AUA Annual Meeting 25-30 april 2009 chicago, illinois usa

American Urological Association Education and Research, Inc.

AUA KONGRESİ SONRASI UYGULAMADA YENİLİKLER

ÜROONKOLOJİ

Dr. Ö. Levent ÖZDAL

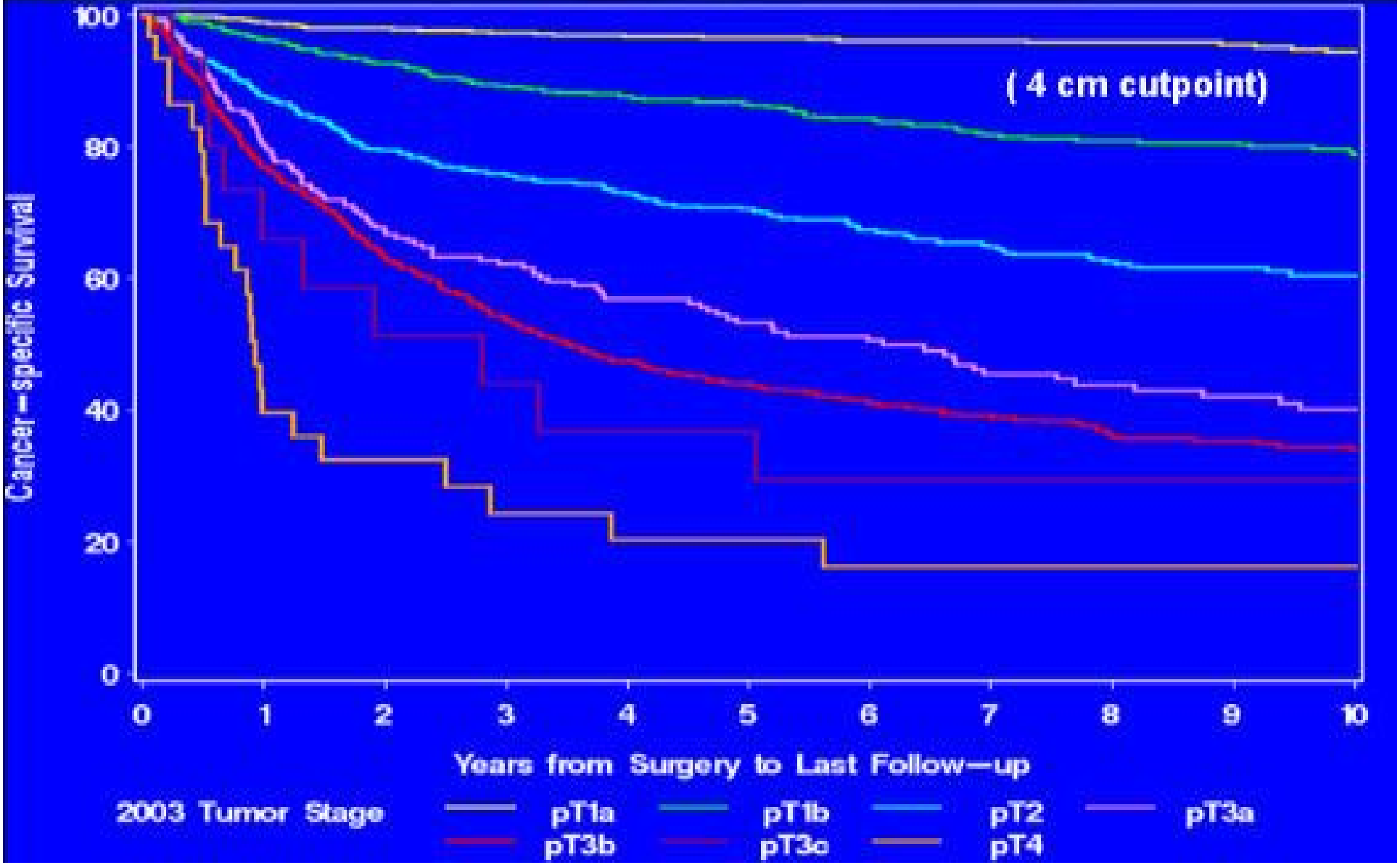
Böbrek Tümörleri

TNM Stage of Renal Cancer

UICC/AJCC 1997		AJCC 2003
T_1	≤7.0 cm, limited to kidney	T_{1a} < 4.0 cm
T_2	>7.0 cm, limited to kidney	T_{1b} 4 - 7 cm
T_{3a}	Perinephric fat, adrenal involved	
T_{3b}	RV, Vena Cava below diaphragm	
T_{3c}	Vena Cava above diaphragm	
T_4	Beyond Gerota's fascia	

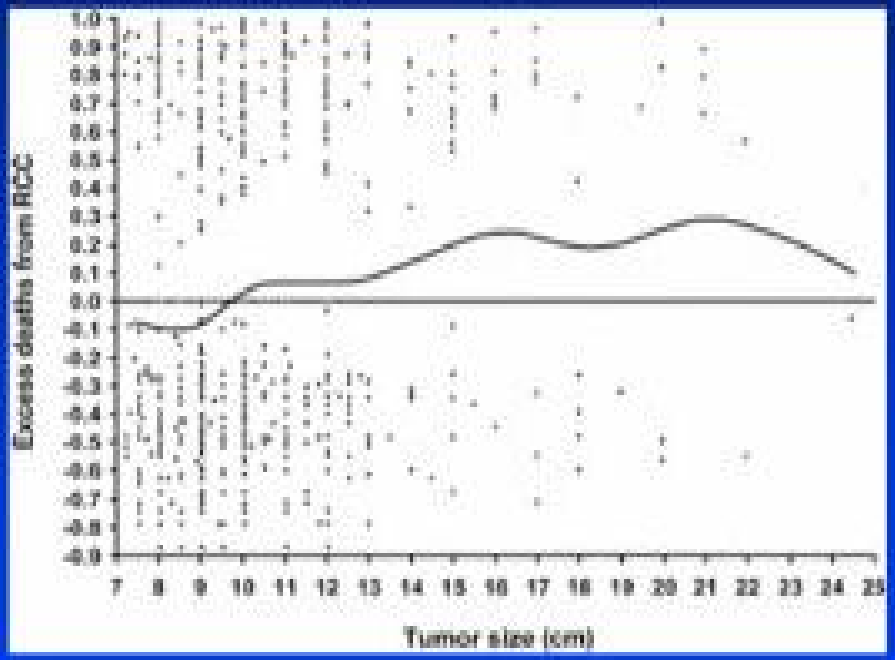
2003 Tumor Classification

Mayo Clinic n= 2,935

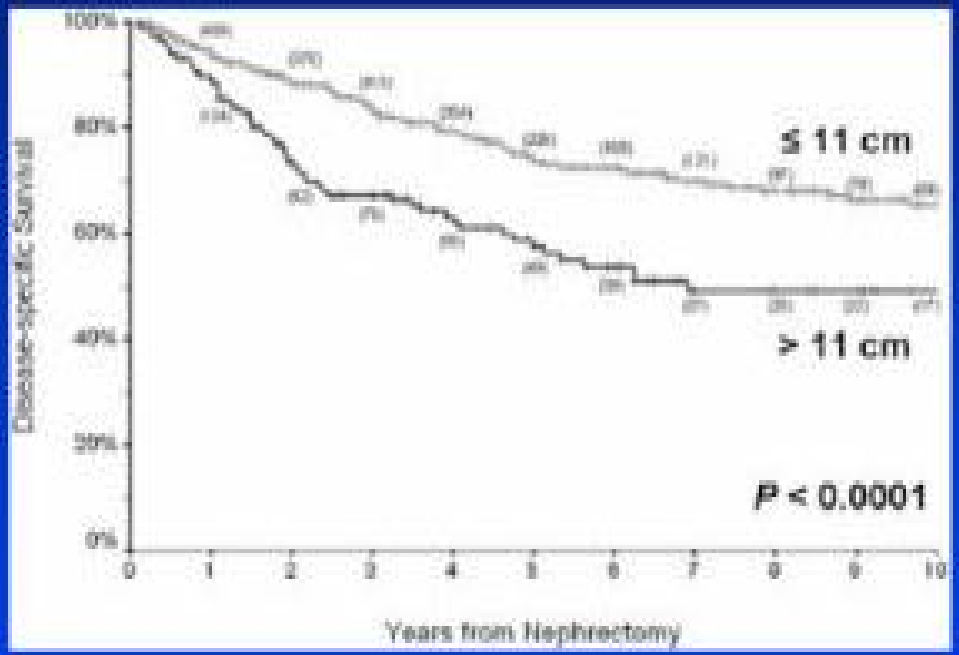


Subdivision of T2

Frank et al, J Urol 2005



Klatte et al, J Urol 2007



Several others

Çağdaş Evreleme ve Prognoz

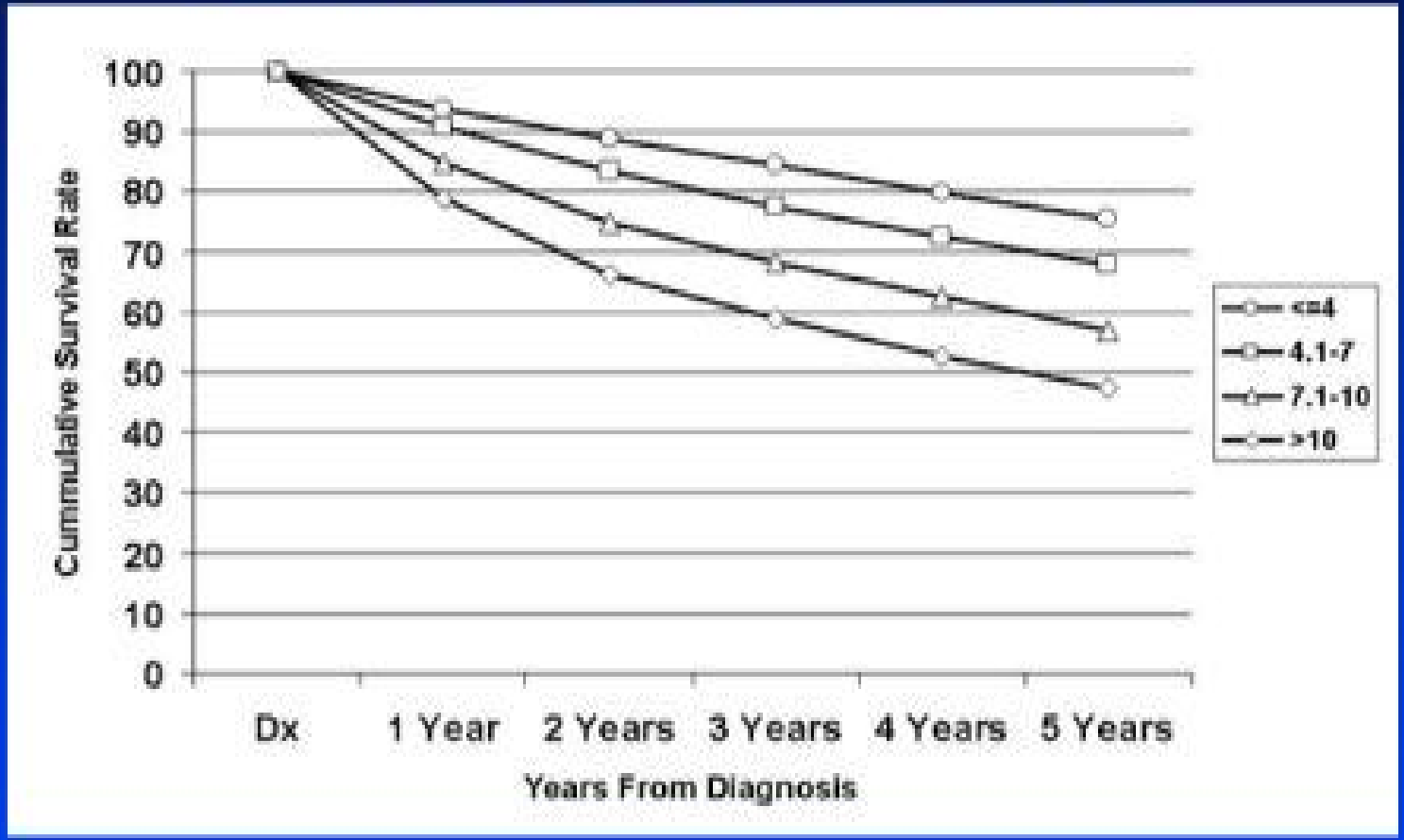
- T2 tümörlerde 10 cm'lik boyutun altında ve üstünde önemli bir prognoz farklılığı gözlenmekte

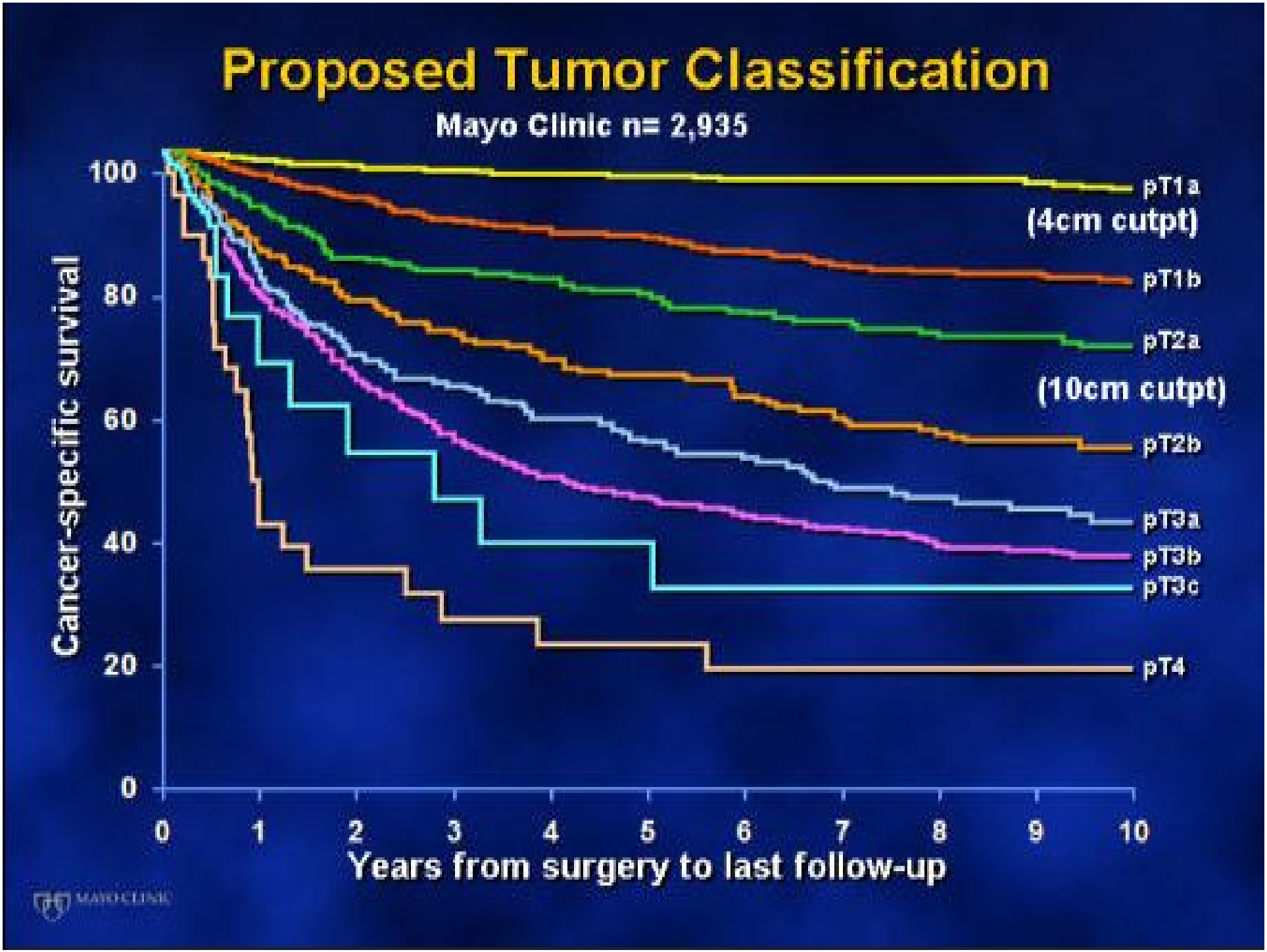
- Amerikan ulusal verilerine göre 2003 pT2 tümör klasifikasyonu
  - 10cm< pT2a
  - 10cm> pT2b

prognostik keskinlik artar

Subdivision of T2

National Cancer Database




Proposed Tumor Classification
Mayo Clinic n= 2,935
Cancer-specific survival
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
10
Years from surgery to last follow-up
pT1a
(4cm cutpt)
pT1b
pT2a
(10cm cutpt)
pT2b
pT3a
pT3b
pT3c
pT4
MAYO CLINIC

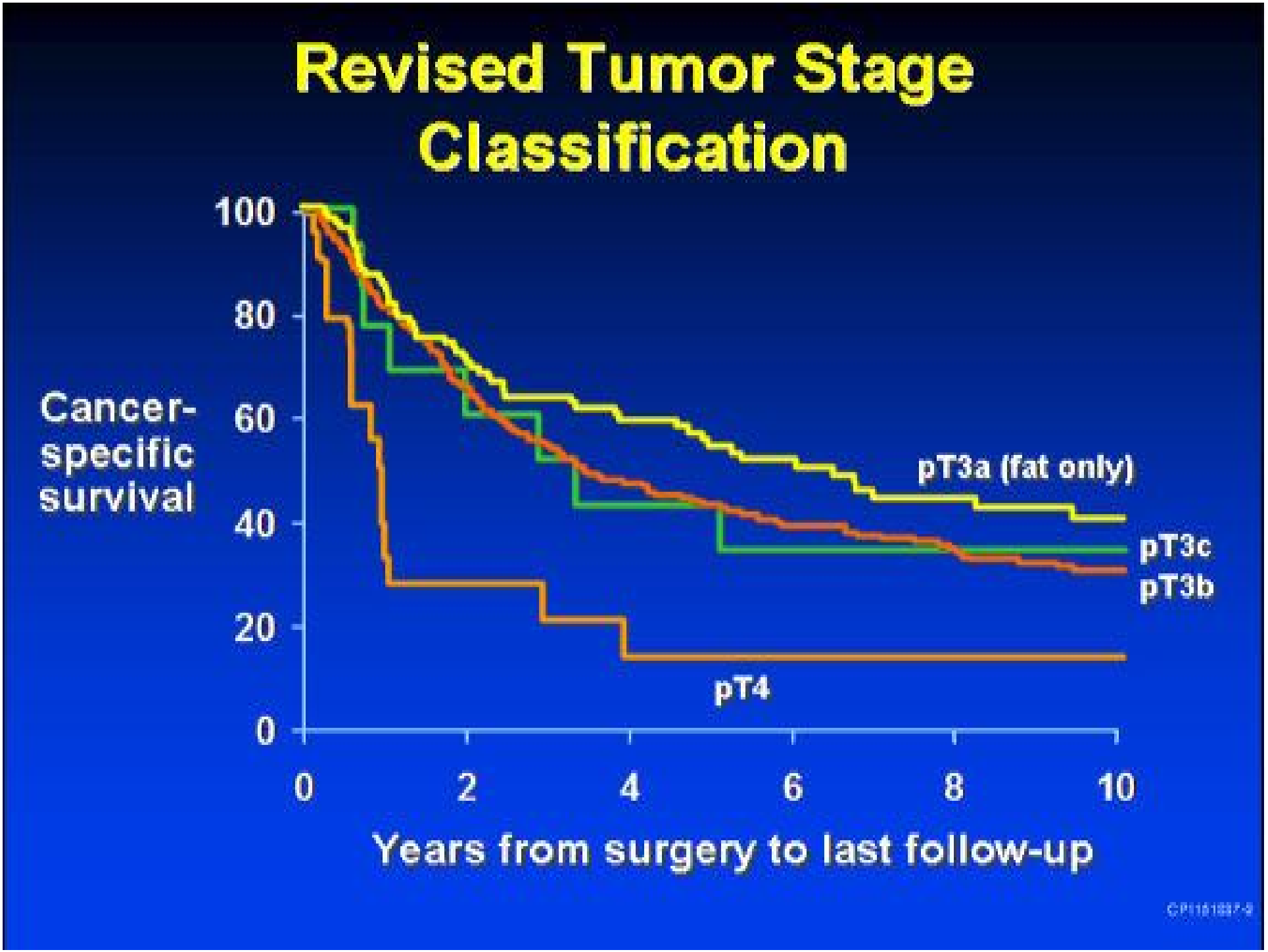
RCC TNM Evreleme

- T3a adrenal, perinefrik yağ veya renal sinus yağ invazyonu
- T3b renal ven veya IVC de trombus (diyafram altı)
- T3c IVC invazyonu, IVC de trombus (diyafram üstü)
  - 2003 AJCC TNM pT3

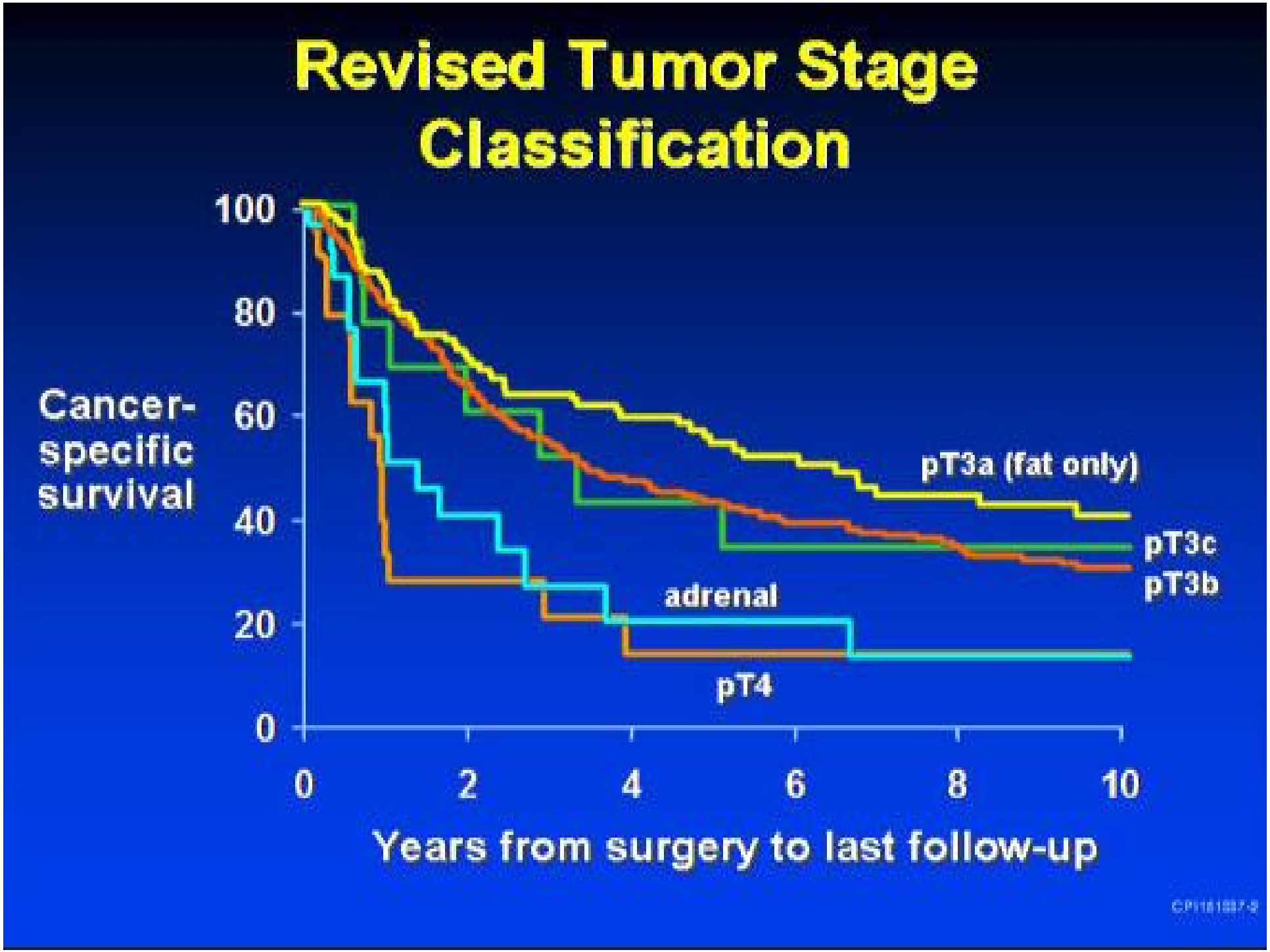
RCC TNM Evreleme

- T3a adrenal tutulumu, perinefrik yağ tutulumuna göre daha kötü prognoza sahip
- Adrenal tutulumu T4 tm' lerle benzer sağkalım özelliği göstermekte
  - Han et al, UCLA, 2003
  - Thompson et al, MAYO, 2005

