Record and Appraisal of Endophytic Tumor Localization Techniques in Minimally Invasive Kidney-Sparing Procedures. A Systematic Review

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Purpose: Review and efficacy assessment of techniques used for intraprocedural endophytic renal mass localization.

Materials and Methods: Advanced search was carried out on PubMed, Cochrane Library, Web of Science and Google Scholar databases up to August 2020. Eligibility criteria were set, according to PRISMA statement. OR (95 % CI) for identification or technical success, positive margins and recurrence, were calculated for completely endophytic tumors. Risk of Bias was evaluated using ROBVIS tool.

Results: 77 studies were used for result synthesis, including 1,317 endophytic tumors, with 758 of them completely endophytic. 356 endophytic tumors were treated laparoscopically and 598 robotically, using ultrasound-based methods, transarterial embolization, dual-source CT, invasive signage, 3D printing, and augmented reality variations. Identification success was 97.8-100%, positive margins 0-12.5 % (completely endophytic: 95 % CI; 0.255-1.971, OR 0.709 in laparoscopic, 95 % CI ; 0.379-3.109, OR 0.086 in robotic partial nephrectomy), recurrences 0-3.9 % (completely endophytic: 0 recurrences in laparoscopic, 95 % CI ; 0.0917-2.25, OR 0.454, in robotic partial nephrectomy), and complications 0-60 % . 363 were treated with ablation techniques using CT-based methods, thermal monitoring, transarterial embolization, ultrasound guidance and invasive signage. Technical success was 33.4-100 % (completely endophytic: 95 % CI ; 0.00157-2.060, OR 0.0569 for invasive and 95 % CI ; 0.598-13.152, OR 2.804 for non-invasive localization techniques) and recurrences were 0-20%.

Conclusion: Ultrasound-based techniques showed acceptable identification success and oncologic outcomes in the laparoscopic or robotic setting. Augmented reality, showed no superiority over conventional techniques. Near infrared fluoroscopy with intravenous indocyanine green, was incapable of endophytic tumor tracking, although when administered angiographic, results were promising, along with other embolization techniques. Percutaneous hook-wire or embolization coil signage, aided in safe and successful tracking of parenchymal isoechoic masses, but data are inadequate to assess efficacy. CT-guidance, combined with ultrasound or thermal monitoring, showed increased technical success during thermal ablation, unlike ultrasound guidance that showed poor outcomes.

Keywords: endophytic, kidney, laparoscopy, neoplasms, robotic surgical procedures, systematic review

INTRODUCTION

Kidney-sparing procedures overrun radical nephrectomy for treating small renal masses. European Association of Urology guidelines 2019, recommend partial nephrectomy for T1 renal cell tumors(1). Not only kidney preservation is important but also maintenance of maximum parenchyma for better functional outcomes, especially in patients with impaired renal function, comorbidities or bilateral tumors(2), indicating a shift from kidney to nephron-sparing procedures. Minimally invasive nephron-sparing procedures were stratified by Gill 2003(3) into three categories: excision, probe ablation, and non-invasive ablation. Excision methods include surgeries such as laparoscopic or robotic-assisted partial nephrectomy(4). Probe ablation methods include RFA, Cryoablation, MWA and IRE (5,6). Finally, non-invasive ablation procedures include HIFU and stereotactic body radiation ablation(5).

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Table 1. Summary of results from studies regarding Laparoscopic-assisted Partial Nephrectomy (LPN) for endophytic tumors.

Overall mean Follow-up months.	39.2	NA	34	6.32	3	26	NA	NA	16	27	NA	NA	NA	6	12	17	NA	18	NA	16	NA	1
Recurrence n.(%)	0	0	0	0	NA	0	NA	NA	0	0	NA	NA	NA	NA	0	0	NA	0	NA	0	0	0
Complications n.(%)	10(19.6)	7(15.2)[b]	2(18)	NA	2(25)	68(18.7)	13(23.6)[d]	19(60)[f]	9(47.4)	NA	NA	NA	0[i]	NA	2(13,3)[j]	0	0	NA	NA	0	0	0[m]
Positive margins n.(%)	1(1.96)	0	1(9)	0	1(12.5)	2(5.4)	0	NA	2(10.5)	0	0	0	0	0	0	0	0	0	NA	0	0	0
Mean endophytic tumor size	25	24.2	16	NA	37	26	23	NA	23.1	NA	NA	NA	27.8	NA	27	NA	38	NA	NA	33	16	NA
identification success n.(%)	51(100)	46(100)	11(100)	2(100)	8(100)	41(100)	55(100)	NA	NA	3(100)	6(100)	15(100)	5(100)	8(100)	15(100)	10(100)	10(100)	25(100)	1(100)	1(100)	1(100)	NA
identification method	IOUS	IOUS	IOUS	IOUS and Hydro-Jet excision	IOUS	IOUS	IOUS	IOUS	IOUS	IOUS and perc needle delineation	AR: 3D reconstruction manual registration	AR: 3D reconstruction manual registration	3D printing physical kidney model navigation	AR: 3D reconstruction manual registration	AR: 3D reconstruction manual registration combined with ILUS aid	AR: manual registration with CBCT and fiducials	AR: Manual registration with CB imaging no fiducials	DSCT angiography	ROLL	Perc Hook-Wire	Perc Hook-Wire	Blue dye embolization
Laparoscopic technique	LPN	retroLPN	retroLPN	LPN	Unclamped hand-assisted LPN	transLPN	retroLPN and transLPN	transLPN	transLPN and retroLPN	LPN	transLPN or retroLPN	LPN	transLPN or retroLPN	3D-retroLPN	retroLPN	transLPN	retroLPN	retroLPN	transLPN	transLPN	transLPN	LPN
Study arms	RAPN VS LPN for completely	TIT VS exophytic	Single arm	Single arm	Single arm	TIT VS any exophytic component	Intraparenchymal VS any other tumor	Single arm	Exophytic VS mesophytic VS Endophytic	LPN VS LRN VS lap Cryoablation	3D reconstruction VS no 3D reconstruc	Single arm	Single arm	3D-MIRGS VS no 3D MIRGS	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm	Single arm
multivariate regression: Statistically significant covariates/outc	R.E.N.A.L. Score/ Pentafecta.	NA	NA	NA	NA	NA	No covariates significant / complicati	NA	NA	NA	Parenchymal mass preserved/ renal function	NA	NA	NA	NA	NA	NA	Tumor location and number of clamped	NA	NA	NA	NA
Endophytic tumors n./total tumors n.	61/112	46/583[a]	11/11[c]	2/35	8/8	41/402[n]	55/800[0]	32/184[e]	19/123[g]	3/50	6/49	15/91[h]	5/5	8/35	15/15	NA/10[l]	10/10	25/125[k]	1/3	1/1	1/1	7/50
Study type	Retrospective compara	Retrospective case-control	Retrospective case-	Prospective case-series	Retrospective case-series	Retrospective case-	Retrospective comparati	Prospective case-series	Retrospective comparativ	Retrospective comparative	Retrospective case-control	Retrospective case-series	Retrospective case-series	Retrospective case-control	Retrospective case-series	Retrospective case-series	Retrospective case-series	Retrospective case-series	Case report	Case report	Case report	Prospective case -series
Study	Gu et al.2020 (12)	Qin et al.2018(13)	Di Pierro et al.2014 (16)	Gao et al.2014 (17)	Engel et al.2013 (18)	Nadu et al.2013 (14)	Chung et al.2011 (15)	Shikanov et al.2009(21)	Venkatesh et al.2006 (19)	Fazio et al.2006 (20)	Wang et al.2019 (42)	Zhang et al.2018(43)	Fan.et al 2018 (31)	Wang et al.2015(44)	Chen et al.2014 (17)	Simpfendorfer et al .2016 (37)	Teber et al.2009 (38)	Shao et al.2012 (30)	Hernandez et al.2017 (45)	Kouriefs et al. 2019 (33)	Mandoorah et al 2018 (32)	Bouvier et al 2020 (34)

a=endophytic refers to totally intrarenal tumors with no exophytic component, b=not included 4 radical nephrectomy conversions and 1 open conversion, c=all endophytic tumors were hilar, d= endophytic tumors were totally intraparenchymal not visualized in the kidney surface, e=endophytic defined as >66% of tumor volume embedded in parenchyma, f=5 conversions to open surgery are included with 14 intraoperative and postoperative complications, g=endophytic defined as <40% of the lesion extending off the kidney surface, h=endophytic defined as <40% mass protruding, i= Clavien ≥II, j=postoperative only, k= lesion extending <40% from the kidney surface,l=the exact number of endophytic were not described, all the masses were characterized as endophytic and complex, m=no complications directly related to dye injection, 9 overall complications

Identification of endophytic renal masses, especially completely endophytic that acquire 3 points in the "(E)-endophytic/exophytic" parameter of R.E.N.A.L nephrometry score(7), can be challenging. Lack of haptic feedback in minimally invasive procedures and visual feedback when treating intraparenchymal masses, are obstacles in tumor localization.

Our rationale is to concisely present and evaluate endophytic tumor identification techniques described during minimally invasive nephron-sparing procedures. We aim to comprise a decision-making guide for the clinician when treating endophytic and especially non-visible completely endophytic renal tumors.

