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Tumor enucleation for the treatment of T1 renal tumors: A systematic review and meta-analysis

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Purpose: To evaluate the clinical efficacy and safety of tumor enucleation (TE) compared with partial nephrectomy (PN) for T1 renal cell carcinoma.

Materials and Methods: According to protocol, we searched multiple data sources for published and unpublished randomized controlled trials and nonrandomized studies (NRSs) in any language. We performed systematic review and meta-analysis according to the Cochrane Handbook for Systematic Reviews of Interventions and rated the certainty of the evidence (CoE) using the GRADE framework.

Results: We are uncertain about the effects of TE on perioperative (mean difference [MD] 3.38, 95% CI 1.52 to 5.23; I^2=68%; 4 NRSs; 942 participants; very low CoE) and long-term (MD 2.31, 95% CI -1.40 to 6.01; I^2=57%; 4 NRSs; 542 participants; very low CoE) residual renal function. TE may result in little to no difference in short-term residual renal function (MD 1.04, 95% CI 0.25 to 1.83; I^2=0%; 2 NRSs; 256 participants; low CoE). We are uncertain about the effects of TE on cancer-specific mortality (risk ratio [RR] 0.90, 95% CI: 0.11 to 7.28; I^2=0%; 2 NRSs; 551 participants; very low CoE) and major adverse events (RR 0.48, 95% CI: 0.30 to 0.79; I^2=0%; 10 NRS; 2,360 participants; very low CoE).

Conclusions: While TE appears to have similar effects on short term postoperative residual renal function, there were uncertainties on mortality and major adverse events. However, we need rigorous RCTs to elucidate the effects of TE as the evidence stems mostly from NRSs.

Keywords: Nephrectomy; Renal cell carcinoma; Systematic review

INTRODUCTION

Renal cell carcinoma (RCC) has a prevalence of approximately 2% to 3% of all adult malignancies, and it is the 13th most common malignancy globally, with an estimated 63,990 new diagnoses in the United States in 2017 [1-3]. Its early clinical manifestations are diverse and nonspecific. Only 10% of patients with RCC present with the classic triad of hematuria, pain, and flank mass. Consequently, most patients with RCC have an advanced stage. More than 50% of pa-

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tients with RCC are accidentally diagnosed when RCC has not metastasized [4] because of the technological advances of diagnostic imaging tools such as computed tomography and magnetic resonance imaging [5,6]. However, urologists are faced with challenges in management because of the increase in the prevalence of small RCCs.

Since 2006, partial nephrectomy (PN) has been the gold standard treatment for T1 renal tumors (tumor diameter <7 cm) according to current guidelines [7,8]. The rationale behind this recommendation mainly stems from the evidence of comparable oncologic outcomes and improved preservation of renal function after PN, compared with radical nephrectomy, as shown in the European Organization for Research and Treatment of Cancer phase 3 prospective randomized controlled trial (RCT) [9-11]. However, tumor enucleation (TE), which involves tumor resection without additional removal of normal renal tissue, has been increasingly used as alternative treatment [12]. Theoretically, TE is useful for preserving renal function in patients with preoperative renal insufficiency, solitary kidney, multiple renal masses, or hereditary renal cancer syndrome. Recent reports have shown that if a tumor is completely excised, the width of the resected margins is not associated with disease progression [13,14]. As a result, several surgeons have begun performing TE within the past few years to maximally preserve healthy parenchymal tissue and reduce the incidence of complications [15,16].

TE is a relatively recent technique, and only a few studies have reported on its efficacy and safety for the treatment of T1 renal tumors. It is not clear whether TE is associated with more clinical benefits and fewer adverse events in clinical practice than PN. Therefore, we aimed to elucidate the effects of TE in the treatment of T1 renal tumors and compare them with those of PN. The findings of this review will be relevant to developers of guidelines and clinicians who make surgical treatment recommendations.

MATERIALS AND METHODS

This study does not require ethical approval because it is a systematic review. We performed this systematic review and meta-analysis according to the protocol published in PROSPERO (CRD42020181115).

We performed a comprehensive search of several databases, including MEDLINE, EMBASE, Cochrane Library, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature, as well as other resources such as ClinicalTrials.gov (https://www.clinicaltrials.gov/), the World Health Organization International Clinical Trials Registry Platform search portal (https://apps.who.int/trialsearch/), and grey literature reports (www.greylit.org/). Supplementary Table 1 presents the search strategy for each database. We also searched the reference lists of selected studies for supplemental studies and contacted their authors for reports of any unpublished or published studies, including new or additional studies or work in progress.

The date of the last search of all the databases was August 12, 2021. Three review authors (TWK, JYL, JHJ) independently screened all potentially relevant records and classified the studies according to the criteria provided in the Cochrane Handbook for Systematic Reviews of Interventions [17]. All disagreements were resolved through discussion. We included all clinical trials, regardless of publication status and language.

1. Participants

Participants were enrolled in the study if they met the following criteria: age of >18 years and a diagnosis of a T1 renal tumor (T1 is further divided into: T1a, the greatest dimension of the tumor is ≤4 cm and the tumor is limited to the kidney; T1b, the tumor size is >4 cm with the greatest dimension being ≤7 cm, and the tumor is limited to the kidney, with no regional lymph node metastasis or distant metastasis) according to the American Joint Committee on Cancer TNM classification [18].

