NCCN Guidelines: Renal Cell Carcinoma: Where does IO stand?

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Disclosures

- Research Collaborative Agreement between UCI and Philips Medical Systems (PI), Teclison Limited (PI), Guerbet SA (PI)
- PI on sponsored research by Sillajen Inc, Sirtex Medical Ltd, Instylla HES, Blackswan vascular Inc,
- Intellectual property and part owner in Bruin Biosciences Inc
- Advisory board for Genentech F. Hoffmann-La Roche Ltd, QED Therapeutics Inc, Eisai, Exelexis, Pfizer, Johnson and Johnson, Medtronic Inc

NCCN Guidelines RCC

- Where does IO stand?
- Where could we stand?

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Kidney Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
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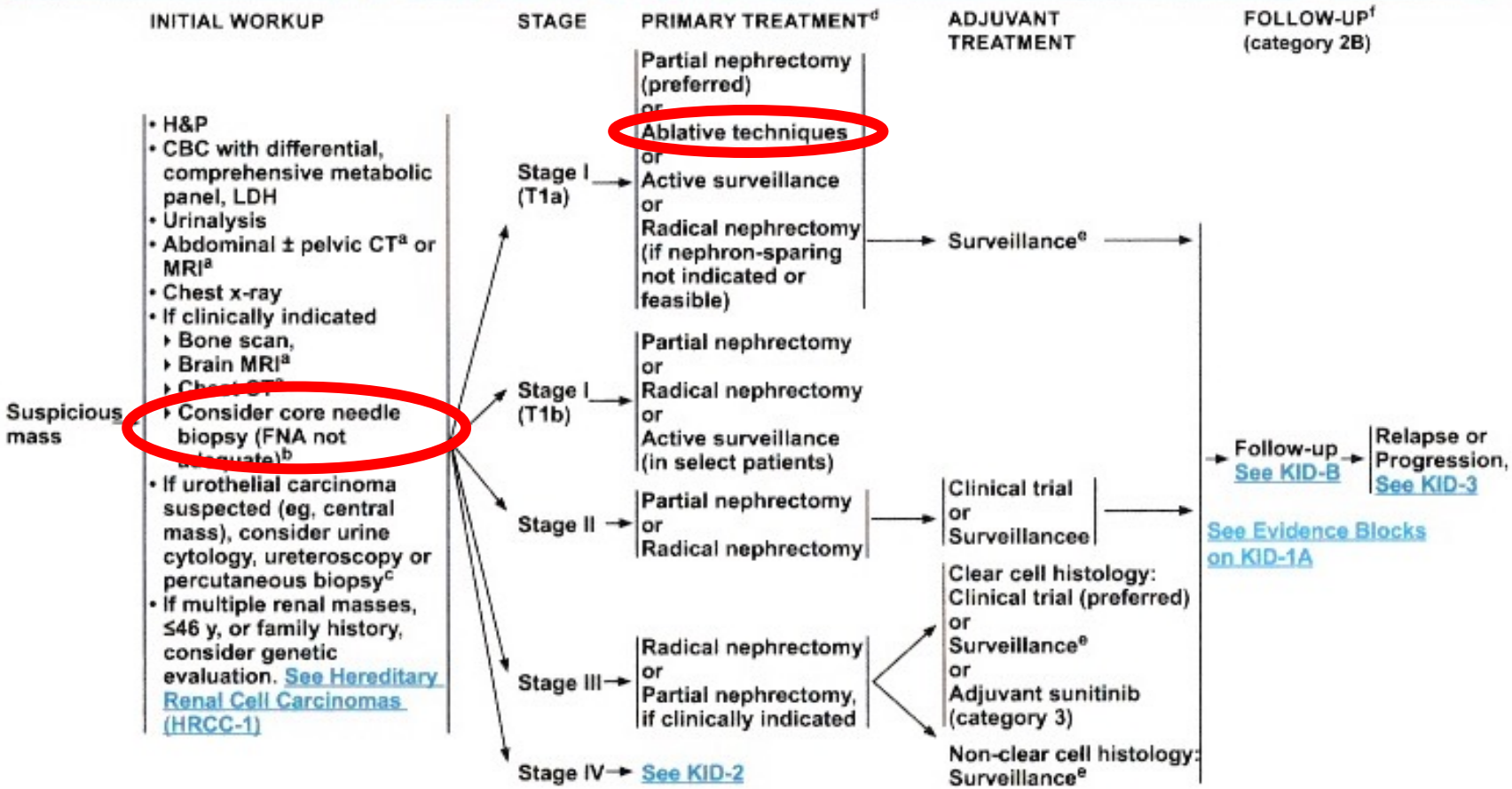
Discussion



Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines

Stage I	Tumor Size		Primary Treatments		Adjuvant Treatments
Limited to kidney Smaller than 7cm	T1a <4cm		Partial nephrectomy *		Active surveillance
			Ablation		
			Active surveillance		
			Radical nephrectomy		
	T1b 4.1-<7cm		Partial nephrectomy *		Active surveillance
			Radical nephrectomy		
			Active surveillance		

NCCN Guidelines

Stage IV	Tumor Size		Primary Treatments		Adjuvant Treatments
Tumor beyond Gerota's fascia & into adrenal gland	Surgery is an option Consider a biopsy		Cytoreductive nephrectomy		Clinical trials or subsequent trials
			Systemic therapy (preferred for poor risk ccRCC)		
	Surgery is not an option Biopsy tumor		Clinical trial supportive care		Clinical trials or subsequent trials
			1st line therapy		
			Metastasectomy or SBRT or Ablation		

Renal Mass Biopsies

- NCCN guidelines:
  - Biopsy may be considered in small lesions before active surveillance or pre-ablation
  - *SIR guidelines recommend biopsy before ablation*
  - Imaging= high diagnostic accuracy therefore needle biopsy is not always needed pre-surgery.

Renal Mass Biopsies

Author Affiliations: Department of Urology, Stanford University Medical Center, Stanford, California (Kim, Khandwala, K. J. Chung, Park, B. I. Chung); Department of Urology, Soonchunhyang University Hospital, Soonchuhyang University Medical College, Seoul, Korea (Kim); Department of Urology and Dermatology, Stanford University Medical Center, Stanford, California (Li); San Diego School of Medicine, University of California, San Diego (Khandwala).

JAMA Surgery | Original Investigation

Association of Prevalence of Benign Pathologic Findings After Partial Nephrectomy With Preoperative Imaging Patterns in the United States From 2007 to 2014

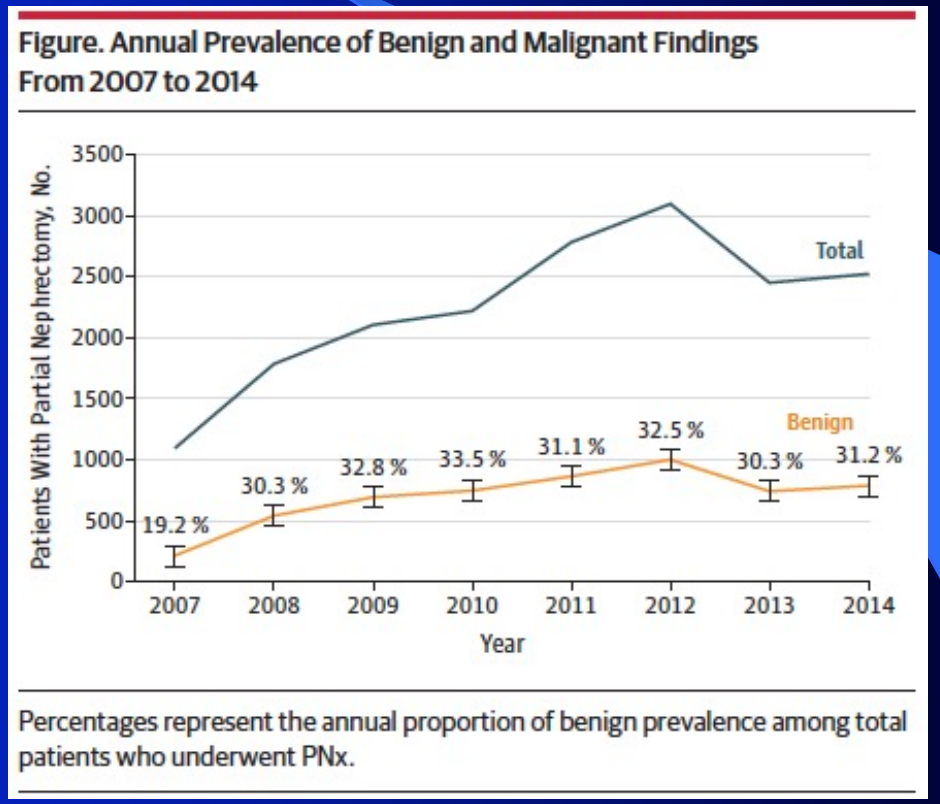
Jae Heon Kim, MD, PhD; Shufeng Li, MS; Yash Khandwala, MD; Kyung Jin Chung, MD, PhD; Hyung Keun Park, MD, PhD; Benjamin I. Chung, MD

