Editorial Commentary

Management of small renal mass: unmet needs and quest for high quality evidence

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In recent decades, the widespread adoption of advanced imaging modalities has led to an increased incidental detection of small (≤4 cm) renal masses (SRMs) (1). On the other end, epidemiological data suggest a plateau in mortality rates for renal cell carcinoma (RCC) despite earlier detection and treatment, fueling the debate linking overdiagnosis to potential overtreatment (2,3). Thus, there is a strong need for high-quality, evidence-based, management strategies.

To date there is still a lack of high-level evidence guiding best treatment choice (4). In particular, the absence of randomized controlled trials (RCTs) comparing the different treatment options certainly stands out. At present, no randomized prospective studies have compared active surveillance (AS) with primary intervention, thermal ablation (TA) techniques with surgery (partial or radical nephrectomy) or compared each TA modality [cryoablation (CRA) versus radiofrequency ablation] (5).

As a matter of fact, previous attempts have been made to fill this gap. Feasibility studies like SURAB (ISRCTN31161700) and CONSERVE (NCT01608165) tested the waters for future RCTs, highlighting viable pathways and uncovering potential stumbling blocks. The CONSERVE trial, a multicenter feasibility study comparing partial nephrectomy (PN) versus TA, was terminated early due to poor accrual (6). The same fate befell the SURAB trial, comparing AS versus CRA (7). Nevertheless, they identified factors directly impacting on trial recruitment: patient and clinician preferences, organizational factors and—for the SURAB trial—the non-inclusion of standard treatment in the study arms.

Taking into consideration these difficulties, the recent brief correspondence published in *European Urology* by Neves *et al.* (8) contributes with an alternative pragmatic trial design to assess the feasibility of a single-center, open-label RCT evaluating percutaneous CRA versus robot-assisted PN for SRMs management. *Table 1* summarizes the main characteristics of these feasibility studies. The novel trial design proposed—which has already found success in other oncology fields (9,10)—consists in the cohort-embedded RCT (ceRCT). It allows recruitment from a pool of patients amenable to research by virtue of recruiting within an observational cohort study.

For SRMs, PN remains the gold standard whenever feasible (11); it yields complete pathological information while preserving renal function and providing similar oncological outcomes when compared to RN (12). Despite nephron sparing surgery offers a definitive treatment, it carries inherent risks such as potential postoperative surgical complications and potential impact on renal function.

In contrast, percutaneous CRA is gaining traction as an alternative to surgery in selected cases of SRMs, such as

Table 1 Feasibility randomized controlled trials on SRMs management

Study characteristics	CONSERVE (6) (NCT01608165)	SURAB (7) (ISRCTN31161700)	NEST (8) (ISRCTN18156881)
Number of centers involved	Multicenter	Multicenter	Single center
Arms	TA[§] *vs.* PN	TA[‡] *vs.* AS	Percutaneous cryoablation *vs.* RAPN
Inclusion criteria	Adults ≥18 years, ASA 1 or 2, radiological confirmation or biopsy-proven SRM <4 cm, no metastases, informed consent	Same as CONSERVE	For the initial cohort: adults ≥18 years, SRM <4 cm, informed consent; for the ceRCT: biopsy-proven RCC, technical feasibility of both treatments, second consent
Exclusion criteria	Same as SURAB plus urosepsis and total endophytic mass	Coagulopathy, unsuitable concomitant disease, multiple SRMs, prior study participation	For the initial cohort: advanced disease; for the ceRCT: specific concurrent medical\ surgical conditions that would lead the SMDT recommend one treatment modality
Planned patient recruitment	60	60	50
Time frame, months	18	3–11*	27[#]
Primary outcome	To assess the proportion of patients who agree to trial registration and accept randomisation	Feasibility of a definitive trial assessed by recruitment and retention rates, and patient experience	Feasibility of recruitment into a ceRCT
Enrolled patients	17[†]	7[†]	50

