I TUMORI DELLE VIE URINARIE

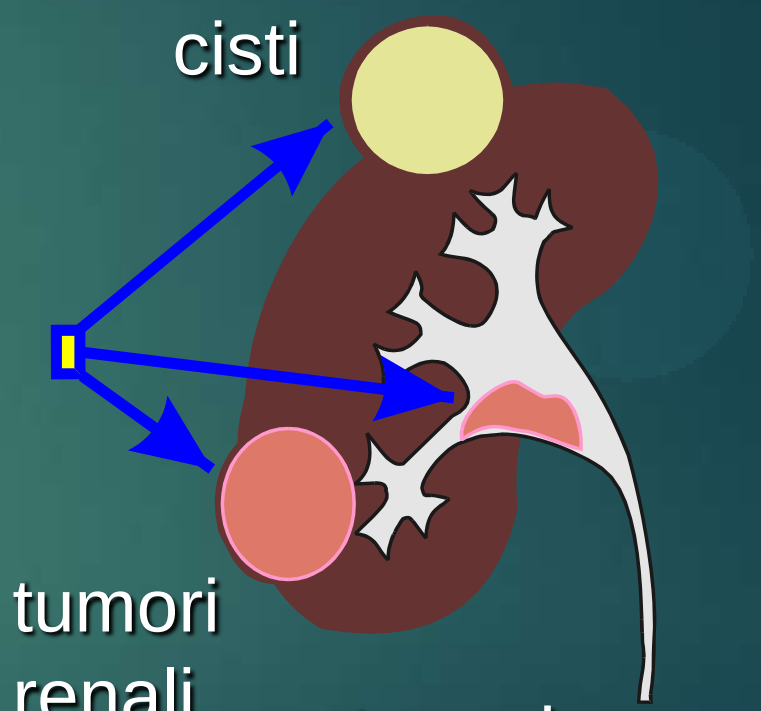
DIAGNOSI E TERAPIA DEI TUMORI DEL PARENCHIMA RENALE

GIANNI CAPPELLI

S.C. NEFROLOGIA DIALISI E TRAPIANTO RENALE – POLICLINICO DI MODENA

Renal Mass

- T. della capsula renale
- T. del parenchima renale maturo
- T. del parenchima renale immaturo
- T. della pelvi renale
- Cisti
- T. vascolari
- T. neurogenici
- T. di tessuto eteroplastico
- T. di derivati mesenchimali
- T. solidi para/perirenali
- T. secondari



Tumori del rene: Classificazione

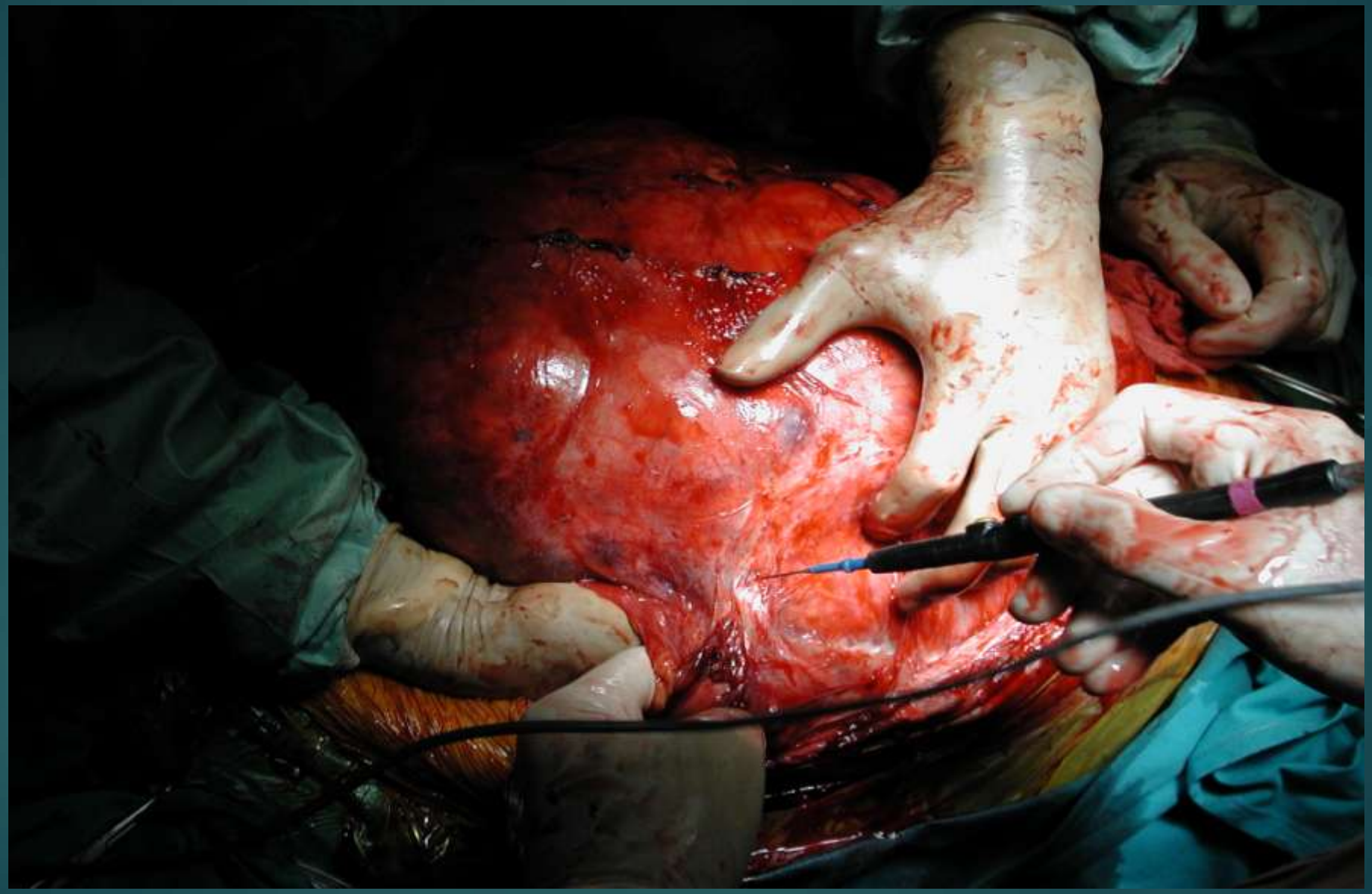
BENIGNI

- adenoma
- oncocitoma
- fibroma
- leiomioma
- angioma
- rabdomioma
- neurofibroma
- cisti dermoide
- endometriosi
- angiomiolipoma

