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Review – Kidney Cancer

Ischemia Techniques in Nephron-sparing Surgery: A Systematic Review and Meta-Analysis of Surgical, Oncological, and Functional Outcomes

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Article info

Abstract

Context: The optimal ischemia technique at partial nephrectomy (PN) for renal masses is yet to be determined.

Objective: To summarize and analyze the current evidence about surgical, oncological, and functional outcomes after different ischemia techniques (cold, warm, and zero ischemia) at PN.

Evidence acquisition: A computerized systematic literature search was performed by using PubMed (MED-LINE) and Science Direct. Identification and selection of the studies were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria. Outcomes of interest were estimated blood loss (EBL), overall complications, positive surgical margins, local tumor recurrence, and renal function preservation. Meta-analysis and forest-plot diagrams were performed. Overall pooled estimates, together with 95% confidence intervals (CIs), of the incidence of all parameters were obtained using a random effect model (RE-Model) on the log transformed means (MLN), proportion, or standardized mean change, as deemed appropriate.

Evidence synthesis: One hundred and fifty-six studies were included. No clinically meaningful differences were found in terms of EBL after cold (mean: 215.5; 95% CI: 154.2–276.8 m), warm (mean: 201.8; 95% CI: 175.0–228.7 ml), or zero (mean: 261.2; 95% CI: 171.0–351.3 ml) ischemia technique. Overall, postoperative complications were recorded in 14.1% (95% CI: 6.7–27.4), 11.1% (95% CI: 10.0–12.3), and 9.7% (95% CI: 7.7–12.2) of patients after cold, warm, and zero ischemia ($p < 0.01$), respectively. Positive surgical margins were recorded in 4.8% (95% CI: 1.9–10.9), 4.0% (95% CI: 3.4–4.8), and 5.6% (95% CI: 3.1–9.8) of patients after cold, warm, and zero ischemia ($p < 0.01$), respectively. Local recurrence was recorded in 3.2% (95% CI: 1.9–5.2) and 3.1% (95% CI: 0.7–11.5) of patients after warm and zero ischemia ($p < 0.01$), respectively. The $\log_2$ of estimated glomerular filtration ratio mean changes were–1.37 (95% CI:–3.42 to 0.68),–1.00 (–2.04 to 0.03), and–0.71 (–1.15 to–0.27) ml/min after cold, warm, and zero ischemia, respectively. Low level of evidence, retrospective nature of most of included studies, a high risk of selection bias, and heterogeneity within included studies limited the overall quality of the analysis.

Conclusions: The effect of ischemia technique at PN is still debatable and subject to confounding by several factors, namely, patients' selection criteria, surgical technique used, and percentage of functional parenchyma spared during surgery. These confounders bias available evidence and were addressed by only a small part of available studies. Unfortunately, the overall quality of literature evidences and the high risk of selection bias limit the possibility about any causal interpretation about the relationship between the ischemia technique used and surgical, oncological, or functional outcomes. Thus, none of the available ischemia technique could be recommended over the other.

Patient summary: The present analysis shows that none of the available ischemia techniques, namely, cold, warm, or zero ischemia, is universally superior to the others, and other factors play a role in the surgical outcome.

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1. Introduction

For the surgical treatment of T1 renal tumors, European [1,2] and North American [3,4] guidelines suggest preference for partial nephrectomy (PN) whenever technically and oncologically safe and feasible. The rationale behind this recommendation mainly stems from the evidence of comparable oncological outcomes [5]—improved renal function preservation following PN compared with radical nephrectomy [6,7], as shown in the European Organization for Research and Treatment of Cancer phase 3 prospective randomized controlled trial [8,9], and a non–cancer-related survival benefit [10–14].

An ideal PN should maximize functional and oncological outcomes while minimizing procedure-related complications. Optimization of functional outcomes relies on two main principles: maximizing parenchymal volume preservation and minimizing ischemia-related nephron damage [15–17]. Different ischemia techniques have been developed to reduce the ischemia-related injury [15,16]. During the "open surgery era," surgeons implemented the induction of hypothermia (so-called "cold ischemia") to reduce kidney metabolism during clamping. Others suggested that the warm ischemia time (WIT) should ideally be limited to 20–25 min [18]. More recently, different "off-clamp" or "selective-clamp" techniques have been explored to limit the ischemic kidney injury, and these are generally defined as "zero ischemia" [15,16].

The choice of one ischemia technique over the others is mainly based on surgeon expertise and tumor characteristics. Generally, cold ischemia is preferred when longer ischemia time is expected and when WIT cannot be limited [18]. Instead, in patients with decreased baseline renal function, minimally ischemic and off-clamp PN is preferred. However, concerns about the safety of these techniques were raised [16].

Despite general recommendations about the use of different ischemia techniques in different settings, the current evidence about the outcomes of PN using different ischemia techniques remains controversial. With the aim of filling this gap in the literature, we performed a systematic analysis of the current evidence about surgical, oncological, and functional outcomes after different ischemia techniques.

2. Evidence acquisition

2.1. Literature search and study selection

The first author (F.G.) established, prior to conducting this systematic review, the selection criteria and research protocol. Thereafter, the protocol was discussed with all the coauthors for approval. The systematic review protocol consisted of five different parts, namely, (1) literature search, (2) study identification and selection, (3) data extraction, (4) study quality assessment, and (5) statistical analysis.

In April 2018, a computerized systematic literature search of papers published up to March 2018 was performed by using PubMed (MEDLINE) and Science Direct. The literature search was carried out adapting the search strategy according to the different research engines. The term "partial nephrectomy" was combined with the keywords "renal cancer," "nephron sparing surgery," "warm ischemia time," "zero ischemia," "clampless," "selective clamp," and "off clamp." The search string used within the PubMed (MEDLINE) engine is specified in the Supplementary material (Search strategy). Additional records on this topic were identified from references cited in the selected manuscripts or in previous review articles on this topic. Literature research was restricted to articles published in the English language. No filters were applied for the date of publication.