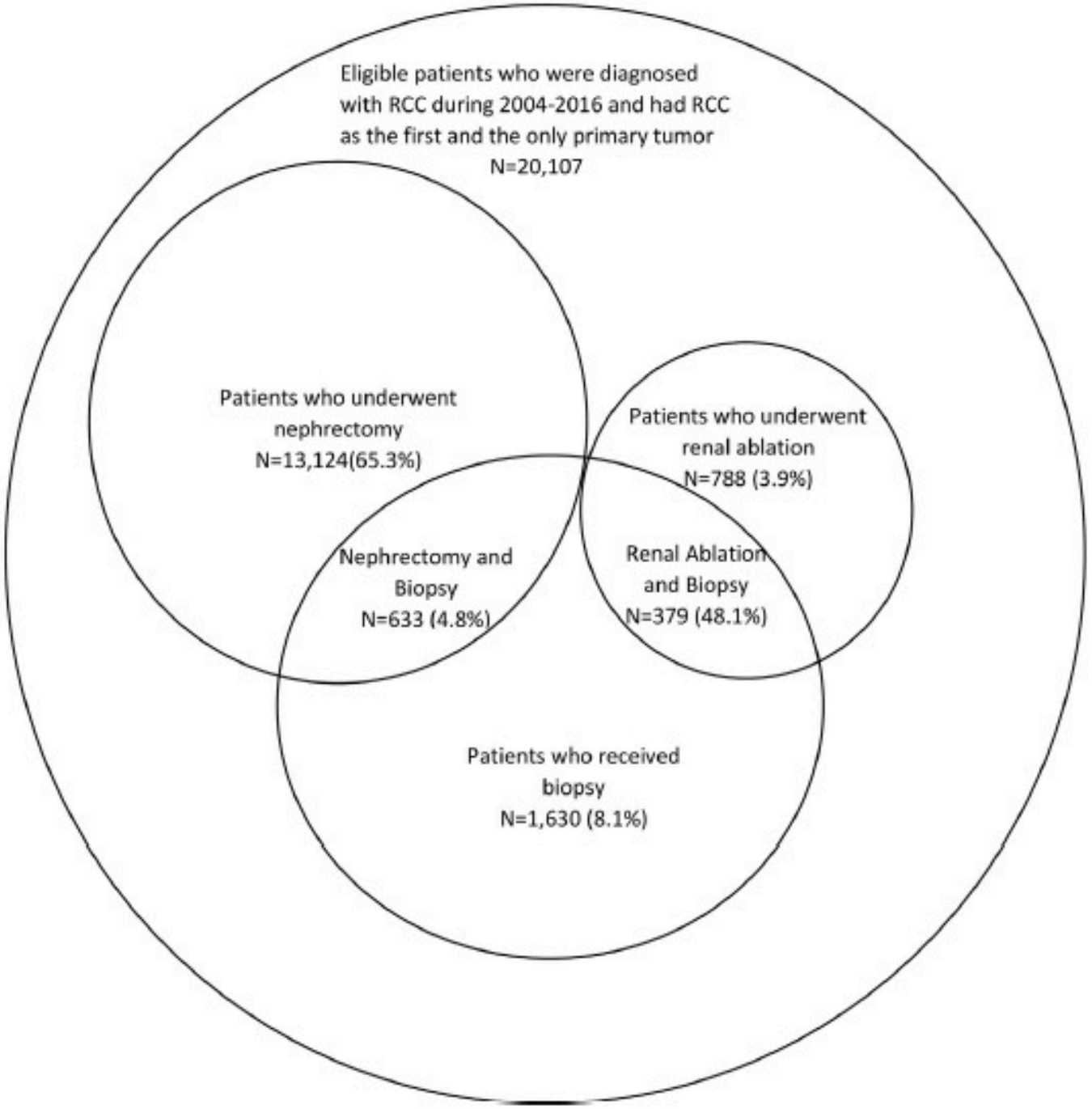
JAMA Surg. 2019;154(3):225-231. doi:10.1001/jamasurg.2018.4602
Published online December 5, 2018.

