

Which factors can influence post-operative renal function preservation after nephron-sparing surgery for kidney cancer: a critical review

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Citation: Di Lascio G, Sciarra A, Del Giudice F, et al. Which factors can influence post-operative renal function preservation after nephron-sparing surgery for kidney cancer: a critical review. Cent European J Urol. 2022; 75: 14-27.

Article history

Submitted: Oct. 20, 2021

Accepted: Dec. 16, 2021

Published online: Jan. 12, 2022

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Introduction The aim of this article was to compare different surgical approaches to perform nephron-sparing surgery (NSS) in terms of preservation of renal function.

Material and methods We critically reviewed the literature from January 2000 to December 2020 including studies comparing different surgical techniques.

Results A total of 51 studies met the inclusion criteria. Functional outcomes were evaluated in terms of percentual change of estimated glomerular filtration rate (eGFR) and impaired renal function (IRF) on scintigraphy. In cases with a mean age <60 years, the mean decrease in eGFR after NSS was 11.7% and that of IRF 10.0%, whereas higher changes were found in cases with a mean age ≥60 years. For open NSS, the mean eGFR and IRF changes were 15.3% and 21.1%, respectively; using the laparoscopic approach, the mean percentual eGFR and IRF changes were 13.9% and 11.1%, respectively; in robotic cases, the mean eGFR and IRF changes were 10.8% and 13.1%, respectively. In cases performed with global ischemia, the mean eGFR and IRF changes were 12.7% and 15.1%, respectively. Similar results were found distinguishing ischemia time ≤20 and >20 minutes, whereas using the off-clamp technique the mean decreases in eGFR and IRF were only 4.2% and 6%, respectively.

Conclusions Patients' age, tumor size, off-clamp technique, and robot-assisted approach were significant independent predictive factors able to influence renal function changes after NSS. A lower reduction of eGFR and IRF after NSS was reported in patients aged <60 years, submitted to a robot-assisted procedure, and using selective and cold ischemia <20 minutes or an off-clamp technique.

Key Words: kidney cancer ↔ nephron-sparing surgery ↔ partial nephrectomy ↔ renal function

INTRODUCTION

International urological guidelines recommend partial nephrectomy (PN) as the gold standard for treatment of small renal masses [1].

The 'trifecta concept' [(i.e., negative surgical margins, no major complications and maximum preservation of renal function (RF)] – is the goal of nephron-sparing surgery (NSS) [2].

In the recent past, open partial nephrectomy (OPN) was considered the most effective surgery approach, yet, due to the improvement of equipments and operator skills, laparoscopic PN (LPN) has been increasingly used with better peri-operative

results. The aim of this article was to compare different surgical approaches to perform nephron-sparing surgery (NSS) in terms of preservation of renal function.

and post-operative morbidity and comparable long-term oncological results for T1 tumors [3].

However, LPN is a technically challenging procedure, especially in those cases with high nephrometric scores, which require longer warm ischemia time (WIT) with risk of impaired post-operative RF [4, 5]. In these cases, robot-assisted PN (RAPN) can offer advantages in solving the LPN 'difficult points', such as tumor excision, hilum preparation and renorrhaphy, moreover with the possibility of selective ischemia, performed to maximize saving of healthy renal parenchyma and residual RF [6].

According to the recent literature, RAPN is considered superior to LPN in terms of complications, WIT – when performed – and RF preservation [7].

In this review, we aimed to compare the three currently available surgical options and some technical variables to perform NSS, in terms of renal function preservation.

MATERIAL AND METHODS

The aim of the present review was to critically analyze and compare results in the literature regarding different approaches of NSS. In particular, we compared OPN with LPN and RAPN in terms of renal function preservation.

Search strategy

We searched in PubMed, Web of Science and Cochrane Library database (primary fields: partial nephrectomy AND open partial nephrectomy AND robot-assisted partial nephrectomy AND laparoscopic partial nephrectomy).

Our search was performed on 10 May 2021 without language restriction between January 2000 and December 2020, following the PRISMA guidelines (Figure 1). Original and review articles were included and critically evaluated. Additional studies were identified from the references of included papers. Meeting abstracts were excluded.

Selection of the studies and inclusion criteria

Collected data were gathered from clinical trials evaluating the surgical approach(es) for NSS concerning tumor size, time and type of ischemia, and related functional outcomes. Two authors (GDL; GDP) independently screened the titles and abstracts of all articles using the predefined inclusion criteria. The full-text articles were examined independently by three authors (GDL; MM; GDP) to determine whether or not they met the inclusion criteria. Discrepancies were solved by all investigators' evaluation discussion.

Inclusion criteria were: (I) analysis on NSS for renal cell carcinoma; (II) open or laparoscopic or robot-assisted procedures; (III) results expressed as surgical data (tumor size, tumor score, surgical technique, time of ischemia) and functional outcomes [change in estimated glomerular filtration rate (eGFR), impaired renal function (IRF) or scintigraphy outcomes].

Articles were excluded if: (I) multiple reports were published on the same population; (II) data provided were insufficient for the analysis; (III) comparison of at least one surgical or functional outcome was not reported.

RESULTS

Search results

The literature search yielded 261 articles. Of these, 104 were subsequently removed due to duplication. Full text articles of 66 articles were then re-evaluated and critically analyzed. Of these, 15 did not meet the inclusion criteria and were excluded. The remaining 51 studies were included in this review (Figure 1). Table 1 shows the characteristics of the included studies [8–58].

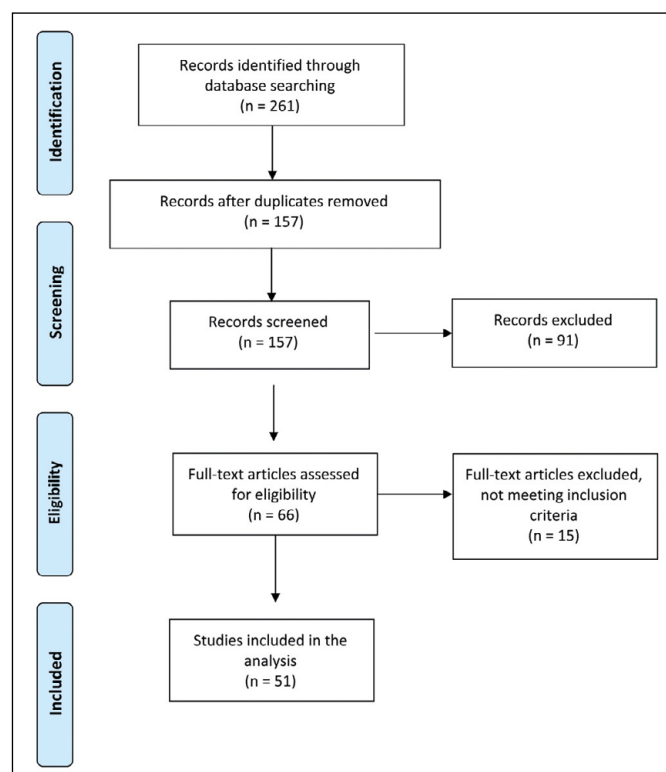


Figure 1. PRISMA flow diagram.

