



IX Congresso Internacional de Uro-Oncologia

IV SIMPÓSIO MULTIPROFISSIONAL DE URO-ONCOLOGIA

1 a 3 de Março de 2018

SHERATON SÃO PAULO WTC HOTEL

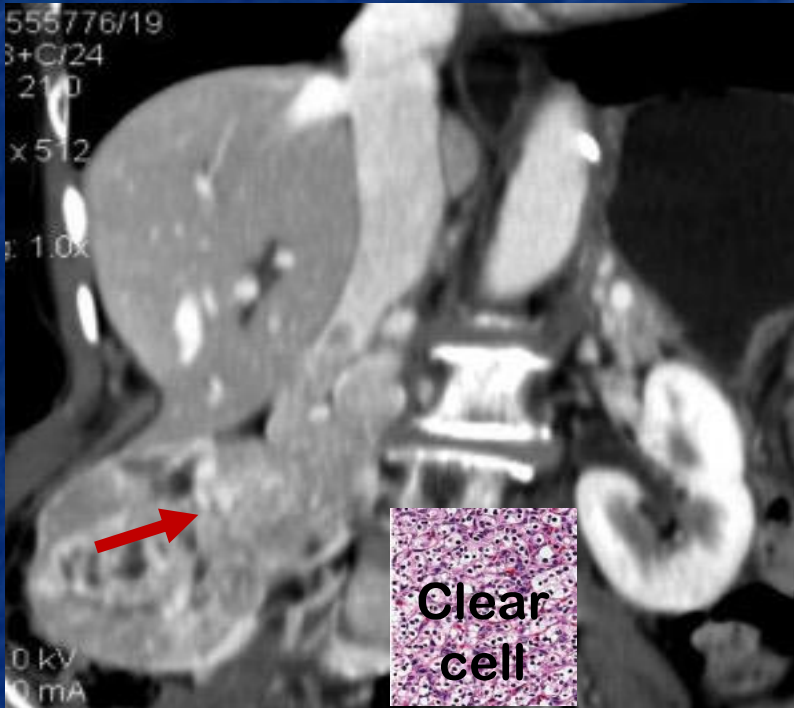


Antonio Carlos Lima Pompeo

Prof. Titular – Disciplina de Urologia – FM-ABC, São Paulo, Brasil

Ca Renal Localmente Avançado

Bases Terapêuticas T3 - T4, N0 - N1, M0



- **T3a**: infiltração peri-renal sem ultrapassar Gerota
- **T3b**: veia renal/cava abaixo do diafragma
- **T3c**: veia cava acima do diafragma
- **T4**: invasão além da *fascia* de Gerota / Adrenal

Prevalência: análise prospectiva (n = 3907)

- **T3**: 32,1%
- **T4**: 1,7% (mets. sincrônicas +++)

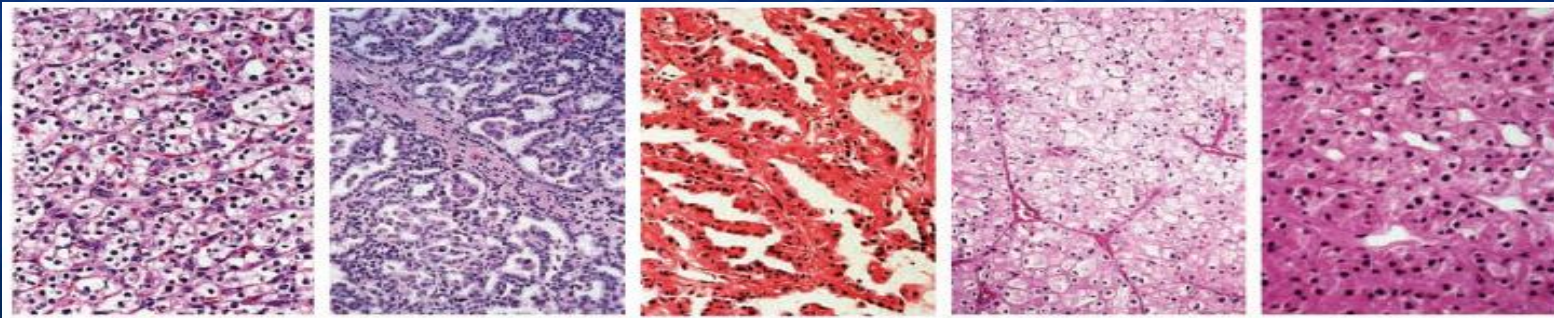
Ca Renal Localizado / Localmente Avançado

Fatores Prognósticos

- Estadio
- Variantes histológicas
- Grau nuclear de Fuhrman
- Condições clínicas

T3-T4 risco ↑↑

Recidiva / progressão



Clear cell

75%

Papillary type 1

5%

Papillary type 2

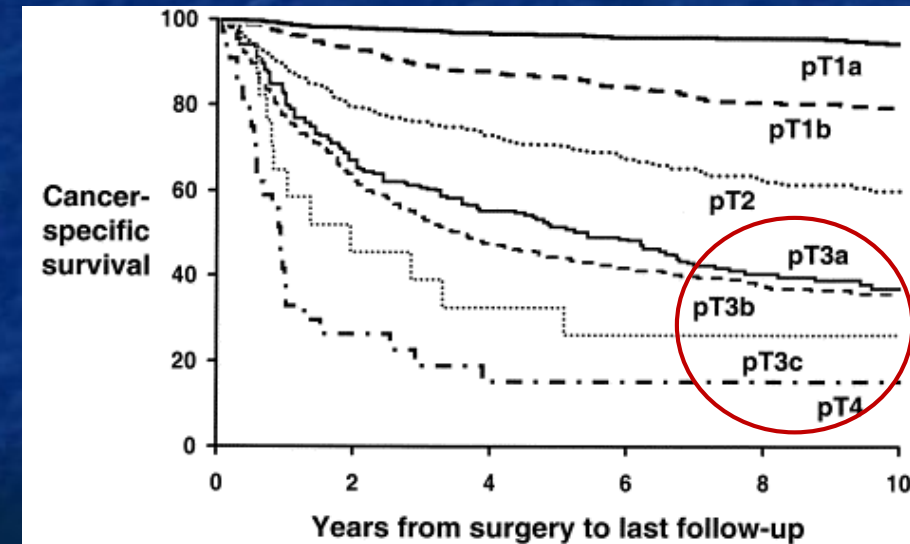
10%

Chromophobe

5%

Oncocytoma

5%



Ca Renal

Fatores Prognósticos

UISS: Algorithm to predict risk

A

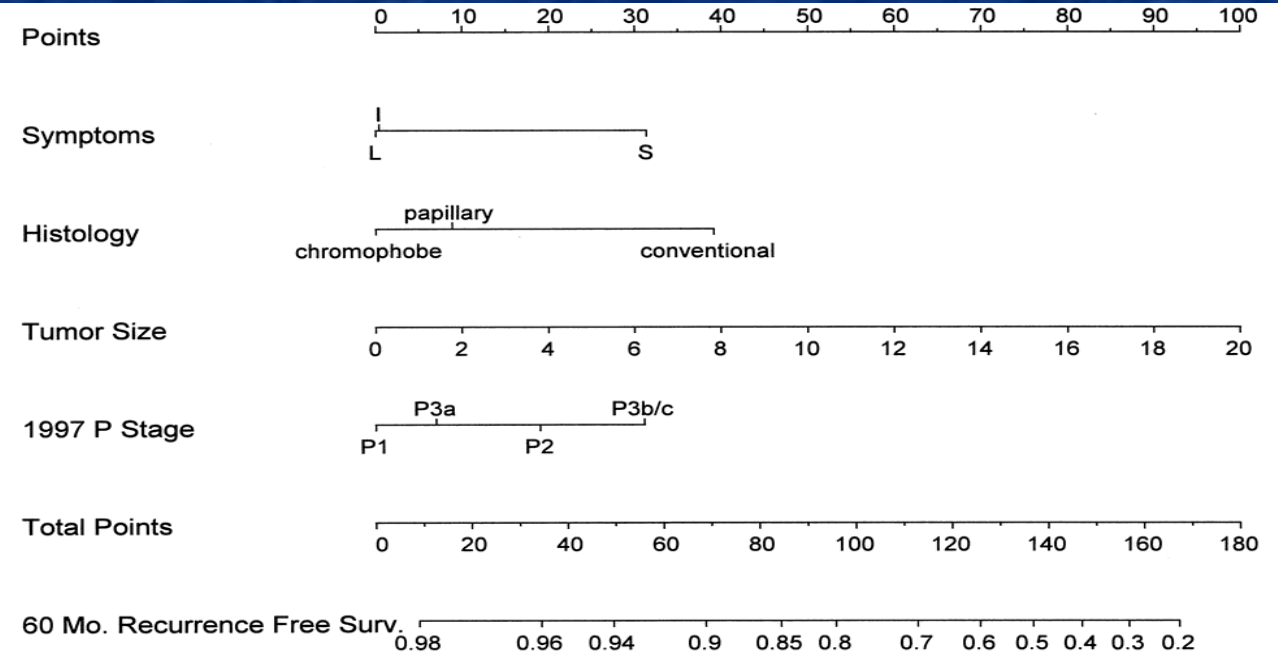
T stage	1		2	3		4
Grade	1-2		3-4	1	>1	
ECOG PS	0	≥1	0	≥1	0	≥1
Risk	Low	Intermediate				High

B

Stage	N1M0	N2M0 / M1					
Grade		1	2	3	4		
ECOG PS		0	≥1	0	≥1	0	≥1
Risk	Low	INTM	Low	INTM		High	

INTM - Intermediate

MSKCC: Postop. prognostic nomogram for RCC



Instructions for Physician: Locate the patient's symptoms (I=incidental, L=local, S=systemic) on the Symptoms axis. Draw a line straight upwards to the **Points** axis to determine how many points towards recurrence the patient receives for his symptoms. Repeat this process for the other axes, each time drawing straight upward to the **Points** axis. Sum the points achieved for each predictor and locate this sum on the **Total Points** axis. Draw a line straight down to find the patient's probability of remaining recurrence free for 5 years assuming he or she does not die of another cause first.