2. Interventions

We compared TE and PN. Concomitant interventions had to be the same in the experimental and comparator groups to establish fair comparisons. TE was defined as blunt dissection of the tumor following the natural cleavage plane between the normal renal parenchyma and tumor pseudo-capsule without an additional resection of normal tissue around the tumor [12,15]. PN was defined as complete excision of the tumor along with a thin rim of normal parenchyma.

3. Outcomes

We did not measure the outcomes assessed in this review as eligibility criteria. The primary outcomes for this study were residual renal function (creatine level or glomerular filtration rate [GFR]), overall mortality (death from any cause), and major adverse events (Clavien–Dindo classification ≥grade III), and the secondary outcomes were cancer-specific mortality, local recurrence, distant metastasis, positive surgical margin, overall adverse events, hospital stay, and postoperative pain. We considered the residual renal function and adverse events assessed within 1 week of randomization as 'postoperative', within 3 months as 'short-term',

and after 3 months as 'long-term'. We planned to also assess oncologic outcomes, such as mortality, recurrence, and metastasis, as time-to-event outcomes. We assessed the positive surgical margin, hospital stay, and pain only postoperatively.

4. Assessment of risk of bias in included studies

Three review authors (TWK, JYL, JHJ) independently assessed the risk of bias in each included study. All disagreements were resolved through discussion.

We assessed the risk of bias for the RCTs using the Cochrane risk of bias tool for randomized trials. The risk of bias domains were "low risk," "high risk," or "unclear risk," and they were evaluated using individual items, as described in the Cochrane Handbook for Systematic Reviews of Interventions [17].

We assessed the risk of bias in nonrandomized studies (NRSs) using ROBINS-I, which is used to assess the risk of bias in NRSs of interventions using the "low risk," "moderate risk," "serious risk," "critical risk," or "no information" domains [19].

5. Data collection and analysis

We extracted the outcome data, as needed for the calculation of summary statistics and measures of variance. For the dichotomous outcomes, we obtained the number of events and their proportions, as well as the summary statistics with corresponding measures of variance. For the continuous outcomes, we obtained the means and standard deviations or other necessary data. We calculated the hazard ratios and corresponding 95% confidence intervals (CIs) for the oncologic outcomes; no study reported these outcomes using time-to-event data. We analyzed the data using a random-effects model. Review Manager 5 software was used for the statistical analysis (The Cochrane Collaboration, Copenhagen, Denmark) [20]. We assessed the impact of heterogeneity on the meta-analysis and interpreted it according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions [21]. We expected the characteristics, such as age, tumor size, and preoperative renal function, to be heterogeneous and planned to carry out subgroup analyses with an investigation of interactions limited to primary outcomes. The sensitivity analyses of the primary outcomes were planned for only RCTs to explore the influence of the risk of bias (when applicable) on effect sizes by excluding studies with high or unclear risks. However, we could not perform secondary analyses because there were no relevant data, and the RCTs were scarce. If we included 10 studies or more in investigating a particular outcome, funnel plots were used to assess small study effects.

6. Summary of findings table

We assessed the overall certainty of the evidence (CoE) for each outcome according to the GRADE framework. Three review authors (TWK, JYL, JHJ) independently rated

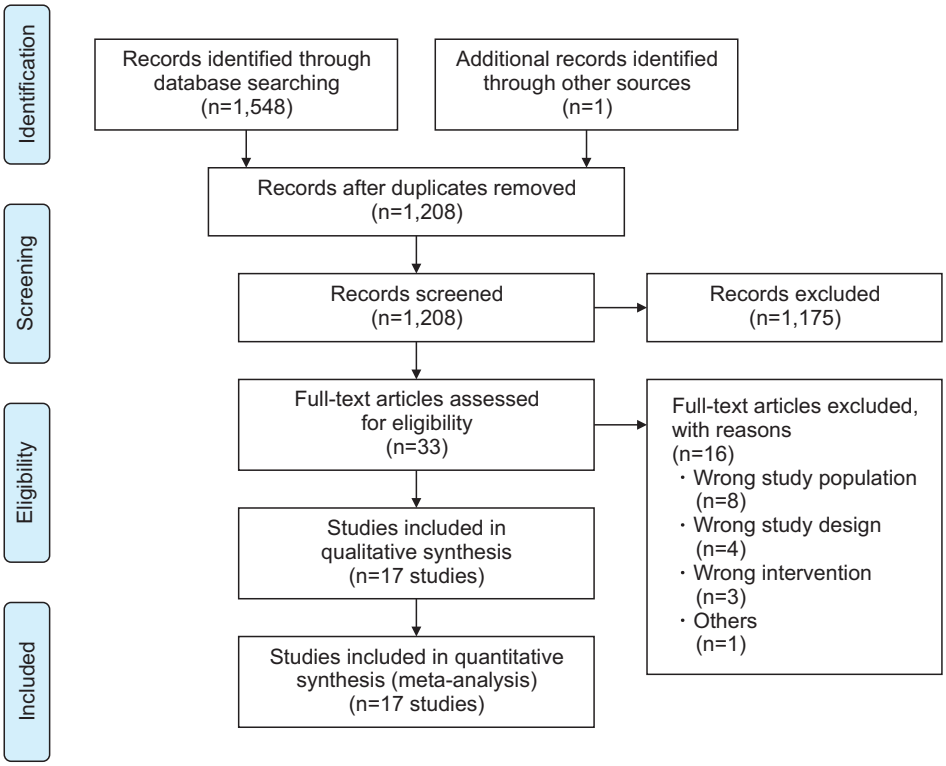

Fig. 1. PRISMA 2009 flow diagram.