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

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Table 1. Baseline characteristics of the included studies (*n* = 51), reporting functional outcomes after partial nephrectomy

Study, authors, year	Study design	Number of cases	Age, years	Comorbidity scores (ASA, CCI scores)	Tumor size, cm	Nephrometry score	Surgical approach
Lane BR et al. 2008 [8]	SC Retrospect	1169	Median (IQR): 61 (52–69)	NR	Median (IQR): 3.0 (2.2–4.1)	NR	OPN: 696 LNP: 473
Funahashi Y et al. 2009 [9]	SC Retrospect	32	Mean (SD): 58 (13)	NR	Mean (SD): 2.7 (0.8)	NR	OPN: 20 LNP: 12
Song C et al. 2009 [10]	SC Retrospect	117	Mean (range): 52.5 (26–75)	NR	Mean (SD): 2.8 (0.8–11.0)	NR	OPN: 52 LNP: 65
Thompson RH et al. 2010 [11]	MC Retrospect	458	Median (range): GI: 62 (19–93) OC: 63 (32–83)	NR	Median (range): GI: 3.4 (0.7–18.0) OC: 2.5 (0.9–8.5)	NR	OPN: 411 LNP: 47
Shikanov S et al. 2010 [12]	Retrospect	401	Median (IQR): 60 (52–68)	NR	Median: 2.5	NR	LPN: 401
Smith GL et al. 2011 [13]	SC Retrospect	308	Median (range): GI: 62 (51–69) OC: 62 (51–70)	NR	Median (range): GI: 2.8 (2.0–3.5) OC: 3.0 (2.5–4.5)	NR	OPN: 308
Pouliot F et al. 2011 [14]	SC Retrospect	56	Mean (SD): 62 (11)	ASA 1: 43; ASA 2: 35; ASA 3: 22	Mean (SD): 3.2 (1.6)	NR	LPN: 56
Lane BR et al. 2011 [15]	MC Retrospect	660 solitary kidney	Median: CI: 64 WI: 61	CCI ≥2: 95	Median (IQR): CI: 4.0 (2.9–5.4) WI: 4.0 (2.8–5.2)	NR	OPN: 660
Simmons MN et al. 2011 [16]	SC Retrospect	39	Median (range): 59 (18–80)	CCI, Median (range): 2 (1–3)	Median (range): 3.5 (1.3–10.1)	NR	OPN: 27 LPN: 11
Thompson RH et al. 2012 [17]	MC Retrospect	362 solitary kidney	Median (range): 62 (19–93)	NR	Median (range): 3.4 (0.7–18.0)	NR	OPN: 319 LNP: 43
Simmons MN et al. 2012 [18]	SC Retrospect	301	Median (range): 59 (18–86)	CCI, Median (range): 4 (1–12)	Median (range): 3.2 (0.8–9.6)	NR	OPN: 141 LNP: 100 RAPN: 60
Porpiglia F et al. 2012 [19]	SC Prosp	54	Mean (SD): 57 (13.9)	CCI, Mean (SD): 0.9 (1.4)	Mean (SD): 3.6 (1.4)	RENAL, Mean (SD): 5.0 (1.4)	LPN: 54
Sankin A et al. 2012 [20]	SC Retrospect	32	Median (IQR): 58 (55–69)	NR	Median (IQR): 3.0 (2–4)	NR	LNP RAPN
Ng CK et al. 2012 [21]	SC Prosp	44 SI+MD: 22 SI-MD: 22	Mean (SD): SI+MD: 56 (7.9) SI-MD: 57 (13.2)	ASA, Median (range): 18.5 (28.5–43.4)	Mean (SD): SI+MD: 4.6 (2.6) SI-MD: 2.3 (1.0)	RENAL, Median (IQR): SI+MD: 8 (4–11) SI-MD: 6 (4–9)	LNP RAPN
Gill IS et al. 2012 [22]	SC Prosp	57	Median (range): 59 (18–86)	Mean (range) ASA: 2.4 (1–3) CCI: 0.6 (0–4)	Median (range): 3.2 (0.9–13.0)	RENAL, Mean (SD): 7.0 (1.9)	LNP: 43 RAPN: 15
Shao P et al. 2012 [23]	SC Retrospect	125	Median (range): 58 (12–81)	NR	Median (range): 3.4 (1.4–7.0)	NR	LPN: 125
Papalia R et al. 2012 [24]	SC Prosp	121	Mean (SD): 59 (14.2)	NR	Mean (SD): 3.9 (1.9)	NR	LNP: 70 RAPN: 51
Mir MC et al. 2013 [25]	SC Retrospect	92	Median (IQR): 61 (55–70)	CCI, Median (IQR): 4 (2–6)	Median (IQR): 3.5 (2.3–4.8)	RENAL, Median (IQR): 8.0 (5.5–9.0)	OPN LNP RAPN
Hillyer SP et al. 2013 [26]	MC Retrospect	26 solitary kidney	Median (IQR): 66 (60–71)	Median (IQR) ASA: 3 (2–3) CCI: 4 (3–4)	Median (IQR): 4.3 (2.9–5.0)	RENAL, Median (IQR): 6.0 (5.0–7.0)	RAPN: 26
Panumatrassamee K et al. 2013 [27]	SC Retrospect	67	Median (IQR): LPN: 61 (50–72) RAPN: 63 (59–69)	ASA 1–2: LPN: 14; RAPN: 6 ASA 3–4: LPN: 35; RAPN: 9	Median (IQR): LPN: 2.8 (2.2–4.3) RAPN: 3.2 (2.5–5.3)	NR	LPN: 52 RAPN: 15
Gupta GN et al. 2013 [28]	SC Retrospect	19	Median (range): 47 (26–76)	NR	Median (range): 5.0 (4.1–15)	RENAL, Median: 9.0	RAPN: 19
Kaczmarek BF et al. 2013 [29]	MC Retrospect	332	Mean (SD): GI: 60.4 (1.5) OC: 60.2 (0.5)	NR	Mean (SD): 2.5 (2.1)	RENAL, Mean (SD): GI: 5.6 (0.2) OC: 5.3 (0.2)	RAPN: 332

