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INTERVENTIONAL

Partial nephrectomy versus ablative techniques for small renal masses: a systematic review and network meta-analysis

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Abstract

Purpose To compare partial nephrectomy (PN), radiofrequency ablation (RFA), cryoablation (CRA) and microwave ablation (MWA) regarding oncologic, perioperative and functional outcomes.

Material and methods The MEDLINE, EMBASE and COCHRANE libraries were searched for studies comparing PN, RFA, CRA or MWA and reporting on any-cause or cancer-specific mortality, local recurrence, complications or renal function. Network meta-analyses were performed.

Results Forty-seven studies with 24,077 patients were included. Patients receiving RFA, CRA or MWA were older and had more comorbidities compared with PN. All-cause mortality was higher for CRA and RFA compared with PN (incidence rate ratio IRR = 2.58, IRR = 2.58, $p < 0.001$, respectively). No significant differences in cancer-specific mortality were evident. Local recurrence was higher for CRA, RFA and MWA compared with PN (IRR = 4.13, IRR = 1.79, IRR = 2.52, $p < 0.05$ respectively). A decline in renal function was less pronounced after RFA versus PN, CRA and MWA (mean difference in GFR MD = 6.49; MD = 5.82; MD = 10.89, $p < 0.05$ respectively).

Conclusion Higher overall survival and local control of PN compared with ablative therapies did not translate into significantly better cancer-specific mortality. Most studies carried a high risk of bias by selecting younger and healthier patients for PN, which may drive superior survival and local control. Physicians should be aware of the lack of high-quality evidence and the potential benefits of ablative techniques for certain patients, including a superior complication profile and renal function preservation.

Key Points

• *Patients selected for ablation of small renal masses are older and have more comorbidities compared with those undergoing partial nephrectomy.*
• *Partial nephrectomy yields lower all-cause mortality, which is probably biased by patient selection and does not translate into prolonged cancer-free survival.*
• *The decline of renal function is smallest after radiofrequency ablation for small renal masses.*

Keywords Kidney neoplasms · Ablation techniques · Nephrectomy · Meta-analysis

Johannes Uhlig and Arne Strauss contributed equally to this work.

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Abbreviations

CRA Cryoablation
GFR Glomerular filtration rate
IRR Incidence rate ratio
MWA Microwave ablation
PN Partial nephrectomy
RFA Radiofrequency ablation

Introduction

The incidence of renal cancer, especially of small renal masses, has risen during the last decade [1, 2]. For primary treatment of small renal masses, guidelines recommend nephron-sparing surgical approaches, such as partial nephrectomy (PN) [3, 4].

Thermal ablation techniques are an alternative treatment option, mainly recommended for frail patients [3, 4]. The most widely applied thermal ablation techniques include radiofrequency ablation (RFA), cryoablation (CRA) and microwave ablation (MWA) [5].

A few reviews have evaluated oncologic and functional outcomes for selected comparisons of partial nephrectomy versus various thermal ablation techniques using traditional, pairwise meta-analysis approaches [6–8]. Still, to the best of our knowledge, there is no review using a network meta-analysis to compare partial nephrectomy versus all commonly implemented ablative techniques.

Network meta-analyses are a statistical advancement allowing for simultaneous assessment of multiple treatments in one analysis [9]. Benefits of network meta-analyses include increased statistical power and precision for comparisons of more than two treatments, incorporating both direct and indirect evidence [10, 11].

Thus, the aim of our study was to conduct a network meta-analysis comparing oncologic and functional outcomes after partial nephrectomy, radiofrequency, microwave and cryoablation for treatment of small renal masses.

Material and methods

Search strategy

This study was prospectively registered at PROSPERO (CRD 42018084320). In December 2017, a systematic literature search was conducted using the MEDLINE, EMBASE and COCHRANE libraries, unrestricted to publication date and language. The full search strategy is provided as supplemental material. Literature lists of review articles and conference proceedings were screened to identify additional publications.

Inclusion/exclusion criteria

Peer-reviewed studies were included if they fulfilled the following criteria: evaluation of PN, RFA, CRA or MWA for treatment of renal masses; comparative study design contrasting at least two different interventions; assessment of at least one of the following end points: all-cause mortality, cancer-specific mortality, local recurrence, complications or change in renal function. Retrospective and prospective studies were included.

Exclusion criteria were: studies on animals; reviews or meta-analyses; pooled results of two or more interventions; insufficient reporting on measures of dispersion (i.e., standard deviation) for changes in renal function. If several publications reported on the same patient cohort, only the most comprehensive study was included to satisfy the independency assumption of meta-analyses.

Data extraction

The following data were extracted independently by two blinded authors: author, year of study, study design, adjustment for potential confounders, type of intervention and separately for each intervention demographic patient variable as well as duration of follow-up. According to Rothman et al, studies that collected data on the intervention and covariates before end points occurred were categorized as prospective [12].

Study quality assessment

The Downs and Black instrument was used for study quality assessment by two independent authors, as recommended by Deeks et al [13, 14]. Study quality is evaluated on five distinct domains, reporting, external validity, bias, confounding and sample size, as a surrogate for statistical power. Sample size was rated 0-5 points, corresponding to < 20, 20-40, 40-80, 80-160, 160-320 and > 320 patients.

The total obtainable Downs and Black score ranged between 0 points (worst study quality) and 32 points (best study quality). Following recommendations of the Cochrane handbook, study quality was separately assessed for each of the five primary end points [15].

Statistical analyses

Any-cause mortality, cancer-specific mortality and local recurrence were evaluated as incidence of death from any cause, renal cancer or local recurrence per patient-month under observation (incidence rate ratio; IRR) multiplying mean follow-up time by patient numbers. Procedural complications were evaluated as the total number of intra- and post-intervention complications using the odds ratios (OR). If available, results of multivariable logistic regression models were included. Change in renal function was analyzed as change from the last pre-intervention to the most recent measurement such as the glomerular filtration rate (GFR) in ml/min/1.73 m^2. All ablative techniques were compared with partial nephrectomy, considered the reference treatment [3, 4].

For outcome comparison, a network meta-analysis approach was chosen: this method simultaneously evaluates treatment effectiveness combining direct and indirect evidence [16]. Random effects meta-analyses were selected because of the expected study heterogeneity from diverging patient populations and study designs.