Instruction to Patient: "Mr. X, if we had 100 men or women exactly like you, we would expect between <predicted percentage from nomogram - 10%> and <predicted percentage + 10%> to remain free of their disease at 5 years following surgery, though recurrence after 5 years is still possible."

RCC - Locally advanced Primary Treatment



National
Comprehensive
Cancer
Network®

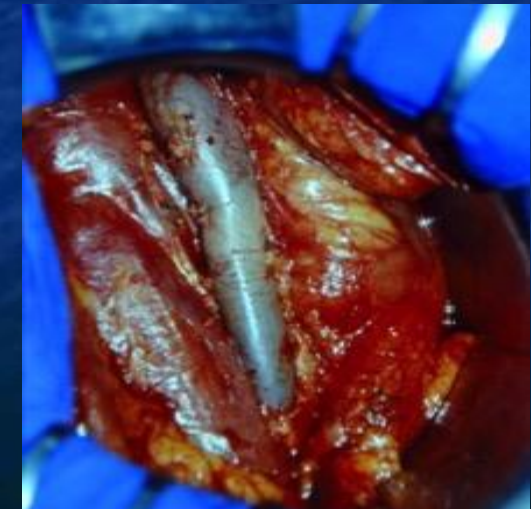
**NCCN Guidelines Version 2.2016
Kidney Cancer**



2016

**Guidelines on
Renal Cell
Carcinoma**

Radical Nephrectomy



2017

**American
Urological
Association**

Ca Renal Localmente Avançado

Tratamento - Controvérsias

- Técnica cirúrgica
 - Aberta / laparoscópica / robótica
 - Linfadenectomia
 - Indicações, extensão, resultados
 - Adrenalectomia
 - Embolização pré operatória ?
- Neo / adjuvância
- Seguimento / fatores prognósticos

65 a, m, cT3-T4 N0 M0



?

Karellas ME et al. BJU Int 2009;103

Kim SP et al. J Urol 2011;185

Ca Renal Localmente Avançado

NR – aberta vs. lap vs. robótica?



- Conclusão: Preferência da equipe cirúrgica
- Fatores a considerar: disponibilidade material, treinamento, custos, etc...

Nefrectomia Radical

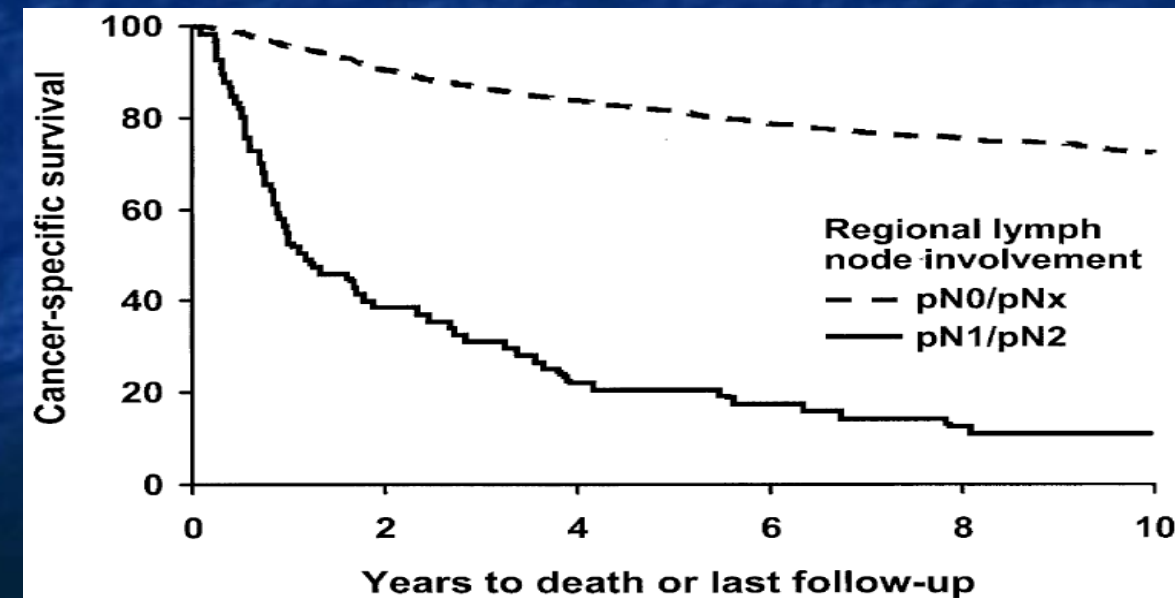
Envolvimento linfonodal

- Influencia negativamente o prognóstico
- Sobrevida 5 anos (T1 – T2)
8% – 32% (N+) **vs.** 85% – 90% (N-)

Mickisch GH – Lymph node dissection for RCC – Urology 1999

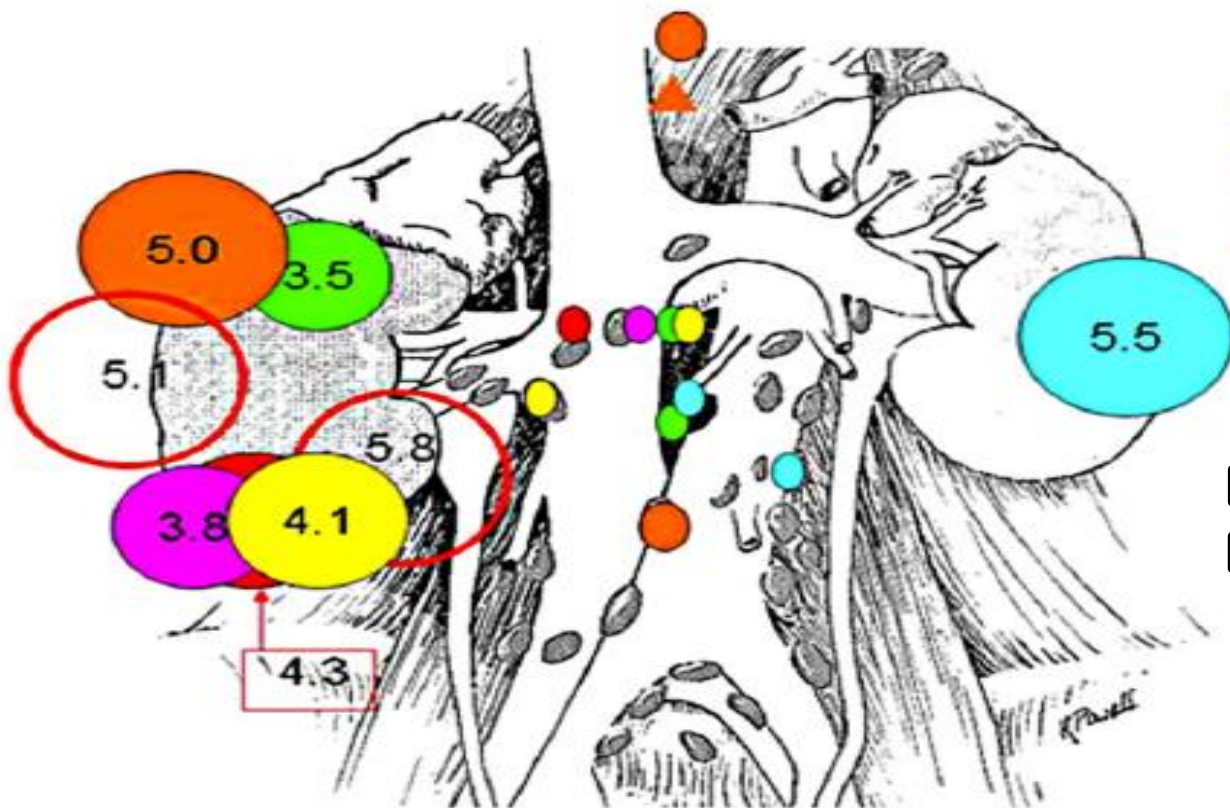
- Incidência aumenta com o estágio
6% (T1-T2); 46,4% (T3); 61,9% (M1)

Giuliani L et al. – Radical extensive surgery for RCC – J Urol 1990;

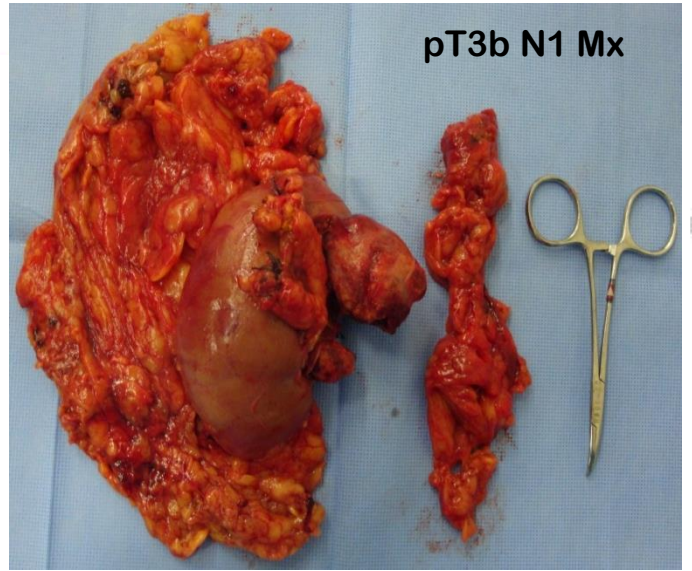


Blute ML et al., J Urol, 2004

Sentinel Lymph Node Mapping



- Patient 1
- Patient 2
- Patient 3
- Patient 6
- Patient 7
- Patient 8



RCC n=8
Lymphoscintigraphy; CT imaging

Sentinel node? "Not yet"

Systematic Review of Adrenalectomy and Lymph Node Dissection in Locally Advanced Renal Cell Carcinoma

Hendrika J. Bekema^a, Steven MacLennan^b, Mari Imamura^b, Thomas B.L. Lam^{b,c,*}, Fiona Stewart^d, Neil Scott^e, Graeme MacLennan^d, Sam McClinton^c, T.R. Leyshon Griffiths^f, Andreas Skolarikos^g, Sara J. MacLennan^b, Richard Sylvester^h, Börje Ljungbergⁱ, James N'Dow^{b,c}

Conclusion: ... there is no robust evidence to suggest superior oncologic outcomes or worse perioperative outcomes for patients who had LND at the time of nephrectomy compared with patients who had nephrectomy alone for cT3–T4N0M0 RCC.