Table 1. Continued

Study, authors, year	Study design	Number of cases	Age, years	Comorbidity scores (ASA, CCI scores)	Tumor size, cm	Nephrometry score	Surgical approach
Shao P et al. 2013 [30]	SC Retrospect	82	Median (IQR): 58 (11–21)	NR	Median (range): 3.0 (1.4–7.0)	RENAL, Mean (SD): 6.7 (1.8)	LPN: 82
Hung J et al. 2013 [31]	SC Retrospect	534	NR	NR	NR	NR	LPN RAPN
Zargar H et al. 2014 [32]	MC Retrospect	125	Mean (SD): OPN: 61.5 (11.4) RAPN: 61.3 (10.7)	NR	Mean (SD): OPN: 3.7 (2.0) RAPN: 2.8 (2.7)	RENAL, Mean (SD): OPN: 7.0 (3.0) RAPN: 6.0 (2.0)	OPN: 85 RAPN: 40
Autorino R et al. 2014 [33]	SC Retrospect	65	Mean (SD): 56.0 (1.4)	NR	Mean (SD): 2.6 (1.0)	RENAL, Mean (SD): 8.7 (1.4)	RAPN: 65
Volpe A et al. 2014 [34]	SC Retrospect	44	Median (IQR): 65 (60–73)	NR	Median (IQR): 4.2 (2.3–5.4)	all PADUA ≥ 10	RAPN: 44
Kaouk JH et al. 2014 [35]	SC Retrospect	11	Median (range): 55 (39–75)	NR	Median (range): 4.0 (2.3–7.1)	RENAL, Median (range): 9.0 (5–11)	RAPN: 11
Peyronnet B et al. 2014 [36]	MC Retrospect	430	Mean (SD): 59.0 (6.0) GI: 59.8 (0.8) GI+EUC: 59.5 (0.8)	NR	Mean (SD): GI: 3.2 (1.0) GI+EUC: 3.5 (1.0)	RENAL, Mean (SD): GI: 6.1 (0.4) GI+EUC: 6.9 (0.4)	RAPN: 430
McClintock TR et al. 2014 [37]	SC Retrospect	84 GI: 42 SI: 42	Mean (SD): GI: 59.4 (12.6) SI: 59.0 (12.2)	NR	Mean (SD): GI: 2.9 (1.6) SI: 2.8 (1.5)	RENAL, Mean (SD): GI: 7.4 (1.9) SI: 6.7 (1.9)	RAPN: 84
Desai MM et al. 2014 [38]	SC Retrospect	122 GI: 63 SI: 59	Median (range): GI: 63 (34–86) SI: 62 (17–88)	NR	Median (range): GI: 2.6 (1.0–6.2) SI: 3.4 (1.0–9.0)	RENAL, Median (range): GI: 7.0 (4.0–10.0) SI: 8.0 (4.0–11.0)	RAPN: 122
Porpiglia F et al. 2015 [39]	SC Retrospect	87	Mean (SD): GI: 57.5 (12.3) OC: 60.6 (12.8)	NR	Mean (SD): GI: 3.4 (1.1) OC: 3.6 (1.4)	PADUA, Mean (SD): GI: 6.9 (1.2) OC: 7.0 (1.5)	LPN: 87
Zargar H et al. 2015 [40]	SC Retrospect	99	Mean (SD): 61.0 (12.9)	NR	Median (IQR): 3.2 (2.0–4.5)	RENAL, Median (IQR): 8.0 (6.0–9.0)	RAPN: 99
Tanaka K et al. 2015 [41]	SC Retrospect	39	Mean (range): RENAL ≤ 6 : 56 (35–78) RENAL ≥ 7 : 65 (39–84)	NR	Mean (SD): RENAL ≤ 6 : 29.5 (10.9) RENAL ≥ 7 : 27.9 (8.9)	NR	RAPN: 39
Maddox M et al. 2015 [42]	SC Retrospect	46	Median (IQR): 55 (51–68)	NR	Median (IQR): 5.0 (4.1–5.2)	RENAL, Median (range): 7.1 (5.0–11.0)	RAPN: 46
Shin TY et al. 2015 [43]	SC Retrospect	117 GI: 97 SI: 20	Mean (SD): GI: 51.2 (12.8) SI: 51.0 (15.1)	NR	Mean (SD): GI: 3.6 (1.7) SI: 3.4 (1.4)	RENAL, Mean (SD): GI: 7.7 (2.0) SI: 7.3 (2.0)	RAPN: 117
Satkunasivam R et al. 2015 [44]	SC Retrospect	179 SI-LC: 70 SI: 60 OC: 49	Median (range): SI-LC: 59 (36–88) SI: 62 (34–88) OC: 62 (17–79)	NR	Median (range): SI-LC: 3.0 (0.9–13.6) SI: 3.4 (1.3–7.9) OC: 3.4 (1.5–14.0)	Median (range): SI-LC: 7.0 (4.0–11.0) SI: 8.0 (4.0–11.0) OC: 9.0 (4.0–11.0)	RAPN: 179
Zargar H et al. 2016 [45]	MC Retrospect	351	Mean (SD): 59.4 (12.1)	NR	Median (IQR): 3.2 (2.4–4.3)	RENAL, Median (IQR): 7.0 (5.0–8.0)	LPN: 135 RAPN: 216
Maurice MJ et al. 2016 [46]	SC Retrospect	880	Median (IQR): 60.5 (52.0–68.3)	NR	Median (IQR): 3.2 (2.3–4.3)	RENAL, Median (IQR): 7.0 (6.0–9.0)	LPN: 284 RAPN: 596
Luciani LG et al. 2016 [47]	SC Retrospect	32	Median (range): 67 (37–79)	NR	Median (range): 4.0 (1.8–7.0)	NR	RAPN: 32
Wang Y et al. 2016 [48]	SC Retrospect	216	Mean (SD): LPN: 63.5 (14.8) RAPN: 61.2 (12.6)	NR	Mean (SD): LPN: 3.6 (1.7) RAPN: 3.8 (2.2)	RENAL, Mean (SD): LPN: 8.1 (1.1) RAPN: 8.3 (0.9)	LPN: 135 RAPN: 81
Andrade HS et al. 2016 [49]	SC Retrospect	104	Mean (SD): LPN: 62.9 (13.2) RAPN: 60.8 (11.1)	NR	Median (IQR): LPN: 5.7 (4.7–6.7) RAPN: 5.1 (4.4–6.2)	RENAL, Median (IQR): LPN: 9.0 (9.0–10.0) RAPN: 9.0 (9.0–10.0)	LPN: 52 RAPN: 52
Novara G et al. 2016 [50]	SC Retrospect	465	Median (IQR): cystic: 62 (54.7–71.2) solid: 58 (49–66)	Charlson C. Index Median (IQR) cystic: 2 (0–3) solid: 1 (0–3)	Median (IQR): cystic: 3.4 (2.1–5.0) solid: 3.2 (2.3–4.0)	PADUA cystic: low 13, interm 28, high 13 solid: low 201, interm 118, high 92	RAPN: 465

Table 1. Continued

Study, authors, year	Study design	Number of cases	Age, years	Comorbidity scores (ASA, CCI scores)	Tumor size, cm	Nephrometry score	Surgical approach
Takagi T et al. 2016 [51]	SC Retrospect	279	Mean (SD): OPN: 58.0 (13.0) RAPN: 57.0 (13.0)	NR	Mean (SD): OPN: 4.2 (\pm 1.5) RAPN: 2.8 (\pm 0.9)	RENAL OPN: low 21, interm 97, high 61 RAPN: low 40, interm 54, high 6	OPN: 179 RAPN: 100
Ramirez D et al. 2016 [52]	SC Retrospect	28	Mean (range): 58.3 (31–76)	NR	Mean (range): 4.6 (3.0–8.0)	RENAL, Median (range) 9.0 (6.0–11.0)	RAPN: 28
Paulucci DJ et al. 2016 [53]	MC Retrospect	665 GI: 589 SI: 76	Median (IQR): GI: 58.0 (49.0–66.0) SI: 58.0 (47.3–65.8)	NR	Median (IQR): GI: 3.1 (2.3–4.1) SI: 2.5 (2.0–3.5)	RENAL, Median (IQR) GI: 7.0 (5.0–9.0) SI: 7.0 (6.0–8.0)	RAPN: 665
Tsai SH et al. 2017 [54]	SC Retrospect	103	Median (IQR): \leq 4 cm: 60 (42–67) $>$ 4 cm: 52 (45–63)	ASA 1: $>$ 4 10; $<$ 4 7 ASA 2: $>$ 4 25; $<$ 4 41 ASA 3: $>$ 4 10; $<$ 4 10	Median (IQR): \leq 4 cm: 8.0 (6.0–8.0) $>$ 4 cm: 9.0 (8.0–10.0)	RENAL, Median (IQR): \leq 4 cm: 9.0 (8.0–10.0) $>$ 4 cm: 8.0 (6.0–8.0)	RAPN: 103
Chang DK et al. 2018 [55]	SC Retrospect	366	Mean RAPN: 53.2 LPN: 53.5 OPN: 53.8	CCI, Median: RAPN: 3.6 LPN: 3.6 OPN: 3.6	Median (IQR) RAPN: 2.8 (2.2–4.8) LPN: 2.7 (1.9–4.3) OPN: 2.5 (2–4.5)	RENAL, Mean: RAPN: 2.8 LPN: 2.7 OPN: 2.5	RAPN: 122 LPN: 122 OPN: 122
Tachibana H et al. 2019 [56]	SC Retrospect	1762	Mean (SD) OPN: 58.0 (\pm 13.0) RAPN: 57.0 (\pm 13.0) LPN: 57.0 (\pm 12.0)	NR	Mean (SD) OPN: 3.7 (\pm 1.5) RAPN: 3.0 (\pm 1.3) LPN: 2.1 (\pm 0.8)	RENAL, Mean (SD) OPN: 8.2 (1.8) RAPN: 7.3 (1.9) LPN: 6.1 (1.5)	OPN: 588 RAPN: 959 LPN: 215
Gu L et al. 2020 [57]	SC Retrospect	112	Mean RAPN: 48.2 LPN: 47.3	ASA 1–2: RAPN 59; LPN 50 ASA 3–4: RAPN 2; LPN 1	Median(IQR) RAPN: 2.3 (2.1–2.8) LPN: 2.5 (1.8–3.0)	RENAL, Median: RAPN: 9.0 LPN: 8.0	RAPN: 61 LPN: 51
Würnschimmel C et al. 2020 [58]	Prosp Randomized	115	Mean (SD) LPN: 63.9 (10.5) RAPN: 62.7 (11.1)	CCI $<$ 2: LPN 3; RAPN 6 CCI 3: LPN 10; RAPN 10 CCI $>$ 4: LPN 41; RAPN 45	Median (IQR): LPN: 3.5 (2.5–4.6) RAPN: 4.0 (2.4–5.0)	RENAL, Median (IQR) LPN: 7 (6–8) RAPN: 7 (5–7) PADUA, Median (IQR) LPN: 8 (7–8) RAPN: 8 (7–9)	LPN: 54 RAPN: 61

