Individualizing Management of the Small Renal Mass with Percutaneous Renal Mass Biopsy

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Renal Mass Biopsy

- **Reasons to Forego Biopsy**
  - **Don't need it - we know it is cancer**
  - **Don't need it - radiographic characteristics (CT, MRI, molecular imaging) are accurate to determine risk**
  - **Biopsy is unsafe**
  - **Biopsy is not accurate**

Renal Mass Biopsy

- **"We Know it is Cancer"**
  - **Wrong! For masses < 4 cm…**
  - **~ 25% are benign**
    - ***Frank et al, J Urol 170:2217, 2003***
  - **~ 20% of malignancies are "aggressive"**
    - ***Thompson et al, J Urol 181:2033, 2009***
  - **> 95% 5-year CSS * if malignant**
    - ***Nguyen & Gill, J Urol 181:1020, 2009***
  - **~ 1% 3-year risk of metastases**
    - ***Thompson et al, J Urol 182:41, 2009***

Renal Mass Biopsy

- **"Radiographic Characteristics are Accurate" Getting better, but not enough…**
  - **Yes: Papillary v clear-cell**
    - ***Sun et al, Radiology 250: 793, 2009***
  - **Yes: Oncocytoma v clear-cell**
    - ***Gorin et al, Eur Urol 69:413, 2016***
  - **No: Papillary type 1 v type 2**
    - ***Egbert et al, AJR 201:347, 2013***
  - **Cannot differentiate clear-cell grades**

Renal Mass Biopsy

- **"Biopsy is Unsafe"**
  - **Wrong!**
  - **Seeding risk estimated < 0.01%**
    - ***Herts & Baker, Curr Opin Urol 10:105, 2000.***
  - **Only 1 seeding report in last 20 years**
    - ***Mullins & Rodriguez, J Can Urol Assoc 7:E176, 2013***
  - **Major complications < 1%**
    - ***Lane et al, J Urol 179:20, 2008***

Renal Mass Biopsy

- **"Biopsy is not Accurate"**
  - **Wrong! Wrong! Wrong!**
  - **For determining malignancy**
    - **~90% sensitivity, ~99% specificity**
      - ***Volpe et al, J Urol 178:379, 2007***
    - **< 1% false -, < 1% false +, ~ 10% indeter**
      - ***Lane et al, J Urol 179:20, 2008***
  - **For determining high v low risk cancer**
    - **96% sensitivity, 100% specificity ***

Renal Mass Biopsy to Risk Stratify

Accuracy of Determining Small Renal Mass Management with Risk Stratified Biopsies: Confirmation by Final Pathology

Schuyler J. Halverson,* Lakshmi P. Kunju,* Ritu Bhalla,* Adam J. Gadzinski,* Megan Alderman,* David C. Miller,† Jeffrey S. Montgomery,* Alon Z. Weizer,* Angela Wu,* Khaled S. Hafez* and J. Stuart Wolf, Jr.*,‡

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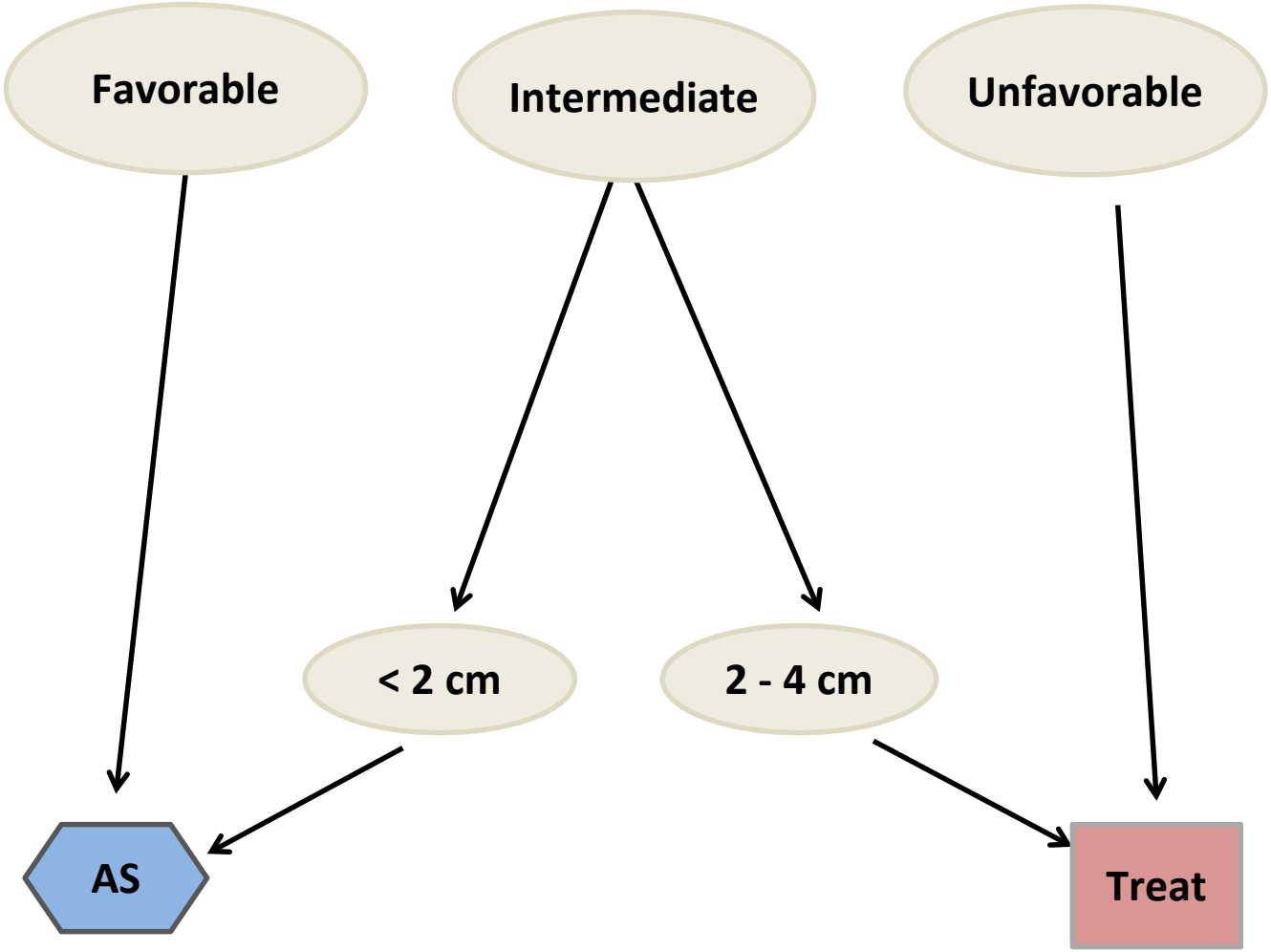
Renal Mass Biopsy to Risk Stratify

- **Histologic Risk Groups**
  - **Benign AML, Oncocytoma**
  - **Favorable Chromophobe, Gr 1 Papillary I**
  - **Intermediate Gr 1 / 2 Clear cell, Gr 2 Papillary I, Oncocytic or Papillary NOS**
  - **Unfavorable Gr 3 / 4 Clear cell, Papillary II, urothelial, unclassified, sarcomatoid, etc**

Renal Mass Biopsy to Risk Stratify



Renal Mass Biopsy to Risk Stratify

- **Is Biopsy Reliable Enough?**
  - **151 patients with core-biopsy and excised small renal mass**
    - **< 2 cm, n = 37; 2 – 4 cm, n = 114**
  - **Compare pathology on renal mass biopsy with final pathology**
  - **Determine management group as directed by biopsy**
  - **Confirm management group using final pathology**

Renal Mass Biopsy to Risk Stratify

- **Biopsy Results**
  - **Indeterminate - 14**
  - **Benign – 4**

    (n = 18, excluded from analysis)
  - **Favorable - 5**
  - **Intermediate - 110**
  - **Unfavorable – 18**

    (n = 133, included in analysis)

Renal Mass Biopsy to Risk Stratify

- **Revised Risk Grouping: ≤ 4 cm (n=133)**

Biopsy Pathology	Final Surgical Pathology	
	Surveillance	Treatment
Surveillance	25	4
Treatment	0	104

Incorrect assignment in 4 / 133 (3.0%)

Kappa = 0.91

Renal Mass Biopsy to Risk Stratify

- **Accuracy of Biopsy Risk Assignment**
  - **Sensitivity (for Treatment)**
    - **104 / 108 (96%)**
  - **Specificity (for Surveillance)**
    - **25 / 25 (100%)**
  - **Positive Predictive Value (Treatment)**
    - **104 / 104 (100%)**
  - **Negative Predictive Value (Surveillance)**
    - **25 / 29 (86%)**

Renal Mass Biopsy to Risk Stratify

Evaluation of Renal Mass Biopsy Risk Stratification Algorithm for Robotic Partial Nephrectomy—Could a Biopsy Have Guided Management?

Haider Rahbar, Sam Bhayani, Michael Stifelman,* Jihad Kaouk, Mohamad Allaf, Susan Marshall, Homayoun Zargar, Mark W. Ball, Jeffrey Larson and Craig Rogers†,‡

From the Vattikuti Urology Institute, Henry Ford Hospital, Detroit, Michigan (HR, CR), Division of Urologic Surgery, Washington University School of Medicine, Saint Louis, Missouri (SB, JL), Department of Urology, New York University Langone Medical Center, New York, New York (MS, SM), The Glickman Urological Institute, Cleveland Clinic, Cleveland, Ohio (JK, HZ), and the James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore, Maryland (MA, MWB)

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http://dx.doi.org/10.1016/j.juro.2014.06.028
Vol. 192, 1337-1342, November 2014
Printed in U.S.A.

Renal Mass Biopsy to Risk Stratify

Materials and Methods: A simplified algorithm of biopsy directed small renal mass management previously reported using risk stratified biopsies was applied to 1,175 robotic partial nephrectomy cases from 5 academic centers. A theoretical assumption was made of perfect biopsies that were feasible for all patients and had 100% concordance to final pathology. Pathology risk groups were benign,

Conclusions: The theoretical application of a biopsy driven, risk stratified small renal mass management algorithm to a large robotic partial nephrectomy database suggests that about half of the patients might have avoided surgery. Despite the obvious limitations of a theoretical assumption of all

Renal Mass Biopsy to Risk Stratify

Comparison with Size Criteria

- Is biopsy any better than using size alone?
- Surveillance if < 2 cm (n = 31) ?
- Treatment if 2 – 4 cm (n = 102) ?

