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Chan, V.W.-S. orcid.org/0000-0002-6108-9315, Ng, H.H.-L. and Wah, T.M. (2024) Image-Guided Ablation of Renal Masses: Challenges to Produce High-Quality Evidence and Future Directions. Seminars in Interventional Radiology, 41 (02). pp. 144-153. ISSN 0739-9529

https://doi.org/10.1055/s-0044-1787163

Image-guided ablation of renal masses – challenges to produce high quality evidence and future directions

Dr. Vinson Wai-Shun Chan[1], MBChB, Dr. Helen Hoi-Lam Ng[1,2], MBChB, Prof. Tze Min Wah[1,2], MBChB, MSc, PhD, FRCR, EBIR, FESUR, FCIRSE, FHEA, PG Cert Clin Educ

[1]Leeds Institute of Medical Research at St James's, Faculty of Medicine and Health, University of Leeds

[2] Division of Diagnostic and Interventional Radiology, Institute of Oncology, St. James's University Hospital, Leeds

Email Addresses:

Dr. Vinson Wai-Shun Chan: V.W.Chan@leeds.ac.uk

Dr. Helen Hoi-Lam Ng: um16hln@leeds.ac.uk

Prof. Tze Min Wah: tze.wah@nhs.net

Corresponding Author:

Prof. Tze Min Wah

Department of Diagnostic and Interventional Radiology, Institute of Oncology, St. James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds LS9 7TF, UK. Tel.: +44 1132066043.

Conflict of interests:

Prof Tze Min Wah received research grant from HistoSonics, Johnson & Johnson, Boston Scientific and Angiodynamics as well as acting as consultant for Angiodynamics. Dr Vinson Wai-Shun Chan and Dr Helen Hoi-Lam Ng has no conflict of interests to report.

Keywords:

Ablation; clinical trial; renal mass; renal cancer

Abstract

Image-guided ablation (IGA) is a rapidly developing field in interventional oncology. There is some evidence suggesting IGA's non-inferiority compared to partial or radical nephrectomy for the treatment of small renal masses (SRM). However, these are mostly limited to retrospective cohort studies.

This review article outlines the evidence comparing IGA to partial nephrectomy by collating the different survival measures and evaluates the challenges of producing clinical trials and high-quality evidence. The main challenges are due to the heterogeneity of SRM, patient selection bias, unstandardised endpoint and outcomes, and the lack of global practice standards.

Despite the evidence thus far demonstrating that IGA stands as a non-inferior treatment modality for SRMs, exhibiting favourable short- and long-term outcomes, further robust research is needed to integrate ablation techniques into routine clinical practice with a multidisciplinary approach. There are emerging evidence to suggest randomised controlled trial in SRMs is possible and technologies such as histotripsy as well as the use of artificial intelligence in IGA.

Introduction

There has been a notable rise in the incidence of renal cell carcinoma (RCC) in the past 3 decades, this is likely attributed to the more frequent use of cross-sectional abdominal imaging. However, this has led to the increased incidental detection of asymptomatic small renal masses (SRM)[1].

Recognizing the predominantly slow-growing nature of most of these lesions, the approach to their management has shifted from the previously aggressive open radical nephrectomy (RN) to less invasive procedures such as laparoscopic and robotic partial nephrectomy (PN), further progressing to minimally invasive percutaneous image-guided thermal ablation (IGA)[2]. Additionally, active surveillance (AS) has emerged as a viable strategy[2,3].

While the latest guidelines from the American Urological Association (AUA) advocate PN as the recommended standard of care for SRM (≤4 cm; clinical stage T1a), they now also endorse AS and IGA as acceptable alternatives for selected patients with specific comorbidities and individual preferences[4]. Specifically, the two types of IGA recommended by the guidelines are radiofrequency ablation (RFA) and cryoablation. It is important to note that there are other modalities including microwave ablation (MWA) and non-thermal ablation such as irreversible electroporation (IRE) and high intensity focused ultrasound (HIFU).

This review article aims to outline the evidence for the role of IGA in the manage of patients with SRM, the challenges in developing high quality evidence for Image-guided ablation for SRM and future directions for IGA.

Evidence vs nephrectomy

Literature comparing image-guided ablation to partial nephrectomy for T1a patients are outlined in table 1 [5].

Overall Survival

Overall survival outcomes exhibit considerable variability in the literature, largely influenced by significant selection bias and patient-specific factors. Notably, a recent study by Lehrer et al. in 2023[6] adopted a restricted approach by including only patients aged over 75. Despite the relatively short mean follow-up period of approximately 22 months, this study demonstrated comparable overall survival between patients undergoing image-guided RFA and robotic-assisted PN. The emphasis on an elderly cohort highlights the potential benefits of IGA over PN, although AS has also become significantly more popular in this population.