MATERIALS AND METHODS

Clinical question and Eligibility Criteria

This review is based on a focused clinical question using P.I.C.O (Population, Intervention, Comparison, and Outcome) Worksheet and Search Strategy Protocol (8) .(P) Endophytic renal masses, (I) Minimally Invasive Kidney-sparing procedures, (C) Tumor localization techniques, (O) Presentation of recorded techniques and evaluation of efficacy and oncologic outcomes. Inclusion criteria were: 1) English language 2) Population: Renal masses characterized as endophytic, completely endophytic, intrarenal, totally intrarenal, intraparenchymal and parenchymal, 3) Study design: Randomized controlled trials and observational studies, as well as systematic reviews/meta-analyses, reviews and case reports 3) Intervention: minimally invasive kidney-sparing treatments (laparoscopic or robotic partial nephrectomy, ablative methods and hybrid techniques). 4) Outcomes: Report, assessment or comparison of different invasive or non-invasive localization techniques used for signage of the aforementioned masses. Exclusion criteria were: 1) Animal, phantom, ex-vivo or cadaveric studies 2) Abstracts or conference announcements and electronic book publications. 3) Studies on upper tract urothelial masses.

Information Sources and Search Strategy

An advanced search was carried out on PubMed, Cochrane Library, Web of Science and Google Scholar databases up to August 2020, with the terms: kidney/renal/nephron sparing OR kidney/renal/nephron preserving OR laparoscopic/3D Laparoscopic/robotic/robotic assisted partial nephrectomy OR ablation OR minimal invasive AND endophytic OR intraparenchymal OR intrarenal OR parenchymal AND renal tumor/mass/lesion/cancer OR kidney tumor/mass/lesion/cancer. Keyword search with the terms: "tumor marking"

Table 2. Summary of results from studies regarding Robotic Assisted Partial Nephrectomy (RAPN) for endophytic tumors.

Study	Study	Endop	multiva	Study	Surgica	Identifi	Identifi	Mean	Positive	Compli	Recurr	Overall
Gu et	Retrosp	61/112	R.E.N.	RAPN	RAPN	IOUS	61(100)	23	2(3,27)	50(82)	0	27,3
Tiryaki	Case	1/1	NA	-	transRA	IOUS	1(100)	24	0	0	0	12
Abdel	Retrosp	52/89	NA	RAPN	transRA	IOUS	NA	28	5(9,6)	17(32,7	2(3,9)[b]	59
Harke	Retrosp	64/140	PADU	RAPN	transRA	IOUS	64(100)	26	0	14(21,9	NA	NA
Gunelli	Retrosp	NA/22	NA	Single	Robotic	RobIO	22(100)	NA	0	0	NA	NA
Kara et	Retrosp	87/143	NA	RAPN	RAPN	IOUS	NA	28	4(5,4)	19(21,8	0	15,2
Curtiss	Retrosp	30/297	NA	Intraren	3 or 4 -	ILUS or	NA	23	0	2(6,67)	0	10,6
Boylu	Retrosp	8/66	NA	RAPN	transRA	IOUS	NA	NA	NA	NA	0	33
Shiroki	Retrosp	4/48	Tumor-	long	Trans or	IOUS	NA	NA	0	0	NA	NA
Kommin	Retrosp	45/225	Age and	Endoph	transRA	ILUS	44(97,8	26	1(2,2)[e]	12(26,7	1(2,2)	48
Autorin	Prospec	65/389	NA	Endoph	transRA	IOUS	65(100)	26	3(4,6)	8(12,3)[g]	1(1,6)	12,6
Kaczma	Retrosp	49/150[h]	NA	Robotic	Trans	RobIO	NA	NA	3(6,1)	NA	0	18[j]
Kaczma	Retrosp	21/22[k]	NA	Single	3 -arm	RobIO	21(100)	NA	0	NA	0	13
Kim et	Retrops	9/65	NA	Comple	Off-	RobIO	9(100)	NA	NA	NA	0	14
White	Retrosp	3/67	NA	Single	transRA	ILUS	3(100)	NA	NA	NA	0	8
Hyams	Prospec	12/53	NA	LDU	RAPN	ILUS	NA	33[l]	NA	0	NA	NA
Rogers	Retrosp	4/14	NA	Single	transRA	ILUS	4(100)	32,5	0	0	0	3
Gong et	Retrosp	12/32	NA	Single	4 -arm	IILUS	NA	NA	0	0	0	15
Ho et	Retrosp	6/20	NA	Single	3-arm	IILUS	6(100)	NA	0	0	0	12
Alenezi	Retrosp	5/61	NA	Global	4-arm	robIOU	5(100)	NA	NA	NA	NA	18,5
Simone	Prospec	10/10	NA	Single	Off-	TAE	10(100)	30	0	0	0	12
Angell	Retrosp	2/79	NA	Single	transRA	IV	0[m]	NA	0	NA	NA	NA
Krane	Prospec	5/47	NA	NIRF-	4-arm	IV	0[n]	NA	NA	NA	NA	5
Porpigli	Retrosp	28/91	NA	3D AR	transRA	AR:	28(100)	NA	NA	NA	0	3
Porpigli	Prospec	12/52	NA	HA3D	transRA	AR:	12(100)	NA	0	NA	NA	NA
Lasser	Retrosp	2/10	NA	Single	RAPN	AR:	2(100)	NA	0	0	NA	4
Reeves	Case	1/1	NA	-	retroRA	Percuta	1(100)	25	0	0	NA	NA

a=5 intraoperative complications (3 conversions, 1 ureteric injury, 1 transfusion), 12 postoperative complications (2 ≥III), b=1 local recurrence, 1 metastasis, c=1 intraoperative, 18 postoperative complications (4 III-IV), d=1 tumor positive frozen biopsy, 97,8% technical success, e= 1 tumor positive frozen biopsies, conversion, f=3 intraoperative (2 conversion, 1 ureteric injury) and 9 postoperative (4 I, 3 II, 2 III), g=2 intraoperative and 6 postoperative (1 III-IV), h=20 tumors >50% endophytic in the laparoscopic IOUS and 29 in robotic IOUS, i= 75 underwent RAPN with robotic IOUS and 75 with laparoscopic IOUS, j=25,7 months in the laparoscopic IOUS and 10,3 months in the robotic IOUS, k=endophytic: ≥50% endophytic component, l=32mm in LDU, 34mm in non LDU, m,n= detection with IOUS, no fluorescence of ICG, o=HA3D identified all endophytic masses before fat detachment allowing no kidney rotation.

"endophytic renal tumor" "minimal invasive" "kidney sparing" was performed synchronously in Google Scholar database. This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement 2009(9).

PubMed and Cochrane Library search resulted in 429, Web of Science in 29 and Google Scholar search in 977 studies. 97 originated from references manual cross-searching in relevant articles. 1,498 studies were screened for eligibility after duplicate extraction. 1,234 studies were initially excluded by title and abstract, 153 studies were secondarily excluded, after full reading, due to eligibility criteria mismatch. Finally, 111 studies were included in our systematic review for evaluation. 77 studies, 1 multi-institutional prospective single arm, 6 prospective case-series, 5 prospective comparative and 59 retrospective and 6 case-reports, were included for narrative results presentation or subgroup analysis. Search results are summarized in PRISMA flow-diagram(**Figure 1**).

Data extraction and Risk of Bias assessment

Data extraction was performed in duplicate and included study type and design, minimally invasive approach, identification method, identification and technical success for ablative techniques, number and size of tumors, marginal status, perioperative complications, recurrence and follow-up. Risk of bias was assessed using ROBVIS tool(10) based on ROBINS-I tool for assessing non-randomized studies of interventions(11). Observational studies with inconclusive information, case reports and reviews were evaluated, although a priori considered critically biased. Risk of bias was evaluated throughout seven domains: confounding, selection of participants, classification of interventions, deviations of intended interventions, missing data, measurement of outcomes, selection of the reported results. For each domain we used a judgment from low to serious. Results are presented in a traffic-light plot (**Figure 2**).

Result synthesis and Statistical Analysis

Results presentation is mainly narrative. A meta-analysis was not performed due to heterogeneity of overall study population. Therefore, percentages of the outcome values for each variable instead of effect measures were calculated.

Table 3. Endophytic tumor localization techniques during ablation procedures.

Table 3. Endophytic tumor localization techniques during ablation procedures.

Study	Study type	Endophytic	Study arms	Ablation	Identificatio	Technical	Endophytic	Complicatio	Recurrence	Overall
		Radiofrequency Ablation (RFA)								
Sommer et	Systematic	NA	-	PRFA	iodized oil	NA	NA	NA	NA	NA
Gupta et	MI	46/163	Single arm	PRFA	G.A and real-	43(93,48)	NA	NA	4(8,7)[a]	20.3
Gervais et	Retrospective	5/100	Single arm	PRFA	CT or US	5(100)	NA	NA	NA	27,6
Farrell et	Retrospective	13/35	Single arm	PRFA	G.A and CT	13 (100)	NA	0[b]	0	9
Veltri et	Retrospective	9/18[e]	Single arm	PRFA	US	9(100)	26,9	0	0[f]	14
Pietryga et	Retrospective	8/46	Coil VS no	PRFA	Embolization	8(100)	NA	0	0	4
Matsumoto et	Retrospective	17/64	Single arm	PRFA/LRFA	CT/IOUS/N	16(94,1)	NA	NA	1 (5,9)	12 [d]
Young E. et	Retrospective	48/316	PRFA VS	(25)	G.A and CT/IOUS and	NA	NA	NA	NA	NA
Wingo et	Prospective	41/146	PRFA VS	(21)PRFA/(2	F-CT/IOUS or	37(90,2)	27	8 (19,5)	4(9,75)	29
Jacomides et	Retrospective	2/17	In situ LRFA	(2) In situ	IOUS	2 (100)	21	0	0	9,8
Zeltser et	Prospective	5/32	Single arm	RFA –	IOUS	4(80)	NA	NA	0	36
Yang et	Retrospective	NA/51	Single arm	LRFA	CEUS	NA	NA	NA	NA	31,5
Wu et	Prospective	31/78	LPN VS RF-	(5) LPN/(26)	ILUS	26(100)	NA	NA	0[g]	7,8
Nadler et	Retrospective	NA/16	Single arm	RFA assisted	ILUS	NA	NA	NA	NA	NA
		Cryoablation								
Murray et	Retrospective	49/49	Single arm	PCA	US or F-CT	49(100)	25	5 (10)[h]	6(13)[i]	56,5
Azevedo et	Retrospective	27/71	Single arm	PCA	US and CT	NA	NA	8(32)[j]	NA	NA
Permpongkos	Retrospective	8/23	Single arm	PCA	F-CT	6(75)	27	1(12,5)	NA	2,7
Michimoto et	Retrospective	17/17	Single arm	PCA	Ethanol and	16(94,12)	26,5	0	5(29,4)[k]	15,4
Kajiwara et	Retrospective	11/13[l]	Single arm	PCA	Ethanol and	11(100)	NA	0	0	11,5
Harmon et	Case report	1/1	Single arm	PCA	polyvinyl alcohol	1(100)	39,9	0	0	4
Atwell et	Retrospective	28/115	Single arm	PCA	US and CT	NA	NA	1(3,57)	NA	13,3
Wright et	Retrospective	3/35	Single arm	LCA	IOUS	1(33,4)	NA	0	0	18
Mues et	Retrospective	38/171	PCA VS	(16)PCA/(22)	F-CT/ILUS	NA	NA	NA	0/NA	NA
Derweesh et	Retrospective	5/60	Ct guided	(2)PCA/(3)L	F-CT/ILUS	5(100)	NA	NA	2 (40), 1 in	12/6