→ 9 of 31 on Surveillance would have unfavorable pathology (4 using biopsy)

→ 3 of 102 Treated would have favorable pathology (0 using biopsy)

Renal Mass Biopsy to Risk Stratify

Comparison with R.E.N.A.L. Nephrometry Score

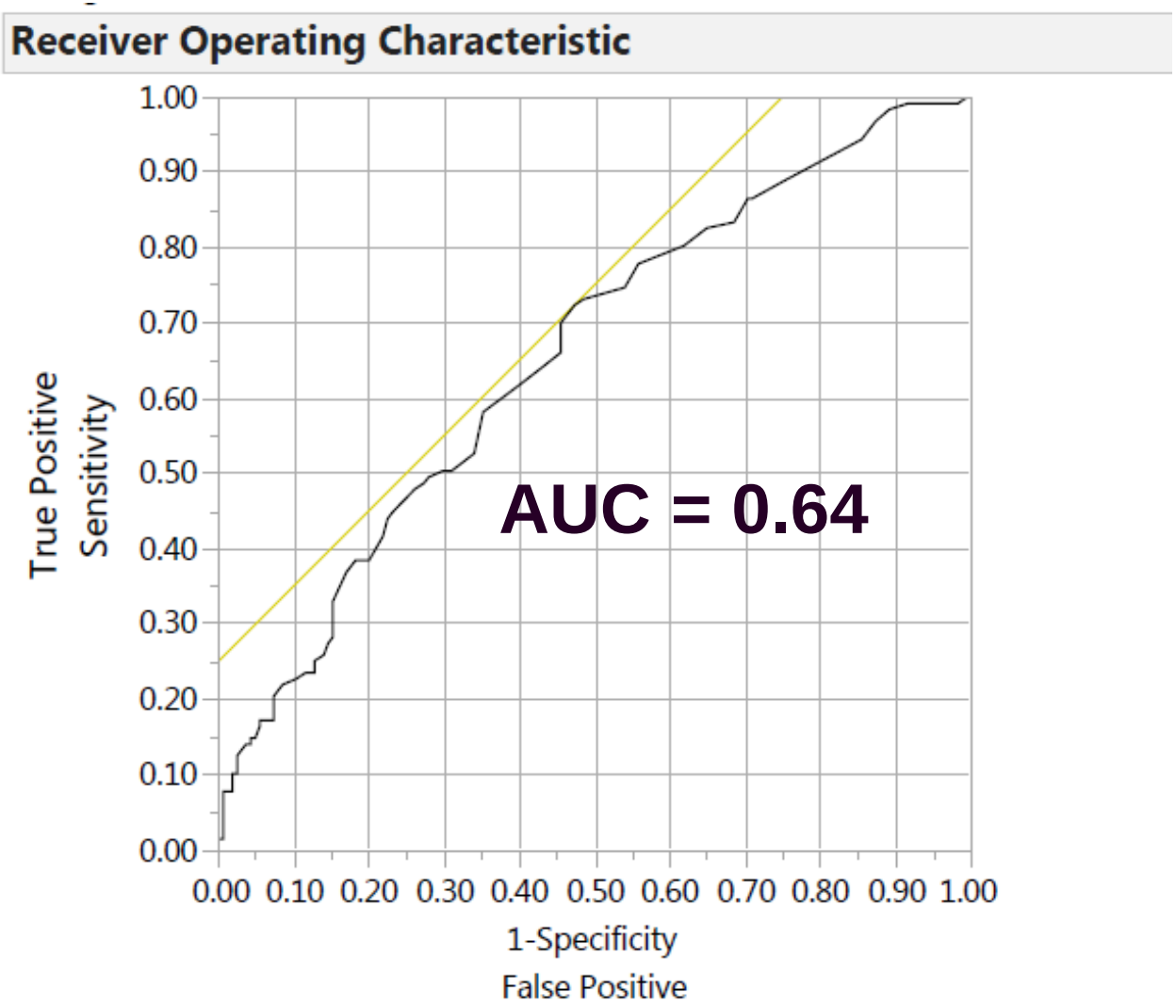
- **Kutikov et al, Eur Urol 2011, 60:241**
- **Nomograms predicting**
  - **benign v malignant (AUC = 0.76)**
  - **favorable v unfavorable (= 0.73)**
- **University of Michigan validation: 281 SRMs with nephrometry score, biopsy and final pathology from excision**

Renal Mass Biopsy to Risk Stratify

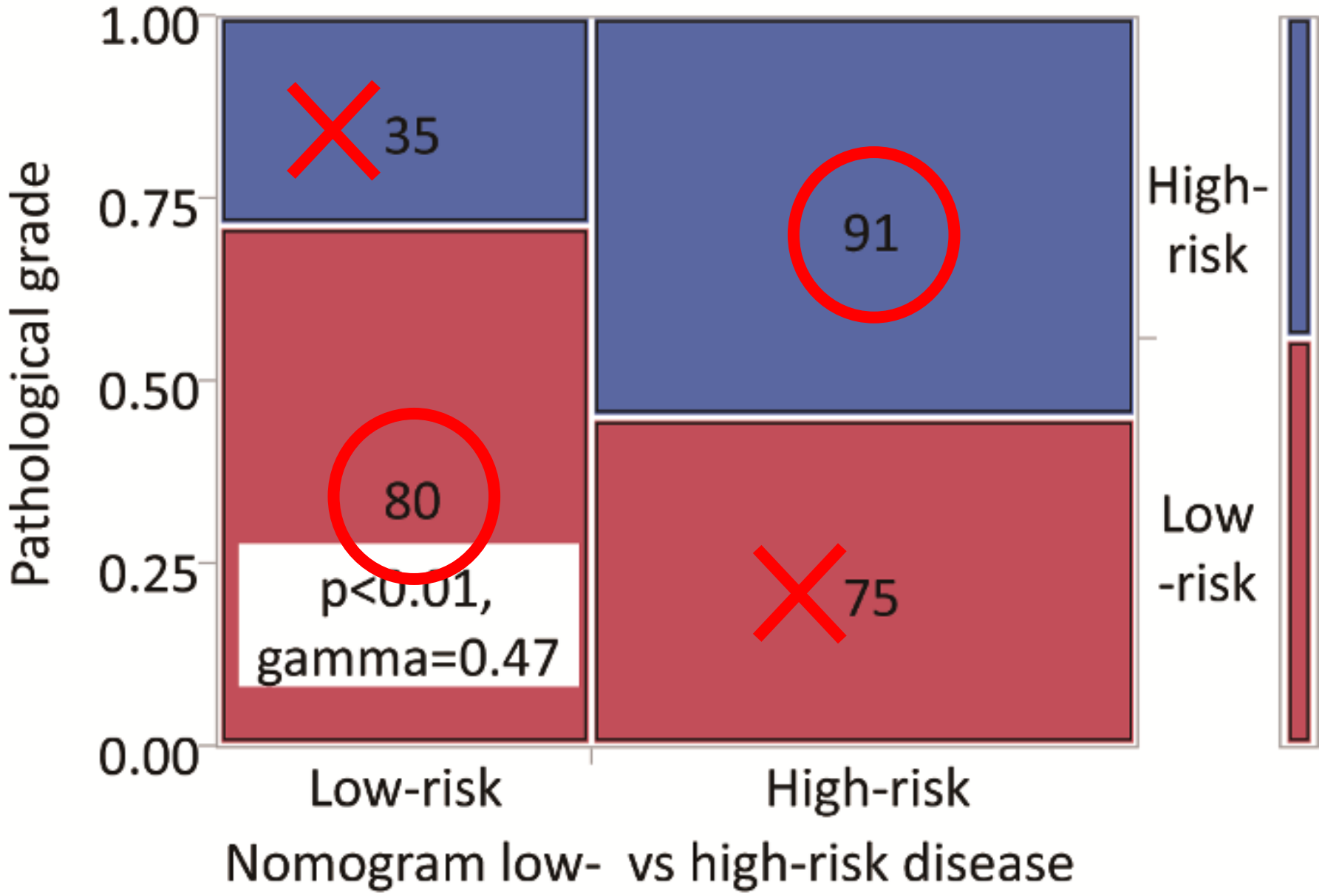
- **Histologic Risk Groups**
  - **Benign AML, Oncocytoma**
  - **Favorable Chromophobe, Gr 1 Papillary I**
  - **Intermediate Gr 1 / 2 Clear cell, Gr 2 Papillary I, Oncocytic or Papillary NOS**
  - **Unfavorable Gr 3 / 4 Clear cell, Papillary II, Urothelial, Unclassified, Sarcomatoid, etc**