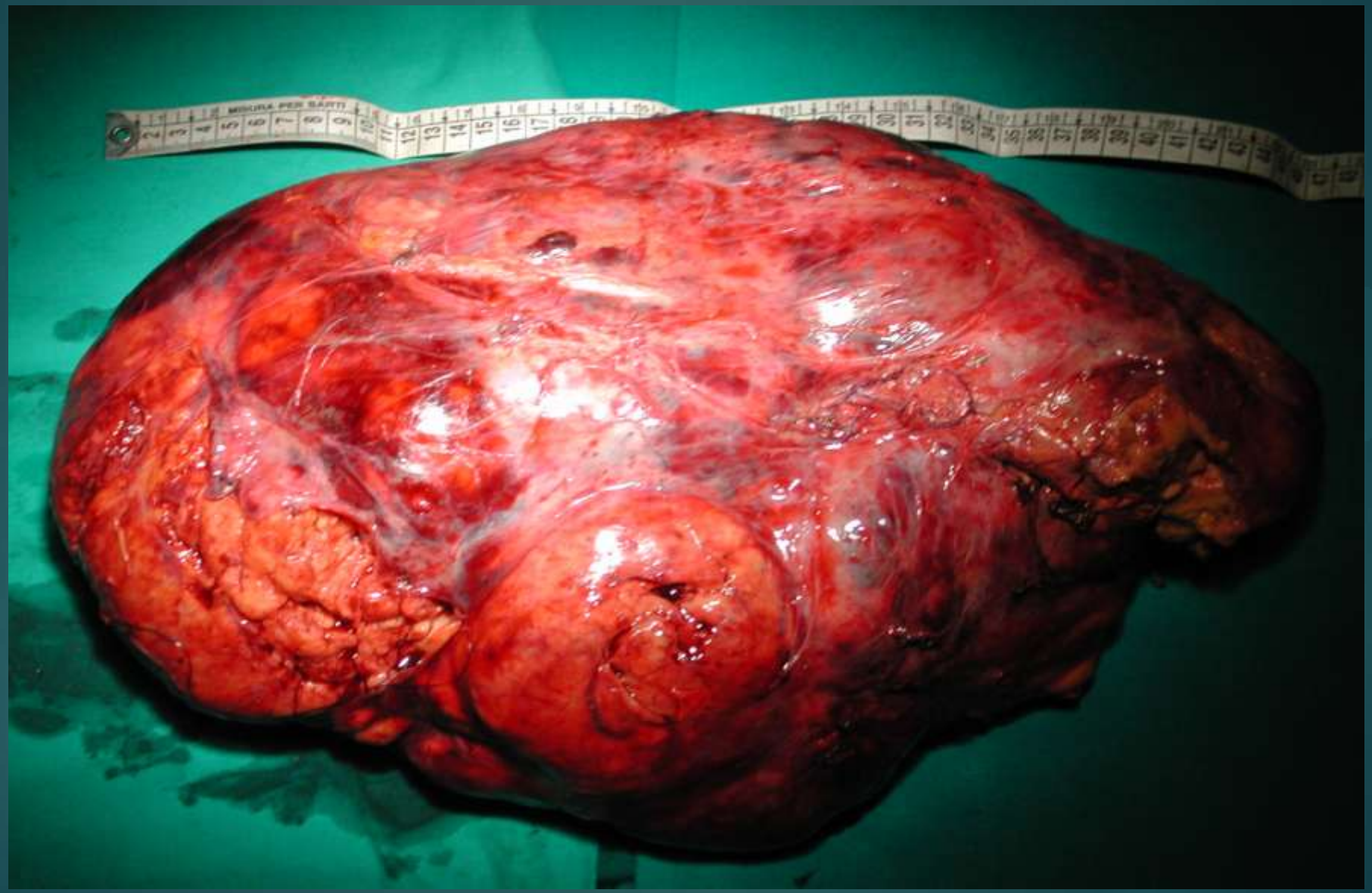
MALIGNI

- nefroblastoma
- carcinoma
- sarcomi
  - fibrosarcoma
  - liposarcoma
  - leiomiosarcoma
  - s. osteogenetico
- linfoblastoma
  - linfomi
  - mieloma
- tumori secondari

Angiomiolipoma



Angiomiolipoma



Tumori del rene: Classificazione

BENIGNI

- adenoma
- oncocitoma
- fibroma
- leiomioma
- angioma
- rabdomioma
- neurofibroma
- cisti dermoide
- endometriosi
- angiomiolipoma

MALIGNI

- nefroblastoma 5-6%
- carcinoma 90%
- sarcomi 1-3%
  - fibrosarcoma
  - liposarcoma
  - leiomiosarcoma
  - s. osteogenetico
- linfoblastoma
  - linfomi
  - mieloma
- tumori secondari

Carcinoma a Cellule Renali

INTRODUCTION

- Renal cell carcinoma (RCC) has increased its incidence at a rate of 2% per year on the last 65 years as well as its mortality on the last 2 decades.
- Partial Surgery is the new option for localized tumors. 20% to 40% of the operated tumors will develop metastases in a future and will require additional therapy.
- RCC are resistant to chemotherapy and radiotherapy. Hormones doesn't work too.
- New target therapy agents are available with great responses & survival benefits.

Overview of RCC

Epidemiology

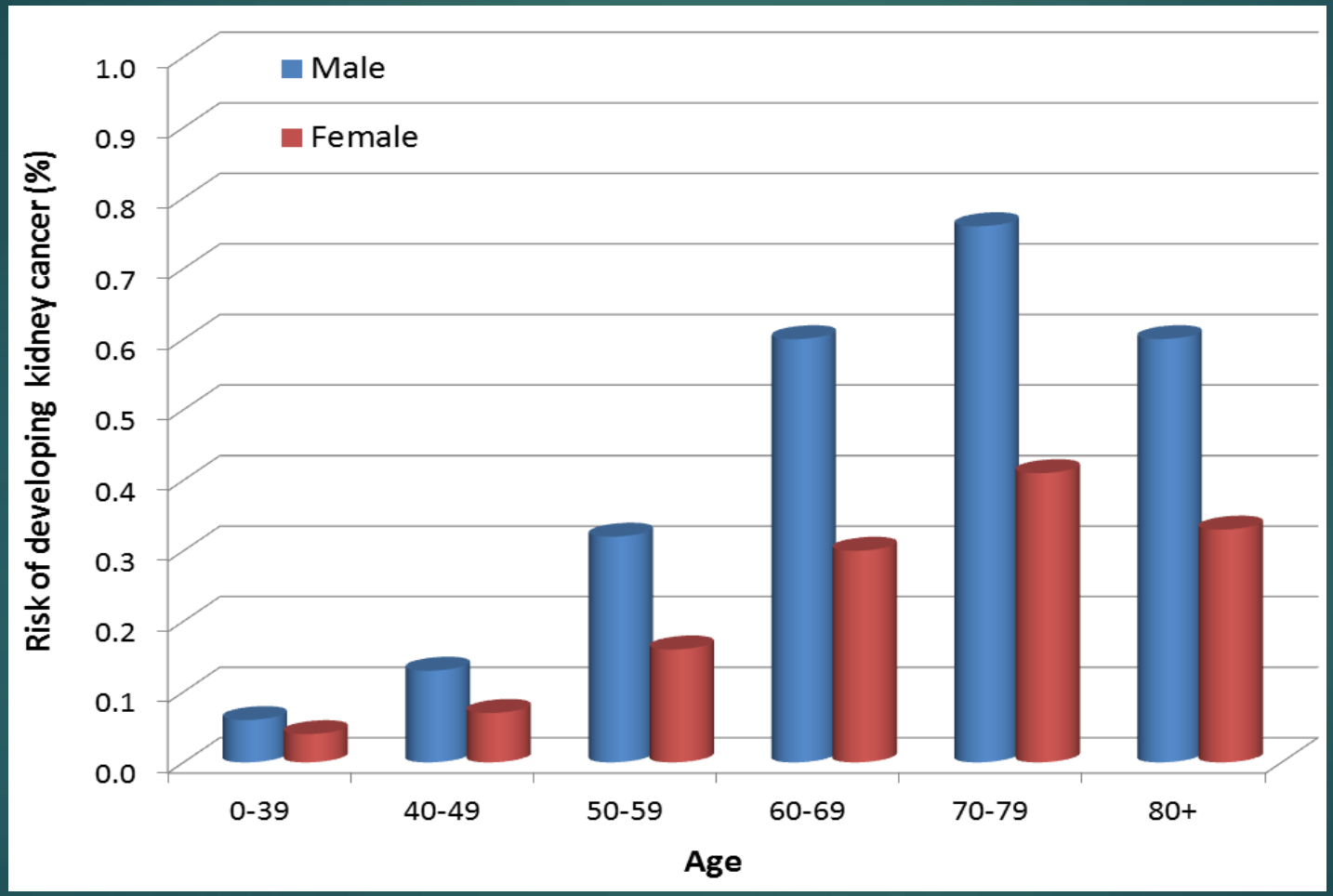
Pathology

Pathogenesis

Epidemiology

- RCC is the responsible of 2% - 3% of all malignancies in adults.
- The incidence peak age is: 60 – 80 years old.
- Men : Women ratio of 2:1
- Incidence & Mortality are rising in African Americans.
- 5-year survival rate of 65% by 1995-2000..