ASA – American Society of Anesthesiology; CCI – Charlson Comorbidity Index; IQR – interquartile range; SD – standard deviation; NR – not reported; SC – single-centre; MC – multi-centre; Prosp – Prospective; Retrospect – Retrospective; GI – global ischemia; OC – off-clamp; SI – selective ischemia; WI – warm ischemia; CI – cold ischemia; SE – simple enucleation; ER – enucleoresection; wedge resection (ie, traditional PN); OPN – open partial nephrectomy; LPN – laparoscopic partial nephrectomy; RAPN – robot-assisted partial nephrectomy; MD – vascular microdissection; EUC – early unclamping

Quality of studies

Of the 51 studies entered into the review, 8 were carried out in Europe, 29 in America, 13 in Asia and 1 in Oceania.

Forty-three of 51 were single centre studies, 46 were retrospective mono or multicentre, and 5 were prospective monocentre; 1 study was randomized [58] (Table 1). Each study reported one or more surgical technique for NSS, comparing them in terms of surgical results and functional outcomes.

Study sample size, mean age and baseline comorbidities

Among the 51 included studies, the whole sample size varied from 11 to 1762 cases (total sample: 12299 cases). The range of mean age across the studies varied from 47.0 to 67.0 years. Comorbidity scores used were Charlson Comorbidity Index (CCI) and Ameri-

can Society of Anesthesiology (ASA) score. Thirty-five studies did not consider comorbidity scores. Across the studies, ASA score varied from 1 to 4, and CCI from 1 to 5. No patients were excluded for comorbidity scores (Table 1).

All studies utilized as inclusion criteria small renal mass or at least one or more renal mass not requiring radical nephrectomy. Few studies also included patients with solitary kidney [15, 17, 26].

Tumor size and nephrometry score

All 51 studies included tumor size in baseline data. Mean tumor size ranged from 2.3 to 5.7 cm. Thirty-three studies used at least one nephrometry score to assess for tumor complexity. In particular, 30 studies used the RENAL score, distinguishing or not between the types of ischemia [19, 21, 22, 25, 26, 28, 29, 30, 32, 33, 35–38, 40, 42–46, 48, 49, 51–58]. Across the studies, RENAL score ranged from 5 to 9,

with a mean value of 7.3. Four studies used the Padua score, which ranged from 6 to >10 (Table 1) [34, 39, 50, 58].

Surgical and ischemia technique

OPN was employed in 15 studies, including a total of 3940 cases [8–11, 13, 15–18, 25, 32, 46, 51, 55, 56], whereas LPN was applied in 27 studies, with a total of 2812 cases [9–12, 14, 16–25, 27, 30, 31, 39, 45, 48, 49, 55–58]. RAPN was analysed in 37 studies, comprising a total of 5661 cases (Table 2) [18, 20, 21, 22, 24–29, 31–38, 40–58]. All the studies reported enucleoresection as the excision technique for PN (Figure 2A).

With regards to the ischemia technique, 32 studies used main renal artery clamping [8–10, 12, 14–17, 19, 20, 25–28, 32–36, 40, 41, 42, 46–49, 51, 52, 54, 56, 57, 58], 5 studies selective ischemia [21–24, 30], 5 studies used both main renal artery and selective ischemia [37, 38, 43, 45, 53], 8 studies compared global ischemia and the off-clamp technique [11, 13, 18, 29, 31, 39, 50, 55], and 1 study selective ischemia and the off-clamp technique [44]. Across the included trials, 42 studies used warm ischemia during the enucleoresection [8–15, 17, 19–24, 26–34, 36–45, 47–50, 53, 54, 55, 58], while 2 trials utilised cold ischemia with iceball [35, 52]; 8 studies used both the cold and warm ischemia [15, 16, 18, 25, 46, 51, 56, 57] (Figure 2B). Across all the studies, mean ischemia time ranged from 13.9 to 45.0 minutes. Considering only the studies with main renal artery clamping, mean ischemia time was 23.7 minutes, whereas in trials with selective ischemia, mean ischemia time was shorter (18.6 minutes); moreover, in the trials using cold ischemia, mean ischemia time was 34.4 minutes, whereas in those with warm ischemia, mean time was 22.3 minutes.

Post-operative functional assessment

Follow-up varied across the included studies from 1 to 64 months, with a mean value of 11.4 months. Functional outcomes were evaluated in terms of percentual change of estimated eGFR and percentual change of IRF using renal scintigraphy. Percentual eGFR variation was estimated in 49 studies, at a mean of 11.6 months of follow-up; values ranged from 0.7% to 37.1%, with a mean value of 12.5%. Fourteen studies reported percentual change of IRF on renal MAG-3 scintigraphy [9, 14, 19, 20, 22, 24, 39, 40, 41, 45, 47, 52, 54, 58]. At a mean follow-up of 7.9 months, IRF changes varied from 1.9% to 28%, with a mean IRF decrease of 13.3%.

Post-operative functional results: influence of age and tumor size

Stratifying our population derived from the 51 studies on the basis of a mean age <60 (5471 cases) or ≥60 (6828 cases) years, some differences were observed. In cases with a mean age <60 years, the decrease in eGFR after surgery ranged from 0.7% to 37.1%, with a mean value of 11.7%, and that of IRF from 2.2% to 22.0%, with a mean value of 10.0%.

In cases with a mean age of ≥60 years, the decrease in eGFR ranged from 1.3% to 27.8%, with a mean value of 13.5%, and that of IRF change from 10.5% to 28.0% with a mean value of 18.7% (Figure 3A).