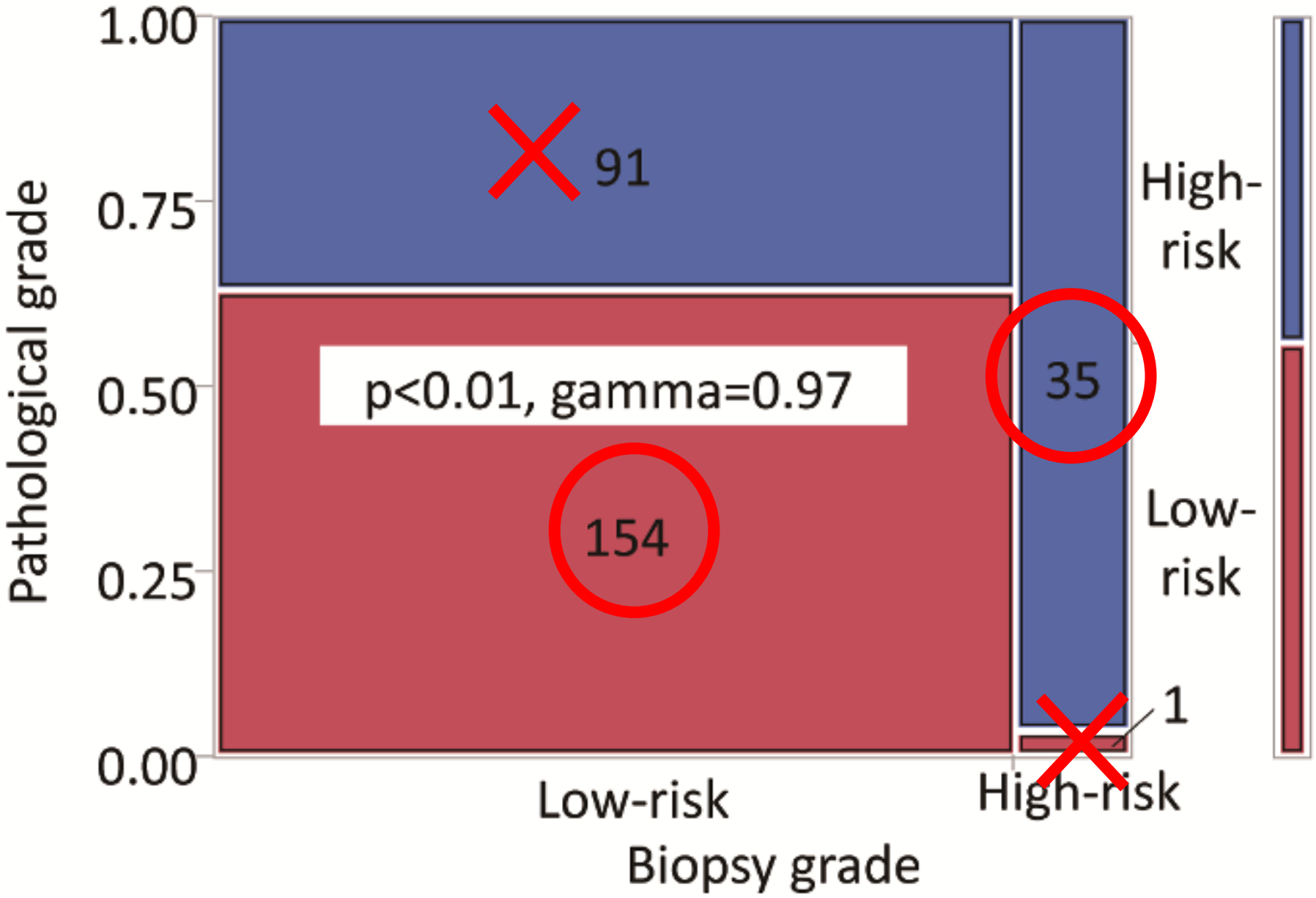
Renal Mass Biopsy to Risk Stratify

- **Collapsed Histologic Risk Groups**
  - **Favorable, n = 157 AML, Oncocytoma, Chromophobe, Gr 1 / 2 Papillary I, Gr 1 / 2 Clear cell, Oncocytic or Papillary NOS**
  - **Unfavorable, n = 124 Gr 3 / 4 Clear cell, Papillary II, Urothelial, Unclassified, Sarcomatoid, etc**



Nephrometry Score Nomogram Predicts Favorable v Unfavorable Pathology


1.00
0.75
0.50
0.25
0.00
Pathological grade
35
91
80
75
p<0.01,
gamma=0.47
High-risk
Low-risk
Low-risk
High-risk
Nomogram low- vs high-risk disease


1.00
0.75
0.50
0.25
0.00
Pathological grade
91
p<0.01, gamma=0.97
154
35
1
High-risk
Low-risk
Low-risk
High-risk
Biopsy grade

Renal Mass Biopsy to Risk Stratify

- **Concern about those "False Negatives"**
  - **Patients incorrectly assigned to surveillance, who in fact harbor worse pathology than suggested by biopsy and should get treated**
  - **14% of those assigned to surveillance**
  - **(17% in updated series)**

Renal Mass Biopsy to Risk Stratify

- **Can we Salvage Patients Incorrectly Assigned to Surveillance?**
  - **Subset of University of Michigan SRM database**
  - **495 treated SRMs from 2009 to 2015**
  - **376 early intervention, 119 delayed intervention**
  - **Impact on Adverse pathology**
    - **Gr 3 / 4 Clear cell, Papillary II, Urothelial, Unclassified, Sarcomatoid, etc.**

Renal Mass Biopsy to Risk Stratify

- **Can we Salvage Patients Incorrectly Assigned to Surveillance?**
  - **Multivariable logistic regression comparing early and delayed intervention groups**
  - **Rates of partial v radical nephrectomy similar (p=0.6)**
  - **Delayed intervention not associated with adverse pathology (p=0.5)**

Renal Mass Biopsy to Risk Stratify

- **Can we Salvage Patients Incorrectly Assigned to Surveillance?**
  - **Multivariable logistic regression comparing early and delayed intervention groups**
  - **In patients who underwent surveillance, faster growth rates associated with adverse pathology**
    - **10% increase in odds of adverse pathology for each 1 mm/yr change in growth rate**

Renal Mass Biopsy to Risk Stratify

- **Can we Salvage Patients Incorrectly Assigned to Surveillance?**
  - **Answer … Yes, we can**
  - **This mitigates some of the concern about "false negatives" of biopsy**

Renal Mass Biopsy to Risk Stratify

- **Summary: Risk Stratification by Biopsy**
  - **Biopsy does not perfectly identify histologic type and grade**
  - **Biopsy does not need to perfectly identify histologic type and grade**
  - **Absolute accuracy not necessary when biopsy is paired with a risk-stratified management algorithm**

Renal Mass Biopsy to Risk Stratify

- ~~Reasons to Forego Biopsy~~
  - ~~Don't need it - we know it is cancer~~
  - ~~Don't need it - radiographic characteristics (CT, MRI, "advanced MRI") are accurate to determine risk~~
  - ~~Biopsy is unsafe~~
  - ~~Biopsy is not accurate~~

Renal Mass Biopsy to Risk Stratify

- **Reasons to Perform Biopsy - #1**
  1) **Avoid intervention in cases of benign or non-aggressive tumor**
     - **Routine for all SRMs?**
       - **Young healthy patients unlikely to accept surveillance**
       - **Unlikely to treat older patients with major comorbidities**
     - **Who are the best candidates?**

Renal Mass Biopsy to Risk Stratify

- **Reasons to Perform Biopsy - #2**

  2) May change treatment plan if aggressive malignancy is found

  - **Radical versus partial in some situations**
  - **Papillary Type 2 – risk of multifocality**
  - **Grade 4 clear cell – concern about margins**

Renal Mass Biopsy to Risk Stratify

- **Biopsy Determines Management**
  - **Subset of University of Michigan SRM database**
  - **854 SRMs from 2007 to 2015**
  - **366 interpretable biopsy, 488 no biopsy**
  - **Impact on initial management**
    - **393 active surveillance**
    - **49 ablative therapy**
    - **275 partial nephrectomy**
    - **37 radical nephrectomy**

Renal Mass Biopsy to Risk Stratify

- **Histologic Risk Groups**
  - **Benign AML, Oncocytoma**
  - **Favorable Chromophobe, Gr 1 Papillary I**
  - **Intermediate Gr 1 / 2 Clear cell, Gr 2 Papillary I, Oncocytic or Papillary NOS**
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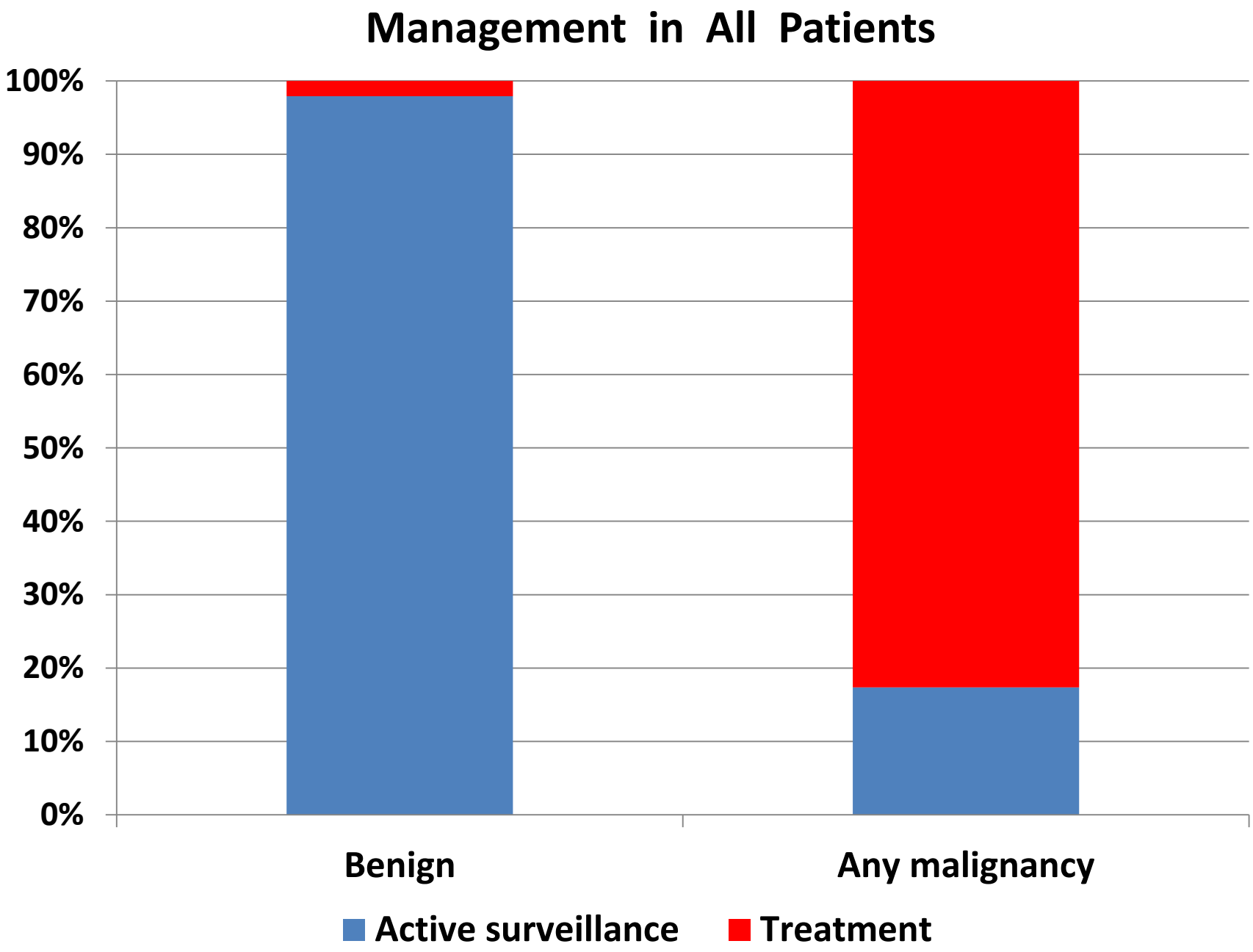
Renal Mass Biopsy to Risk Stratify