Revised Tumor Stage Classification



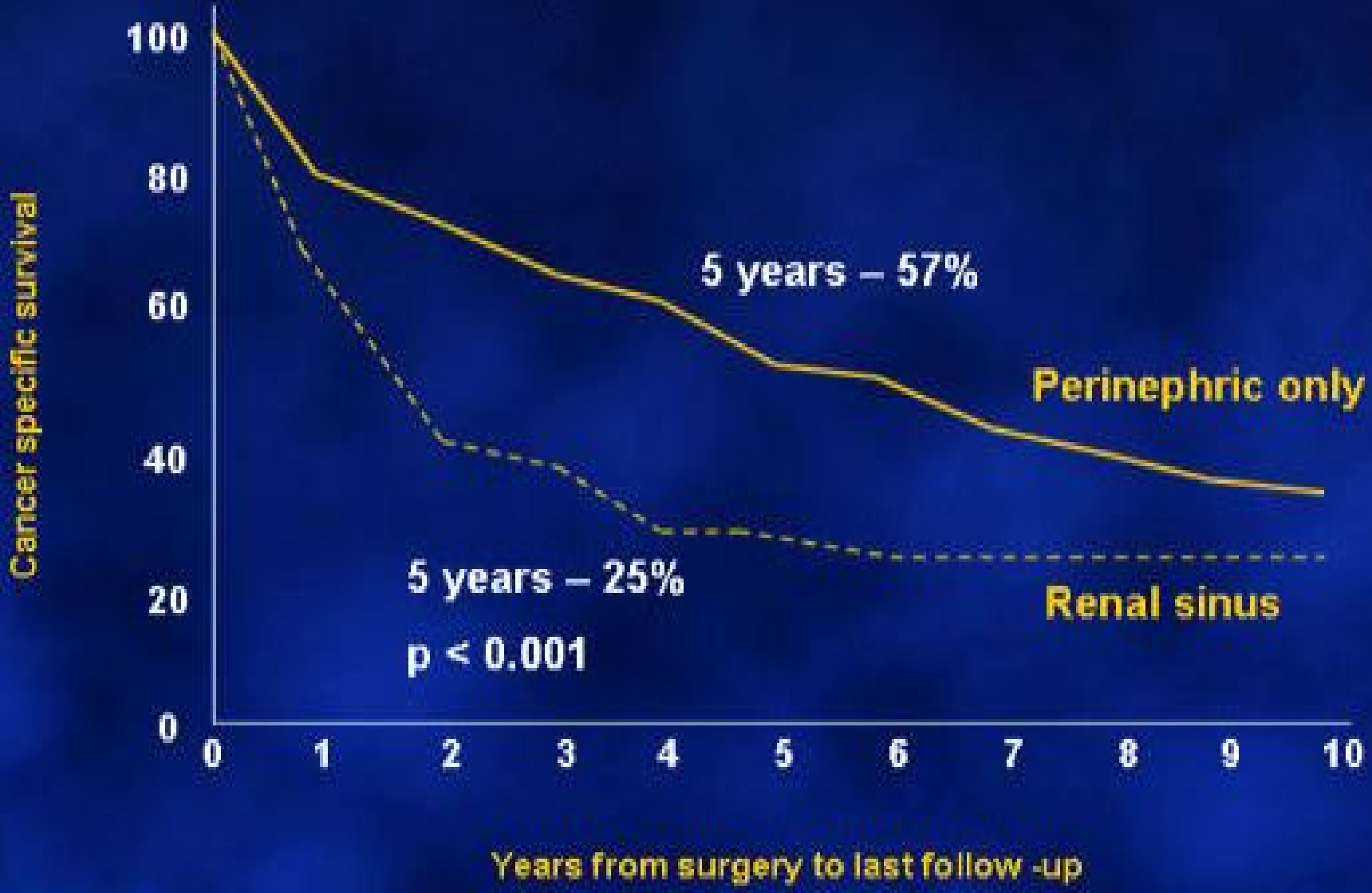
Revised Tumor Stage Classification



RCC TNM Evreleme

- Renal sinüs invazyonu gösteren tümörler sadece perinefrik yağ invazyonu gösteren tümörlere göre daha kötü prognoza sahip

Association of renal sinus fat invasion with death from RCC for 205 patients with pT3a clear cell renal cell carcinoma



MAYO CLINIC

Proposed TNM v7: T stage

Tx: Primary tumor cannot be assessed

T0: No evidence of primary tumor

T1a: Tumor ≤ 4cm, limited to kidney

T1b: Tumor > 4cm ≤ 7cm, limited to kidney

T2a: Tumor > 7cm ≤ 10cm, limited to kidney

T2b: Tumor > 10 cm, limited to kidney

T3a: Perirenal fat and/or renal sinus fat and/or invasion of renal vein or segmental branches (muscle containing)

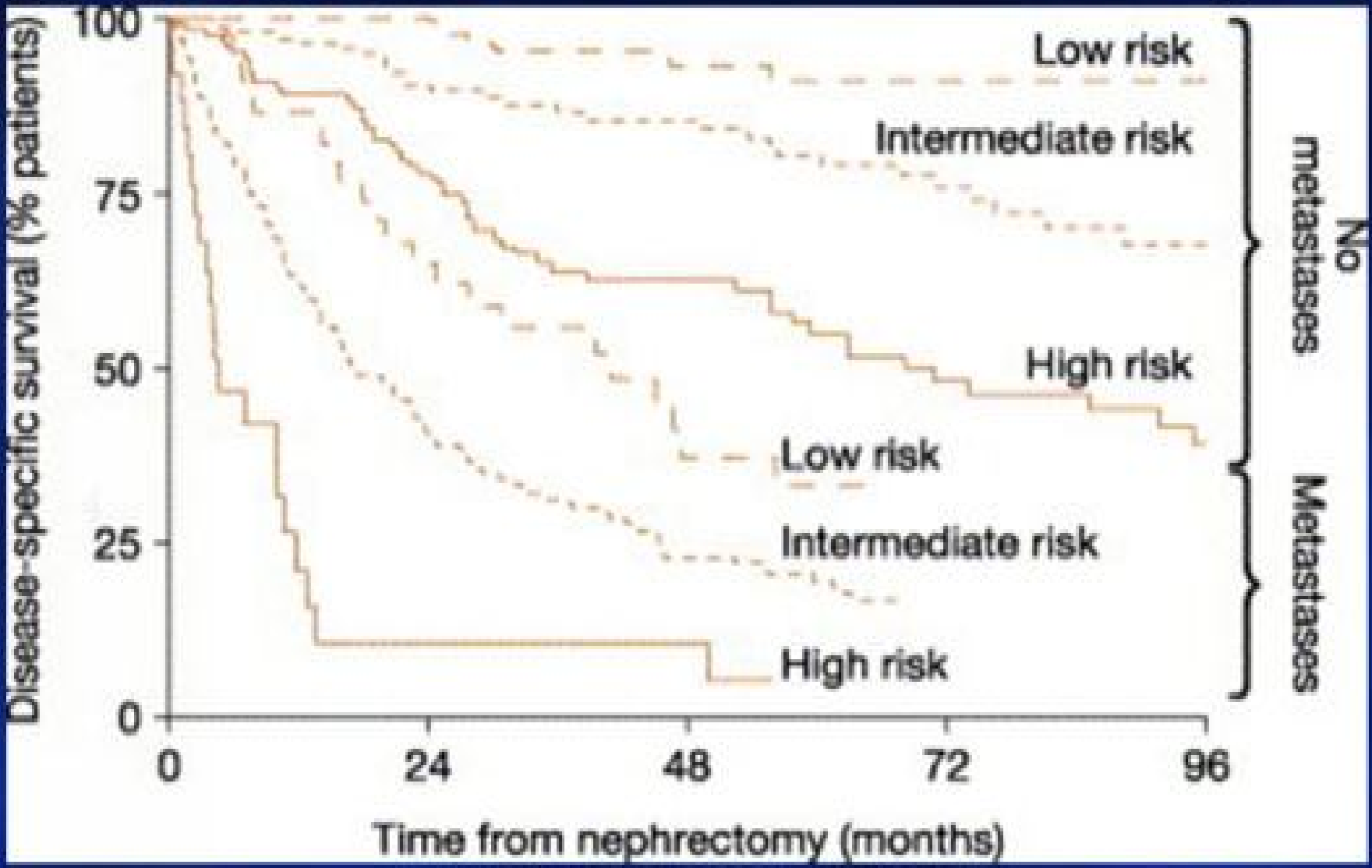
T3b: Venous invasion of IVC below the diaphragm

T3c: IVC above diaphragm; invasion of IVC wall

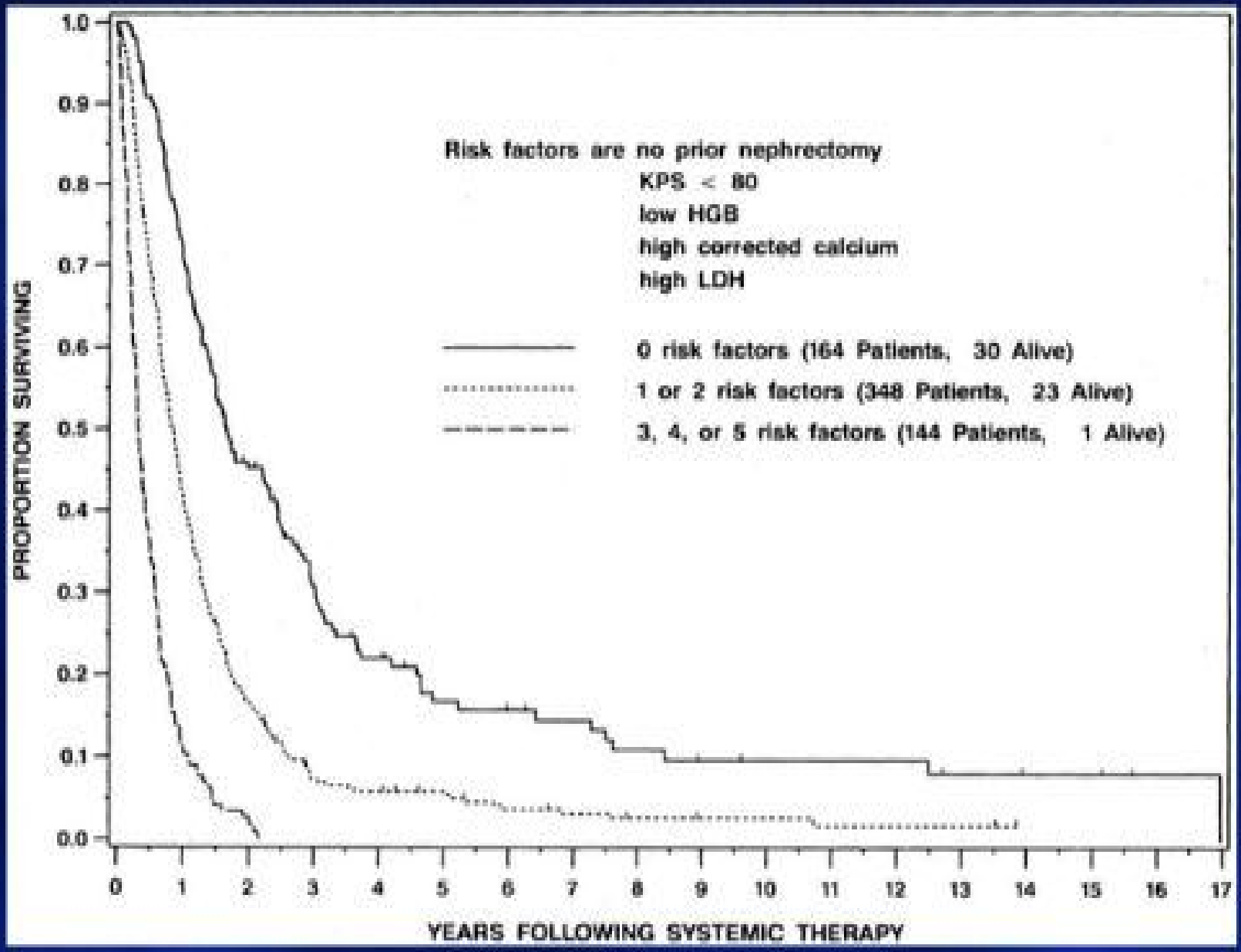
T4: Tumor invades beyond Gerota's fascia or contiguous extension involving the ipsilateral adrenal

RCC TNM Güncel Evreleme Sistemleri

- UCLA entegre evreleme sistemleri
- MAYO Klinik SSIGN skoru
- MSKCC Kattan postop Nomogram/Motze Kriteri M+RCC



Disease specific survival of patients with localized (N0M0) or metastatic (N1/N2M0 or any M1) RCC according to UCLA prognostic groups (Kaplan-Meier analysis)



Memorial Sloan-Kettering Model n=670 pts with advanced RCC

Mayo Clinic SSiGN

Feature		Score
1997 T Stage	T1	0
	T2	1
	T3	**2**
	T4	0
1997 N Stage	NX	0
	N0	**0**
	N1	2
	N2	2
1997 M Stage	**M0**	**0**
	M1	4
Nuclear Grade	1	0
	2	0
	3	**1**
	4	3
Necrosis	**No**	**0**
	Yes	2
Tumor Size ≥ 5cm	No	0
	Yes	**2**
Total		5

Estimated Cancer-Specific Survival Rates

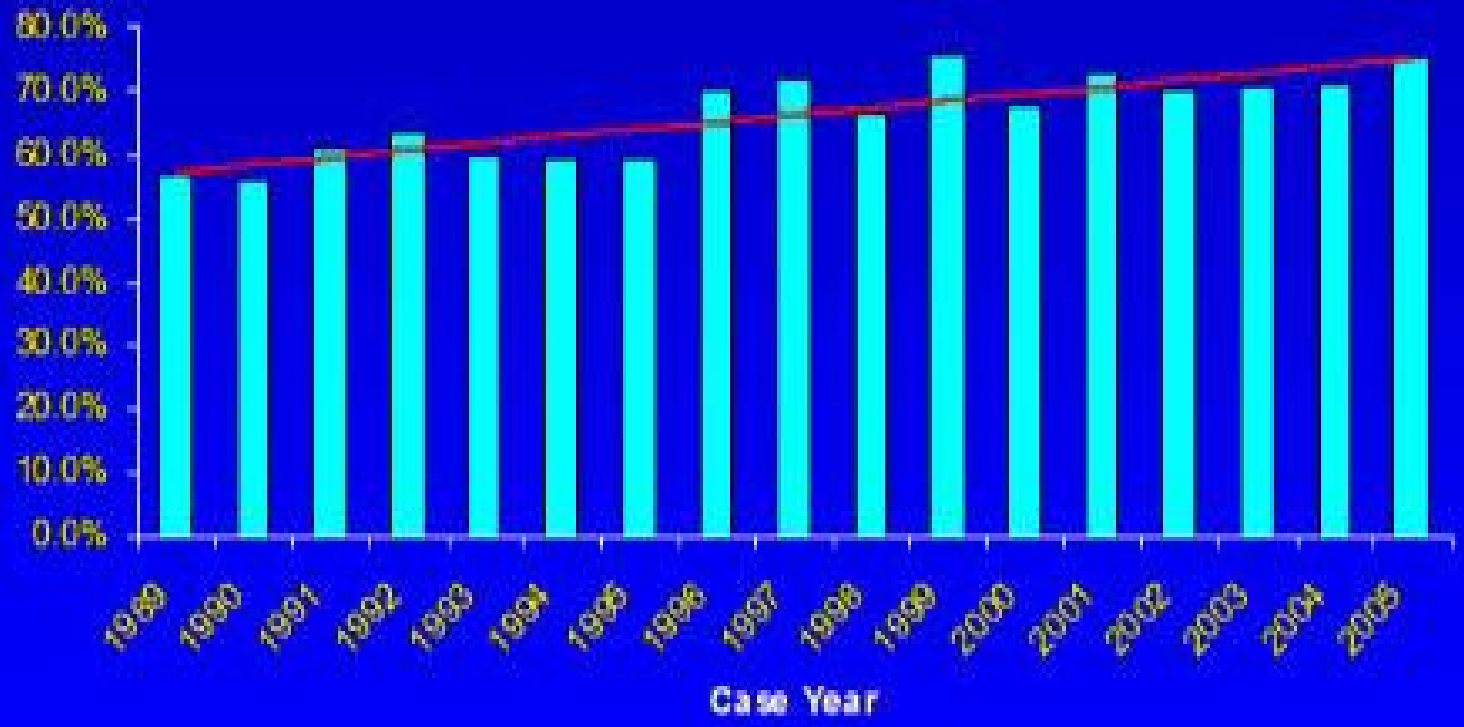
Score	Year				
	1	3	5	7	10
0-1	100.0	99.7	99.4	98.7	97.1
2	99.1	95.9	94.8	90.3	85.3
3	97.4	90.3	87.8	81.8	77.9
4	95.4	87.1	79.1	70.8	66.2
5	91.1	71.3	65.4	57.1	50.0
6	87.0	69.8	54.0	46.4	38.8
7	80.3	52.4	41.0	34.0	28.1
8	65.1	38.9	23.6	12.7	12.7
9	60.5	26.8	19.6	18.1	14.8
≥10	36.2	11.9	7.4	4.6	4.6

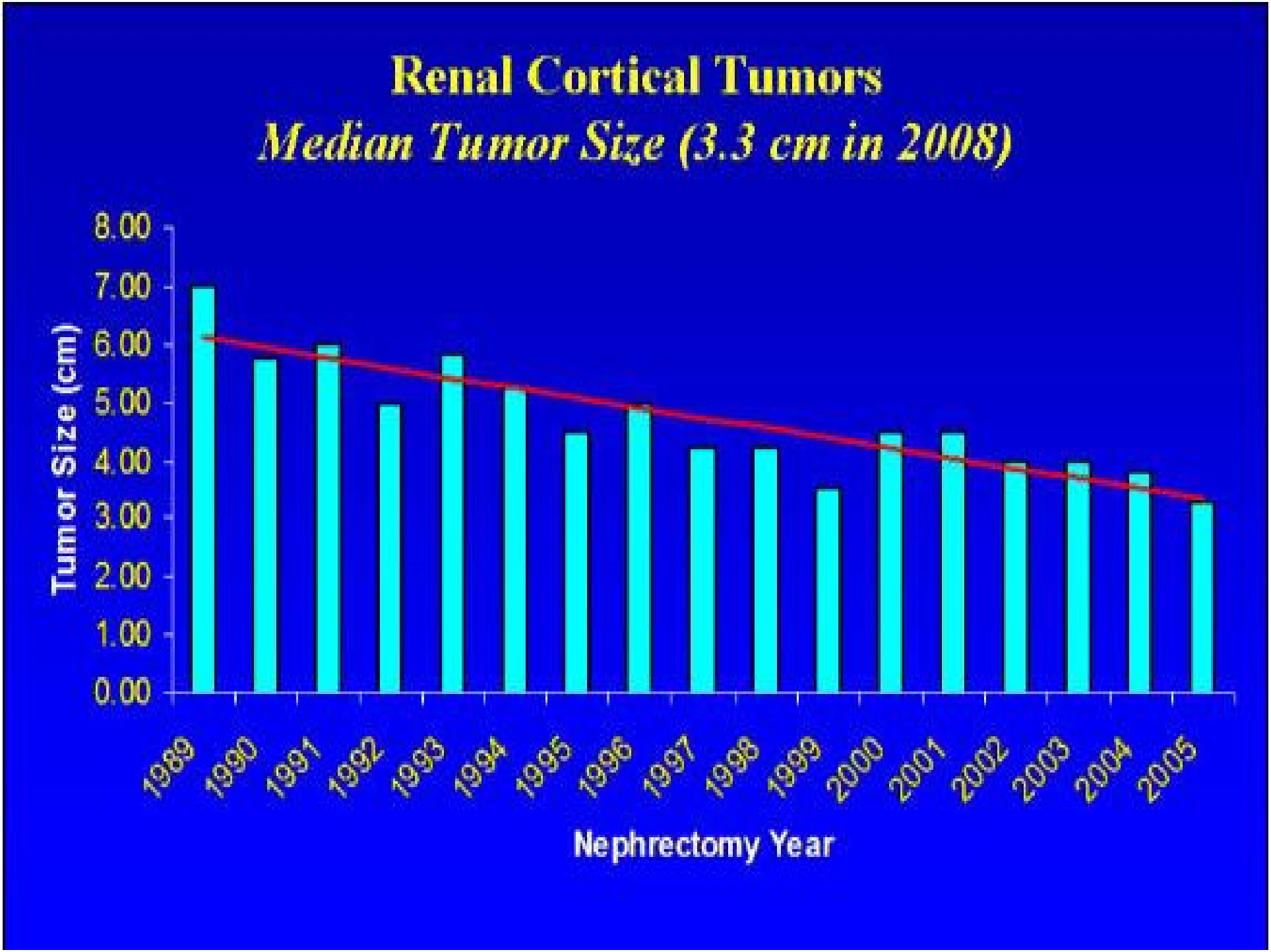
Prognoz ve Tedaviye Yönelik Potansiyel Markerlar

- Survivin
- B7-H1
- EphA2
- CA IX
- IGF-1
- Ki-67
- EpCAM
- PTEN
- p53
- VEGF/VEGF-R