Lymph Node Dissection in Renal Cell Carcinoma

EUROPEAN UROLOGY 60 (2011) 1212–1220

Umberto Capitanio^{a,}, Frank Becker^b, Michael L. Blute^c, Peter Mulders^d, Jean-Jacques Patard^e, Paul Russo^f, Urs E. Studer^g, Hein Van Poppel^h*



Systematic Review concerning the role of LND in RCC staging and outcome

Conclusions

- The evidence suggests LND (extended) **may be beneficial in pts T3-T4** and/or unfavorable clinical/pathologic characteristics (↑Fuhrman grade, large tumors, sarcomatoid and/or Tu necrosis)
- **T1-T2** clinically (-) LN offers **limited** staging information and **no oncological benefit**

Linfadenectomia no Cancer Renal

Fatores Preditivos de LN (+)

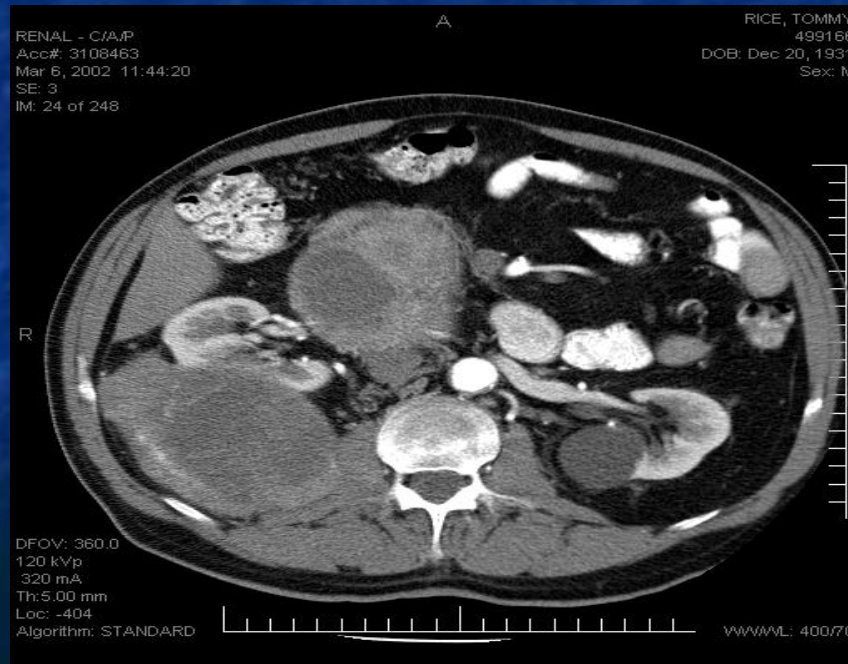
Tu > 10 cm

Fuhrman 3 e 4

Componente sarcomatóide

Tumor localmente avançado

Necrose tumoral



Capitanio et al. Eur Urol, 2011

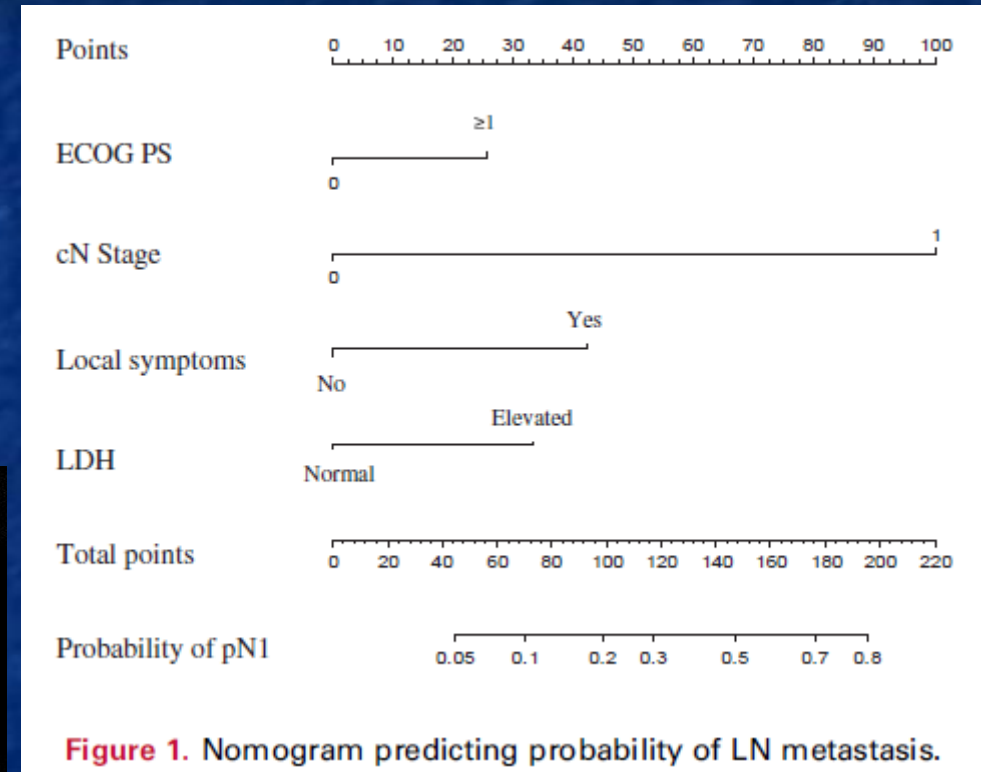


Figure 1. Nomogram predicting probability of LN metastasis.

Babaian K, et al., J Urol, 2015

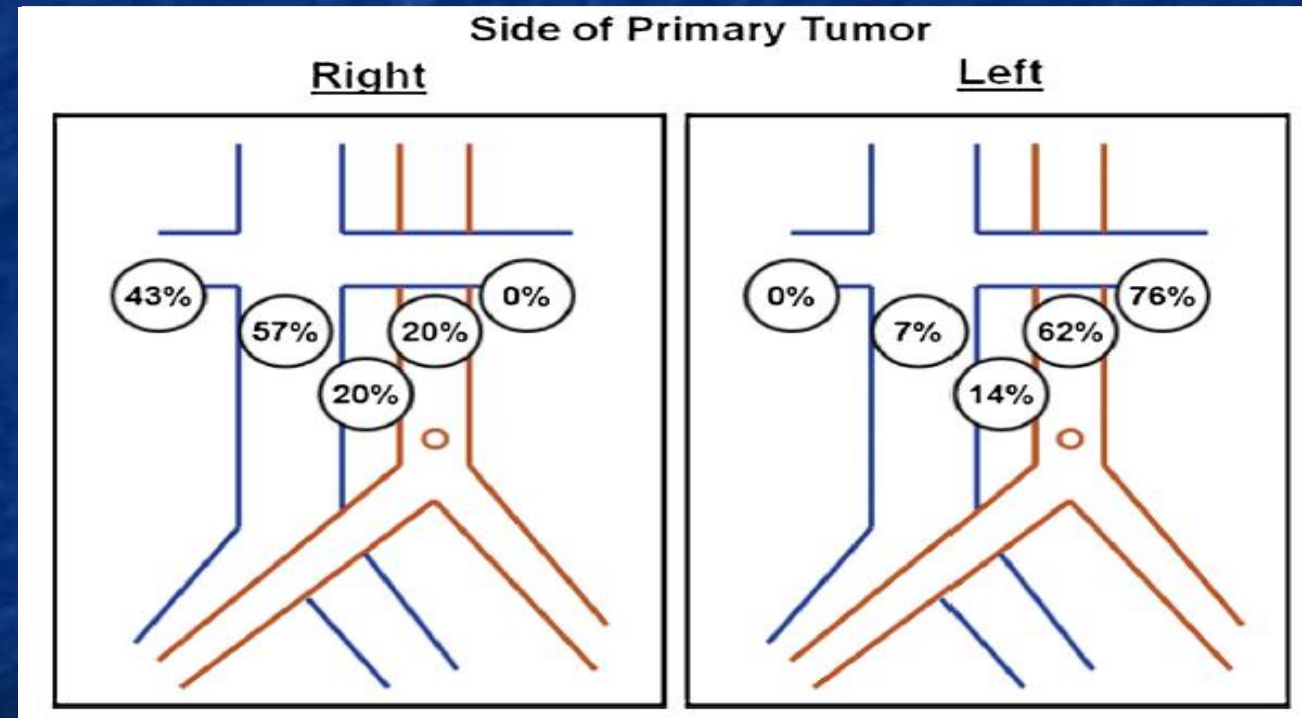
Kidney Cancer

Lymph Node Dissection at the Time of Radical Nephrectomy for High-Risk Clear Cell Renal Cell Carcinoma: Indications and Recommendations for Surgical Templates

Paul L. Crispen^a, Rodney H. Breau^a, Cristine Allmer^b, Christine M. Lohse^b, John C. Cheville^c, Bradley C. Leibovich^a, Michael L. Blute^{a,*}

Quando indicada LND:

- **Lado direito:** remoção de LN – hilares, paracavais e inter-aortocavais
- **Lado esquerdo:** hilares, para-aórticos e inter-aortocavais
- Desde a crura do diafragma até a artéria ilíaca comum



Localização de +LN baseado na lateralidade tumoral. Porcentagem representa frequência de envolvimento da localização em pts com positividade linfonodal

LND em câncer renal

Tendências – *Take Home Messages*

- Tumores localizados (T1-T2)
incidência 0,4% - 3%
 - Nefrectomias parciais
 - Tto. minimamente invasivo
- Alto risco de envolvimento nodal
(fatores independentes)**

T3/T4

Tus > 10 cm

Fuhrman III/IV

Diferenciação sarcomatóide

Citoredução

Imagem suspeita - necrose

→ LND rotina **NÃO**



→ **SIM**

Capitanio U et al. Eur Urol 2011

Pompeo A, Sadi MV, Wroclawski E - Algoritmos em Urologia 2007

**Obs.: a literatura dá respaldo à
linfadenectomia estendida**

Systematic Review of Adrenalectomy and Lymph Node Dissection in Locally Advanced Renal Cell Carcinoma

