Editorial Commentary

Reconsidering nephron-sparing strategies for the management of small renal tumors: a call for the inclusion of level 1 evidence in the debate

Zine-Eddine Khene^, Isamu Tachibana, Raj Bhanvadia, Yair Lotan, Vitaly Margulis

Department of Urology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Correspondence to: Zine-Eddine Khene, MD. Department of Urology, University of Texas Southwestern Medical Center, 2001 Inwood Road, 4th Floor, WCB3, Dallas, TX 75390, USA. Email: zineddine.khene@gmail.com.

Comment on: Neves JB, Warren H, Santiapillai J, *et al.* Nephron Sparing Treatment (NEST) for Small Renal Masses: A Feasibility Cohort-embedded Randomised Controlled Trial Comparing Percutaneous Cryoablation and Robot-assisted Partial Nephrectomy. Eur Urol 2024;85:333-6.

Keywords: Kidney cancer; renal cell carcinoma; partial nephrectomy; study design

Submitted Dec 19, 2023. Accepted for publication May 05, 2024. Published online Jun 11, 2024.
doi: 10.21037/tau-23-661
View this article at: https://dx.doi.org/10.21037/tau-23-661

In the complex field of renal surgery and invasive therapies, the choice of one procedure over another is influenced by the surgeon's assessment of the patient. This decision-making process includes various factors such as the surgeon's expertise, the hospital volume, the patient's preference, and the patient's specific medical and surgical history (1-3). The inherent subjectivity of these decisions presents significant challenges in the design of clinical trials.

Understanding the true effects of different surgical interventions ideally requires randomized clinical trials (RCTs), which are the gold standard in research. However, RCTs in surgery are infrequent due to several factors identified in the literature. Firstly, new surgical techniques often do not mandate RCTs for approval, unlike medical treatments. Secondly, the high costs and limited availability of funding often deter researchers from undertaking these comprehensive studies. Thirdly, the complexity of designing and executing surgical RCTs poses additional challenges, including randomization, blinding, enrolling, variability in surgeon skills, patient diversity, and a lack of consensus on defining surgical outcomes. These factors collectively contribute to the scarcity of RCTs in the field of surgery (4,5).

Neves and colleagues conducted a study to evaluate the feasibility of recruitment for a cohort-embedded randomized controlled trial comparing cryoablation (CRA) with robotic partial nephrectomy (RPN) (6). The primary endpoint of the study was to determine the feasibility of randomization, defined by a consent rate of 30% for the intervention arm. Interestingly out of 200 participants recruited for the cohort, only 50 patients were eligible for the RCT. In the CRA intervention arm, 84% consented [with a 95% confidence interval (CI) of 64–95%], and 76% (95% CI: 55–91%) underwent CRA. In contrast, 100% (95% CI: 86–100%) of patients in the control arm received RPN. This feasibility study successfully met its primary endpoint, demonstrating the practicality of recruitment for an open-label cohort-embedded RCT of CRA versus RPN for small renal masses. The trial's design presents a potentially pragmatic approach to addressing recruitment challenges in interventional surgical trials. However, it also suggests that the design will need to include the likelihood of many screen failures in patients with small renal masses since only 25% of patients were eligible.

Partial nephrectomy is recognized as the optimal treatment for clinically localized renal cancer suitable for nephron-sparing techniques, associated with over a 90% disease-specific survival for stage T1a tumors (7).

^ ORCID: 0000-0002-4124-789X.

Moreover, ablation therapy and active surveillance have also proven to be effective management strategies for T1a renal cancers (8), although they are currently underutilized. An increasing number of studies have been investigating thermo-ablation (TA) techniques, such as radiofrequency ablation and cryoablation, for treating these tumors. Overall, TA has been found to be safe for treating small renal masses, showing equivalent long oncological outcomes with minimal complications (9,10). However, many of these studies have faced criticism for a high or uncertain risk of bias, largely due to their retrospective nature, poorly matched control groups, or being single-arm case series with limited follow-up periods. Additionally, these studies often lack detailed methodologies and clear comparative analyses (11). To overcome these limitations, RCT comparing RPN to TA have been attempted over the past decade. However, trials like SURAB (ISRCTN31161700) and CONSERVE (ISRCTN23852951) have struggled to meet their enrollment targets, perpetuating the lack of high-level evidence in this field.

An alternative to the traditional randomized controlled trial design is the cohort embedded RCT approach. In this model, the process begins by identifying all patients eligible for the study within a larger cohort. From this pool of eligible patients, a subset is randomly chosen and offered the trial intervention. Following the intervention, outcomes of these randomly selected patients with those of the eligible patients who were not chosen for the intervention was compared. This approach allows for a controlled comparison within a broader patient population.