Epidemiology

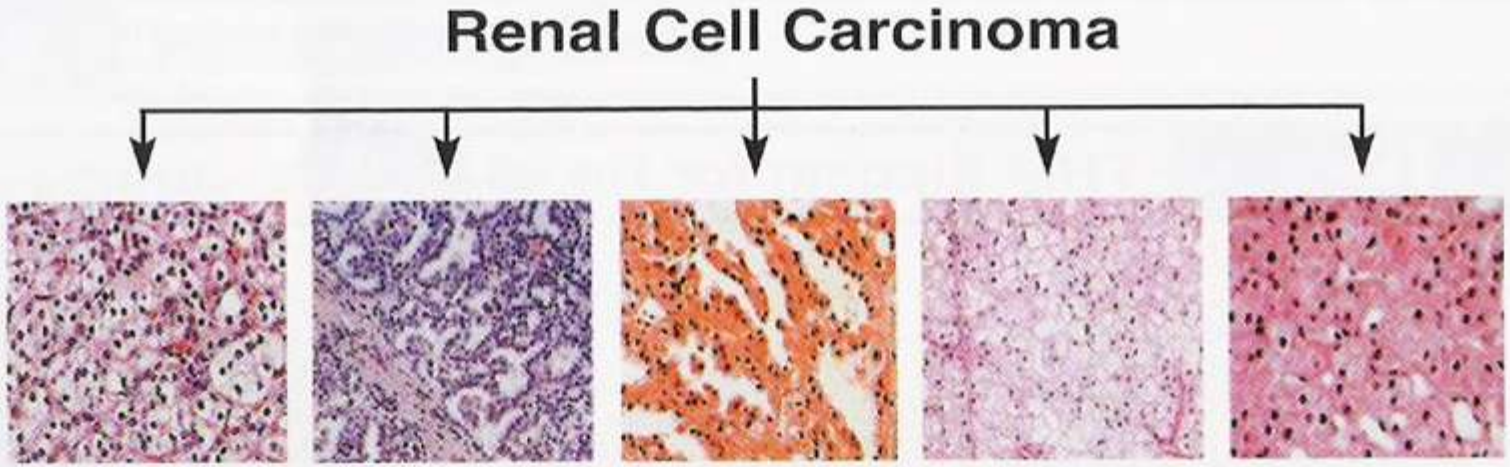


- RCC affects more than 150,000 people annually worldwide, resulting in 78,000 deaths each year.
- Individuals with positive family history of RCC have a 2.5-fold greater chance for developing renal cancer during their life time.
- Patients with a family history comprise about 4% of all cases of RCC.

Pathology

Clear cell (non-papillary) carcinoma is the most common.

FIGURE 1 **Histologic Classification of Human Renal Epithelial Neoplasms**



Type	Clear cell	Papillary type 1	Papillary type 2	Chromophobic	Oncocytoma
Incidence (%)	75	5	10	5	5

(Reprinted with permission; Linehan et al., 2003)

Renal cell carcinomas arise from the renal epithelium, the most common histology is clear cell and accounts for approximately 75% of renal cancers.

Renal Cancer and Gene Mutation

Gene	Hereditary Syndrome
VHL	Von Hippel-Lindau
c-Met (receptor tyrosine kinase)	Hereditary papillary Renal Carcinoma type I
FH (fumarate hydratase)	Hereditary leiomyomatosis and Renal Cell Carcinoma
BDH	Birt-Hogg-Dubè Syndrome

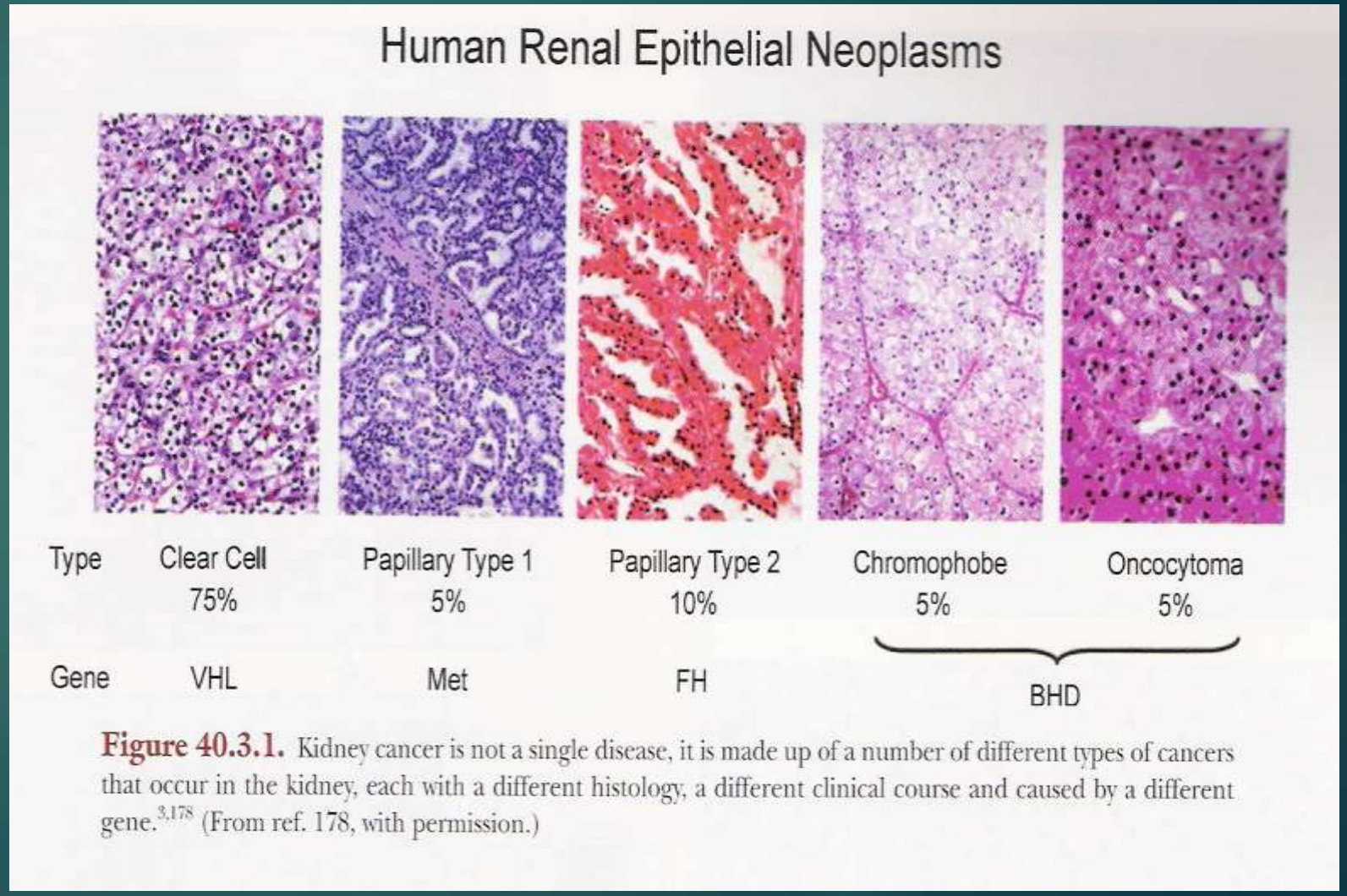


Figure 40.3.1. Kidney cancer is not a single disease, it is made up of a number of different types of cancers that occur in the kidney, each with a different histology, a different clinical course and caused by a different gene.[3,178] (From ref. 178, with permission.)

Pathogenesis

A number of environmental, hormonal, cellular, and genetic factors have been studied as possible causes of RCC.

Etiology

- Tobacco
- Obesity
- Chronic arterial hypertension
- Diabetes mellitus
- End-Stage Renal Disease on hemodialysis
- High fat, high protein diet, fried food, red meat
- Use of phenacetin chronically as analgesics
- Amphetamines
- Petroleum products
- Cadmiun
- Asbestos
- Aromatic hydrocarbons

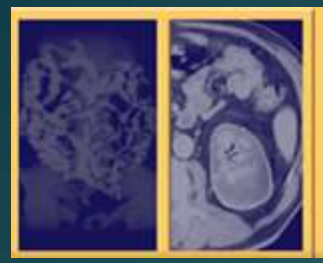
- Smoking: 30% in men, 24% in women.
- Obesity: Increased BMI is related with RCC, but more favorable prognosis.