Stratifying the population according to the mean tumor size, in studies with ≤4 cm (11395 cases), the decrease of eGFR ranged from 0.7% to 37.1% (with a mean value of 12.4%) and the IRF change from 2.2% to 28.0% (with mean value of 12.7%). In studies with a mean tumor size >4 cm (904 cases), the decrease of eGFR ranged from 2.4% to 31.5%, with a mean value of 18.3%, and IRF

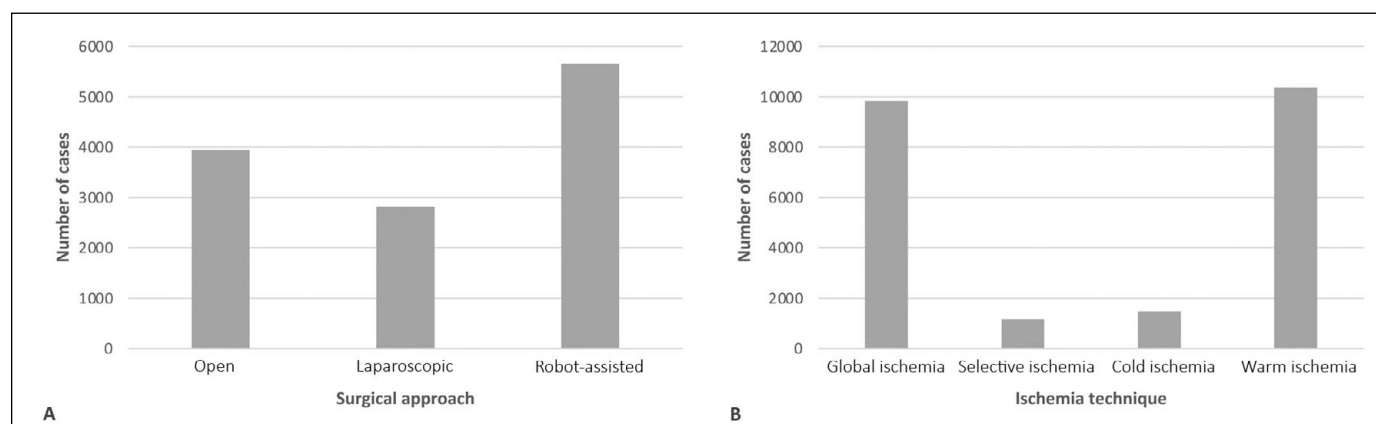


Figure 2. Surgical approach (open, laparoscopic or robot-assisted) (A) and ischemia technique (global, selective, warm or cold ischemia) (B) used in the whole population of the 51 included studies.

Table 2. Operative data and follow-up data of the included studies (*n* = 51), reporting functional outcomes after partial nephrectomy

Study, authors, year	Surgical approach, n° of cases	Ischemia technique	Ischemia type	Ischemia time, minutes	Excision technique	Change in eGFR, %	Change in IRF on scintigraphy, %	Length of follow-up, months (median)
Lane BR et al. 2008 [8]	OPN: 696 LNP: 473	GI	WI	Median (IQR): 25 (18–33)	ER	-8.8	NR	18
Funahashi Y et al. 2009 [9]	OPN: 20 LNP: 12	GI	WI	Mean (SD): 24.4 (6.8)	ER	Mean: -3.0	Mean: -21.1	6
Song C et al. 2009 [10]	OPN: 52 LNP: 65	GI	WI	Mean (range): 33.5 (13–75)	ER	Mean: OPN: -33.2 LNP: -29.9	NR	6.5
Thompson RH et al. 2010 [11]	OPN: 411 LNP: 47	GI: 362 OC: 96	WI	Mean: 32	ER	Median: GI: -26.3 OC: -1.3	NR	GI: 18 OC: 48
Shikanov S et al. 2010 [12]	LPN: 401	GI	WI	Median (IQR): 29 (22–34)	ER	Median (IQR): -11 (-2-0)	NR	12
Smith GL et al. 2011 [13]	OPN: 308	GI: 116 OC: 192	WI	Median (range): 23 (15–29)	ER	Median (range): GI: -12.3 OC: -9.8	NR	12
Pouliot F et al. 2011 [14]	LPN: 56	GI	WI	Mean (SD): 30 (9)	ER	Mean: -19.2	Mean: -14.0	3
Lane BR et al. 2011 [15]	OPN: 660	GI	CI: 300 WI: 360	Median (IQR): CI: 45 (35–60) WI: 22 (17–29)	ER	Median: CI: -21.0 WI: -22.0	NR	3
Simmons MN et al. 2011 [16]	OPN: 27 LPN: 11	GI	CI: 18 WI: 17	Median (range): CI: 38.5 (28–61) WI: 24.5 (16–60)	ER	Median: -13.4	NR	12
Thompson RH et al. 2012 [17]	OPN: 319 LNP: 43	GI	WI	Median (range): 21 (4–55)	ER	Median: -20.0	NR	1
Simmons MN et al. 2012 [18]	OPN: 141 LNP: 100 RAPN: 60	GI: 282 OC: 19	CI: 57 WI: 223	Median (range): CI: 40 (25–77) WI: 21 (17–60)	ER	Median: -9.0	NR	1.4
Porpiglia F et al. 2012 [19]	LPN: 54	GI	WI	Mean (SD): 27.9 (11.1)	ER	Mean: -1.1	Mean: -4.8	48
Sankin A et al. 2012 [20]	LNP RAPN	GI	WI	Median (IQR): 27 (19–36)	ER	Mean: -4.0	Mean: -6.0	200 days
Ng CK et al. 2012 [21]	LNP RAPN	SI+MD: 22 SI-MD: 22	–	0	ER	Median (range): SI+MD: -10.2 (-57.0–23.9) SI-MD: -11.2 (-48.3–21.0)	NR	2
Gill IS et al. 2012 [22]	LNP: 43 RAPN: 15	SI	–	0	ER	Mean: -11.4	Mean: -4.0	6
Shao P et al. 2012 [23]	LPN: 125	SI	WI	Median (range): 24 (12–40)	ER	Mean: -35.1	NR	18
Papalia R et al. 2012 [24]	LNP: 70 RAPN: 51	SI	–	0	ER	Mean: ≤4 cm: -1.8 >4 cm: -0.7	Mean: ≤4 cm: -1.9 >4 cm: -2.5	3
Mir MC et al. 2013 [25]	OPN LNP RAPN	GI	WI CI	Median (IQR): 24 (17–29)	ER	Median: -21.0	NR	4–12
Hillyer SP et al. 2013 [26]	RAPN: 26	GI	WI	Median (IQR): 17 (12–28)	ER	Median: -15.8	NR	6
Panumatrassamee K et al. 2013 [27]	LPN: 52 RAPN: 15	GI	WI	Median (IQR): LPN: 19 (15–34) RAPN: 15 (0–24)	ER	Median: LPN: -20.0 RAPN: -23.0	NR	LPN: 15.6 RAPN: 5.9
Gupta GN et al. 2013 [28]	RAPN: 19	GI	WI	Median (range): 36 (17–61)	ER	Median: -3.5	NR	12
Kaczmarek BF et al. 2013 [29]	RAPN: 332	GI: 283 OC: 49	WI	Mean (SD): GI: 18.5 (0.4)	ER	Mean (SD): GI: -6.2 (1.3) OC: -1.6 (2.7)	NR	3