Statistical analysis, was performed for the distinctive subgroup of completely endophytic tumors (intraparenchymal, parenchymal, totally intrarenal, endophytic non-visible during surgery), which showed low clinical and methodological heterogeneity. Pooled Odds Ratios (OR) under random effects, using Cochran-Mantel-Haenszel test, were calculated with MedCalc-version 19.7.1 software, and forest-plots were used for presentation (**Figures 3-7**). Measured outcomes were, positive margins and recurrences for laparoscopic and robotic or technical success for ablation procedures, due to adequacy of data. We have not used adjusted ORs, since they were not provided in all relevant studies and if applied, covariates were not the same in each study. All tumor localization techniques in laparoscopic and robotic procedures were non-invasive ultrasound-based, whereas in ablation procedures such techniques were heterogeneous (invasive and non-invasive) therefore separate analysis was performed respectively. Publication bias was assessed using Egger's linear regression test and Begg's rank test, and presented in funnel-plots (**Figures 3-7**). Statistical heterogeneity was quantified, using Cochran's Q test and I2 statistic index ($P < .05$ as statistically significant, $I^2 \leq 50\%$ for low heterogeneity). The latter was used to assess if the amount of variance across studies was likely to be real and not due to sampling errors. Results were presented along with forest-plots(**Figures 3-7**).

"R package meta" in R (programming language) was used to perform subgroup meta–regression analysis and determine sources of heterogeneity. Only confounding covariates present in all studies, either defined from authors of each study or determined according to our experience, were used for meta-regression. Results showed that positive margins in robotic approach were negatively related to patient B.M.I. Successful ablation was also negatively related to the number of thermal ablation needles used, as concluded from the negative meta-regression slope(**Table 4**).

RESULTS

Laparoscopic Assisted Partial Nephrectomy

Data from 22 studies regarding 363 endophytic masses that underwent Laparoscopic Partial Nephrectomy (LPN), were collected (**Table 1**).

Described techniques were, Intraoperative Ultrasound (IOUS) (n = 265), Intraoperative dual-source CT (DSCT) (n = 25), Three dimensional printing physical kidney model technique (3Dp k.m) (n = 5), Intraoperative ultrasound guidance combined with 22 Gauge needles for tumor delineation (needle-IOUS) (n = 3), Intratumoral CT-guided percutaneous Hook-Wire insertion for tumor signage (Hook-Wire) (n = 2), selective intra-arterial blue dye embolization (blue dye TAE) (n =

Table 4. Results of meta-regression subgroup analysis for the five individual meta-analysis scopes. The model slope is presented in separate columns for the binary variables depending on their value (YES or NO). Statistically significant p values are presented in bold.

											For binary repressor variables			
Scope	Regression variable	τ^2 (estimated amount of residual heterogeneity)	p (test for residual heterogeneity)	I^2 (residual heterogeneity / unaccounted variability)	H^2 (unaccounted variability / sampling variability)	R^2 (amount of heterogeneity accounted for)	Model intercept	intercept p	Model slope	Slope p	Model slope (NO)	Slope (NO) p	Model slope (YES)	Slope (YES) p
Positive margins laparoscopic	Tumor size	0	0.7848	0.00%	1.0	0%	-2.3	0.5769	0.69	0.6315				
	Tumor location (anterior, posterior, central, hilar)	No data												
	B.M.I	No data												
	R.E.N.A.L score	No data												
	Ischemia Time	0	0.7324	0.00%	1.0	0%	0.3	0.9761	-0.02	0.1280				
	Resection time	No data												
Positive margins robotic	Tumor size	0.2	0.2936	18.46%	1.2	0%	-0.6	0.8380	0.34	0.7406				
	Tumor location (anterior, posterior, central, hilar)	No data												
	B.M.I	0	0.7973	0.00%	1.0	100%	10.1	**0.0231**	-0.37	**0.0294**				
	R.E.N.A.L score	0.2	0.3088	16.29%	1.2	0%	2.3	0.5080	-0.30	0.5596				
	PADUA score	No data												
	Ischemia Time	0	-		1.0	-3.9	0.2	0.1887	0.19	0.1442				
	Resection time	No data												
Recurrence robotic	Positive margins	No data												
	Tumor location (anterior, posterior, central, hilar)	No data												
	R.E.N.A.L score	No data												
	Histological type	No data												
	Stage	No data												
	Grade	No data												
	Age	No data												
Recurrence	Due to no recurrences reported in the studies, meta-analysis/regression was not performed													
Technical success ablation	Tumor size	3.5	0.0534	57.11%	2.3	0%	-0.6	0.6611	0.04	0.6572				
	Intraoperative fluoroscopy	3.5	0.0521	57.40%	2.4	0%	0.4	0.8200			-0.88	0.686		
	Procedures under General Anesthesia	4.5	**0.0431**	63.16%	2.7	0%	1.3	0.6389			-0.86	0.7937	-2.13	0.4551
	Preoperative CT Hounsfield units	No data												
	Hydro-dissection	3.5	0.0559	56.60%	2.3	0%	-0.4	0.7158					1.27	0.6351
	Number of Ablation probe insertions	No data												
	Number of needles	0	0.5271	0.00%	1.0	100%	6.1	**0.0314**	-2.80	**0.0118**				
	Ablation time	3.3	0.0604	55.69%	2.3	0%	1.2	0.6507	-0.07	0.5729				
	Ablation power applied (Kw)	No data												

Tables's abbreviationsCE-CT=Contrast enhanced CT, NA= Not Assessed, data absent or inconclusive, n. =number, OPN= Open partial nephrectomy, perc=percutaneous, RFA= Radiofrequency ablation RF-RCPN= Radiofrequency ablation –assisted robotic clampless partial nephrectomy, retro= retroperitoneal, TIT= Totally intraparenchymal tumors, trans= trans peritoneal, VSP= Virtual surgical planning, VS= Versus, WIT= Warm ischemia time

7), Augmented Reality (A.R.) (n = 54), Radio-Guided Occult Lesion Localization (ROLL) (n = 1).

Results on IOUS were extracted from retrospective comparative studies[12-15], retrospective single arm studies[16-20] and a prospective case-series study[21]. Identification success rate was 100%, mean tumor size was 16-37 mm, positive margin rate was 1.96 % -12.5 % , recurrence rate was 0 % in a mean 3-39.2 months follow-up and complication rate was 15.2 % -60 % . Various observational studies[22-25] and reviews[26-29] highlighted the importance of IOUS for the identification of intrarenal masses, precise delineation of size and depth, and presence of satellite renal masses or collecting system infiltration.

DSCT was used in a retrospective study[30] for retroperitoneal LPN. Overall accuracy of feeding artery orientation was 93.6 %, tumor identification success was 100 %, no positive margins or recurrences occurred in a mean 18-month follow-up.