The identification and selection of the studies were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria and the Population, Intervention, Comparator, Outcomes (PICO) methodology [19,20] (www.prisma-statement.org). PICO was defined as follows: population consisted of patients with renal masses (P) who underwent PN (I). Different ischemia techniques, namely, cold, warm, and zero ischemia, were compared (C). Outcomes of interest were estimated blood loss (EBL), surgical complications, positive margins, local recurrence, and renal function (as assed by the change of estimated glomerular filtration rate [eGFR] after surgery compared with that before; O).

After reviewing the titles and assessing the abstracts to ascertain whether they met the inclusion criteria, full-text articles were read exhaustively. Articles that reported data about at least one of the outcomes of interest were included in our analysis. Studies without original or primary data (ie, reviews, commentaries, and letters) were excluded. Similarly, duplicate or repeated cohorts were excluded from the analyses; moreover, only cohort and case-control or case series studies were included in our analyses. In addition, studies that did not clearly specify the ischemia technique used or had mixed ischemia techniques were excluded. Furthermore, articles that did not report or report renal function in other way than pre- and postoperative eGFR values or were conducted in patients with solitary kidney were excluded. Two authors (F.G. and R.A.) performed independently the literature search and study selection according the aforementioned strategy. A third author (H.V.P.) resolved eventual discrepancies.

2.2. Data extraction and level of evidence assessment

For each selected study, the following items were recorded in an Excel (Microsoft, Redmond, WA, USA) sheet: first author's name, year of publication, number of patients, median tumor diameter (cm), median operative time (min), median WIT (min), median ischemia time (min), median EBL (ml), postoperative complications (*n*), pre- and postoperative eGFR (ml/min), local recurrence (*n*), and margin status (*n*). Ischemia technique was defined as cold, warm, or zero ischemia. Specifically, all the procedures where any cooling technique was used to limit ischemic damage after artery clamping were considered as cold ischemia PN; otherwise, ischemia was classified as warm [15]. During zero ischemia PN, the hilar vessels were not clamped [21]. Finally, the level of evidence for each outcome was assessed according to the Oxford Centre of Evidence Based Medicine criteria [22].

2.3. Statistical analysis

Overall pooled estimates, together with 95% confidence intervals (CIs), of the incidence of all parameters were obtained using a random effect model (RE-Model) on the log transformed means (MLN), proportion, or standardized mean change, as deemed appropriate.

In addition, we aimed to test the effect of different ischemia types within different subgroups of patients. These subgroups were defined according to the median tumor size. Thus, sensitivity analyses tested the effect of different ischemia types within different groups defined according to the tumor size (<4 and ≥4 cm). Furthermore, we tested the effect of WIT, stratified as <25 and ≥25 min, on all the outcomes of interest. Finally, we explored the effect of different surgical approaches, namely, open PN (OPN), laparoscopic PN (LPN), and robotic-assisted PN (RAPN), in the different case scenarios. In all the analyses, local recurrences that occurred within 1 yr were included. Moreover, the eGFR change was evaluated at 3 mo.

A funnel plot was used to examine the potential publication bias. Two statistical tests, trim and fill methods, were assessed if there was evidence of a publication bias [23]. The rank correlation test [24] evaluated whether the effect estimates and sampling variances for each study are related. If meta-analyses were smaller than 25 studies Egger's regression test was used [25]. Analyses were performed using the R software environment for statistical computing and graphics (http://www.r-project.org/). R packages and functions, as well as all the literature references, are noted in the Supplementary material (Search strategy).

3. Evidence synthesis

3.1. Study characteristics

After the removal of duplicates, our search identified 617 manuscripts. Of these, 291 were full-text screened for eligibility. Finally, 156 studies were included in the current synthesis after exclusion according to the aforementioned strategy [8,21,26–177]. The selection process of the studies is resumed according to the PRISMA flow chart [19] (Supplementary Fig. 1).

Overall, 22 626 patients were included in the current study. After stratification according to surgical technique, 1704 patients underwent OPN, 12 648 underwent LPN, and 1828 underwent RAPN. Median tumor size ranged from 1.9 to 8.7 cm. After stratification according to the tumor size, 19 115 and 2 850 patients had renal masses <4 and ≥4 cm, respectively (Supplementary Table 1).

3.2. Surgical outcomes

3.2.1. Estimated blood loss
Overall, the mean EBL was 218.5 (95% CI: 189.3–247.7) ml. No clinically meaningful differences were found when cold (mean EBL: 215.5 ml), warm (mean EBL: 201.8 ml), or zero (mean EBL: 261.2 ml) ischemia technique was analyzed in subgroup analyses (Fig. 1).

Similarly, no clinically meaningful differences were found when EBL was examined in patients with renal masses <4 cm. Specifically, EBL means were 175.0, 185.5, and 192.0 ml after cold, warm, and zero ischemia PN, respectively (Supplementary Fig. 2). Moreover, no clinically meaningful differences were found when EBL was examined in patients with renal masses ≥4 cm. Specifically, EBL means were 228.2, 254.6, and 150.0 ml after cold, warm, and zero ischemia PN, respectively (Supplementary Fig. 3).

Moreover, analyses focusing on the effect of WIT on EBL showed that EBL means were 209.6 and 237.1 ml for WIT <25 and ≥25 min, respectively (Supplementary Fig. 4 and 5). The $\log_2$ means of EBL meaningfully varied according to the surgical technique used. Specifically, lower EBL was recorded after RAPN (mean EBL: 147.2 ml) than after LPN (mean EBL: 192.6 ml) or OPN (mean EBL: 237.0 ml; Supplementary Fig. 6).

Overall, the quality of studies and the study design of included evidence were low according to the Oxford Centre of Evidence Based Medicine criteria (level of evidence 4).

