Improving Diagnosis & Surgical Outcomes of Early Kidney Cancer

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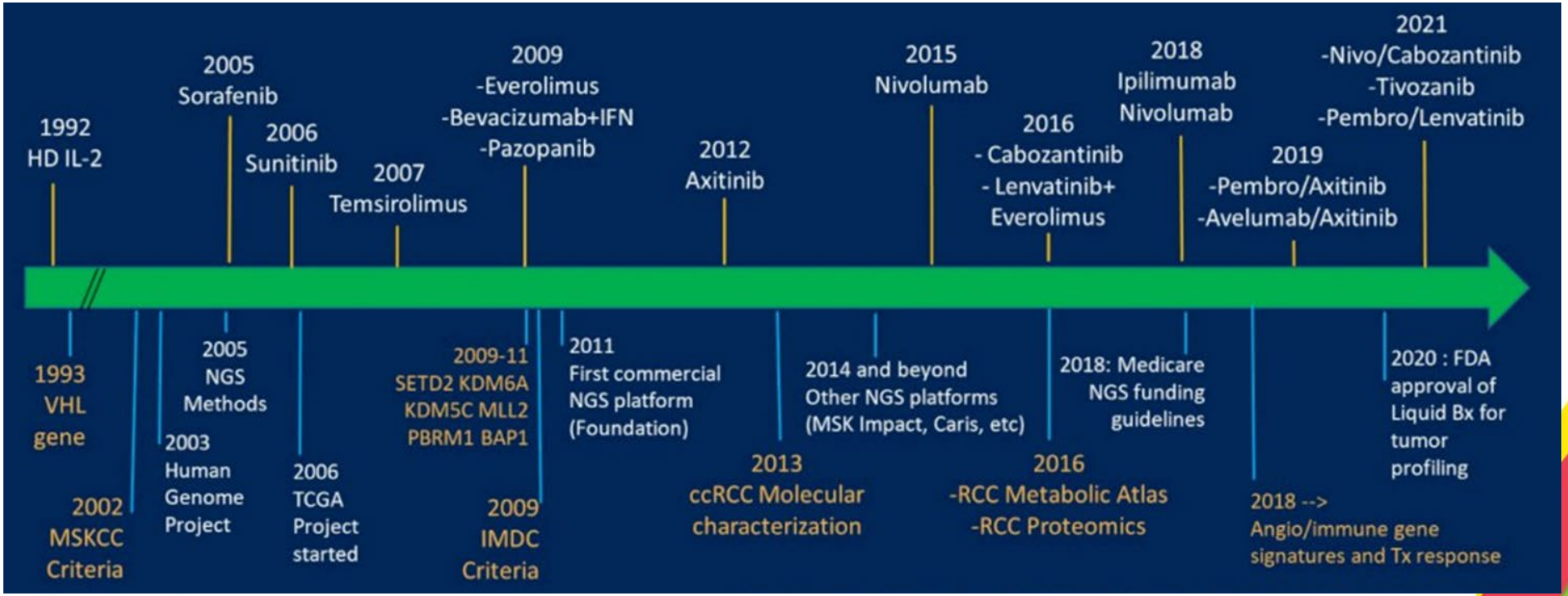
Kidney Cancer

- A surgical disease
- Chemo-resistant / Radio-resistant

- Recent advances in systemic treatment
  - Targeted therapy
    - Tyrosine kinase inhibitors (-tinib)
    - mTOR kinase inhibitors (-limus)
    - Monoclonal antibodies (-mab)
  - Immunotherapy
    - Immune checkpoint inhibitors (-mab)

Evolution in Therapeutic Landscape



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JR Merchan, presented at ASCO GU 2022

Kidney Cancer 5-Year Survival

SEER* stage	5-year relative survival rate
Localized	93%
Regional	74%
Distant	17%
All SEER stages combined	78%

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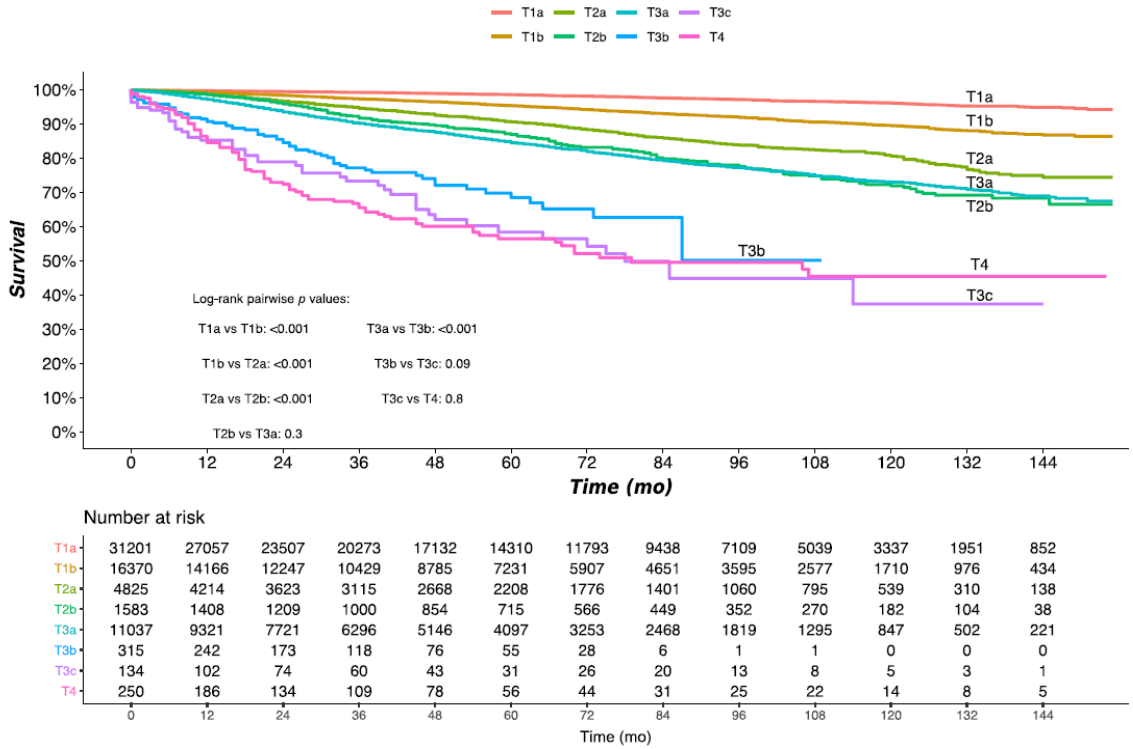
*SEER = Surveillance, Epidemiology, and End Results
Source: American Cancer Society on 1 May 2024