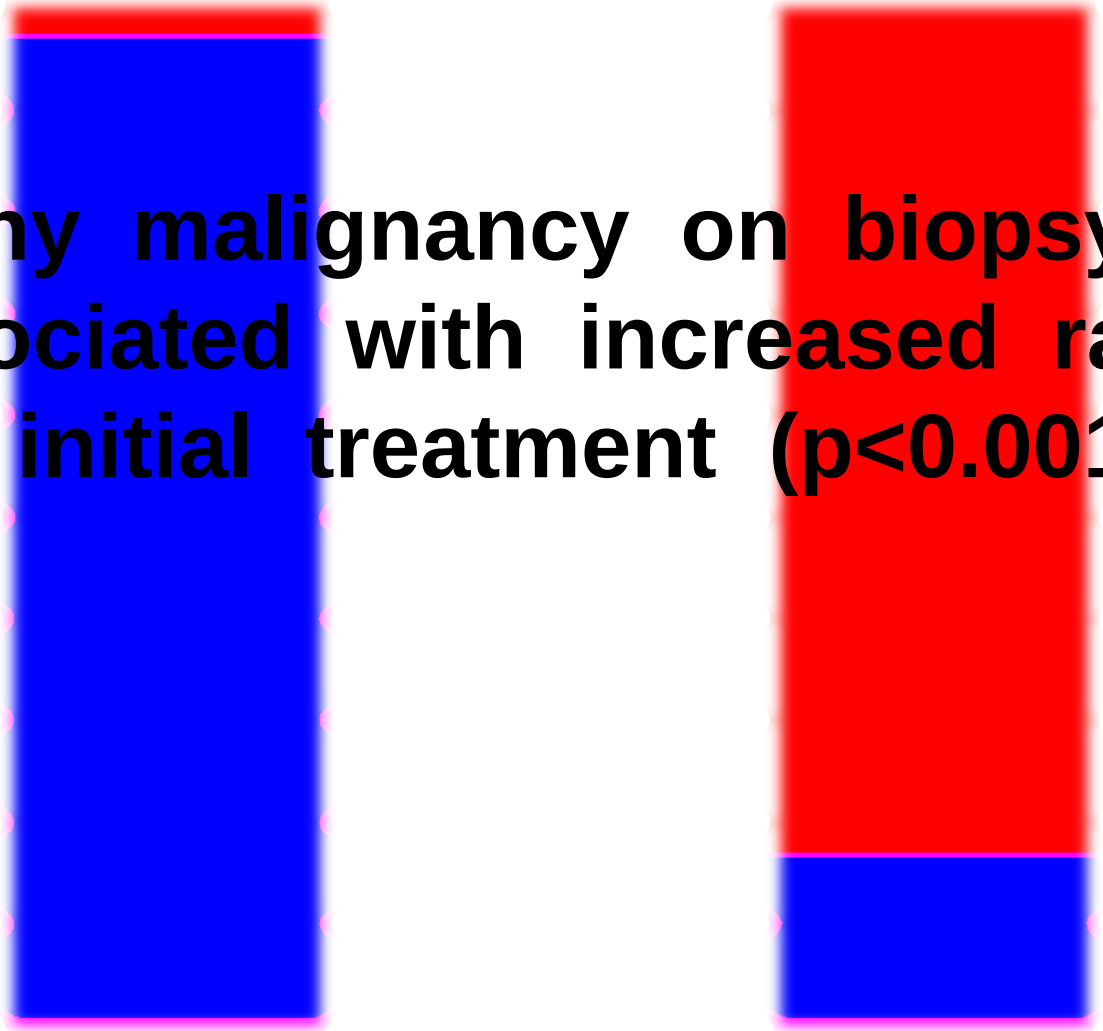
- **Collapsed Histologic Risk Groups**
  - **Benign AML, Oncocytoma**
  - **Favorable / Intermediate Chromophobe, Gr 1 / 2 Papillary I, Gr 1 / 2 Clear cell, Oncocytic or Papillary NOS**
  - **Unfavorable Gr 3 / 4 Clear cell, Papillary II, Urothelial, Unclassified, Sarcomatoid, etc.**

Renal Mass Biopsy to Risk Stratify

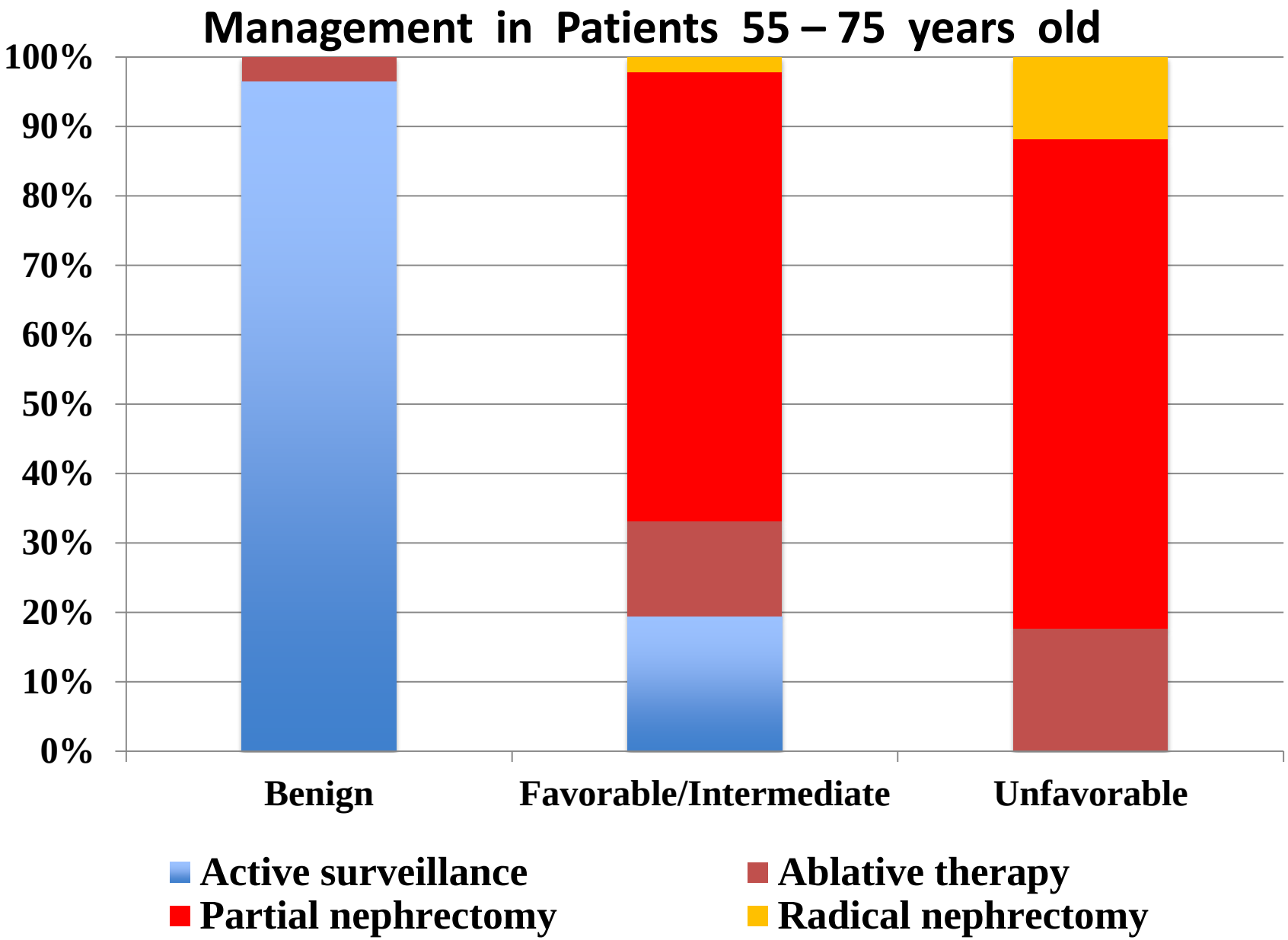
- **Biopsy Determines Management**
  - **Multivariable logistic analyses on initial management decision**
    - **Intervention vs Active Surveillance**
    - **Specific type of intervention**
  - **Factors**
    - **Age, gender, race, BMI, initial tumor size, and biopsy result**