- 18k underwent PNx b/w 2007-2014 from Truven Health MarketScan Research database
- Prevalence of benign pathology= 30% prevalence every year of study

Renal Mass Biopsies

- Study noted female and adv age-> higher tendency for benign path post PNx
- MRI & biopsy significantly reduced benign path post PNx vs CT which did not
  - CT is still the Dx method of choice and recommended by NCCN




Eligible patients who were diagnosed with RCC during 2004-2016 and had RCC as the first and the only primary tumor
N=20,107
Patients who underwent nephrectomy
N=13,124(65.3%)
Patients who underwent renal ablation
N=788 (3.9%)
Nephrectomy and Biopsy
N=633 (4.8%)
Renal Ablation and Biopsy
N=379 (48.1%)
Patients who received biopsy
N=1,630 (8.1%)

Renal Mass Biopsies

- Underutilized although most societal guidelines recommend greater recourse to renal mass Bx

Ablation

- Ablation vs active surveillance
  - 5-yr analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: The DISSRM registry 2015
  - CSS & MFS 98-100%
  - OS 69-94% older pop, comorbidities
  - Of note, all pts requiring delayed interventions were still eligible for nephron sparing options

Ablation

Population-based assessment of cancer-specific mortality after local tumour ablation or observation for kidney cancer: a competing risks analysis

BJU Int 2016; **118:** 541–546

Alessandro Larcher*,†, Vincent Trudeau*,‡, Maxine Sun*, Katharina Boehm*,§, Malek Meskawi*,‡, Zhe Tian*,¶, Nicola Fossati†,**, Paolo Dell'Oglio*,†, Umberto Capitanio†, Alberto Briganti†, Shahrokh F. Shariat††, Francesco Montorsi† and Pierre I. Karakiewicz*,‡

- 1860 pts 2000-2009 AS vs TA
- CSM > AS vs TA (9.1% vs 3.5%, respectively; HR ¼ 0.47; 95% CI, 0.25–0.89)

Ablation

Comparative Effectiveness of Thermal Ablation, Surgical Resection, and Active Surveillance for T1a Renal Cell Carcinoma: A Surveillance, Epidemiology, and End Results (SEER)–Medicare-linked Population Study

Radiology 2018; 288:81–90

Minzhi Xing, MD • Nima Kokabi, MD • Di Zhang, BS • Johannes M. Ludwig, MD • Hyun S. Kim, MD

- Database 2002-2011, 1yr f-up PSM T1aN0M0 RCC
- 10k pts 2.8k PN, 4.5k RN, 989 TA, 1978 AS
- CSS + OS < w/ AS. No statistical diff b/w TA, RN or PN for CSS @ 9yrs

Cardiovasc Intervent R
DOI 10.1007/s00270-0

CLINICAL INV

CrossMark

ONCOLOGY

Treatment
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n:

Annemarie Uhlig[1]
Lutz Trojan[1] · Re

- SEER
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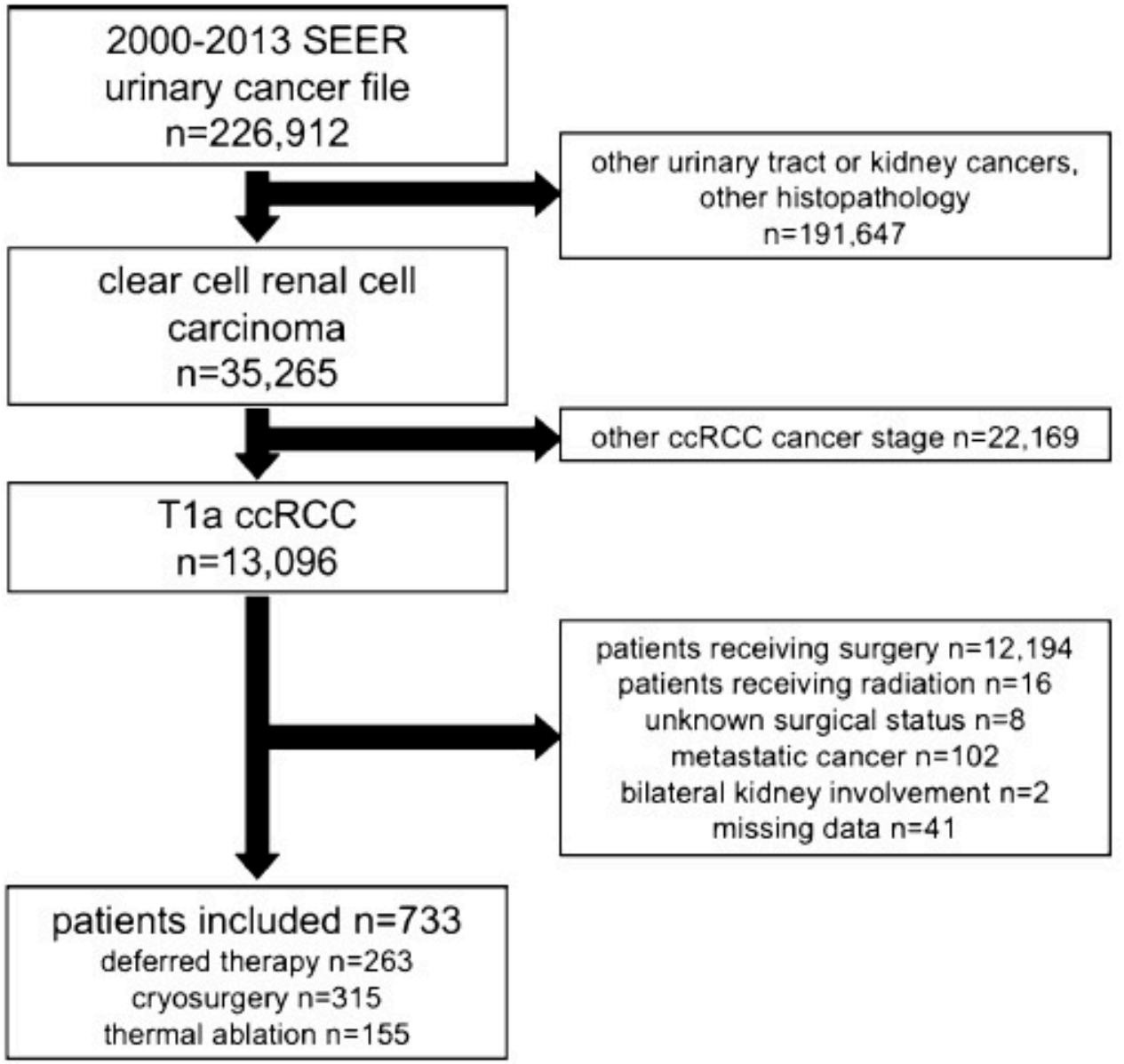
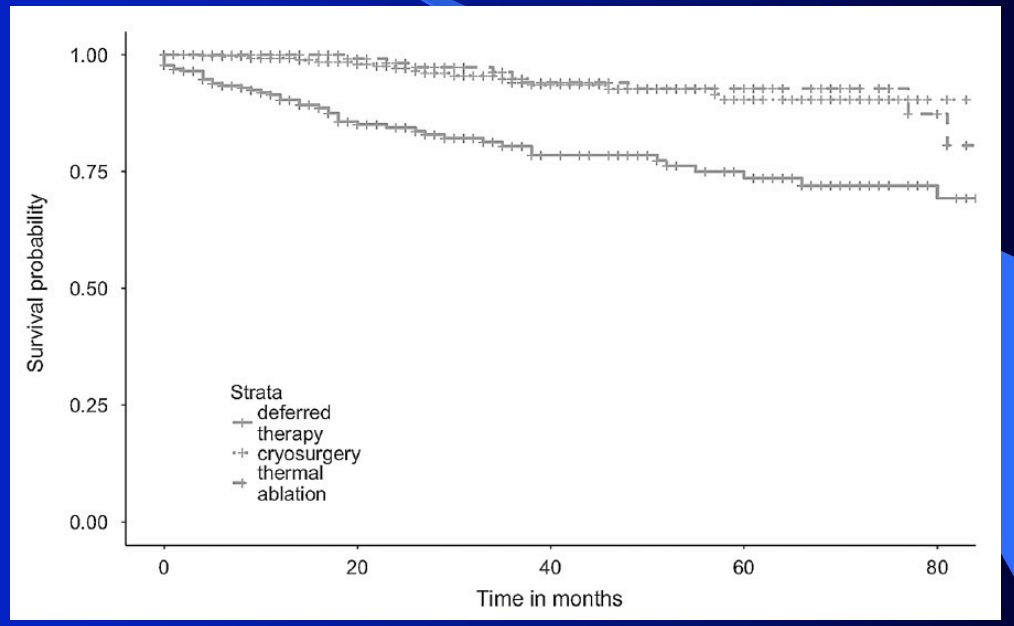


- T1a ccRCC undergoing CA or MWA/RFA improved CSS vs deferred therapy
- CA vs deferred
  - HR: 0.25 (95%CI 0.14-0.45 p<0.001)
- MWA/RFA vs deferred
  - HR:0.27 (95%CI: 0.13-0.55 p<0.001)
- CA vs MWA/RFA
  - HR: 1.03 (95%CI 0.45-2.33 p=0.95)



Ablation

- Several population-based studies seem to favor ablation vs. active surveillance for RCC
- Prospective multicenter RCT may change guidelines

- Ablation vs. surgery?