Similarly, a more extensive investigation with a follow-up duration of up to 100 months reported no significant differences in overall survival rates among patients treated with image-guided cryoablation, RFA, or laparoscopic PN[7]. This study included a significantly older and comorbid cohort in the IGA group, yet overall survival outcomes are similar between the three modalities.

On the other hand, it is essential to acknowledge a pivotal 2019 study from the USA, which compared IGA with PN and found a significant superiority in overall survival in the PN group[8].Furthermore, a more recent comprehensive systematic review and meta-analysis revealed that patients undergoing PN had significantly better overall survival outcomes compared to those opting for ablative therapy (not limited to image-guided)[5]. The results from these should be interpreted with caution as selection bias in favour of PN due to patients' age is significant.

Cancer-specific survival

The same systematic review and meta-analysis has brought to light consistent findings of equivalence regarding cancer-specific survival (CSS) when comparing IGA with PN[5]. This pattern holds true across subgroup analyses and sensitivity assessments, particularly in studies with a follow-up duration of 5 years or longer. A noteworthy investigation utilizing the United States Surveillance, Epidemiology, and End Results (SEER) database, albeit lacking specification on the ablation approach (laparoscopic or image-guided), reported comparable cancer-specific survival between ablation and PN over a 9-year follow-up period involving more than 1,300 patients[9]. Additionally, extensive long-term studies conducted by Chan et al. [7]and Andrews et al.[8] consistently highlighted the similarity in CSS among patients undergoing image-guided cryoablation, RFA, and PN.

As for modalities currently not supported by the AUA guidelines, in particular the microwave modality, a 2020 study by Yu et al. in China, involving 1,955 patients, showed comparable CSS outcomes in individuals who underwent image-guided MWA compared to those who opted for PN[10].

These collective findings from diverse studies and populations provide robust support for the comparable efficacy of IGA and PN in preserving CSS, suggesting the developing role of IGA to achieve good oncological control comparable to PN.

Local-recurrence free survival (LRFS)

The existing evidence in the majority of studies consistently points towards IGA being associated with a significantly inferior LRFS compared to PN. However, it is crucial to contextualize this observation within the limitations of current research, which predominantly features studies with relatively short follow-up durations. A systematic review and meta-analysis have further revealed a substantially worse LRFS outcome in patients undergoing any form of IGA compared to those opting for PN (HR 2.55, 95% CI 1.68-3.88, $p<0.001$) [5]. It's important to note, however, that when scrutinizing only studies with a follow-up period exceeding 5 years in subgroup analyses, LRFS did not exhibit a significant difference between IGA and PN[5].

In more recent investigations, LRFS has consistently demonstrated no significant difference between patients treated with IGA or PN. Noteworthy studies, such as the 2018 South Korean study by Park et al.[11], reported that percutaneous RFA exhibited either significantly higher or equivalent LRFS rates compared to PN over a 20-month follow-up period ($p=0.029$). Similarly, studies by Chang et al.[12] and Olweny et al.[13] from China and the USA, respectively, both conducted over approximately 6 years, found LRFS to be similar between patients undergoing laparoscopic or image-guided RFA and those undergoing laparoscopic or open PN. A 2019 study by Anglickis et al.[14] comparing percutaneous MWA with open PN reported no recurrences in either group over a median follow-up of 40 months. Last but not least, long-term investigations by Chan et al.[7] and Andrews et al.[8] align in their findings of similar LRFS rates among patients undergoing IGA and PN. These collective outcomes emphasize the evolving landscape of LRFS comparisons, urging a cautious interpretation of the data and recognition of the advancements in IGA outcomes over time.

Metastasis-free survival (MFS)

The most recent systematic review in this domain has yielded a consistent observation—there is no discernible difference in MFS between patients treated with IGA and those undergoing PN[5]. Another pivotal study by Andrews et al. [8] stands as a cornerstone for the similarity in MFS outcomes among patients who opted for laparoscopic PN and those undergoing image-guided RFA or cryoablation. Echoing these findings, long-term investigations by Chan et al.[7], Chang et al.[12] and Olweny et al.[13] have reported akin MFS outcomes in patients treated with laparoscopic or image-guided RFA compared to open or laparoscopic PN. This aligns with earlier studies, such as that conducted by Lucas et al. [15] in 2008 in the USA, over a 2-year follow-up period. The consistency in MFS outcomes from various populations solidifies the robustness of this metric in the evaluation of treatment efficacy for SRM.