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Table 1A. Baseline characteristics of the included studies

Study name	Design/setting/country	Population				
		Inclusion criteria	No. of participants (TE/PN)	Age (TE/PN, y, mean±SD)	Tumor size (TE/PN, cm, mean±SD)	Baseline GFR (TE/PN, mL/min/1.73 m^2, mean±SD)
Blackwell et al., 2017 [53]	Case control/single center/USA	Patients who had appropriate pre- and postoperative studies for analysis of parenchymal mass preservation specific to the operated kidney	110 (57/53)	60.1/57.6 (median)	3.0/2.5 (median)	73.1/78.3 (median)
Calaway et al., 2017 [54]	Case control/single center/USA	Patients with sporadic clear cell RCC	47 (34/13)	NR	NR/NR	NR/NR
Dobrota et al., 2020 [51]	Prospective cohort/ single center/ Romania	Patients with clinical stage T1 RCC	83 (28/55)	NR	NR/NR	85.1±23.5/77.3±20.2
Gayarre-Abril et al., 2020 [40]	Case control/single center/Spain	Patients with clinical T1 tumor	48 (26/22)	64.2±10.1/61.5±11.1	NR/NR	NR/NR
Giulioni et al., 2020 [50][b]	Case control/NR/Italy	Localized renal masses (cT1-2N0M0)	312 (274/38)	NR	NR/NR	86.6/78.9
Longo et al., 2014 [49]	Case control/ multicenter/Italy	Patients with clinical T1 tumor that was clinically and pathologically staged according to the American Joint Committee on Cancer	396 (198/198)	62.8±11.5/62.4±12.2	3.1±1.2/3.2±1.3	85.6±23.0/82.3±21.9
Lu et al., 2017 [42]	Case control/single center/China	Patients with clinical localized renal tumor	385 (280/105)	54.9±13.6/53.0±14.5	3.7±1.4/3.6±1.6	112.2±30.0/107.7±25.2
Lu et al., 2019 [43]	Case control/single center/China	Patients with highly complex renal tumors	166 (94/72)	51.3±13.3/52.3±13.4	4.6 ±1.1/4.7±1.0	107.6±14.2/99.4±18.5
Lu et al., 2020 [46][b]	RCT/single center/ China	Age 18–80 years with clinical T1 RCC	180 (90/90)	NR	NR/NR	NR/NR
Minoda et al., 2021 [48]	Case control/single center/Japan	Patients who underwent RAPN with endophytic tumor	Overall: 144 (72/72) Matching: 90 (45/45)[a]	54.0±14/53.0±13	2.7±1.1/2.6±1.3	67.0±17.0/67.0±19
Mukkamala et al., 2014 [55]	Case control/single center/USA	Patients with nonfamilial and unifocal tumors	602 (86/516)	57.0±14.0/58.0±13.0	2.9±1.6/2.9±1.4	79.0±22.0/79.0±23.0
Pogosyan et al., 2020 [41]	Case control/single center/Russia	Patients who underwent PN	109 (19/90)	57.7±4.5/61 (median)	3.0/3.4 (median)	75.7±21.5/78 (median)
George Rahota et al., 2021 [52]	Prospective cohort/ single center/ Romania	Patients who underwent 3D laparoscopic NSS for clinical T1 renal tumor	84 (38/46)	58.8±12.0/57.2±12.8	NR/NR	73.37±16.7/84.2±21.5
Takagi et al., 2017 [47]	Case control/single center/Japan	Patients who underwent robot-assisted laparoscopic PN	Overall: 282 (48/234) Matching: 90 (45/45)[a]	57.0±13.0/58.0±14.0	3.4±1.0/2.8±1.0	71.0±16.0/66.0±18.0

Table 1A. Continued

Study name	Design/setting/country	Population				
		Inclusion criteria	No. of participants (TE/PN)	Age (TE/PN, y, mean±SD)	Tumor size (TE/PN, cm, mean±SD)	Baseline GFR (TE/PN, mL/min/1.73 m^2, mean±SD)
Wang et al., 2017 [56]	Case control/single center/USA	Patients with renal tumors who underwent TE and PN	117 (59/58)	57.7/62.1 (median)	2.9/3.0 (median)	NR/NR
Zhang et al., 2005 [44]	Case control/single center/China	Patients who underwent retroperitoneal laparoscopic nephron-sparing surgery	32 (11/21)	53.0 (overall mean)	2.8 (overall mean)	NR/NR
Zhao et al., 2021 [45]	Case control/single center/China	Patients treated with MRASE or RAPN for clinical T1b renal tumors	203 (139/64)	55.7±13.3/53.7±14.4	4.5±1.0/4.8±1.1	100.1±17.9/101.9±19.9

[a]:Propensity score matching. [b]:Only abstracts have been published.
TE, tumor enucleation; PN, partial nephrectomy; GFR, glomerular filtration rate; RCC, renal cell carcinoma; NR, not recorded; RAPN, robot-assisted PN; 3D, three-dimensional; NSS, nephron-sparing surgery; MRASE, modified robot-assisted simple enucleation.

the CoE for each outcome, and we resolved any discrepancies by consensus. For the RCTs, we considered the criteria related to internal validity (risk of bias, inconsistency, imprecision, and publication bias), as well as external validity, such as the directness of results [22,23]. For the NRSs, we also considered three criteria for upgrading the CoE, which were the large magnitude of effects, all plausible confounding that would reduce a demonstrated effect or suggest a spurious effect when results showed no effect, and the dose-response gradient [22,23]. When RCTs and NRSs were considered together, we followed the current GRADE guidelines [23].