3.2.2. Postoperative complications
Overall, 11.0% (95% CI: 10.0–12.1%) of patients had postoperative complications (Fig. 2). Subgroup analyses for each ischemia technique revealed postoperative complication proportions of 14.1%, 11.1%, and 9.7% for cold, warm, and zero ischemia procedures, respectively (chi-square test on proportion $p < 0.01$; Fig. 2). Moreover, sensitivity analyses focusing on patients with renal masses <4 cm revealed postoperative complication proportions of 10.5%, 10.1%, and 10.4% for cold, warm, and zero ischemia procedures, respectively (chi-square test on proportion $p < 0.01$; Supplementary Fig. 7). Analysis focusing on patients with renal mass ≥4 cm showed postoperative complication proportions of 21.7%, 9.7%, and 5.9% for cold, warm, and zero ischemia procedures, respectively (chi-square test on proportion $p < 0.01$; Supplementary Fig. 8).

Moreover, analyses focusing on the effect of WIT on postoperative complications showed that the proportion of patients with complications were 11.9% and 17.4% for WIT <25 and ≥25 min, respectively (chi-square test on proportion $p < 0.01$; Supplementary Fig. 9 and 10).

Proportion of complications varied according to the surgical technique used. Specifically, complications were recorded, respectively, in 12.1%, 8.4%, and 10.2% of patients in whom LPN, OPN, and RAPN were performed (Supplementary Fig. 11).

Overall, the quality of studies and the study design of included evidence were low according to the Oxford Centre of Evidence Based Medicine criteria (level of evidence 4).

3.3. Oncological outcomes

3.3.1. Surgical margins
Overall, 4.2% (95% CI: 3.6–4.9%) of patients had positive surgical margins (Fig. 3). Subgroup analyses for each ischemia technique revealed positive margin proportions of 4.8%, 4.0%, and 5.6% for cold, warm, and zero ischemia procedures, respectively (chi-square test on proportion

Study	EBL loss	No. of patients	Mean	95% CI	Weights
Ischemia type = Cold ischemia					
(26)_Palacios_2013	235.3	23	235.3	(235.3; 235.3)	1.5%
(29)_Gschwend_1995	428	10	428.0	(427.9; 428.1)	1.5%
(57)_Minervini_2013	221	5	221.0	(220.8; 221.2)	1.5%
(78)_Tatsugami_2011	110	12	110.0	(110.0; 110.0)	1.5%
(79)_Ilbeigi_2005	126	16	126.0	(126.0; 126.0)	1.5%
(80)_Kallingal_2016	200	12	200.0	(200.0; 200.0)	1.5%
(83)_KC.Koo_2015	220	22	220.0	(220.0; 220.0)	1.5%
(104)_Matsuda_2004	150	11	150.0	(149.9; 150.1)	1.5%
(134)_Parekh_2013	249.4	27	249.4	(249.4; 249.4)	1.5%
Random effects model			*215.5*	*[154.2; 276.8]*	*13.2%*
Heterogeneity: I^2 = 100%, p = 0					
Ischemia type = Warm ischemia					
(32)_McDougall_1998	217	9	217.0	(216.9; 217.1)	1.5%
(34)_Hoznek_1999	72	13	72.0	(72.0; 72.0)	1.5%
(38)_Huyghe_2006	150	29	150.0	(150.0; 150.0)	1.5%
(39)_Porpiglia_2007	198.5	44	198.5	(198.5; 198.5)	1.5%
(43)_Haseebuddin_2010	135	38	135.0	(135.0; 135.0)	1.5%
(49)_Sammon_2011	150	30	150.0	(150.0; 150.0)	1.5%
(50)_Bazzi_2012	147.5	31	147.5	(147.5; 147.5)	1.5%
(55)_Tobis_2012	295	19	295.0	(295.0; 295.0)	1.5%
(57)_Minervini_2013	192.5	275	192.5	(192.5; 192.5)	1.5%
(61)_Abukora_2005	212	49	212.0	(212.0; 212.0)	1.5%
(63)_Benway_2008	140.3	50	140.3	(140.3; 140.3)	1.5%
(64)_D'Urso_2014	250	4	250.0	(249.8; 250.2)	1.5%
(66)_Gong_2008	202.3	78	202.3	(202.3; 202.3)	1.5%
(68)_Porpiglia_2012	164.27	76	164.3	(164.3; 164.3)	1.5%
(70)_Bermudez_2003	290	19	290.0	(290.0; 290.0)	1.5%
(72)_LS.Krane_2016	100	40	100.0	(100.0; 100.0)	1.5%
(78)_Tatsugami_2011	141.5	25	141.5	(141.5; 141.5)	1.5%
(79)_Ilbeigi_2005	194	16	194.0	(194.0; 194.0)	1.5%
(80)_Kallingal_2016	200	25	200.0	(200.0; 200.0)	1.5%
(83)_KC.Koo_2015	220	106	220.0	(220.0; 220.0)	1.5%
(85)_Pahernik_2011	500	2	500.0	(499.3; 500.7)	1.5%
(87)_Kondo_2002	427	24	427.0	(427.0; 427.0)	1.5%
(88)_HJ.Koo_2010	159	4	159.0	(158.8; 159.2)	1.5%
(89)_Papalia_2012	200	20	200.0	(200.0; 200.0)	1.5%
(91)_Bollens_2007	150	39	150.0	(150.0; 150.0)	1.5%
(93)_Petrasz_2012	354	25	354.0	(354.0; 354.0)	1.5%
(106)_Springer_2013	165	14	165.0	(165.0; 165.0)	1.5%
(108)_Bahler_2015	100	15	100.0	(100.0; 100.0)	1.5%
(115)_Porpiglia_2014	152.4	44	152.4	(152.4; 152.4)	1.5%
(117)_Shao_2010	197.5	75	197.5	(197.5; 197.5)	1.5%
(126)_Weizer_2011	100	16	100.0	(100.0; 100.0)	1.5%
(134)_Parekh_2013	249.4	13	249.4	(249.4; 249.4)	1.5%
(141)_Brown_2007	112	50	112.0	(112.0; 112.0)	1.5%
(148)_IS.Gill_2003	200	10	200.0	(199.9; 200.1)	1.5%
(151)_Jain_2013	220	5	220.0	(219.8; 220.2)	1.5%
(152)_J-H.Zheng_2009	105	48	105.0	(105.0; 105.0)	1.5%
(153)_Kang_2013	273.5	18	273.5	(273.5; 273.5)	1.5%
(158)_Gettman_2001	125	10	125.0	(124.9; 125.1)	1.5%
(159)_Moinzadeh_2006	219	50	219.0	(219.0; 219.0)	1.5%
(160)_Nohara_2008	380	18	380.0	(380.0; 380.0)	1.5%
(151)_Jain_2013	220	5	220.0	(219.8; 220.2)	1.5%
(170)_Tugcu_2018	196.5	80	196.5	(196.5; 196.5)	1.5%
Random effects model			*201.8*	*(175.0; 228.7)*	*61.8%*
Heterogeneity: I^2 = 100%, p = 0					
Ischemia type = Zero ischemia					
(64)_D'Urso_2014	250	19	250.0	(250.0; 250.0)	1.5%
(68)_Porpiglia_2012	201.46	41	201.5	(201.5; 201.5)	1.5%
(71)_CP.Hou_2016	100	19	100.0	(100.0; 100.0)	1.5%
(76)_IS.Gill_2012	206	54	206.0	(206.0; 206.0)	1.5%
(85)_Pahernik_2011	800	3	800.0	(799.6; 800.4)	1.5%
(85)_Pahernik_2011	500	5	500.0	(499.8; 500.2)	1.5%
(86)_Kobayashi_2008	133.8	5	133.8	(133.6; 134.0)	1.5%
(87)_Kondo_2002	572	10	572.0	(571.9; 572.1)	1.5%
(88)_HJ.Koo_2010	165	11	165.0	(164.9; 165.1)	1.5%
(89)_Papalia_2012	200	40	200.0	(200.0; 200.0)	1.5%
(93)_Petrasz_2012	135	13	135.0	(135.0; 135.0)	1.5%
(95)_Kaczmarek_2012	210	44	210.0	(210.0; 210.0)	1.5%
(96)_Loertzer_2013	75	11	75.0	(74.9; 75.1)	1.5%
(107)_TS.Kim_2014	243	24	243.0	(243.0; 243.0)	1.5%
(115)_Porpiglia_2014	290.6	42	290.6	(290.6; 290.6)	1.5%
(150)_IS.Gill_2010	150	15	150.0	(150.0; 150.0)	1.5%
(154)_Khoder_2012	208	36	208.0	(208.0; 208.0)	1.5%
Random effects model			*261.2*	*(171.0; 351.3)*	*25.0%*
Heterogeneity: I^2 = 100%, p = 0					
Random effects model			**218.5**	**(189.3; 247.7)**	**100.0%**
Heterogeneity: I^2 = 100%, p = 0					