The network's heterogeneity was tested using Higgins's I^2, with percentages above 75% rated as considerable heterogeneity [17]. The network consistency assumption was statistically assessed using Cochran's Q statistics and visually evaluated via net heat plots, depicting changes in heterogeneity in a matrix layout [18]. For each end point, interventions were ranked using frequentist "*p* score" methods [19]. The *p* scores indicate the extent of certainty that a given treatment is better than the average of competing treatments. Publication bias was visually assessed via funnel plots for all pairwise comparisons that included at least five individual studies.

All statistical analyses were conducted using R version 3.4.2 and RStudio version 1.1.383 implementing R-packages "meta" and "netmeta" [20–23]. *p* values are two-sided. An alpha level < 0.05 was considered statistically significant.

Results

Study characteristics

Of 2293 studies screened, 47 published from 2005-2017 fulfilled the inclusion criteria (Fig. 1). Characteristics of included studies are summarized in Table 1. A total of 24,077 patients were analyzed: 15,238 receiving PN, 6,618 receiving CRA, 1877 receiving RFA and 344 receiving MWA. Sixteen studies evaluated overall survival, 15 studies cancer-specific survival, 37 studies local recurrence, 36 studies complications and 21 studies renal function. Four studies were multi-arm trials with three treatment arms: two studies reported on PN, RFA and CRA [65, 66]; one study reported on RFA, MWA and CRA [31] and another study on MWA, CRA and PN [47]. The remaining 43 studies contrasted two treatments. Seven studies were available as congress abstracts only [25, 31, 40–59, 67]. Figure 2 summarizes the number of comparative studies separately for each end point.

The majority of studies were of retrospective design. Only 13 studies were conducted in a prospective manner [26, 29, 38, 39–51, 65]. Most studies did not account for potential confounding factors, except one study comparing PN with MWA in a prospective randomized controlled setting [42]. Another seven studies used matching procedures to adjust for confounders [29, 32, 33–54]. Two studies reported multivariable adjusted odds ratios for complications [43, 68].

Among those studies reporting patient age for different interventions, patients were youngest in the PN group with mean age 59 years compared with RFA (64.8 years), CRA (67.9 years) and MWA (64.2 years). Mean tumor size was comparable across intervention groups, with the largest

Fig. 1 Flow chart showing study inclusion and exclusion, adapted from the PRISMA statement

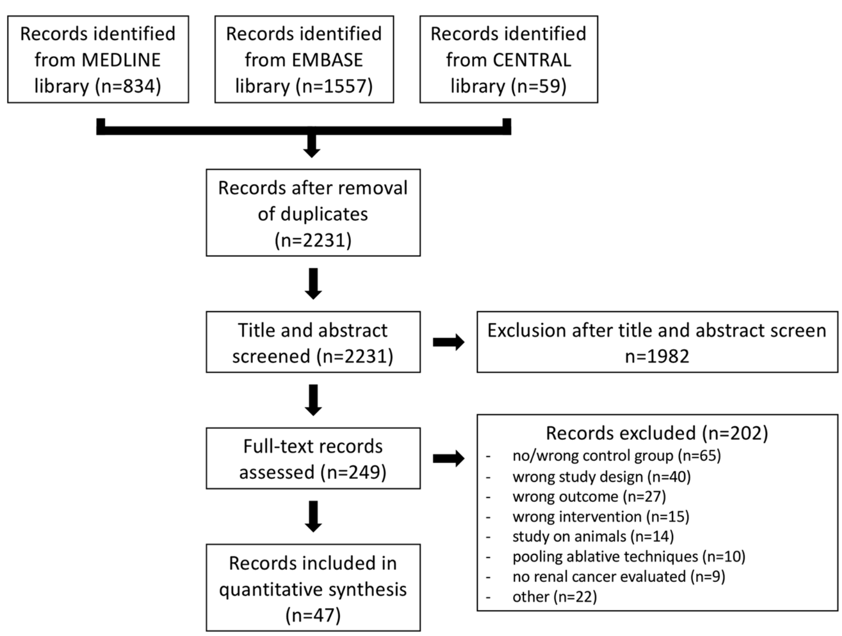

Table 1 Study characteristics of included studies

Author	Year	End points	Therapy	Number of patients	Mean age	Mean tumor size	Comorbidities	Follow-up (months)	Study design	Confounders adjustment
Abboud [24]	2017	Recurrence, complications	MWA	17	All 66	NA	NA	12	Retrospective	No
			RFA	61		NA	NA	41		
Alekseev [25]	2017	Complications	RFA	70	69	2.8	Prevalence of comorbidities with impact on renal function: 33%	NA	Retrospective	No
			PN	738	56	3	Prevalence of comorbidities with impact on renal function: 10%	NA		
Arnoux [26]	2013	Survival, recurrence, complications	RFA	36	79.2	2.8	Mean ASA score 3	22	Prospective	No
			PN	14	62.5	3.6	Mean ASA score 2	22		
Atwell [27]	2013	Recurrence, complications	RFA	222	68.8	1.9	NA	38	Retrospective	No
			CRA	163	68.2	2.3	NA	22		
Bensalah [28]	2007	Survival, recurrence, complications	RFA	40	62	2.3	53% ASA score ≥ 3	25	Retrospective	No
			PN	14	57	2.6	26% ASA score ≥ 3	15		
Bhindi [29]	2017	Complications, renal function	CRA	54	65	3.5	Median CCI: 2	47	Propensity score matched prospective	Yes (propensity score matching)
			PN	64	63	3.7	Median CCI: 2	47		
Bird [30]	2009	Survival, recurrence, complications, renal function	RFA	36	75	2.8	Mean ASA score 2.8	12	Retrospective	No
			PN	33	58	3.1	Mean ASA score 2.2	27		
Camacho [31]	2016	Recurrence, complications	RFA	35	All 65	1.95		61	Retrospective	No
			CRA	51		2.38		61		
			MWA	58		2.26		61		
Caputo [32]	2017	Survival, recurrence, complications	CRA	31	68	4.3	Mean CCI: 6, mean ASA score: 3	30	Prospective	Yes (propensity score matching)
			PN	31	68	4.6	Mean CCI: 6, mean ASA score: 3	13		
Chang [33]	2015	Survival, recurrence, complications, renal function	RFA	45	53	3	Mean ASA score 1.7	68	Retrospective	Yes (propensity score matching)
			PN	45	53	3	Mean ASA score 1.7	69		
Chang [34]	2015	Survival, recurrence, complications, renal function	RFA	27	64	4.7	Mean ASA score 2.1	66	Retrospective	Yes: adjusted OR for cancer recurrence RFA vs. PN: 1.77, 0.06 - 51.92
			PN	29	57	5.2	Mean ASA score 1.5	70		
Chehab [35]	2016	Recurrence, complications	CRA	37	69	2.1	Mean CCI 7.1	22	Retrospective	No
			PN	128	61	2.6	Mean CCI 5	28		
Cooper [36]	2015	Recurrence, renal function	RFA	9	51	4.1	NA	NA	Retrospective	No
			PN	9	53	2.7	NA	NA		
Danzig [37]	2015	Renal function	CRA	14	69	2.1	Mean CCI 1.2	18	Prospective	No