[§], including: percutaneous radiofrequency ablation, laparoscopic or percutaneous cryoablation; [‡], including: percutaneous radiofrequency ablation, laparoscopic or percutaneous cryoablation and percutaneous microwave ablation; *, depending on recruiting institution; [#], initial planned time frame of 24 months, 3 months were added due to COVID-19 pandemic; [†], terminated earlier due to poor patient accrual. SRM, small renal mass; TA, thermal ablation; PN, partial nephrectomy; AS, active surveillance; RAPN, robot-assisted partial nephrectomy; ASA, American Society of Anesthesiologists physical status classification system; ceRCT, cohort-embedded randomized controlled trial; RCC, renal cell carcinoma; SMDT, specialist multidisciplinary team; COVID-19, coronavirus disease 2019.

elderly patients, genetic predisposition to develop multiple tumors or contraindication to surgery (13). It demonstrated lower complication rates, preservation of long-term renal function and equivalent long-term oncological outcomes compared to surgical resection in selected patients (14-16). However, current guidelines recommend informing patients about the higher chance of tumor persistence or recurrence after primary TA techniques during counseling (17).

Acknowledging the previously outlined issues, Neves *et al.* established "the feasibility of randomization"—defined as a consent rate of 30% for the intervention arm—as their primary endpoint.

To overcome the inherent reluctance among patients to accept treatment allocation based on chance—especially when there is a lack of clinical equipoise between the treatment options—they performed a two-stage consent. The first consent allowed to create a prospective cohort of patients with SRM; the second-stage consent represented—for patients with biopsy-proven RCC—agreement to a 1:1 randomization. During a 27-months recruitment period, 200 patients (57% of the patients approached) consented to be included in the cohort (first consent). Of these, only 50 patients (25% of the cohort) were eligible for the ceRCT.

Eligibility for each patient required a cross-disciplinary team consensus on their suitability for both treatment options. Additionally, renal mass biopsy (RMB) was performed when deemed that it could impact treatment decisions, resulting in a 61% of the initial cohort undergoing RMB.

This reflects a significant shift from past practices, where biopsies were not routinely performed due to concerns over their accuracy, capacity to affect clinical management and potential complications. However, improved biopsy techniques and patient selection criteria and a better understanding of renal mass histopathology have established biopsies as a valuable tool for risk stratification (18-20), a point this study emphasizes.

The authors observed that through the adoption of this

decision-making strategy, the remaining 75% of the cohort had patient-, tumor-, or clinician-related factors favoring a particular management option. Nevertheless, after 1:1 randomization of the eligible cohort, they achieved an 84% consent rate (second consent) to undergo CRA (intervention arm). Moreover, clinical follow-up retention in the ceRCT was 90% (95% confidence interval: 79–96%) at 6 months, demonstrating its feasibility in this regard as well.

In our opinion, this methodology efficiently considers both SRMs characteristics and patient's perspective, aligning with the growing emphasis on shared decision-making. Even though it is an RCT, by informing patients of the individualized management considerations, they are actively involved in selecting a treatment that suits their expectations and needs. This strategy aims not just to enhance the efficacy of recruitment but also to minimize side effects by avoiding a one-size-fits-all strategy (21).

However, the present study inevitably presents some limitations. The single center design presupposes that any potential future definitive trial should include an internal pilot to ensure that recruitment outside the lead site is met, and authors have recognized it. Furthermore, they suggested restricting eligibility criteria for the initial cohort in future studies; by including only patients suitable for active treatment, they anticipate increased trial efficiency. Considering this factor, the lack of definitive inclusion criteria could represent a limit for the reproducibility of this trial design.

Despite these considerations, we must be grateful to authors for presenting insights into successful trial structuring, highlighting the importance of clinical adaptability in research methodology. As we grapple with the nuances of SRM treatment, it is the rigor of feasibility studies like this that will illuminate the path forward for the successful delivery of surgical RCTs.

Although this is not the focus of this study, we believe this data may also encourage future similar trial design on AS versus standard of care. Notably, more than half of the not-eligible patients in the cohort were managed with initial AS. While the authors acknowledge an impact of the COVID-19 pandemic during the study period as a possible factor, this highlights a shift towards AS in recent years (22,23).

It is upon us—the clinical and research communities—to take these insights and translate them into larger trials that can decisively improve current guidelines and influence SRM management. Thus, feasibility studies—the first step towards obtaining high quality data—do not merely answer the question "can we proceed?" but also "how should we proceed?": a guiding light towards evidence-based, patient-centered care.

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