Resection before Mets is the Key



Nocera L, et al. Eur Urol Focus. 2022 Jan;8(1):182-190

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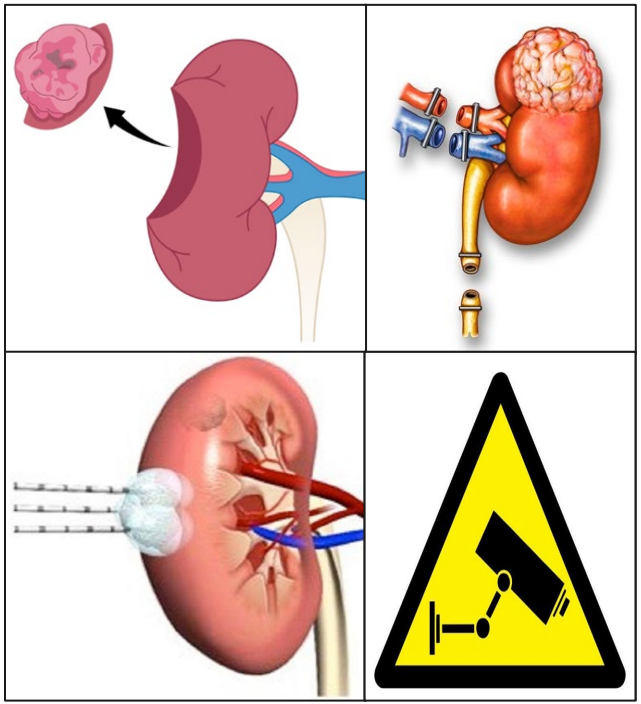
Options for Early Kidney Cancer

- Partial nephrectomy
- Radical nephrectomy
- Thermal ablation
- Surveillance



American Urological Association Guidellines 2021

Ways to Improve Outcomes

- Reduce risk of +ve margins
  - ➔ improve long term oncologic clearance
- Reduce collateral damage to adjacent normal tissues
  - ➔ improve post-operative renal function
- Reduce need for invasive procedures / anesthesia
  - ➔ improve peri-operative outcomes
- Reduce missed diagnosis
  - ➔ improve pre-operative patient selection

Do +ve Margins Matter?

- US National Cancer Database
- 20762 patients over 6 years eligible for PS matching ➔ 1265 matched cases in each group
- Age, gender, race, comorbidity, tumor size, histology, grade

ELSEVIER

CrossMark

UROLOGIC ONCOLOGY

Urologic Oncology: Seminars and Original Investigations 36 (2018) 90.e15–90.e21

Original article

Impact of positive surgical margins on overall survival after partial nephrectomy—A matched comparison based on the National Cancer Database

Cheuk Fan Shum, M.B.B.S., M.Med (Surgery), F.A.M.S. (Urology), Clinton D. Bahler, M.D., M.Sc., Chandru P. Sundaram, M.D., F.R.C.S.*

Department of Urology, Indiana University School of Medicine, Indianapolis, IN

Received 9 May 2017; received in revised form 9 November 2017; accepted 12 November 2017

Abstract

Introduction: The impact of positive surgical margins (PSM) in partial nephrectomy (PN) has been a controversy. Previous studies on the relationship between PSM and overall survival (OS) were either underpowered or had highly dissimilar groups. We used the National Cancer Database with propensity score matching to determine the association between PSM and OS after PN.

Materials and methods: We identified patients with T1/T2 N0M0 renal cancer treated with PN between 2004 and 2009, and divided them into 2 groups based on their margin status. We used propensity score matching to ensure similarities in age, comorbidity score (CCI), tumor size, histology, and grade between groups. Covariates were compared by χ^2 test. Cox multiple regression was used to estimate the hazard ratios (HR) for all-cause mortality. OS between matched groups were compared by log-rank, Breslow and Tarone-Ware tests.

Results: After excluding those with missing data on margin or survival status, 20,762 patients were eligible for matching. Each matched group had 1,265 patients, similar in age, sex, race, CCI, tumor size, histology, and grade. There were 386 recorded all-cause mortalities over a median follow-up duration of 72.6 months. Cox multiple regression showed a higher risk of all-cause mortality among cases with PSM (HR: 1.393, $P = 0.001$). Old age, high CCI, and large tumors had higher risks, while papillary and chromophore histologic subtypes had lower risks. PSM was associated with significantly worse OS by log-rank, Breslow, and Tarone-Ware tests.