Table 1 (continued)

Author	Year	End points	Therapy	Number of patients	Mean age	Mean tumor size	Comorbidities	Follow-up (months)	Study design	Confounders adjustment
			PN	65	61	2.5	Mean CCI 0.8	18		
Desai [38]	2015	Survival, recurrence, complications	CRA	78	66	2.1	ASA 3/4 75%	25	Prospective	No
			PN	153	61	2.3	ASA 3/4 46%	6		
Emara [39]	2014	Survival, recurrence, complications, renal function	CRA	56	70	2.6	NA	31	Prospective	No
			PN	47	61	3.3	NA	17		
Evans [40]	2017	Complications	MWA	79	70	2.5	NA	20	Retrospective	No
			RFA	136	68	2.6	NA	57		
Foyil [41]	2008	Renal function	CRA	49	68	2.5	73% of patients with DM or hypertension	6	Retrospective	No
			PN	55	61	2.4	56% of patients with DM or hypertension	6		
Guan [42]	2012	Survival, recurrence, complications, renal function	MWA	48	46	3.1	Mean ASA score 2.4	32	Prospective RCT	Yes: RCT
			PN	54	46	2.8	Mean ASA score 2.5	36		
Guillotreau [43]	2012	Recurrence, complications, renal function	CRA	226	67	2.2	ASA 3/4 80%	45	Retrospective	Yes (multivariable logistic regression for complications)
			PN	210	58	2.4	ASA 3/4 51%	5		
Haber [44]	2011	Survival, recurrence, complications, renal function	CRA	30	61	2.6	Mean CCI 2.0, mean ASA score 2.8	43	Prospective	No
			PN	48	61	3.2	Mean CCI 1.7, mean ASA score 2.7	60		
Haramis [45]	2012	Survival, recurrence, complications	CRA	75	69	2	Mean ASA score 1.9	14	Prospective	No
			PN	92	59	1.9	NA	22		
Hegarty [46]	2006	Complications	CRA	161	66	2.6	Mean ASA score 2.9	36	Retrospective	No
			RFA	72	67	2.5	Mean ASA score 2.8	12		
Hinshaw [47]	2016	Recurrence	MWA	110	"MWA and CRA significantly older"	"Comparable tumor diameter"	"Significantly higher CCI for MWA and CRA versus PN"	14	Retrospective	No
			CRA	77				37		
			PN	182				29		
Ji [48]	2016	Recurrence, complications	RFA	105	64	2.2	Mean ASA score 2.3	78	Retrospective	No
			PN	74	57	2.9	Mean ASA score 1.7	82		
Kim [49]	2015	Survival, recurrence, complications, renal function	RFA	27	59	1.8	ASA 2: 48%	17	Retrospective propensity score matched	Yes (propensity score matching)
			PN	27	60	1.8	ASA 2: 4%	11		
Klatte [50]	2011	Recurrence, complications, renal function	CRA	41	75	2.5	Median CCI: 6	34	Retrospective	Yes (propensity score matching)
			PN	82	70	2.5	Median CCI: 6	34		

Table 1 (continued)

Author	Year	End points	Therapy	Number of patients	Mean age	Mean tumor size	Comorbidities	Follow-up (months)	Study design	Confounders adjustment
Liu [51]	2017	Complications	RFA	115	67	3.1	Median ASA score: 2	77	Retrospective	No
			PN	149	58	3.4	Median ASA score: 1	80		
Lucas [52]	2008	Recurrence, renal function	RFA	86	62	2.3	ASA score > 2: 21%	40	Retrospective	No
			PN	85	56	2.6	ASA score > 2: 6%	44		
Lughezzani [53]	2009	Complications	CRA	118	NA	2.4	NA	42	NA	No
			PN	83	NA	2.2	NA	36		
Mason [54]	2017	Renal function	CRA	389	68	3.2	Matching on comorbidities	3	Retrospective	Yes (propensity score matching)
			PN	389	67	3.1	Matching on comorbidities	3		
Omalley [55]	2007	Recurrence, complications	CRA	15	76	2.7	ASA 3/4: 62%	12	Retrospective	Yes: matching
			PN	15	76	2.5	ASA 3/4: 53%	10		
Olweny [56]	2012	Recurrence	RFA	37	64	2.1	ASA score 3: 38%	78	Prospective	No
			PN	37	55	2.5	ASA score 3: 19%	73		
Pantelidou [57]	2016	Recurrence, complications, renal function	RFA	63	61	2.1	ASA 3/4: 14%	48	Retrospective	No
			PN	63	54	2.9	ASA 3/4: 11%	18		
Panumatrassamee [58]	2013	Survival, recurrence, complications, renal function	CRA	43	64	2.2	ASA 3/4: 83%	41	Retrospective	No
			PN	33	60	2.9	ASA 3/4: 59%	17		
Psutka [59]	2013	Survival, recurrence	RFA	186	71	3.1	Mean CCI 5.6	58	NA	No
			PN	194	57	2.6	Mean CCI 3.5	65		
Raman [60]	2010	Recurrence, renal function	RFA	47	66	2.7	Median ASA score: 3	18	Retrospective	No
			PN	42	60	3.5	Median ASA score: 2	30		
Stern [61]	2007	Recurrence, complications	RFA	40	61	2.4	NA	30	Retrospective	No
			PN	37	56	2.4	NA	47		
Sung [62]	2012	Recurrence, complications, renal function	RFA	40	60	2.4	CCI > 2: 60%	37	Prospective	No
			PN	110	53	2.2	CCI > 2: 16%	37		
Takaki [63]	2010	Recurrence, complications, renal function	RFA	51	70	2.4	Comorbidities in 90% in patients	34	Retrospective	No
			PN	10	64	1.9	Comorbidities in 80% in patients	26		
Tanagho [64]	2013	Recurrence, complications, renal function	CRA	267	69	2.5	Mean CCI: 6.5	40	Retrospective	No
			PN	233	57	2.9	Mean CCI: 2.1	22		
Thompson [65]	2015	Survival, recurrence	RFA	180	71	2.9	Median CCI: 2.1	35	Prospective	No
			CRA	240	72	2.1	Median CCI: 2	17		
			PN	1383	60	2.5	Median CCI: 1.2	60		