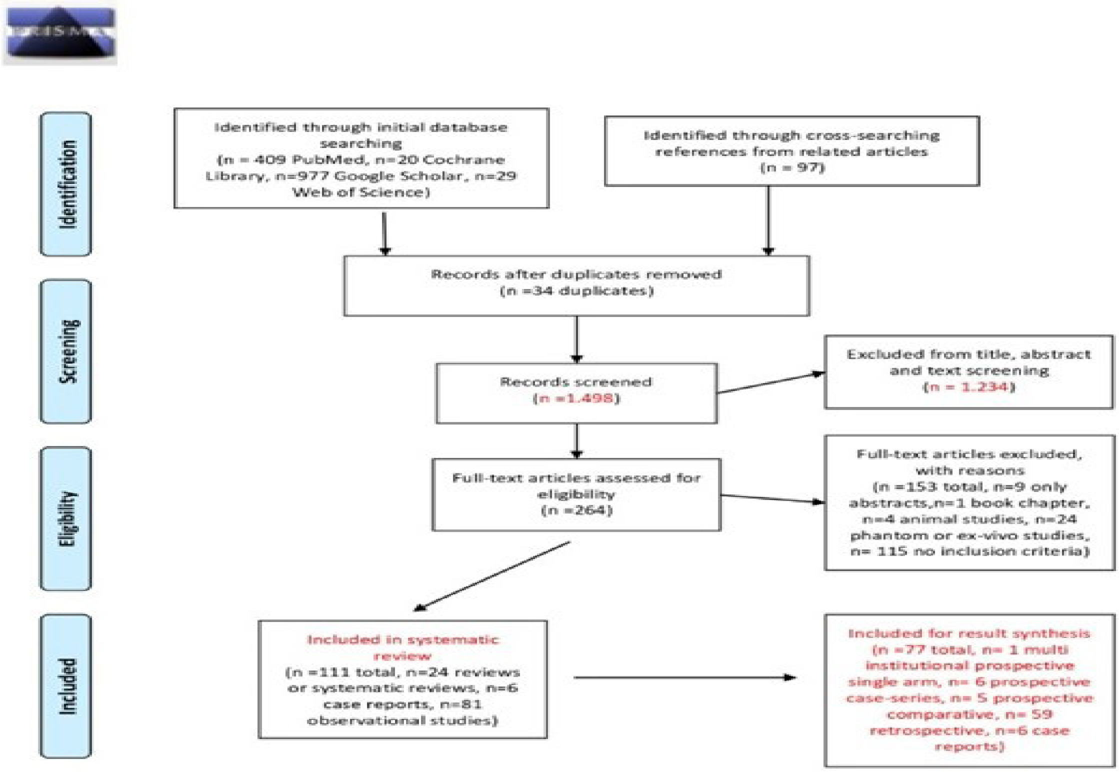
3Dp k.m[31] used markers orientated by anatomical landmarks, labeled on a kidney-model surface. Navigation intraoperatively was performed using kidney-model's distance measurements. Mean tumor size was 27.8 mm, treated with trans or retro peritoneal LPN. Identification rate was 100 % . No complications or positive margins were reported.

Needle IOUS assisted de novo identification of an unidentified intraparenchymal lesion with IOUS-only guidance. Neither positive surgical margins nor recurrences were reported in 27-month follow-up.

Hook-Wire was applied in 2 intraparenchymal tumors [32,33]. Identification success was 100 % , no complications or positive surgical margins were reported, and a 16-month follow-up in one case showed no recurrence.

Blue dye TAE, followed by super selective tumor embolization with glue or micro coils was presented in a prospective study[34]. No complications related to dye injection occurred nor positive surgical margins were present. All tumors were successfully embolized. Data regarding identification success were inconclusive. Early Follow-up imaging showed no recurrences.

A.R. summarizes a spectrum of techniques, all based on superimposing pre/intraoperative images, onto endoscopic scene. Intraoperative imaging or preoperative 3D-reconstructions can be registered within surgical view in three ways: 1) surface-based registration using a stylus or a range scanner tool, 2) manual registration using fiducials and markers, 3) 3D to 3D registration using stereoscopic robotic camera ability[35,36]. 10 masses were identified with Real-time imaging like cone-beam CT (CBCT) combined with fiducial aid technique [37-39]. CBCT helps to resolve the tissue deformation issue, due to natural organ movement, that can cause imprecise image fusion[40]. 44 tumors were identified with 3D reconstructed preoperative image fused with 2D or 3D laparoscopic view[41-44]. Identification rate was 100% and no positive surgical margins were reported



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 1. Search strategy presented with PRISMA flow-chart

for both techniques. CBCT showed no complications while 3D reconstruction technique had 0-13.3 % complication rate.

ROLL successfully used gamma camera for one intraparenchymal tumor in an experimental setting(45), this was the only case reported in English literature(46).

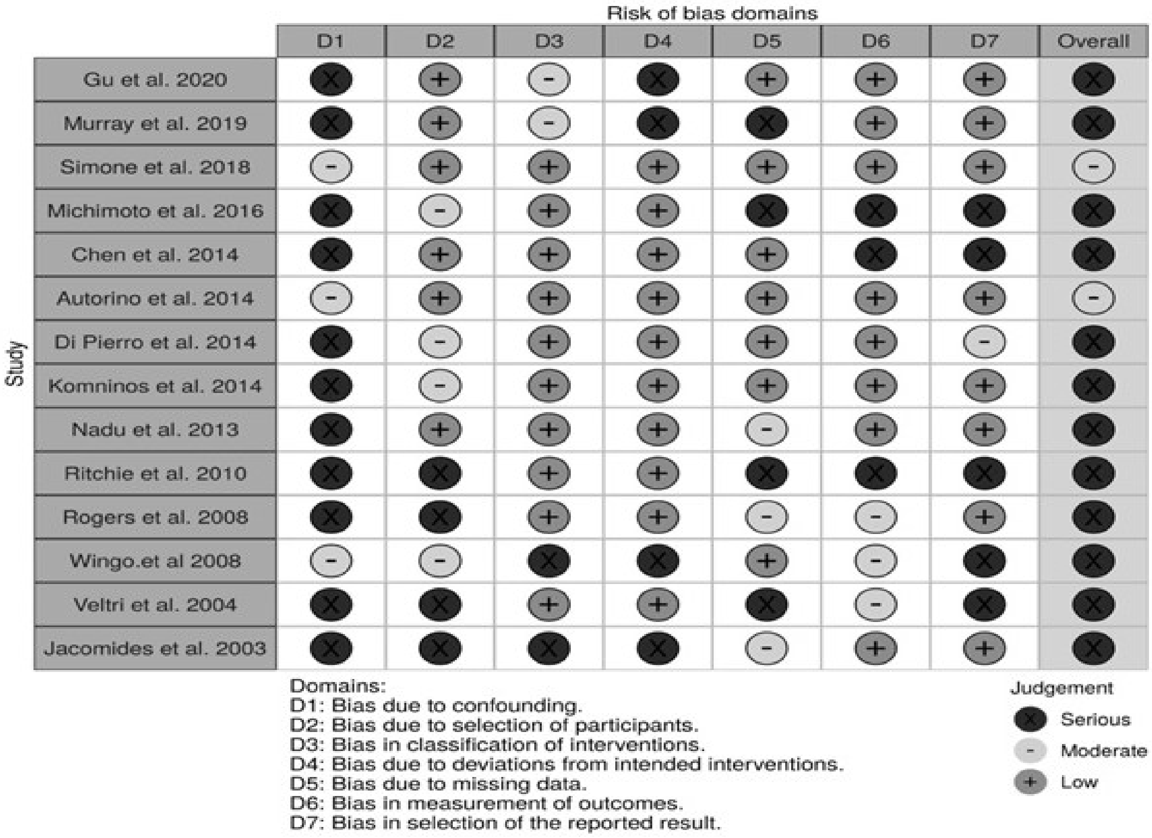
Completely endophytic subgroup analysis for LPN

Data were extracted from 12 studies (6 retrospective comparative, 3 retrospective single arm, 3 case-reports) (12,42,13,31,41,18,14,15,20,32,33,45). From 239 tumors, 17 were identified with A.R., 5 with 3Dp k.m, 211 with IOUS, 3 with needle IOUS, 2 with Hook-wire and 1 with ROLL. Intraparenchymal growth showed no correlation to identification success among methods. All techniques had 100 % successful identification rates both for intervention and control groups. Odds Ratio was 95 % CI ; 0.255-1.971, OR 0.709, *P* = .510, with low heterogeneity (Q = 1.355, 95 % CI ; 0.00-41.36, I2 0.00 % , *P* = .8553) for positive margins with IOUS guidance or A.R. navigation in LPN(**Figure 3**).

Positive margins with IOUS guidance had 95%CI; 0.0519-6.701, OR 0.590 in LPN compared to RAPN. Consecutive studies showed 95 % CI; 0.0201-5.756, OR 0.340 ; 95 % CI ; 0.179-3.589, OR 0.790 and 95 % CI ; 0.0251-7.191, OR 0.425 for an exophytic compared to an intrarenal mass to have positive margins. Positive margins for 3D reconstruction A.R. techniques, such as 3D-medical image reconstructing and guiding system (MIRGS), over control group had 95 % CI ; 0.116-115.805, OR 3.667 for totally intraparenchymal tumors. Local recurrence rate using IOUS, was 0 % in 5 comparative studies(12-14,20,41) with a mean 12-39.2 months follow-up, but data were insufficient for statistical analysis.

Robotic Assisted Laparoscopic Partial Nephrectomy

Data from 27 studies regarding 598 endophytic masses that underwent Robotic Assisted Laparoscopic Partial Nephrectomy (RAPN), were collected(**Table 2**). IOUS was the cornerstone of identification methods during RAPN(47,48). 365 masses were identified with IOUS. Other sonography-based methods were, IOUS combined with frozen sample biopsies from tumor bed (frozen-sample IOUS) (n = 161), Intraoperative laparoscopic Ultrasound enhanced with color Doppler modality (LDU) (n = 7) and Intraoperative Contrast Enhanced Ultrasound (CEUS) (n = 5). Apart from ultrasonography, embolization techniques such as iodized oil Trans arterial embolization in tumor feeding-artery (iodized oil TAE), TAE with Near infrared Fluoroscopy imaging using indocyanine Green (TAE NIRF-ICG) (n = 10),



Risk of bias domains

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Gu et al. 2020	X	+	-	X	+	+	+	X
Murray et al. 2019	X	+	-	X	X	+	+	X
Simone et al. 2018	-	+	+	+	+	+	+	-
Michimoto et al. 2016	X	-	+	+	X	X	X	X
Chen et al. 2014	X	+	+	+	+	X	X	X
Autorino et al. 2014	-	+	+	+	+	+	+	-
Di Pierro et al. 2014	X	-	+	+	+	+	-	X
Komninos et al. 2014	X	-	+	+	+	+	+	X
Nadu et al. 2013	X	+	+	+	-	+	+	X
Ritchie et al. 2010	X	X	+	+	X	X	X	X
Rogers et al. 2008	X	X	+	+	-	-	+	X
Wingo.et al 2008	-	-	X	X	+	-	X	X
Veltri et al. 2004	X	X	+	+	X	-	X	X
Jacomides et al. 2003	X	X	X	X	-	+	+	X

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
X Serious
- Moderate
+ Low

Figure 2. Risk of Bias Traffic-light plot created with ROBVIS tool. Assessment of bias for each non-randomized study throughout seven domains of bias (D1-D7). Domains are stratified with a judgment from low to serious.