RESULTS

1. Search results

We identified 1,548 studies through electronic database searching and one other study from other sources. After removing duplicates, we screened the titles and abstracts of 1,208 studies and excluded 1,175. We screened the full text of 33 articles and excluded 16 [24-39] (Supplementary Table 2). We included 1 RCT (abstract) and 16 NRSs that ultimately met the inclusion criteria for the qualitative synthesis. The assessment process is illustrated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Fig. 1).

2. Included studies

Fifteen of the 17 studies were published in English; the other 2 were published in Spanish [40] and Russian [41], respectively. The countries of origins of the included studies were China [42-46], Japan [47,48], Italy [49,50], Spain [40], Romania [51,52], Russia [41], and the United States [53-56]. We attempted to contact the corresponding authors of the included studies to obtain additional information on the study methodology and results and received replies for two studies [53,55].

Table 1A and B show the baseline characteristics of the included studies with a total of 3,300 participants. The mean (or median) age of the patients ranged from 51.3 to 64.2 years. The mean (or median) tumor size ranged from 2.5 to 4.8 cm. The mean (or median) preoperative GFR ranged from 66.0 to 112.2 mL/min/1.73 m^2. The interventions were mainly minimally invasive, and they included laparoscopic and robotic approaches. Three studies used various surgical techniques for nephrectomy (two studies [40,49], open or laparoscopic; one study [50], open, laparoscopic, or robot-assisted). Two studies did not describe the interventions in detail [41,56]. The mean duration of surgery ranged from 70 to 241 minutes. The mean (or median) duration of warm ischemia

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Table 1B. Baseline characteristics of the included studies

Study name	Intervention/comparator			Study period (median, mo)
	Procedure	Operation time (min, mean±SD)	Warm ischemic time (min, mean±SD)	
Blackwell et al., 2017 [53]	Robot-assisted	NR/NR	24/26.5 (median)	12
Calaway et al., 2017 [54]	Robot-assisted	NR/NR	NR/NR	NR
Dobrota et al., 2020 [51]	3D Laparoscopic	NR/NR	NR/NR	NR
Gayarre-Abril et al., 2020 [40]	Open or laparoscopic	NR/NR	NR/NR	NR
Giulioni et al., 2020 [50][b]	Open, laparoscopic, or robot-assisted	140/148	4/4 (median)	NR
Longo et al., 2014 [49]	Open or laparoscopic	121±44/147±42	18±5/17±6	NR
Lu et al., 2017 [42]	Laparoscopic	182±52/192±53	23±6/25±6	18
Lu et al., 2019 [43]	Robot-assisted	107±10/121±11	17±3/20±3	36 (TE)/37 (PN)
Lu et al., 2020 [46][b]	Robot-assisted	162±50/169±50	18±9/21±9	NR
Minoda et al., 2021 [48]	Robot-assisted	140±44/167±40	23±14/21±8	NR
Mukkamala et al., 2014 [55]	Minimally invasive[a]	159±58/191±58	23±10/27±11	34
Pogosyan et al., 2020 [41]	Not defined	NR/NR	20/20 (median)	NR
George Rahota et al., 2021 [52]	3D Laparoscopic	158±33/169±17	0/18	NR
Takagi et al., 2017 [47]	Robot-assisted	190±39/180±41	25±12/18±6	NR
Wang et al., 2017 [56]	Not defined	181/241	25/25	22 (TE)/19 (PN)
Zhang et al., 2005 [44]	Laparoscopic	70/96	NR/NR	13
Zhao et al., 2021 [45]	Robot-assisted	197±54/215±61	21±6/24±6	32 (TE)/30 (PN)

[a]:Not defined. [b]:Only abstracts have been published.
3D, three-dimensional; NR, not reported; TE, tumor enucleation; PN, partial nephrectomy.

ranged from 4 to 27 minutes. The residual renal function measured by GFR was reported perioperatively [43,48,52,55], within 3 months of surgery [43,47], and at 3 months after surgery [43,45,48,51]. Two NRSs reported cancer-specific mortality (follow-up: median 18 to 37 months), but no study reported overall mortality [42,43]. Major adverse events were reported in 10 NRSs [42-45,47-50,52,55]. Local recurrence was reported in 6 studies including 1 RCT [42-46,52]. Distant metastasis was reported in three studies [42,43,52]. A positive surgical margin was reported in 15 studies including 1 RCT [40-50,52-55]. Overall adverse events were reported in 13 NRSs [40-45,47-50,52,55,56]. Six NRSs reported hospital stays [40,42,43,45,47,48].

Six of 17 studies specified funding sources: 3 studies reported that they had no relevant financial interests [40,41,53], and 3 studies were funded by institutions [44,49,55]. Ten studies reported their conflicts of interest: 1 study reported that the corresponding author was the paid chairman of the AUA Practice Guidelines Committee and a paid consultant for the Urology Times [55] and 9 studies reported no conflicts of interests [40-43,45,47-49,56].

3. Effect of the intervention

We included 17 studies (1 RCT and 16 NRSs) involving 3,300 participants (TE, 1,553; PN, 1,747) (Table 2).