Post-operative complication rate

IGA emerges as a markedly less invasive alternative in stark contrast to PN, as substantiated by the aforementioned systematic review and meta-analysis[5] with a significantly lower risk of post-operative complications in patients undergoing any ablation (image-guided or laparoscopic), with a notable risk ratio of 0.72 (95% CI 0.55-0.94, p=0.004). Intriguingly, this advantage did not extend to a comparative advantage of image-guided ablation over partial nephrectomy, with both groups exhibiting a comparable incidence of minor and major complications[5]. It is paramount to note that this observation is circumscribed by a relatively small sample size and a limited number of studies reporting complication rates.

Complication rates, being a multifaceted metric, pose a challenge for the direct comparison of IGA and PN, particularly given the steep learning curve associated with both procedures. An insightful perspective emerges from the Nephron Sparing Treatment for Small Renal Masses (NEST) feasibility cohort-embedded randomized control trial (RCT)[16], where, among the 25 patients in each arm, only 12% of those undergoing image-guided cryoablation experienced post-operative complications, in contrast to 29% in the robotic PN group. The generalizability of this finding, however, is restricted by the trial's small sample size. Larger-scale studies present a more nuanced picture, with some demonstrating comparable complication rates between the two modalities. For instance, a study by Chan et al.[7] involving 238 patients found no significant difference in complication rates between image-guided RFA, cryoablation, and laparoscopic PN. This is reflective in another study encompassing 1955 patients, comparing image-guided MWA with laparoscopic PN, which revealed no significant disparity in complications between the two groups[10].

Contrastingly, findings from the 2018 SEER study[9] presented a noteworthy exception. The authors observed a significantly ($p<0.05$) higher complication rate in patients undergoing PN compared to IGA. Nonetheless, it is essential to acknowledge the study's limitations: the non-inclusion of the modality of PN and the amalgamation of various ablation approaches (open, laparoscopic, and image-guided) in the analysis.

Preservation of Renal function

Another notable advantage of IGA over PN lies in the preservation of renal parenchyma, consequently safeguarding renal function post-procedure. The recent systematic review and meta-analysis[5] underscored this advantage, revealing a significantly smaller change in post-operative estimated glomerular filtration rate (eGFR) among patients undergoing ablative (image-guided or laparoscopic) therapies compared to PN, with a mean difference of -7.42 (95% CI -13.15 to –1.70, p=0.01). However, this benefit did not persist when compared exclusively between PN and IGA, likely attributable to the scarcity of studies reporting pre- and post-operative eGFR.

Studies by Takaki [17] and Park [11] did not identify a significant difference in the drop in post-operative eGFR when comparing image-guided RFA and robotic or laparoscopic PN. Contrastingly, more recent investigations have presented divergent findings. Chan et al. [7] reported a significantly smaller drop in eGFR in patients undergoing image-guided cryoablation (-2.19%) and image-guided RFA (-3.44%) compared to laparoscopic PN (-9.35%) (p<0.001). Lehrer et al. [6] on another hand, found that patients undergoing image-guided RFA exhibited a significantly smaller increase in post-operative serum creatinine compared to those receiving robotic-assisted partial nephrectomy (1.9% vs. 10.1%, p=0.03). Looking at microwave technology, Yu et al.[10], compared 1995 patients receiving image-guided MWA and laparoscopic PN, found significantly smaller decline in renal function in patients undergoing MWA (p<0.01).

These findings suggest that advancements in different modalities of IGA show significantly better renal preservation compared to PN. It must be noted that the number of studies in the literature elucidating lifelong renal function outcomes in the two patient groups are limited, emphasizing the need for future research in this domain.

Challenges in developing high quality evidence for Image-guided ablation for small renal masses.

Heterogeneity of small renal masses (SRM), patient selection and endpoints

SRM is defined as an incidental, contrast-enhancing solid or cystic lesion of size ≤4cm. Conducting a clinical trial poses considerable challenges due to the characteristics of the SRM and the patient population. When standardising the inclusion and exclusion criteria, it would be particularly difficult to create a homogenous study as SRM would exhibit heterogeneity in terms of size, location, and characteristics. In particularly, the histological subtypes of SRMs make it challenging to create meaningful clinical studies without limiting to biopsy-proven histological subtypes. SRM can typically be representative of RCC, which typically possess malignant characteristics and oncocytomas or angiomyolipomas are both typically benign. In patients undergoing surgery for SRM, up to 30% of patients are reported to have a benign histology in oppose to a malignant histology [18] and up to 21% of patients undergoing cryoablation have a benign histology[19]. Renal tumour biopsies are found to be 90% diagnostic with minimal rates of complication and seeding[20,21]. It has also been shown that routine biopsies in a separate session prior to treatment reduces the rate of benign treatments in patients undergoing either surgery or IGA[22]. Despite this, biopsy prior to treatment is not standard practice in most centres. A high benign rate of SRM presents a challenge in clinical trials evaluating treatment options of SRM due to variable outcomes as a result of a variety of histology. It is noted in the SURAB (Surveillance versus ablation for incidentally diagnosed small renal tumours) feasibility RCT that the standardisation of pretreatment renal tumour biopsy is one of the challenges to recruitment in an RCT setting[23]. It is recommended that future clinical studies to include only SRM with a biopsy or histology proven RCC.