Hendrika J. Bekema^a, Steven MacLennan^b, Mari Imamura^b, Thomas B.L. Lam^{b,c,*},
Fiona Stewart^d, Neil Scott^e, Graeme MacLennan^d, Sam McClinton^c,
T.R. Leyshon Griffiths^f, Andreas Skolarikos^g, Sara J. MacLennan^b, Richard Sylvester^h,
Börje Ljungbergⁱ, James N'Dow^{b,c}

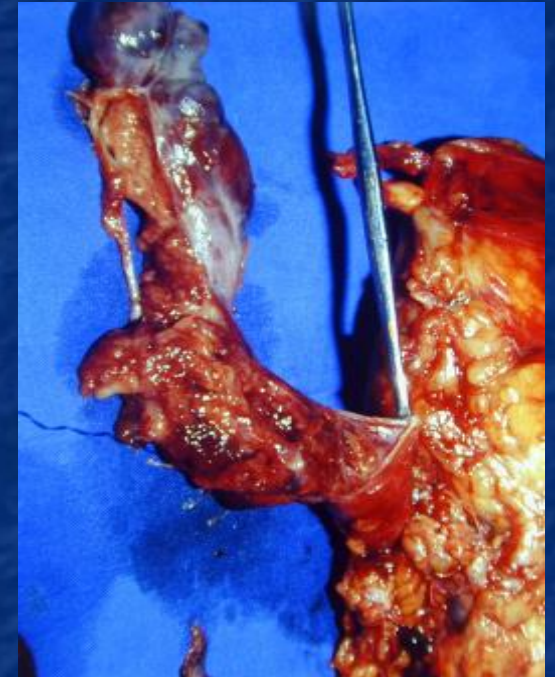


Conclusions: There is insufficient evidence to draw any conclusions on oncologic outcomes for... **ipsilateral adrenalectomy** compared with patients having RN alone for cT3–T4N0M0 RCC. Further research... is needed ...

Ca Renal Localmente Avançado

Invasão Vascular - Tratamento

- Não tratados: evolução ➔ óbito
- Tratamento cirúrgico: nefrectomia radical +
 - Retirada do trombo
 - Remoção de segmento caval quando infiltrada
 - Casos complexos
 - Circulação extracorpórea
 - Hipotermia profunda
 - Mobilização do trombo
 - Princípio básico: controle vascular (hemorragia-tromboembolismo)
- SV Ca-específica: 10 a **15%** ➔ **50%**



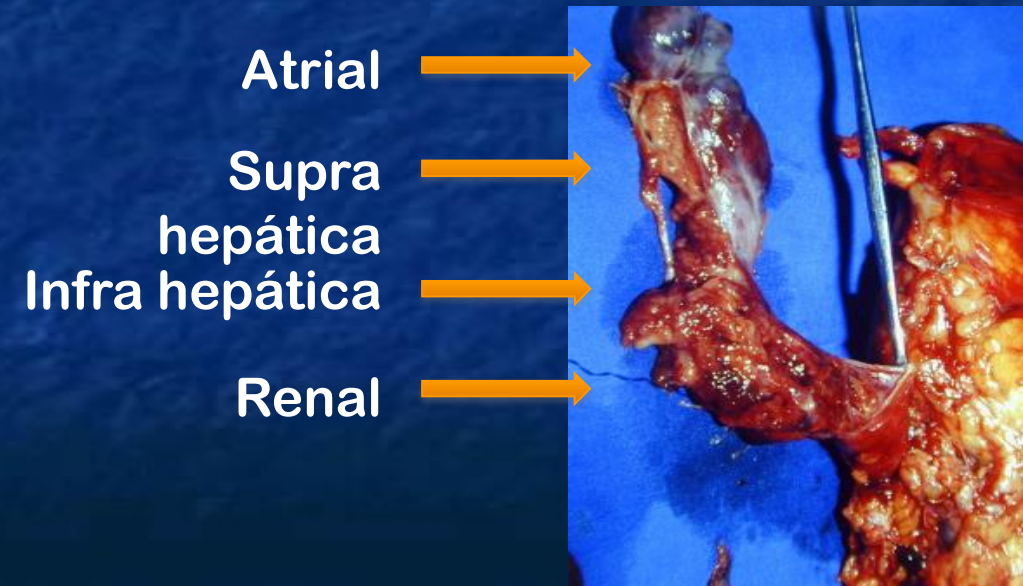
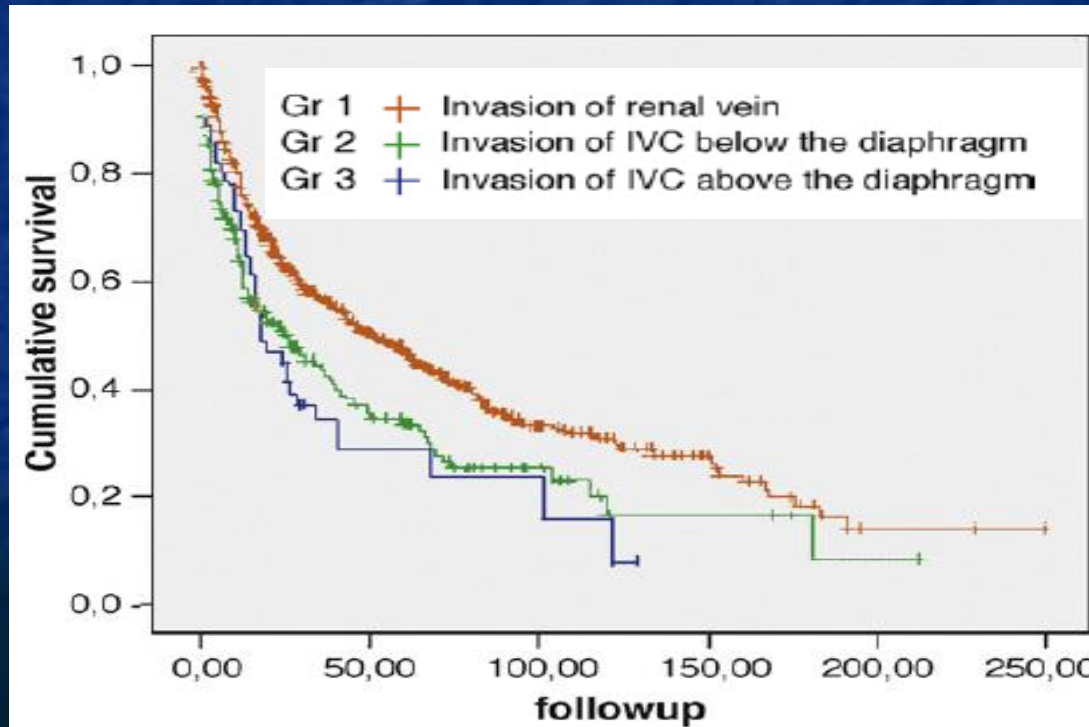
Ca Renal - Invasão Vascular

Extensão do trombo – Prognóstico

- Estudo retrospectivo. (n=1192 nefrect.) - pT3b / pT3c
SG > em pts com trombo na veia renal vs. veia cava
- Estudo prospectivo. (n=134) SCE > pts com trombo em nível infra-hepático vs. trombo ao nível das hepáticas ou mais altos

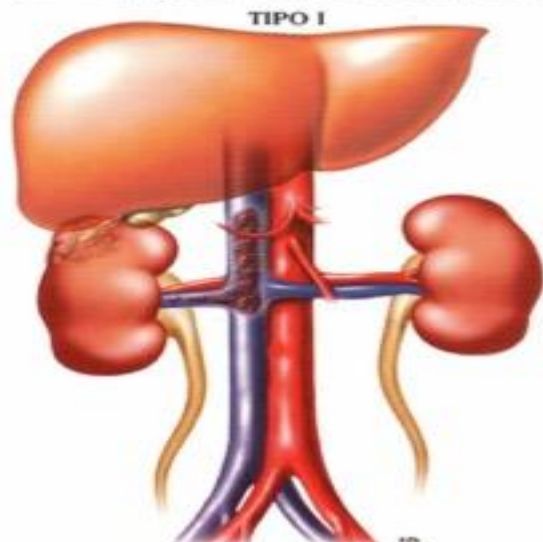
Wagner B et al Eur Urol 2009;55

Haferkamp A et al J Urol 2007;177

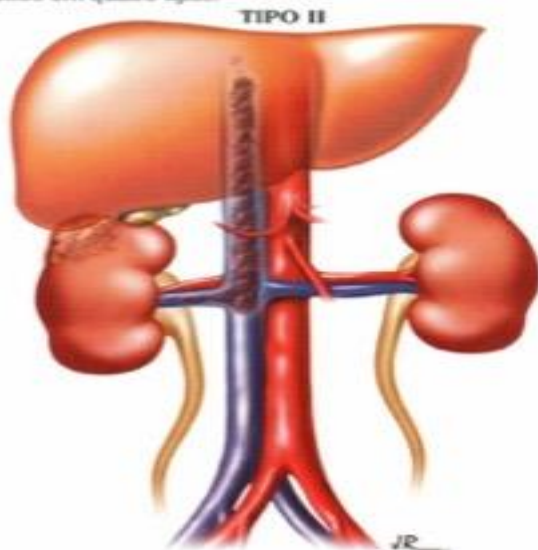


Tumor renal com invasão vascular – Variações técnicas

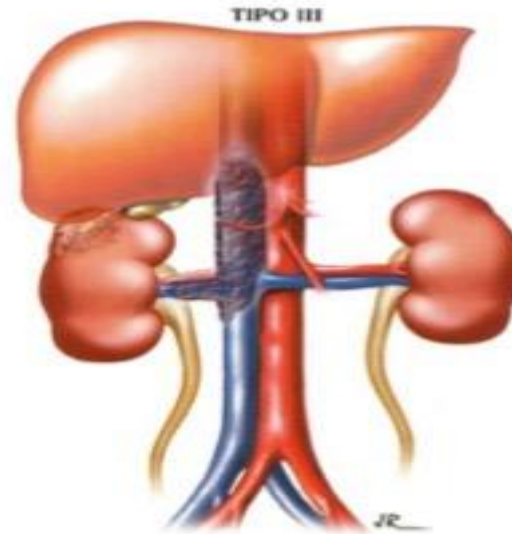
Quanto à topografia, o trombo da veia cava pode ser classificado em quatro tipos:



Infra hepático



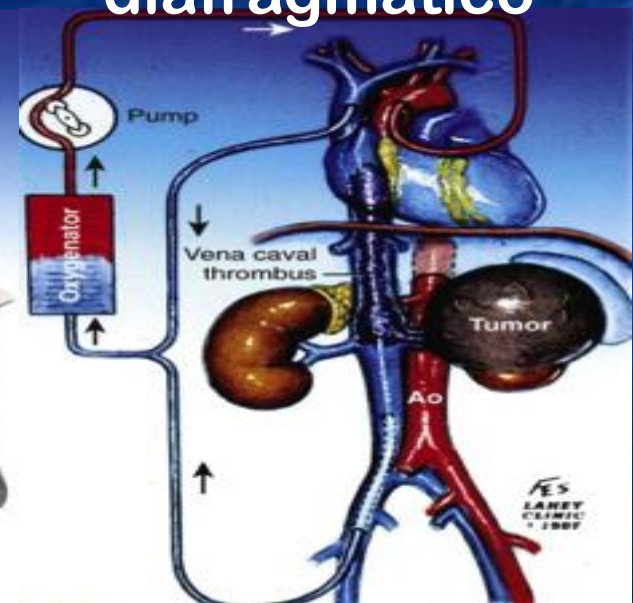
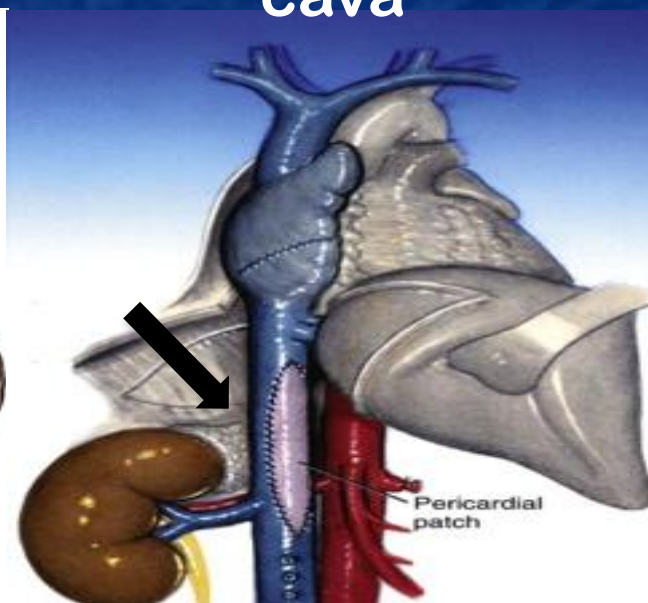
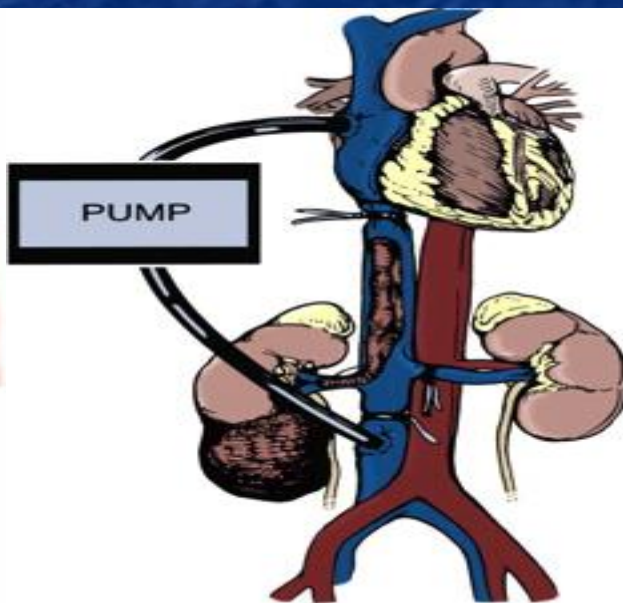
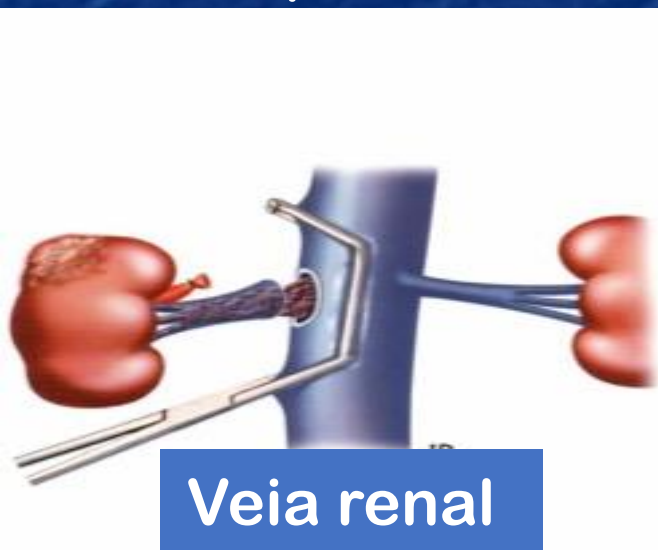
Retro hepático



Infiltração parede cava



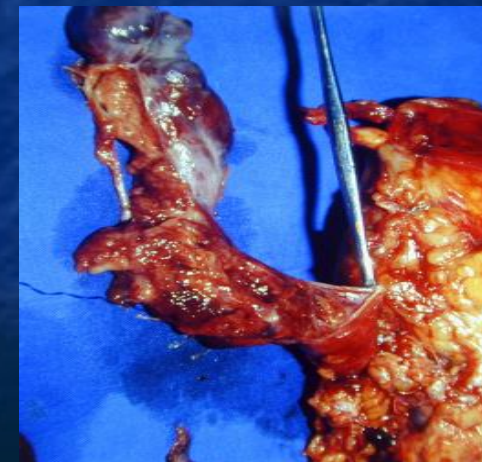
Supra diafragmático



Ca Renal com Invasão Atrial

Técnica Cirúrgica

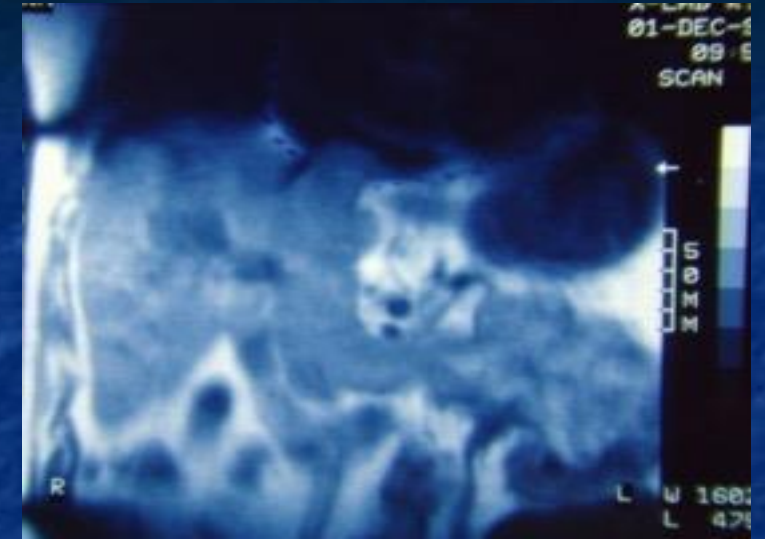
- Incisão mediana abdominal ou *Chevron* bilateral com extensão cranial
- Completa mobilização do rim tumoral e cava antes da anticoagulação
- Externotomia e Bypass cardio-pulmonar; canulação da aorta e v. Cava sup.
- A seguir duas técnicas:
 - Parada cardio-resp com hipotermia (28° C) e circulação com bomba de perfusão
 - Parada cardio-resp com hipotermia acentuada (14° C) e completa exsanguinação por período não superior a 30 minutos
- Abertura atrial, da veia cava e retirada do rim + trombo. Linfadenectomia



Tumores Renais com Invasão Atrial



Resultados
n = 12



Nº	Remoção completa	SED	Seguimento (meses)	Óbitos*
8 RCC	6/8 (75%)	4/8 (50%)	8 - 81	3
4 Wilm's	100%	3/4 (75%)	36 - 91	-

*PO tardio 2
Intra-op 1

Ca Renal com Invasão Vascular

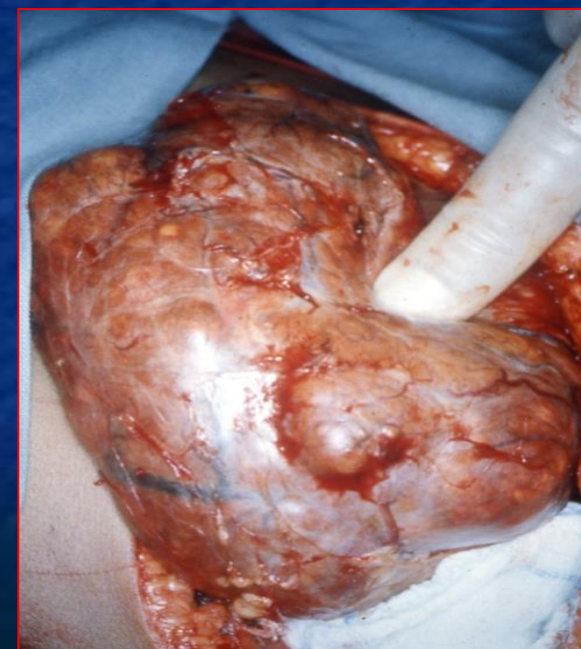
Take Home Messages

- Pode ser removido cirurgicamente com segurança
- Controle vascular é **medida mandatória** que permite excisão tumoral sem perdas sanguíneas significativas
- Complicações pós-operatórias são aceitáveis
- Potencial expressivo de sobrevida a longo prazo para pacientes **sem infiltração linfonodal (fator prognóstico ↓↓↓)**
- Infiltração parede vascular (**prognóstico ↓**)
- Casos complexos – necessidade de equipe multidisciplinar
- A indicação de tto sistêmico (neo/adjuvante) é controversa

Embolização Arterial Seletiva*

- Eficaz no controle da hematúria
- Nefrectomias tecnicamente mais fáceis
- Menor perda sangüínea
- Eficaz no tratamento de fístulas artério-venosas

n = 19



*Pompeo ACL Tese de Mestrado FMUSP, 1979

Ca Renal localmente avançado

Embolização arterial

- *“in pts unfit for surgery with massive haematuria, or flank pain, embolisation can be a beneficial palliative approach”*

Ca Renal Localmente Avançado

Tratamento – Neo/Adjuvância*

- **Adjuvância – Racional**
 - Diminuir risco de recorrência local / sistêmica
 - Nomogramas prognósticos: SSIGN. UISS ...
- **Neoadjuvância - Racional**
 - Redução tumoral. Tus. inop. → op.
 - Ressecções menos extensas → NSS
 - Redução 10%-20% do tamanho tu.