Conclusion: PSM is associated with significantly worse OS after PN.

Do +ve Margins Matter?

- Cox multiple regression showed a higher risk of all-cause mortality among cases with PSM (HR: 1.393, P=0.001)
- Old age, high CCI, and large tumors had higher risks
- Papillary and chromophore histologic subtypes had lower risks
- PSM was associated with significantly worse OS

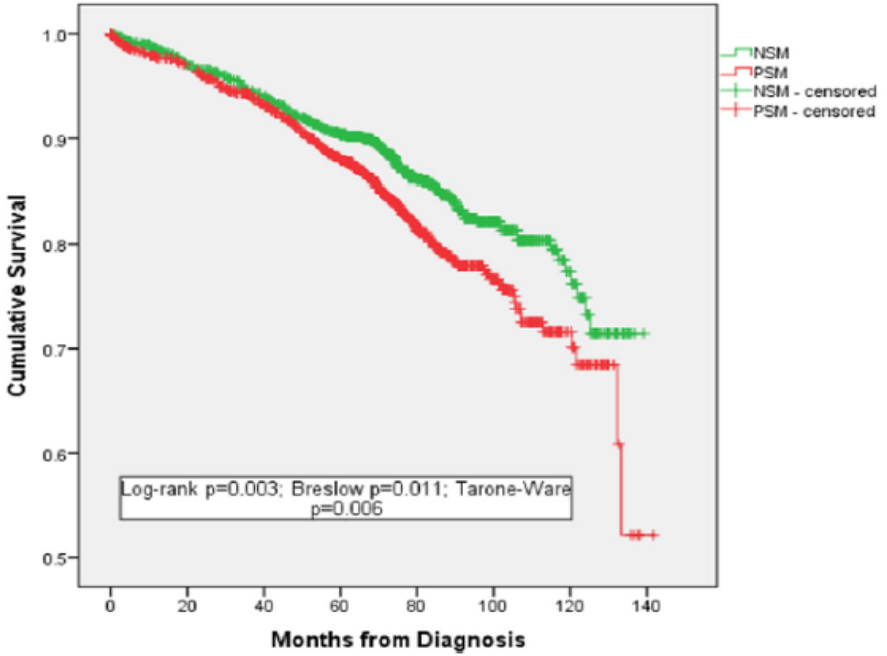


Fig. 2. Kaplan-Meier curves showing OS stratified by surgical margin status. NSM = negative surgical margins; PSM = positive surgical margins.

Reducing Risk of +ve Margins

- Ways to reduce +ve margins in conventional PNx
  - Intra-operative ultrasound
  - Frozen section
  - Near-infra-red fluorescence imaging
- RCC has lower folate receptor expression than normal kidney tissues
- Near-infrared fluorescence imaging using indocyanide green tagged to a folate analogue
- Real-time visual identification of tumor margins during resection

Reducing Risk of +ve Margins

JOURNAL OF ENDOUROLOGY CASE REPORTS
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Mary Ann Liebert, Inc.
Pp. 189–197
DOI: 10.1089/cren.2016.0104

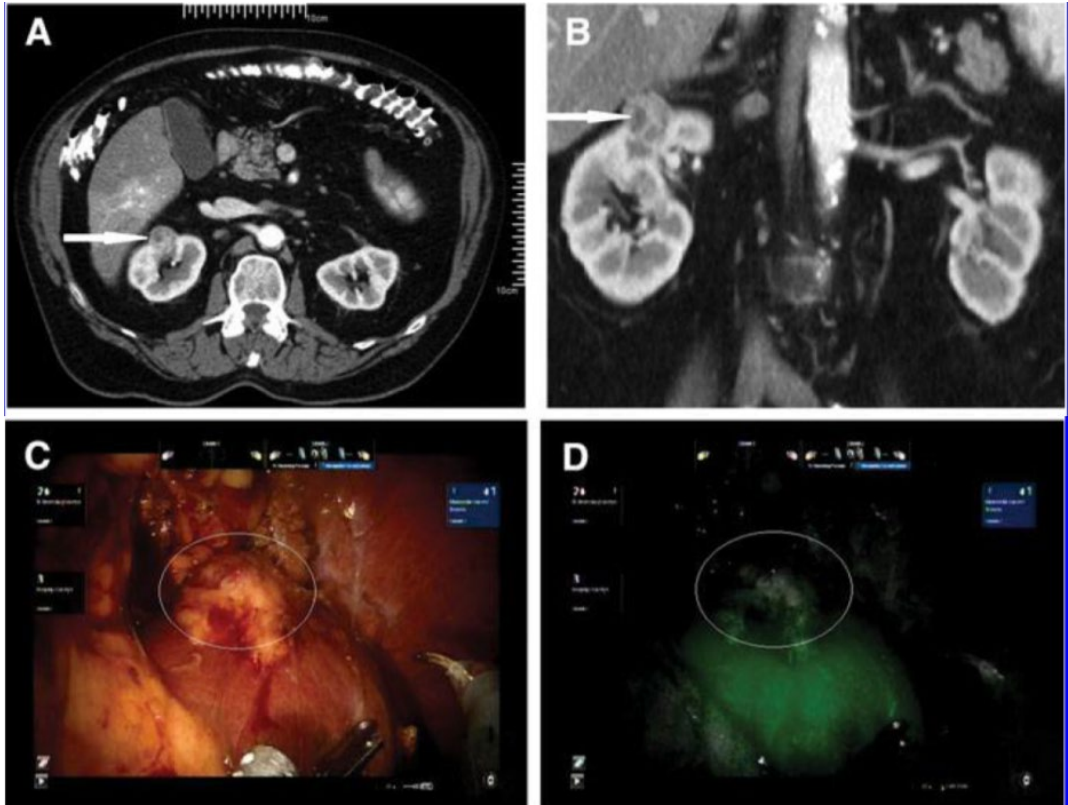
Case Report

Novel Use of Folate-Targeted Intraoperative Fluorescence, OTL38, in Robot-Assisted Laparoscopic Partial Nephrectomy: Report of the First Three Cases