Patient selection bias is often another key factor that poses a challenge to clinical trials as the choice offered between IGA and PN is often influenced by patient-specific factors such as age, comorbidities, and individual preferences. As a result, more morbid patients with poorer prognoses are often only included in IGA arms but not PN arms, leading to significant bias in the literature[5].

Defining specific end points in measuring these outcomes can itself be challenging. While short-term outcomes, such as perioperative complications, can be easy to measure, defining relevant long-term endpoints, such as quality of life, renal function preservation, or overall survival, requires careful consideration. Cancer-specific survival, for example, proves challenging to employ as a reliable metric in research of SRM. The challenge stems from the inherent nature of the disease, where the overall mortality rate from renal cancer is relatively low. This low incidence of mortality leads to difficulty in detecting slight differences in cancer-specific survival rates, often necessitating a large sample size or a surrogate outcome for statistical significance. Another important endpoint that requires further evidence is the effect of IGA on renal function in patients with known chronic kidney disease and the safety to perform IGA in this group of patients. It is also important to utilise population-based data to establish long term renal function and cardiovascular outcomes of patients undergoing IGA or nephrectomy towards later stages of life.

Inherent Bias in Retrospective Data:

Whilst it is possible to avoid the issues with prospective trials by using retrospective data, retrospective data itself comes with bias issues related to data collection, patient selection, and treatment allocation. These could introduce inherent biases thus making the study difficult to draw replicable conclusions from.

Standardisation of Techniques:

IGA encompasses various modalities, as mentioned above, including but not limited to RFA, cryoablation and MWA. In ensuring the highest quality of trial, there would need to be a standardised protocol for these diverse modalities across the different study sites. Developing such protocols can be time consuming and difficult for teams to adopt to a new flow of work. Variations in operators' experience may also further impact the consistency of results. Ensuring adherence to study protocols, particularly in a multicentre trial, is essential for the reliability and validity of the results. Variability in adherence, otherwise, may introduce confounding factors that could compromise the internal validity of the trial. To do so, an international consensus panel may allow international experts and the multidisciplinary team to convene and outline the optimal indication, approach and research priorities for IGA, while a consensus panel on the research priorities for IGA is performed in 2010, this is now outdated and may warrant an up to date consensus meeting[24].

Future directions, research goals and anticipated developments in image-guided ablation of renal masses

Changing Landscape of Interventional Techniques and energy source:

Another exciting challenge would be the rapid advancements in technology and evolving interventional techniques within interventional oncology. The developments may introduce variability during the course of a clinical trial. Changes in the standard of care or the emergence of new technologies may influence the relevance of the study results over time, proposing a significant challenge in equipoise and applicability of trial results once long-term follow up has completed. With anticipation, histotripsy is a developing non-invasive therapeutic focused ultrasound which instead of utilising thermal energy, induces acoustic cavitation of the tissue cells and mechanical destruction of cancer cells[25]. This has been proven feasible and safe in the HOPE4LIVER trial for liver tumours [25] and the highly anticipated CAIN (The HistoSonics Investigational System for Treatment of Primary Solid Renal Tumors Using Histotripsy; NCT05432232) trial will inform us of the feasibility and the safety profile of histotripsy for renal masses[26].

Artificial Intelligence (AI) and robotics

The use of AI and robotic systems can theoretically standardise treatment and improve outcomes of IGA: guiding evaluation of the effectiveness in the form of multicentre trials. Indeed, the histotripsy system pioneered by HistoSonics incorporates a sophisticated robotic arm endowed with multifaceted manoeuvring capabilities[26,27]. Their design enables the administration of treatment in even the most challenging anatomical configurations, thereby facilitating therapeutic interventions in clinically demanding scenarios. Furthermore, Levy et al. reported a use of the CT-guided robotic system for percutaneous biopsy reduced radiation dose by about 90% compared to conventional CT-guided biopsy[28]. Despite this, these robotic systems are mostly in prototype and formal feasibility and safety trials are highly anticipated. Navigation systems are currently used in practice in conjunction with fusion images to improve accuracy and technical success of the procedure. Amalou and Wood have described a case of renal tumour ablation in a patient with von Hippel Lindau syndrome using an electromagnetic tracker and a fusion of real time ultrasound, CT and MRI images to aid targeting[29]. Furthermore, the application of radiomics, while not directly related to the intervention, can aid the diagnosis of renal cancer, especially the differentiation between angiomyolipoma, oncocytoma and RCC[30].