Renal Cortical Tumors

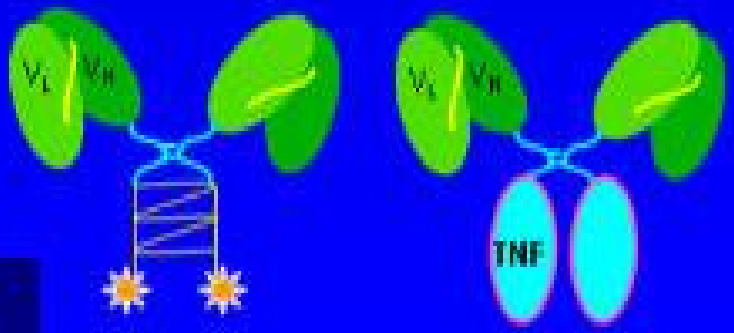
Incidental Detection (70% in 2008)

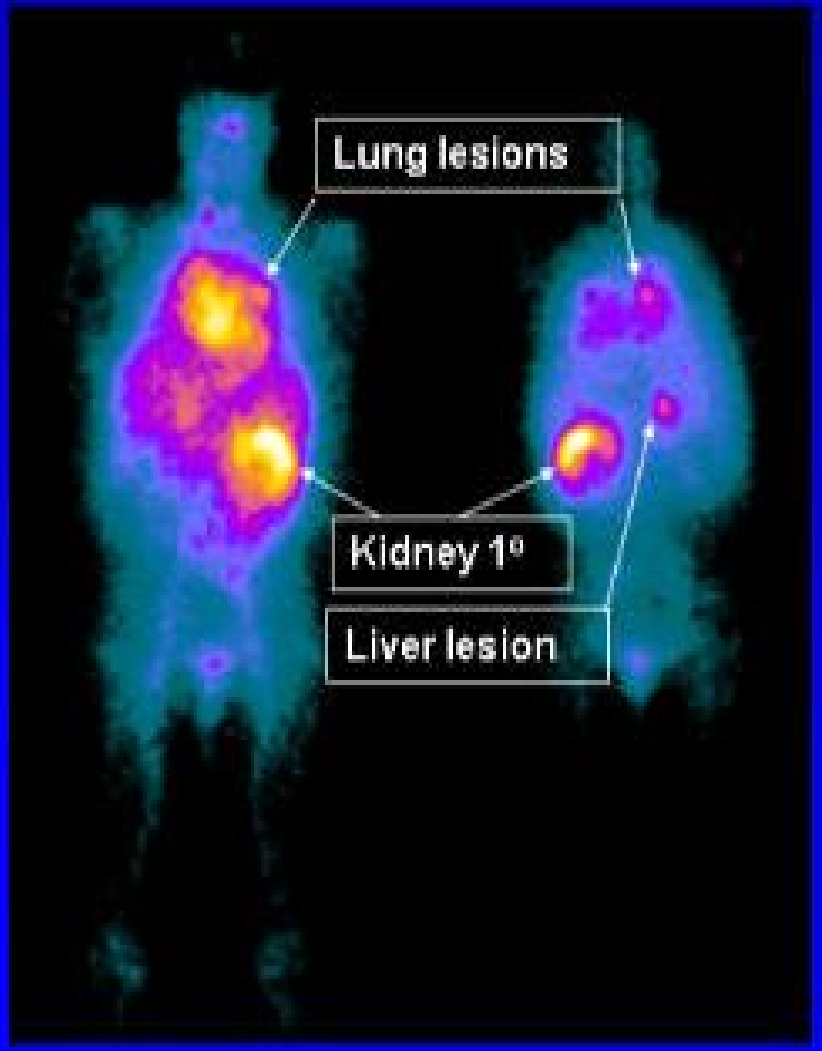



Renal Cortical Tumors
Median Tumor Size (3.3 cm in 2008)
Tumor Size (cm)
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
Nephrectomy Year

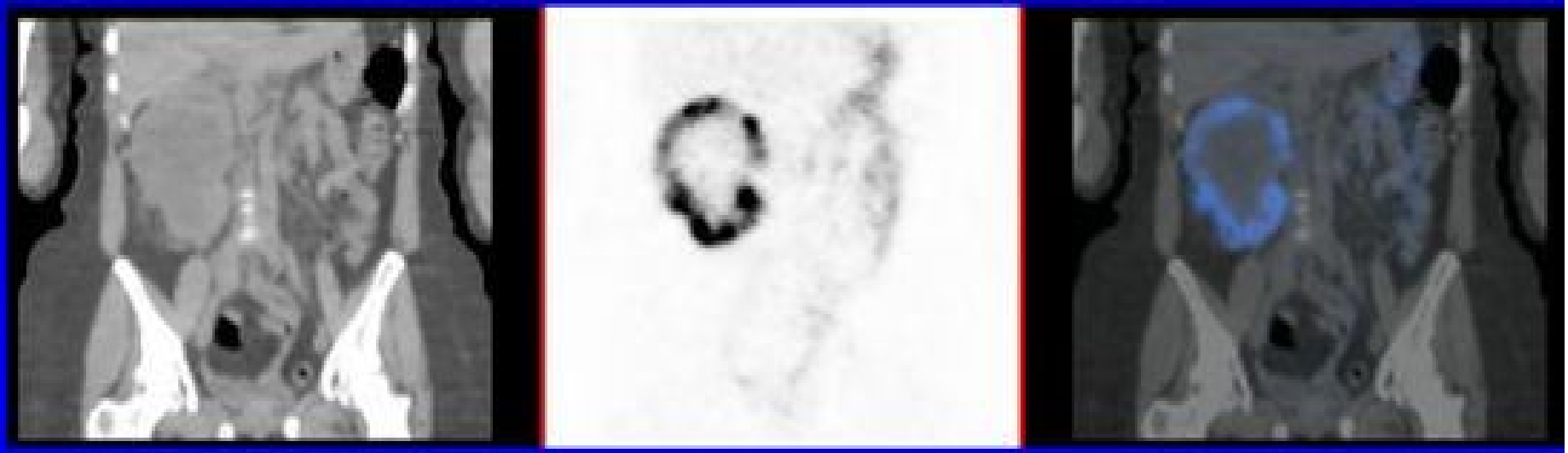
cG250 antibody for pre-op imaging

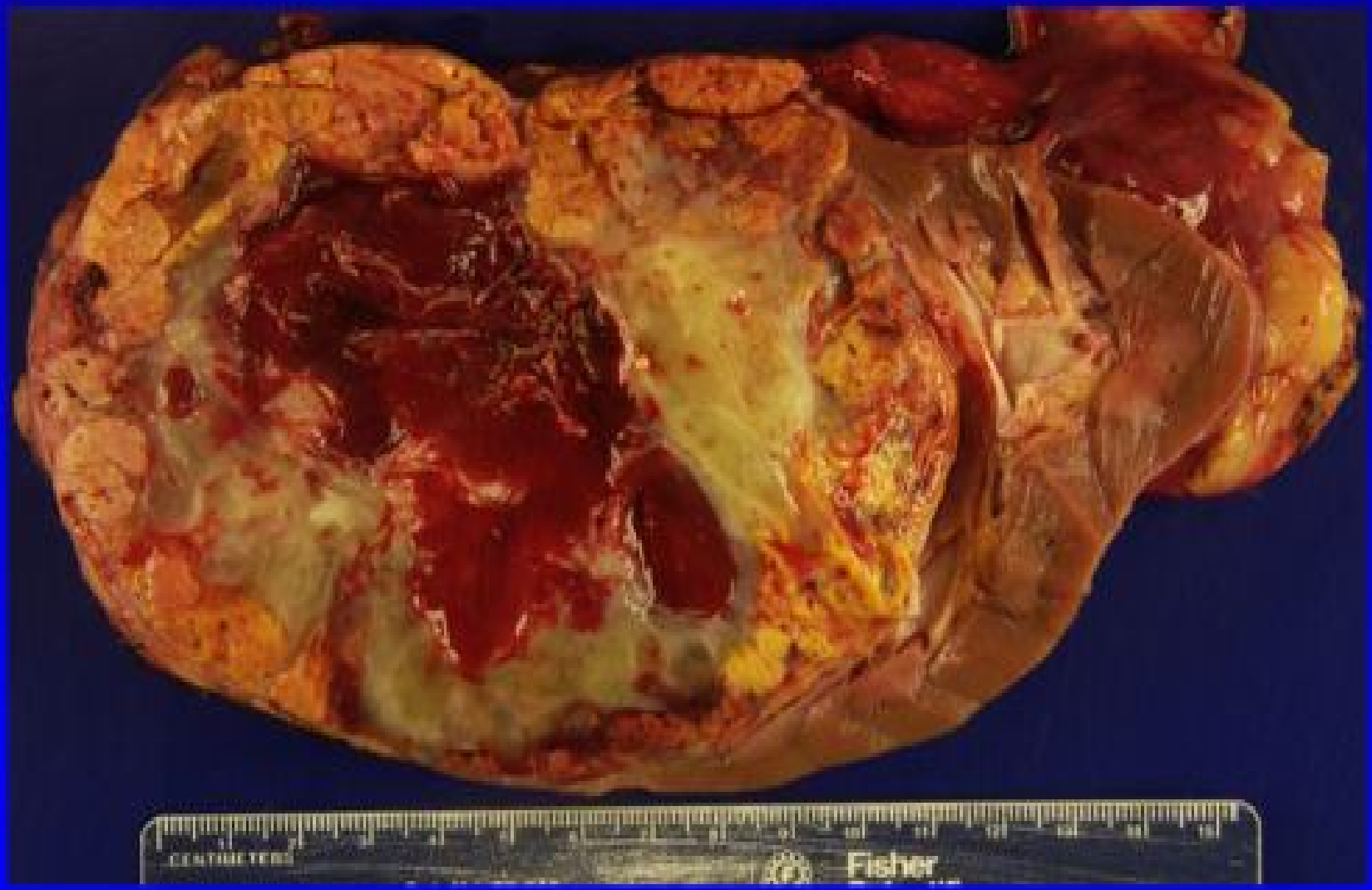
- Reacts only to clear cell renal carcinomas
- Antigen: Carbonic anhydrase-IX
- Normal tissue cross-reactivity – bile duct – saturable

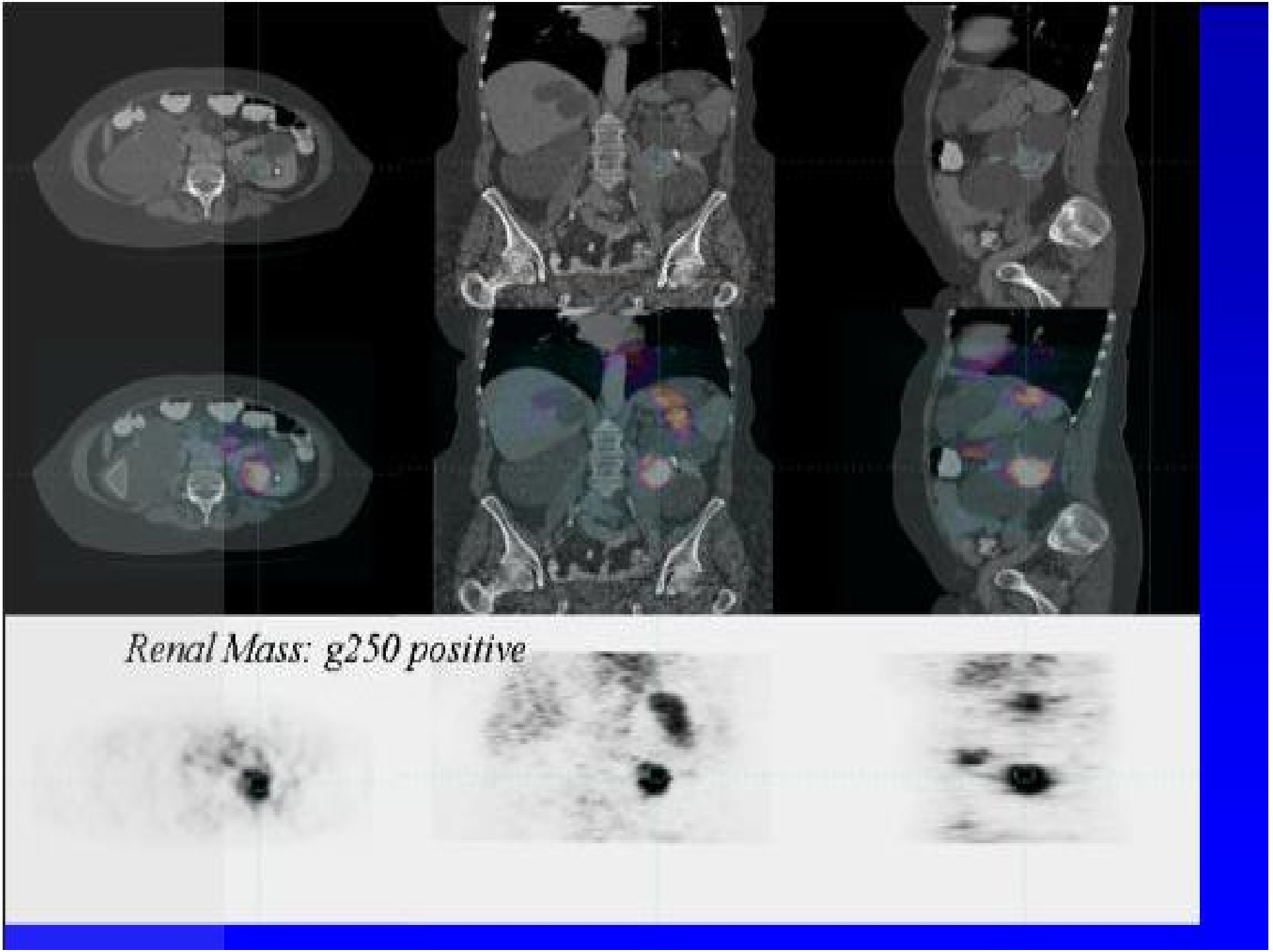




Ludwig Institute for Cancer Research




Fisher


Renal Mass: g250 positive

Phase 1 Trial: cG250 antibody for imaging MSKCC 2005-2006

Lancet Oncology 2007; 8:304-310.

Number of Patients on Protocol

Total Number of Patients Accrued	26
Injected with ^{124}I-cG250	26
PET and Resection	26

PET vs. Pathology Results:

13/14 Pet + clear cell, 1 false negative (sarcomatoid)

12/12 PET- : all non clear cell

Renal Kortikal Tümörlerde Tedavi

- Radikal Nx (LAP veya Açık)
- Parsiyel Nx (LAP veya Açık)
- Ablatif tedaviler (Perkütan veya LAP)
- Gözlem

Küçük Renal Kitlelerde Aktif İzlem

- 286 hasta, 10 çalışma meta-analizi
- Medyan Tm boyutu 2.48cm (1.73-4.8cm)
- 131/286 (%46) RCC
- Büyüme hızı 0.28cm/yıl
- 3/286 Met hastalık <%1

Yaşlı Hastalarda Aktif İzlem

- Kontrastlanma gösteren renal kitleli 110 hasta
- Medyan yaş 81 (76-95)
- Medyan tm boyutu 2.5cm (0.9-11.2)
- Medyan takip 24ay
- Ortalama tm büyüme hızı 0.26cm/yıl
- 34 hasta diğer sebeplerden ex
- Hiç bir hasta RCC'den ölmemiş

J Urology 190:505-509, 2008

RN vs PN Böbrek fxn Etkisi

- 662 hasta normal Kr (<1.4mg/dl) ve normal karşı böbrek
- Elektif PN, n=409
- RN, n=290
- Her iki grupta tm boyutu <4cm
- Preop GFR %20 hastada <60ml/dk ve KBY
- PN grubunda 3 yıl boyunca GFR'nin <60ml/dk düşmekten kurtulma ihtimali %80 iken,
- RN grubunda bu oran %35

Lancet Oncology 2006

- KBY ihtimali arttıkça mortalite ↑
- KBY tek başına kardiyovasküler hastalık için bağımsız risk faktörü

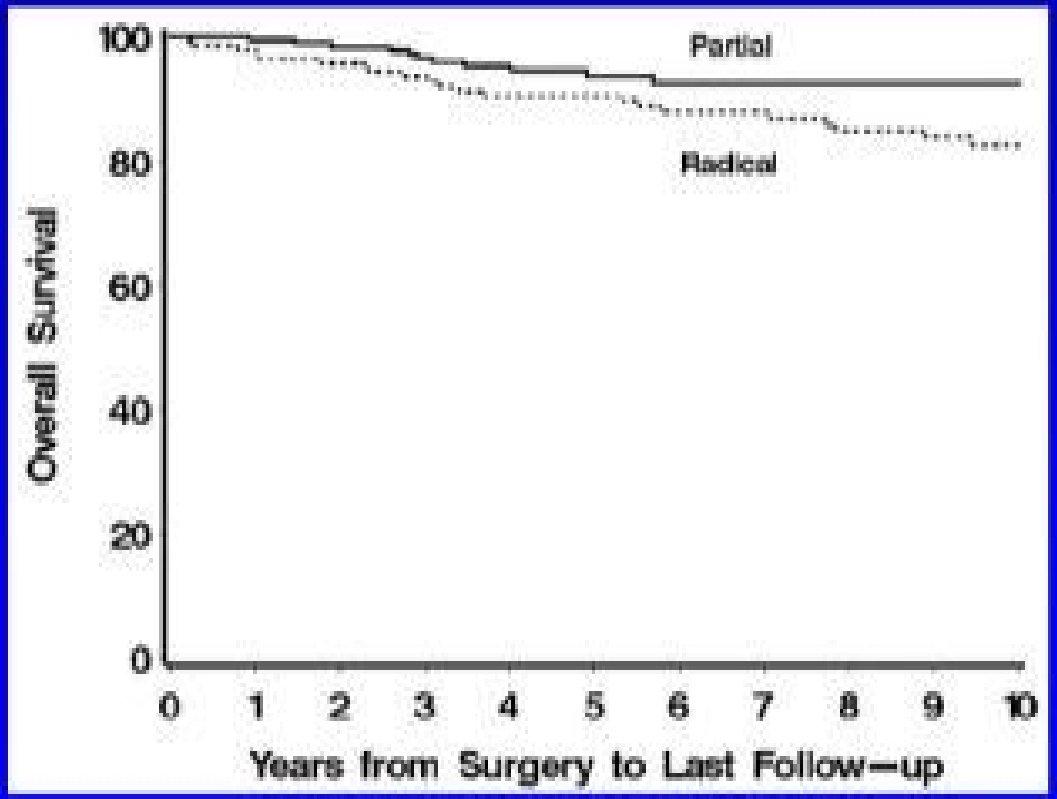
T1a Tm'de RN daha kötü sağkalımla ilişkili

- 648 hasta T1a tm (<4cm)
- 358 PN
- 290 RN
- RN <65yaş hastalarda anlamlı (p=0.02) olarak herhangi bir sebepten ölümle ilişkili
- Bu ilişki preop Kr, Chalson Romano indexi, tümör histolojisi, semptomlar ve DM için ayarlandığında da geçerli

Radical Nephrectomy for pT1a Renal Masses May be Associated With Decreased Overall Survival Compared With Partial Nephrectomy

R. Houston Thompson,* Stephen A. Boorjian, Christine M. Lohse, Bradley C. Leibovich, Eugene D. Kwon, John C. Cheville and Michael L. Blute

From the Departments of Urology (RHT, SAB, BCL, EDK, MLB), Health Sciences Research (CML) and Laboratory Medicine and Pathology (JCC), Mayo Medical School and Mayo Clinic, Rochester, Minnesota



J. Urol 179: 468, 2008

RN Artmış KVO ve Mortaliteyle İlişkili

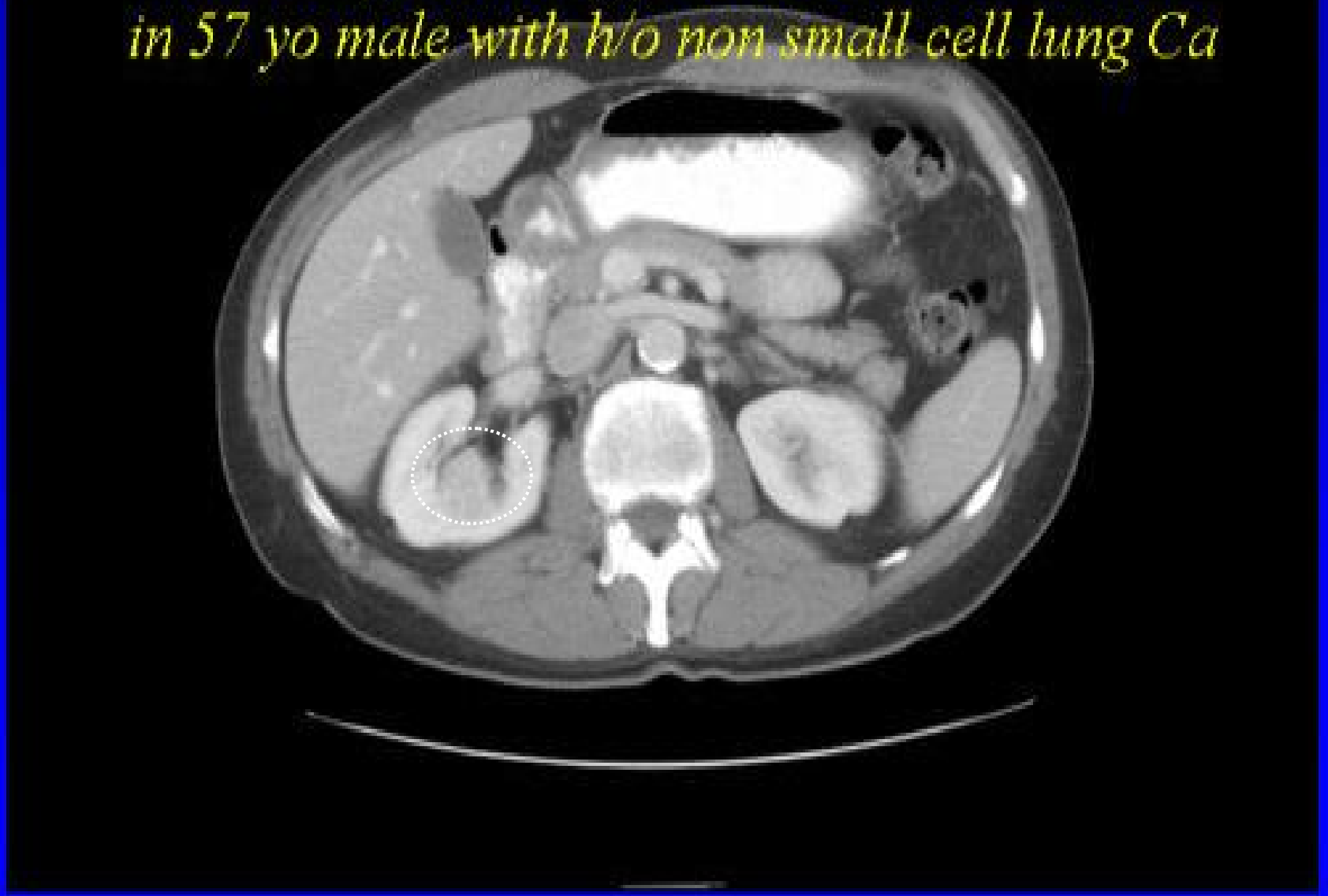
- 2991 hasta (81.41 RN, %18.59 PN)
- Preop KBY ve KVH yönünden fark yok
- PN hastaları daha genç, erkek ve evli?
- 609 hasta postop KVO yaşamış
  - PN %15.11, RN %21.%6 p=0.007
- 892 hasta ex
  - PN %19.78 , RN %32.11 (p<0.001)