This approach is characterized by three main elements: (I) recruitment of a large cohort of patients; (II) continuous and comprehensive monitoring of relevant outcomes across the entire cohort over a prolonged period. For instance, in managing small renal tumors, both renal function and cancer outcomes would be systematically monitored. (III) Facilitation of multiple, sequential randomized controlled trials. For example, an initial RCTs might compare focal therapy with partial nephrectomy, followed by another examining radiotherapy or active surveillance, and a third assessing the efficacy of regular computed tomography scans in monitoring disease progression during active surveillance (12).

Analyzing cohort RCTs may present more challenges than standard RCTs (13). A significant concern is the impact of patient refusal rates on outcome measures and the identification of suitable statistical methods to address this. Since only patients in one arm of the RCT can refuse the assigned treatment, imbalances in baseline characteristics, such as disease severity or comorbidities, might arise between the randomly selected group and the non-selected control group. The potential for significant variability within the control group, part of the larger cohort, is another issue. While this heterogeneity may mirror actual clinical practice, enhancing the study's external validity, it presents challenges in data analysis. Lastly, there is concern among research teams conducting Phase II/III studies with the same patient population that a comprehensive cohort RCT could disrupt the recruitment for their ongoing trials, potentially impacting their results (for instance adjuvant therapy in renal cell carcinoma).

Cluster randomized trials (CRT) offer another alternative, randomizing entire groups or institutions, which may be particularly relevant when interventions are system-wide or when individual randomization is impractical (14). However, CRTs may require larger sample sizes due to intra-cluster correlation. Adaptive design trials introduce a dynamic element that allows for adjustments based on interim results, which may be particularly beneficial in rapidly evolving fields such as surgical oncology (15). Finally, pragmatic trials focus on the effectiveness of interventions in "real-world" clinical settings, providing valuable insight into how surgical innovations perform outside of controlled research environments (16). Each of these RCT designs has distinct advantages and limitations and the choice of design should be guided by the specific research question.

The cohort embedded RCT approach can be considered a significant methodological advancement in oncology research. It aims to integrate the rigor of RCTs into the framework of cohort studies. This design addresses several key challenges of traditional randomized trials, including slow patient accrual, high dropout rates, and limited external validity. It leverages pre-existing observational cohort infrastructures for trial randomization and execution. Particularly in the field of oncology, where patient responses and treatments are highly diverse, nuanced study designs are necessary. As noted by Kessels *et al.*, this design enhances feasibility and applicability. However, it also introduces unique methodological considerations, such as handling non-compliance and the implications for statistical power, which require careful planning and execution (17). By adopting this innovative trial design, researchers can potentially overcome longstanding barriers in clinical research, leading to more patient-centered, efficient, and generalizable study outcomes in oncology.

In the field of oncology, many studies have utilized the cohort embedded RCT approach. An example is the MEDOCC-CrEATE trial, which investigates the willingness of patients to receive adjuvant chemotherapy based on the detection of circulating tumor DNA after surgical resection of colon cancer (18). This study is conducted within the Prospective Dutch ColoRectal Cancer cohort. Shortly after their surgical procedures, eligible patients who had previously agreed to possible randomization in future studies are assigned to either the intervention or control group. Only individuals in the intervention group are asked to provide informed consent for the immediate assessment of their circulating tumor DNA from a recent post-operative blood sample. Patients with detectable circulating tumor DNA are offered adjuvant chemotherapy, which they can either accept or decline. Patients who decline, as well as those who lack detectable circulating tumor DNA or did not consent to its immediate analysis, receive standard post-operative care. Individuals in the control group are not informed of the trial details and their post-surgical blood samples are not immediately tested for circulating tumor DNA.

In conclusion, this study has highlighted a viable approach to addressing the recruitment challenges commonly encountered in interventional surgical trials. The urgent requirement for the development of randomized comparative effectiveness research models in surgical oncology is underscored, particularly in the context of kidney cancer surgery. Currently, many surgical practices in this area rely on limited empirical evidence, often based on individual experiences, retrospective study results, or subjective perceptions and assumptions. In line with the stringent evaluation protocols established in medical oncology and the pharmaceutical industry, where meticulous assessments are a prerequisite prior to the administration of any medication, it is imperative to apply equally rigorous standards in evaluating surgical techniques. This approach is crucial to optimize patient outcomes and to advance the practice of surgical oncology on a foundation of solid, evidence-based medicine.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Andrology and Urology*. The article has undergone external peer review.