Nephron Sparing Treatment (NEST) Cohort-Embedded Randomised Controlled Trial

Most importantly, in order to overcome most challenges in developing optimal evidence for level one evidence in the form of an RCT is desperately needed. However, recruitment to randomised trials involving IGA has proven to be difficult, with multiple failed attempts in the past, noted particularly the SURAB trial[23] and the CONSERVE[31], due to difficulty in recruitment. The NEST (Nephron Sparing Treatment) is an interesting study in the form of a cohort embedded RCT proposed in attempt to compare image-guided ablation and robotic partial nephrectomy[32]. A cohort embedded RCT is an innovative established concept where a patient enrols into an observational cohort study for outcome measurement within the cohort study. Eligible patients are then randomised to be contacted to be invited to the undergo an intervention or not to be contacted and receive standard of care treatment[33]. In the NEST Trial all eligible patients (SRM < 4cm) are consented to join the cohort study with long term follow-up, biobanking, patient reported outcome measures and future randomised invites to consider new intervention or tests. Those that are eligible for both robotic partial nephrectomy or cryoablation are randomly allocated in a 1:1 ratio to be invited to undergo cryoablation as a treatment or not to be contacted and undergo standard treatment (robotic partial nephrectomy). This group forms the intention-to-treat and the randomised group to provide much needed answers on the effectiveness of IGA compared to partial nephrectomy. The NEST Feasibility trial was proved to be a success, with 200 patients consented to join the cohort. 25/50 of the eligible patients were invited to undergo image-guided cryoablation and 21 patients accepted the invitation, with 19 patients undergoing image-guided cryoablation and 29 patients undergoing partial nephrectomy ultimately. A further two patients were found not suitable to have cryoablation after being invited to undergo cryoablation and have had partial nephrectomy or active surveillance instead[33]. The full multicentre NEST trial is currently in planning and the launch is highly anticipated to provide much needed level one evidence in the area.

Conclusion

The evidence thus far demonstrates that IGA stands as a non-inferior treatment modality for SRMs, exhibiting favourable short- and long-term outcomes. To solidify its place in clinical practice, further robust research efforts are warranted to confirm its outcomes and efficacy across diverse patient populations. Clinicians are encouraged to adopt a comprehensive, multi-disciplinary approach when considering treatment options for patients. Addressing the challenges inherent in producing high-quality data for IGA necessitates overcoming obstacles such as the heterogeneity of SRMs, precise patient selection, standardised endpoints, outcome determination, and the establishment of global practice standards. Moreover, the integration of ablation techniques with emerging technologies such as histotripsy or artificial intelligence presents promising avenues for advancing the field of interventional oncology. Collaboration within multidisciplinary teams is paramount in enhancing outcomes for patients with SRM and producing much needed level 1 evidence in the area. Cohort embedded studies such as the NEST (Nephron Sparing Treatment) study is proven feasible, and the full study is highly anticipated.

