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Brief Correspondence

Nephron Sparing Treatment (NEST) for Small Renal Masses: A Feasibility Cohort-embedded Randomised Controlled Trial Comparing Percutaneous Cryoablation and Robot-assisted Partial Nephrectomy

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Abstract

There is a paucity of high-level evidence on small renal mass (SRM) management, as previous classical randomised controlled trials (RCTs) failed to meet accrual targets. Our objective was to assess the feasibility of recruitment to a cohort-embedded RCT comparing cryoablation (CRA) to robotic partial nephrectomy (RPN). A total of 200 participants were recruited to the cohort, of whom 50 were enrolled in the RCT. In the RCA intervention arm, 84% consented (95% confidence interval [CI] 64–95%) and 76% (95% CI 55–91%) received CRA; 100% (95% CI 86–100%) of the control arm underwent RPN. The retention rate was 90% (95% CI 79–96%) at 6 mo. In the RPN group 2/25 (8%) were converted intraoperative to radical nephrectomy. Postoperative complications (Clavien-Dindo grade 1–2) occurred in 12% of the CRA group and 29% of the RPN group. The median length of hospital stay was shorter for CRA (1 vs 2 d; $p = 0.019$). At 6 mo, the mean change in renal function was −5.0 ml/min/1.73 m^2 after CRA and −5.8 ml/min/1.73 m^2 after RPN. This study demonstrates the feasibility of a cohort-embedded RCT comparing CRA and RPN. These data can be used to inform multicentre trials on SRM management.

Patient summary: We assessed whether patients with a small kidney tumour would consent to a trial comparing two different treatments: cryoablation (passing small needles through the skin to freeze the kidney tumour) and surgery to remove part of the kidney. We found that most patients agreed and a full trial would therefore be feasible.

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Small renal masses (SRMs) are tumours <4 cm with an imaging appearance consistent with stage T1a, as defined by the Union for International Cancer Control/American Joint Committee on Cancer [1]. Active treatment options include robot-assisted partial nephrectomy (RPN) and percutaneous cryoablation (CRA), with observational data suggesting equivalent oncological control at 9 yr [2] and lower costs for CRA [3]. Previous classical randomised control trials (RCTs) comparing RPN to CRA failed to reach accrual targets (SURAB, ISRCTN31161700; and CONSERVE, ISRCTN23852951), resulting in a lack of level 1 evidence.

European Association of Urology guidelines recommend surgery as the standard of care, reserving CRA for elderly or comorbid patients in whom surgery is high risk [4]. It is not clear if more patients might benefit from CRA for SRMs.

Standard interventional RCTs are notoriously challenging to design and deliver. Lessons from previous trials highlight a lack of clinical equipoise and an inherent reluctance among patients to accept treatment allocation based on chance [5]. An alternative pragmatic design that allows effective comparison of treatments is the cohort-embedded RCT (ceRCT) [6].

We performed a single-centre, prospective, open-label, feasibility ceRCT of CRA versus RPN with two-stage consent. The study protocol was prospectively registered (ISRCTN18156881) and has been published [7]. The primary endpoint was the feasibility of randomisation, defined as a consent rate of 30% for the intervention arm. Analysis was on an intention-to-treat basis. Further information on the study design is provided in the Supplementary material.

During a 27-mo recruitment period (May 2019–July 2021), 200 patients consented to inclusion in the cohort from 348 approached (57%, 95% confidence interval [CI] 52–63%), and 478 eligible patients (42%, 95% CI 37–46%). This included a 3-mo extension to compensate a 3-mo recruitment pause imposed by COVID-19 pandemic restrictions. Reasons for non-enrolment are summarised in Figure 1.

Fifty patients were eligible for the ceRCT (25% of the cohort, 95% CI 19–36%). Of these, 25 participants were randomised to consider CRA, of whom 21 completed second-stage consent (84%, 95% CI 64–95%) and four (16%) declined and opted for RPN. CRA was completed in 19/25 patients (76%, 95% CI 55–91%) as two patients were deemed unsuitable on positioning because of proximity to the