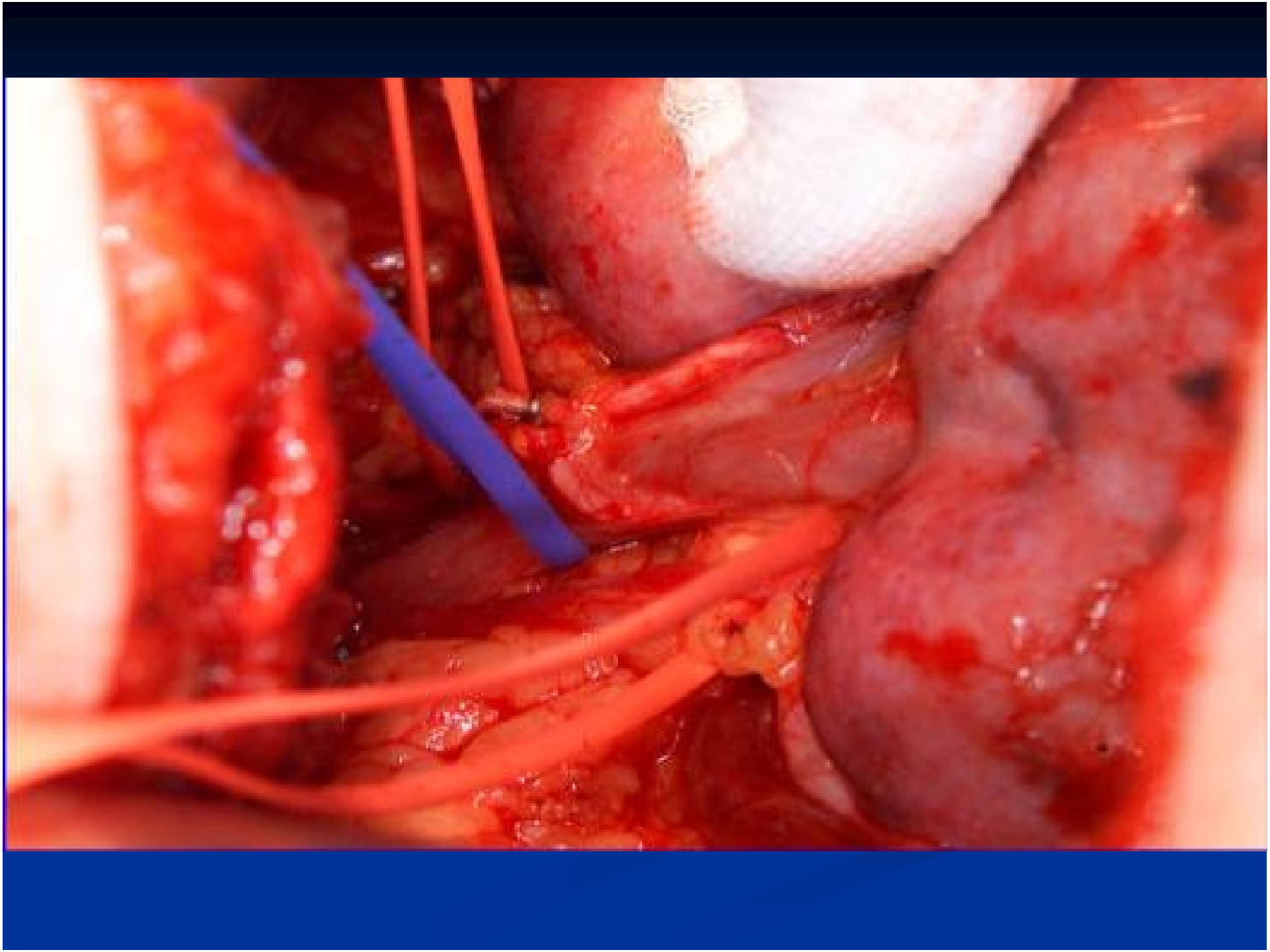
MSKCC 2008 Böbrek Koruyucu Cerrahi Protokolü

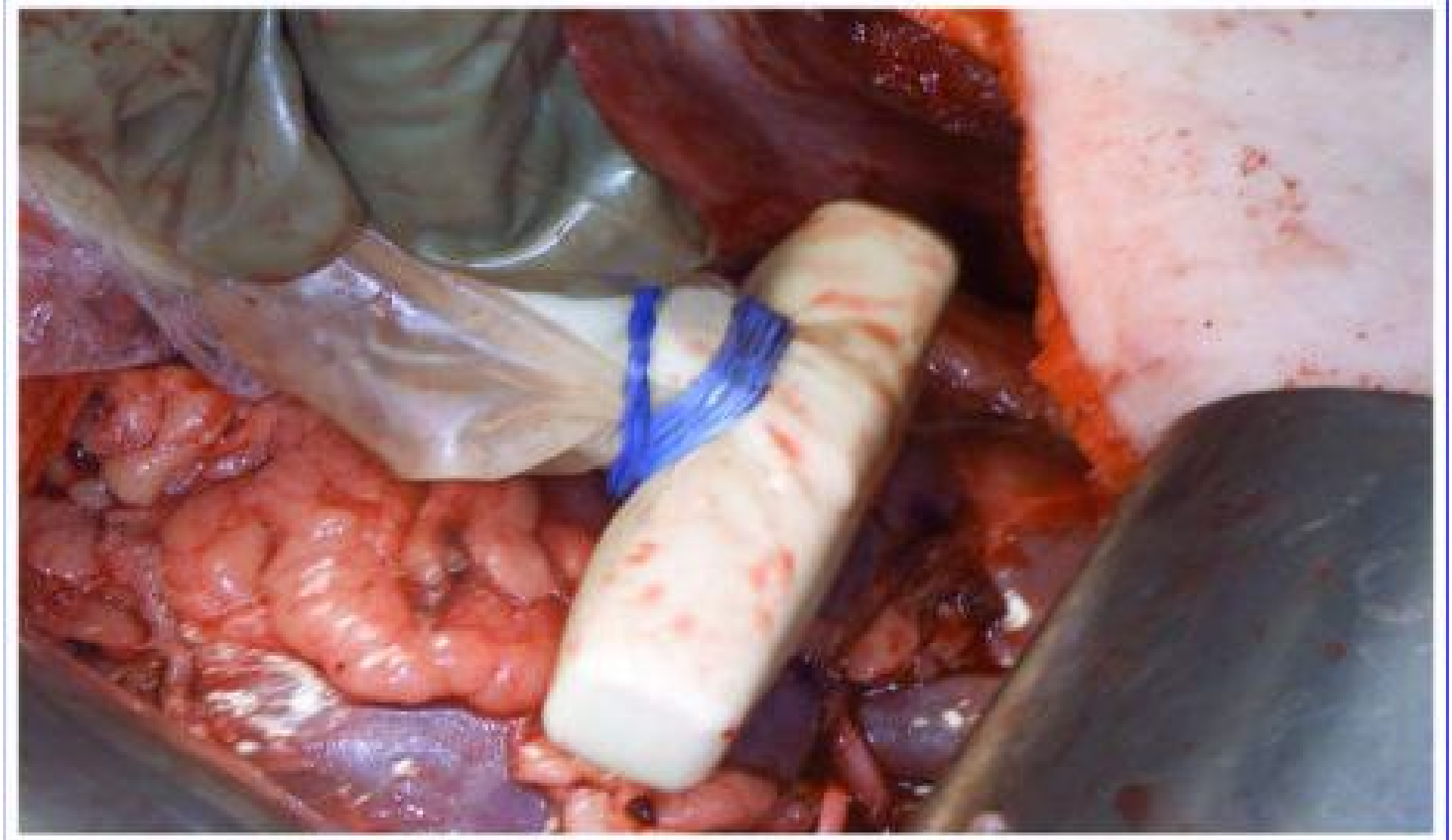
- <7cm tm PN planlanmış
- Teknik: LAP ve Açık
- PN rutin hiliyer ve endofitik tümörlerin rezeksiyonu
- İntraoperatif USG, kompleks vasküler ve toplayıcı sistem onarımı
- Extended PN

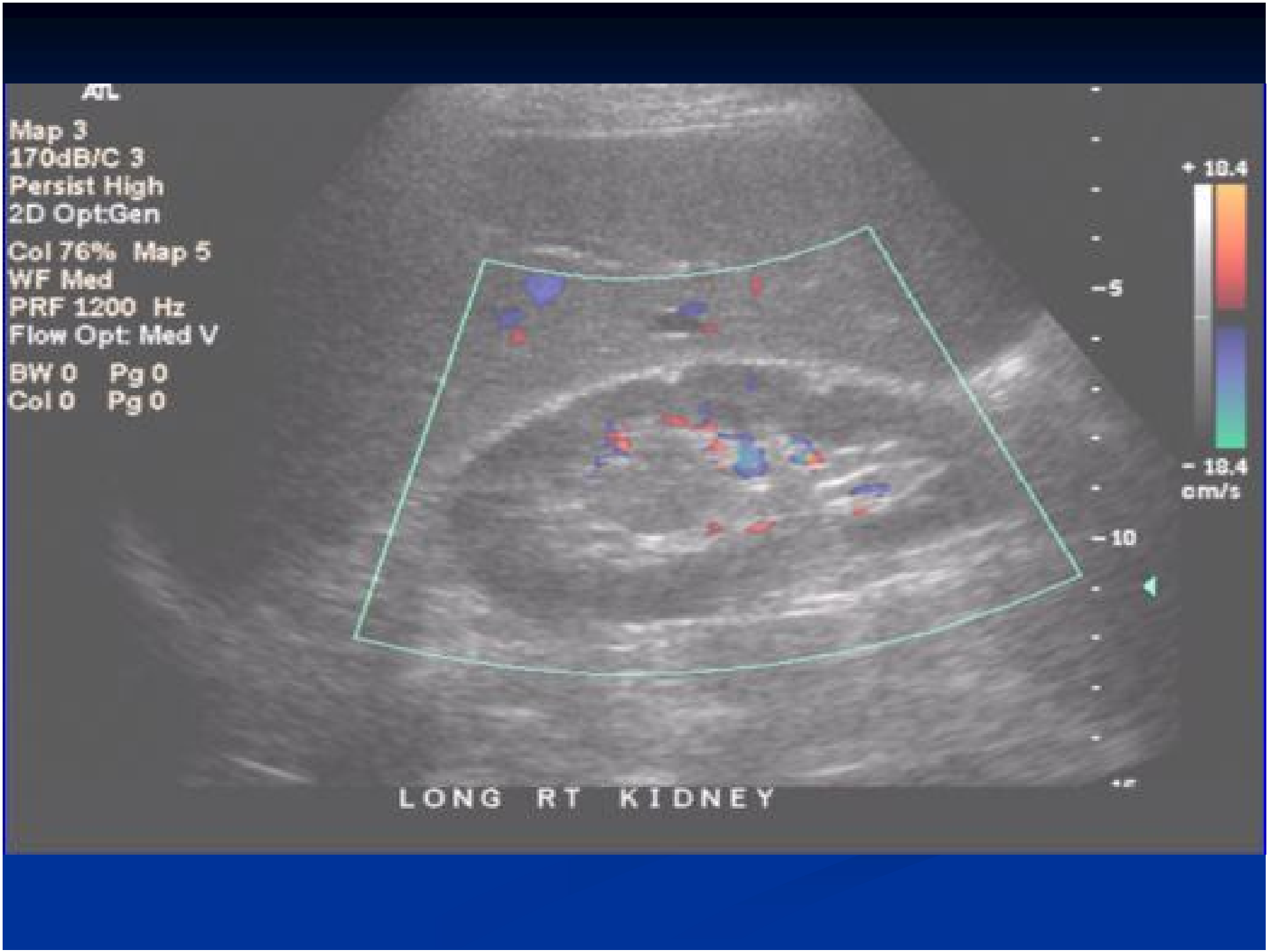
EXTENDED PARTIAL NEPHRECTOMY

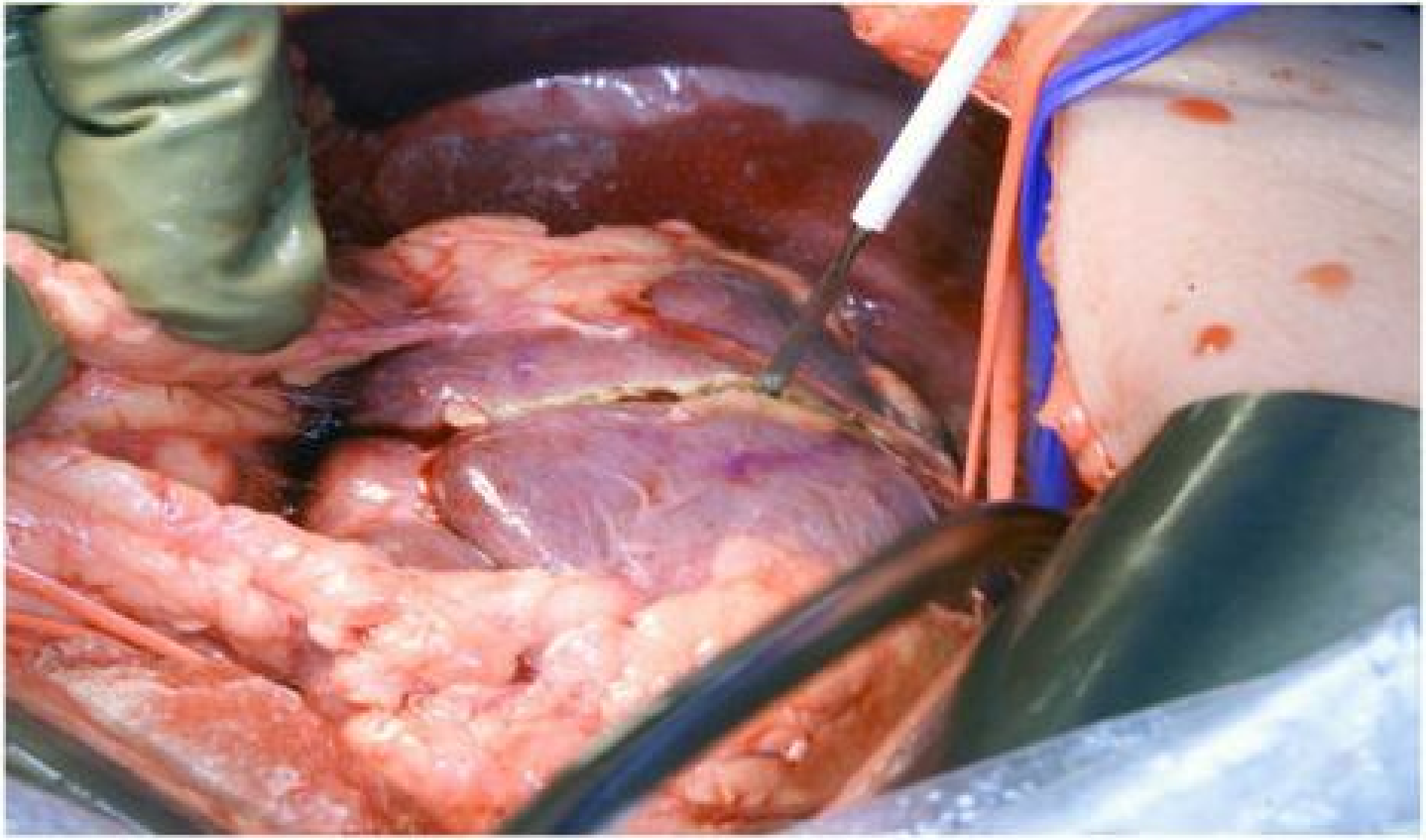
Partial Nephrectomy for Renal Sinus Tumor
in 57 yo male with h/o non small cell lung Ca