4. Primary outcomes

1) Residual renal function

(1) Perioperative (within 1 wk)

We are uncertain about the effects of TE on residual renal function measured by GFR (mean difference [MD] 3.38, 95% CI 1.52 to 5.23; I^2=68%; 4 NRSs; 942 participants; very low CoE) [43,48,52,55].

(2) Short-term (up to 3 mo)

TE may result in little to no difference in residual renal function measured by GFR (MD 1.04, 95% CI 0.25 to 1.83; I^2=0%; 2 NRSs; 256 participants; low CoE) [43,47].

(3) Long-term (beyond 3 mo)

We are uncertain about the effects of TE on residual renal function measured by GFR (MD 2.31, 95% CI -1.40 to 6.01; I^2=57%; 4 NRS; 542 participants; very low CoE) [43,45,48,51]. After excluding the study that reported the final result of GFR with a marginal baseline difference ($p<0.1$), TE may result in little to no difference in residual renal function (MD 0.29, 95% CI -0.16, 0.74; I^2=0%; 3 NRS; 459 participants; low CoE) [43,45,48].

2) Overall mortality

No study reported this outcome.

Table 2. Summary of findings table

Outcome	No. of participants (studies)	Certainty of the evidence (GRADE)[a]	Relative effect (95% CI)[b]	Anticipated absolute effects	
				Risk with PN	Risk difference with TE
Residual renal function (GFR, mL/min/1.73 m^2) Follow-up: perioperative MCID: 5[i]	942 (4 NRSs)	⊕○○○ VERY LOW[c,d]	-	The mean change of GFR ranged from -2.3 to -12.6	MD 3.38 higher (1.52 higher to 5.23 higher)
Residual renal function (GFR, mL/min/1.73 m^2) Follow-up: 1 to 3 months MCID: 5[i]	256 (2 NRSs)	⊕⊕○○ LOW[c]	-	The mean change of GFR ranged from -6.2 to -8.0	MD 1.04 higher (0.25 higher to 1.83 higher)
Residual renal function (GFR, mL/min/1.73 m^2) Follow-up: beyond 3 months MCID: 5[i]	542 (4 NRS)	⊕○○○ VERY LOW[c,d]	-	The mean change of GFR ranged from -3.7 to -15	MD 2.31 higher (1.4 lower to 6.01 higher)
Overall mortality (not reported)	-	-	-	-	-
Major adverse events Follow-up: median 13 to 37 months MCID: 3% absolute risk difference	2,360 (10 NRSs)	⊕○○○ VERY LOW[c,d,e]	RR 0.48 (0.30 to 0.79)	Study population 57 per 1,000	30 fewer per 1,000 (40 fewer to 12 fewer)
Cancer-specific mortality Follow-up: median 18 to 37 months MCID: 3% absolute risk difference	551 (2 NRSs)	⊕○○○ VERY LOW[c,d]	RR 0.90 (0.11 to 7.28)	Study population 6 per 1,000	1 fewer per 1,000 (5 fewer to 35 more)
Local recurrence Follow-up: median 13 to 37 months MCID: 3% absolute risk difference	180 (1 RCT)	⊕○○○ VERY LOW[f,g,h]	Not estimable	Study population -	-
	870 (5 NRSs)	⊕○○○ VERY LOW[c,d]	RR 1.33 (0.35 to 4.98)	Study population 10 per 1,000	3 more per 1,000 (6 fewer to 39 more)
Distant metastasis Follow-up: median 18 to 37 months MCID: 3% absolute risk difference	635 (3 NRSs)	⊕○○○ VERY LOW[c,d]	RR 0.75 (0.22 to 2.56)	Study population 18 per 1,000	6 fewer per 1,000 (14 fewer to 28 more)
Positive margin Follow-up: perioperative MCID: 5% absolute risk difference	180 (1 RCT)	⊕⊕○○ LOW[d,f]	RR 0.67 (0.11 to 3.90)	Study population 33 per 1,000	11 fewer per 1,000 (30 fewer to 97 more)
	2,528 (14 NRSs)	⊕⊕○○ LOW[c]	RR 0.72 (0.44 to 1.17)	Study population 50 per 1,000	14 fewer per 1,000 (28 fewer to 8 more)
Overall adverse events Follow-up: median 13 to 37 months MCID: 5% absolute risk difference	2,634 (13 NRSs)	⊕○○○ VERY LOW[c,d,e]	RR 0.69 (0.57 to 0.83)	Study population 250 per 1,000	78 fewer per 1,000 (108 fewer to 43 fewer)

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Table 2. Continued

Outcome	No. of participants (studies)	Certainty of the evidence (GRADE)[a]	Relative effect (95% CI)[b]	Anticipated absolute effects	
				Risk with PN	Risk difference with TE
Hospital stay (days) Follow-up: perioperative MCID: 1	982 (6 NRSs)	⊕⊕◯◯ LOW[c]	-	The mean hospital stay ranged from 5.0 to 8.7	MD 0.71 days lower (0.91 lower to 0.51 lower)