TABLE 40.1.1 Hereditary Renal Cancer Syndromes

Syndrome	*Chromosome Location*	*Predisposing Gene*	*Renal Manifestations*	*Other Manifestations*
Von Hippel-Lindau (VHL)	3p25	*VHL*	Clear cell renal carcinoma: solid and/or cystic, multiple and bilateral	Retinal and central nervous system hemangioblastomas; pheochromocytomas; pancreatic cysts and neuroendocrine tumors; endolymphatic sac tumors; epididymal and broad ligament cystadenomas
Hereditary papillary renal carcinoma type1(HPRC)	7q31	*MET*	Papillary renal carcinoma type 1: solid, multiple and bilateral	None
Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)	1q42-43	*FH*	Papillary renal carcinoma type 2, collecting duct carcinoma: solitary, aggressive	Uterine leiomyomas and leiomyosarcomas; cutaneous leiomyomas
Birt-Hogg-Dubé syndrome (BHD)	17p11.2	*BHD*	Hybrid oncocytic renal tumors, chromophobe and clear cell renal carcinomas, oncocytomas: multiple, bilateral	Benign tumors of hair follicle (fibrofolliculomas); lung cysts, spontaneous pneumothoraces
Constitutional chromosome 3 translocation	3p	Not known; *VHL* somatic mutations in renal tumors	Clear cell renal carcinoma: multiple, bilateral	None

Familiar type RCC & von Hippel Lindau

- Suppressor gene in the short arm of chromosome 3 as autosomic dominant.
- 1 in 30,000 births.
- Age of early symptoms: 26.3 years old.
- Penetrance age of 60 years old.
- RCC: bilateral low staging.
- Associated features: retinal angiomas, cerebelar & spinal cord hemagioblastomas, cysts and/or angiomas of solid organs, pheochromocytomas.



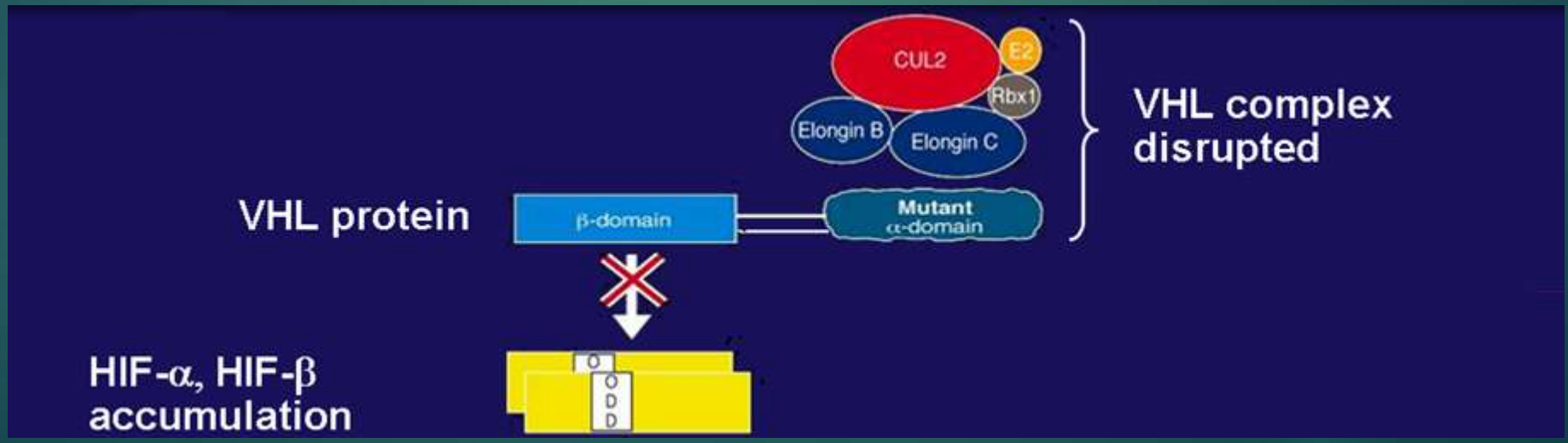
VHL Gene Mutation in Clear-Cell RCC

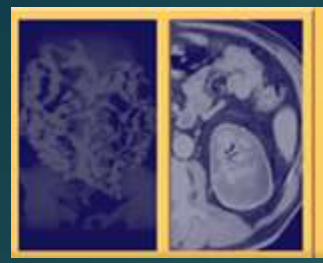
Clues to the pathogenesis of RCC have been identified through study of von Hippel Lindau (VHL) syndrome, an autosomal dominant disorder with inherited susceptibility to clear-cell RCC and other tumors.

VHL syndrome is associated with overexpression of various growth factors that have been linked with tumorigenesis, including VEGF and PDGF

- In VHL syndrome, VHL gene inactivation due to gene mutation or methylation leads to defective VHL protein function.

VHL protein normally earmarks another protein called hypoxia inducible factor-1α (HIF-1α) for metabolic degradation, so loss of VHL protein function leads to an accumulation of HIF-1α





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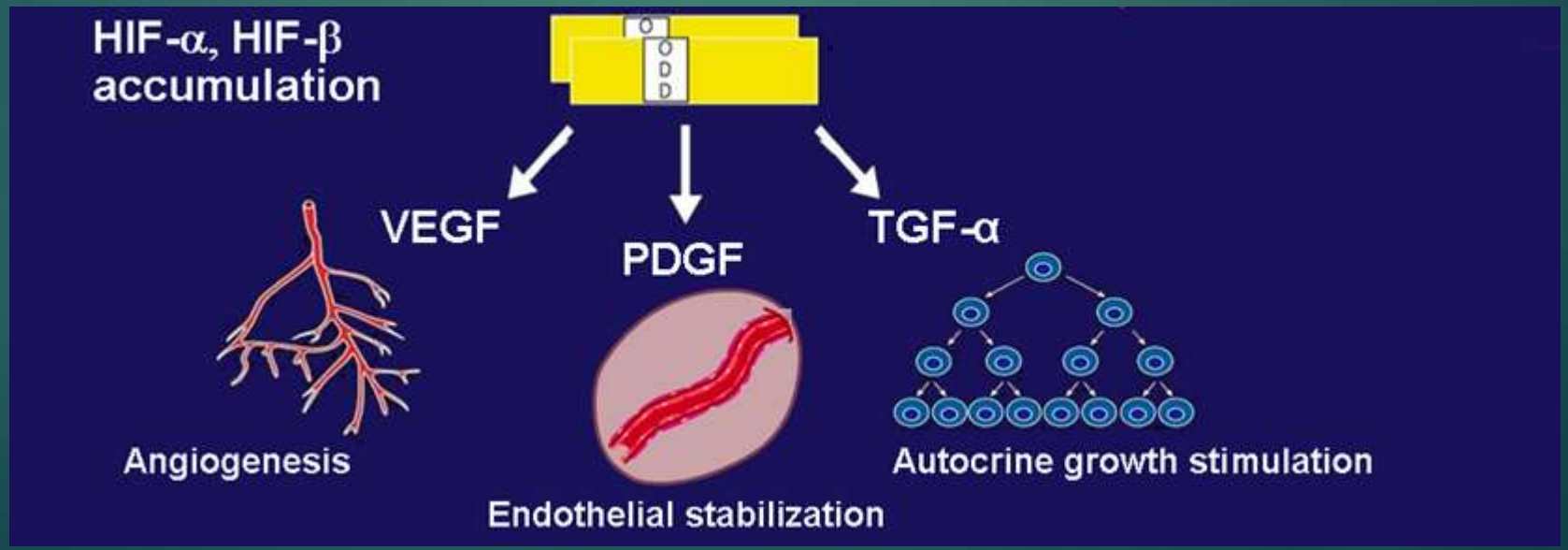
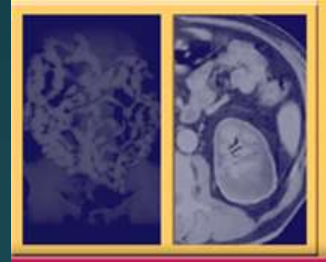
VHL syndrome is associated with overexpression of various growth factors that have been linked with tumorigenesis, including VEGF and PDGF