Table 1 (continued)

Author	Year	End points	Therapy	Number of patients	Mean age	Mean tumor size	Comorbidities	Follow-up (months)	Study design	Confounders adjustment
Turna [66]	2009	Survival, recurrence, complications, renal function	CRA	36	64	2.5	ASA score > 3: 78%	24	Retrospective	No
			RFA	29	61	2.6	ASA score > 3: 69%	24		
			PN	36	60	3.7	ASA score > 3: 67%	43		
Wan [67]	2017	Recurrence, complications	RFA	31	NA	2.6	NA	34	Retrospective	No
			PN	97	NA	2.6	NA	34		
Weinberg [68]	2015	Complications	CRA	4241	Age > 70 years: 42%	NA	CCI > 2: 57%	NA	Prospective	Yes (multivariable logistic regression)
			PN	10,034	Age > 70 years: 16%	NA	CCI > 2: 46%	NA		
Youn [69]	2013	Recurrence, complications	RFA	41	59	2.3	ASA score 2: 71%	51	Prospective	No
			PN	14	54	2.4	ASA score 2: 68%	50		
Zechlinski [70]	2016	Recurrence, complications	MWA	32	74	3.1	NA	30	Retrospective	No
			CRA	126	67	2.3	NA	33		

ASA American Society of Anesthesiologists, *CCI* Charlson Comorbidity Index, *CRA* Cryoablation, *MWA* Microwave ablation, *NA* Not applicable, *PN* Partial nephrectomy, *RFA* Radiofrequency ablation

tumors treated via PN (2.84 cm), followed by MWA (2.74 cm), RFA (2.63 cm) and CRA (2.53 cm).

The degree and severity of comorbid diseases (measured by the Charlson Comorbidity Index [CCI] and American Society of Anesthesiologists [ASA] score) were higher among patients undergoing RFA, CRA or MWA compared with PN, except for randomized or matched study cohorts [29, 32, 33, 42, 50, 54, 55].

Histologic assessment of renal masses was reported in 42 of 47 included studies (89.4%). In 39 of these studies, benign and malignant renal masses were equally distributed among the different treatment arms. The studies by Lucas et al and Thompson et al demonstrated significantly larger proportions of benign renal masses in the ablation subgroups [52, 65]. Tanagho et al reported a significantly lower number of renal cell carcinomas in the CRA subgroup without specifying the malignancy of remaining histologic assessments [64].

Renal mass location, polarity, depth and aspect were provided in 22 of 47 included studies. Another nine studies reported the RENAL score and two studies the PADUA score as surrogates for renal mass location. Significant differences were reported in six studies: for the respective ablation subgroups, Alekseev et al described a higher proportion of exophytic masses [25], Arnoux et al a lower median RENAL score [26], Guillotreau et al a higher proportion of lateral masses [43], Haramis et al a lower proportion of exophytic masses [45], Tanagho et al a lower proportion of lateral, exophytic as well as mid-pole masses [64] and Turna et al a higher proportion of anterior masses [66].

CT-guided approaches were used in 16 studies on RFA, 8 studies on CRA and 3 studies on MWA. Laparoscopic approaches were chosen in 4 studies on RFA, 13 studies on CRA and 2 studies on MWA. The technical approach was not specified in 11 studies [25, 40, 47, 51, 54, 59, 65, 67, 36–63].

Study quality

Included studies were of moderate quality and showed relevant risk of bias with mean Downs and Black scores ranging between 21.7 and 22.6 of a maximum score of 32 points, depending on the end point. Only one study implemented a randomized design and yielded a high study quality of 27 points [42]. The main reasons for low study quality were inadequate adjustment for potential confounders and statistical analyses not accounting for differences in follow-up time between intervention groups. In tendency, the mean Downs and Black score was higher for complications and renal function. Study quality across the five end points is summarized in the supplemental tables.