Patient or population: patients with T1 renal tumor. Setting: retrospective study design/China, Japan, Italy, and USA. Intervention: TE. Comparison: PN.
CI, confidence interval; PN, partial nephrectomy; TE, tumor enucleation; GFR, glomerular filtration rate; MCID, minimal clinically important difference; NRS, nonrandomized study; MD, mean difference; RR, risk ratio; RCT, randomized controlled trial.
[a]:GRADE Working Group grades of evidence: (1) High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. (2) Moderate certainty: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. (3) Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. (4) Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
[b]:The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[c]:Downgraded by two levels for study limitations (NRS).
[d]:Downgraded by one level for imprecision (cross assumed threshold).
[e]:Downgraded by one level for publication bias.
[f]:Downgraded by one level for study limitations (RCT).
[g]:Downgraded by two levels for imprecision: very rare event.
[h]:No event in either group.
[i]:Mayne TJ, Nordyke RJ, Schold JD, Weir MR, Mohan S. Defining a minimal clinically meaningful difference in 12-month estimated glomerular filtration rate for clinical trials in deceased donor kidney transplantation. Clin Transplant 2021;35:e14326.

3) Major adverse events

We are uncertain about the effects of TE on major adverse events (risk ratio [RR] 0.48, 95% CI 0.30 to 0.79; I^2=0%; 10 NRS; 2,360 participants; very low CoE) [42-45,47-50,52,55]. This would correspond to 30 fewer major adverse events per 1,000 men (95% CI 40 fewer to 12 fewer).

5. Secondary outcomes

1) Cancer-specific mortality

We are uncertain about the effects of TE on mortality (RR 0.90, 95% CI 0.11 to 7.28; I^2=0%; 2 NRSs; 551 participants; very low CoE) [42,43]. This would correspond to 1 fewer cancer-specific mortality events per 1,000 men (95% CI 5 fewer to 35 more).

2) Local recurrence

Based on 1 RCT with 180 participants (TE: 90, PN: 90), there was no local recurrence in either group [46].

Based on 5 NRSs with 870 participants (TE: 562, PN: 308), we are uncertain about the effects of TE on local recurrence (RR 1.33, 95% CI 0.35 to 4.98; I^2=0%; 5 NRSs; 870 participants; very low CoE) [42-45,52]. This would correspond to 3 more local recurrences per 1,000 men (95% CI 6 fewer to 39 more).

Based on the entire body of evidence, we are uncertain about the effects of TE on local recurrence.

3) Distant metastasis

We are uncertain about the effects of TE on distant metastasis (RR 0.75, 95% CI: 0.22 to 2.56; I^2=0%; 3 NRSs; 635 participants; very low CoE) [42,43,52]. This would correspond to 6 fewer distant metastasis events per 1,000 men (95% CI 14 fewer to 28 more).

4) Positive surgical margin

Based on 1 RCT with 180 participants (TE: 90, PN: 90), TE may result in little to no difference in the positive surgical margin (RR 0.67, 95% CI 0.11 to 3.90; 1 RCT; 180 participants; low CoE) [46]. This would correspond to 11 fewer positive surgical margins per 1,000 men (95% CI 30 fewer to 97 more).

Based on 14 NRSs with 2,528 participants (TE: 1,328, PN: 1,200), TE may result in little to no difference in the positive surgical margin (RR 0.72, 95% CI 0.44 to 1.17; I^2=13%; 14 NRSs; 2,528 participants; low CoE) [40-45,47-50,52-55]. This would correspond to 14 fewer positive surgical margins per 1,000 men (95% CI 28 fewer to 8 more).

Based on the entire body of evidence, TE may result in little to no difference in the positive surgical margin.

5) Overall adverse events

We are uncertain about the effects of TE on the overall adverse events (RR 0.69, 95% CI 0.57 to 0.83; I^2=0%; 13 NRSs; 2,634; very low CoE) [40-45,47-50,52,55,56]. This would correspond to 78 fewer overall adverse events per 1,000 men (95% CI 108 fewer to 43 more).

6) Hospital stay

TE may result in little to no difference in the duration of hospital stay (MD -0.71, 95% CI -0.91 to -0.51; I^2=0%; 6 NRSs; 982 participants; low CoE) [40,42,43,45,47,48].

7) Postoperative pain

No study reported this outcome.

6. Secondary analysis

We were unable to perform any secondary analyses because the included studies did not report relevant data or the reported data were limited.

7. Risk of bias

1) RCT

We found one RCT that compared TE with PN. and we summarized the risk of bias assessment in Fig. 2.

While we judged detection bias and attrition bias for oncologic outcomes such as local recurrence and positive surgical margin as being low risk, we judged the other risk of bias as unclear risk because there were no relevant descriptions in the study [46].

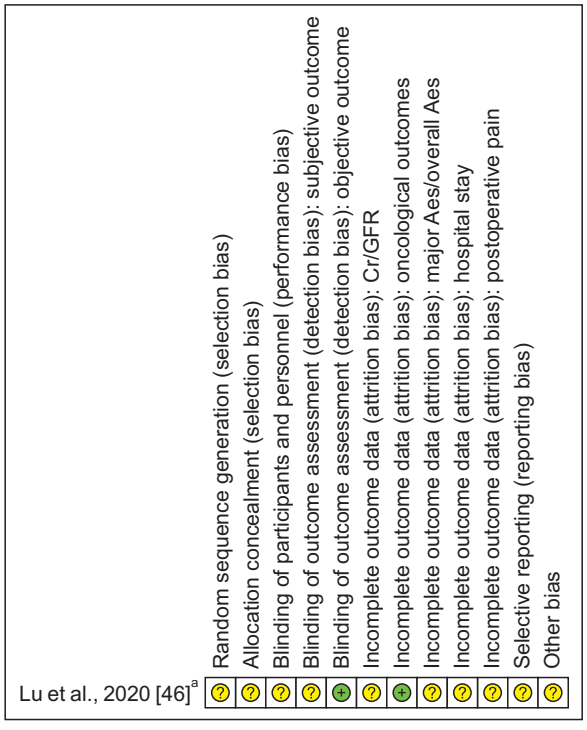

Fig. 2. Risk of bias summary. Review authors' judgements about each risk of bias item for each included study. Cr, creatinine; GFR, glomerular filtration rate. [a]:Only abstracts have been published.