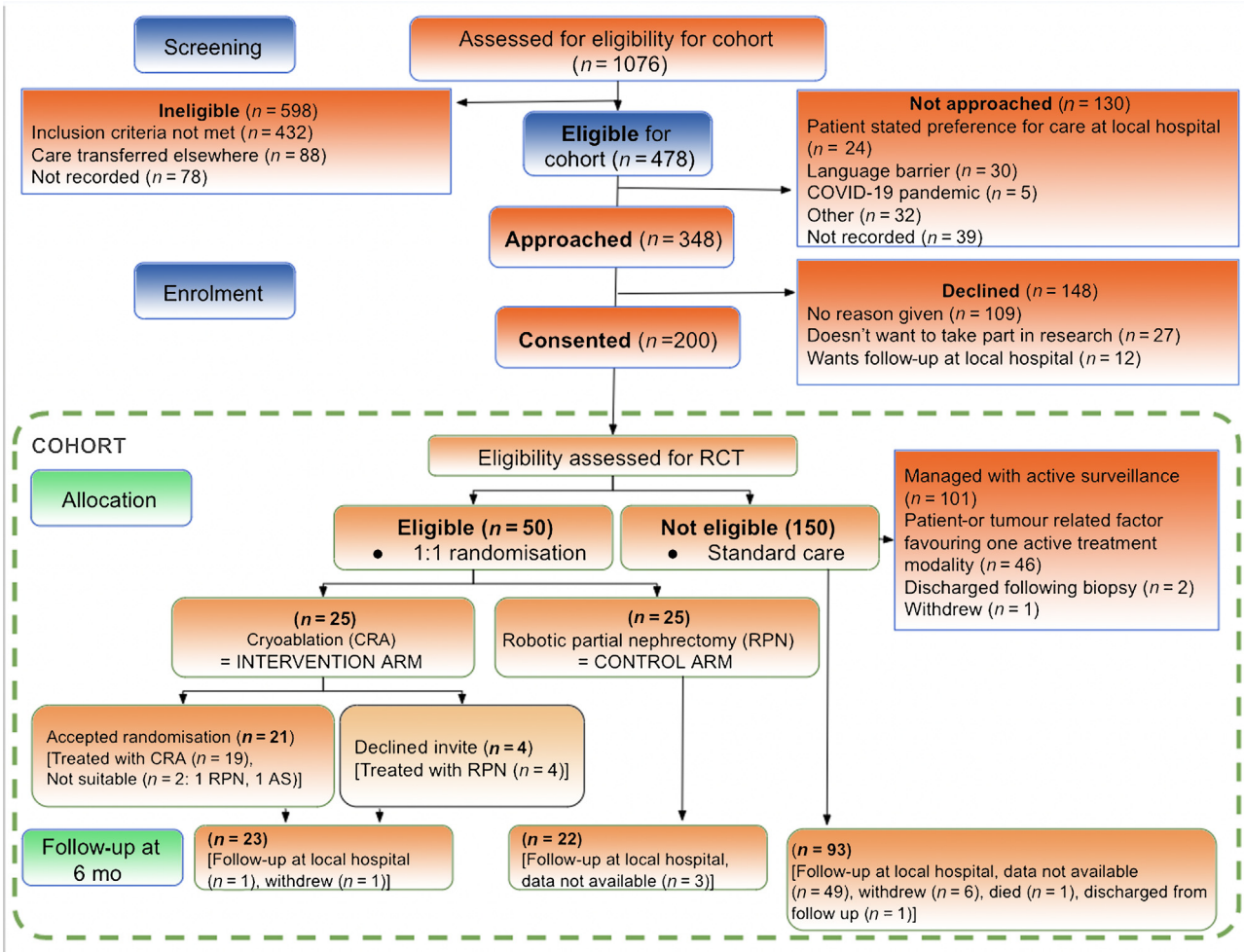

Fig. 1 – Study CONSORT diagram showing screening, enrolment, allocation, and follow-up for study participants. RCT = randomised controlled trial; AS = active surveillance.

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bowel, one of whom subsequently underwent RPN and the other opted for active surveillance. All patients allocated to the standard-care arm consented to RPN (100%, 95% CI 86–100%). Participant demographics and tumour characteristics are reported in Table 1. The initial management strategy chosen is described in Supplementary Table 1. Demographics of the cohort participants undergoing initial active treatment or active surveillance are reported in Supplementary Table 2.

There were two intraoperative conversions to radical nephrectomy in the RPN group, one for bleeding and the other because of tumour extension to the renal sinus fat and segmental renal vein. Postoperative complications at 30 d are listed in Supplementary Table 3; all were Clavien-Dindo grade ≤2 (minor).

The median length of hospital stay was 1 d for CRA and 2 d for RPN ($p = 0.019$). The mean change in eGFR at 6 mo was −5.0 ml/min/1.73 m^2 (standard deviation 10.3) after CRA and −5.8 ml/min/1.73 m^2 (standard deviation 15.4) after RPN.

Clinical follow-up retention in the ceRCT was 90% (95% CI 79–96%) at 6 mo. Disruption caused by the COVID-19 pandemic resulted in incomplete data sets for quality-of-life analyses. In addition, participants reported that the Client Service Receipt Inventory instrument was too complicated and intrusive, resulting in very few completed inventories, which limited the health economic analyses. Alternative, more patient-friendly instruments should be considered for future trials in this setting.

The ceRCT approach is an evolution of postrandomisation consent RCTs, first described by Zelen [8], that overcome ethical concerns [9] by asking cohort participants to consent to be the "control" arm and receive the standard of care in embedded trials. The ceRCT design allows recruitment from a pool of patients amenable to research by virtue of recruiting within an observational cohort study. This is reflected in the overwhelming acceptance of CRA treatment by patients randomised to the intervention arm in NEST.