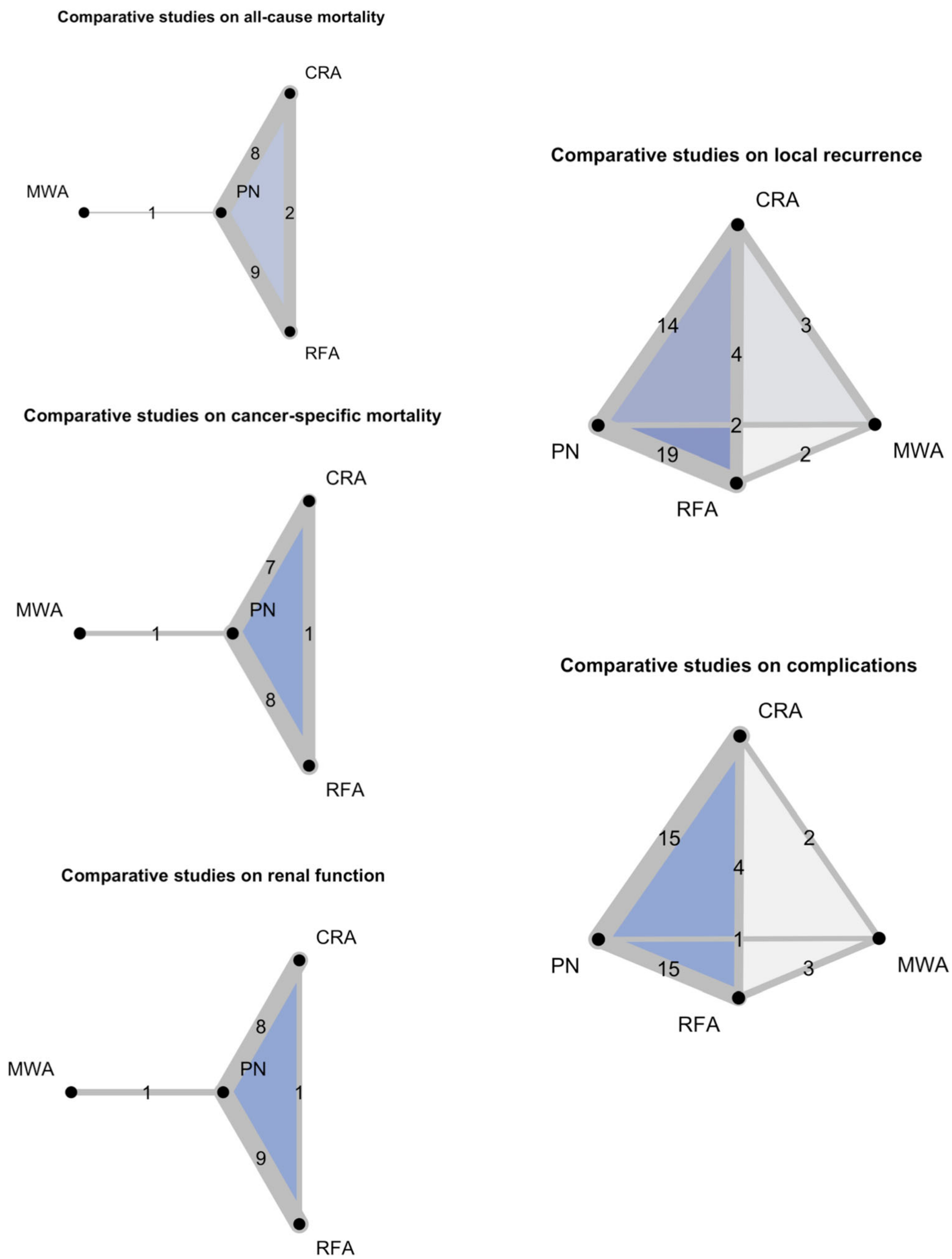

Fig. 2 Number of comparative studies for each end point. Pairwise comparisons are depicted by bars with bar thickness correlating to the number of studies. Shaded areas indicate multi-arm studies

Network meta-analysis: all-cause mortality

The network meta-analysis for the end point all-cause mortality was based on 20 pairwise comparisons from 16 distinct studies. Compared with PN, all-cause mortality was higher for CRA (IRR = 2.58, 95% CI: 1.92-3.46, $p < 0.001$) and RFA (IRR = 2.58, 95 % CI: 1.9-3.51, $p < 0.001$). No significant difference was found comparing PN and MWA (IRR = 3.8, 95% CI: 0.15-93.2, $p = 0.414$). A league table summarizing all pairwise comparisons between interventions is shown in Table 2; Table 3 highlights associated p scores.

There was no evidence for between-study heterogeneity (I^2: 0%, $p = 0.968$). The net-heat plot (supplemental material) and Cochran´s Q statistics did not reveal inconsistencies (Q = 0.61, df = 2, $p = 0.738$). A forest plot demonstrating all-cause mortality for PN versus CRA, MWA and RFA is depicted in Fig. 3.

Network meta-analysis: cancer-specific mortality

The network meta-analysis for cancer-specific mortality was based on 17 pairwise comparisons from 15 distinct studies. Comparing each intervention to partial nephrectomy, cancer-specific mortality did not show statistically significant differences, as summarized in Table 2. There was no evidence for between-study heterogeneity using the I^2 statistic (I^2: 0%, $p = 0.8283$). Neither the net-heat plot (supplemental material) nor

Table 2 League table showing pairwise comparisons for all interventions and the end points any-cause mortality, local recurrence, complications and renal function