Cheuk Fan Shum, MBBS, MMed (Surgery), FAMS (Urology),[1] Clinton D. Bahler, MD, MS,[1] Philip S. Low, PhD,[2] Timothy L. Ratliff, PhD,[3] Steven V. Kheyfets, MD,[1] Jay P. Natarajan,[1] George E. Sandusky, DVM, PhD,[4] and Chandru P. Sundaram, MD[1]

This paper is part of a Festschrift for Arthur D. Smith, MD

Phase 2 trial with OTL38 (Pafolacianine)
FDA approval in Nov 2021



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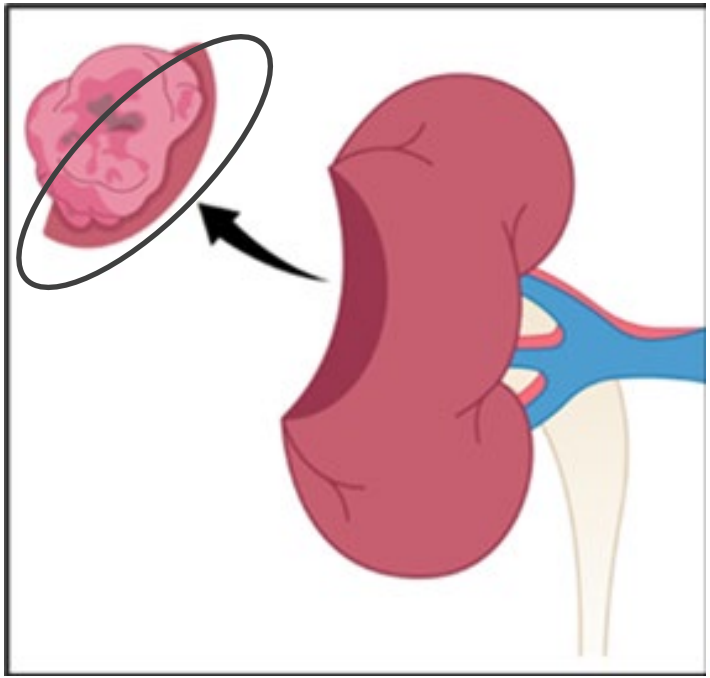
Ways to Improve Outcomes

- Reduce risk of +ve margins
  - ➔ improve long term oncologic clearance
- Reduce collateral damage to adjacent normal tissues
  - ➔ improve post-operative renal function
- Reduce need for invasive procedures / anesthesia
  - ➔ improve peri-operative outcomes
- Reduce missed diagnosis
  - ➔ improve pre-operative patient selection

Reducing Collateral Damage

- What is the perfect margin?

- PNx: to achieve same oncologic outcomes as RNx without compromising renal function
- Thin margin ➔ risk of +ve margin
- Thick margin ➔ risk of CKD



Importance of Preserving Renal Volume

- US National Cancer Database
- 9254 patients over 6 years eligible for PS matching ➔ 527 matched cases in each group
- Age, gender, race, comorbidity, tumor size, histology, grade
- Minimum 5 years of follow-up

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Volume 31, Number 8, August 2017

Pp. 800–805
DOI: 10.1089/end.2017.0190

General Research

Matched Comparison Between Partial Nephrectomy and Radical Nephrectomy for T2 N0 M0 Tumors, a Study Based on the National Cancer Database

Cheuk Fan Shum, MBBS, MMed (Surgery), FAMS (Urology), Clinton D. Bahler, MD, MSc, and Chandru P. Sundaram, MD

Abstract

Objectives: To compare overall survival (OS) and immediate postoperative outcomes between partial and radical nephrectomy (RN) for T2 N0 M0 tumors and identify significant factors for poor OS.
Patients and Methods: Using the National Cancer Database, we identified patients with T2 N0 M0 renal cancer between 2004 and 2009 who were treated with partial or radical nephrectomy. The partial and RN groups were statistically matched by demographics and tumor characteristics. We used Cox multiple regression to identify significant factors for all-cause mortality and plotted survival curves for both groups. We compared immediate postoperative outcomes between groups by χ^2 test and independent samples *t*-test.
Results: After statistical matching, there were 527 patients in each group, with high similarities in age, gender, race, comorbid status, tumor size, histology, and grade. RN was associated with a higher risk of all-cause mortality (hazard ratio: 5.289; $p < 0.001$) than partial nephrectomy (PN), after adjusting for all available covariates. PN had significantly better OS than RN, with log-rank, Breslow, and Tarone-Ware tests consistently showing *p*-values of <0.001. Old age, high comorbidity index, and high Fuhrman grade were associated with increased risks of all-cause mortality, while papillary and chromophobe tumors had decreased risks. PN was associated with more positive surgical margins (PSM) than RN (4.4% *vs* 2.5%, $p < 0.001$).
Conclusion: T2 N0 M0 tumors treated with PN had better OS than those treated with RN, despite more PSM. Age, comorbidity index, histologic subtypes, and Fuhrman grade had significant impacts on OS.