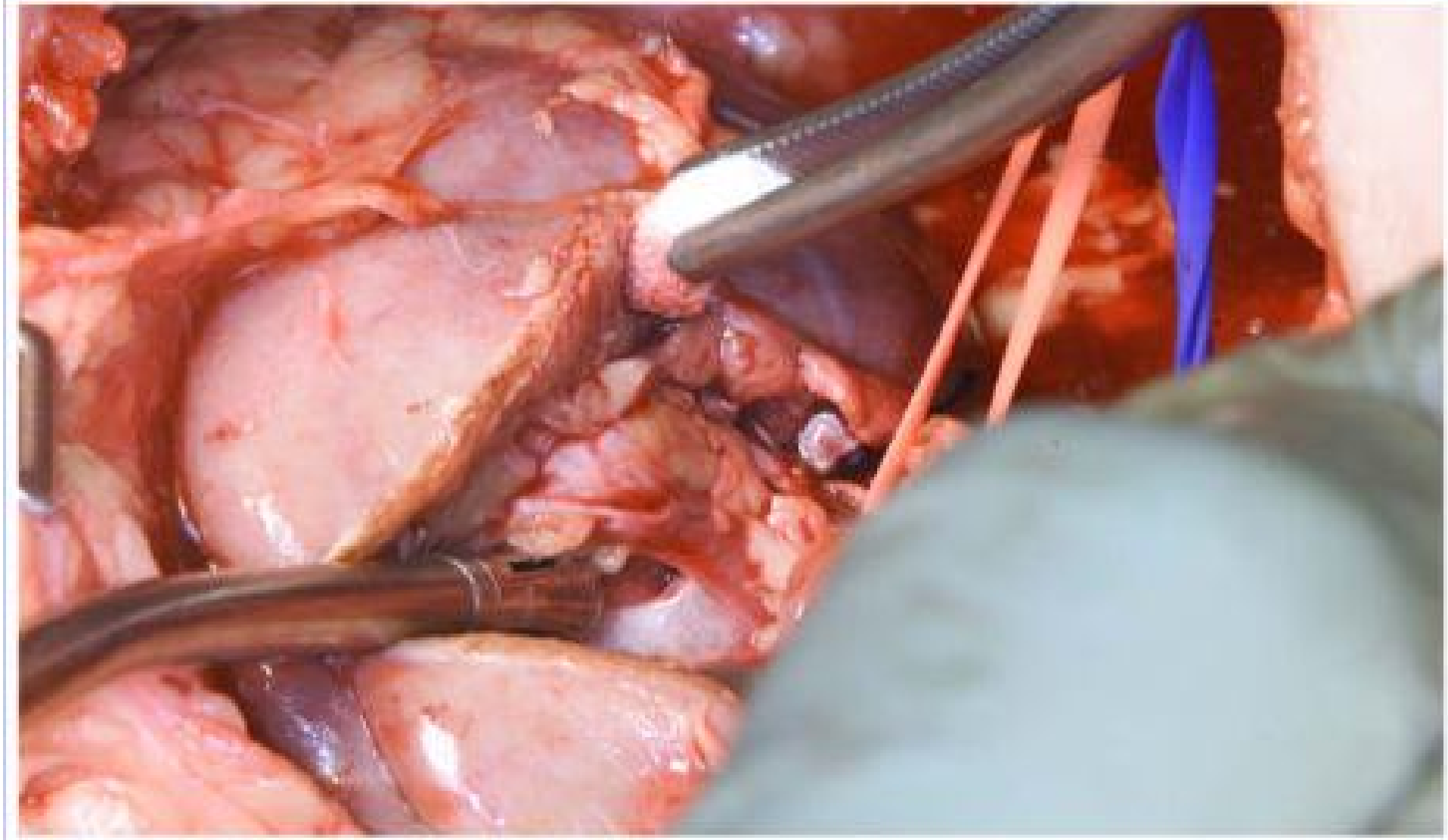


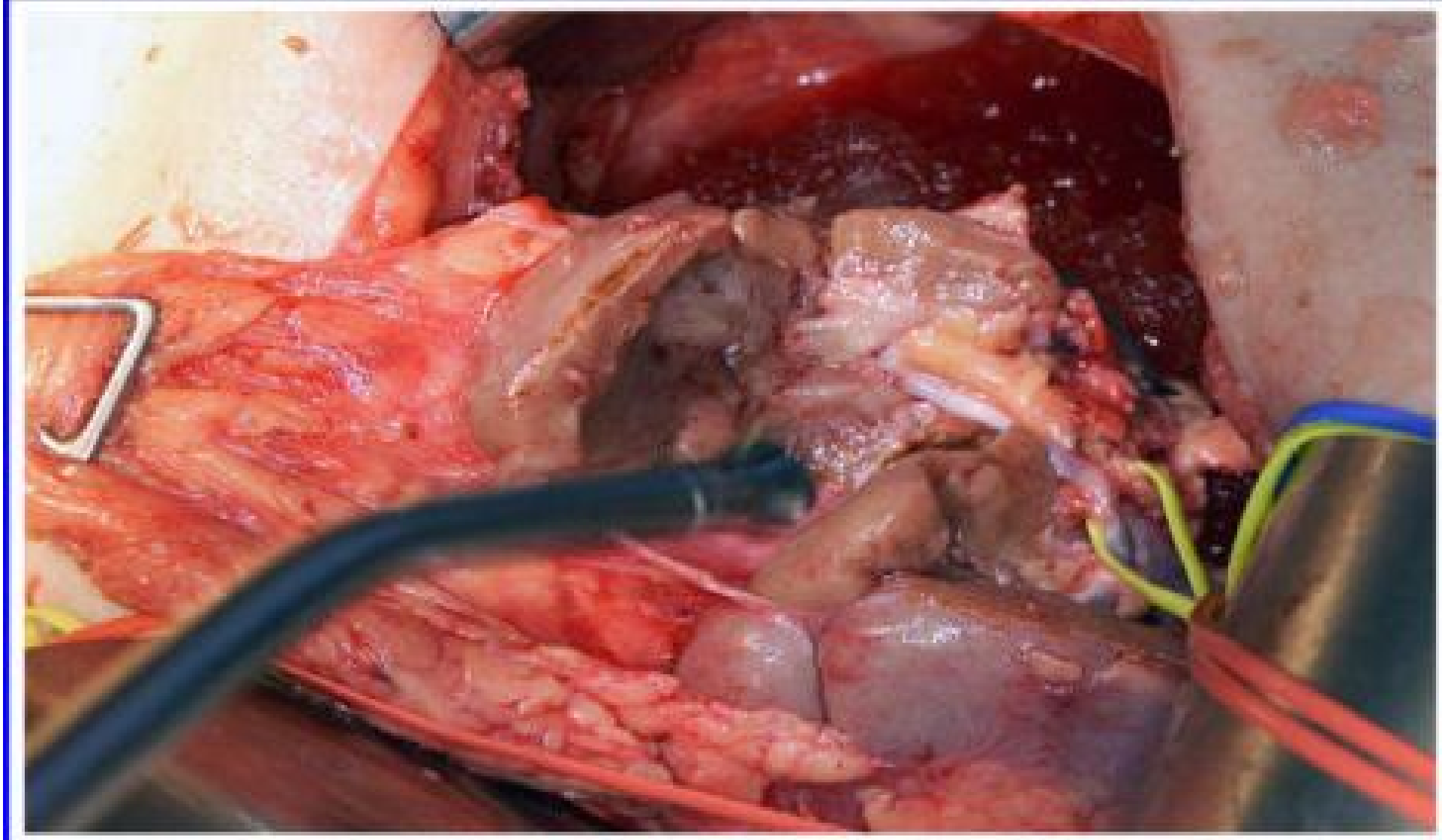


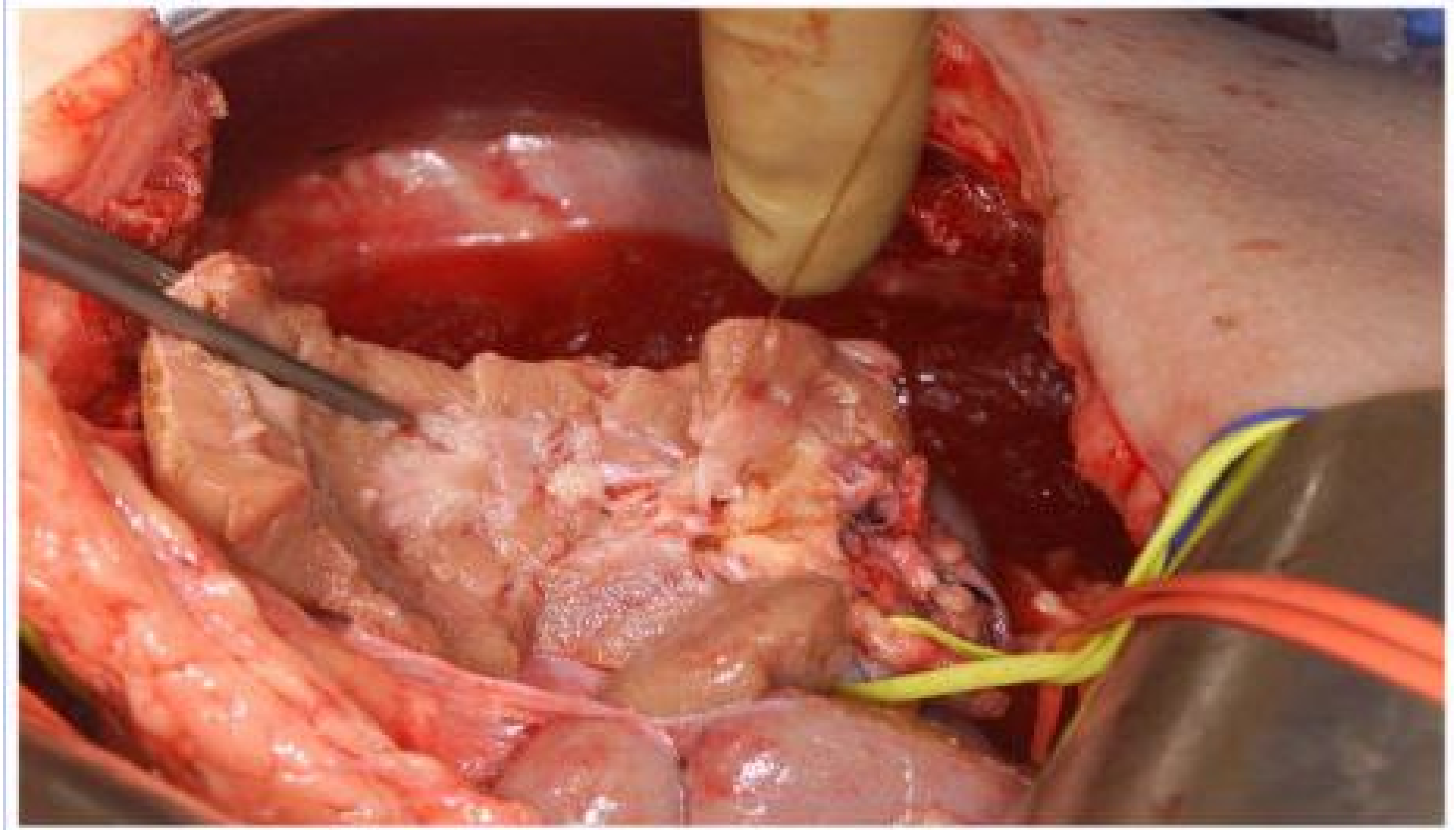



ATL
Map 3
170dB/C 3
Persist High
2D Opt:Gen
Col 76% Map 5
WF Med
PRF 1200 Hz
Flow Opt: Med V
BW 0 Pg 0
Col 0 Pg 0
+ 18.4
- 18.4
cm/s
-5
-10
LONG RT KIDNEY

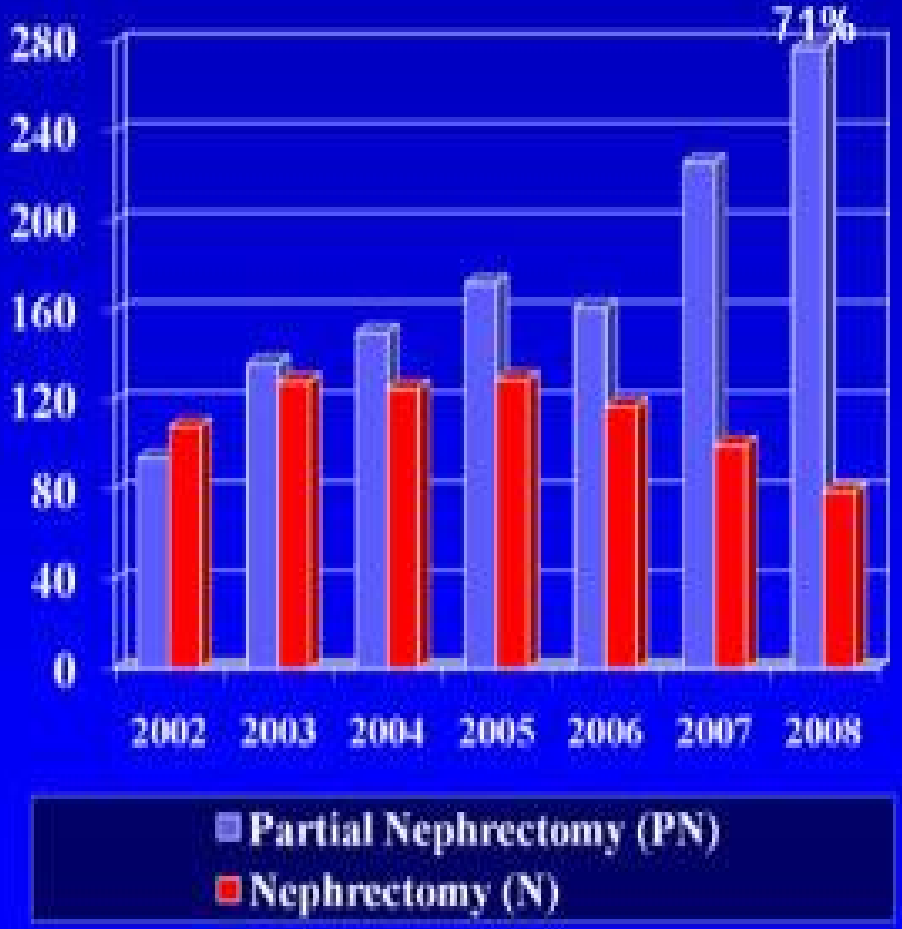








MSKCC Renal Surgical Case Report
2002 – 2008



Year	# PN	#RN
2002	94	108
2003	136	128
2004	150	125
2005	172	129
2006	161	117
2007	226	100
2008	277	79

Renal Tümör Ablasyonu

- Radyofrekans ve Kriyoablasyon
- Güvenilirliği FDA onaylı
- Onkolojik etkinliği (-)
- Uygulama
  - Açık
  - LAP
  - Perkütan
- Ablasyon öncesi ve sonrası patolojik konfirmasyon eksikliği

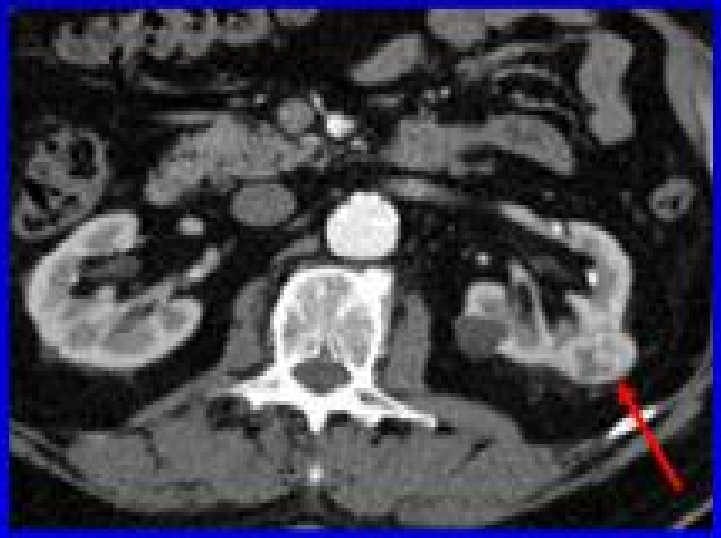
Renal Tümör Ablasyonu

- Lezyonun CT/MRI değişikliklerine ve kontrastlanma paternlerine göre tedavi başarısı belirleniyor
- Rutin tedavi sonrası biyopsi (-)
- Başarısızlıkta ne yapılacağına yönelik bir görüşbirliği yok
- Kanser spesifik sağkalımda patoloji raporu yok

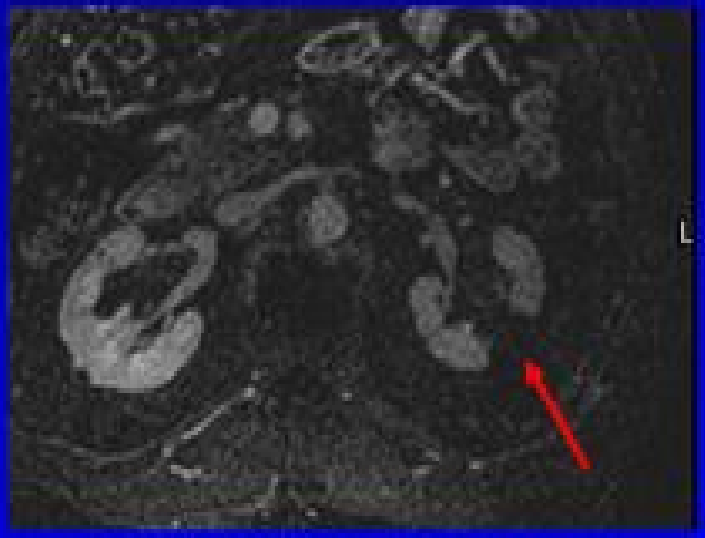
Renal Tümör Ablasyonu

- Endikasyonları
  - Cerrahiye uygun olmayan renal tümörlü hastalar (*Kavoussi/Solomon J Urol 2008*)
  - Yüksek riskli hastalardaki başarısına dayanarak, hastanın durumuna bakılmaksızın küçük tm lerde uygulanmakta *(Clayman J Urol 2008)*

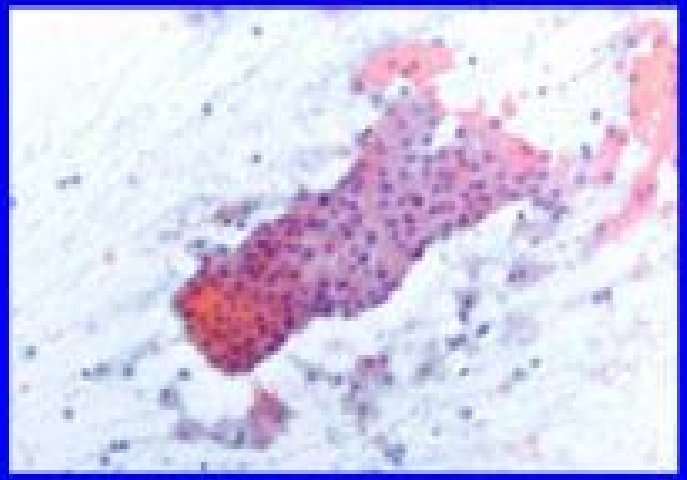
Positive Biopsy with No MRI Enhancement Following RFA

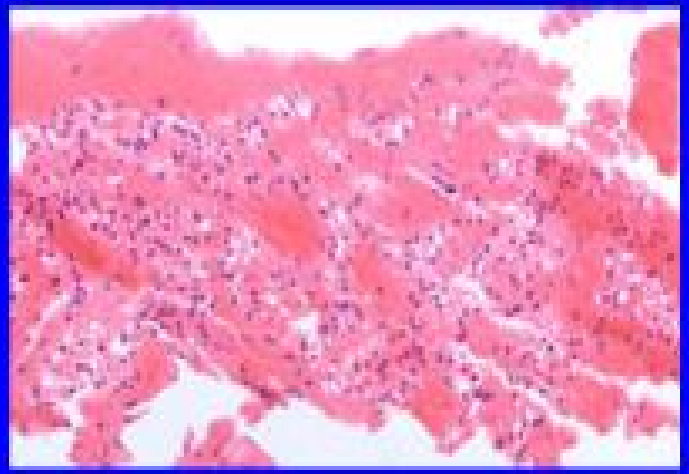


Pre-RFA



6 months Post-RFA





Complications

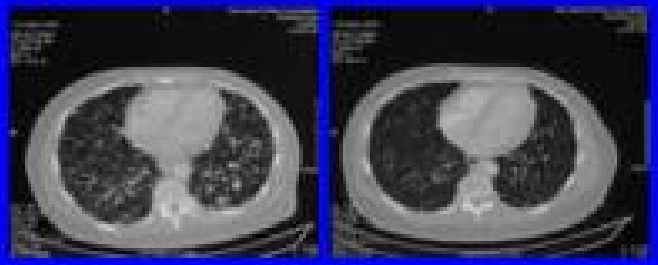
	Major GU Comp Comp	Maj NonGu Compl	Conversion Rate	Incomplete ablation rate
PN	6.3%	2.2%	0.5%	NA
Cryo	4.9%	4.9%	3.5%	4.2%
RFA	6.0%	4.4%	1.6%	14.2%

Metastatik RCC'da Yeni Tedaviler

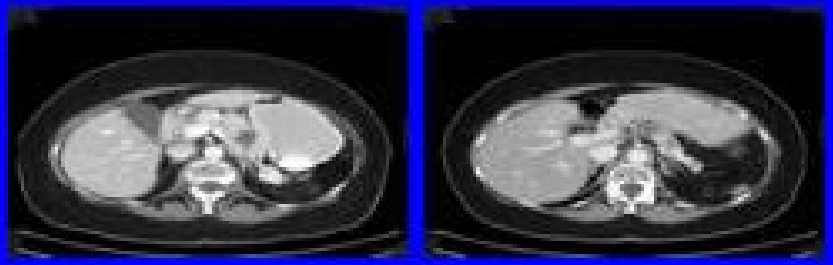
Tedavi Almamış Metastatik RCC

Phase III First-Line Sunitinib vs. IFN: Efficacy Summary

	Sunitinib (n=375)	IFN-a (n=375)	P value[1]
Objective Response[2]	39% (47%)[3]	8% (12%)	< .000001
Median PFS[2]	11 months	5 months	< .000001



Response of Pulmonary Metastases



Response of Pancreatic Metastases

[1] Log Rank test, [2]Independent review , [3] Investigator assessed

Figlin, ASCO 2008, abstract #5024

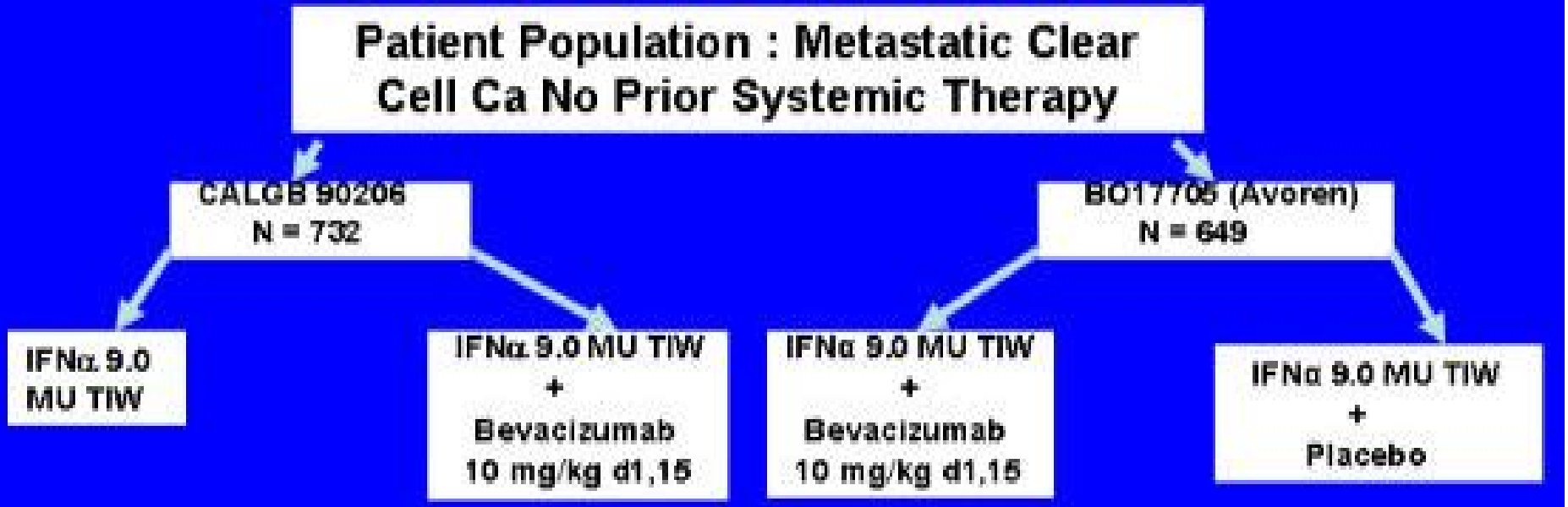
Phase III First-Line Sunitinib vs. IFN: Efficacy Summary

	Sunitinib (n=375)	IFN-a (n=375)	P[1]
Objective Response[2]	39% (47%)[3]	8% (12%)	< .000001
Median PFS*	11 months	5 months	< .000001
Median OS (Intent to treat)	26.4 months	21.8 months	.051
Median OS, censored placebo (n=25)	26.4 months	20 months	.0362
Median OS, no post study treatment	28.1 months (n=193)	14.1 months (n=162)	.0033

[1] Log Rank test, [2]Independent review , [3] Investigator assessed

Figlin, ASCO 2008, abstract #5024

Bevacizumab : Phase 3 Trials in Renal Cell Carcinoma



	CALGB 90206[1]		AVOREN[2]	
Therapy	IFNα	IFNα + Bev	IFNα + Bev	IFNα + Placebo
ORR (%)	13.1%	25.5%	31%	13%
PFS (median)	5.2 mos.	8.5 mos.	10.2 mos.	5.4 mos.

[1] Rini, B , et al. J Clin Oncol, 2008; [2] Escudier, B et al : The Lancet, 2007

Comparative PFS in Prognostic Groups in Frontline mRCC Randomized Trials

Risk Group	Sunitinib vs IFNα[1]	AVOREN[2]	CALGB 90206[3]
Favorable:			
Sunitinib or Bev/IFNα	14.0 mos	12.9 mos	11.1 mos
IFNα	8.0 mos	7.6 mos	5.7 mos
Intermediate:			
Sunitinib or Bev/IFN	11.0 mos	10.2 mos	8.4 mos
IFNα	4.0 mos	4.5 mos	5.3 mos
Poor:			
Sunitinib or Bev/IFN	3.0 mos	2.2 mos	3.3 mos
IFNα	1.0 mos	2.1 mos	2.6 mos

1. Mozter et al, JCO 2009; 2. Escudier et al, The Lancet, 2007; 3. Rini et al, JCO 2009.

Cytokine Refractory mRCC : Comparative Results

Agent	Sorafenib[1]	Sunitinib[2]	Bevacizumab[3]
Dose	400 mg bid	50 mg/d 4/6 wks	10 mg/kg IV q2wks
Type Trial	Phase 3	Phase 2	Phase 2
Patient Nos.	451	168	39
ORR %	10%	34%	10%
PFS (mos)	5.8	8.4	4.8
Median OS (mos)	17.3	19.9	15.5

[1] Bukowski et al, ASCO, 2007; [2] Rosenberg et al, ASCO, 2007 ; [3] Yang et al, NEJM, 2002

New Standards for Clear Cell RCC Therapy- Recommendations

Setting		Phase III	Phase II
1st-Line Therapy	Good or intermediate risk*	Sunitinib	HD IL-2
		Bevacizumab + IFNα	
	Poor risk*	Temsirolimus	Sunitinib
2nd-Line Therapy	Prior cytokine	Sorafenib	Sunitinib Bevacizumab
	Prior VEGFR inhibitor	Everolimus Clinical Trial	? Sequential TKI's ? Temsirolimus
	Prior mTOR inhibitor	No Data	No Data

*MSKCC risk status

Atkins. ASCO 2006 Plenary session; Bukowski, ASCO 2007 Plenary session; Rini ASCO 2008

Böbrek Tümörlerinde Sitoredüktif Nefrektomi ve Metastatektomi

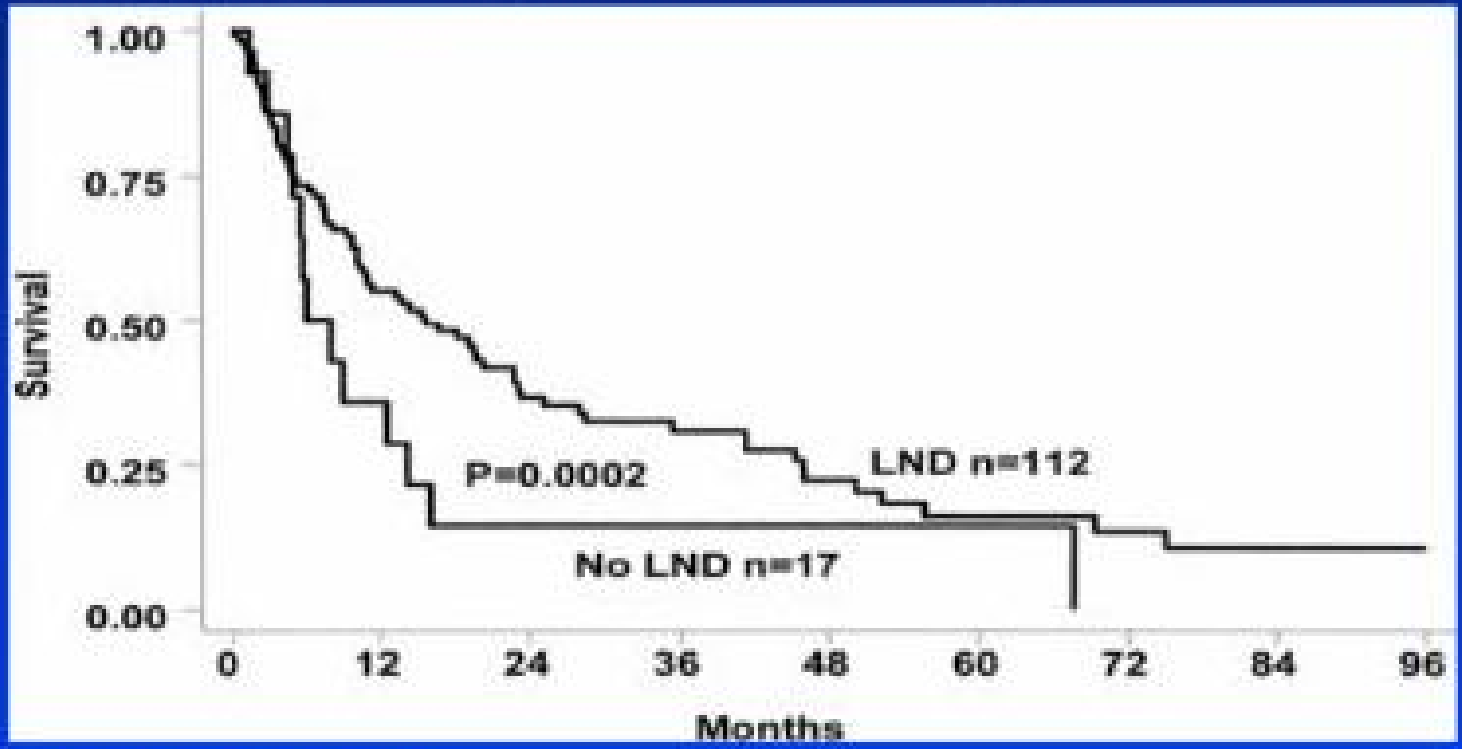
Design: Nephrectomy followed by IFN-a vs IFN-a alone