* Sunitinibe, Pazopanibe, Sorafenibe, mTOR, Girentuximabe, anti PD1 antibody, Nivolumab, tumor cell vaccines, etc

Resultados? PFS. OS?

Silberstein JL et al. BJU Int 2010;106
Cowey CL et al. J Clin Oncol 2010;28
EAU 2016 Guidelines; ESMO 2016

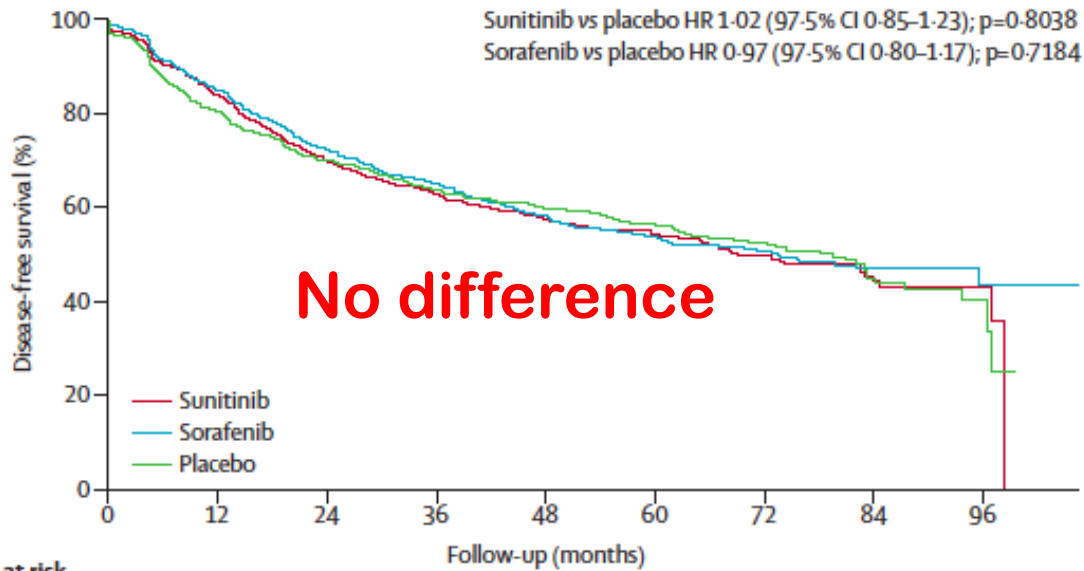
RCC Adjuvant Trials

Clinical Trial	Study Intervention	Duration (years)	N	Clear Cell	Patient Population	Primary Endpoint	Time	Stratification during Study	Imaging	NCT Identifier
ASSURE	Sunitinib vs. sorafenib vs. placebo	1	1943	Or nccRCC	pT1b (G3-4), pT2-4, pN+	DFS	Apr 2006-Sep 2010	Histology, Surgery, ECOG PS, Risk	q4.5mo x 1 yr, then q6mo x 2 yr, then q12mo	NCT00326898
S-TRAC	Sunitinib vs. placebo	1	615	Only	pT3-4, pN+	DFS	Jul 2007-Nov 2015	UISS Risk, ECOG PS, Country of residence	q3mo x 3 yr, then q6mo	NCT00375674
ARISER	Girentuximab vs. placebo	0.5	864	Only	pT1b-2 (G3-4), pT3-4, pN+	DFS + OS	Jun 2004-Apr 2013	UISS Risk, Region of the world	q3mo x 2 yr, then q6mo x 2 yr, then q12mo	NCT00087022
PROTECT	Pazopanib vs. placebo	1	1540	Only	pT2 (G3-4), pT3-4, pN+	DFS	Nov 2010-Oct 2015	Surgery, Risk	~q4mo x 1 yr, then q6mo x 4 yr, then q12mo	NCT01235962
EVEREST	Everolimus vs. placebo	1	1545	Or nccRCC	pT1b (G3-4), pT2-4, pN+	DFS	Apr 2011-Oct 2021	Histology, ECOG PS, Risk	q4mo x 1yr, then q6mo x 2yr, then q12mo	NCT01120249
SORCE	Sorafenib (1 vs 3 y) vs. placebo	1	1656	Or nccRCC	Intermediate- or high-risk RCC (Leibovich score, 3-11)	DFS	Jun 2007-Aug 2012	Yes (factors N/A)	q6mo x 3 yr	NCT00492258
ATLAS	Axitinib vs. placebo	3	700	Only	pT2-4, pN+	DFS	Apr 2012-Jun 2017	N/A	N/A	NCT01599754
IMmotion 010	Atezolizumab vs. placebo	1	664	Or sarcomatoid dedifferentiation	pT2 (G3-4), pT3a (G4), pT3b-4, pN+, NED after mets surgery	DFS	Jan 2017-Jun 2024	Risk, Region of the world, PD-L1 IHC	q3mo x 3 yr, then q6mo	NCT03024996
PROSPER	Nivolumab (neoadj+adj) vs. observation	0.8	766	Or nccRCC	cT2-4, cN+	RFS	Feb 2017-July 2022	Histology, cT, cN	q4.5mo twice, then q6mo x 1 yr, then q12mo	NCT03055013

Resultados ? DFS ? OS ?

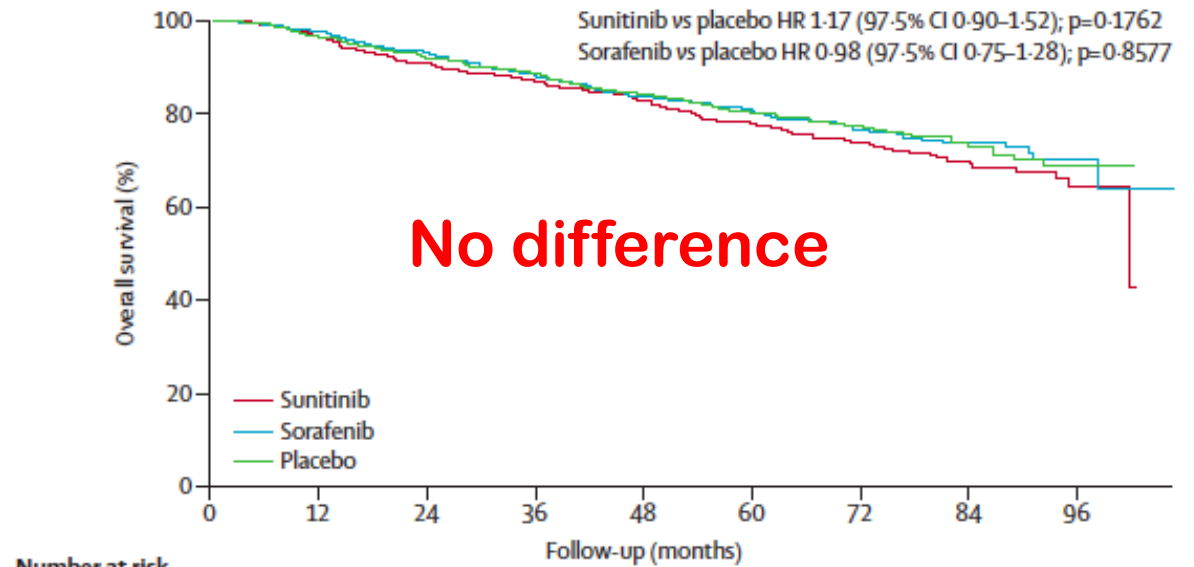
ASSURE: Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ECOG 2805)

Disease-Free Survival



Number at risk	0	12	24	36	48	60	72	84	96
Sunitinib	647	500	397	338	279	194	102	42	7
Sorafenib	649	517	423	357	297	199	114	48	11
Placebo	647	499	414	360	312	200	111	48	7

Overall Survival

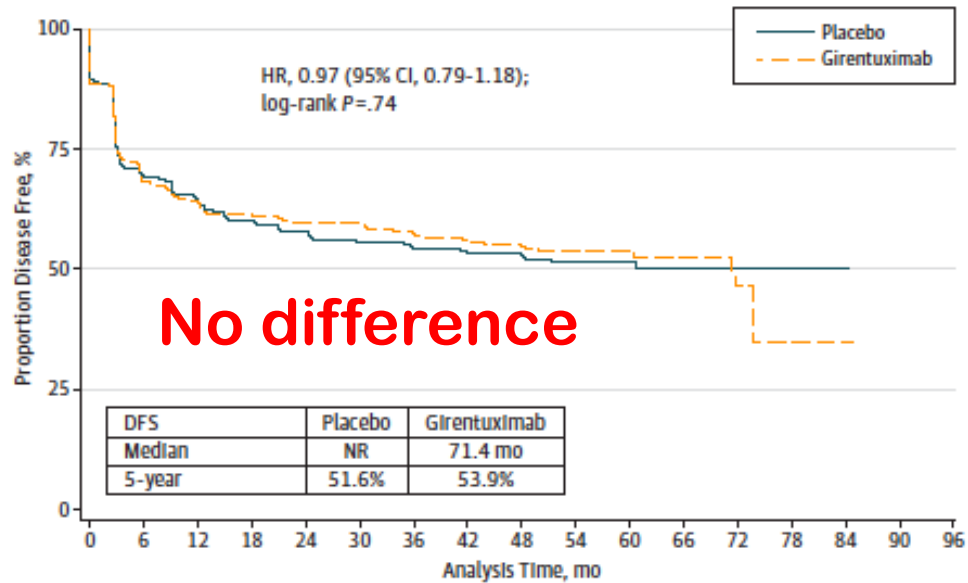


Number at risk	0	12	24	36	48	60	72	84	96
Sunitinib	647	586	543	503	458	332	190	89	22
Sorafenib	649	597	562	514	474	353	203	97	26
Placebo	647	606	569	533	482	349	211	104	22