2) NRS

For reporting purposes, we split the risk of bias assessments for the outcomes into six sets. Within each set of outcomes, the risk of bias assessments were the same across all domains (set 1: GFR [perioperative], cancer-specific mortality, local recurrence, and distant metastasis; set 2: GFR [short-term]; set 3: GFR [long-term]; set 4: major adverse events; set 5: positive surgical margin; set 6: overall adverse events and hospital stay). No study reported the overall mortality (no information). The bias due to confounding was serious or critical for all the review outcomes because of the inherent limitations of NRSs, even though the author likely used an appropriate analysis method (e.g., propensity score matching) to control confounding factors. All review outcomes were judged to have moderate risk of bias due to selection of participants and in classification of interventions. All review outcomes were judged as serious risk of bias due to deviations from the intended interventions. The bias due to missing data was moderate for sets 2 and 3 for the study by Lu et al. [43] and critical for set 5 for two studies [53,55]. The remaining studies had a low risk of bias because most of the study participants were likely included in the analysis. The risk of bias in measurement of outcomes and selection of the reported result were moderate or serious because of unblinding of the participants or investigators and the lack of information on the published protocol. The overall risk of bias for all review outcomes across the included studies was critical or serious (Fig. 3).

8. Publication bias

For outcomes such as major adverse events, positive surgical margin, and overall adverse events reported by 10 or more studies, there was no suspected publication bias on visual inspection and sensitivity analysis using comparison of random-effects and fixed-effect meta-analysis.

DISCUSSION

The current guidelines recommend that TE can be considered in patients with familial RCC, multifocal disease, or severe chronic kidney disease to optimize parenchymal tissue preservation. However, the clinical benefits and negative effects of this surgical technique remain controversial [37,49,55,57].

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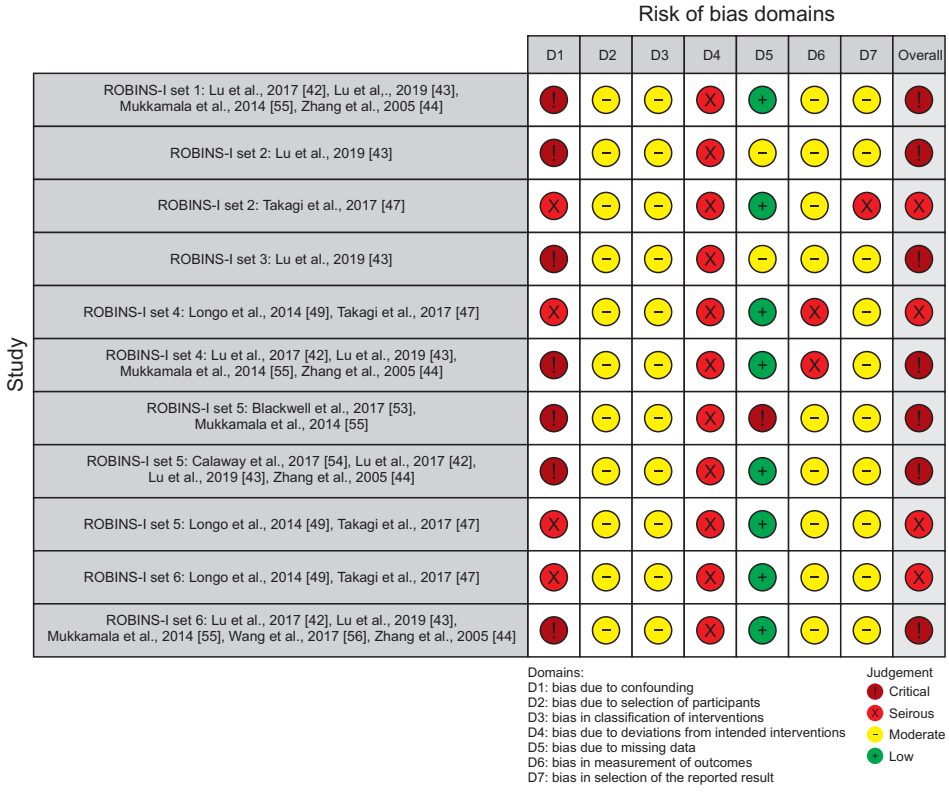

Fig. 3. Risk of bias summary. ROBINS-I outcome set 1: glomerular filtration rate (perioperative), cancer-specific mortality, local recurrence, distant metastasis; set 2: glomerular filtration rate (short-term); set 3: glomerular filtration rate (long-term); set 4: major adverse events; set 5: positive surgical margin; set 6: overall adverse event, hospital stay. Figure created using robvis: https://www.riskofbias.info/welcome/robvis-visualization-tool.