A.R. (n = 42) and percutaneous placement of embolization coils inside the mass for tumor signage (embolization coils) (n = 1) were used.

Endophytic tumor size in IOUS techniques(12,49-62) was 23-32,5mm. Identification success rate was 100%, complication rate varied 0-21.8% and positive margin rate ranged 0 -6.1 % . Recurrence rate varied among studies 0-1.6 % , in 8-48 months follow-up.

Frozen sample IOUS studies(63-65) included masses sized 26-28mm. Identification success rate was 97.8 % - 100 % . Positive margin rate was 0-9.6 % . Complication rate was 21.9 % -32.7 % , and distal or local recurrence rate was 2.2 % -3.9 % in a mean 48-59 months follow-up.

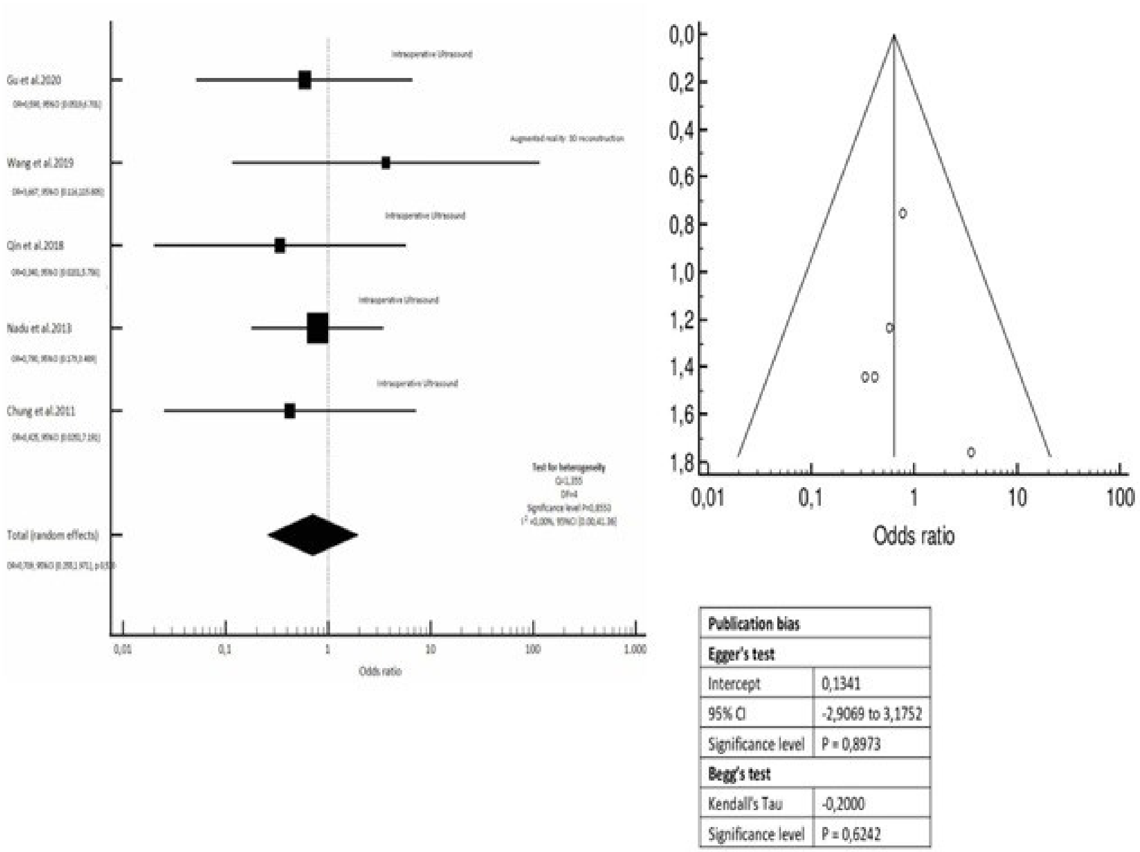
LDU(61,66), was used, not only to locate tumor but to identify the resection margin, and tumor distance from collecting system(67) and to track adjacent vessels(60). Identification success was 100 % , without complications.

CEUS was an alternative sonographic method to drop-in robotic ultrasound for in situ renal blood flow mapping after contrast agent injection(68). It allowed occlusion angiography after mapping vasculature and scanning the tumor along with its position and intraparenchymal depth assessment. Tumor identification rate was 100 %(69).

Efficacy of embolization techniques, such as iodized oil TAE and TAE NIRF-ICG, in localizing endophytic tumors was specified in one study(70-72). Mean tumor size was 30mm, identification success rate was 100 % , with no positive margins or recurrences at 12-month follow-up and no need for ultrasonography assistance.

A.R. techniques with real-time 3D to 3D registration were: Hyperaccuracy 3-dimensional reconstruction (HA3D)(73,74) and Inverse Realism technique using NVIDIA Quadro DVP hardware(75). Comparing HA3D to 2D IOUS techniques, both showed 100 % identification success rates, but with improved maneuverability, enhanced surgical movement and visualization of other hidden structures such as vessels or calyces for the HA3D arm. HA3D aided in 90% successful selective clamping versus 39 % successful pedicle management in non-HA3D group without positive margins in both arms. 3D to 2D image fusion utilizing vascular pulsation cues for guiding preoperative to intraoperative registration(76) was used for occluded structures tracking such as endophytic tumors or vessels occluded by fat during RAPN. IOUS 2D images and 3D reconstructed images integrated in surgical console, but not overimposed to endoscopic view were also described without further numerical data provided. VSP, used reconstructions created preoperatively, and IOUS real-time imaging both projected simultaneously within surgical view (77). Tumor identification rate was 100 % , showing no positive margins or complications. This technique could be helpful in cases with intraparenchymal or hilar tumors accompanying complicated renal vessels(78).

IOUS-tracked embolization coils, were used in an en-



Publication bias	
Egger's test	
Intercept	0,1341
95% CI	-2,9069 to 3,1752
Significance level	P = 0,8973
Begg's test	
Kendall's Tau	-0,2000
Significance level	P = 0,6242

Figure 3. Odds Ratio Forest-plot for positive surgical margins after Laparoscopic partial nephrectomy for completely endophytic tumors. OR calculated overall and separately for positive margins using different localization techniques. I2 shows low heterogeneity of data. Funnel-plot, Egger's test and Begg's test were used for publication bias evaluation.

dophytic isoechoic tumor during retroperitoneal RAPN (79). Identification success 100 % , and negative marginal status or complications, might suggest this as a method of choice when dealing with isoechoic intraparenchymal lesions.

Completely endophytic subgroup analysis for RAPN

Data were extracted from 13 studies (7 retrospective comparative, 3 retrospective single arm, 3 prospective studies)(51,63,65,12,50,62,64,57,70,80,77,73,81). In 366 tumors, identification success rates were 100 % for A.R. (n = 1), 100 % for IOUS (n = 158), 99.08 % for frozen sample IOUS (n = 109), 100 % for TAE NIRF-ICG (n = 10), and 0 % for intravenous (I.V.) NIRF-ICG (n = 7), (t-test, P = .9730). Intraparenchymal growth showed no significant correlation to warm ischemia time(62). Analysis for positive margins in IOUS guided RAPN and A.R. navigation for completely endophytic tumors with or without frozen biopsies had total 95 % CI ; 0.379-3.109, OR 1.086, *P* = .878, with moderate heterogeneity (I2 = 46.39 % , *P* = .0826) (**Figure 4**).