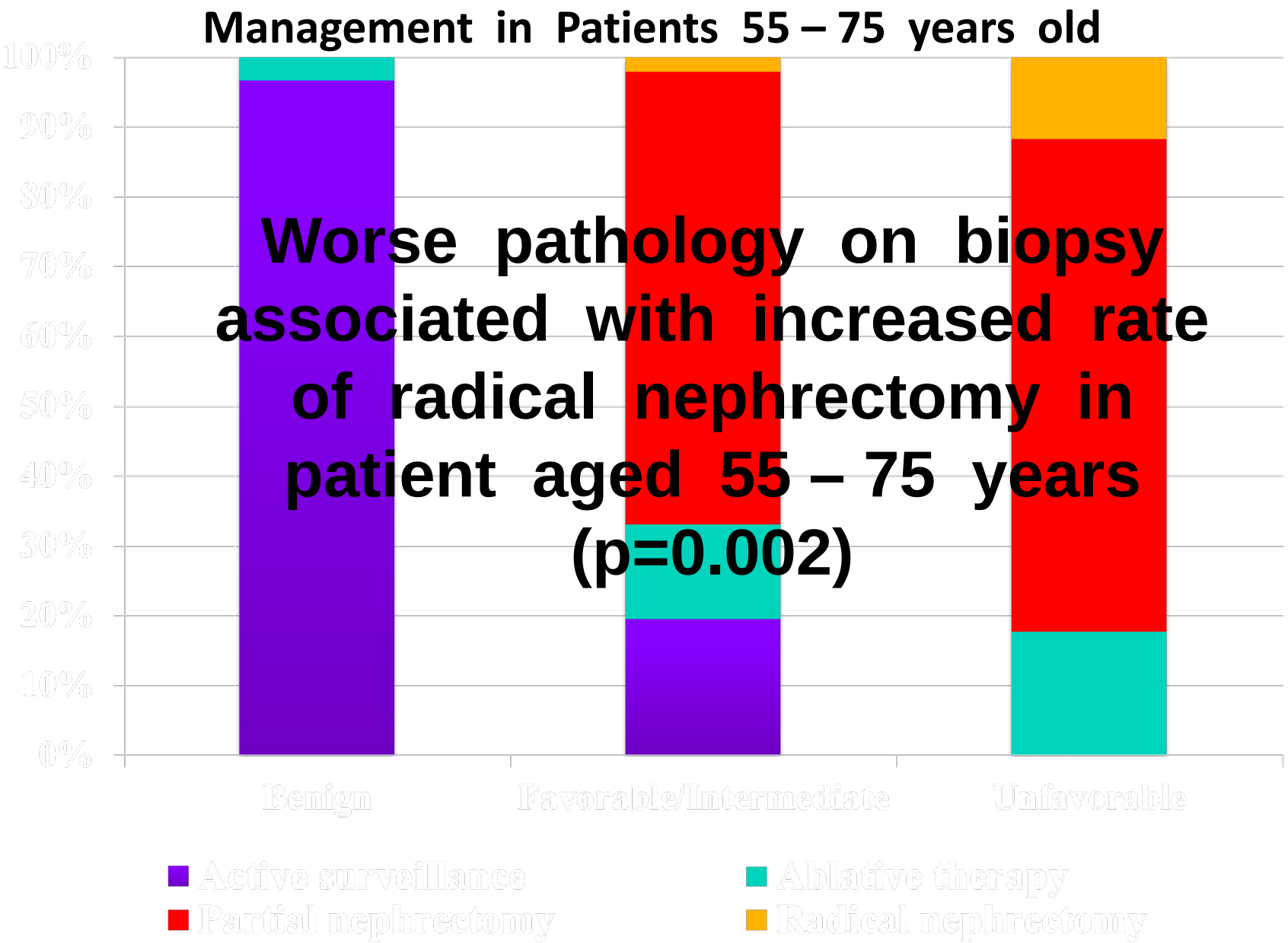

Management in All Patients
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Benign
Any malignancy
Active surveillance
Treatment

Management in All Patients

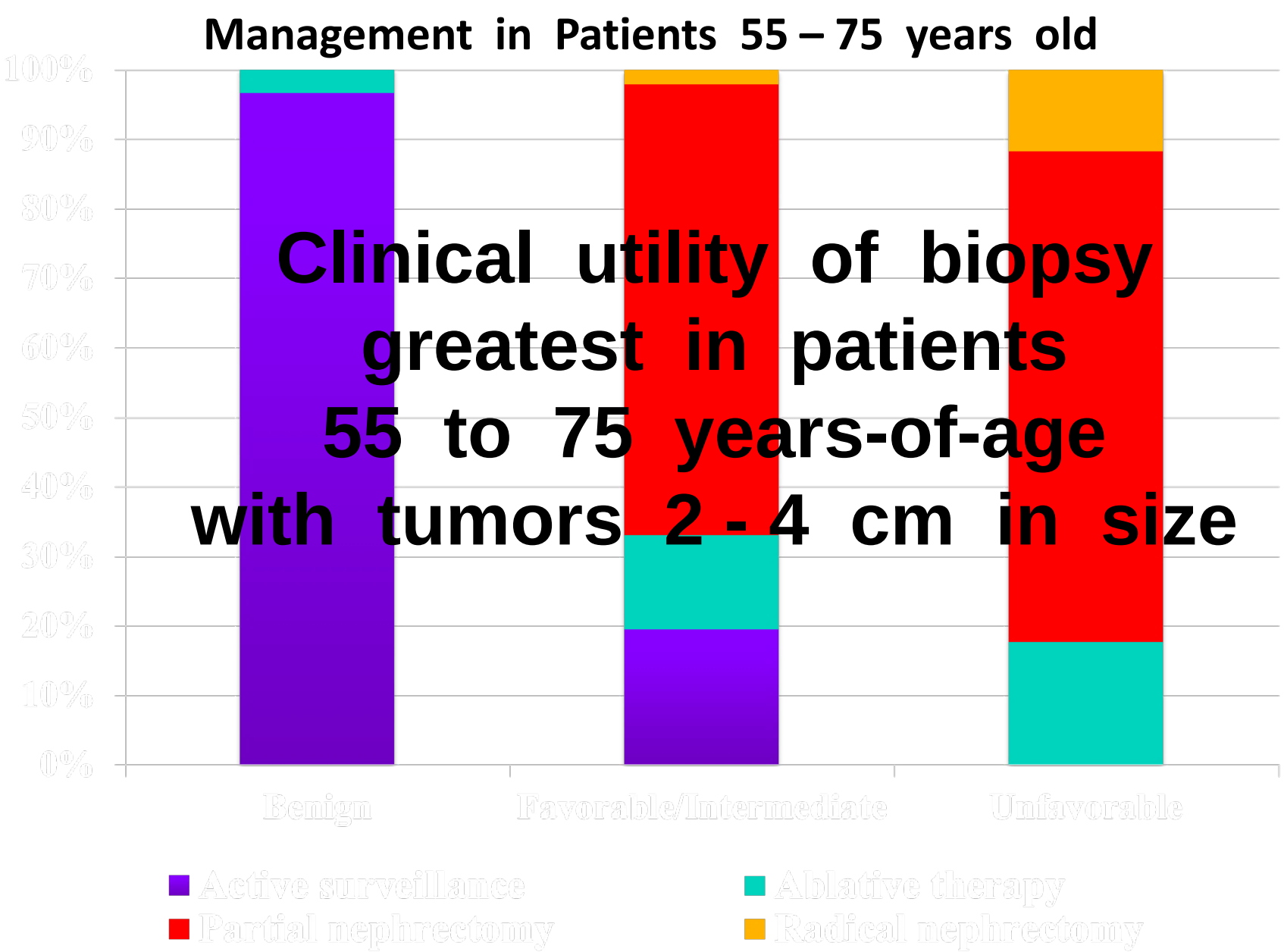


Any malignancy on biopsy associated with increased rate of initial treatment ($p<0.001$)

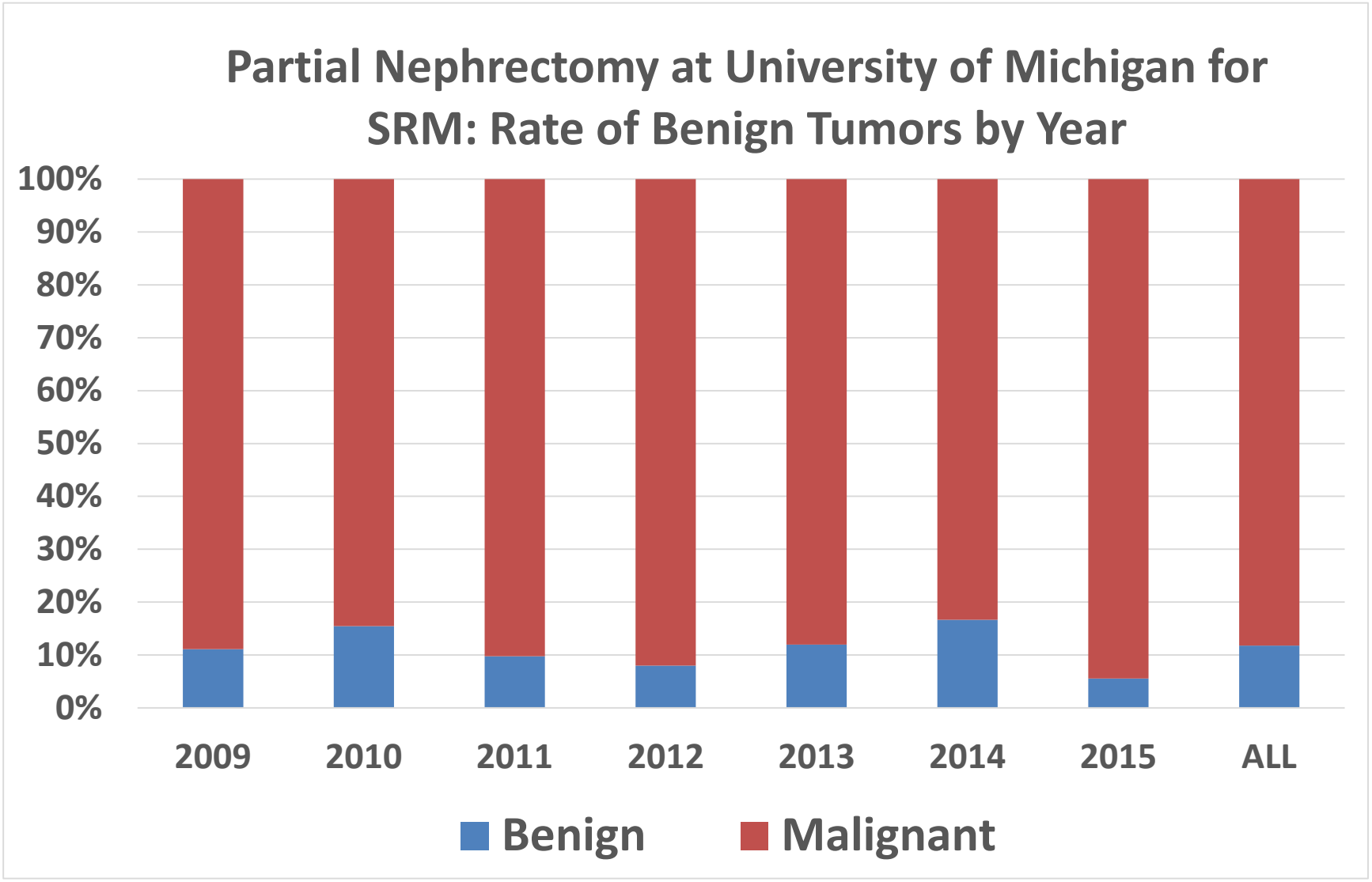

Management in Patients 55 – 75 years old
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Benign
Favorable/Intermediate
Unfavorable
Active surveillance
Ablative therapy
Partial nephrectomy
Radical nephrectomy