In our review, we included 1 RCT and 16 NRSs involving 3,300 participants aged 51.3 to 64.2 years. The mean (or median) tumor size ranged from 2.5 to 4.8 cm. Whereas TE appears to have similar effects on residual renal function up to 3 months, we are uncertain about the effects after 3 months. However, we are uncertain about the effects of TE on major adverse events, cancer-specific mortality, local recurrence, distant metastasis, and overall adverse events. Regarding the positive surgical margin and hospital stay, TE and PN may demonstrate little to no difference. The evidence was mainly based on NRSs with a small sample (wide CI) that were conducted over a relatively short duration.

Recently, Xu et al. [58] performed a systematic review and meta-analysis of 13 studies, including 3 RCTs. They suggested that TE was a less traumatic and recovery-beneficial technique compared with PN that was better for preserving renal function. However, two studies (one prospective observational multicenter study [59] and one retrospective study [37]) in the review were misclassified as RCTs. More importantly, the RCT performed radiofrequency ablation before TE to maximize the effects of TE; therefore, we excluded those studies because of the indirectness of our review question [38]. Recently, two more RCTs comparing radiofrequency ablation with TE and PN have been published. On the basis of the results of these RCTs, we performed meta-analyses for residual renal function (up to 3 months [MD 8.40, 95% CI 2.34 to 14.46; 1 RCT; 89 participants], beyond 3 months [MD 6.60, 95% CI 0.15 to 13.05; 1 RCT; 89 participants]), major adverse events (RR 0.98, 95% CI 0.15 to 6.60; I^2=0%; 2 RCTs; 272 participants), local recurrence (no event in either group), positive surgical margin (RR 0.67, 95% CI 0.11 to 3.90; I^2=0%; 3 RCTs; 452 participants), overall adverse events (RR 0.88, 95% CI 0.42 to 1.84; I^2=0%; 2 RCTs; 272 participants), and hospital stay (RR -0.50, 95% CI -0.89 to -0.11; 1 RCT; 183 participants).

Two more systematic reviews were published in 2017. Cao et al. [60] evaluated the safety and efficacy of TE and compared them with of the same variables for PN for T1 RCC. They included seven studies, including one RCT, and suggested that TE is effective and safe for T1 RCC and is acceptable for early oncologic outcomes. However, the review did not account for RoB in individual studies when interpreting the results of the review. In addition, the RCT in the systematic review was the same study by Huang et al. [38], who performed radiofrequency ablation with TE. Another study reported that TE was noninferior to PN based on the positive surgical margins and local recurrence rates in patients with malignant renal tumors [61]. However, this conclusion was based on indirect evidence using single-arm studies. In addition, they did not assess the potential impact of the risk of bias in individual studies on the basis of the results of the meta-analysis. Finally, both reviews searched a limited database and excluded studies based on publica-

tion status (e.g., abstract) or the language of publication (e.g., other than English).

We arrived at a conclusion that was consistent with those of previous reviews. However, we believe that our review is the first to use the same rigorous methodology as in the Cochrane Review. We registered an explicit statement that the review methods were established before the review in PROSPERO and focused on outcomes important to patients such as mortality and adverse events. In addition, we performed a comprehensive literature search of multiple databases, as well as trial registries, other sources of gray literature, and conference proceedings, with no restrictions on the language of publication or publication status. Most importantly, we rated the risk of bias of the included studies and evaluated the CoE to assess the potential impact of the risk of bias on our results according to GRADE.

Our review has some limitations regarding what can be applied to current practice. First, most of the evidence stems from the NRSs, and their inherent limitations are carried over; these studies only provided evidence with low or very low certainty. Second, the ability to assess the long-term outcomes of TE compared with conventional PN was limited, given that the median follow-up duration was 37 months or less. Third, almost all studies were conducted at single centers. Due to the lack of RCTs, similar studies performed by the investigators in multiple centers around the world would be valuable in validating these findings. Finally, adjusted estimates using multivariate analysis need to be presented to resolve the confounding bias in NRSs. However, the outcomes in the included studies were reported without adjustment. In addition, we were unable to perform any of our predefined secondary analyses for factors such as patient age, tumor size, and preoperative renal function, which may be important effect modifiers.

In summary, there is insufficient evidence to elucidate the effects of TE in routine clinical practice. Given the low and very low CoE found for TE, additional studies of better quality, namely RCTs comparing TE and conventional PN, appear essential. Future trials should be conducted according to higher methodologic standards, and long-term data should be provided.

CONCLUSIONS

TE and PN seem to be associated with comparable short-term postoperative residual renal function. However, we are uncertain about the perioperative and long-term postoperative residual renal function. We are also not certain about the other patient outcomes, such as oncologic outcomes and adverse events, associated with TE. Therefore, there is a need for methodologically rigorous RCTs to elucidate the outcomes of TE in patients with T1 renal tumors.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Tae Wook Kang and Jae Hung Jung. Data acquisition: Hyun Chul Chung, Tae Wook Kang, and Young Hwan Kim. Statistical analysis: Tae Wook Kang, Joon Young Lee, and Jae Hung Jung. Data analysis and interpretation: Tae Wook Kang and Jae Hung Jung. Drafting of the manuscript: Hyun Chul Chung, Tae Wook Kang, and Jae Hung Jung. Critical revision of the manuscript: Eu Chang Hwang and Ki Don Chang. Supervision: Hong Jun Park and Jun Eul Hwang. Approval of the final manuscript: Jae Hung Jung.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20210361.

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