A limitation of this work is the single-site recruitment at an academic institution, which may not be reproducible in other centres and settings. Any potential future definitive trial should include an internal pilot to ensure that recruitment outside the lead site is met.

It is notable that only 25% of patients presenting with an SRM were eligible for the embedded RCT. This means that there was equipoise in selecting treatment with CRA or RPN for only a minority of the patients and that the majority (75%) had patient-, tumour-, or clinician-related factors such as age, comorbidities, and tumour location or proximity to vital structures favouring a particular management strategy.

We note that more than half of participants in the cohort were managed with initial active surveillance. To the best of our knowledge, UK population-level data on contemporary initial management for SRMs is lacking. According to data from the Surveillance, Epidemiology and End Results-Medicare linked database in the USA, 19.4% of SRMs were managed with initial surveillance between 2002 and 2011 [2]. While it is likely that there has been a shift towards active surveillance for SRMs owing to new evidence supporting its safety [10], it is possible that the COVID-19 pandemic resulted in a higher proportion of patients with SRMs managed with initial active surveillance because of limited elective procedural capacity, COVID-imposed prioritisation initiatives, and patient desire to avoid contact with health services. A future definitive trial might consider restricting eligibility criteria for the cohort to include only those suitable for active treatment in order to increase trial efficiency.

While this feasibility study was not powered to detect differences in outcomes between CRA and RPN, our data, along with other published literature [2], will help to inform sample size calculations for future studies.

In conclusion, this feasibility study met its primary endpoint and demonstrated the feasibility of recruitment to an open-label ceRCT of CRA versus RPN for SRM. The trial design offers a potential pragmatic solution to recruitment

Table 1 – Participant demographics and tumour characteristics in the NEST cohort and embedded randomised controlled trial

Parameter [a]	Intervention arm CRA ($n = 25$)	Control arm RPN ($n = 25$)	NEST cohort ($n = 200$)
Gender			
Male, *n* (%)	17 (68.0)	14 (56.0)	120 (60)
Age at enrolment (yr)	58.8 (10.8)	57.2 (8.8)	63 (12)
Ethnicity, *n* (%)			
Asian	1 (4.0)	3 (12.0)	17 (8.5)
Black	2 (8.0)	5 (20.0)	17 (8.5)
White	21 (84.0)	15 (60.0)	146 (73)
Not known	1 (4.0)	2 (8.0)	19 (9.5)
History of smoking, *n* (%)			
Yes	14 (56.0)	7 (28.0)	61 (30.5)
No	11 (44.0)	17 (68.0)	116 (58.0)
Unknown	0 (0)	1 (4.0)	23 (11.5)
Charlson comorbidity index, *n* (%)			
>3	0 (0)	0 (0)	14 (7)
≤3	25 (100)	25 (100)	182 (91)
Unknown	0 (0)	0 (0)	4 (2)
Baseline eGFR (ml/min/1.73 m^2)	84.7 (15.9)	83.7 (18.1)	78.3 (21.1)
Number of lesions, *n* (%)			
1 lesion	25 (100)	24 (96.0)	191 (95.5)
≥2 lesions	0 (0)	1 (4.0)	9 (4.5)
Left-sided index tumour, *n* (%)	17 (68.0)	12 (48.0)	112 (56.0)
Tumour size (mm)	29 (5)	27 (6)	26 (8) [b]
RENAL score for the index tumour, *n* (%)			
Low	5 (20.0)	11 (44.0)	86 (43.2)
Moderate	19 (76.0)	12 (48.0)	98 (49.2)
High	1 (4.0)	2 (8.0)	15 (7.5)
Position of the index tumour, *n* (%)			
A	11 (44.0)	9 (36.0)	92 (46.2)
P	10 (40.0)	14 (56.0)	76 (38.2)
X	4 (16.0)	1 (4.0)	25 (12.6)
H	0 (0)	1 (4.0)	6 (3.0)
Missing			1 (0.5)
Bosniak score for cystic tumours, *n* (%)			
3	0 (0)	1 (4)	8 (4)
4	0 (0)	3 (12)	9 (4.5)

CRA = cryoablation; RPN = robotic partial nephrectomy; eGFR = estimated glomerular filtration rate.
[a] Continuous variables are reported as the mean (standard deviation).
[b] Range 8–40 mm.

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challenges faced by interventional trials in general. Future work may include a multicentre trial of a similar design that takes into account lessons learnt during the feasibility trial.

Author contributions: Maxine G.B. Tran had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tran, Neves.
Acquisition of data: Neves, Warren, Santiapillai, Rode, Cullen, Ranieri.
Analysis and interpretation of data: Warren, Pavlou.
Drafting of the manuscript: Warren, Neves, Tran.
Critical revision of the manuscript for important intellectual content: Walkden, Patki, Barod, Mumtaz, Aitchison, Bandula, Pizzo, Ranieri, Williams, Wildgoose, Gurusamy, Bex.
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Peer Review Summary

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