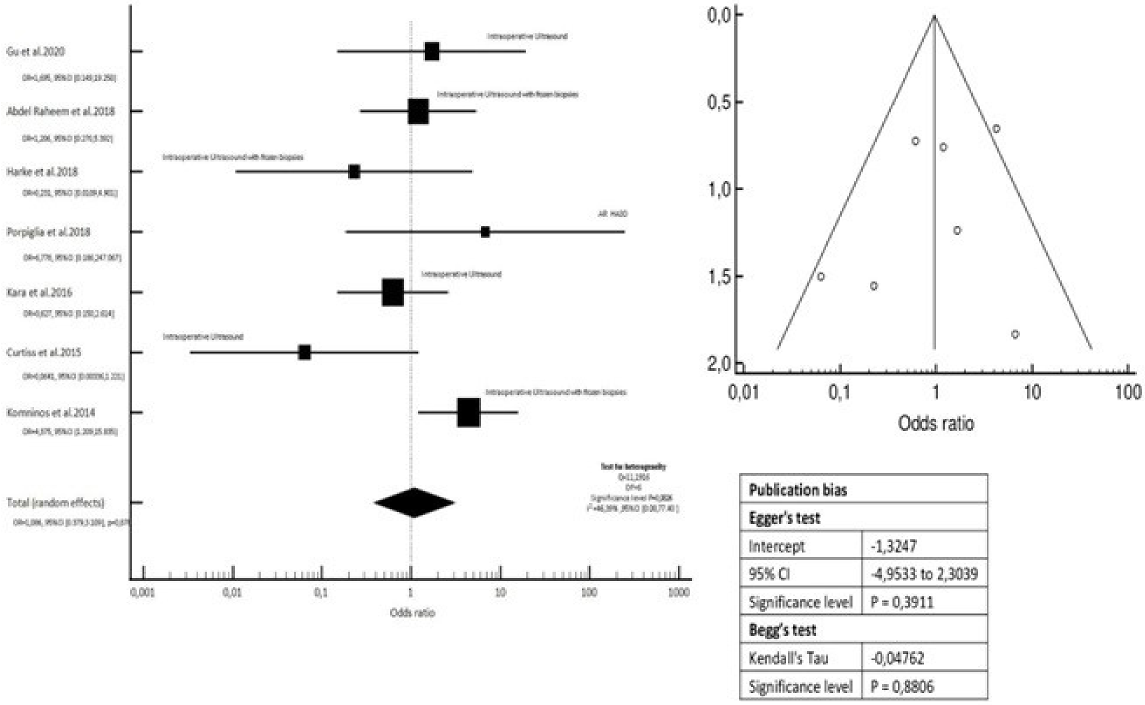
Positive margins using IOUS RAPN for intrarenal versus exophytic tumors had 95%CI; 0.00336-1.221, OR 0.0641. Positive margins with frozen sample IOUS had 95%CI; 1.209-15.835, OR 4.375, for completely endophytic versus mesophytic or exophytic masses in LPN compared to RAPN. Positive margins for A.R. techniques such as HA3D compared to IOUS control group, had 95 % CI ; 0.186-247.067, OR 6.778.

Total 95 % CI ; 0.0917-2.251, OR 0.454, *P* = .0334 with low heterogeneity (I2 = 0.00 % , *P* = .07645) was estimated for recurrence in frozen sample IOUS RAPN for intrarenal tumors, as other identification techniques showed insufficient data for further analysis. Frozen sample IOUS had 95 % CI ; 0.0299-3.932, OR 0.343 for recurrence after RAPN compared to OPN and 95 % CI ; 0.0673-4.686, OR 0.562 for recurrence after RAPN when comparing intrarenal to mesophytic or exophytic tumors(**Figure 5**).

Radiofrequency Ablation

Data from 14 studies, with 225 endophytic renal masses that underwent Radiofrequency Ablation (RFA), were collected(**Table 3**). 127 neoplasms underwent percutaneous RFA (PRFA), 55 underwent Laparoscopic RFA (LRFA), and 26 underwent RFA assisted RAPN. Hybrid laparoscopic and robotic RFA assisted partial nephrectomy was described in literature without specific data recorded.

Localization methods described during PRFA were: CT guidance alone or combined with CT guidance under general anesthesia (G.A-CT) and Fiber optic thermal monitoring (FOTM)(82-85), Fluoroscopy CT (F-CT) guidance with embolization coil markers (n = 8)(86), Ultrasound (US)-only guidance (n = 9)(87) and iodized oil TAE(88). RFA with GA-CT and FOTM (n = 43) was the only method with 93.48 % technical success rate and 8.7 % recurrence rate compared to 100 % success rate and 0 % recurrence rate of other modalities. Tumor size data were only provided for US RFA, showing mean



Publication bias	
Egger's test	
Intercept	-1,3247
95% CI	-4,9533 to 2,3039
Significance level	P = 0,3911
Begg's test	
Kendall's Tau	-0,04762
Significance level	P = 0,8806

Figure 4. Odds Ratio Forest-plot for positive surgical margins after Robotic partial nephrectomy for completely endophytic tumors. OR calculated overall and separately for positive margins using different localization techniques. I2 shows moderate heterogeneity of data. Funnel-plot, Egger's test and Begg's test were used for publication bias evaluation.

size 26.9mm. Complication rate 0% was announced for US and F-CT embolization coil methods. TAE was used for difficult-to-detect endophytic tumors, but concise numerical data regarding success rate and surgical outcomes were not provided.

LRFA was facilitated either by IOUS-alone(85,89-91) or combined with visual guidance and FOTM(92-93) or CEUS (94) for tumor localization. IOUS-alone technical success rate was 80 % -100 % and recurrence rate was 0 % overall. RFA assisted robotic clamp-less partial nephrectomy for 26 endophytic tumors had 100 % technical success rate and 0 % recurrence rate using IOUS alone(95). Results were inconclusive for IOUS-FOTM and CEUS.

Cryoablation

Data from 10 studies including 187 endophytic tumors treated with Cryoablation were collected (**Table 3**). 159 masses underwent with percutaneous Cryoablation (PCA) and 28 were treated with Cryoablation during laparoscopy (LCA). 88 were completely endophytic.

Identification techniques used in PCA were: F-CT only or combined with US (n = 112)(96-99) and TAE (n = 29) combined with CT guidance such as iodized oil and absolute ethanol TAE (100) , iodized oil and gelatin particles TAE(101), or polyvinyl alcohol particles in iodinated contrast agent TAE(102).

Combined US and intermittent CT imaging during ablation for 76 masses showed 100% technical success rate, complication rates were 10 % -32 % . Recurrence rate was 13 % in one retrospective single arm study with long term follow-up. F-CT only method, had 75 % technical success rate and 12.5 % recurrence rate in a retrospective study including 8 endophytic tumors with mean size 27mm.

Iodized oil and absolute ethanol TAE showed inferior results compared to other TAE techniques, with technical success rate 94.12 % , and 29.4 % recurrence rate, versus 100 % technical success rate and 0 % recurrence rate respectively. Outcomes were comparable despite small study samples.

IOUS was the only identification method described during LCA. A retrospective single arm study(103) showed 33.4 % technical success rate, 0 % complication and recurrence rate in mid-term follow-up during LCA for 3 completely endophytic non-visible tumors. Limited data, indicated ultrasonography signage inexpediency for treating intrarenal tumors. Retrospective comparative studies analysis on CT guided PCA and IOUS guided LCA(104-105) showed 100 % technical success and 20 % recurrence rates for both arms, while limitations such as small sample size and restrictions in definitions of technical success, persistent enhancement and recurrence, obscured safe statistical conclusions.

Microwave Ablation

Data regarding Microwave Ablation (MWA) were collected (**Table 3**). Yu et al. 2012(106) reviewed intermediate-term outcomes after MWA with US and FOTM sensors for 44 endophytic masses, mean size 18mm. 26 had parenchymal and 18 had endophytic growth patterns with 17.9-19.8 months median-follow up. Parenchymal nodules showed 100 % technique efficacy and no recurrences. Endophytic masses showed 94.4 % technique efficacy, and 15 % showed recurrence.

Retrospective comparative studies(107-109) on CT percutaneous thermal ablation for 165 endophytic masses

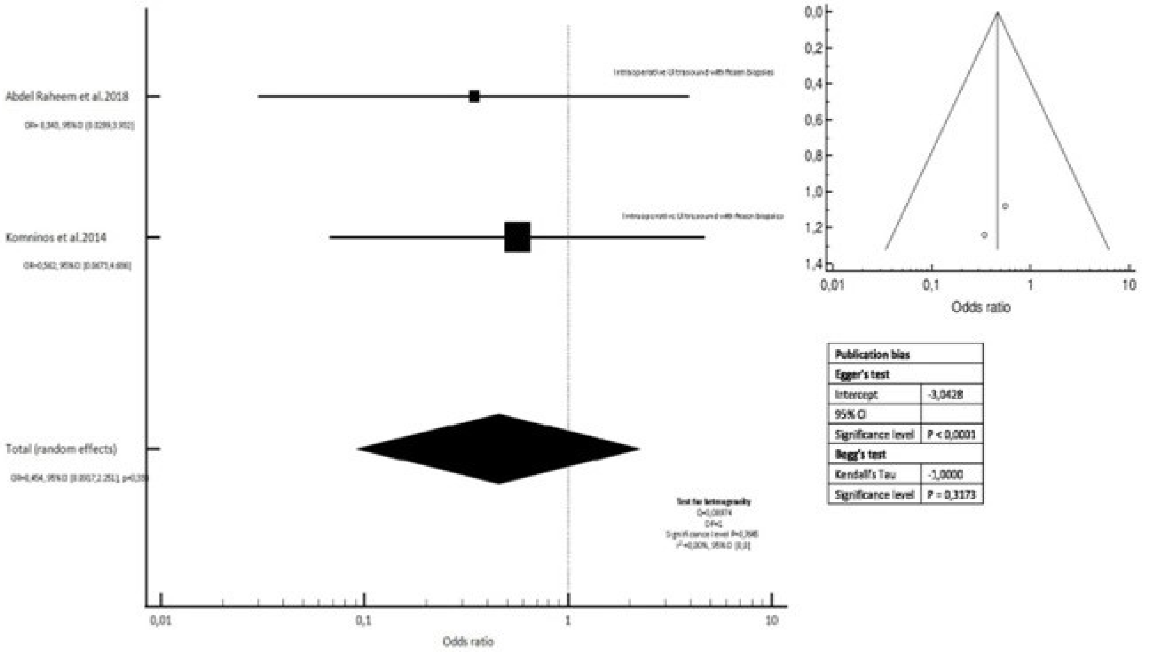


Figure 5. Odds Ratio Forest-plot depicting likelihood for tumour recurrence using intraoperative ultrasound guidance with frozen samples from tumor bed in Robotic Partial Nephrectomy for completely endophytic tumours. I2 shows low heterogeneity of data. Funnel-plot, Egger's test and Begg's test were used for publication bias evaluation.

showed overall 100 % technical success rate for all intervention types. In MWA group, no urothelial injury or Clavien-Dindo II-IV complications occurred.