Ablation

- A Feasibility Study for a Multicenter Randomized Controlled Trial to Compare Surgery With Needle Ablation Techniques in People With Small Renal Masses (CONSERVE)=> terminated early due to poor accrual
- Comparison Between Partial Nephrectomy and Ablation for Renal Tumor => recruiting but NO status update since 2017

Percutaneous Microwave Ablation versus Laparoscopic Partial Nephrectomy for cT1a Renal Cell Carcinoma: A Propensity-matched Cohort Study of 1955 Patients

Jie Yu, MD • Xu Zhang, MD • Hong Liu, MS • Ruiming Zhang, MS • Xiaoling Yu, MD • Zhigang Cheng, MD • Zhiyu Han, MD • Fangyi Liu, MD • Guoliang Hao, MD • Meng-juan Mu, MD • Ping Liang, MD

Radiology 2020; 294:698–706

- All pts tx w/ perc microwave ablation (MWA) vs laparoscopic partial nephrectomy (LPN) b/w 04/06-11/17
- Retrospective study single center but large # of pts
- Inclusion: histologic confirmation of RCC + RCC $\leq$ 4cm
- Exclusion: vascular invasion or extrarenal spread

MWA vs PN cT1a RCC

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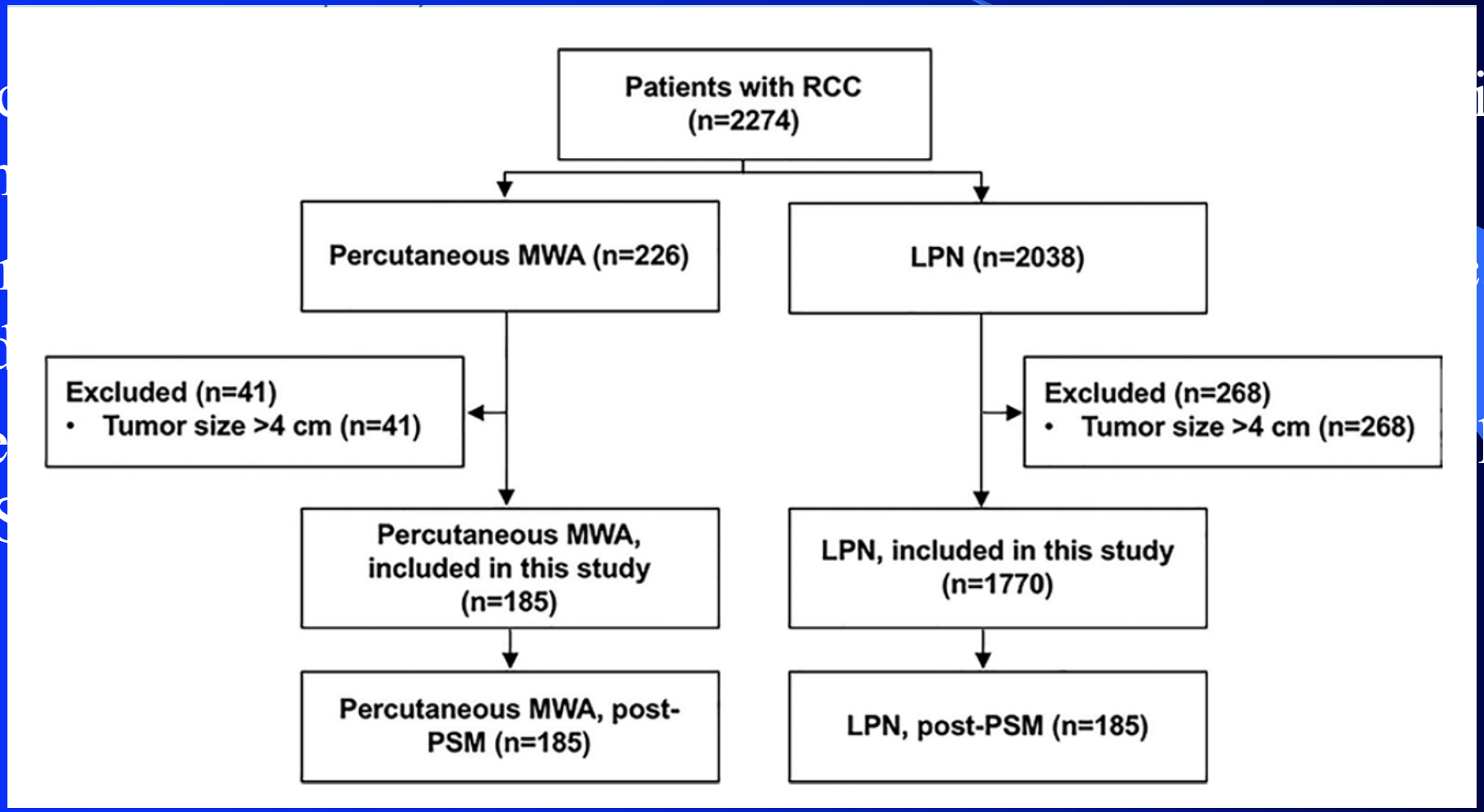