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Importance of Preserving Renal Volume

- Cox multiple regression showed a higher risk of all-cause mortality among RNx (HR: 5.289, P<0.001)
- PNx was associated with significantly better OS despite a higher PSM rate

	PN (n = 527) %	*RN* (n = 527) %	p
Surgical margins			
Negative	486 (92.2)	508 (96.4)	0.01
Positive	23 (4.4)	13 (2.5)	
Unknown	18 (3.4)	6 (1.1)	
Postoperative length of stay (day)	4.75 ± 3.88	5.03 ± 5.42	0.352
30-day unplanned readmission			
No	493 (93.5)	493 (93.5)	0.874
Yes	22 (4.2)	24 (4.6)	
Unknown	12 (2.3)	10 (1.9)	

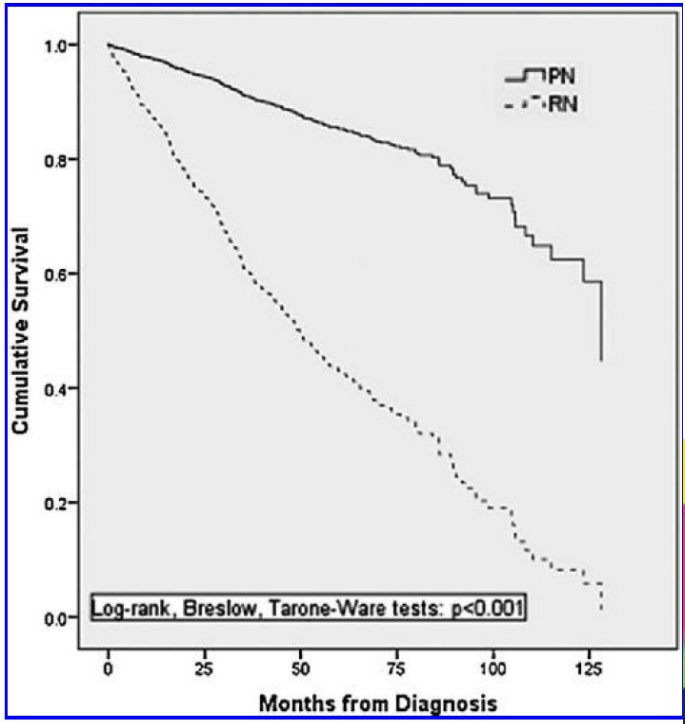
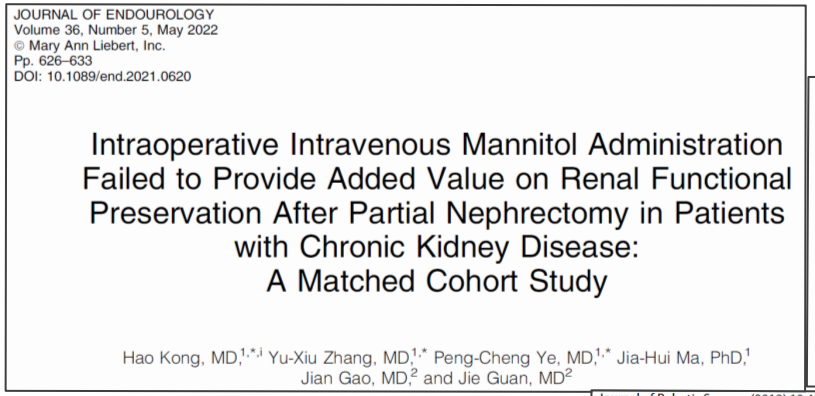


FIG. 2. OS curves for the matched PN and RN groups, at mean values of all other covariates. OS = overall survival.

Reducing Collateral Damage

- Residual renal volume is the key
  - ‘There is no replacement for displacement’



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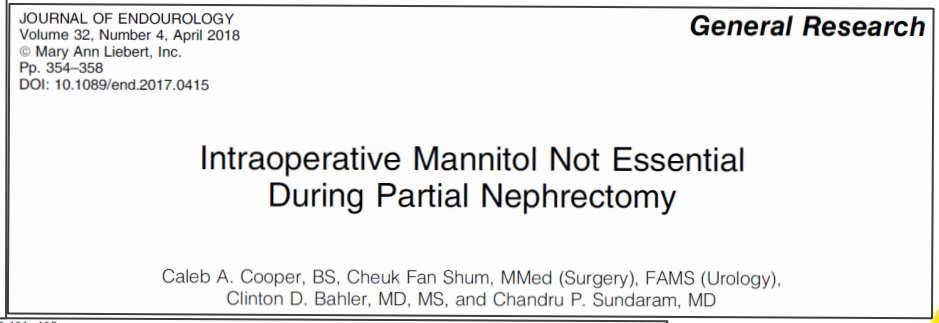
Intraoperative Intravenous Mannitol Administration Failed to Provide Added Value on Renal Functional Preservation After Partial Nephrectomy in Patients with Chronic Kidney Disease: A Matched Cohort Study

Hao Kong, MD,[1,*,†] Yu-Xiu Zhang, MD,[1,*] Peng-Cheng Ye, MD,[1,*] Jia-Hui Ma, PhD,[1] Jian Gao, MD,[2] and Jie Guan, MD[2]