Irreversible Electroporation

One study from Diehl et al. (110) reported the use of Irreversible Electroporation (IRE) in endophytic tumors, but data were inconclusive (**Table 3**).

Completely endophytic subgroup analysis for thermal ablation

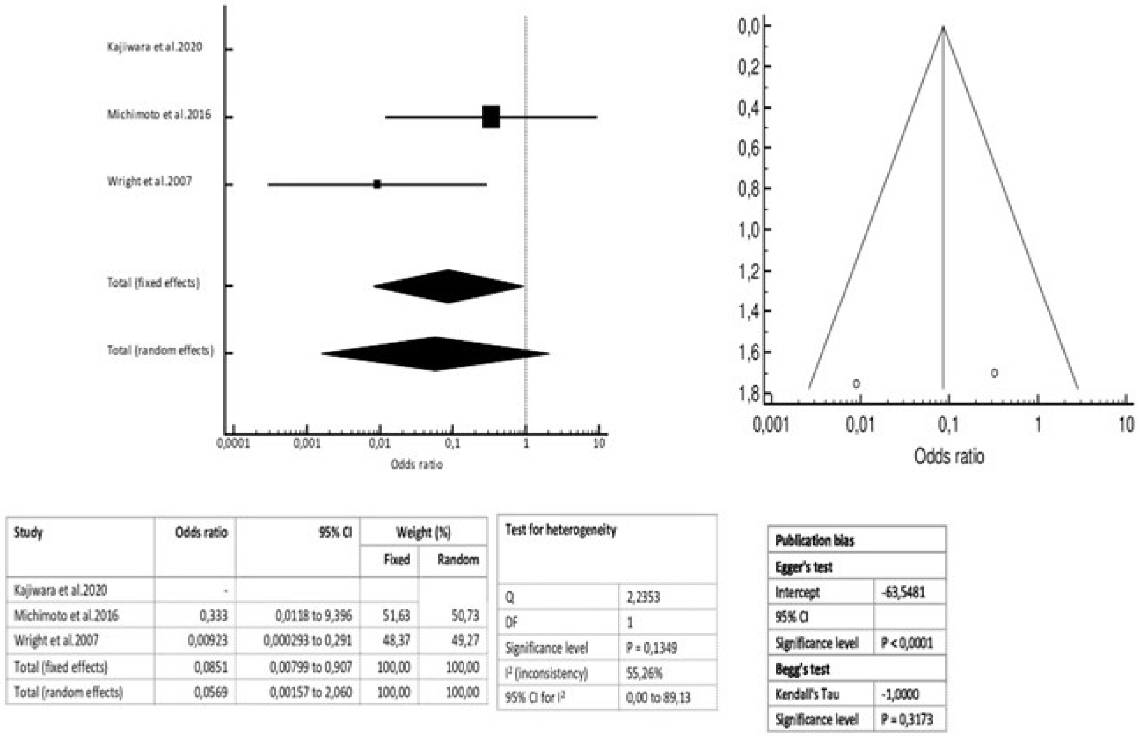
Data were extracted from 11 studies (9 retrospective single arm, 1 retrospective comparative, 1 prospective) (83,84,87,86,93,96,100,101,99,103,106) including 153 completely endophytic tumors. Localization methods during PRFA were: CT guidance alone or combined with US (n = 18), US-alone (n = 9), and F-CT with embolization coil markers (n = 8). Deep endophytic tumors during LRFA were identified with FOTM IOUS. Identification techniques during PCA were: CT guidance alone or combined with US (n = 77) and iodized oil TAE (n = 12), while IOUS was the only localization modality used during LCA (n = 3). US with FOTM was used for 26 tumors during percutaneous MWA. Total OR for technical success after thermal ablation procedures was 95 % CI ; 0.137-5.167, OR 0.842, *P* = .853.

We applied separate pooled OR reporting for invasive (Figure 6.) and non-invasive (Figure 7) localization techniques regarding technical success in ablation procedures, in order to avoid heterogeneous data analysis. Invasive techniques: Iodized TAE in PCA, 95 % CI ; 0.0118-9.39), OR 0.333 and laparoscopic IOUS guidance in PCA, 95 % CI ; 0.000293-0.291, OR 0.00923 both showed less likelihood for technical success, total random effect 95 % CI ; 0.0157-2.060, OR 0.05690, fixed effect 95 % CI ; 0.00799-0.907, OR 0.0851, P = .041, with significant heterogeneity of data 95 % CI ; 0.00-89.13, I2 55.26 % . Non-invasive techniques: All non-invasive imaging techniques showed increased likelihood for success with total random effects 95 % CI ; 0.598-13.152, OR 2.804 and low heterogeneity of data 95 % CI ; 0.00- 25.11, I2 0.00 % . US guidance in percutaneous RFA, 95 % CI ; 0.262- 152.872, OR 6.333 and combined CT and US guidance, especially when performed under FOTM, in MWA : 95 % CI ; 0.137 -91.090, OR 3.533, in PCA: 95 % CI ; 0.118- 47.114, OR 2.361 and PRFA: 95 % CI ; 0.0696- 26.205, OR 1.35, showed increased likelihood for success.

Comparison between thermal ablation methods showed that endophytic growth pattern attributed to hematoma formation with Mean Relative Risk (RR) 95 % CI ; 0.90-1.51, RR 1.15 and to residual disease with Mean 95 % CI ; 1.10-1.87, RR 1.30(107-109). Overall estimated cumulative incidence of recurrence was 95 % CI ; 1-19, 5 % , at 3 years and 95 % CI ; 4-27, 10 % at 5 years for PCA using combined CT and US guidance for completely endophytic tumors(96). Wingo et. al.2008 (93), contrariwise, failed to predict increased risk for recurrence due to endophytic location (chi-square = .81 < 5.99) for CT-FOTM PRFA or IOUS LRFA.

High Intensity Focused Ultrasound

Ritchie et al.(111) evaluated 5 entirely endophytic tumors, mean size 20,4mm treated with High Intensity Focused Ultrasound (HIFU). US was used for tumor localization, surgical planning and real time evaluation. All were successfully identified. Technical success rate was



Study	Odds ratio	95% CI	Weight (%)	
			Fixed	Random
Kajiwara et al.2020	-			
Michimoto et al.2016	0,333	0,0118 to 9,396	51,63	50,73
Wright et al.2007	0,00923	0,000293 to 0,291	48,37	49,27
Total (fixed effects)	0,0851	0,00799 to 0,907	100,00	100,00
Total (random effects)	0,0569	0,00157 to 2,060	100,00	100,00

Test for heterogeneity	
Q	2,2353
DF	1
Significance level	P = 0,1349
I² (inconsistency)	55,26%
95% CI for I²	0,00 to 89,13

Publication bias	
Egger's test	
Intercept	-63,5481
95% CI	
Significance level	P < 0,0001
Begg's test	
Kendall's Tau	-1,0000
Significance level	P = 0,3173

Figure 6. Invasive techniques in Ablation procedures. Forest-plot depicting odds ratios for technical success during thermal ablation procedures for completely endophytic tumors. Cochran's Q test and I2 statistic are calculated for heterogeneity. Funnel-plot, Egger's test and Begg's test show publication bias.

20 %. No major complications occurred. Recurrence rate was 25 % in a mean 36-month follow-up.

DISCUSSION

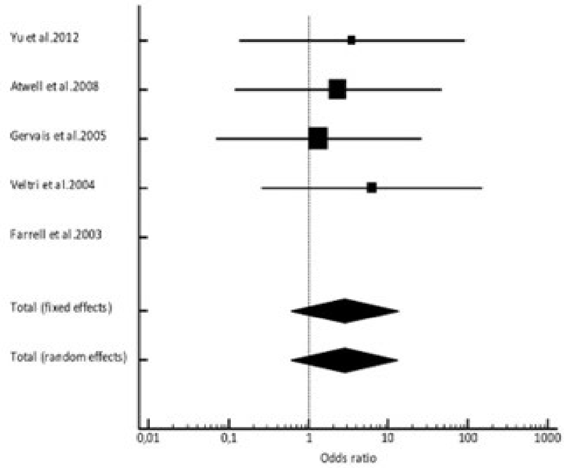
Evidence on excision techniques showed that IOUS was widely applied identification method, with high identification rates, and recurrence rates up to 1.6 % in follow up period up to 60 months. Positive margin rates were 1.96-12.5 % in LPN and 0-6.1 % in RAPN, while complication rates varied from 0 % in LPN to 0-21.8 % in RAPN. Kaczmarek et al.2013(54) showed similar efficacy between Laparoscopic and Robotic IOUS probes, Robotic group though, excelled in autonomy, maneuverability, cost effectiveness and practicality when depicting challenging tumor angles. Frozen sample IOUS during RAPN, showed increased complications, without improving positive margin or recurrence rates; making it questionable whether it should be performed. LDU or CEUS showed insufficient data regarding tumor tracking but aided in identifying hidden vasculature, defining safe excisional margins or contact with the collecting system. DSCT combined high identification success rate with efficient tumor feeding artery orientation.

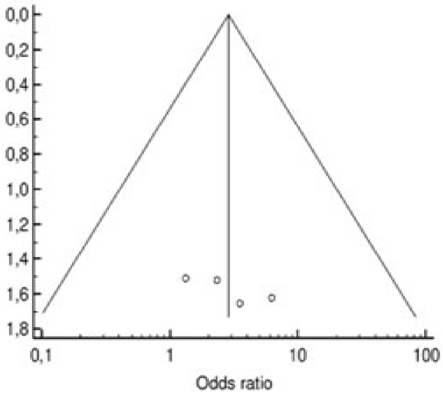
A.R. was useful in identification, especially within a robotic setting. Overlapped 3D onto real- time endoscopic image, enhanced anatomical structures(112). Despite high identification success rates, data were inconclusive to support superiority over conventional techniques. Findings are compatible with international literature (113,114). Only HA3D showed superiority compared to IOUS during RAPN regarding surgical autonomy, and selective artery clamping.