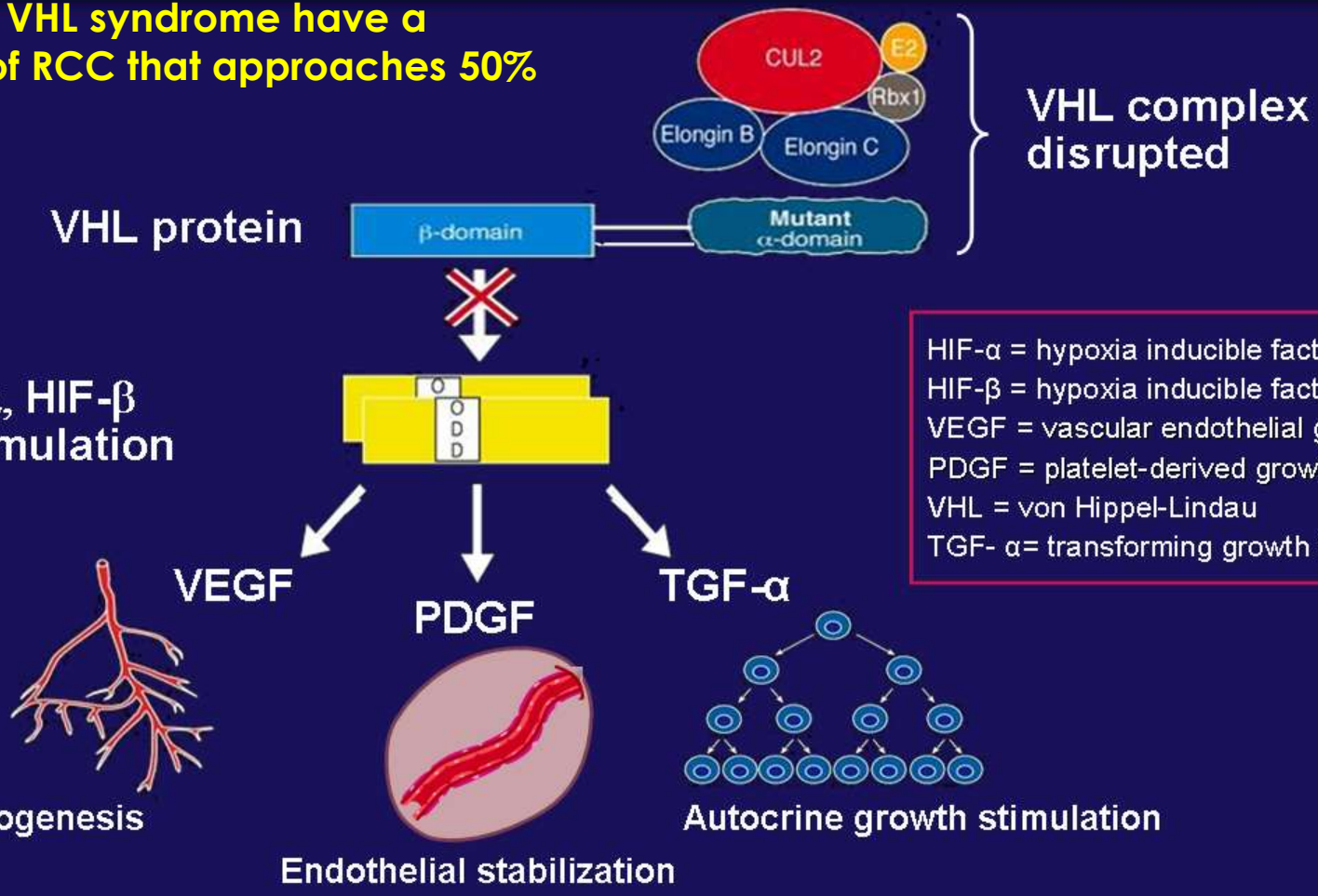
- HIF-α forms a complex with HIF-β that regulates gene transcription, including the genes encoding VEGF, PDGF, and TGF-α.
- Hence, accumulation of HIF-α in VHL syndrome leads to overexpression of VEGF, PDGF, and TGF-α





VHL Gene Mutation in Clear-Cell RCC

Patients with VHL syndrome have a lifetime risk of RCC that approaches 50%



HIF-α = hypoxia inducible factor-α
HIF-β = hypoxia inducible factor-β
VEGF = vascular endothelial growth factor
PDGF = platelet-derived growth factor
VHL = von Hippel-Lindau
TGF- α= transforming growth factor alpha.

Rini BI, Small EJ. *J Clin Oncol.* 2005;23:1028-1043.
Hicklin DJ, Ellis LM. *J Clin Oncol.* 2005;23:1011-1027.
De Paulsen N et al. *Proc Nat Acad Sci U S A.* 2001;98:1387-1392.
Please see full prescribing information.

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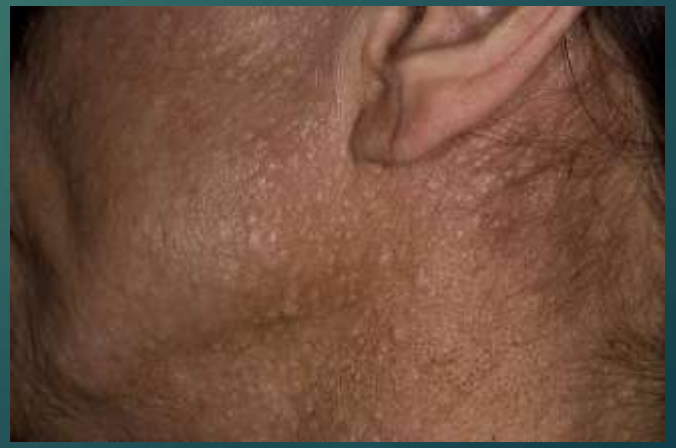
TABLE 40.1.2 Subclassification of von Hippel-Lindau (VHL): Genotype-Phenotype Correlations

Subclass	*VHL Mutation Type*	*Molecular Defect*	*VHL Phenotype*
Type 1	Large deletions, truncating mutations, missense mutations that affect pVHL folding or stability	Up-regulation of HIF and its target genes	Hemangioblastomas Low risk of pheochromocytoma **High risk of RCC**
Type 2A	Missense	Up-regulation of HIF and its target genes	Hemangioblastomas High risk of pheochromocytomas **Low risk of RCC**
Type 2B	Missense	Up-regulation of HIF and its target genes	Hemangioblastomas High risk of pheochromocytomas **High risk of RCC**
Type 2C	Missense	pVHL binds and degrades HIF; decrease in fibronectin binding, defective fibronectin matrix assembly	Pheochromocytomas only

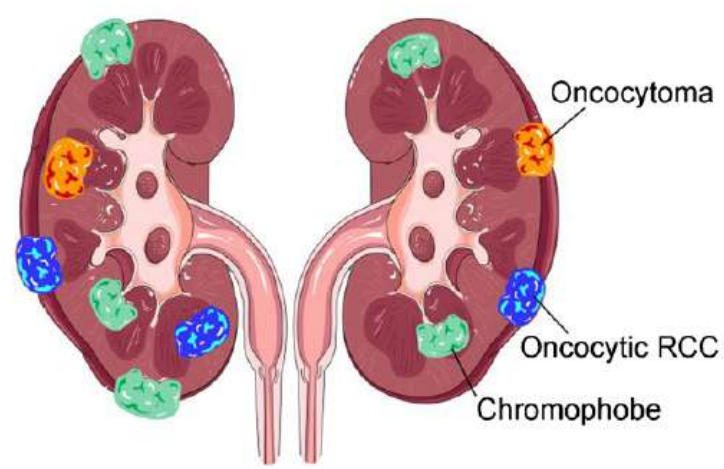
pVHL, the von Hippel-Lindau protein; HIF, hypoxia-inducible factor; RCC, renal cell carcinoma.