ARISER: Adjuvant Rencarex[®]* Immunotherapy Trial to Study Efficacy in Non-Metastatic RCC

A DFS

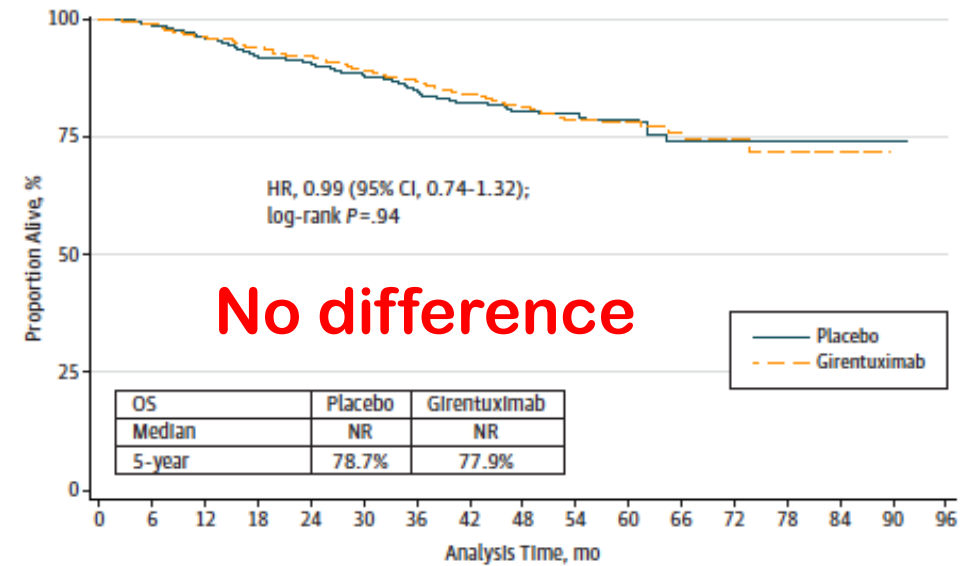
Disease-Free Survival



No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Placebo	431	283	262	237	227	215	203	194	167	76	64	15	12	3	3	0	0
Girentuximab	433	280	259	243	228	221	210	194	167	88	74	18	12	3	2	0	0

B OS

Overall Survival



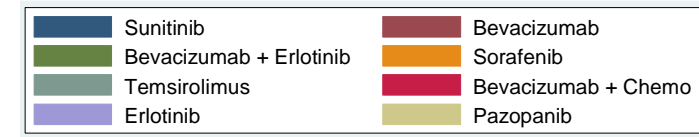
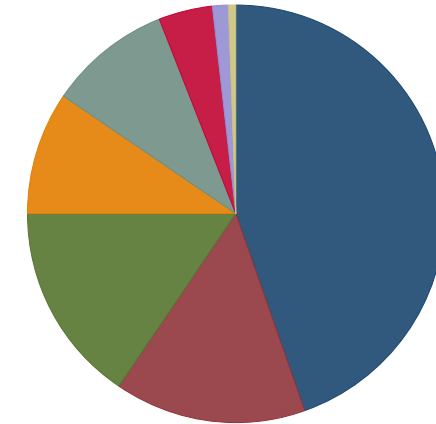
No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Placebo	431	416	402	378	372	359	344	328	297	218	128	45	26	12	5	1	0
Girentuximab	433	421	407	393	382	365	353	335	301	220	132	56	29	10	4	0	0

* Girentuximab

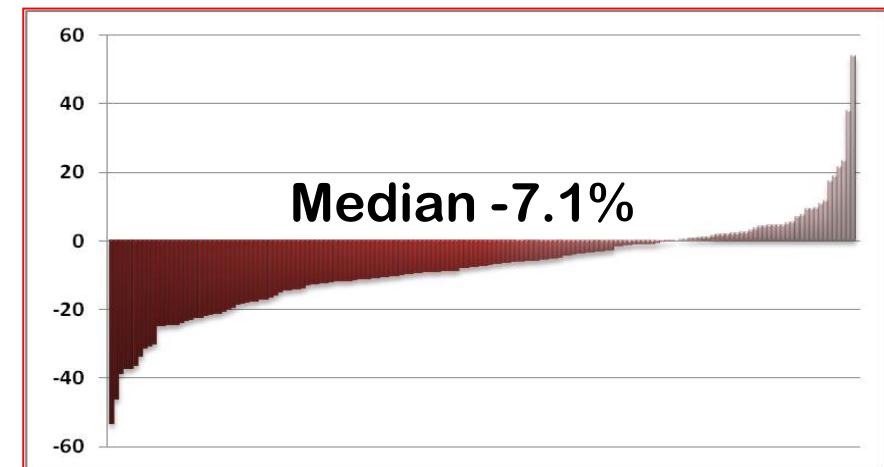
Types of targeted therapy – RESULTS – Neoadj

	N	%
sunitinib	75	44.6
bevacizumab	25	14.9
bevacizumab/ erlotinib	26	15.5
sorafenib	16	9.5
temsirolimus	16	9.5
bevacizumab/ chemo	7	4.2
erlotinib	2	1.2
pazopanib	1	0.6
Total	168	100

Abel et al., Eur Urol, 2011



Maximum overall response in primary tumor



Immune Checkpoint Modulators

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

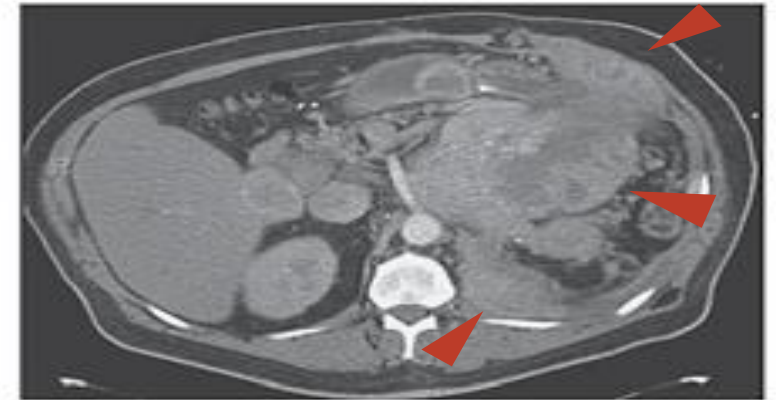
JUNE 28, 2012

VOL. 366 NO. 26

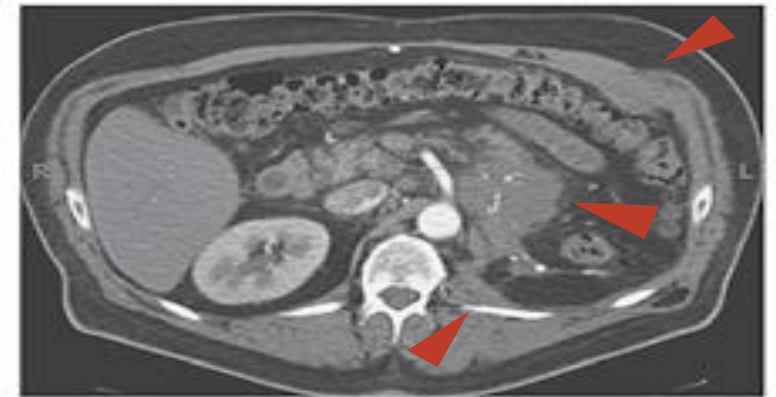
Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

B Patient with Renal-Cell Cancer Before Treatment



6 Months



Sunitinibe e Sorafenibe

Efeitos adversos

- Mucosite
- Síndrome mão-pé
- Diarréia, náuseas e vômitos
- Fadiga
- Mielosupressão
- Alteração na cor dos cabelos
- Hipertensão