Acknowledgements

None

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Author	Country of Study	Study Design	Comparison	Average Age (Years)	Average Tumour Size (cm)	Average R.E.N.A.L Nephrometry Score	Tumour Locations	Comorbidities	Number of Participants (Intervention/ Control)	Duration of Follow-up (Months)	Outcomes
Neves 2023 (NEST Study)	United Kingdom	Cohort-Embedded RCT	Percutaneous CRYO vs robotic-assisted PN	Mean [SD] CRYO: 58.5 (10.8) PN: 57.2 (8.8)	Mean [SD] CRYO: 29 (5) PN: 27 (6)	Cryo: Low: 5 (20%) Moderate: 19 (76%) High: 1(4%) PN: Low: 11 (44%) Moderate: 12 (48%|)| High: 2 (8%)	CRYO: A: 11 (44%) P: 10 (40%) X: 4 (16%) H: 0 (0%) PN: A: 9 (36%) P 14 (56%) X: 1 (4%) H 1 (4%)	CCI CRYO: >3: 0 (0%) ≤3: 25 (100%) PN: >3: 0 (0%) ≤: 25 (100%)	25/25	6 months	84% consent rate Post-oeprative complication rate: 12% (Cryo) vs 29% (PN).
Lehrer 2023	France	RCS	Percutaneous RFA vs robot-assisted PN	Mean [SD] RFA: 80.4 [3.7] PN: 79 [3.7]	Mean [SD] RFA: 2.7 [0.7] PN: 3.2 [0.9]	Mean [SD] RFA: 6.1 [1.3] PN: 3.2 [0.9]	NR	Renal function impairment: RFA: 12.1% PN: 5.6% Cardiovascular disease: RFA: 77.3% PN: 80.1% Other cancer: RFA: 37.9% PN: 5.6%	66/142	Mean [SD] RFA: 22 [15.5] PN: 22 [16.1]	Overall complication rate: Similar between two groups Increase in serum creatinine: Significantly higher in PN group 10.1% vs 1.9% (p=0.03) LRFS: 12.9% vs 4.8% (p=0.13) PFS: Similar (p=0.11) OS: Similar (p=0.08) DFS: Similar (p=0.09)
Chan 2022	United Kingdom	RCS	Percutaneous RFA/ CRYO vs laparoscopic PN	Median [IQR] CRYO: 72 [62-76] RFA: 73 [66-78] PN: 59 [49-67]	Median [IQR] CRYO: 2.85 [2.5-3.45] RFA: 2.8 [2.4 – 3.4] PN: 2.5 [2.1-3.0]	Median [IQR] CRYO: 6 [5-7] RFA: 6 [5-8] PN: 5[4-7]	NR	CCI : Median [IQR] CRYO: 3 [2-4.5] RFA: 4 [3-5] PN: 2 [1-4]	72 (Cryo)/ 87 (RFA)/ 79	Median [IQR] CRYO: 75.6 [66.8 – 86.5] RFA: 106.0 [61.2 – 135.1] PN: 72 [64.6 - 99.7]	No significant difference for OS, CSS, LRFS, MFS. Similar complication rate. Significantly better renal function preservation in CRYO and RFA compared to PN. (p<0.0001)
Yu 2020	China	Propensity-matched RCS	Percutaneous MWA vs laparoscopic PN	Mean [SD] Unmatched MWA: 63.2 [15.2] LPN: 50.9 [13.2] Matched MWA: 63.2 [15.2] LPN: 60.4 [14.1]	Unmatched MWA: 2.3 [0.5] LPN: 2.3 [0.8] p=0.86 Matched MWA: 2.3 [0.5] LPN: 2.3 [0.9] p=0 .67	NR	Tumour location unmatched MWA, LPN, matched MWA, LPN (IQR) 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)	CCI Median [Range] Unmatched MWA: 4.0 [2.3-4.0] LPN: 1.0 [0-3.0] Matched MWA: 4.0 [2.3-4.0] LPN: 1.0 [0-3.0]	185/185	Median [Range] MWA: 42.0 [23.5-69.3] LPN: 40.6 [25.1-63.4]	CSS: No significant differences between MWA and PN (p=0.24) OS and DFS: Worse in MWA (p=0.049; p=0.003) Decline in renal function: Lesser in MWA (p<0.01) Complications: No significant difference between MWA and PN (p=0.17)
Alam 2019	USA	Registry-based RCS (DISSRM)	Unspecified approach of PN, RN and ablation vs active surveillance	Median [IQR] AT: 71.8 [62-74.8] PN: 61.3 [52.9-67.3]	Median [IQR] AT: 2.1 [1.7-2.5] PN: 2.4 [1.8-3.2]	RENAL Nephrometry Score (%) Low Complexity (4-6)	NR	CCI (%) n (%) AT 0: 16 (59.3%) 1-3: 8 (29.6%)	27/231	Median [IQR] Full cohort: 36 [19.2-60]	OS and CSS : No significant differences between AT and PN (p=0.3; p=0.5)