Table 1: Baseline Participant Characteristics

Parameter	Unmatched Cohort			Matched Cohort		
	MWA (n = 185)	LPN (n = 1770)	P Value	MWA (n = 185)	LPN (n = 185)	P Value
Age (y)	63.2 ± 15.2	50.9 ± 13.2	<.001	63.2 ± 15.2	60.4 ± 14.1	.07
No. of female patients	48 (26.0)	411 (23.3)	.41	48 (26.0)	47 (25.4)	.91
Charlson comorbidity index	4.0 (2.3–4.0)	1.0 (0–3.0)	.001	4.0 (2.3–4.0)	1.0 (0–3.0)	<.001
Preoperative creatinine level ≥ 0.85 mg/dL	102 (55.1)	885 (50)	.002	102 (55.1)	111 (61.6)	.21
Preoperative eGFR ≥ 120 mL/min/1.73 m^2	126 (68.1)	229 (12.9)	.003	126 (68.1)	119 (64.3)	.44
Maximal tumor size (cm)	2.3 ± 0.5	2.3 ± 0.8	.86	2.3 ± 0.5	2.3 ± 0.9	.67
Tumor side			.054			.68
Left	81 (43.8)	907 (51.2)		81 (43.8)	85 (45.9)	
Right	104 (56.2)	863 (48.8)		104 (56.2)	100 (54.1)	
Tumor location			<.001			.050
Upper segment	54 (29.2)	629 (35.5)		54 (29.2)	60 (32.4)	
Middle segment	80 (43.2)	468 (26.4)		80 (43.2)	58 (31.4)	
Lower segment	51 (27.6)	673 (38.0)		51 (27.6)	67 (36.2)	
Tumor histologic type			.56			>.99
Clear cell carcinoma	174 (94.1)	1622 (91.6)		174 (94.1)	174 (94.1)	
Papillary carcinoma	5 (2.7)	70 (4.0)		5 (2.7)	5 (2.7)	
Chromophobe cell carcinoma	6 (3.2)	57 (3.2)		6 (3.2)	6 (3.2)	
Cystic carcinoma	0	17 (1.0)		0	0	
Granular cell carcinoma	0	4 (0.2)		0	0	

Table 2: Comparison of Intraoperative and Postoperative Outcomes between the Percutaneous MWA and LPN Groups

	Unmatched Cohort			Matched Cohort		
Parameter	MWA (n = 185)	LPN (n = 1770)	P Value	MWA (n = 185)	LPN (n = 185)	P Value
Postoperative hospitalization time (d)	5.1 ± 2.6	6.9 ± 3.0	<.001	5.1 ± 2.6	6.9 ± 2.8	<.001
Procedure time (h)	0.5 ± 0.1	1.9 ± 0.7	<.001	0.5 ± 0.1	1.8 ± 0.6	<.001
Estimated blood loss (mL)	4.5 ± 1.3	63.1 ± 83.4	<.001	4.5 ± 1.3	54.2 ± 69.2	<.001
Percentage decrease in eGFR at discharge	6.2	17.0	<.001	6.2	16.4	<.001
Cost (U.S. dollars)	3150 ± 2970	6475 ± 3660	<.001	3150 ± 2970	6045 ± 1860	<.001
Major complication	4 (2.2)	79 (4.5)	0.15	4 (2.2)	9 (4.9)	0.17
Fever > 38°C	30 (16.2)	1250 (70.6)	<.001	30 (16.2)	135 (73.0)	<.001