-400 -200   0   200 400 600 800
EBL loss

Fig. 1 – Forest plot of meta-analyses of mean estimated blood loss after partial nephrectomy and after stratification according to each ischemia type (cold, warm, and zero ischemia, respectively, from the top to the bottom of the plot). CI = confidence interval; EBL = estimated blood loss.
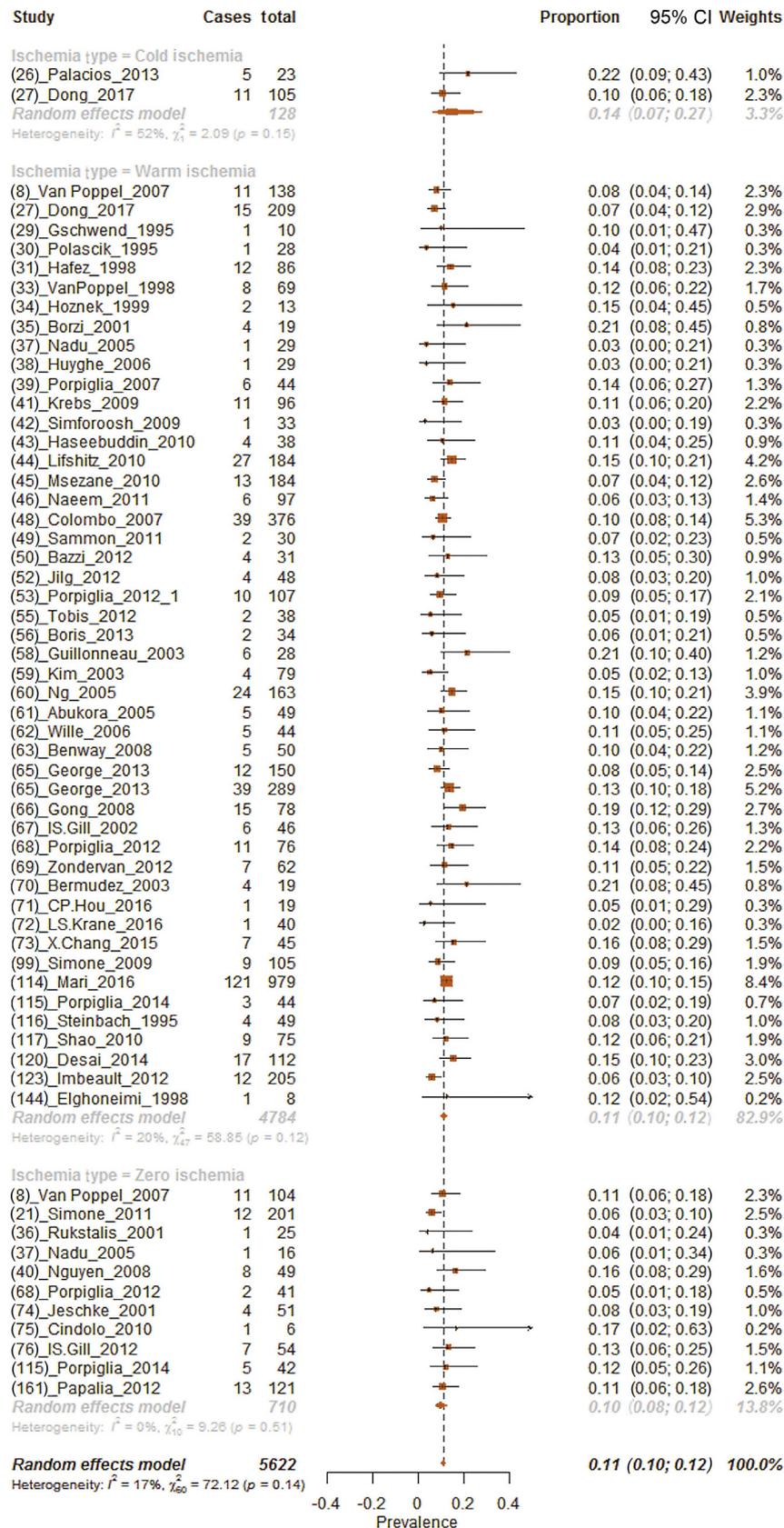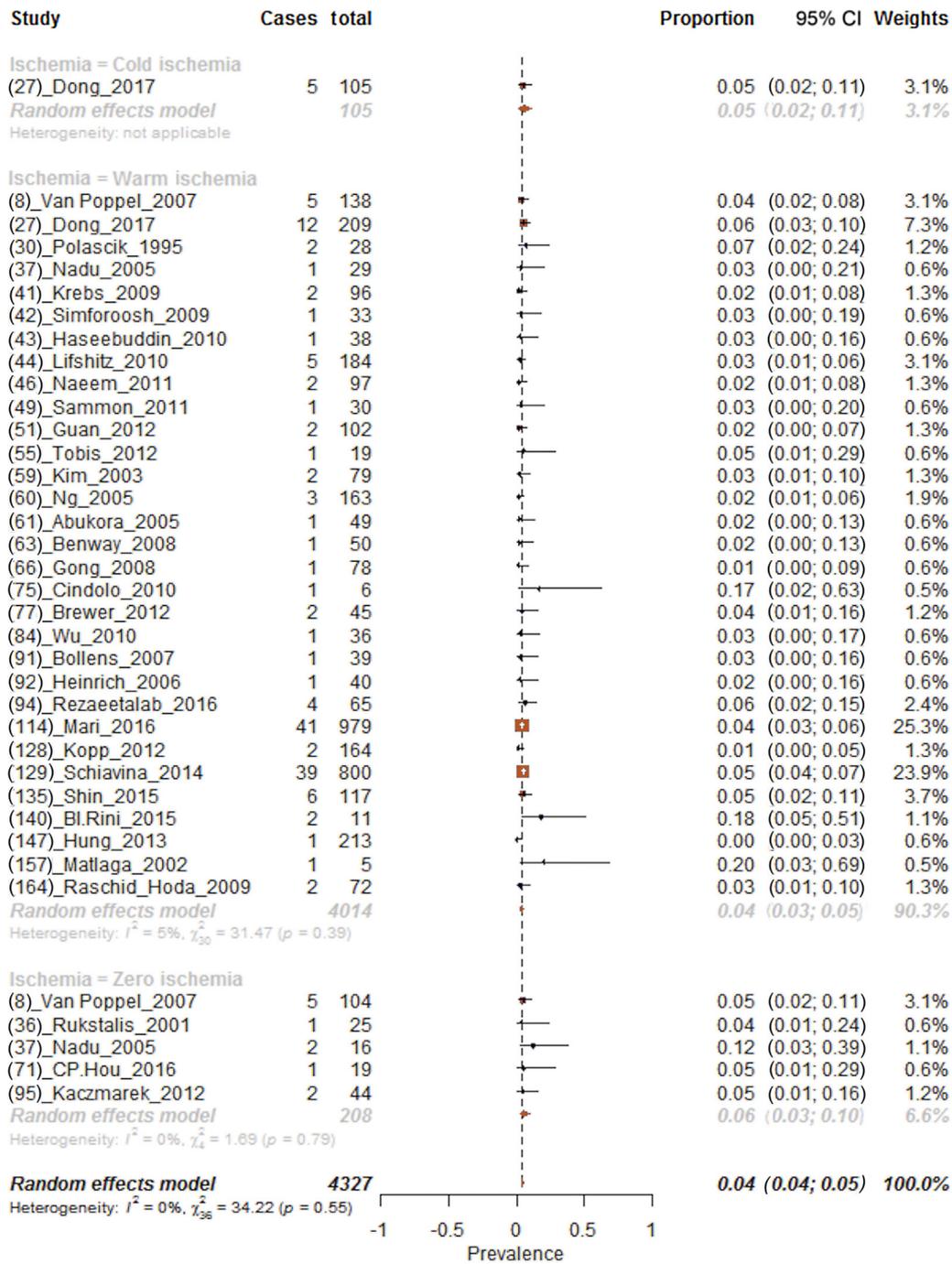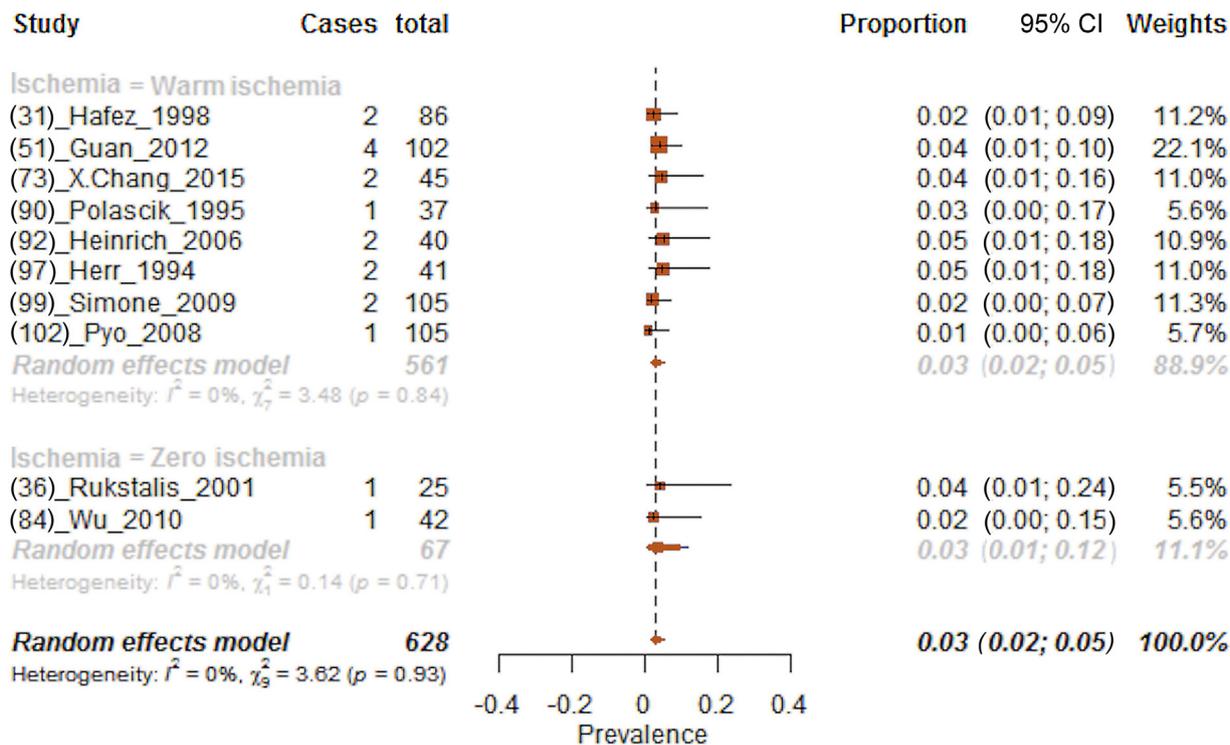
Fig. 2 – Forest plot of meta-analyses of proportions of postoperative complications after partial nephrectomy and after stratification according to each ischemia type (cold, warm, and zero ischemia, respectively, from the top to the bottom of the plot). CI = confidence interval.