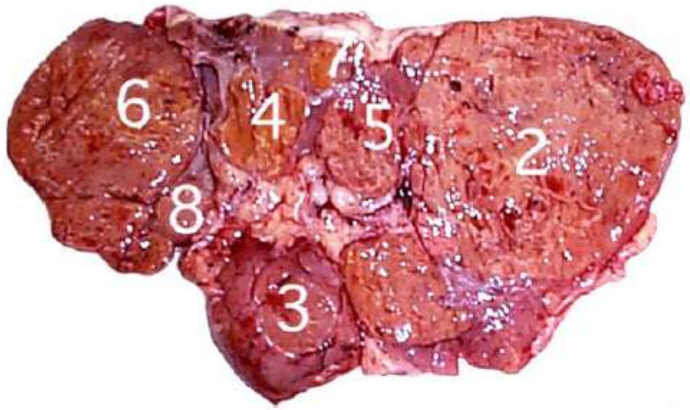
Birt-Hogg-Dubé Syndrome

- Rare autosomal dominant
- Gene located at the short arm of the chromosome 17
- Chromophobe RCC with low metastatic potential
- Fibrofolliculomas trichodiscomas (benign hamartomas of the hair follicule), pulmonary cysts, spontaneous pneumothorax



Birt-Hogg-Dubé Syndrome





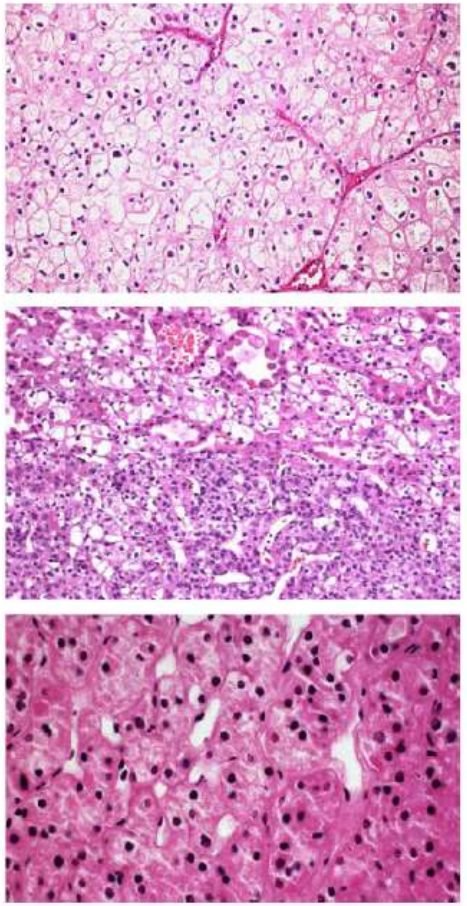


Fig. 4. Patients affected with Birt–Hogg–Dubé (BHD) are at risk for the development if bilateral, multifocal kidney cancer (left upper and left lower panels) with chromophobe (upper right panel), hybrid oncocytic (right middle panel) and oncocytoma (right lower panel).
From Linehan et al. [1].

Clinical Manifestations

Evaluation and Staging of RCC

Clinical Presentation

- Small tumors as incidental findings
- Hematuria
- Abdominal pain
- Palpable abdominal mass

- Paraneoplastic syndrome:

(↑ Prostaglandins, Calcitriol, Renin, Erytropoietin, PTH-like, Glucagon-like, Insulin-like, chorionic gonadotropin-like)

  - Bone pain
  - Hypercalcemia
  - Fever
  - Weight loss
  - Polycythemia
  - Neuromyopathy
  - Amyloidosis

TABLE 40.3.6 Presenting Symptoms, Laboratory Abnormality, or Abnormality on Physical Examination and Relationship to Survival in 309 Consecutive Patients Undergoing Nephrectomy for Renal Carcinoma

Presenting Symptom, Abnormal Laboratory Findings, or Abnormality on Physical Examination	*Patients (n = 309)*	*Patients Surviving 5 Years*
Classic triad (gross hematuria, flank mass, pain)	29 (9%)	9/29 (31%)
Hematuria	* 183 (59%)	74/183 (40%)
Pain	* 127 (41%)	56/127 (44%)
Abdominal mass	* 139 (45%)	49/139 (35%)
Fever	21 (7%)	8/21 (38%)
Weight loss	85 (28%)	29/85 (39%)
Anemia	64 (21%)	24/64 (38%)
Erythrocytosis	10 (3%)	4/10 (40%)
Hypercalcemia	11 (3%)	4/11 (35%)
Acute varicocele	7 (2%)	3/7 (43%)
Tumor calcification on x-ray film	39 (13%)	18/39 (46%)
Symptoms of metastases	31 (10%)	1/31 (3%)
Cancer, incidental finding	20 (7%)	13/20 (65%)

(Modified from ref. 179, with permission.)

- 30% presented with metastatic disease, 25% with locally advanced disease, and 45% with localized disease.

- 75% of metastatic disease presents with pulmonary lesions, 36% to soft tissues, 20% to the bones, 18% to the liver, 8% to the skin, and 8% to the CNS.

Diagnostic tests

- History & Physical Exam
- Laboratory: Complete Blood Count, Routine biochemical screen, LDH, C Reactive Protein, Erythrocyte Sedimentation Rate, Urinalysis
- Chest X Ray, Abdomino-pelvic Ultrasound / CT Scan
- MRI if Inferior Vena Cava thrombosis suspected
- Angiography
- Aspiration cytology
- Bone scan if bone metastases suspected
- PET/CT is controversial

TNM Classification

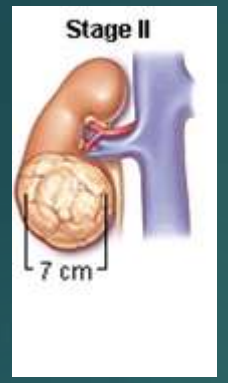


TABLE 40.3.7 Tumor, Node, Metastasis Classification: Kidney Cancer

PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to kidney, <7 cm in greatest diameter
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T3	Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
T3a	Tumor directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or vena cava below the diaphragm
T3c	Tumor grossly extends into vena cava above diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia
NODAL INVOLVEMENT (N)	
	The regional lymph nodes are the para-aortic and paracaval nodes. The juxtaregional lymph nodes are the pelvic nodes and the mediastinal nodes.
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in a single regional lymph node
N2	Metastasis in more than one regional lymph node
DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

(From ref. 180, with permission.)

Prognosis and Treatment of RCC

Prognostic factors

- Symptomatic presentation
- Weight loss
- Poor performance status
- Erythrocite Sedimentation Rate > 30 mm/hr
- Anemia
- Elevated alkaline phosphatase
- Tumor size, positive margins, liver & lung metastases, Sarcomatoid tumors