Trial	No.	Response Rates	Overall Survival (Months)
SWOG	246	3.6% vs 3.3%	11.1 vs 8.1 (p=0.05)
EORTC	85	19% vs 12%	17 vs 7 (p=0.03)
Combined analysis	331	6.9% vs 5.7% (p=0.60)	13.6 vs 7.8 (p=0.002)

Sitoredüktif Nefrektomi

- Genel sağkalım anlamlı olarak artmakta
- Ciddi komplikasyon %5 ve mortalite %1.4

mRCC'de LND



Pantuck et al J Urol 2003

mRCC’de LND

- <13 lenf nodu çıkartıldığında %10 LN (+)
- >13 lenf nodu çıkartıldığında %21 LN (+)
- Perop gross LN çıkarılmalıdır

M+ RCC Metatstatektomi

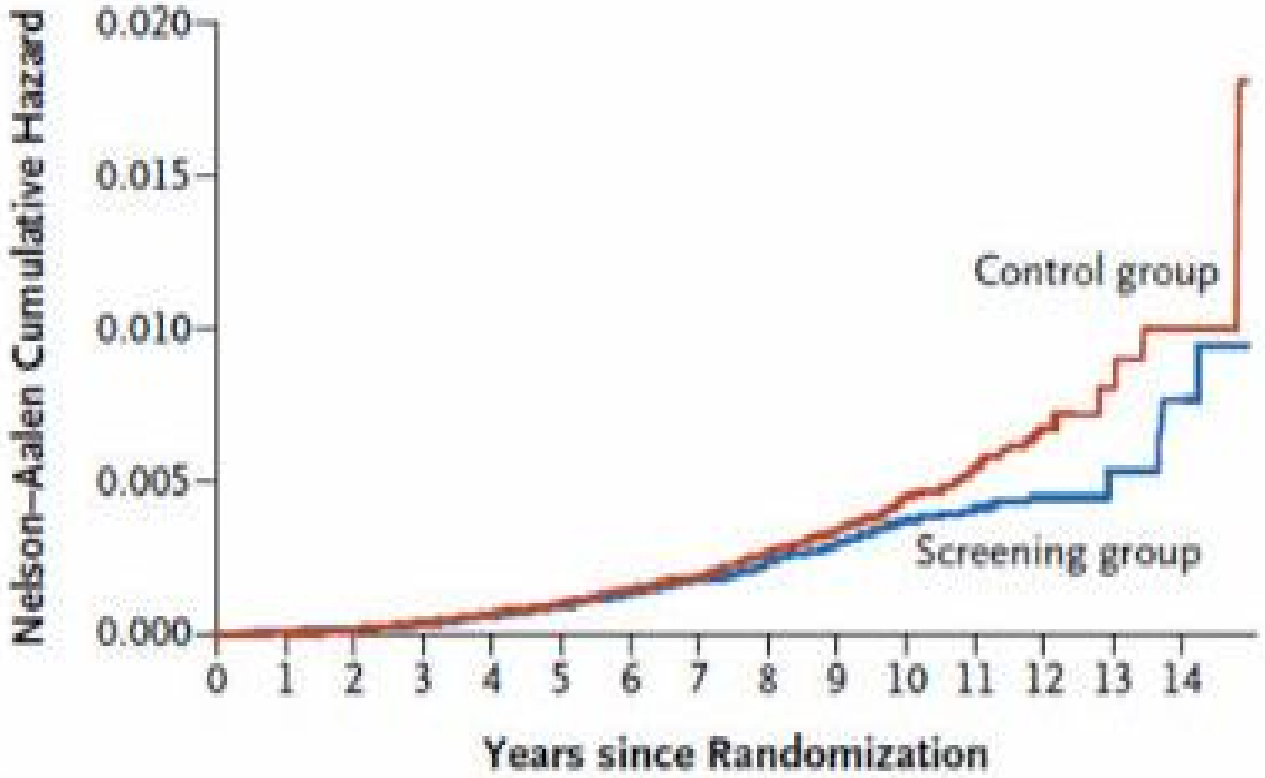
- N=692 RN uygulanmış
- 125 hastada komplet metastatektomi
- Genel sağkalım
  - 1, 5 ve 10 yıl
  - %64, %14 ve %6 (medyan 1.6yıl)

Prostat Kanseri

Methods I – European Randomized Study of Screening for Prostate Cancer (ERSPC)

- Tarama grubu 72.890 erkek
- Kontrol grubu 89.353
- 20.437 (%16.2) pozitif test sonucu
- 17.543(%85.8) biyopsi
- Tarama kolu 5990 PCa (%8.2), 214 PCa bağlı ölüm
- Kontrol grubu 4307 PCa(%4.8), 326 PCa bağlı ölüm
- Ortalama takip 8.8, medyan 9 yıl

Cumulative risk of death from prostate cancer



No. at Risk			
Screening group	65,078	58,902	20,288
Control group	80,101	73,534	23,758

Schröder,Hugosson Roobol et al. NEJM 2009

Prostat Kanseri-PSA taraması

- Tanıda geç kalındığında ileri hastalık+
- Çok ileri hastalığın tedavisi yok
- Tarama ile mortalitede azalma
- ERSPC çalışmasında hastalığa bağlı mortalitede %20 azalma
- Tedavi mortaliteyi düşürebilir

PLCO Çalışması

- Large Number Pre – screened
- Heavy Contamination of Control Group
- Follow – up Limited
- Used Single Cut – Point

N Engl J Med. **360**: 1310-19. 2009

PCa taramasının Riskleri ve Faydaları

- ERSPC çalışmasında; 48 hastayı PCa nedenli tedavi etmek ve 10 yılda 1 PCa bağlı ölümü engellemek için;
  - 1410 erkek taramadan geçmelidir
- Taramada tespit edilen kanserlerin çoğuna hemen tedavi gerekmemektedir
- Tarama gerekenden fazla tanı ve tedaviyle ilişkilidir

PROSTATE SCREENING 2009

Organization	Recommendation
American Urological Association (AUA)	Men who are in good health: annual PSA testing starting at age 50, or 40 if high-risk (AA, or with a father, brother or son with prostate cancer.)
American Cancer Society (ACS)	Offer to men > 50 who expect to live another 10 years, and high risk if they're age 45 and older.
Centers for Disease Control and Prevention (CDC)	Considers evidence "insufficient to determine whether the benefits outweigh the harms".
U.S. Preventive Services Task Force (USPSTF)	Do not screen > 75 and older, or in men who will probably live 10 years or fewer. For men under 75, the evidence insufficient to determine whether the benefits outweigh the harms. (Am J Prev Med 2008;34(2):164)
American College of Preventive Medicine (ACPM)	Discuss risks/benefits. The need for screening questionable in elderly men with other chronic illnesses and men with life expectancies of less than 10 years.

REDUCE Çalışması

- Hipotez: Dual 5-ARI dutasteride PCa geliştirme için yüksek risk taşıyan grupta biyopsi ile tanı konabilen PCa'ni önlemektir

- Faz III BPH çalışmalarında plaseboya oranla %51 daha az PCa görülmüştür

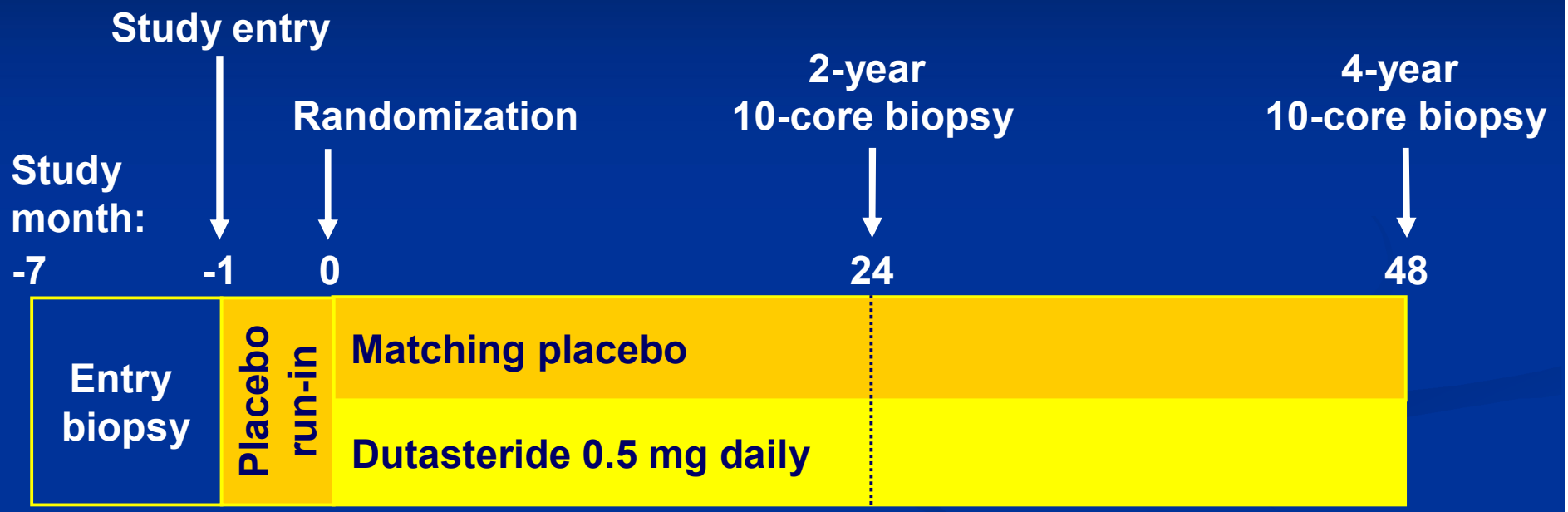
- PCa de BPH ya oranla daha fazla tip I 5AR enzimi tespit edilmiştir

1. Andriole *et al.* Urology 2004; 64: 537–41;
2. Thomas *et al*. Prostate 2005; 63: 231–9

Çalışmaya Giriş Kriterleri

- 50-75 yaş erkekler
- <60 yaş PSA 2.5–10 ng/mL veya
- >60 yaş PSA 3.0–10 ng/mL
- Son 6 ayda tek negatif prostat biyopsisi (6-12 kor, ASAP, HG-PIN veya PCa olmayan)
- Prostate hacmi ≤80 cc

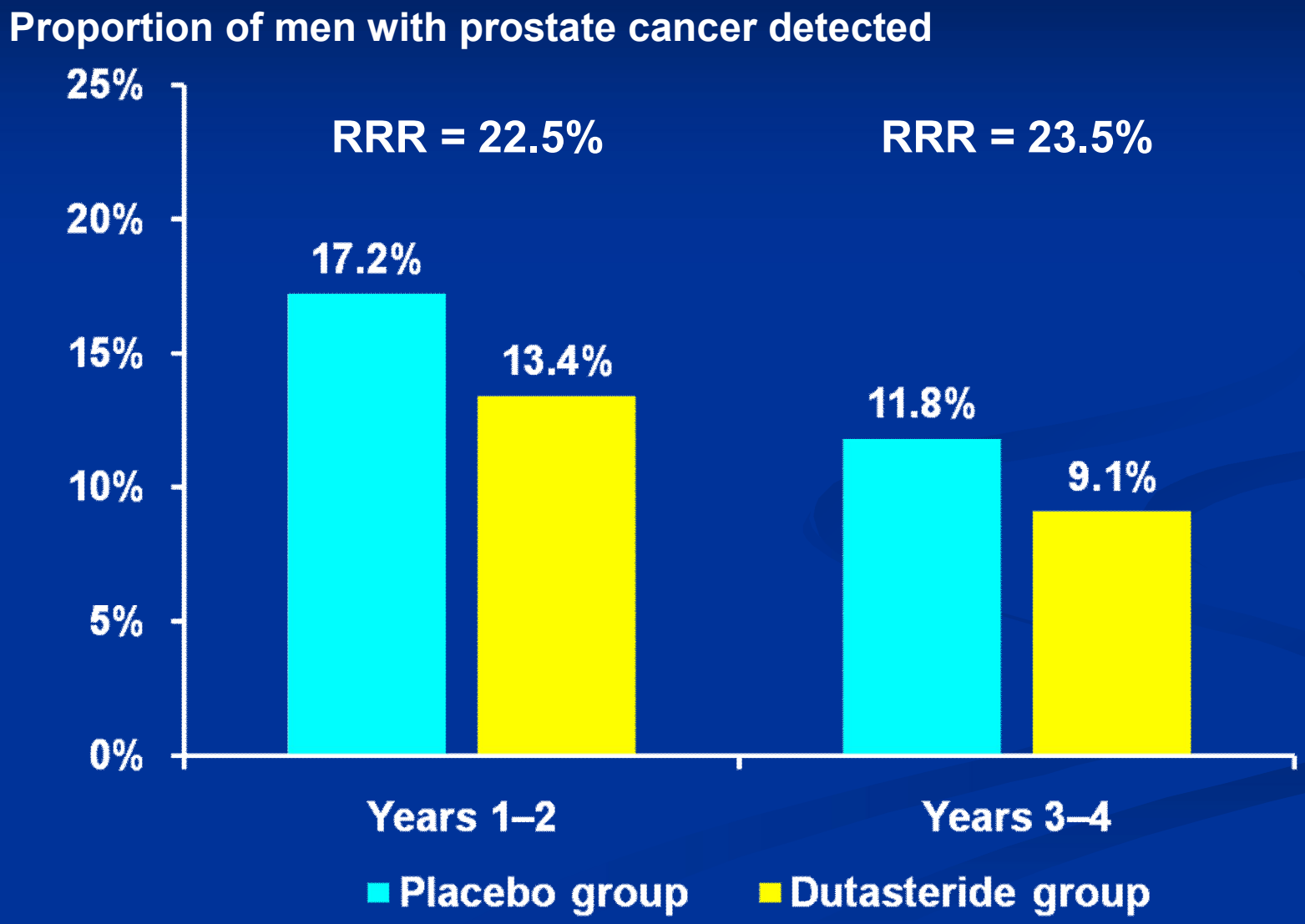
REDUCE: Study design



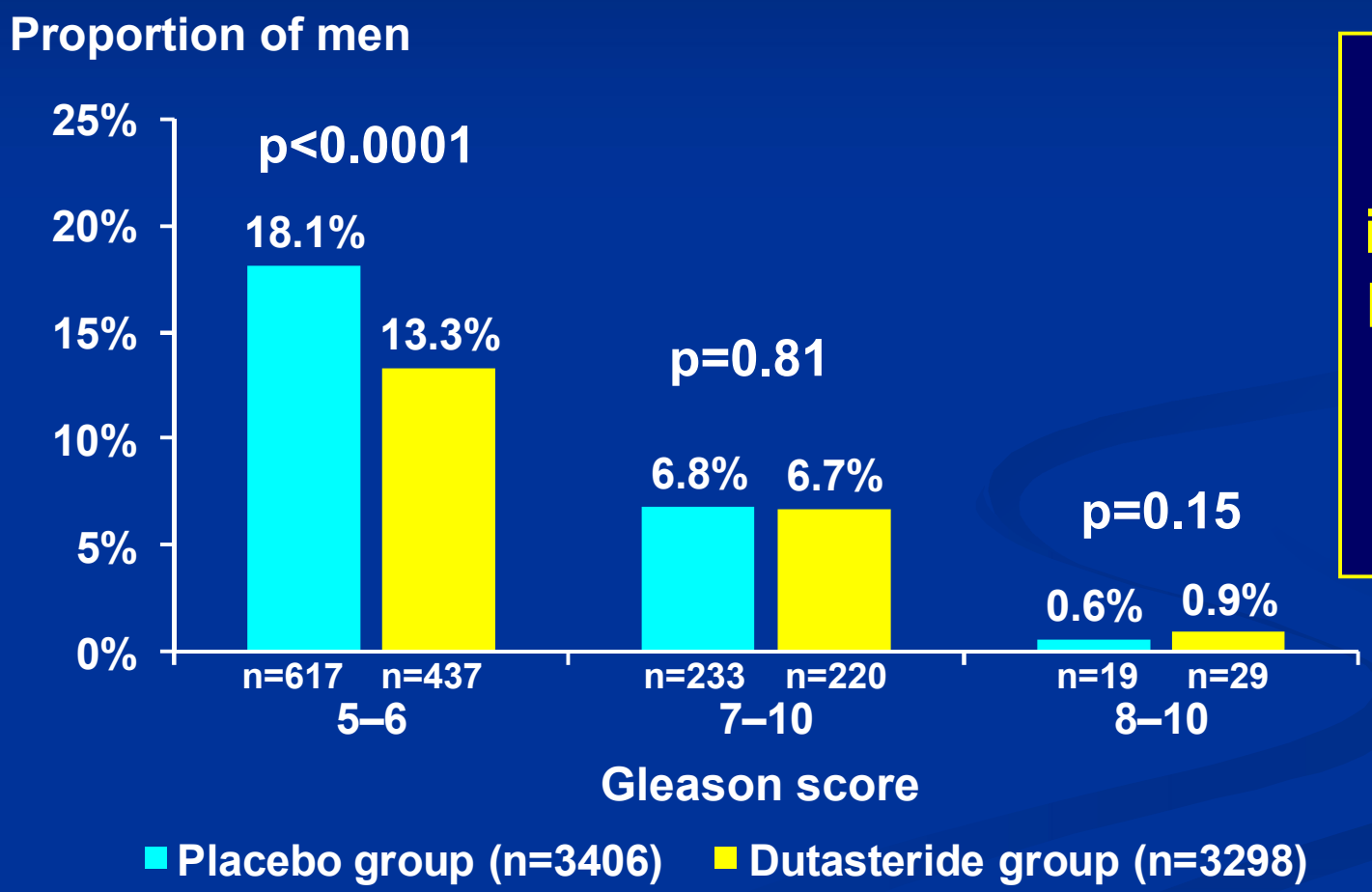
Protocol-independent biopsies could occur as indicated

Andriole *et al.* J Urol 2004; 172: 1314–7

REDUCE: Primary endpoint



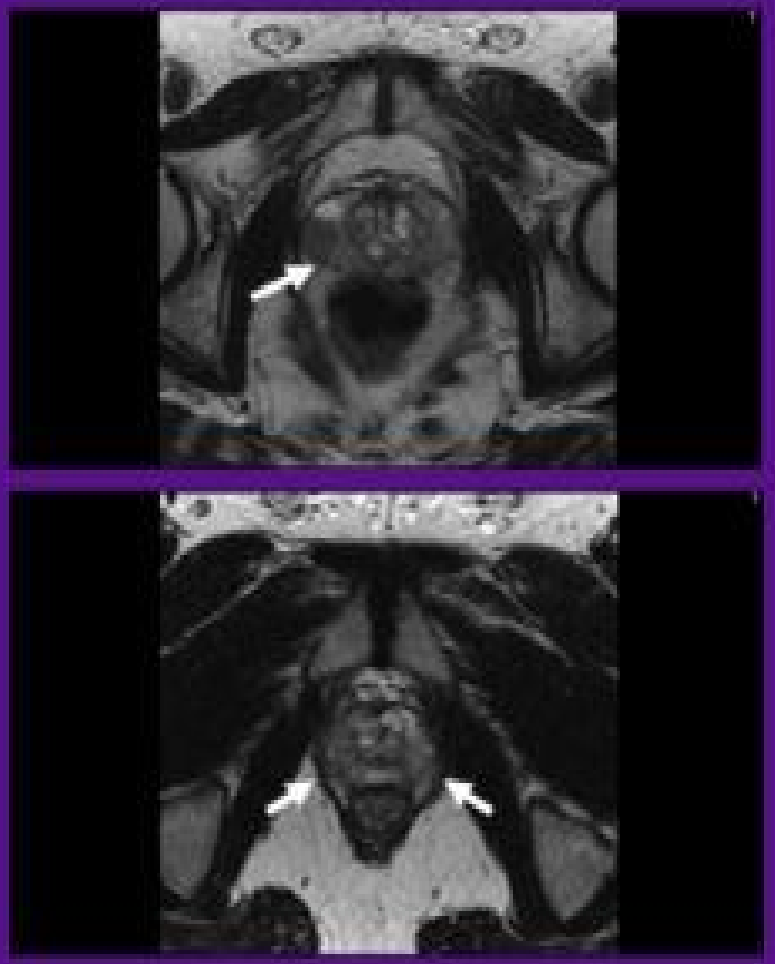
REDUCE: Gleason score distribution



No significant increase in high-grade tumors over 4 years

Focal Therapy

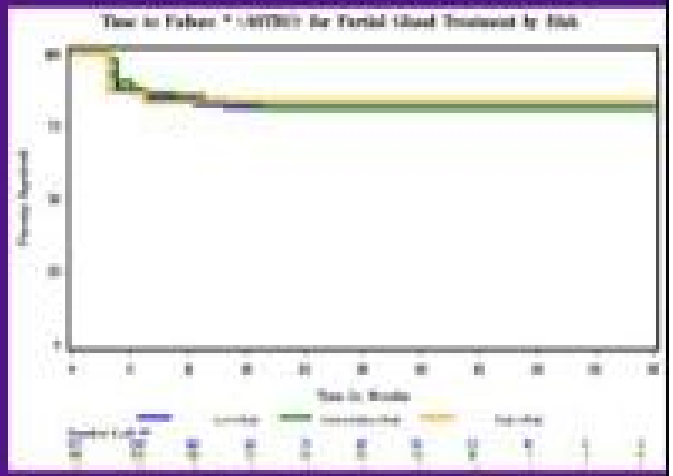
- Tareen, et al (abstract 490)
- 41 men with unilateral positive biopsy
- Specimen re-reviewed and 'mapped' for cancer location
- NPV for uninvolved lobe:
  - Biopsy 46.7%
  - MRI 71.4%
  - Both 100 %