Study	Cases	total		Proportion	95% CI	Weights
Ischemia = Cold ischemia						
(27)_Dong_2017	5	105		0.05	(0.02; 0.11)	3.1%
Random effects model		105		0.05	(0.02; 0.11)	3.1%
Heterogeneity: not applicable						
Ischemia = Warm ischemia						
(8)_Van Poppel_2007	5	138		0.04	(0.02; 0.08)	3.1%
(27)_Dong_2017	12	209		0.06	(0.03; 0.10)	7.3%
(30)_Polascik_1995	2	28		0.07	(0.02; 0.24)	1.2%
(37)_Nadu_2005	1	29		0.03	(0.00; 0.21)	0.6%
(41)_Krebs_2009	2	96		0.02	(0.01; 0.08)	1.3%
(42)_Simforoosh_2009	1	33		0.03	(0.00; 0.19)	0.6%
(43)_Haseebuddin_2010	1	38		0.03	(0.00; 0.16)	0.6%
(44)_Lifshitz_2010	5	184		0.03	(0.01; 0.06)	3.1%
(46)_Naeem_2011	2	97		0.02	(0.01; 0.08)	1.3%
(49)_Sammon_2011	1	30		0.03	(0.00; 0.20)	0.6%
(51)_Guan_2012	2	102		0.02	(0.00; 0.07)	1.3%
(55)_Tobis_2012	1	19		0.05	(0.01; 0.29)	0.6%
(59)_Kim_2003	2	79		0.03	(0.01; 0.10)	1.3%
(60)_Ng_2005	3	163		0.02	(0.01; 0.06)	1.9%
(61)_Abukora_2005	1	49		0.02	(0.00; 0.13)	0.6%
(63)_Benway_2008	1	50		0.02	(0.00; 0.13)	0.6%
(66)_Gong_2008	1	78		0.01	(0.00; 0.09)	0.6%
(75)_Cindolo_2010	1	6		0.17	(0.02; 0.63)	0.5%
(77)_Brewer_2012	2	45		0.04	(0.01; 0.16)	1.2%
(84)_Wu_2010	1	36		0.03	(0.00; 0.17)	0.6%
(91)_Bollens_2007	1	39		0.03	(0.00; 0.16)	0.6%
(92)_Heinrich_2006	1	40		0.02	(0.00; 0.16)	0.6%
(94)_Rezaeetalab_2016	4	65		0.06	(0.02; 0.15)	2.4%
(114)_Mari_2016	41	979		0.04	(0.03; 0.06)	25.3%
(128)_Kopp_2012	2	164		0.01	(0.00; 0.05)	1.3%
(129)_Schiavina_2014	39	800		0.05	(0.04; 0.07)	23.9%
(135)_Shin_2015	6	117		0.05	(0.02; 0.11)	3.7%
(140)_Bl.Rini_2015	2	11		0.18	(0.05; 0.51)	1.1%
(147)_Hung_2013	1	213		0.00	(0.00; 0.03)	0.6%
(157)_Matlaga_2002	1	5		0.20	(0.03; 0.69)	0.5%
(164)_Raschid_Hoda_2009	2	72		0.03	(0.01; 0.10)	1.3%
Random effects model		4014		0.04	(0.03; 0.05)	90.3%
Heterogeneity: $I^2 = 5\%$, $\chi^2_{30} = 31.47$ ($p = 0.39$)						
Ischemia = Zero ischemia						
(8)_Van Poppel_2007	5	104		0.05	(0.02; 0.11)	3.1%
(36)_Rukstalis_2001	1	25		0.04	(0.01; 0.24)	0.6%
(37)_Nadu_2005	2	16		0.12	(0.03; 0.39)	1.1%
(71)_CP.Hou_2016	1	19		0.05	(0.01; 0.29)	0.6%
(95)_Kaczmarek_2012	2	44		0.05	(0.01; 0.16)	1.2%
Random effects model		208		0.06	(0.03; 0.10)	6.6%
Heterogeneity: $I^2 = 0\%$, $\chi^2_4 = 1.69$ ($p = 0.79$)						
Random effects model		**4327**		**0.04**	**(0.04; 0.05)**	**100.0%**
Heterogeneity: $I^2 = 0\%$, $\chi^2_{36} = 34.22$ ($p = 0.55$)						