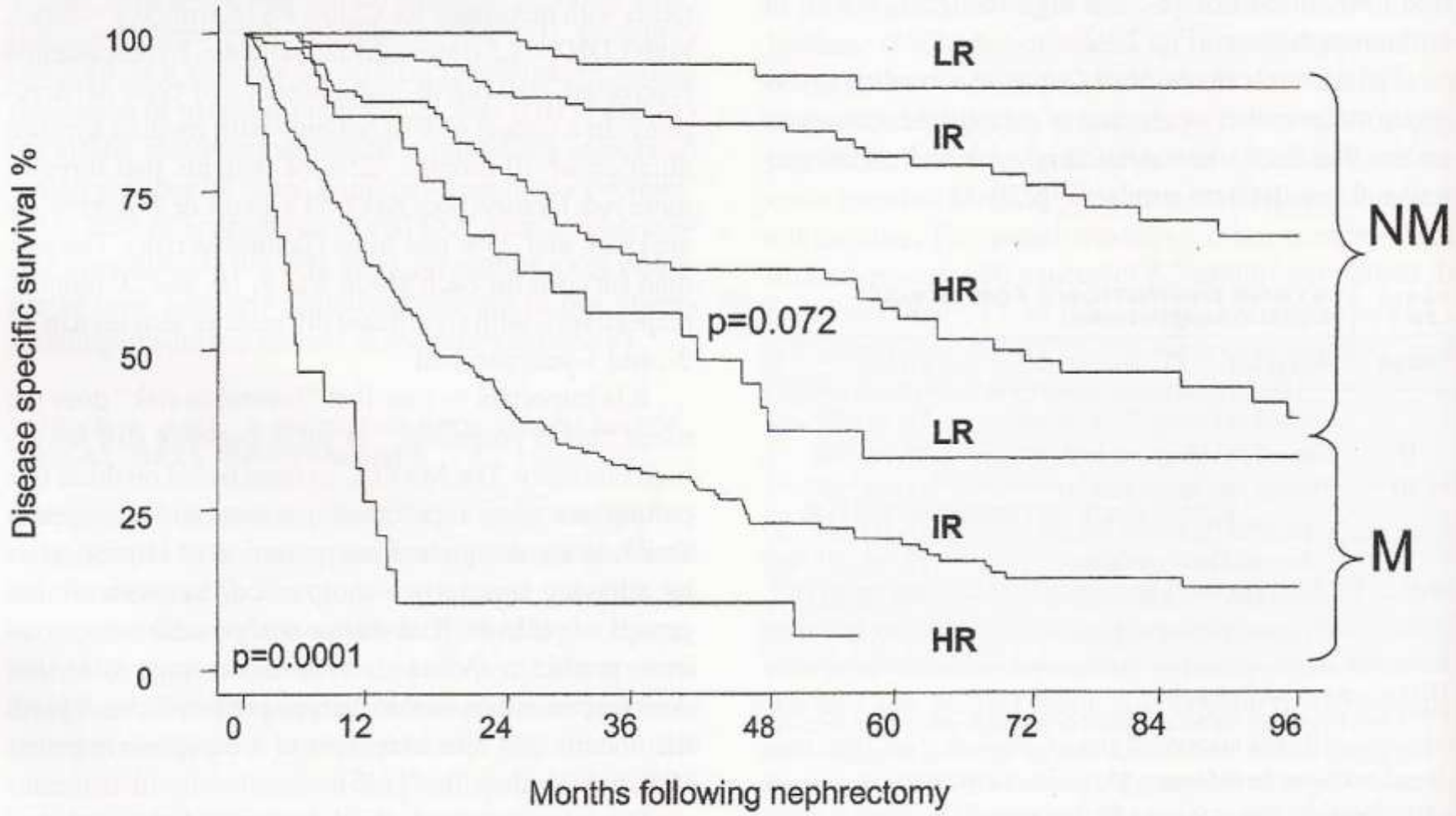


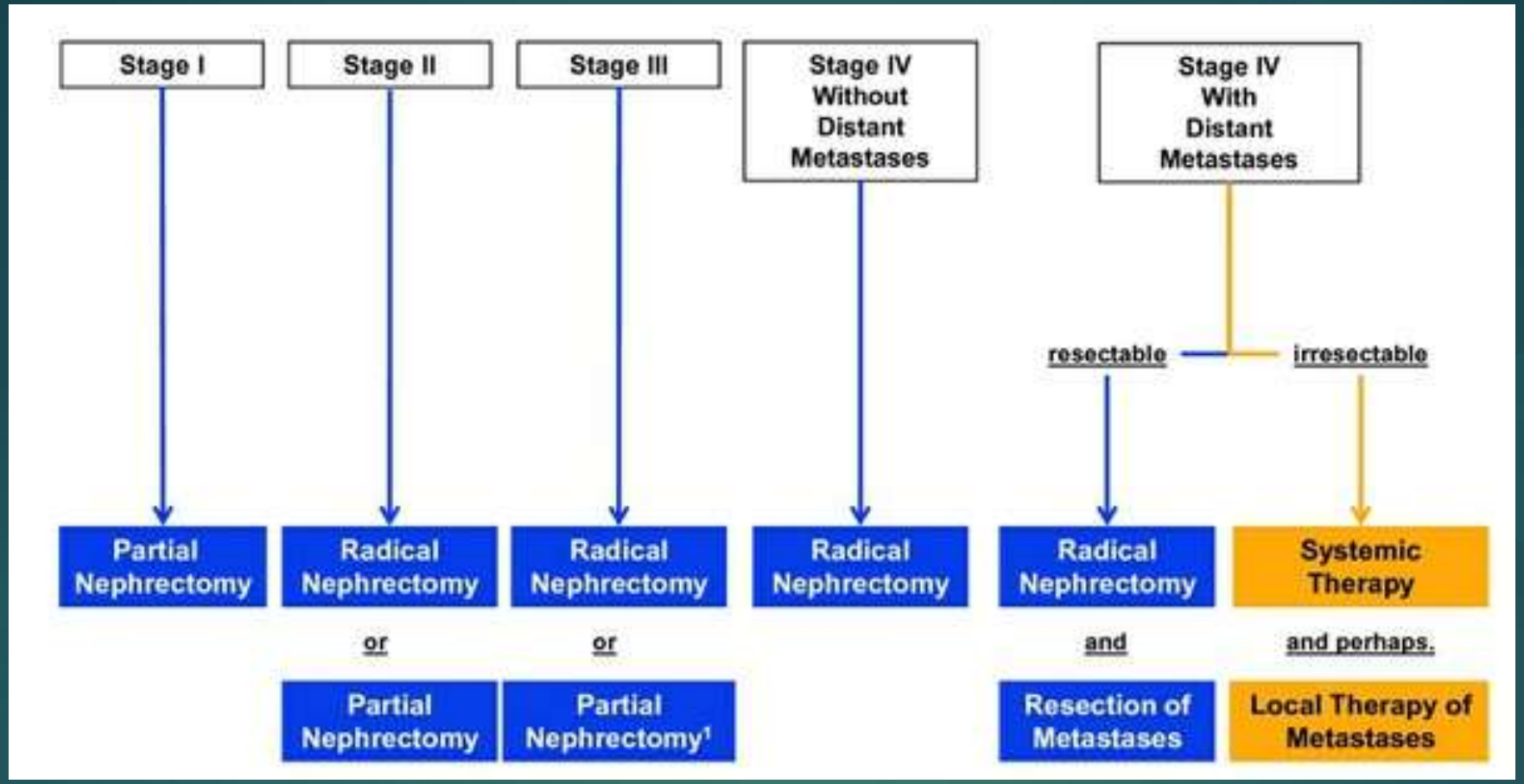
FIGURE 29-3 Disease-specific survival comparison for risk groups segregated according to metastatic or nonmetastatic RCC at the time of nephrectomy. [*From Zisman et al.* (42). *With permission.*]

Surgery in RCC

- Urologists are moving from Radical nephrectomy to Partial nephrectomy using laparoscopy.

- To minimize positive margins in partial nephrectomy:
  - Intraoperative sonography
  - Use of cold scissors for parenchymal transection
  - Hilum control to avoid vascular leak (bleeding).

- The first nephrectomy was performed on June 4th of 1861. Since then, there have been significant advances in surgical techniques.
- The most common procedure today for treatment of localized renal carcinoma > 4 cm is radical nephrectomy.
- Laparoscopic nephrectomy has become the standard of care for management of most renal tumors not amenable to nephron-sparing surgery.



Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

DGHO ÖGHO SSMO SSOM SGMO

- At present, lymphadenectomy is a safe adjunct to radical nephrectomy and is primarily used for staging.

Angioinfarction

- **Embolization of the renal artery: only for palliation. No definitive benefit.**

Chemotherapy

- **NO ROLE !!!!!**
- **Combination of Vinblatine + Toremifene/ Verapamil/ Nifedipine/ Cyclosporin ????? (Due to inhibition of p-glycoprotein 1 which is the responsible for chemo-resistance).**

IMMUNOTHERAPY

- **4% SPONTANEOUS REGRESSION RATE.**
- **IL-2 & IFN-**alpha 2a **and** 2b **alone or in combinations: poor response rates (5-20%).**
- **Effector cell therapies: very complex and expensive with low response rates**

  TILs cells(autologous Tumor-Infiltrating Lymphocytes),

  LAK cells (Lymphokine-activated killer cells),

  Dendritic cells (dendritic cell vaccination)

Adjuvant Therapy

Adjuvant Therapy: Rationale

- **Patients with recurrent disease following nephrectomy have micrometastatic disease at the time of surgery**
- **There is a 35%-65% recurrence rate* with locally aggressive tumors**
- **Use of effective therapy may reduce the risk of relapse**