Worse pathology on biopsy associated with increased rate of radical nephrectomy in patient aged 55 – 75 years (p=0.002)



Clinical utility of biopsy greatest in patients 55 to 75 years-of-age with tumors 2 - 4 cm in size


Partial Nephrectomy at University of Michigan for SRM: Rate of Benign Tumors by Year
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
2009
2010
2011
2012
2013
2014
2015
ALL
Benign
Malignant

Renal Mass Biopsy to Risk Stratify

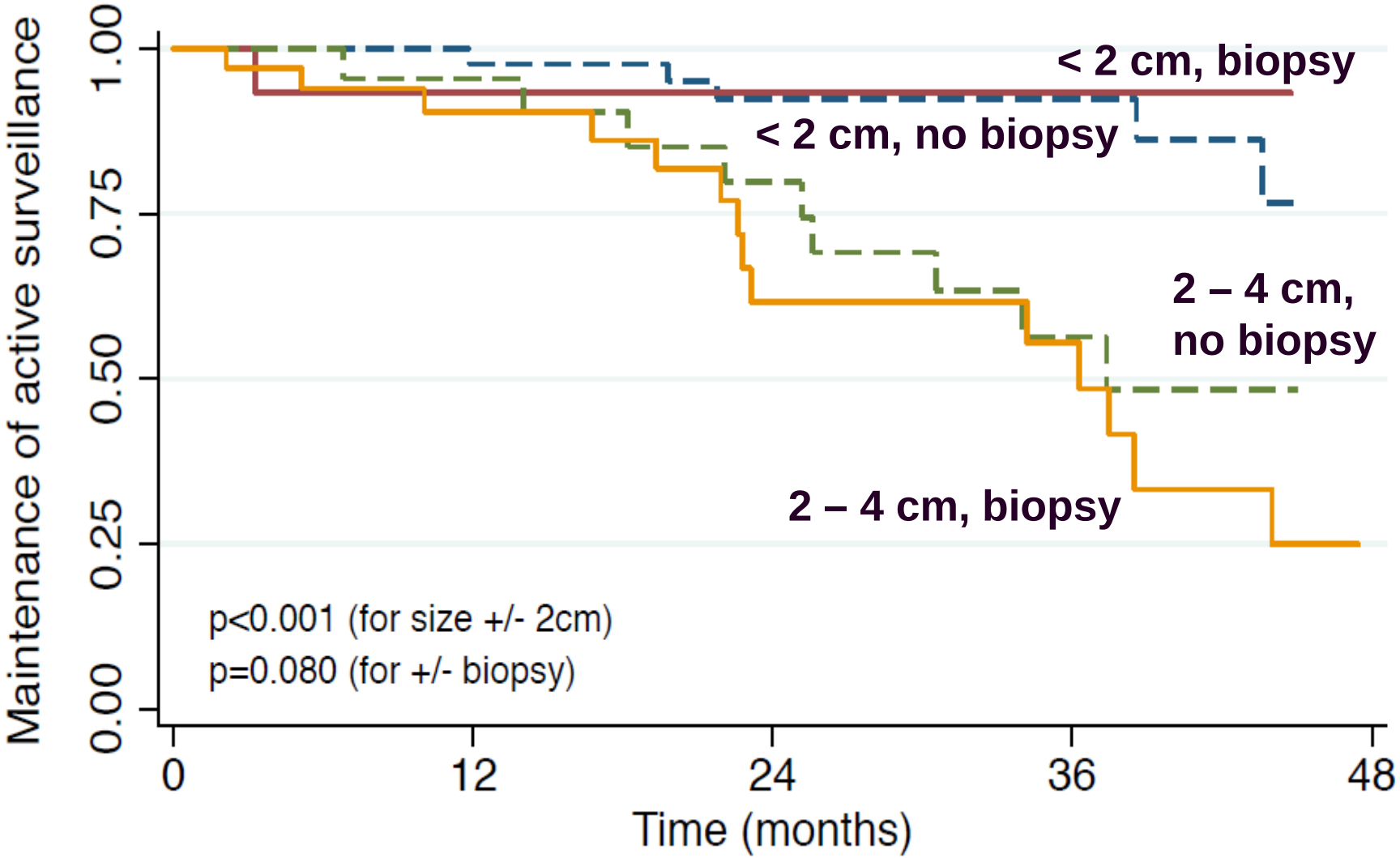
- **Reasons to Perform Biopsy - #3**
  - **3) ? More assurance on active surveillance**
    - **? improve patient acceptance**
    - **? increase urologist confidence**
    - **Still follow benign lesions, but different endpoints**
      - **Angiomyolipoma**
      - **Oncocytoma**

Renal Mass Biopsy to Risk Stratify

- **Biopsy and Active Surveillance**
  - **Subset of University of Michigan SRM database**
  - **118 SRMs initiating active surveillance from 2009 to 2011, > 5 months radiologic follow-up (unless limited by unexpected death or intervention)**
  - **Median radiologic follow-up of 29.5 months**
  - **Multivariable analysis on delayed intervention**

Renal Mass Biopsy to Risk Stratify

- **Biopsy and Active Surveillance**
  - **Increased risk of delayed intervention**
    - **Size > 2 cm (HR 3.65, p=0.015)**
    - **Growth rate, mm/yr (HR 1.26, p<0.001)**
    - **<u>Not</u> biopsy (p=0.29)**


Maintenance of active surveillance
0.00
0.25
0.50
0.75
1.00
0
12
24
36
48
Time (months)
< 2 cm, biopsy
< 2 cm, no biopsy
2 – 4 cm, no biopsy
2 – 4 cm, biopsy
p<0.001 (for size +/- 2cm)
p=0.080 (for +/- biopsy)

Renal Mass Biopsy to Risk Stratify

- **Biopsy and Active Surveillance**
  - **So even at University of Michigan, don't use biopsy to full potential**
    - ☑ **Select patients for surveillance**
    - ☑ **Select patients for treatment**
    - ☑ **Select type of treatment**
    - ☒ **Maintain patients on surveillance**

Renal Mass Biopsy to Risk Stratify

- **But, biopsy only going to get better…**
  - **"Prognostic Utility of a Multi-gene Signature (The Cell Cycle Proliferation Score) in Patients with Renal Cell Carcinoma after Radical Nephrectomy"**
  - **Morgan TM, Mehra R, Tiemeny P, Wolf JS, Orr B, Wu S, Sangale Z, Stone S, Wu C-L & Feldman AS**
  - **University of Michigan, Massachusetts General Hospital and Myriad Genetics**
  - **AUA Abstract 2016, MP78-20**

Renal Mass Biopsy to Risk Stratify

- **CCP Score and Resected RCC**
  - **CCP score**
    - **RNA-base expression of 46-gene-panel, from paraffin-embedded tissue, validated prognostic marker of cancer specific mortality (CSM) from prostate cancer**
  - **Karakiewicz nomogram**
    - **post-resection risk stratification**

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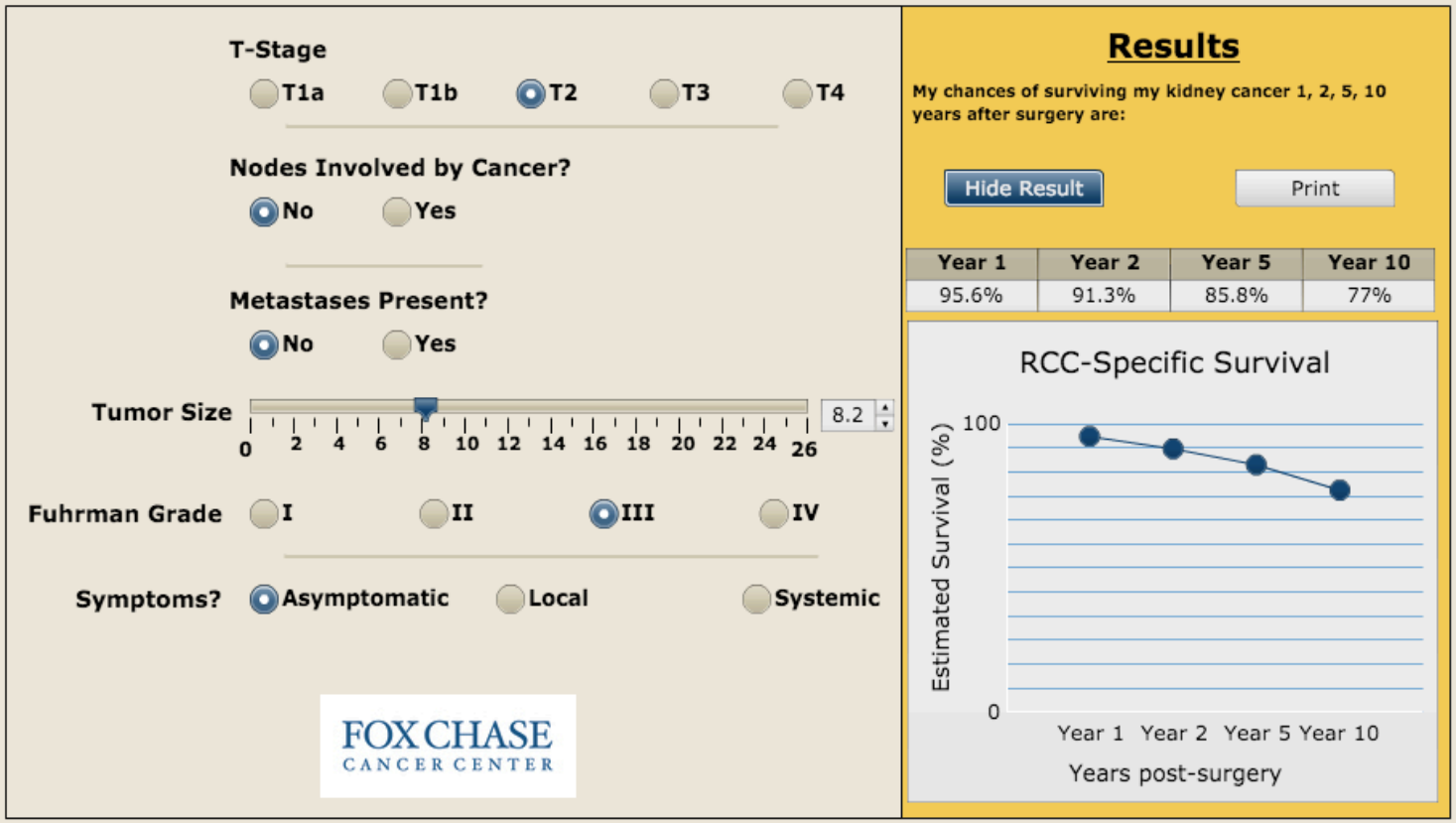
ORIGINAL REPORT