-1   -0.5   0   0.5   1
Prevalence

Fig. 3 – Forest plot of meta-analyses of proportions of positive surgical margins after partial nephrectomy and after stratification according to each ischemia type (cold, warm, and zero ischemia, respectively, from the top to the bottom of the plot). CI = confidence interval.

$p < 0.01$; Fig. 3). In addition, sensitivity analyses focusing on patients with renal masses <4 cm revealed positive margin proportions of 4.8%, 3.8%, and 5.6% for, respectively, cold, warm, and zero ischemia procedures (chi-square test on proportion $p < 0.01$; Supplementary Fig. 12). Analysis focusing on positive surgical margin proportions after PN in patients with renal masses ≥4 cm could be performed only within patients who underwent warm ischemia PN. Here, positive surgical margins were reported in 5.4% of patients (Supplementary Fig. 13).

Moreover, analyses focusing on the effect of WIT on positive surgical margins showed that the proportion of patients with positive surgical margins were 5.1% and 1.9%, respectively, for WIT <25 and ≥25 min (chi-square test on proportion $p < 0.01$; Supplementary Fig. 14 and 15).

Proportion of positive surgical margins varied according to the surgical technique used. Specifically, positive surgical margins were recorded, respectively, in 4.3%, 12.5%, and 3.8% of patients in whom LPN, OPN, and RAPN were performed (Supplementary Fig. 16).

Fig. 4 – Forest plot of meta-analyses of proportions of local recurrence after partial nephrectomy and after stratification according to each ischemia type (warm and zero ischemia, respectively, from the top to the bottom of the plot). CI = confidence interval.

Overall, the quality of studies and the study design of included evidence were low according to the Oxford Centre of Evidence Based Medicine criteria (level of evidence 4).

3.3.2. Local recurrence

The effect of local recurrence was tested according to all the ischemia techniques; however, data availability allowed the inclusion of results after warm and zero ischemia only. Local recurrence was recorded in 3.2% (95% CI: 2.0–5.0%) of patients (Fig. 4). More specifically, 3.2% and 3.1% of patients experienced local recurrence after warm and zero ischemia, respectively. In sensitivity analyses according to renal mass size, the proportions of patients with local recurrence were 1.8 and 3.1, respectively, after warm and zero ischemia in renal masses <4 cm (Supplementary Fig. 17). Moreover, proportion of patients with local recurrence was 4.2% after warm ischemia PN for renal masses ≥4 cm (chi-square test on proportion $p < 0.01$; Supplementary Fig. 18).

Furthermore, analyses focusing on the effect of WIT on local recurrence showed that the proportion of patients with local recurrence were 6.9% and 1.1% for WIT <25 and ≥25 min, respectively (chi-square test on proportion $p < 0.01$; Supplementary Fig. 19 and 20).

Proportion of local recurrence varied according to the surgical technique used. Specifically, local recurrence was recorded, respectively, in 4.0% and 6.0% of patients in whom LPN and RAPN were performed (Supplementary Fig. 21).

Overall, the quality of studies and the study design of included evidence were low according to the Oxford Centre of Evidence Based Medicine criteria (level of evidence 4).

3.4. Functional outcomes

Overall, the $\log_2$ eGFR standardized mean change was–0.98 (95% CI:–1.61 to–0.36) ml/min (Fig. 5). Subgroup analyses for each technique revealed $\log_2$ eGFR standardized mean changes of–1.37,–1.00, and–0.71 ml/min for cold, warm, and zero ischemia procedures, respectively (Fig. 5).

Sensitivity analyses stratified according to tumor size were also performed; however, these analyses could include only a very small number of studies. Thus, results were not reliable, were biased, and were not included (results not shown).

Moreover, analyses focusing on $\log_2$ eGFR standardized mean change according to WIT showed standardized mean changes of–11.65 and–11.63 for, respectively, for WIT <25 and ≥25 min (Supplementary Fig. 22 and 23). However, these analyses could include only a small number of studies, and thus no conclusions could be reached based on these results.

The $\log_2$ eGFR standardized mean changes were–1.52 and–1.56 after OPN and LPN, respectively (Supplementary Fig. 24).

Overall, the quality of studies and the study design of included evidence were low according to the Oxford Centre of Evidence Based Medicine criteria (level of evidence 4).