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-661/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-661/coif). Y.L. reports consulting fees from Nanorobotics, Photocure, AstraZeneca, Merck, Fergene, Abbvie, Nucleix, Ambu, Seattle Genetics, Hitachi, Ferring Research, verity pharmaceutics, virtuoso surgical, Stimit, Urogen, Vessi medical, CAPs medical, Xcures, BMS, Nonagen, Aura Biosciences, Inc., Convergent Genomics, Pacific Edge, Pfizer, Phinomics Inc., CG oncology, Uroviu, On target lab, Promis Diagnostics, Valar labs, Uroessentials. V.M. serves as an unpaid editorial board member of *Translational Andrology and Urology* from December 2022 to November 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Khene ZE, Peyronnet B, Bernhard JC, et al. A preoperative nomogram to predict major complications after robot assisted partial nephrectomy (UroCCR-57 study). Urol Oncol 2019;37:577.e1-7.
2. Larcher A, Muttin F, Peyronnet B, et al. The Learning Curve for Robot-assisted Partial Nephrectomy: Impact of Surgical Experience on Perioperative Outcomes. Eur Urol 2019;75:253-6.
3. Peyronnet B, Tondut L, Bernhard JC, et al. Impact of hospital volume and surgeon volume on robot-assisted

partial nephrectomy outcomes: a multicentre study. BJU Int 2018;121:916-22.
4. Pronk AJM, Roelofs A, Flum DR, et al. Two decades of surgical randomized controlled trials: worldwide trends in volume and methodological quality. Br J Surg 2023;110:1300-8.
5. Robinson NB, Fremes S, Hameed I, et al. Characteristics of Randomized Clinical Trials in Surgery From 2008 to 2020: A Systematic Review. JAMA Netw Open 2021;4:e2114494.
6. Neves JB, Warren H, Santiapillai J, et al. Nephron Sparing Treatment (NEST) for Small Renal Masses: A Feasibility Cohort-embedded Randomised Controlled Trial Comparing Percutaneous Cryoablation and Robot-assisted Partial Nephrectomy. Eur Urol 2024;85:333-6.
7. Almdalal T, Sundqvist P, Harmenberg U, et al. Clinical T1a Renal Cell Carcinoma, Not Always a Harmless Disease-A National Register Study. Eur Urol Open Sci 2022;39:22-8.
8. Renal Mass and Localized Renal Cancer: Evaluation, Management, and Follow Up (2021) - American Urological Association. [cited 2023 Dec 18]. Available online: https://www.auanet.org/guidelines-and-quality/guidelines/renal-mass-and-localized-renal-cancer-evaluation-management-and-follow-up
9. Xing M, Kokabi N, Zhang D, et al. 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.
10. Chan VW, Abul A, Osman FH, et al. Ablative therapies versus partial nephrectomy for small renal masses - A systematic review and meta-analysis. Int J Surg 2022;97:106194.
11. Abu-Ghanem Y, Fernández-Pello S, Bex A, et al. Limitations of Available Studies Prevent Reliable Comparison Between Tumour Ablation and Partial Nephrectomy for Patients with Localised Renal Masses: A Systematic Review from the European Association of Urology Renal Cell Cancer Guideline Panel. Eur Urol Oncol 2020;3:433-52.
12. Relton C, Torgerson D, O'Cathain A, et al. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. BMJ 2010;340:c1066.
13. Ergina PL, Cook JA, Blazeby JM, et al. Challenges in evaluating surgical innovation. Lancet 2009;374:1097-104.
14. Esserman D, Allore HG, Travison TG. The Method of Randomization for Cluster-Randomized Trials: Challenges of Including Patients with Multiple Chronic Conditions. Int J Stat Med Res 2016;5:2-7.
15. Pallmann P, Bedding AW, Choodari-Oskooei B, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. BMC Med 2018;16:29.
16. Sox HC, Lewis RJ. Pragmatic Trials: Practical Answers to "Real World" Questions. JAMA 2016;316:1205-6.
17. Kessels R, May AM, Koopman M, et al. The Trial within Cohorts (TwiCs) study design in oncology: experience and methodological reflections. BMC Med Res Methodol 2023;23:117.
18. Schraa SJ, van Rooijen KL, van der Kruijssen DEW, et al. Circulating tumor DNA guided adjuvant chemotherapy in stage II colon cancer (MEDOCC-CrEATE): study protocol for a trial within a cohort study. BMC Cancer 2020;20:790.

Cite this article as: Khene ZE, Tachibana I, Bhanvadia R, Lotan Y, Margulis V. Reconsidering nephron-sparing strategies for the management of small renal tumors: a call for the inclusion of level 1 evidence in the debate. Transl Androl Urol 2024;13(6):1049-1052. doi: 10.21037/tau-23-661