Table 2. Continued

Study, authors, year	Surgical approach, n° of cases	Ischemia technique	Ischemia type	Ischemia time, minutes	Excision technique	Change in eGFR, %	Change in IRF on scintigraphy, %	Length of follow-up, months (median)
Shao P et al. 2013 [30]	LPN: 82	SI	WI	Mean (SD): 24.0 (6.3)	ER	Mean (SD): -37.1 (16.1)	NR	20
<10% eGFR (n°pt. groups)								
Hung J et al. 2013 [31]	LPN RAPN	GI	WI	NR	ER	1. 64 2. 95 3. 64 4. 56	NR	NR
Zargar H et al. 2014 [32]	OPN: 85 RAPN: 40	GI	WI	Median (IQR): OPN: 23 (19) RAPN: 15 (9)	ER	Median: OPN: -26.0 RAPN: 2–19.7	NR	OPN: 14 RAPN: 7.8
Autorino R et al. 2014 [33]	RAPN: 65	GI	WI	Mean (SD): 21.7 (9.3)	ER	Mean (SD): -9.4 (17.4)	NR	12.6
Volpe A et al. 2014 [34]	RAPN: 44	GI	WI	Median (IQR): 16.0 (13.8–18.0)	ER	Mean: -25.2	NR	6
Kaouk JH et al. 2014 [35]	RAPN: 11	GI	CI	Median (range): 27.1 (18–49)	ER	Median: -19.0	NR	12 days
Peyronnet B et al. 2014 [36]	RAPN: 430	GI: 208 GI+EUC: 222	WI	Mean (SD): GI: 22.3 (0.5) GI+EUC: 16.7 (0.5)	ER	Mean: GI: -5.5 GI+EUC: -10.6	NR	GI: 16.7 GI+EUC: 6.7
McClintock TR et al. 2014 [37]	RAPN: 84	GI: 42 SI: 42	WI	Mean (SD): GI: 22.9 (8.8) SI: 20.4 (7.0)	ER	Mean: GI: -14.6 SI: -3.1	NR	3
Desai MM et al. 2014 [38]	RAPN: 122	GI: 63 SI: 59	WI	Median (range): GI: 19 (9–37) SI: 0	ER	Median: GI: -17.0 SI: -11.0	NR	GI: 6 SI: 4
Porpiglia F et al. 2015 [39]	LPN: 87	GI: 44 OC: 43	WI	Mean (SD): GI: 18.0 (5.8) OC: –	ER	Mean: GI: -1.7 OC: -0.7	Mean: GI: -5.0 OC: -6.0	3
Zargar H et al. 2015 [40]	RAPN: 99	GI	WI	Median (IQR): 20.0 (16–25)	ER	Median: -16.2	Median: -28.0	6
Tanaka K et al. 2015 [41]	RAPN: 39	GI	WI	Mean (SD): RENAL ≤6: 19.9 (6.8) RENAL ≥7: 23.9 (8.3)	ER	Mean (SD): RENAL ≤6: -9.1 (11.1) RENAL ≥7: -7.2 (10.8)	Mean (SD): RENAL ≤6: -7.0 (20.2) RENAL ≥7: -14.1 (22.7)	eGFR: 12 IRF: 3
Maddox M et al. 2015 [42]	RAPN: 46	GI	WI	Median (IQR): 20.5 (17–25)	ER	Mean (SD): -2.4 (21.1)	NR	24.3
Shin TY et al. 2015 [43]	RAPN: 117	GI: 97 SI: 20	WI	Mean (SD): GI: 27.4 (9.9) SI: –	ER	Mean (SD): GI: -10.4 (14.9) SI: -0.0 (15.8)	NR	3
Satkunasivam R et al. 2015 [44]	RAPN: 179	SI-LC: 70 SI: 60 OC: 49	WI	–	ER	Median (range): SI-LC: -7.6 (-72–53) SI: -0.0 (-74–74) OC: -3.0 (-55–127)	NR	1
Zargar H et al. 2016 [45]	LPN: 135 RAPN: 216	GI: 300 SI: 51	WI	Median (IQR): GI: 20.0 (16–25) SI: –	ER	Median (IQR): -2.8 (7.7–5.4)	Median (IQR): -13.7 (22.9–5.4)	3–6
Maurice MJ et al. 2016 [46]	OPN: 284 RAPN: 596	GI	CI: 225 WI: 655	Median (IQR): 60.5 (52.0–68.3)	ER	Median (IQR): -14.1 (24.2–2.8)	NR	18.0
Luciani LG et al. 2016 [47]	RAPN: 32	GI	WI	Median (range): 24 (8–37)	ER	NR	Mean: -22.4	1
Wang Y et al. 2016 [48]	LPN: 135 RAPN: 81	GI	WI	Mean (SD): LPN: 22.3 (8.4) RAPN: 20.5 (7.6)	ER	Mean (SD): LPN: -10.0 (9.2) RAPN: -8.7 (7.6)	NR	LPN: 16.5 RAPN: 31.4
Andrade HS et al. 2016 [49]	LPN: 52 RAPN: 52	GI	WI	Median (IQR): LPN: – RAPN: 27.5 (21.0–34.0)	ER	Median (IQR): LPN: -31.5 (-40.3–23.6) RAPN: -24.2 (-36.1–6.3)	NR	21

Table 2. Continued

Study, authors, year	Surgical approach, n° of cases	Ischemia technique	Ischemia type	Ischemia time, minutes	Excision technique	Change in eGFR, %	Change in IRF on scintigraphy, %	Length of follow-up, months (median)
Novara G et al. 2016 [50]	RAPN: 465	GI	WI	Median: cystic: 18 solid: 17	ER	Median (IQR): cystic: -3.0 (1–6) solid: -3.0 (6–7)	NR	cystic: 10 solid: 6
Takagi T et al. 2016 [51]	OPN: 179 RAPN: 100	GI	OPN: CI RAPN: WI	Mean (SD): OPN: 43.0 (18.0) RAPN: 18.0 (6.4)	ER	Mean (SD): OPN: -8.0 (14.0) RAPN: -5.0 (10.0)	NR	4–6
Ramirez D et al. 2016 [52]	RAPN: 28	GI	CI	Mean (range): 32.0 (18–56)	ER	Median (range): -9.0 (6–38)	Median (range): -22.0 (0–40)	6
Paulucci DJ et al. 2016 [53]	RAPN: 665	GI: 589 SI: 76	WI	Median (IQR): GI: 15.6 (12.0–20.0) SI: 13.9 (10.9–18.0)	ER	Median (IQR): GI: -12.3 (-24.5–1.1) SI: -10.4 (-21.1–1.7)	NR	GI: 11.5 SI: 5
Tsai SH et al. 2017 [54]	RAPN: 103	GI	WI	Median (IQR): ≤4 cm: 21 (15–28) >4 cm: 32 (25–41)	ER	Median (IQR): ≤4 cm: -6.7 (15.6–3.7) >4 cm: -10.8 (21.1–0)	Median (IQR): ≤4 cm: -10.5 (26.3–3.7) >4 cm: 12.5 (21.4–1.4)	≤4 cm: 11 >4 cm: 15
Chang DK et al. 2018 [55]	RAPN: 122 LPN: 122 OPN: 122	GI Unclamp	WI	Median RAPN: 22 LPN: 24.3 OPN: 27.1	ER	Median RAPN: -6 LPN: -18 OPN: -8	NR	RAPN: 60 LPN: 60 OPN: 64
Tachibana H et al. 2020 [56]	OPN: 588 RAPN: 959 LPN: 215	GI	WI (LPN, RAPN) CI (OPN)	Mean (SD) OPN: 42.0 (±20) RAPN: 20.0 (±9) LPN: 30.0 (±16)	ER	Mean: OPN: -19.3 RAPN: -9.4 LPN: -13.1	NR	6
Gu L et al. 2020 [57]	RAPN: 61 LPN: 51	GI	WI CI	Median RAPN: 20.0 LPN: 20.0	ER	Median % (IQR): RAPN: -9.8 (2.1–19.6) LPN: -10.6 (5.4–17.0)	NR	RAPN: 27.3 LPN: 39.2
Würnschimmel C et al. 2020 [58]	LPN: 54 RAPN: 61	GI	WI	Mean (SD) LPN: 21.1 (6.1) RAPN: 19.6 (7.7)	ER	Median (IQR): LPN: -14.0 (7–23.5) RAPN: -16.0 (4.5–20.0)	Median (IQR): LPN: -18.0 (-26–11) RAPN: -20.0 (-33–12.0)	6

IQR – interquartile range; SD – standard deviation; NR – not reported; GI – global ischemia; OC – off-clamp; SI – Selective ischemia; WI – warm ischemia; CI – cold ischemia; ER – enucleoresection; OPN – open partial nephrectomy; LPN – laparoscopic partial nephrectomy; RAPN – robot-assisted partial nephrectomy; MD – vascular microdissection; EUC – early unclamping; eGFR – estimated glomerular filtration rate; IRF – impaired renal function

change ranged from 10.5 to 22.0 with mean of 15.0% (Figure 3B).