End point		CRA (reference)	MWA (reference)	PN (reference)	RFA (reference)
All-cause mortality (IRR)	**CRA (comparator)**	-	0.68 (0.03-16.9), $p = 0.813$	2.58 (1.92-3.46), $p < 0.001$	1 (0.68-1.46), $p = 0.996$
	MWA (comparator)	1.47 (0.06-36.63), $p = 0.813$	-	3.8 (0.15-93.2), $p = 0.414$	1.47 (0.06-36.64), $p = 0.814$
	PN (comparator)	0.39 (0.29-0.52), $p < 0.001$	0.26 (0.01-6.47), $p = 0.414$	-	0.39 (0.29-0.53), $p < 0.001$
	RFA (comparator)	1 (0.69-1.46), $p = 0.996$	0.68 (0.03-16.93), $p = 0.814$	2.58 (1.9-3.51), $p < 0.001$	-
Cancer-specific mortality (IRR)	**CRA (comparator)**	-	1.79 (0.03-103.78), $p = 0.778$	2.27 (0.79-6.49), $p = 0.126$	1.12 (0.36-3.42), $p = 0.848$
	MWA (comparator)	0.56 (0.01-32.27), $p = 0.778$	-	1.27 (0.03-63.78), $p = 0.906$	0.62 (0.01-34.84), $p = 0.817$
	PN (comparator)	0.44 (0.15-1.26), $p = 0.126$	0.79 (0.02-39.82), $p = 0.906$	-	0.49 (0.2-1.23), $p = 0.128$
	RFA (comparator)	0.9 (0.29-2.75), $p = 0.848$	1.61 (0.03-90.02), $p = 0.817$	2.03 (0.81-5.08), $p = 0.128$	-
		CRA (reference)	**MWA (reference)**	**PN (reference)**	**RFA (reference)**
Local recurrence (IRR)	**CRA (comparator)**	-	1.64 (0.76-3.55), $p = 0.209$	4.13 (2.28-7.47), $p \leq 0.001$	2.31 (1.27-4.18), $p = 0.006$
	MWA (comparator)	0.61 (0.28-1.32), $p = 0.209$	-	2.52 (1.09-5.83), $p = 0.031$	1.41 (0.61-3.22), $p = 0.419$
	PN (comparator)	0.24 (0.13-0.44), $p < 0.001$	0.4 (0.17-0.92), $p = 0.031$	-	0.56 (0.36-0.86), $p = 0.009$
	RFA (comparator)	0.43 (0.24-0.79), $p = 0.006$	0.71 (0.31-1.63), $p = 0.419$	1.79 (1.16-2.76), $p = 0.009$	-
		CRA (reference)	**MWA (reference)**	**PN (reference)**	**RFA (reference)**
Complications (OR)	**CRA (comparator)**	-	2.55 (1.12-5.81), $p = 0.027$	0.67 (0.48-0.92), $p = 0.013$	0.75 (0.47-1.2), $p = 0.231$
	MWA (comparator)	0.39 (0.17-0.9), $p = 0.027$	-	0.26 (0.11-0.6), $p < 0.001$	0.3 (0.12-0.71), $p = 0.006$
	PN (comparator)	1.5 (1.09-2.06), $p = 0.013$	3.82 (1.67-8.72), $p < 0.001$	-	1.13 (0.75-1.69), $p = 0.559$
	RFA (comparator)	1.33 (0.83-2.12), $p = 0.231$	3.39 (1.41-8.13), $p = 0.006$	0.89 (0.59-1.33), $p = 0.559$	-
		CRA (reference)	**MWA (reference)**	**PN (reference)**	**RFA (reference)**
Renal function (MD of GFR)	**CRA (comparator)**	-	5.06 (-5.36-15.48), $p = 0.341$	0.66 (-3.18-4.51), $p = 0.736$	-5.82 (-11.1--0.55), $p = 0.03$
	MWA (comparator)	-5.06 (-15.48-5.36), $p = 0.341$	-	-4.4 (-14.08-5.28), $p = 0.373$	-10.89 (-21.22--0.55), $p = 0.039$
	PN (comparator)	-0.66 (-4.51-3.18), $p = 0.736$	4.4 (-5.28-14.08), $p = 0.373$	-	-6.49 (-10.1--2.87), $p < 0.001$
	RFA (comparator)	5.82 (0.55-11.1), $p = 0.03$	10.89 (0.55-21.22), $p = 0.039$	6.49 (2.87-10.1), $p < 0.001$	-

CRA Cryoablation, *GFR* Glomerular filtration rate, *IRR* Incidence rate ratio, *MD* Mean difference, *MWA* Microwave ablation, *OR* Odds ratios, *PN* Partial nephrectomy, *RFA* Radiofrequency ablation

Table 3 *P* scores ranking interventions for each end point, indicating the extent of certainty that a given treatment is superior to the average of all competing treatments (1: highest certainty)

	PN	CRA	RFA	MWA
All-cause mortality	0.9310	0.3651	0.3636	0.3402
Cancer-specific mortality	0.8065	0.5519	0.3496	0.2920
Local recurrence*	0.9933	0.0359	0.5973	0.3735
Complications*	0.0956	0.6305	0.2797	0.9943
Renal function*	0.3939	0.4922	0.9884	0.1255

*After sensitivity analyses as described in detail in the corresponding paragraphs

Cochran's Q statistics demonstrated inconsistencies (Q = 2.13, df = 2, $p = 0.3448$). Figure 3 provides a forest plot comparing interventions with PN.

Network meta-analysis: local recurrence

A total of 36 studies with 44 pairwise comparisons contributed to the network meta-analysis on the end point local recurrence.

The initial network meta-analysis showed that local recurrence was higher for CRA (IRR = 2.76, 95% CI: 1.5-5.08, $p < 0.001$) and RFA (IRR = 1.73, 95% CI: 1.05-2.84, $p = 0.03$) compared with PN, while differences did not reach statistical significance for MWA (IRR = 1.81, 95% CI: 0.67-4.93, $p = 0.244$). No relevant and statistically significant heterogeneity was evident (I^2: 29.4%, $p = 0.6784$), but the net heat plot indicated network inconsistencies supported by Cochran's Q statistics (Q = 28.83, df = 9, $p < 0.001$). Visual assessment of the net heat plot (supplemental material) suggested that the design contributing most to the network's inconsistencies were three-arm studies contrasting PN, CRA and RFA [65, 66]. After exclusion of these studies, no network inconsistencies or heterogeneity was evident (supplemental material; Q = 10.18, df = 7, $p = 0.179$; I^2: 0%, $p = 0.973$).

Higher local recurrence rates for CRA, RFA and MWA compared with partial nephrectomy were observed in the reduced network meta-analysis, as shown in Fig. 3 and the corresponding league table (Table 2). The *p* scores are provided in Table 3.

Network meta-analysis: complications

A total of 36 studies with 40 pairwise comparisons evaluated complications of renal interventions.

Compared with PN, the likelihood of complications was lower for CRA (OR = 0.63, 95% CI: 0.43-0.93, $p = 0.02$) and MWA (OR = 0.43, 95% CI: 0.19-1, $p = 0.05$), while differences did not reach statistical significance for RFA (OR = 0.69, 95% CI: 0.44-1.09, $p = 0.113$). Moderate heterogeneity was observed (I^2: 59.9%, $p = 0.003$). The net heat plot suggested that the designs contributing most to network inconsistencies (Q = 34.67, df = 7, $p < 0.001$) compared CRA, PN and RFA as well as MWA and RFA (supplemental material). Sensitivity analyses were conducted excluding the studies by Turna et al and Evans et al [40, 66], resulting in no higher-degree network inconsistencies (Q = 5.27, df = 5, $p = 0.384$; supplemental material). Only moderate heterogeneity was noted in the network meta-analysis after sensitivity analyses (I^2: 42.2%, $p = 0.004$).

The reduced network meta-analysis showed lower likelihood of complications for CRA and MWA compared with PN, as depicted in Table 3 and Fig. 3.

To further assess potential sources of heterogeneity, congress abstracts were excluded [25, 31, 40–59, 67]. Still, significant heterogeneity was evident after study exclusion (I^2: 44.1%, $p = 0.003$).