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General Research

Intraoperative Mannitol Not Essential During Partial Nephrectomy

Caleb A. Cooper, BS, Cheuk Fan Shum, MMed (Surgery), FAMS (Urology), Clinton D. Bahler, MD, MS, and Chandru P. Sundaram, MD

Journal of Robotic Surgery (2019) 13:401–405
https://doi.org/10.1007/s11701-018-0868-4

ORIGINAL ARTICLE

CrossMark

Intraoperative mannitol during robotic-assisted-laparoscopic partial nephrectomy

Kellen Choi[1] · Sharon Hill[2] · Nathan Hale[2] · Stephen Phillips[3] · Samuel Deem[2]

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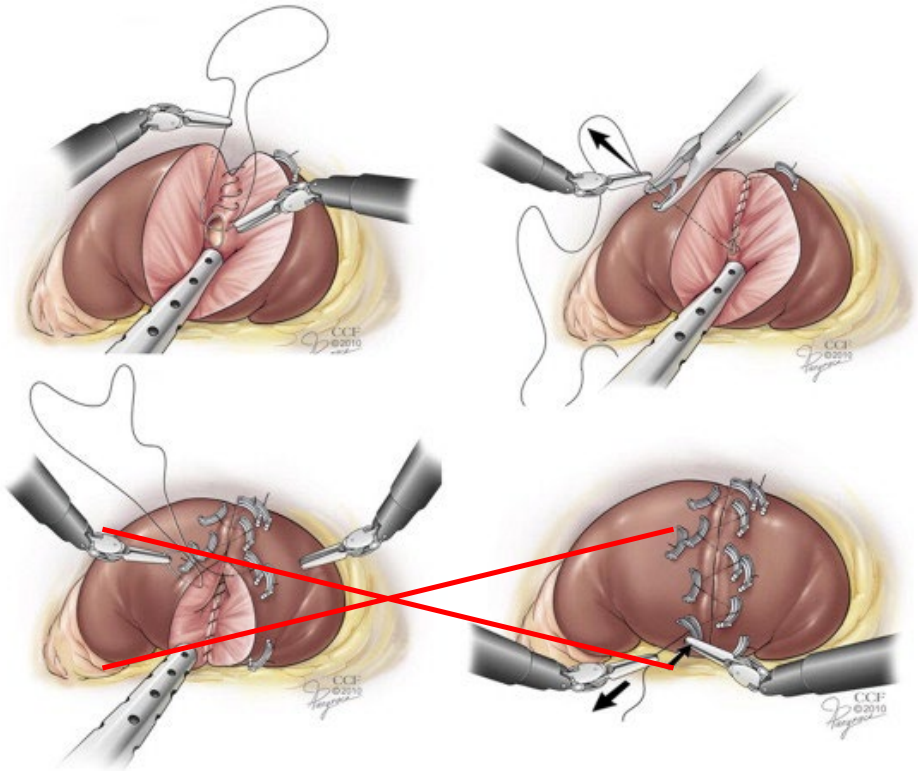
Modified Renorrhaphy



BJUI
BJU International

Systematic Review & Meta-Analysis

Suture techniques during laparoscopic and robot-assisted partial nephrectomy: a systematic review and quantitative synthesis of peri-operative outcomes

Riccardo Bertolo*, Riccardo Campi†, Tobias Klatte‡, Maximilian C. Kriegmair§, Maria Carmen Mir¶, Idir Ouzaid**, Maciej Salagierski††, Sam Bhayani‡‡, Inderbir Gill§§¶¶, Jihad Kaouk*, and Umberto Capitanio‡‡§§§***†††, On behalf of the Young Academic Urologists (YAU) Kidney Cancer working group of the European Urological Association (EAU)

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R.B. and R.C. equally contributed to this work.

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available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

Systematic Review and Pooled Analysis of the Impact of Renorrhaphy Techniques on Renal Functional Outcome After Partial Nephrectomy

Riccardo Bertolo [a,], Riccardo Campi [b], Maria Carmen Mir [c], Tobias Klatte [d,e], Maximilian C. Kriegmair [f], Maciej Salagierski [g], Idir Ouzaid [h], Umberto Capitanio [i,j], on behalf of the Young Academic Urologists Kidney Cancer Working Group of the European Urological Association*

[a] Department of Urology, Cleveland Clinic Foundation, Cleveland, OH, USA; [b] Department of Urology, University of Florence, Florence, Italy; [c] Department of Urology, Fundacion Instituto Valenciano de Oncologia, Valencia, Spain; [d] Department of Urology, Royal Bournemouth and Christchurch Hospitals NHS Trust, Bournemouth, UK; [e] Department of Surgery, University of Cambridge, Cambridge, UK; [f] Department of Urology, University Medical Centre Mannheim, Mannheim, Germany; [g] The Faculty of Medicine and Health Sciences, University of Zielona Góra, Zielona Góra, Poland; [h] Department of Urology, Bichat Hospital, APHP, Paris Diderot University, Paris, France; [i] Department of Urology, San Raffaele Scientific Institute, Milan, Italy; [j] Division of Experimental Oncology/Unit of Urology, URI, IRCCS San Raffaele Hospital, Milan, Italy

Ways to Improve Outcomes

- Reduce risk of +ve margins
  - ➔ improve long term oncologic clearance
- Reduce collateral damage to adjacent normal tissues
  - ➔ improve post-operative renal function
- Reduce need for invasive procedures / anesthesia
  - ➔ improve peri-operative outcomes
- Reduce missed diagnosis
  - ➔ improve pre-operative patient selection