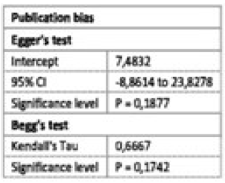
Isoechoic intraparenchymal mass tracking was achieved using embolization coils during RAPN. Further studies are needed to confirm whether embolization coil or hook wire techniques could be the gold standard for such tumors.

Unlike TAE NIRF-ICG, I.V. NIRF-ICG was contraindicated for endophytic tumors(115,40). Studies(80,81) showed no identification success. The only utility for intraparenchymal lesions, was tumor delineation once surrounding normal parenchyma was first incised(116-119). Regarding excision methods for completely endophytic tumors, identification success rates were high, regardless of identification technique, both for LPN and RAPN. Positive margins showed 40% less likelihood in IOUS guided LPN compared to RAPN and significantly decreased odds for IOUS guided LPN or RAPN for totally intraparenchymal tumors compared to masses with exophytic component. Odds for positive margins were increased in A.R. techniques compared to IOUS during laparoscopic or robotic procedures for intrarenal masses. Chances for recurrence were in favor of IOUS LPN compared to RAPN, LCA or laparoscopic radical nephrectomy and increased odds for recurrence were found during laparoscopy for intraparenchymal versus exophytic masses. Frozen sample IOUS showed increased likelihood for positive margins in intrarenal compared to exophytic tumors and 45% less likelihood for recurrence of parenchymal masses compared to mesophytic or other exophytic lesions.

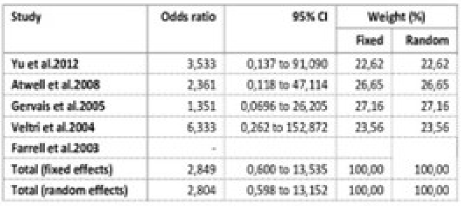
Evidence on ablation procedures suggest that, CT was preferred to US during all thermal ablation procedures



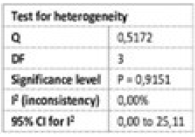




Publication bias	
Egger's test	
Intercept	7,4832
95% CI	-8,8614 to 23,8278
Significance level	P = 0,1877
Begg's test	
Kendall's Tau	0,6667
Significance level	P = 0,1742



Study	Odds ratio	95% CI	Weight (%)	
			Fixed	Random
Yu et al.2012	3,533	0,137 to 91,090	22,62	22,62
Atwell et al.2008	2,361	0,118 to 47,114	26,65	26,65
Gervais et al.2005	1,351	0,0696 to 26,205	27,16	27,16
Veltri et al.2004	6,333	0,262 to 152,872	23,56	23,56
Farrell et al.2003	-			
Total (fixed effects)	2,849	0,600 to 13,535	100,00	100,00
Total (random effects)	2,804	0,598 to 13,152	100,00	100,00



Test for heterogeneity	
Q	0,5172
DF	3
Significance level	P = 0,9151
I^2 (inconsistency)	0,00%
95% CI for I^2	0,00 to 25,11

Figure 7. Non-invasive techniques in Ablation procedures. Forest-plot depicting odds ratios for technical success during thermal ablation procedures for completely endophytic tumors. Cochran's Q test and I2 statistic are calculated for heterogeneity. Funnel-plot, Egger's test and Begg's test show publication bias.

due to improved anatomic resolution, ancillary maneuver permeability and periprocedural complication evaluation(109). CT guided PRFA had technical success rate 93.48 % -100 % and recurrence rate 0-8.7 % in 2-year follow-up. G.A aided in better targeting and minimizing complications risk. Wingo et al.2008(93) showed that FOTM RFA, improved success rate. Gupta et al.2009 (82) showed that OR, an endophytic lesion compared to non-endophytic to be incompletely treated, was 95 % CI ; 0.65-24.8, OR 4.0. RR of developing any recurrence for endophytic lesions compared to non-endophytic was 95 % CI ; 0.6-11.7, RR 2.6, *P* = .20. Endophytic tumors were more resistant to ablation because of the "heat sink" effect caused by blood vessels surrounding the tumor.

Endophytic central masses had the highest risk for recurrence (Hazard Ratio HR, 6.3; *P* = .016). Matsumoto et al.2005.(120) stated that, endophytic lesions, hardly localized during open partial nephrectomy and technically challenging for LPN, were easily targeted and ablated with CT-guided RFA. Pietryga et al.2012(86) showed that use of marker coils in poorly visualized tumors, such as intraparenchymal and isoechoic lesions, facilitated CT PRFA, by 58 % reduction in CT fluoroscopy time, showing equivalent technical outcomes with non-coil group. TAE as add-on to PRFA for difficult-to-detect endophytic tumors, reviewed by Sommer et al.2017 (88), showed that residual post ablation positive margins were more common for endophytic tumors.

IOUS LRFA, showed technical success 80-100%. Yang et al.2014(94) showed that CEUS, improved tumor outline visibility prior to ablation, allowed enhancement status evaluation after ablation, required no warm ischemia and allowed increased parenchymal preservation.

CT PCA showed technical success 75 % , reaching 100 % when combined with US. Recurrence rate was approximately 13 % in short-term follow-up, and complication rate was 10-32 %. TAE PCA, technical success rate was comparable (94.12 % to 100 %) but with higher percentage for recurrences (29.4 %). Harmon et al.2018(102) showed that pre ablation adjuvant embolization allowed better tumor demarcation, reduced cryoneedles needed and minimized procedural cost and complications.

The "poor visualization phenomenon" concerning intraparenchymal or partly endophytic renal masses in unenhanced CT was a factor compromising PCA success. Therefore, Kajiwara et al.2020(101) proposed a five-tier visualization score based on Hounsfield units. Mean visualization score, solely for endophytic and parenchymal tumors, after TAE PCA was 4, representing a tumor margin visibility 75-90 % . Data on IOUS LCA, showed technical success 33.4 % , probably due to ultrasonography signage inexpediency(103). Multivariate analysis revealed that only endophytic status is a predictor of failure. Derweesh et al.2008(105) compared LCA to PCA for endophytic tumors and showed that they had significant association with tumor persistence. Nisbet et al. 2009(121) proposed a decision tree on whether to perform IOUS LCA or LPN for small renal masses. Endophytic tumors were predicted to have better results when treated with LCA.

Results on completely endophytic subgroup for ablation procedures, showed that non-invasive imaging techniques had increased likelihood of success. CT PRFA had slightly increased odds for technical success between totally intrarenal and endophytic tumors (95 % CI ; 0.0696- 26.205, OR 1.351). Technical success during US PRFA was also in favor of intraparenchymal masses. Combined CT and US PCA, favored success over completely endophytic lesions compared to other endophytic tumors. US MWA with FOTM, increased likelihood of success when applied to intrarenal masses compared to endophytic. Contrariwise, invasive techniques showed less likelihood for success. TAE PCA showed 33 % less likelihood of success for intrarenal masses compared to masses with exophytic components. Chances of success for completely endophytic tumors were significantly lower compared to masses with exophytic component during IOUS LCA (95 % CI ; 0.000293-0.291, OR 0.00923). Data on recurrence after ablation were contradictive and therefore inconclusive.

Our limitations were 1) Study selection bias from English language restriction: Additional database search resulted in 6 studies eligible for further evaluation according to abstract, written in Russian, Spanish, French and Hebrew. As authors were incapable of translating, we avoided including non-English literature due to bias of misinterpretation. 2) Further databases could have been searched, such as Scopus, which was not searched due to limited access. 3) Serious uncontrolled confounding bias due to unmeasured confounders. 4) Sparse data bias: unrealistic huge pooled OR estimates and confidence limits, observed in subgroup analysis, suggest that sparse data is an important source of bias. 5) Bias deriving from study design: No randomized controlled studies and limited number of prospective studies were included (6 comparative, 5 single arm studies and 1 multi-institutional), the majority were retrospective, making data extraction strenuous due to ambiguous reporting quality. 6) Missing data within studies: Data were partially missing or inconclusive in 58 studies, while 19 had complete data for extraction. 7) Heterogeneity in terminology: Variance in definitions of terms was a major drawback. The term endophytic described a variety of masses, ranging from totally intraparenchymal to masses protruding up to 50% from capsule. Other definitions such as technical success rate, tumor response rate and recurrence, were diverse among studies resulting in bias during the interpretation of outcomes, although Goldberg et al.2003(122) proposed a protocol for Standardization of Terms and Reporting Criteria for image guided ablation. 8) Small study samples. Low level of evidence, inconsistent reporting of data, bias in study design or subgroup analysis, small samples and heterogeneity of definitions led us to perform a narrative systematic review instead of meta-analysis.

CONCLUSIONS

IOUS in LPN and RAPN was an adequately evaluated method for tumor localization with high identification rates and acceptable oncologic outcomes. A.R., although showing increased surgical maneuverability and autonomy, showed no superiority regarding identification success, positive margins and recurrences. I.V NIRF-ICG, was not an appropriate option for successful endophytic tumor tracking.

CT alone or combined with FOTM and US, showed increased technical success for endophytic and intraparenchymal tumors during thermal ablation. US alone during LCA, had discouraging results regarding technical success. Limited evidence on isoechoic endophytic masses, suggest that more invasive localization methods such as hook-wire or embolization coil techniques, might rise as method of choice for such tumors.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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