Network meta-analysis: renal function

Renal function was evaluated by a total of 17 studies with 19 pairwise comparisons.

Decline of renal function was lower for RFA versus PN (mean difference MD = 5.31, 95% CI: 1.77-8.85, $p = 0.003$). There was no significant difference in renal function comparing PN and CRA (MD = -0.19, 95% CI: -3.94-3.56, $p = 0.921$) or MWA (MD = -4.4, 95% CI: -14.5-5.7, $p = 0.393$). There was considerable heterogeneity between studies (I^2: 91.8%, $p < 0.001$). The net heat plot showed that the design contributing most to network inconsistencies (Q = 21.89, df = 2, $p < 0.001$) compared CRA, PN and RFA (supplemental material). After exclusion of the three-arm study by Turna et al, only direct comparisons were available in the network (a net heat plot could thus not be implemented). Even after study exclusion, considerable and statistically significant heterogeneity was evident ($I^2 = 91.9\%$, $p < 0.001$).

Results of the network after sensitivity analyses supported our initial results, as demonstrated in the forest plot (Fig. 3) and league table (Table 2). Corresponding *p* scores are shown in Table 3.

Publication bias

Among all end points, only the comparison of CRA and RFA versus PN yielded enough individual studies to allow for assessment of publication bias. Visual assessment of the funnel plots did not indicate marked asymmetries, as shown in the supplemental material.

Discussion

So far, there is no comprehensive review on the distinct nephron-sparing techniques for treatment of small renal masses regarding oncologic, perioperative and functional outcomes.

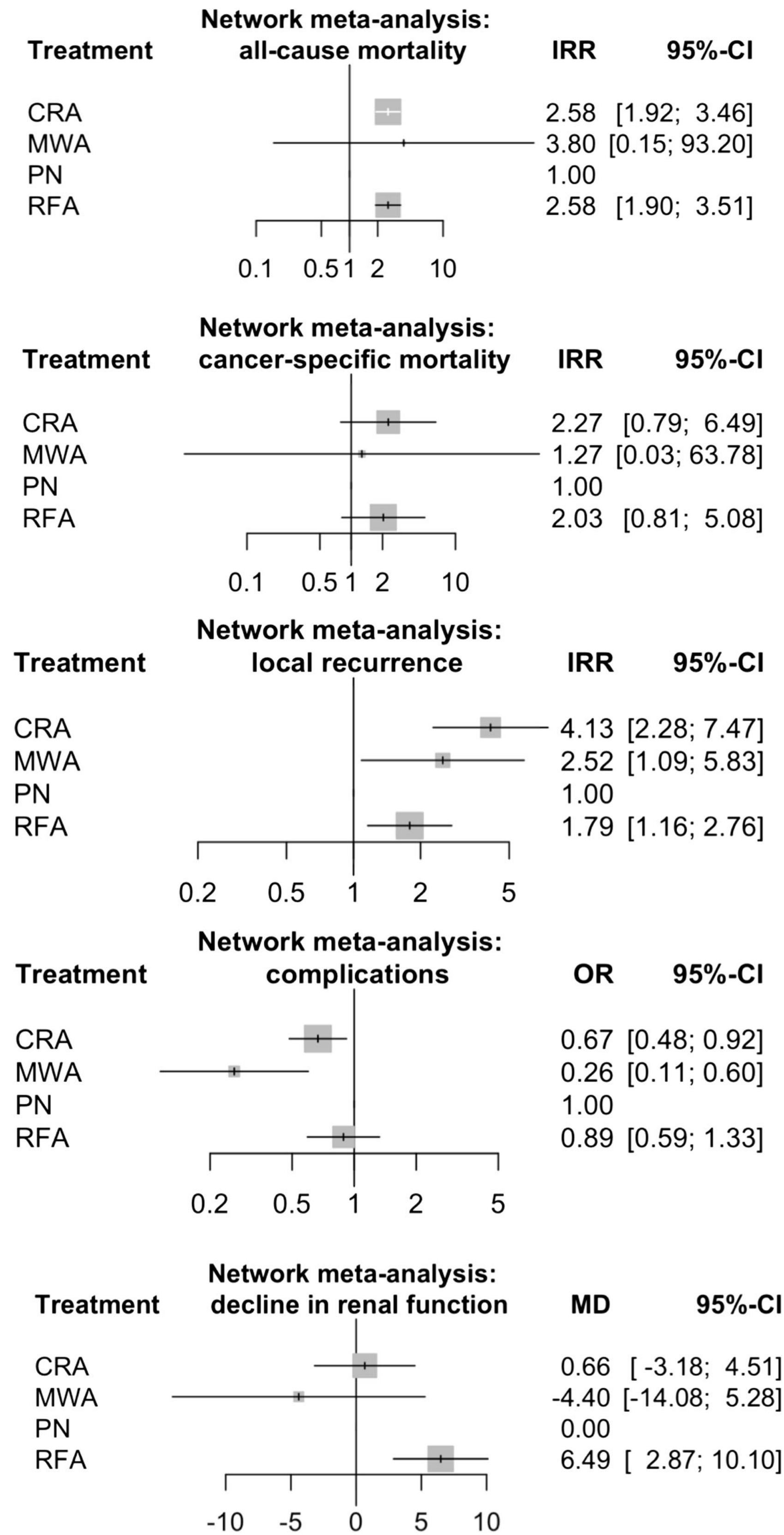

Fig. 3 Forest plots of the pooled estimates for the end points all-cause mortality, local recurrence, complications and renal function. PN (partial nephrectomy) is considered the reference category versus CRA (cryoablation), MWA (microwave ablation) and RFA (radiofrequency ablation). *IRR* incidence rate ratio, *OR* odds ratio, *MD* mean difference in GFR

Using a network meta-analysis approach, our review shows that no intervention consistently outperforms all alternatives. In general, patients treated by PN were younger and had fewer or less severe comorbidities, except for randomized or matched studies, probably reflecting current guidelines [3, 4]. Treatment choice was mostly based on surgeons' and patients' preferences, as well as surgical risk. Thompson et al and Youn et al detailed patient selection for RFA based on peripheral tumors with diameter < 3 cm and without involvement of the collecting system, renal calyx or major vessels [65, 69]. Although larger tumors tended to be treated via PN, tumor diameter was comparable across the different interventions, with mean diameters ranging from 2.84 cm (PN) to 2.53 cm (CRA). Renal mass location, polarity, depth, aspect and nephrectomy scores were only provided by 33 of 47 included studies, of which 6 reported statistically significant differences between the PN and ablation subgroups. In only three of those studies could significant discrepancies in renal mass parameters have favorably biased ablation outcomes, for example, reporting a higher proportion of peripherally located renal masses in the ablation versus PN subgroup that might yield lower complication rates [25, 26, 43].