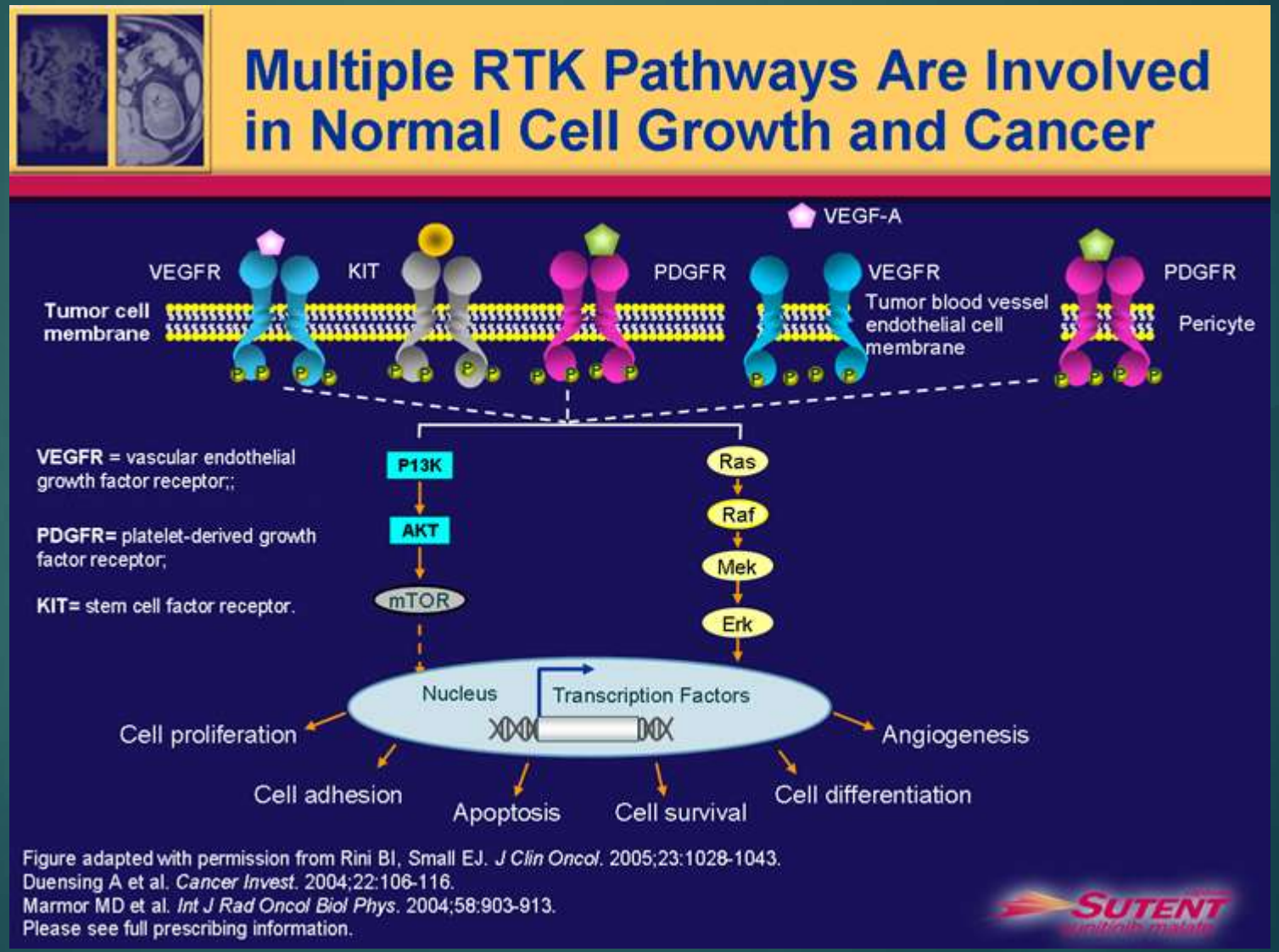
*Depending on pathologic stage Lam JS, et al. BJU Int. 2005

Adjuvant Therapy

- To date, **all** adjuvant therapy trials have failed to demonstrate Disease Free Survival or Overall Survival advantage
  - High-dose (HD) IL-2
  - Interferon
  - Autologous tumor cells + BCG vaccine
  - Vitespen vaccine (tumour-derived heat-shock protein (glycoprotein 96)—peptide complex; HSPPC-96)
- Radiation therapy
- Megestrol acetate

Targeted Therapies for RCC

New Class of Agents Used in RCC to address Receptor Tyrosine Kinases (RTK) transduction pathway



New Class of Agents Used in RCC: Tyrosine Kinase Inhibitors (TKI's)

- **Sorafenib** : Approved by FDA in 2005 (Europe 2006) for advanced RCC (survival (months) 5.5 vs. 2,8 in placebo. *N. Engl. J. Med. 2007*)
- **Sunitinib** : Approved in 2006 for metastatic RCC
  (median progression-free survival 11 months vs. 5 months for IFNa; overall survival NOT statistically significant)
- **Temsirolimus** *(mTOR inhibitor)*: Approved in 2007 for advanced RCC
  (survival (months) 10,9 vs. 7,3 for IFN-a. *N. Engl. J. Med. 2007*)

Table 1. Major Phase III Trials for Drugs Approved for Treatment of mRCC

Drug	Targets	Administration	Dose	Eligibility	Study Design	N	Experimental Arm	Control Arm	Median PFS (months)	Median OS (months)	Reference
Monoclonal antibody											
Bevacizumab	VEGF	IV	10 mg/kg, every 2 weeks	First-line	Double-blind RCT	649	IFN-α (9 MU, s.c., 3 times a week) + bevacizumab	IFN-α (9 MU, s.c., 3 times a week)+ placebo	10.2 vs. 5.4*	23.3 vs. 21.3	Escudier et al., 2007b; Escudier et al., 2010
Bevacizumab	VEGF	IV	10 mg/kg, every 2 weeks	First-line	RCT	732	IFN-α (9 MU, s.c., 3 times a week) + bevacizumab	IFN-α (9 MU, s.c., 3 times a week)	8.5 vs. 5.2*	18.3 vs. 17.4	Rini et al., 2008; Rini et al., 2010
TKI											
Sunitinib	VEGFR-1, -2, and -3; PDGFR -α and -β; c-Kit; FLT3; RET	Oral	50 mg/day, 4 weeks-on/2 weeks-off	First-line	RCT	750	Sunitinib	IFN-α (9 MU, s.c., 3 times a week)	11 vs. 5*	26.4 vs. 21.8	Motzer et al., 2007a; Motzer et al., 2009
Sorafenib	VEGFR-2 and -3; PDGFR-α and -β; c-Kit; FLT3; RET; RAF	Oral	2x400 mg/day	Second-line	Doube-blind RCT, cross-over	903	Sorafenib	Placebo	5.5 vs. 2.8*	17.8 vs. 15.2	Escudier et al., 2007a; Escudier et al., 2009a
Pazopanib	VEGFR-1, -2, and -3; PDGFR -α and -β; c-Kit	Oral	800 mg/day	Second-line, first-line	Double-blind RCT, 2:1 ratio	435	Pazopanib	Placebo	9.2 vs. 4.2*	n.d.	Sternberg et al., 2010
mTOR inhibitor											
Temsirolimus	mTOR	IV	25 or 15 mg/week	First-line	RCT	626	Temsirolimus (25 mg) or temsirolimus (15 mg) + IFN-α (3-6 MU, s.c., 3 times a week)†	IFN-α (3-9-18 MU, s.c., 3 times a week)‡	5.5* and 4.7 vs. 3.1	10.9* and 8.4 vs. 7.3	Hudes et al., 2007
Everolimus	mTOR	Oral	10 mg/day	≥ Second-line	Double-blind RCT, 2:1 ratio, cross-over	416	Everolimus	Placebo	4.9 vs. 1.9*	14.8 vs. 14.4	Motzer et al., 2010; Motzer et al., 2008

TKI, tyrosine kinase inhibitor; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet derived growth factor; FLT3, FMS-like tyrosine kinase-3; c-Kit, c-Kit protein; IV, intravenous; RCT, randomized controlled trial; IFN-α, interferon-α; MU, million U; s.c., subcutaneously; PFS, progression-free survival; OS, overall survival; vs., versus; n.d., not determined.
*, indicates significant difference in outcome.
†, Starting dose of 3 MU 3 times a week for the first week, raised to 9 MU 3 times a week for the second week, and raised to 18 MU 3 times a week for the third week. Patients unable to tolerate these doses received the highest tolerable dose.
‡, Starting dose of 3 MU 3 times a week for the first week, raised to 6 MU 3 times a week thereafter.

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