Post-operative functional results: influence of surgical and excision technique

All studies utilized enucleoresection as the excision technique.

In cases submitted to OPN, the decrease of eGFR ranged from 3.0% to 33.2%, with a mean value of 15.3%. Only 1 study using open surgical technique reported the IRF change, with a value of 21.1%.

In cases submitted to LPN, the decrease of eGFR percentage change ranged from 1.1% to 37.1%, with a mean value of 13.9%, whereas the percentual IRF change ranged from 2.2% to 21.1%, with a mean value of 11.1%.

In RAPN, the decrease of eGFR ranged from 1.1% to 25.2%, with a mean value of 10.8%, and the IRF change from 2.2% to 22.4%, with a mean value of 13.1% (Figure 3C).

Post-operative functional results: influence of ischemia technique, type and time

In cases submitted to global ischemia during enucleoresection (9834 cases), the decrease of eGFR ranged from 1.1% to 27.8% (with a mean value of 12.7%), whereas IRF change ranged from 4.8% to 28.0% (with a mean value of 15.1%).

In cases with selective ischemia techniques (1161 cases), the decrease of eGFR ranged from 1.1% to 37.1% (with a mean value of 12.8%), and the IRF

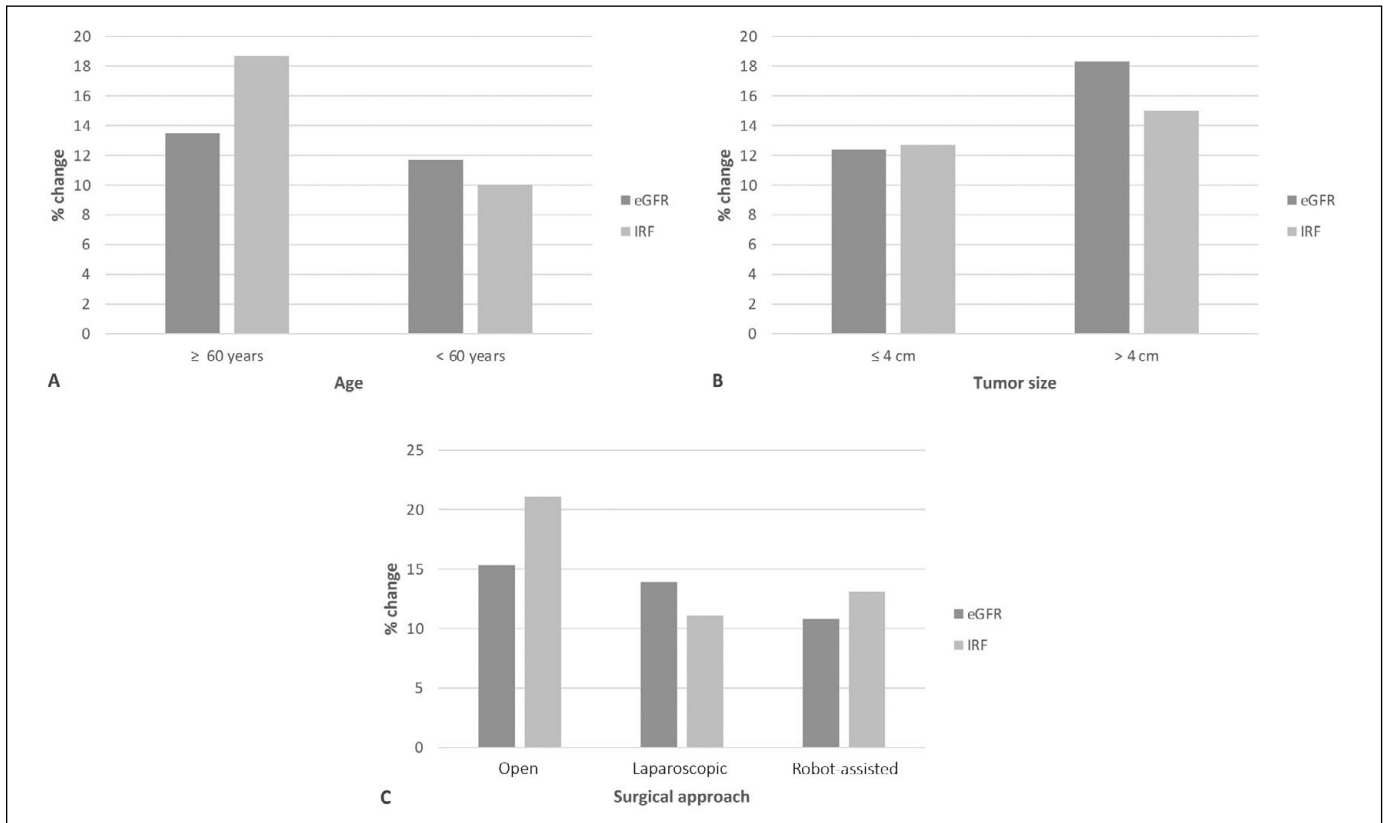


Figure 3. eGFR and IRF percentual change stratified by patient's age (≥ 60 or < 60 years) (A), tumor size (≤ 4 or > 4 cm) (B), and surgical approach (open, laparoscopic or robot-assisted) (C) in the whole population of the 51 included studies.

eGFR – estimated glomerular filtration rate; IRF – impaired renal function

change from 2.2% to 13.7% (with a mean value of 6.6%).

In patients submitted to cold ischemia (1466 cases), the decrease in eGFR change ranged from 8.0% to 21.5%, with a mean value of 14.4%, whereas mean IRF percentual change was 22.2% (only one study reported the IRF percentual change). In patients submitted to warm ischemia (10348 cases), the decrease of eGFR ranged from 1.1% to 37.1% (with a mean value of 12.5%), and the IRF percentual change from 4.8% to 28.0% (with a mean value of 13.4%) (Figure 4A).

Stratifying the population on the basis of an ischemia time ≤ 20 or > 20 minutes, in cases with mean ischemia time ≤ 20 minutes (3095 cases), the decrease of eGFR ranged from 1.2% to 25.2% (with a mean value of 11.0%), whereas IRF change ranged from 5.5% to 13.7% (with a mean value of 15.7%).

In patients with mean ischemia time > 20 mins (8719 cases), the decrease of eGFR ranged from 1.1% to 37.1% (with a mean value of 13.5%), and the IRF change from 2.2% to 22.0% (with a mean value of 11.5%) (Figure 4B).