Most studies failed to adjust for key confounders and were conducted retrospectively. Only ten publications used an adequate study design or statistical methods to control for age and comorbidities. Accordingly, the overall study quality was only moderate, yielding a high risk of bias. In particular, results on all-cause mortality and local control carry strong potential bias according to patient age and comorbidities.

Partial nephrectomy was superior to RFA and CRA concerning all-cause mortality, whereas no differences were found comparing ablative techniques between each.

A surrogate for the degree of confounding by patient age and comorbidities might be given by studies that adjust for key confounders: here, no mortality differences for PN and ablative techniques were observed. One prospective, randomized trial comparing MWA to PN by Guan et al reported no differences in all-cause mortality (3-year overall survival 91.3% versus 96%, $p = 0.5414$) [42]. Accordingly, Chang et al and Kim et al demonstrated no difference in all-cause mortality for RFA versus PN using propensity score matching [33, 49]. Caputo et al showed a numerically higher proportion of deaths among patients undergoing CRA versus PN after propensity score matching, but results failed to reach statistical significance because of longer CRA follow-up (IRR = 5.63, 95% CI: 0.32-100, $p = 0.359$) [32].

Furthermore, network meta-analyses of cancer-specific mortality did not show significant differences among all interventions. They corroborate the concern that differences in all-cause mortality might be driven by older and frail patients rather than factors associated with treatment and the renal mass itself.

Local recurrence was lower for PN compared with RFA, CRA and MWA. The heat sink effect associated with thermal ablation might be one explanation: especially for hypervascularized renal masses or those adjacent to major vessels, thermal effects might dissipate [71]. Here, target temperatures can be insufficient for complete ablation. On the other hand, age > 60 years is a predictor for local recurrence of renal cell carcinoma [72]. Thus, higher patient age among the thermal ablation patients observed in our review may at least partially explain the higher recurrence rates.

Our review included studies reporting on ablation and PN for both malignant and benign renal masses, the former accounting for the majority of lesions. Therefore, recurrence rates reported in our meta-analysis might be an underestimation of those for malignant lesions. Further, three studies reported a higher proportion of benign lesions in the ablation subgroups, which might have slightly distorted our results in favor of ablative techniques.

Overall complications were less likely for CRA and MWA compared with PN. Among the different thermal ablation techniques, MWA demonstrated the lowest complication rates, although only a small number of studies evaluated this technique. Patient age and comorbidities have been described as clinically relevant predictors of complications following surgical treatment of localized kidney cancer [73]. These findings are in line with the literature, showing low CRA operation time and estimated blood loss [8].

Assessing complication rates, the elderly and more comorbid population undergoing thermal ablation has to be highlighted, underlining the high tolerability and low risk-profile of ablative approaches. However, the exact location of the renal masses was unavailable for most publications.

Renal function preservation is one of the key outcomes after kidney intervention: Studies suggest decreased survival associated with a deterioration of renal function [74, 75]. All interventions were associated with a net decrease in renal function after treatment, with the lowest deterioration of renal function for RFA, which might be associated with its mode of action [76]. Greater decline of renal function in PN patients might partly be attributable to renal vessel clamping, resulting in renal ischemia [77]. Still, our results on renal function are limited by the comparably small number of studies, non-standardized time of GFR assessment and missing adjustment for baseline GFR values.

Our findings are contradictory to a recent meta-analysis reporting no differences in renal function change after PN versus thermal ablation, although a tendency toward higher preservation among thermal ablation patients was evident [7]. However, the authors pooled distinct thermal ablation techniques in one analysis group and might therefore have failed to identify technique-specific discrepancies.

Our review is not devoid of limitations. Most included studies were conducted in a retrospective manner, increasing risk of bias and limiting study quality. To obtain a comprehensive review and unbiased estimates, seven abstracts were included in our meta-analysis that did not provide a high level of detail, resulting in low study quality. Missing statistical adjustment for confounders, in particular patient age and comorbidities, may have distorted our results, especially for all-cause mortality. Further, only a small number of studies evaluated renal function with inconsistent follow-up periods, resulting in a heterogeneous network. Finally, the included studies did not provide sufficient information to compare laparoscopic and CT-guided ablative techniques, which might lead to residual bias in our presented results. Future reviews should address not only ablative techniques but also chosen approaches to enhance clinical decision-making processes for small renal masses.

So far, comparisons between RFA, CRA and MWA have not been established. Our study is the first review to evaluate nephron-sparing approaches for small renal masses using a network meta-analysis approach with a combination of direct and indirect evidence. For the first time, pooled effect sizes for different outcomes are presented to facilitate individual treatment decisions. The large number of studies and patients strengthen our results.

Conclusion

Our review indicates that PN is associated with higher overall survival and local control over ablative therapies, but results did not translate into significantly better cancer-specific mortality. In general, ablative therapies were superior to PN regarding complications and renal function. Consistently, patients treated by PN were younger and had less comorbidity compared with thermal ablation. The majority of studies carried a high risk of bias. In particular, selection of younger and healthier patients for PN may drive superior survival and local control. Physicians should be aware of the lack of high-quality evidence for preferring PN over thermal ablation for small renal masses. Potential benefits and harms associated with the different nephron-sparing approaches must be considered for each patient individually.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Annemarie Uhlig.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry Three of the authors have significant statistical expertise.

Informed consent Written informed consent was not required for this study because of the meta-analysis study design.

Ethical approval Institutional Review Board approval was not required because of the meta-analysis study design.

Study subjects or cohorts overlap Study subjects or cohorts have been previously reported as detailed in the references.

Methodology
• observational

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