Reducing Need for Invasive Procedures

- Thermal ablation
  - Cryoablation
  - Radio-frequency ablation
  - Microwave ablation
  - High intensity focused U/S (HIFU)
    - Tissue destruction based on thermal necrosis
    - Thermal damage to surrounding tissues
    - Thermal diffusion ➔ limited usage in vascular tissues (such as kidneys)

Reducing Need for Invasive Procedures

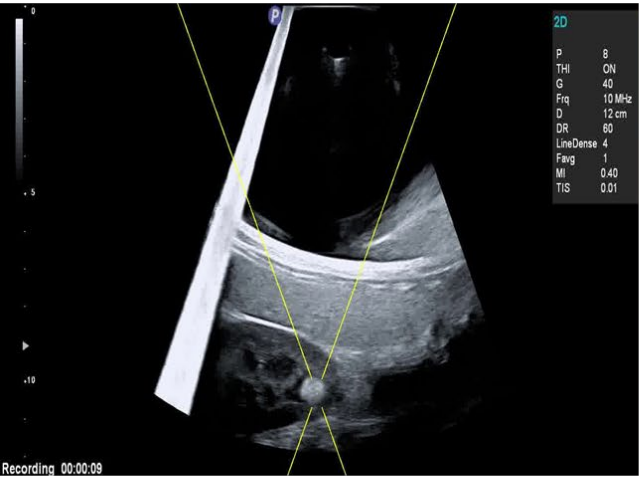
- Extension of ultrasound ablation ➔ histotripsy
  - Boiling histotripsy
    - Shockwaves based on nonlinear propagation effects to produce millimeter-sized boiling bubbles within milliseconds, leading to mechanical shear stress around bubbles for tissue destruction

Histotripsy for Urologic Tumors

- PUCA (Pulsed Ultrasound Cavitation Ablation System)
- Noninvasive, non-ionizing, non-thermal
- Minimal collateral thermal damage
- Real-time ultrasound monitoring of treatment
- Intended use for kidney cancer, prostate cancer and BPH

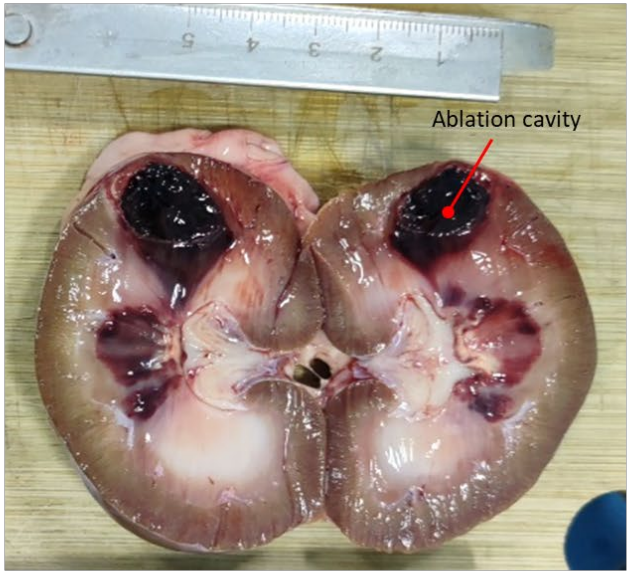
PUCA in Dog Model

1. US monitoring & feedback



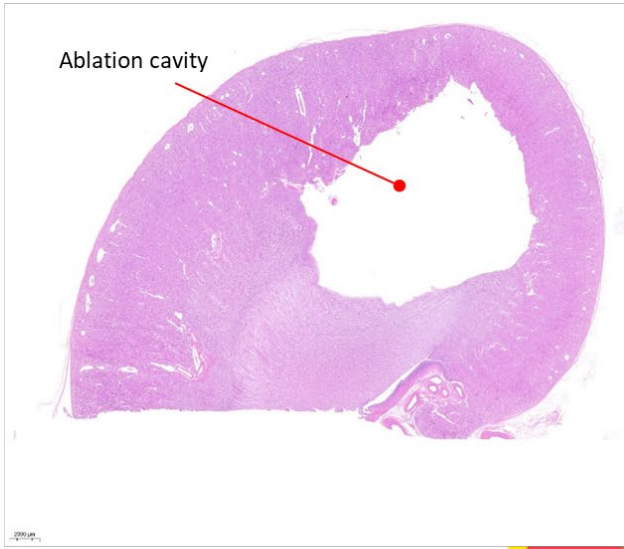
Cavitation cloud formation (Hyperechoic area)

2. Post-Ablation Dissection (≤ 9 days)



Ablation cavity was clearly detected within the treatment area

3. H&E Pathological Examination



H&E showed a well-defined ablation cavity and demarcated boundary

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Courtesy of Creative MedTech Solutions

