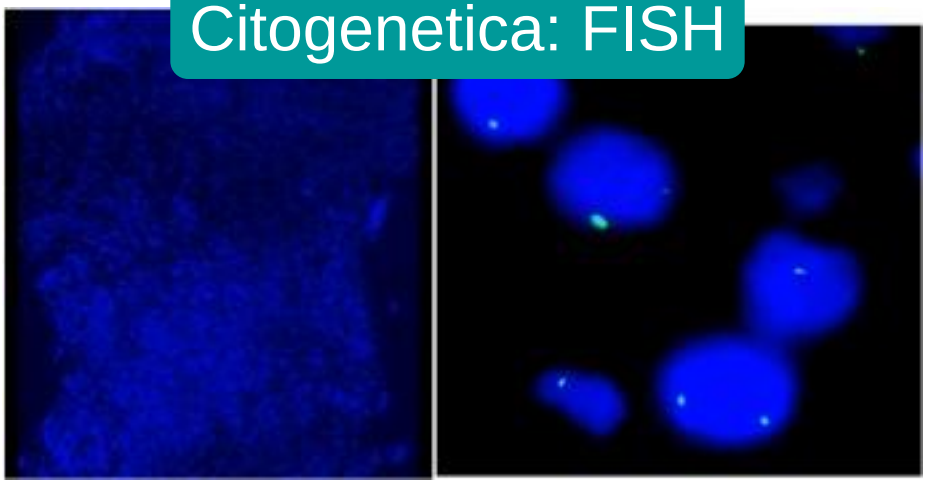
Ficarra V. et al. Pathology 2011; 43:149-155



Morfologia



Immunoistochimica



Citogenetica: FISH

Role of Immunohistochemistry in the Evaluation of Needle Core Biopsies in Adult Renal Cortical Tumors: An Ex Vivo Study

Hikmat A. Al-Ahmadie, MD, Darym Alden,* Samson W. Fine, MD,* Anuradha Gopalan, MD,* Karim A. Touijer, MD,† Paul Russo, MD,† Victor E. Reuter, MD,* and Satish K. Tickoo, MD**

TABLE 1. Diagnosis and Classification by H&E Only

Cases (N)	Adequate Material for Interpretation (%)	Diagnosis Correct on H&E in Cases With Adequate Material (%)
Clear cell RCC (83)	66 (80)*	64 (97)*
Papillary RCC (18)	18 (100)	17 (94)
Chromophobe RCC (14)	13 (93)	8 (62)
Oncocytoma (11)	6 (55)	4 (67)
RCC, unclassified type (4)	4 (100)	0 (0)
Angiomyolipoma (4)	3 (75)	2 (67)
Urothelial carcinoma of renal pelvis (3)	3 (100)	2 (67)
Miscellaneous tumors†(8)	6 (86)	2 (33)
Total (n = 145)	119 (82)	99 (83)

*In 3 additional cases, the diagnosis of carcinoma was rendered but the small amount of tumor cells precluded specific tumor typing.

†Miscellaneous tumors are detailed in Table 3.

RCC indicates renal cell carcinoma.

Role of Immunohistochemistry in the Evaluation of Needle Core Biopsies in Adult Renal Cortical Tumors: An Ex Vivo Study

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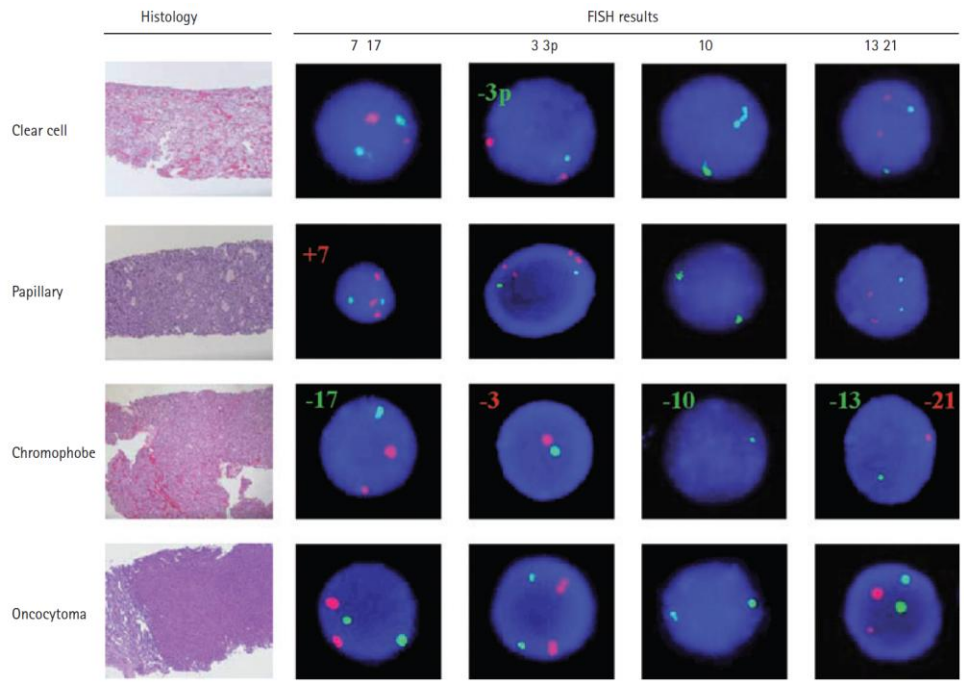
TABLE 2. Results of Interpretation of Needle Biopsy Material of the 4 Most Common Renal Cortical Tumors (Excluding RCC, Unclassified Type): Combined H&E and IHC

Cases (N)	Adequate Material for Interpretation (%)	Diagnosis Correct in Cases With Adequate Material (%)	
		H&E Only	After IHC
Clear cell RCC (n = 83)	66 (80)	64 (97)	66 (100)
Papillary RCC (n = 18)	18 (100)	17 (94)	18 (100)
Chromophobe RCC (n = 14)	13 (93)	8 (62)	12 (92)
Oncocytoma (n = 11)	6 (55)	4 (67)	6 (100)
Total (n = 126)	103 (82)	93 (90)	102 (99)

RCC indicates renal cell carcinoma.

Renal cell carcinoma sub-typing by histopathology and fluorescence *in situ* hybridization on a needle-biopsy specimen

Daniel A. Barocas, Susan Mathew, Joseph J. DelPizzo, E. Darracott Vaughan Jr, R. Ernest Sosa, Ronnie G. Fine, Mohamed Akhtar and Douglas S. Scherr



Needle core	Final pathology: Clear cell	Papillary	Chromophobe	MTSCC	Oncocytoma
N at final pathology	20	7	3	1	5
Histological diagnosis					
Clear Cell	13	0	0	0	0
Papillary	0	6	0	0	0
Chromophobe	2	1	2	0	0
MTSCC	0	0	0	1	0
Oncocytoma	0	0	1	0	5
Not readable	5	0	0	0	0
FISH findings*					
Loss of 3p	9	1	0	0	0
Trisomy 7 or 17	6	6	0	0	0
Widespread losses	0	0	2	0	0
Normal	5	1	1	0	3
Other abnormality	2	0	0	1	2
Not readable	5	0	0	0	0
Histology +FISH					
Clear cell	16	0	0	0	0
Papillary	1	7	0	0	0
Chromophobe	0	0	2	0	0
MTSCC	0	0	0	1	0
Oncocytoma	0	0	1	0	5
Not readable	3	0	0	0	0

2006 BJU INTERNATIONAL | 99, 290–295