Multi-Institutional Validation of a New Renal Cancer–Specific Survival Nomogram

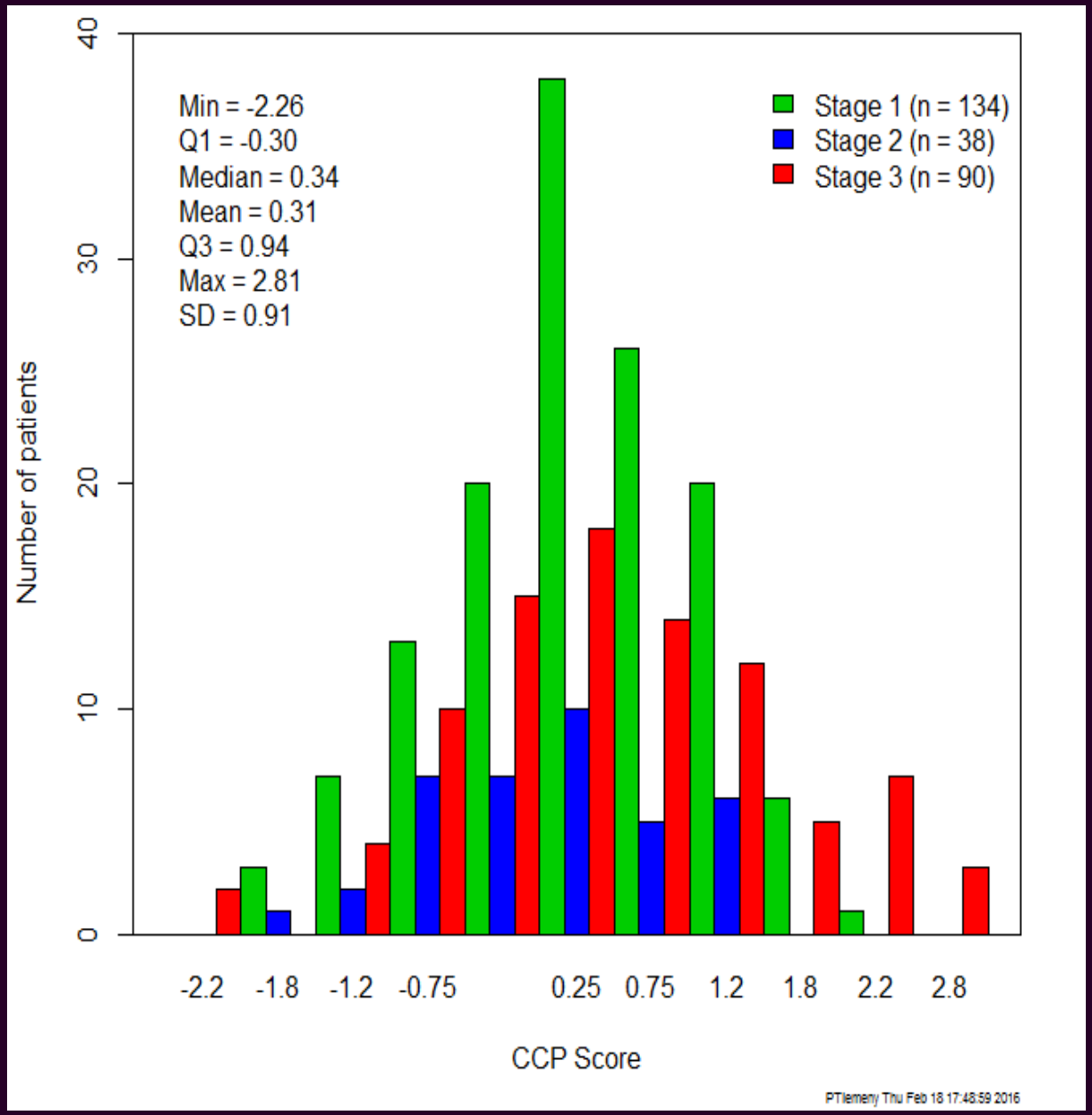
Pierre I. Karakiewicz, Alberto Briganti, Felix K.-H. Chun, Quoc-Dien Trinh, Paul Perrotte, Vincenzo Ficarra, Luca Cindolo, Alexandre De La Taille, Jacques Tostain, Peter F.A. Mulders, Laurent Salomon, Richard Zigeuner, Tommaso Prayer-Galetti, Denis Chautard, Antoine Valeri, Eric Lechevallier, Jean-Luc Descotes, Herve Lang, Arnaud Mejean, and Jean-Jacques Patard



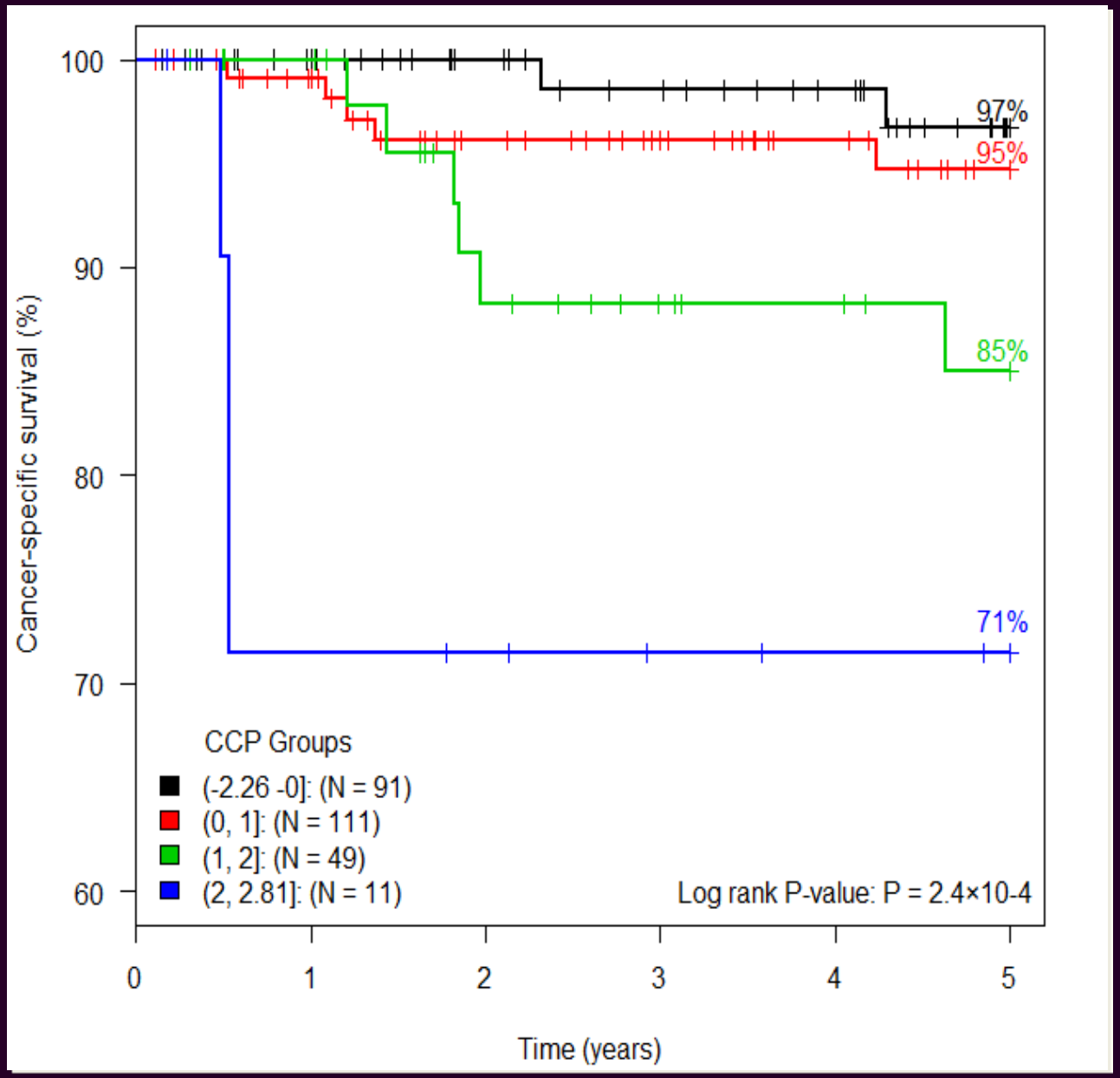
Renal Mass Biopsy to Risk Stratify

- **CCP Score and Resected RCC**
  - **CCP score cut-offs, and optimal combination with Karakiewicz nomogram, derived after radical nephrectomy in 303 patients treated at MGH from 2000 to 2007**
  - **Validated using 345 patients treated at U-M from 2000 to 2009**
  - **Similar demographics, rate of informative CCP, etc.**

CCP Score distributed across stage (validation cohort)