Ways to Improve Outcomes

- Reduce risk of +ve margins
  - ➔ improve long term oncologic clearance
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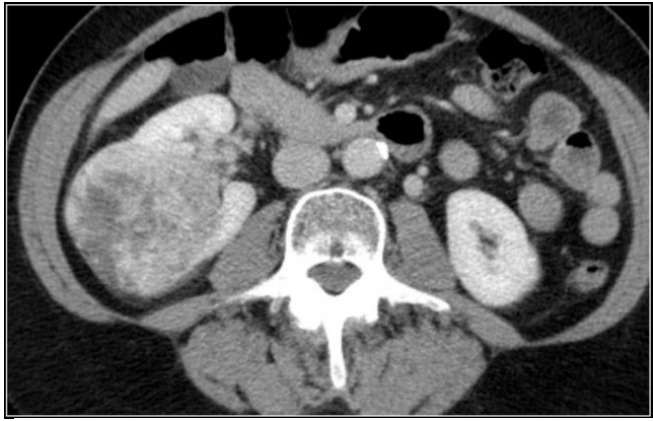
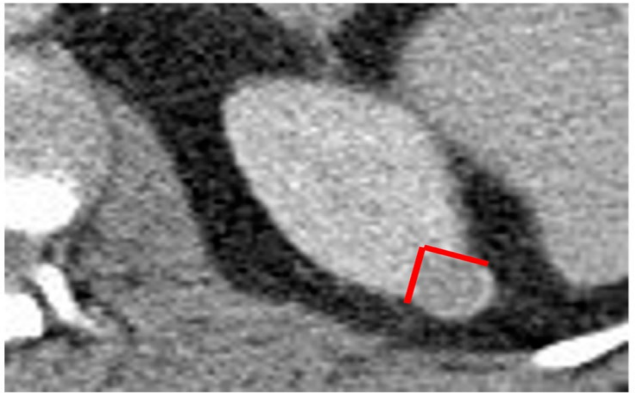
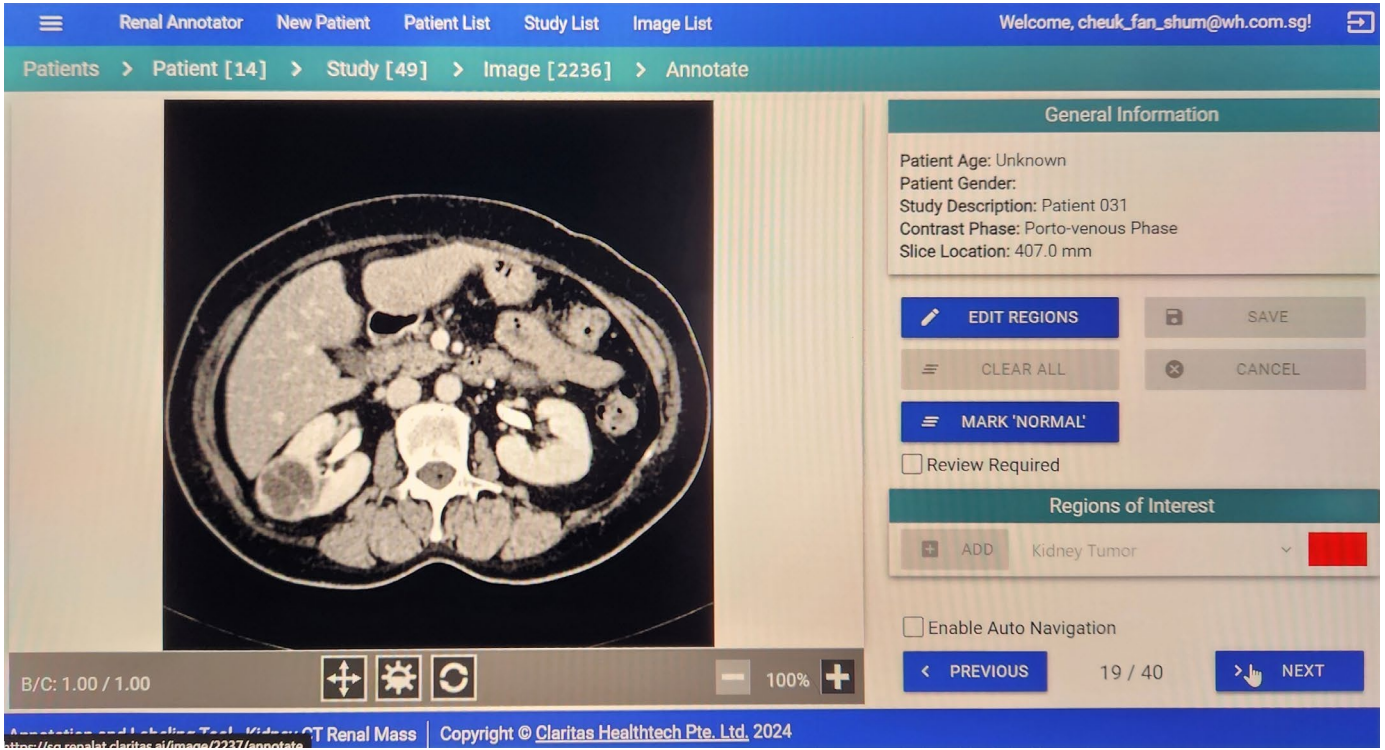
Reducing Missed Diagnosis

- Most small renal tumors are incidental findings on imaging
- Heavy responsibility on radiologists to identify small renal tumors
- Equivocal findings ➔ prolonged follow-up or biopsy
  - Prolonged follow-up ➔ anxiety, healthcare resources
  - Biopsy ➔ risk of complications





Use of Artificial Intelligence



Courtesy of Claritas HealthTech

Conclusion

- Kidney cancer treatment has evolved at various aspects over time

- Research and innovation work hand-in-hand to improve diagnosis and surgical outcomes
- Clinicians and engineers work hand-in-hand to improve diagnosis and surgical outcomes

Thank you

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