In cases submitted to off-clamp technique (448 cases), the decrease of eGFR ranged from 0.7% to 9.8%,

with a mean value of 4.2%, while the IRF was reported in only one study (43 cases), with a value of 6%.

Multivariable analysis of variables influencing post-operative renal function results

A total of 17 studies performed a multivariable analysis to show which pre-operative or surgical technique variable significantly predicted the post-operative renal function outcome [8, 10, 11, 12, 14, 17, 18, 19, 25, 32, 39, 40, 47, 49, 52, 56, 57]. With regards to pre-operative data, 7 studies reported as a significant predictor of functional change the tumor size [8, 12, 25, 40, 47, 56, 57]. According to those studies, a smaller tumor size was associated with higher preservation of eGFR, with an effect of -27 (95%CI -38.3–5.0; p 0.04) in the study by Mir et al. [25], and of -0.66 (95%CI -1.32, 0.0077; p 0.047) in that of Lane et al. [8]. Moreover, Tachibana et al. reported an odd ratio (OR) of 1.29 (95%CI 1.17–1.43; p 0.01) [56] for the risk of post-operative acute kidney injury related to tumor size, while Gu et al. an OR of 0.62 (95%CI 0.45–0.86; p 0.05) [57] related to tumor size for achieving the 'pentad' [negative surgical margin, an ischemia time

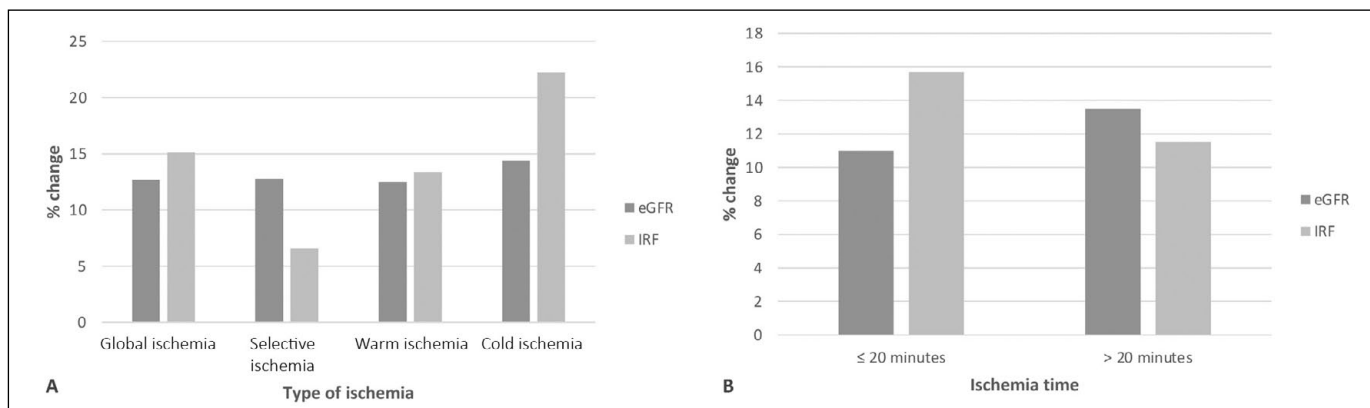


Figure 4. eGFR and IRF percentual change stratified by ischemia type (global, selective, warm or cold ischemia) (A), and ischemia time (≤20 or >20 minutes) (B) in the whole population of the 51 included studies.

eGFR – estimated glomerular filtration rate; IRF – impaired renal function

≤25 minutes, no peri-operative complications, return of eGFR to >90% from baseline, and no chronic kidney disease (CKD) upstaging].

Three studies found patients' age as an independent predictor of post-operative functional renal change [8, 10, 19].

With regards to operative data, 6 studies showed a shorter ischemia time as positive predictor of minor renal function change during the follow-up [8, 12, 14, 17, 19, 32]. For instance, the study by Thompson et al. [17] found a hazard ratio (HR) of 2.27 (95%CI 1.00–5.13; p 0.04) for post-operative new-onset stage IV CKD in surgery with WIT >25 minutes.

One study considered the off-clamp technique more effective to reduce post-operative IRF, reporting an OR of 2.70 (95%CI 1.27–5.78; p 0.01) with warm ischemia versus clampless for post-operative ARF (acute renal failure) [11]; two studies showed a superiority of cold versus warm ischemia technique [25, 52], with an effect of 31.0 (95%CI 12.7–41.9; p 0.02) reported by the study of Mir et al. [25] as a predictor factor of eGFR preservation in operated kidney. Ramirez et al. confirmed that cold ischaemia was associated with 12.9% greater preservation of eGFR in the immediate post-operative period [52].

Concerning the surgical technique, one study found that RAPN was significantly superior to LPN in terms of renal function preservation, with a HR of 4.26 (95%CI 1.80–10.12; p-value 0.001) [49] for predicting CKD upstaging.

CONCLUSIONS

Critical analysis and conclusions

Currently, NSS is the gold standard treatment of small renal masses, and according to the 'trifecta

concept', the maximum preservation of RF is one of its goals [1, 2, 59]. PN can be performed with either an open, laparoscopic or robot-assisted approach, yet LPN and RAPN have recently shown better peri-operative and post-operative morbidity outcomes [3, 6, 60]. The aim of the present review was to compare the three currently available surgical approaches in terms of renal function results.

The included studies were retrospective and prospective trials and only one was a randomized trial. This methodological aspect makes results less statistically relevant. Moreover, there was a great variability among the different populations in terms of sample sizes, and even more when stratifying results according to the surgical techniques. Also, the heterogeneity of populations and sample sizes contribute in reducing the statistical power of the analysis. Nevertheless, summarizing results from the different studies, some relevant conclusions can be drawn. Age, comorbidities and tumor size were found to be independent factors which negatively influenced the preservation of renal function post-operatively. Indeed, patients aged <60 years and with a tumor size of <4 cm showed a better preservation of their renal function after NSS. A nephrometry score was not used in all studies (33/51) and eGFR results were not reported according to this parameter which could be significantly related to results in terms of renal function. We analyzed results in studies from a long period of time (more than 10 years) in which surgical techniques significantly evolved from an open approach to a laparoscopic or robot-assisted procedures. Concerning operative data, LPN and RAPN demonstrated a higher effectiveness in the preservation of post-operative renal function, when compared to OPN. Considering the

different types of ischemia, selective ischemia showed to be a better approach compared to main renal artery clamping in decreasing post-operative eGFR and IRF. Cold ischemia versus warm ischemia – in particular the off-clamp technique – showed a higher percentual rate of conserving indexes of renal function.

In conclusion, a lower reduction of percentage change in terms of eGFR and IRF after NSS was reported in patients aged <60 years, submitted to RAPN using a selective and cold ischemia technique <20 minutes or an off-clamp technique. A future meta-analysis could be undertaken in consideration to better analyze results; however a relevant percentage of studies are retrospective.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

A. Sciarra: conceptualization, writing – original draft preparation; G. Di Lascio: conceptualization, formal analysis and investigation; F. Del Giudice: formal analysis and investigation; S. Saliccia: methodology; G.P. Ricciuti: methodology, formal analysis and investigation; G.B. Di Pierro: writing – review and editing, G.M. Busetto: formal analysis and investigation; E. De Berardinis: writing – review and editing; D. Castellani: writing – review and editing; G. Pirola: formal analysis and investigation; M. Maggi: writing – original draft preparation, formal analysis and investigation, A. Gentilucci: formal analysis and investigation; S. Cattarino: formal analysis and investigation; G. Mariotti: formal analysis, review and editing; P. Casale: conceptualization, investigation.

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