Grau 1



Grau 2



Grau 3



Grau 4

Motzer RJ, NEJM 356:115-24, 2007

Pazopanibe - efeitos adversos ↓

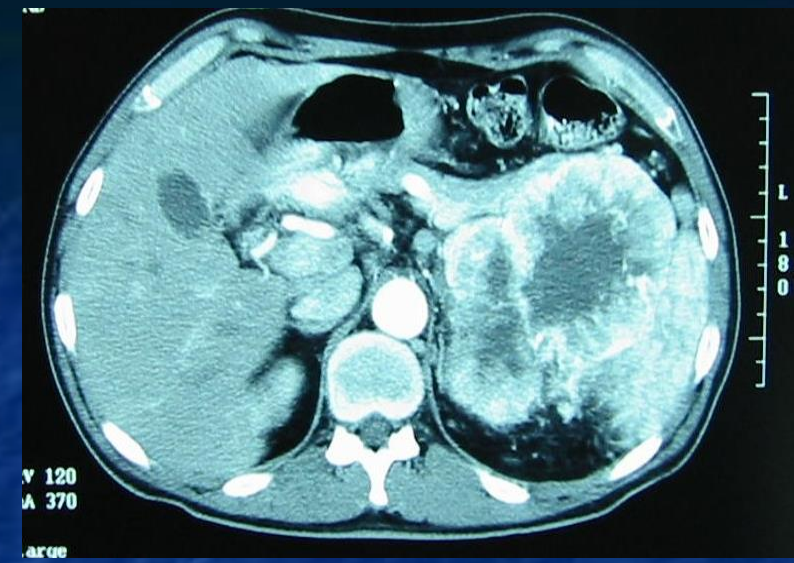
Sternberg CN, JCO 28;1061-8, 2010

Ca Renal Localmente Avançado Neo/Adjuvância - Take Home Messages

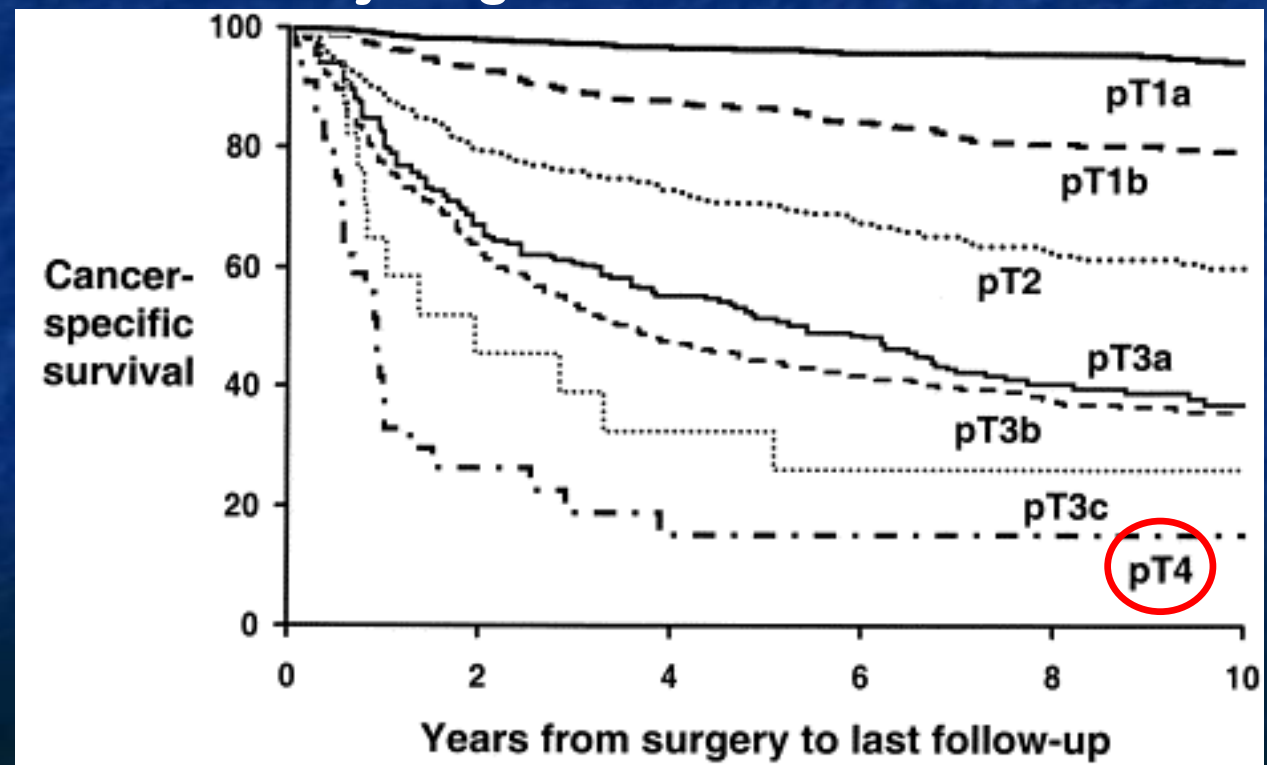
- **Até o momento não existe agente efetivo aprovado para neo/adjuvância no RCC**
- **Dados insuficientes relativos à DFS, CES e OS**
- **Terapia ainda “investigacional”**

Ca Renal Localmente Avançado pT4 - Considerações

- História natural variável
- cT4 = pT4? Falha de exames de imagem em 50%
- Maior potencial de agressividade
- Terapia sistêmica?



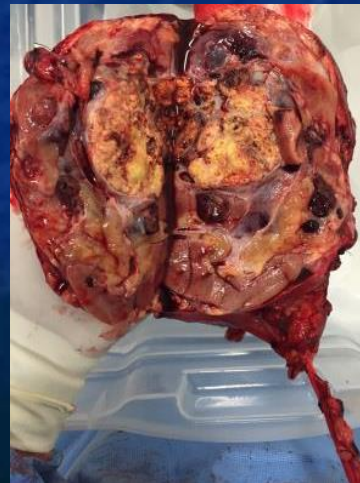
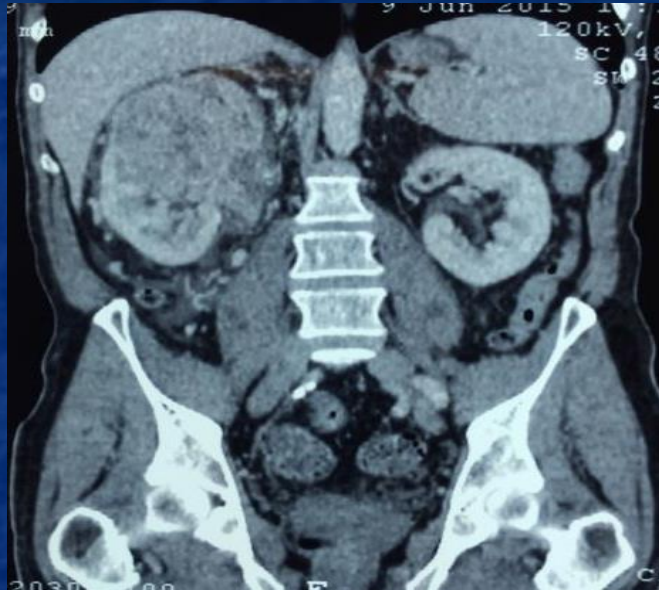
Survival by stage: T4 renal cell carcinoma



59 a, m, bco.

Hematúria macro (1 m)

DM tipo 1. Tabagista, perda ponderal (15 kg 4 m)



RCC Fuhrman IV

- pT3bN0Mx
- 18 LN (-)
- margem (-)

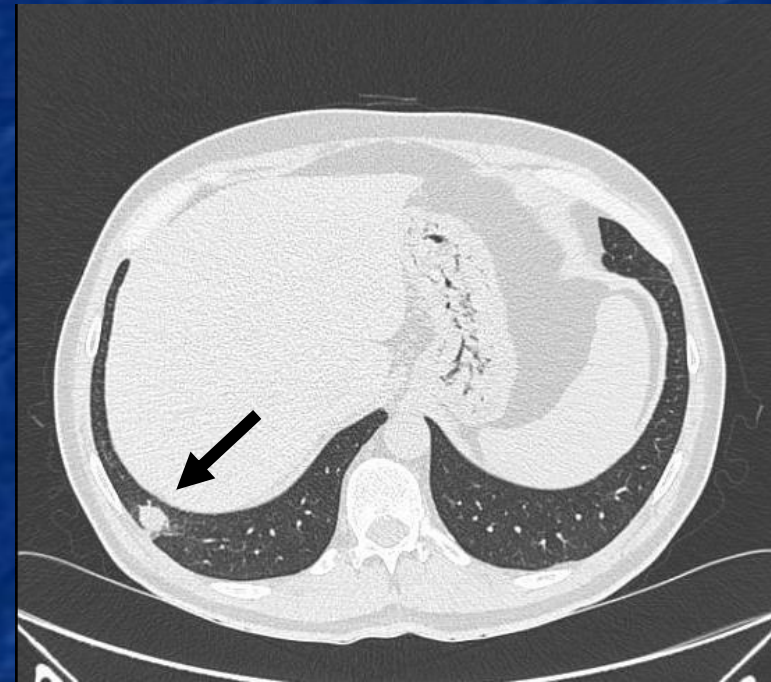
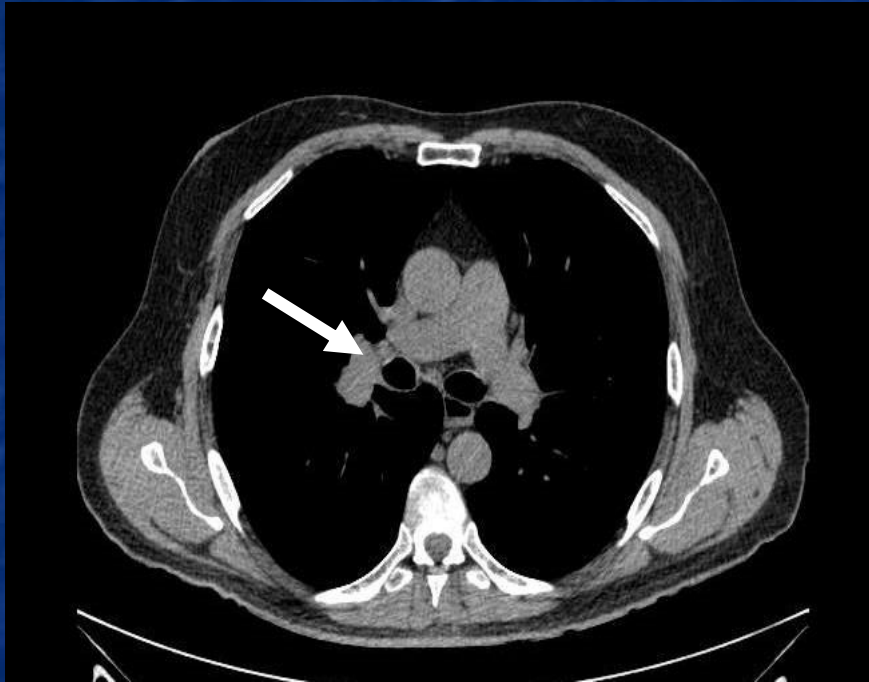
Adjuvância?

59 a, m, bco.

Hematúria macro (1 m)

DM tipo 1. Tabagista, perda ponderal (15 kg 4 m)

Nefrectomia radical + LND há 3 a. pT3bN0Mx. Não fez adjuvância



Iniciou tto pazopanibe

Ca Renal Localmente Avançado

Conclusões

- Tratamento cirúrgico radical quando factível, é mandatório
- O papel da LND permanece controverso. A baixa morbidade e o potencial benefício → tendência de realizá-la
- A adrenalectomia pode ser evitada em casos selecionados
(TC – achados cirúrgicos)
- Neo / adjuvância aguardam resultados mais consistentes para sua indicação rotineira. O potencial terapêutico é significativo



Obrigado!