						Intermediate Complexity (7-9) High Complexity (10-12) PN: 87 (68.5%) 30 (23.6%) 10 (7.9%) AT: 17 (89.5%) 2 (10.5%) 0 (0.0%)		≥4: 3 (11.1%) PN: 0: 146 (63.2%) 1-3: 80 (34.6%) ≥4: 5 (2.2%)			
Andrews 2019	USA	RCS	Percutaneous RFA or percutaneous CYRO vs PN in T1a	Median [IQR] PN: 62 [52-69] RFA: 72 [64-78] CYRO: 72 [65-79]	Median [IQR] PN: 2.4 [1.8-3.1] RFA: 1.9 [1.5-2.5] CYRO: 2.8 [2.4-3.4]	NR	NR	CCI Median [IQR] PN: 1 [0-2] RFA: 1 [0-3] CYRO: 2 [0-3]	360 (RFA: 180, CYRO: 187) /1055	Median [IQR] (Years) PN: 9.4 [7.2-11.9] RFA: 7.5 [4.9-11.6] CYRO: 6.3 [4.4-8.3]	OS: Superior in PN CSS, LRFS and MFS: No significant differences between the 3 groups
Anglickis 2019	Switzerland	RCS	Percutaneous Microwave thermal ablation vs open PN	Median [IQR] MWA: 75 [71-79] PN: 71.5 [70-75]	Median [IQR] MWA: 3.2 [2.35–3.4] OPN: 3 [IQR: 2.5–3.5]	MWA: 6 (IQR: 4.5–6) PN: 5 (IQR: 4–6)	MWA vs OPN Upper: 3 vs 5 Middle: 8 vs 4 Lower: 4 vs 9	CCI MWA: 7.5 [IQR: 5-10] PN: 5.2 [IQR: 5-6]	15/18	Median [IQR] MWA: 40 [34-37] PN: 40.10 [38-43]	Recurrence or metastasis: None seen in both MWA and PN Change in renal function: No significant differences between MWA and PN (p=0.30)
Kitley 2019	USA	Registry-based propensity-matched RCS (NCDB)	Non-specified ablative therapy vs PN vs RN	Median [IQR] Unmatched CYRO: 68 [59-75] PN: 58 [49-67] Matched CYRO: 66.5 [11.7] PN: 66.3 [11.4]	Mean [SD] Unmatched CYRO: 2.5 [7.6] PN: 2.4 [8.3] Matched CYRO: 2.5 [7.6] PN: 2.5 [8.2]	NR	NR	CCI (%) CYRO % vs PN (% Unmatched CYRO 0: 66 1: 24 2: 10 PN 0: 73 1: 21 2: 6 Matched CYRO 0: 66.1 1: 24.0 2: 9.3 PN 0: 65.2 1: 25.6 2: 9.9	Unmatched 6701/51135 Matched 6229/6229	NR	OS: Lower in CYRO on adjusted analysis (p<0.001)
Park 2018	South Korea	Propensity-matched RCS	Percutaneous RFA vs robotic PN	Mean [SD] RFA: 57.1 [13.1] PN: 57.7 [10.8]	Mean [SD] RFA: 2.1 [0.5] PN: 2.0 [0.6]	Mean [SD] RFA: 7.2 [1.5] PN: 7.1 [1.7]	Anterior: 67 Posterior: 59	ASA RFA: 1.8 ± 0.7 PN: 1.8 ± 0.3	63/63	Median [Range] RFA: 21 [1-65] PN: 24.6 [1-90]	LRFS: Lower in RFA (p=0.029) Change in renal function and complication rate: No