Table 3: Oncologic Outcomes and Recurrence

	Unmatched Cohort				Matched Cohort			
Outcome	MWA (n = 185)	LPN (n = 1770)	Hazard Ratio*	P Value	MWA (n = 185)	LPN (n = 185)	Hazard Ratio*	P Value
Local tumor progression	6 (3.2)	17 (1.0)	1.0 (0.4, 2.5)	.92	6 (3.2)	1 (0.5)	6.0 (0.7, 50.2)	.10
Distant metastasis†	8 (4.3)	39 (2.2)	0.9 (0.4, 2.0)	.81	8 (4.3)	8 (4.3)	0.8 (0.3, 2.5)	.76
Disease-free survival	155 (82.9)	1674 (94.6)	5.1 (3.3, 8.0)	<.001	155 (82.9)	169 (91.4)	3.1 (1.5, 6.6)	.003
Death from any cause	19 (10.3)	46 (2.6)	3.8 (2.2, 6.5)	<.001	19 (10.3)	7 (3.8)	2.4 (1.0, 5.7)	.049
Death from RCC†	4 (2.2)	40 (2.3)	0.8 (0.3, 2.3)	.68	4 (2.2)	7 (3.8)	0.5 (0.1, 1.6)	.24

Ablation

- Growing for T1b but not consistent w/ some studies finding TA good option while others favoring robotic assisted PN
- All these studies are retrospective and poor quality

UROLOGY 135: 88–94, 2020. © 2019 Elsevier Inc.
Clinical Genitourinary Cancer, Vol. 18, No. 2, 138-47

SR/MA	Pr re	ent f ion bias ed?	Overall rating of confidence in results of review
Aboumarzouk et al (2018)	No		Critically low
Choi et al (2018)	No		Critically low
Deng et al (2019)	No		Critically low
Hu et al (2019)	No		Low
Patel et al (2017)	Ye		Low
Pessoa et al (2017)	No		Critically low
Prince et al (2017)	Ye		Critically low
Rai et al (2018)	No		Critically low
Rivero et al (2017)	No		Critically low
Uhlig et al (2019)	No		Critically low
Yoon et al (2019)	No		Critically low

MA = meta-analysis; RoB = ris
AMSTAR2 rating:
High—zero or one noncritical
address the question of inter
Moderate—more than one n
summary of the results of th
Low—one critical flaw with o
the available studies that add
Critically low—More than one
provide an accurate and com
* Multiple noncritical weakne
confidence.

of the available studies that

lt may provide an accurate

comprehensive summary of

d should not be relied on to

down from moderate to low

1 Design better-quality prospective studies with protocol-driven inclusion and exclusion criteria, using appropriate controls (which must include standard practice), using validated and standardised outcome measures based on standardised definitions and thresholds, and with adequate follow-up, to enable robust comparative assessments. In this regard, the principles set forth by the IDEAL Collaboration [13] can be followed. Novel study designs, such as the proposed cohort embedded randomised controlled trial comparing nephron-sparing treatment for small renal masses [6,14], should be strongly encouraged and supported.

2 Evidence synthesis (ie, SRs and meta-analyses) must also be protocol driven and conducted in accordance with PRISMA guidance. The AMSTAR template should also be followed to maintain methodological rigour.

3 Preoperative biopsy should probably be systematically performed in older patients with comorbidities before any decision is made. In case of benign histology, these patients would probably be better served by surveillance.

Fig. 2 – Summary of literature search. Lap = laparoscopy; MA = meta-analysis; PN = partial nephrectomy; RN = radical nephrectomy; SR = systematic review; TA = thermal ablation.

Ablation

Current Management of Small Renal Masses, Including Patient Selection, Renal Tumor Biopsy, Active Surveillance, and Thermal Ablation

J Clin Oncol 36:3591-3600.

Alejandro Sanchez, Adam S. Feldman, and A. Ari Hakimi

THERMAL ABLATION

To date, no randomized prospective studies have compared TA techniques with surgery (PN or RN) or compared each TA modality (cryoablation *v* radiofrequency ablation). The CONSERVE

Conclusions

- TA can play bigger role with better evidence
- Biopsy should play a bigger role

Thank you

Questions