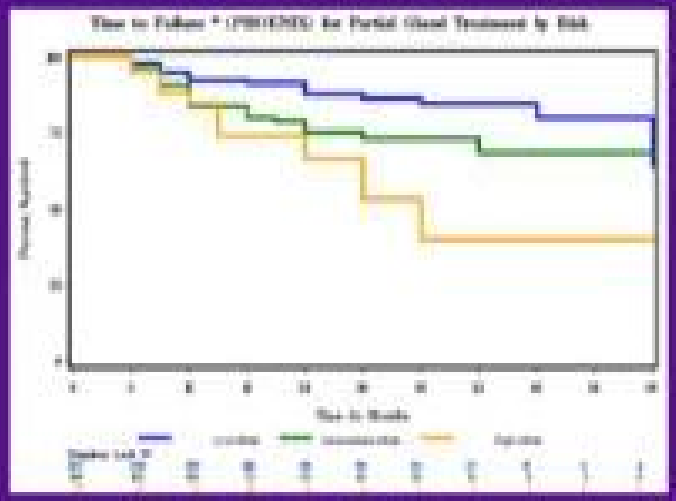


Outcomes of Partial Gland Ablation

Dhar, et al (abstract 1975)

- 795 men in COLD registry
  - 72% ≤ Gleason 6
  - 90% T1c/T2a
  - 47% low risk
- Complications
  - fistula 0.4%
  - Incontinence 0.8%
  - Impotence 35%
- Follow-up biopsy in 144
  - 36 (25%) positive

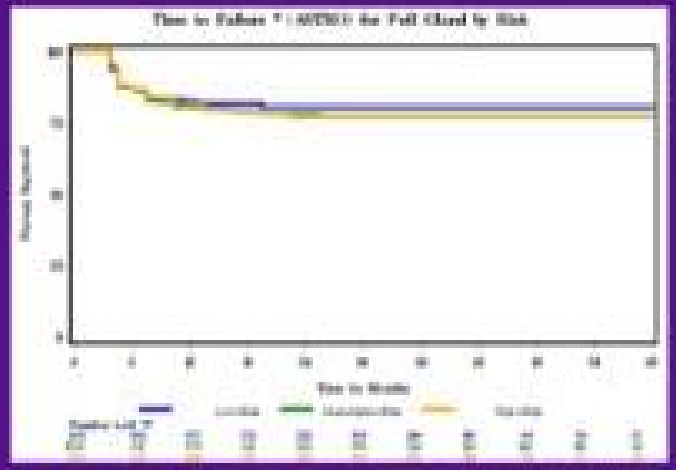


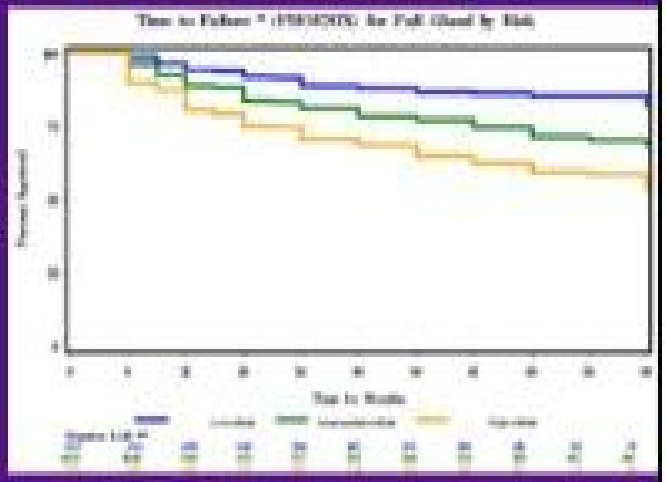


Ablative Whole Gland Therapy

Dhar, et al (abstract 631)

- 3209 men undergoing primary cryotherapy within the COLD registry
- Biochemical failure was defined according to the original ASTRO & PHOENIX def.
- Biopsy at physician discretion in 806 men with a 120 positive (14.9%)
- 67% impotence among men potent prior
- 2.2% incontinence
- 0.3% rectal fistula

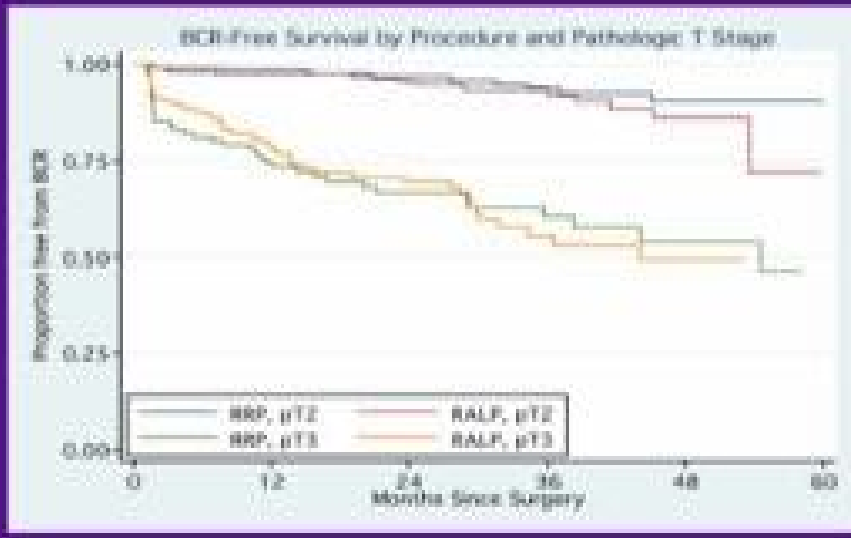




Robotic Radical Prostatectomy: Oncologic Outcomes

- Barocas, et al (abstract 1278)
- Comparison of 1411 RARP and 491 open RP performed between 2002-2008
- More adverse pathology in open group
- Equivalent three year biochemical outcomes

Pathologic Characteristic		RRP (n=491)	RALP (n=1,411)	p value
Pathologic Stage	pT2	342 (69.6)	1,136 (80.5)	<0.01
	pT3	144 (29.3)	268 (19.0)	
ECE	(pct)	103 (27.1)	253 (17.9)	<0.01
SVI	(pct)	38 (7.7)	68 (3.8)	<0.01
SM+	(pct)	145 (29.1)	281 (19.9)	<0.01
Gleason Score	≤ 6	321 (65.3)	773 (81.8)	<0.01
	7	213 (43.4)	557 (41.2)	
	8-10	54 (11.1)	94 (6.7)	



Robotic/Lap Radical Prostatectomy

Sutherland, et al (abstract 1283)

- Randomized study of standard anastamosis vs. posterior rhabdosphincter reconstruction (Rocco stitch) among 94 men undergoing RARP by one of 3 surgeons
- 6 wk and 3 mo. outcomes compared by EPIC questionnaire
- No difference in urinary continence
- Social continence (0-1 pads) in 40% and 70% at 6 weeks and 3 months, respectively

Radikal Prostatektomi

- RRP ve RARP kısa dönem onkolojik sonuçları kıyaslanabilir
- Kısa dönem inkontinans verileri kıyaslanabilir
- Robotik cerrahinin komplikasyonları genelde olduğundan daha az rapor edilmekte
- Sıklıkla hafif komplikasyonlar olmakta fakat ciddi komplikasyon oranı %5

Pozitif Cerrahi Sınırda RRP Sonrası Radyoterapi Zamanlaması

- RP sonrası ölçülemeyen PSA varsa %50 progresyon, %50 kürden bahsedilebilir
- Tüm hastalar RT alırsa bunların ½'si gereksiz tedavi almış olacaktır
- RP sonrası ölçülen PSA varsa erken veya geç RT konusundaki çelişki devam etmekte

Androjen Bağımsız Prostat Kanseri Androjen Bağımsız Değil!

Pca Rekürensi İçin Yeni Teoriler

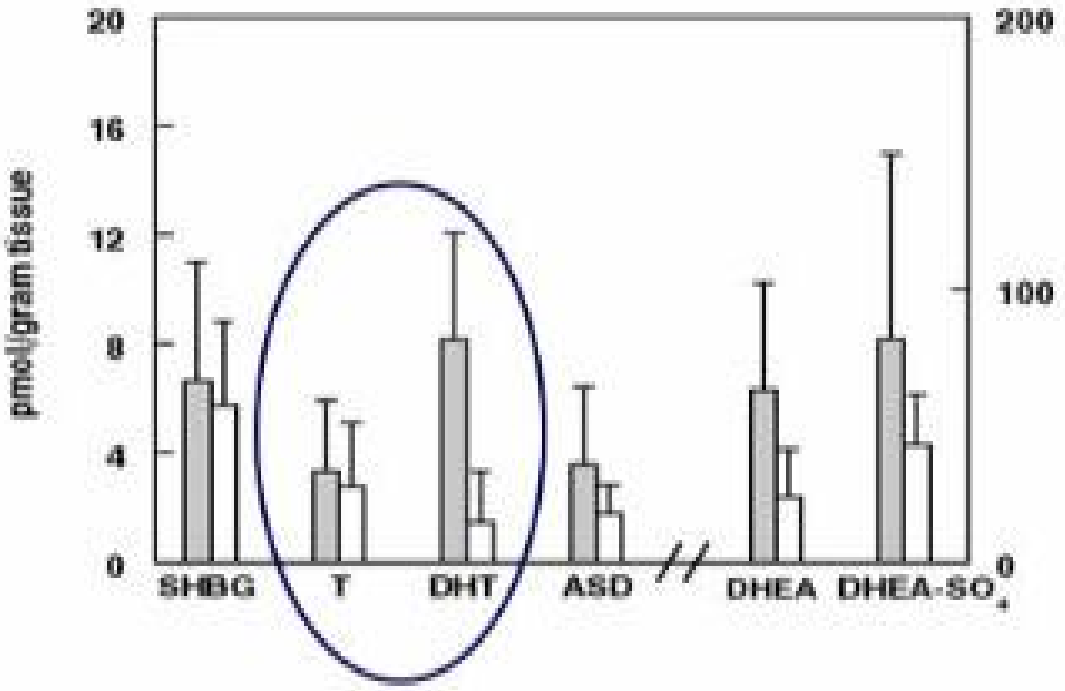
- AR'leri kastrasyona, çok düşük seviyelerde androjenlere karşı hipersensitivite oluşturan moleküler ve biyokimyasal değişikliklerle cevap verir

- Pca kastrasyona daha zayıf androjenlerden ve/veya kolesterolden DHT sentezleyerek cevap verir

AR Hipersensitizasyonu

- Androjen bağımsız LNcaP lerinde androjen sensitif olan hücrelere göre 10.000X fazla sensitivite göstermektedir

Tissue Androgen Levels using RIA in Benign Prostate (n=32;gray) vs. Castration-Recurrent CaP (n=23;white)



Mohler, Clin Cancer Res, 2004

Benign Prostate (n=18)		Castration-Recurrent CaP (n=18)		
T (nM)	DHT (nM)	ADT	T (nM)	DHT (nM)
3.4	23.6	LHRH+flu	1.6	0.0
0	14.5	orch	3.7	0.0
1.2	16.8	orch+flu	13.6	4.9
1.8	11.3	LHRH	1.2	4.6
2.5	12	LHRH+flu	1.7	0.0
2.9	20.5	orch	3.8	7.8
13.0	17.1	LHRH	5.4	3.9
1.2	13.2	orch	8.6	6.7
2.9	9.8	1° hypogonad	9.8	2.8
1.4	14.3	flu	11.4	1.2
1.6	11.2	orch	1.1	0.0
2.0	6.5	orch	2.5	0.4
2.7	10.7	LHRH→DES	7.2	1.3
2.8	13.7	Lupron	0.0	0.0
2.8	13.7	orch	1.6	0.7
3.2	20.3	orch	6.7	5.2
3.3	38.3	DES→orch	9.1	1.5
3.9	12.4	flu→DES	1.1	0.0
Mass Spec	2.8	13.7	3.8	1.3
RIA	3.2	8.1	2.8	1.5

Titus, Clin Cancer Res, 2005

Kastre-Rekürren Pca'de Tedavi Ne Olmalı?

- Doku androjenlerinin sentezinin engellenmesi
- Doku androjenlerinin parçalanmasının artırılması
- Prostatik vasküler yapının harap edilmesi
- AR aktivasyonunun önlenmesi…

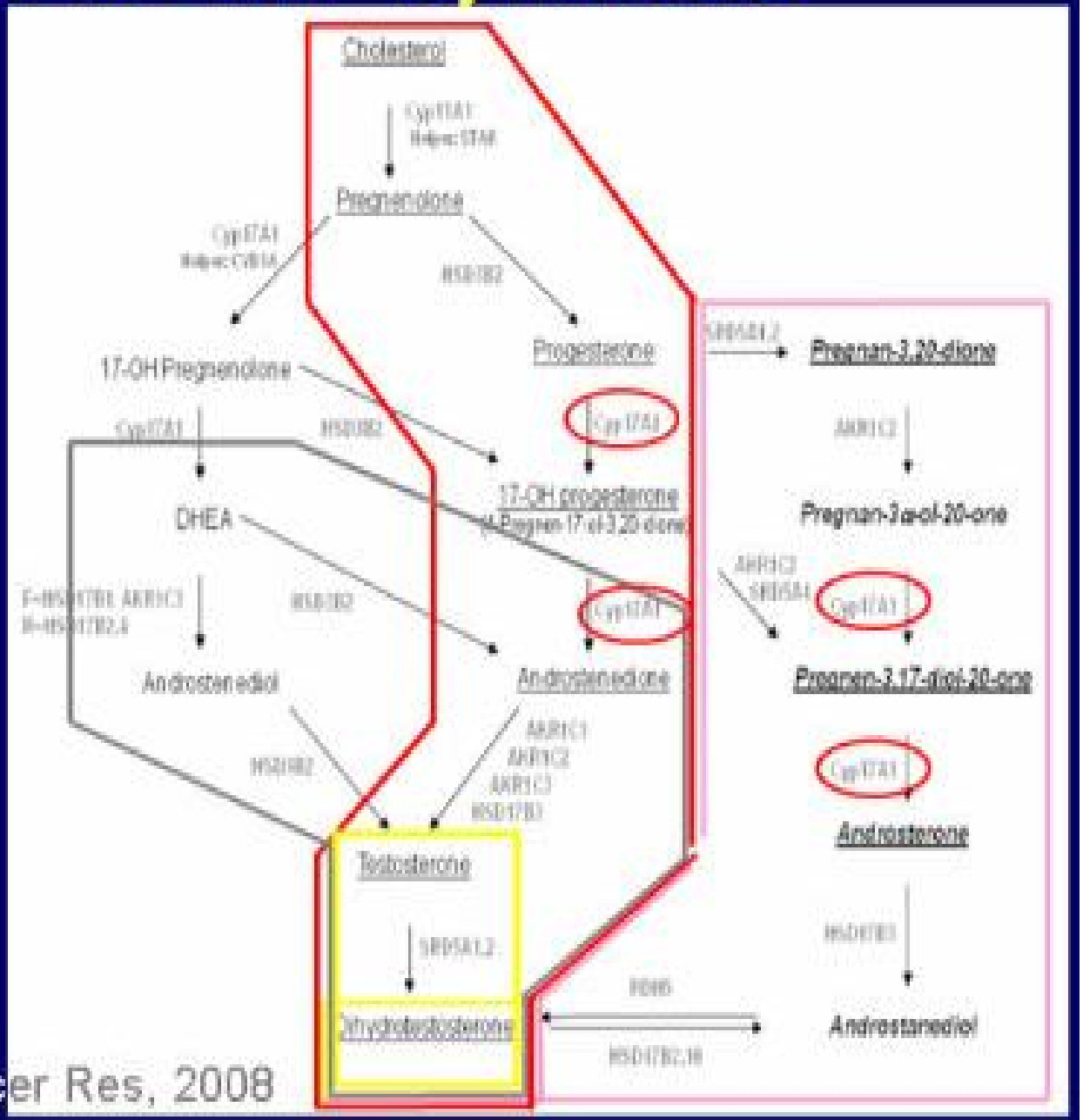
Pathways to DHT Synthesis

Intact pathway

Adrenal androgen pathway

Cholesterol pathway

Backdoor pathway



Modified from Locke, Cancer Res, 2008

PHASE II STUDY OF DUTASTERIDE IN PROSTATE CANCER RECURRENT DURING ANDROGEN DEPRIVATION THERAPY

- 25 evaluable men with asymptomatic castration-recurrent CaP (mean age 70, PSA 62, GS 8 and 15 M1b)
- Safety
  - grade 3 or higher adverse events using NCI criteria in 8 men
  - all judged unrelated to treatment
- Responses
  - 14 progressed
  - 9 stable (3, 3, 3, 4, 4, 5, 5, 9, 9 mo)
  - 2 partial response [PSA decline > 50%] (5, 11 mo)

Shah, J Urol, 2009

5α-Reductase Type 3

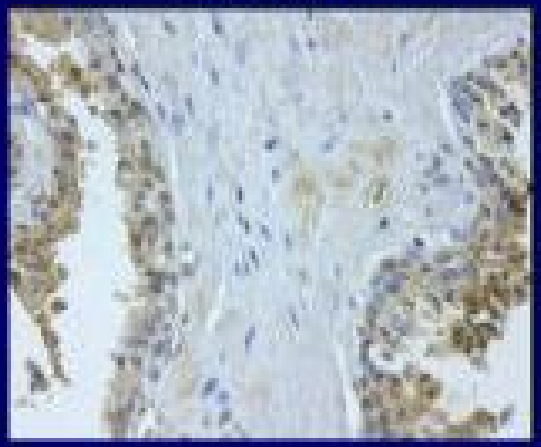
5α-reductase activity shifts from Type 2 in AS-BP → Type 1 in AS-CaP → Type 3 in CR-CaP

qRT-PCR

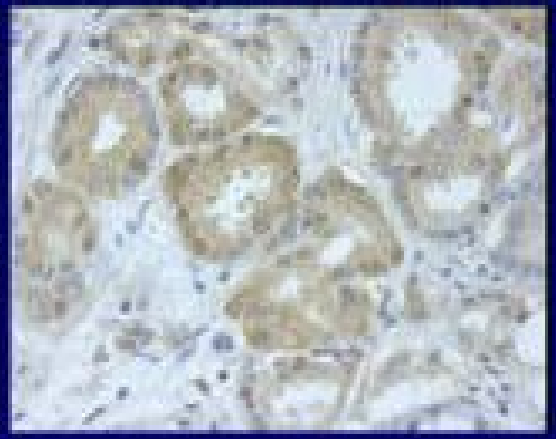
	Type 1	Type 2	Type 3
AS-CaP	0.71 ± 0.55	0.047 ± 0.032	0.69 ± 0.36
CR-CaP	0.26 ± 0.11	0.003 ± 0.006	0.56 ± 0.15

IHC

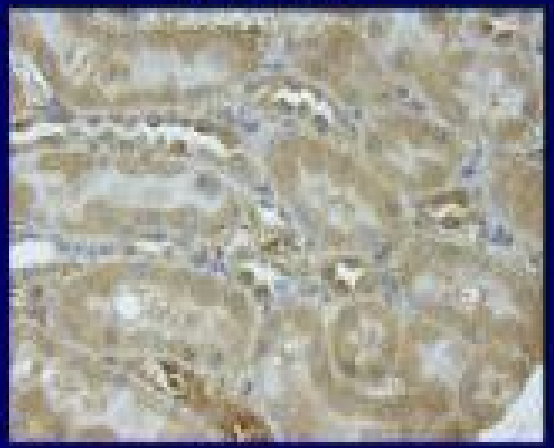
AS-BP



AS-CaP



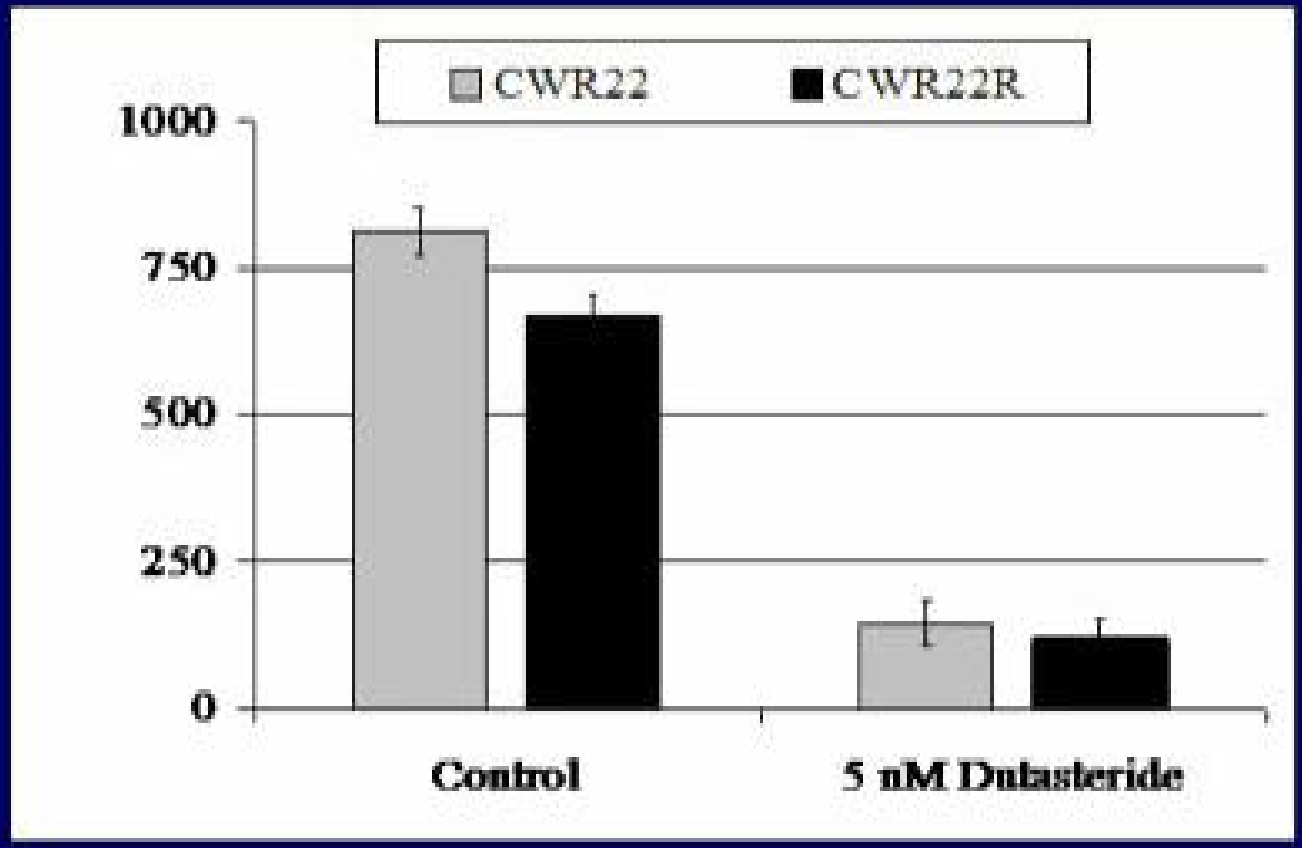
CR-CaP



5α-Reductase Type 3

not inhibited by finasteride or dutasteride

Metabolism of T to DHT (pmol/mg/min)