											significant differences between RFA and PN
Xing 2018	USA	Registry-based propensity-matched RCS (SEER)	Open or laparoscopic or percutaneous Thermal ablation vs non-specified PN	66-74 years: 367 (53.1%), 371 (53.5%) ≥75 years: 324 (46.9%), 320 (46.3%) n of TA (% TA), n of PN (% PN)	Mean [IQR] TA: 2.7 [1.4-3.9] PN: 2.8 [1.5-3.9]	NR	NR	CCI n(%) TA 0: 406 (58.5) 1: 183 (26.5) >2: 102 (14.8) PN 0: 400 (57.9) 1: 183 (26.5) >2: 108 (15.6)	691/691	Median TA: 44.8 PN: 44.6	9-yr CSS and OS: No significant differences between TA and PN (CSS: p=0.07) Complication rate: Higher in PN (p<0.05)
Liu 2017	China	RCS	Percutaneous RFA vs open or laparoscopic PN in T1	Median [Range] ccRCC PRFA: 68 [35-85] PN: 58.5 [23-83] nccRCC PRFA: 65.5 [33-84] PN: 55 [24-84]	Median (Range) ccRCC PRFA: 2.7 [1-4] PN: 2.9 [1-4] nccRCC PRFA: 2.4 [1-3.3] PN: 3.1 [1-4]	Median [Range] ccRCC PRFA: 8 [5–11] PN: 8 [5–11] nccRCC PRFA: 9.5 [5–10] PN: 7 [5–11]	NR	ASA Median [Range] ccRCC PRFA: 2 [1-3] PN: 1 [1-3] nccRCC PRFA: 2 [1-3] PN: 1 [1-3]	115/149	Median [Range] Full cohort: 78 [8-132]	10-year OS and DFS: Comparable between PRFA and PN Postoperative complications: No significant differences between PRFA and PN (ccRCC p=0.791, nccRCC p=0.577)
Chebab 2016	USA	RCS	Percutaneous CYRO (PCA) vs open or robot-assisted PN	Mean PCA: 69.1 OPN: 61.2 RPN: 59	Mean [Range] PCA: 2.11 [1-4] OPN: 2.59 [1.2-4] RPN: 2.32 [1.1-4]	Mean PCA: 6.48 OPN: 6.34 RPN: 5.67	NR	CCI PCA: 7.14 [SD ± 1.398 OPN: 5.0 ± 1.020 RPN: 4.98 ± 1.335	34/126	Mean Full cohort: 22.1	Complication rates: No significant differences between PCA vs OPN (p=0.0235) or vs RPN (p=0.348)
Larcher 2016	Canada	Registry-based RCS (SEER)	Laparoscopic or percutaneous local thermal ablation (LTA) vs laparoscopic or robotic PN	Median [IQR] LTA: 76 [71-81] PN: 72 [69-77]	25 (20-30)	NR	NR	CCI Median [IQR] LTA: 2.1 [0-3.6] PN: 2.0 [0-3.5]	514/1962	NR	Complication rate: Lower in LTA
Chang 2015	China	Propensity-matched RCS	Laparoscopic or percutaneous RFA vs open or laparoscopic PN	Mean [SD] RFA: 52.9 [13.9] PN: 52.8 [12.9]	Mean [SD] RFA: 3.0 [0.6] PN: 3.0 [0.7]	Mean [Range] RFA: 8.0 (6-10) PN: 8.0 (5-10)	NR	ASA Mean [Range] RFA: 1.7 [1.3] PN: 1.7 [1.3]	45/45	Median [Mean] RFA: 66 [67.6 +/- 6.0] PN: 72 [69.0 +/-12.9]	OS, CSS, DFS, LRFS, and MFS: No significant differences between RFA and PN Change in GFR: Significant difference (p=0.0001)
Olweny 2012	USA	RCS	Percutaneous or laparoscopic RFA vs open or laparoscopic PN	Median [IQR] RFA: 63.8 [56.3-69.1] PN: 54.8 [47.8-59.1]	Median [IQR] RFA: 2.1 [1.8-2.8] PN: 2.5 [1.7-3.1]	NR	NR	ASA, n RFA 1: 2 2: 21 3: 14 PN 1: 9 2: 21 3: 7	37/37	Median [IQR] RFA: 6.5 [5.8-7.1] PN: 6.1 [5.4-7.3]	5-yr OS, CSS, DFS, LRFS and MFA: Comparable between RFA and PN (p=0.31; p=0.31; p=0.78; p=0.96; p=0.35)
Takaki 2010	Japan	RCS	Percutaneous RFA vs PN	Mean [SD] RFA: 69.4 [9.6] PN: 64.0 [9.6]	Mean [SD] RFA: 2.4 [0.7] PN: 1.90 [0.7]	NR	Number [%] Right-sided RFA: 31 [60.8]	Comorbid disease n(%)	51/10	Mean [SD] RFA: 34.0 [23.2] PN: 26.0 [16.9]	OS: Lower in RFA CSS and DFS: Comparable in RFA and PN (p=0.13)

							PN: 7 [70] Central RFA: 24 [47.1] PN: 1 [10]	RFA No: 5 (9.8) Yes: 46 (90.2) PN No: 2 (20) Yes: 10 (80)			Change in renal function: Comparable in RFA and PN (p=0.73)
Lucas 2008	USA	RCS	RFA vs PN vs RN	Median [IQR] RFA: 61.5 [14] PN: 56.2 [19]	Mean [95%CI] RFA: 2.34 [2.18–2.51] PN: 2.63 [2.45–2.80	NR	NR	CCI, n RFA 0: 26 1-2: 35 >2: 21 PN 0: 39 1-2: 37 >2: 6	86/85/71(RN)	Median [IQR] RFA: 22.0 [26] PN: 24.0 [26] RN: 45.5 [44]	RFS and MFS: Similar in all groups
Stern 2007	USA	RCS	RFA vs open or laparoscopic PN	Mean [SD] RFA: 60.5 [13.5] PN: 56.4[12.5]	Mean [SD] RFA: 2.41 [0.70] PN: 2.43 [0.80]	NR	NR	NR	40/37	Mean [Range] RFA: 29.8 [13-42] PN: 46.7 [24-93]	3-yr RFS: Similar in RFA and PN (p=0.67) Major complications: 1 (PN) vs 3 (RFA) Minor complications: 2 (PN) vs 2 (RFA)
Hruby 2006	USA	RCS	Laparoscopic CYRO vs laparoscopic PN	Mean LCA: 68 LPN: 52 p=0.02	1.9 (Range 0.9-2.7)	NR	NR	NR	11/12	Mean LCA: 12 LPN: 11.3	Local recurrence: None found in both groups Complications: 6 patients experienced 9 complications in LPN group while none occurred in LCA group

Table 1 – Outline of studies comparing ablation to nephrectomy for small renal masses. Adapted from Chan et al. [5].