CCP Score & CSM (validation cohort)



Renal Mass Biopsy to Risk Stratify

CSM Multivariable analysis (validation)

Characteristic	HR (95% CI)	p-value
CCP (per 1.0 increase)	2.20 (1.25 – 3.87)	<0.001
Tumor size	1.16 (0.96 – 1.39)	0.12
T stage (referent: T1)		0.56
T2	3.69 (0.24 – 56.32)	
T3	2.92 (0.30 – 28.46)	
Fuhrman grade (High vs Low)	1.67 (0.34 – 8.16)	0.51
Lymphovascular invasion	9.82 (2.75 – 35.09)	<0.001
Symptoms (referent: none)		0.024
Local	3.09 (0.17 – 56.72)	
Systemic	9.50 (1.12 – 80.78)	
Positive surgical margins	0.83 (0.23 – 3.04)	0.78

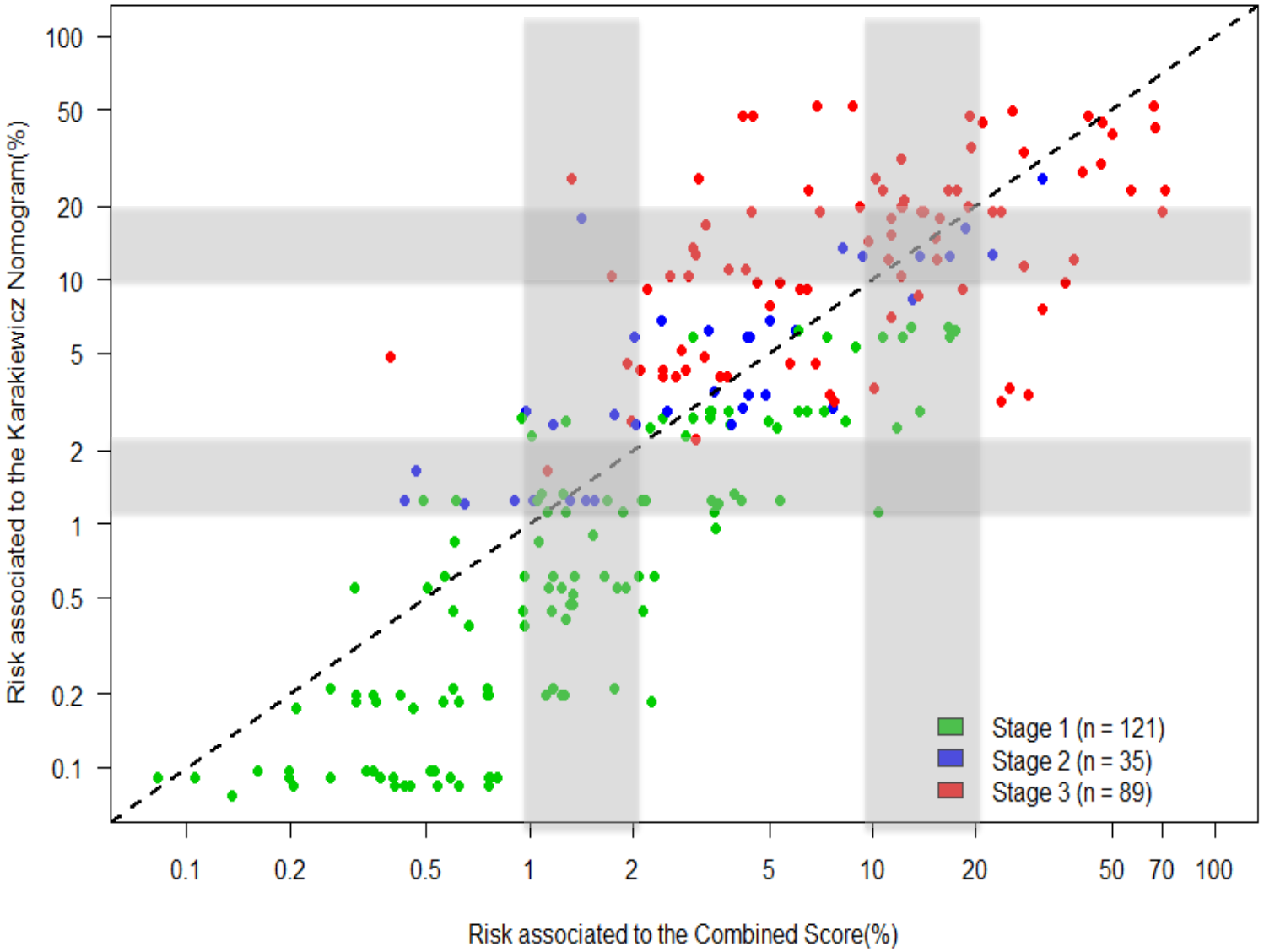
Renal Mass Biopsy to Risk Stratify

CSM Combined Score Validation
CCP + Karakiewicz Nomogram

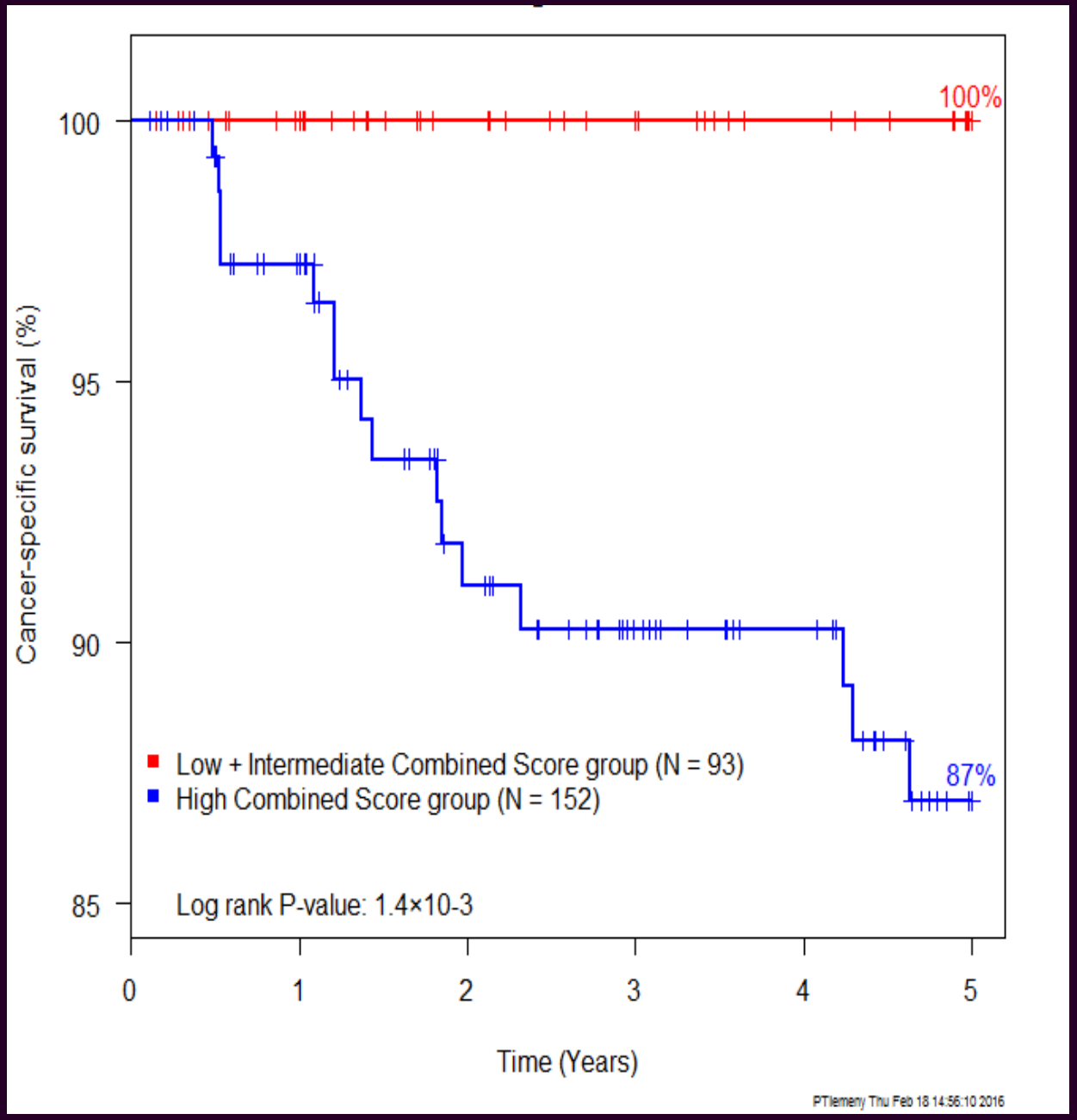
Combined Score = 1.09*CCP + 0.023*Karakiewicz

	Univariate		Bivariate	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Combined score	9.40 (3.94 – 22.44)	<0.001	3.78 (1.10 – 12.93)	0.027
Karakiewicz score	19.79 (5.13 – 76.31)	<0.001	6 (0.98 – 36.63)	0.05

5-year CSM Risk: Comb. Score vs. Nomogram



Combined Score Risk Group



Renal Mass Biopsy to Risk Stratify

- **CCP Score and RCC**
  - **CCP score powerful predictor of CSM following radical nephrectomy**
    - **Most effective at identifying low risk group (100% CSM)**
  - **Next step: Obtain CCP from pre-operative biopsies**
    - **Correlate with CCP score from final pathology**
    - **Correlate with CSM**

Renal Mass Biopsy to Risk Stratify

- **Conclusion**
  - **Reasons to avoid biopsy are weak**
  - **Reasons to perform biopsy are strong**

- **University of Michigan SRM Team**
  - Urology
    - Ganesh Palapattu
    - Alon Weizer
    - Jeff Montgomery
    - Todd Morgan
    - David Miller
    - Khaled Hafez
    - Sapan Ambani
    - Scott Hawken
    - Naveen Krishnan
    - Takahiro Osawa
    - Adam Gadzinski
    - Sky Halverson
    - Bruce Jacobs
    - Ray Tan
  - Radiology & Pathology
    - Elaine Caoili
    - Jim Ellis
    - Lakshmi Kunju