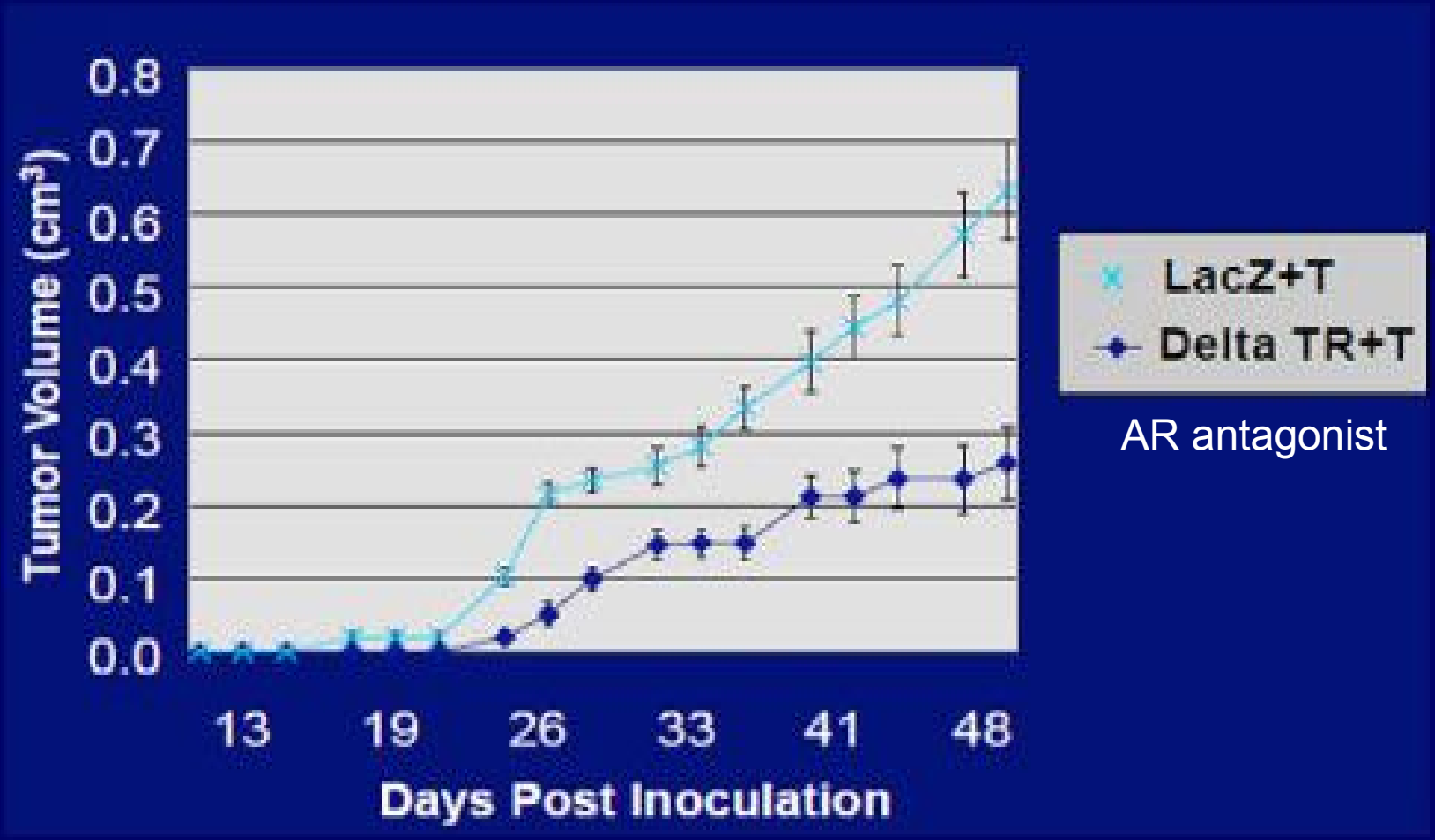


AR'nin AntiAndrojenlerle İnaktivasyonu

- Eski ve relatif etkisiz ilaçlar
  - Flutamid
  - Bikalutamid
  - Nilutamid
- Yeni ve muhtemel daha etkili moleküller

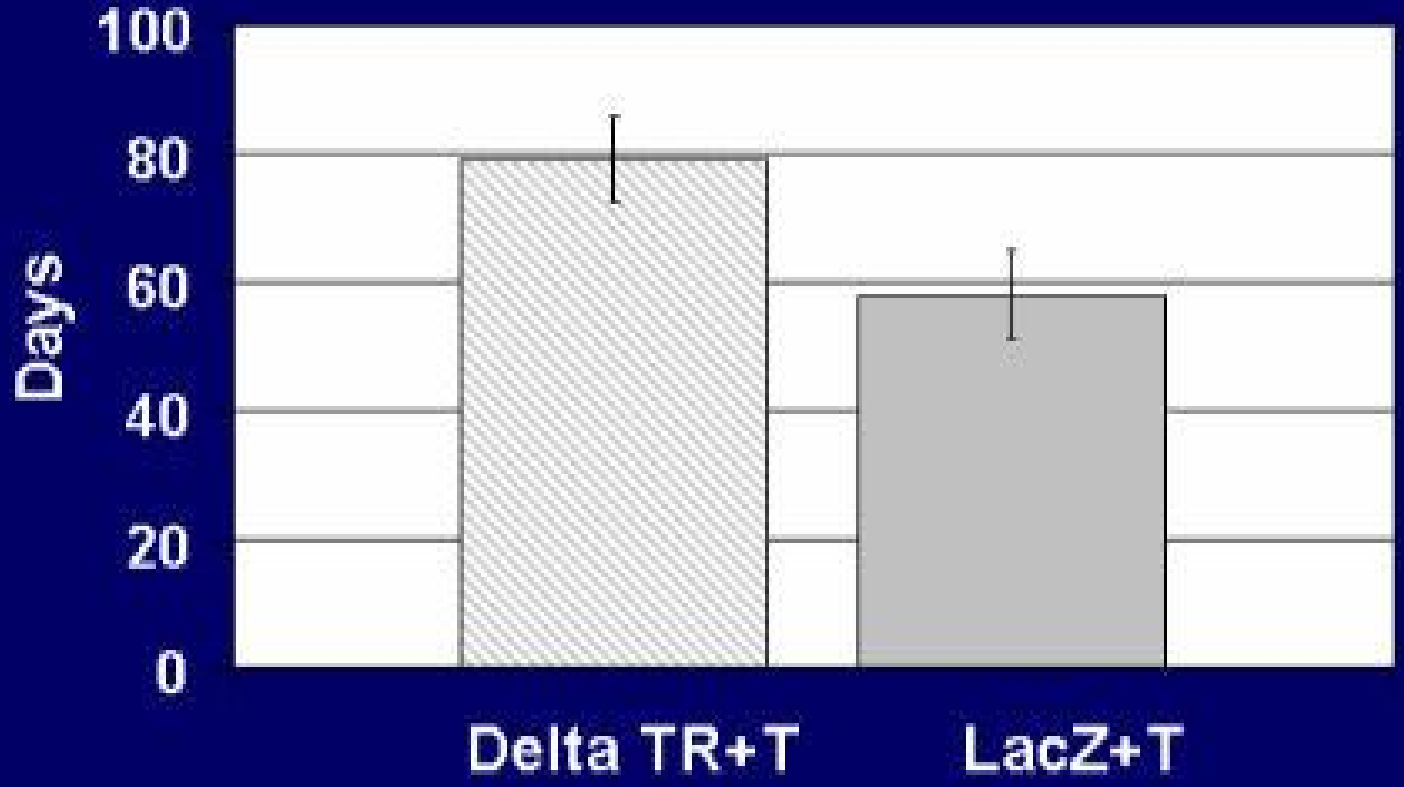
- AR antagonisti
  - MDV3100
- AR- spesifik histon deasetilaz inhibitörü
  - Vorinostat
  - Panobinostat
  - Romidepsin

Median Tumor Volume (to 1st Death)

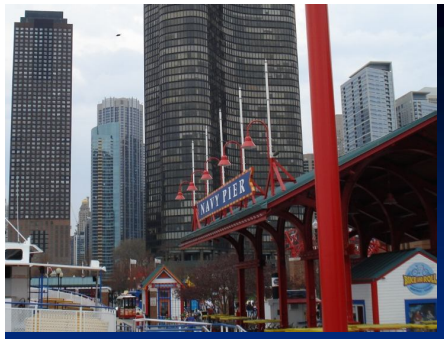


AR antagonist

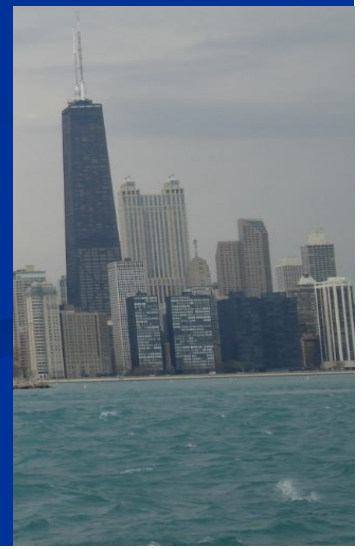
Survival

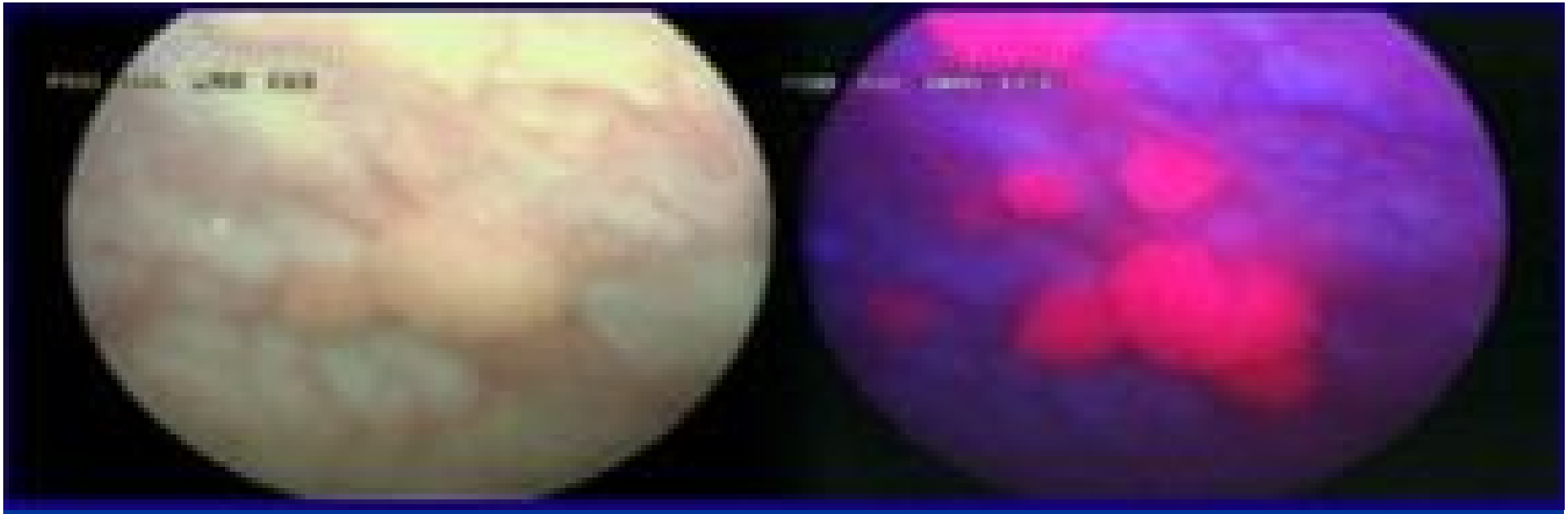


(P = 0.033)



Mesane Tümörleri

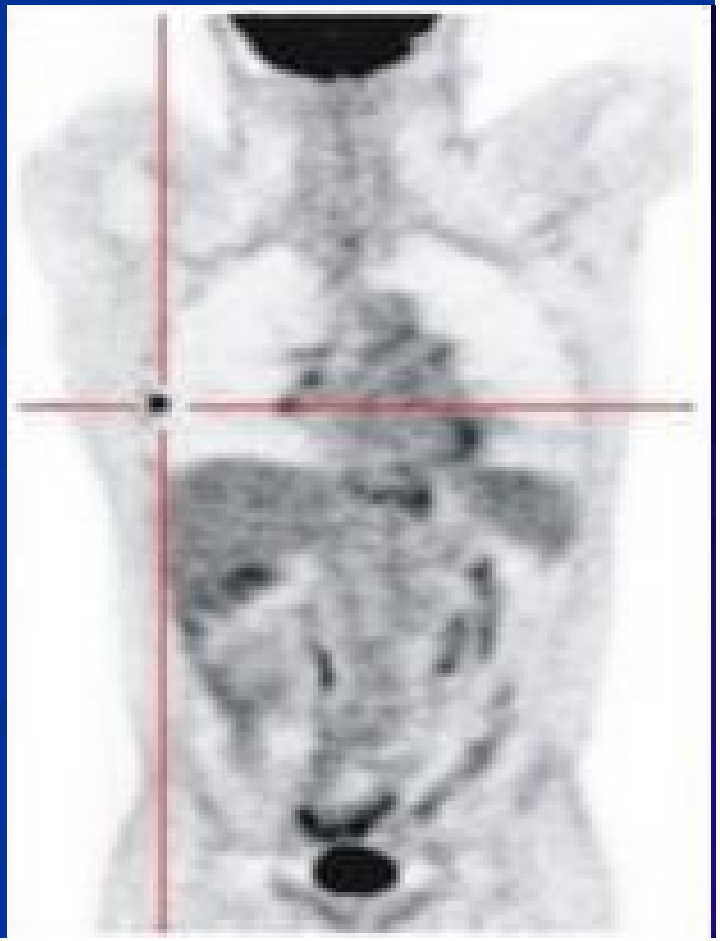




- Hexvix Fluorosein sistoskopi (n=766)
  - %45 daha fazla CIS tespiti
  - 9 ayda rekürens %46 > %36
- ALA Fluorosein sistoskopi (n=300)
  - Tanı oranı ↑
  - Rekürenste fark yok

FDG PET/CT

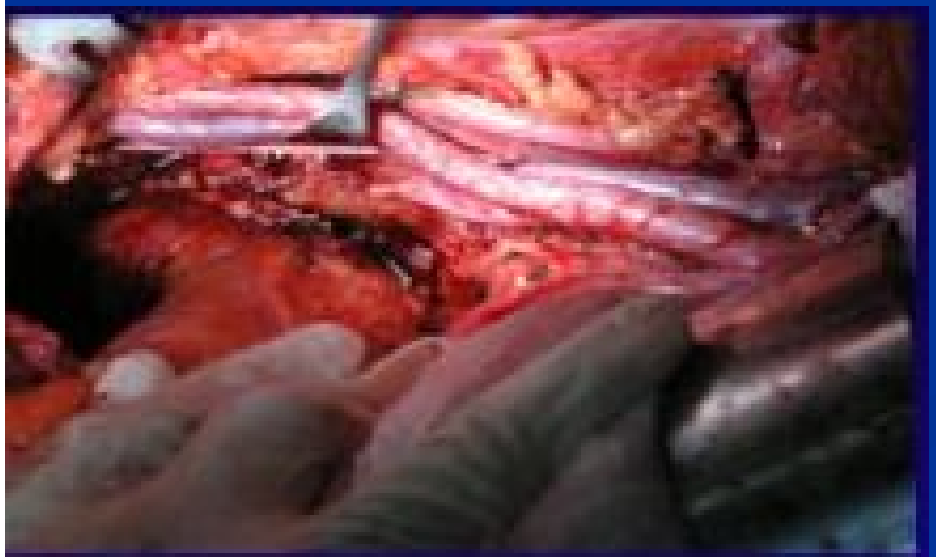
- FDG PET/CT Mesane Tm Evrelemesinde faydalı
- Pelvik nodlarda sensitivite %53-70
- NPV %90

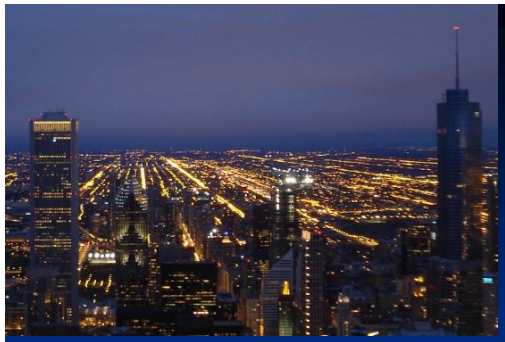


- IV tek doz kemoterapi artık altın standart değildir
- Toplamda %17'lik bir rekürens azaltma etkisi mevcut
- Extended lenfadenektomi hala standart değildir
  - Mark SOLOWAY

Lenfadenektomi

- Daha kapsamlı lenf nodu diseksiyonu sağkalım avantajını işaret etmekte
- %90 LN+ hastayı tespit etmek için extended LND 27< LN çıkarmak gerekli

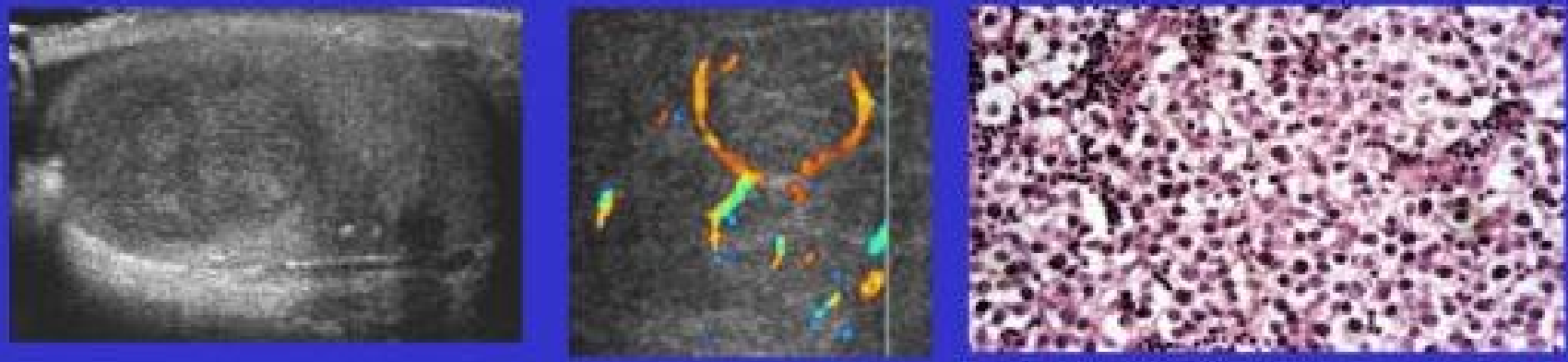




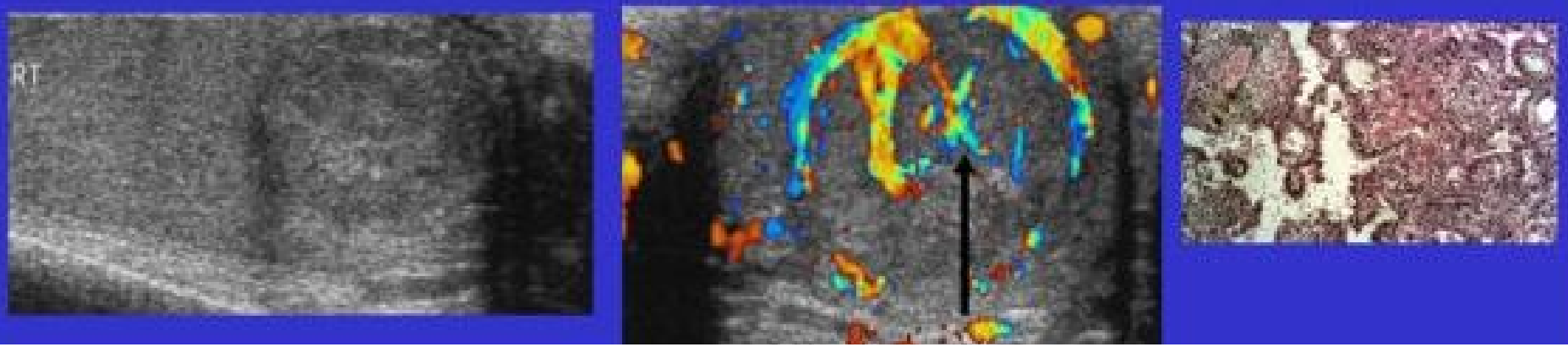
Testis Tümörleri

Tanı

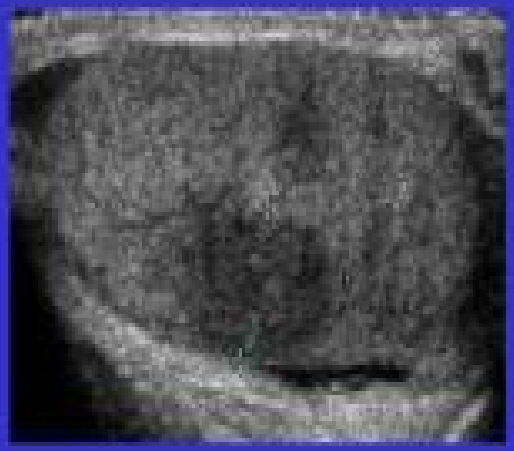
'Criss - Cross' Sign - Seminoma

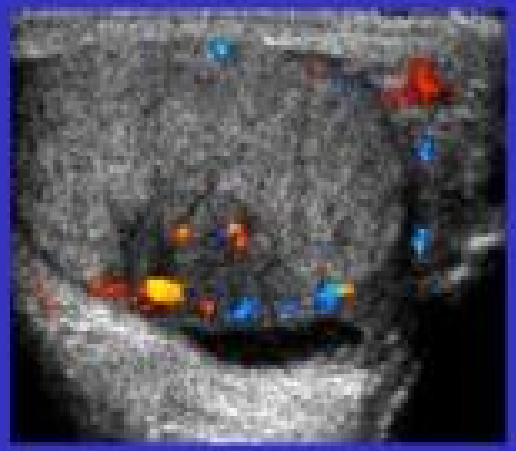


'Criss - Cross' Sign -teratoma

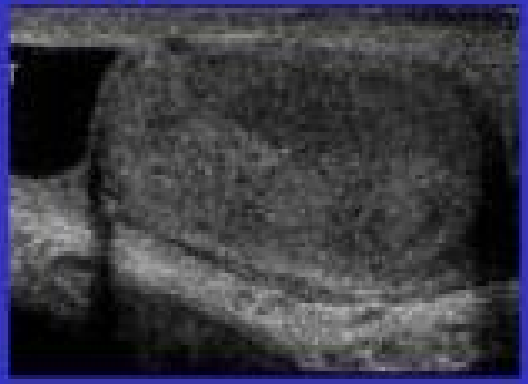


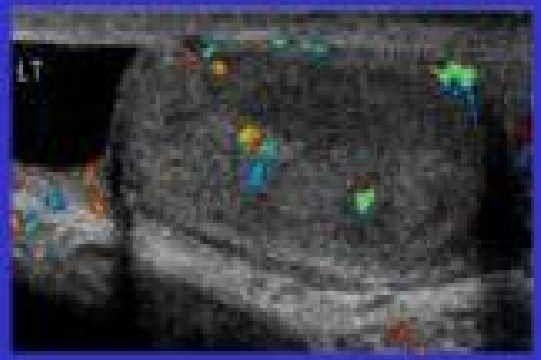
No vascular pattern - Secondary from Leukemia





No vascularity – Acute Segmental Testicular Infarction (ASTI)





Teşekkürler...

- Prostat kanseri taraması Türkiye'de yapılmalı mı? Evet ise ne zaman?

1. Hayır yapılmamalı
2. Evet yapılmalı, 40 yaştan itibaren
3. Evet yapılmalı, 50 yaştan itibaren
4. Evet yapılmalı, 60 yaştan itibaren