3.5. Publication bias

We did not find evidence of publication bias upon inspection of funnel plots. Moreover, regression test and
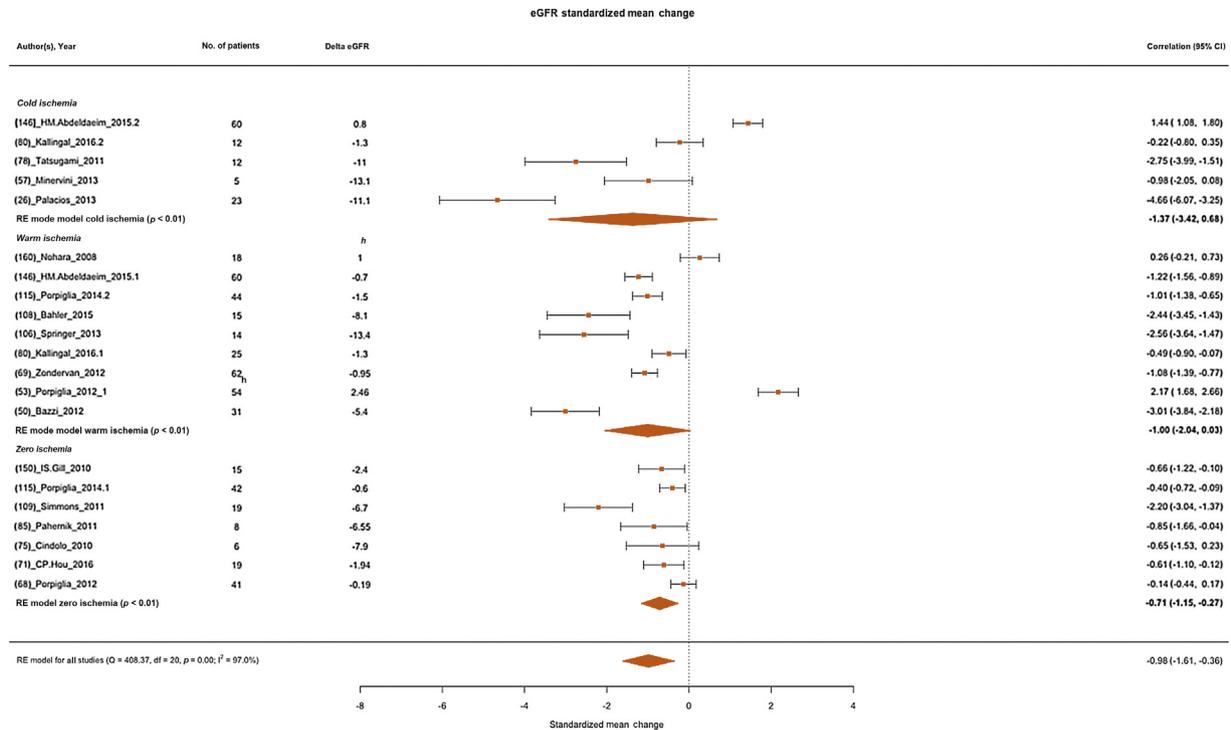
Fig. 5 – Forest plot of meta-analyses of standardized mean change of estimated glomerular filtration rate (as $\log_2$ transformed) after partial nephrectomy and after stratification according to each ischemia type (cold, warm, and zero ischemia, respectively, from the top to the bottom of the plot). CI = confidence interval; eGFR = estimated glomerular filtration rate; RE = random effect.

rank correlation test for funnel plot asymmetry refused the hypothesis of publication bias (all $p > 0.05$; Supplementary material, Publication biases).

3.6. Interpretation of results

We hypothesized that different ischemia techniques may have a different effect on EBL, surgical complications, positive surgical margins, local tumor recurrence, and renal function preservation. After a systematic review of the literature, we performed a formal meta-analysis of available evidence. Results showed several important findings.

First, results on surgical outcomes showed similar EBL across different surgical techniques, with no clinical meaningful differences. In addition, analyses on postoperative complication proportions showed statistically significant different rates of complications according to different ischemia techniques. Indeed, the complication proportions were higher after cold (14.1%) than after warm (11.1%) or zero (9.7%) ischemia. However, these differences may be related to a selection bias. Indeed, complications may be associated with the mass size and not with the ischemia approach by itself. Thus, the stronger driver in postoperative complication rates might be the renal mass size. It seems reasonable to affirm that all these results could be explained considering that cold ischemia is generally indicated for more challenging procedures (eg, large renal masses) that may require longer ischemia time (>30 min) [178], while the zero ischemia approach is mostly used in very small renal masses. Last but not least, these results derive from only a small number of studies that could be included in our analysis.

Second, our analyses looking at the oncological safety of different ischemia techniques showed higher proportions of positive surgical margins after zero ischemia (5.6%) than after cold (4.8%) or warm (4.0%) ischemia. Conversely, similar rates of local recurrence were recorded after zero versus warm ischemia (3.1% vs 3.4%). However, when only renal masses <4 cm were considered, lower rates of positive surgical margins and local recurrence were recorded after warm ischemia compared with the other techniques.

That said, we still could hypothesize that the ischemia technique by itself may influence the resection technique, resulting in higher positive surgical margins and local recurrence rates. Unfortunately, this hypothesis could not be tested in our analyses because of the inherent selection bias within retrospective series [179], paucity of resection technique standardization (pure enucleation, enucleoresection, or wedge resection) [180], and poor ischemia technique standardization [15,16,181]. Finally, we were not able to verify whether the local recurrences reported were true local recurrences in the resection bed or recurrences elsewhere in the kidney. The aforementioned limitations within our results do not allow inferring of any causality.

Moreover, the impact of positive surgical margins on local recurrence after PN is still controversial, and clinical relevance of a positive surgical margin is still being scrutinized [182]. Indeed, historical multi-institutional analysis showed no effect of positive surgical margins on

recurrence after multivariable adjustment [183]. More recently, Shah et al. [184] showed that positive surgical margins were associated with an increased recurrence risk. Interestingly, in high-risk patients (pT2-3 and/or Fuhrman grade III–IV) positive surgical margins were still associated with recurrence, while no association was found in a low-risk patient subgroup.

Third, none of ischemia technique outperforms the other in terms of renal function preservation. Noteworthy, the eGFR standardized mean change was similar throughout different ischemia techniques, and differences may be considered clinically marginal or not meaningful. Nonetheless, these findings should be interpreted cautiously due to the availability of a small number of studies. In particular, sensitivity analyses showed the paucity of studies stratifying according to tumor size and WIT. Moreover, authors would like to emphasize the low level of evidence derived from institutional retrospective studies and the inherent selection bias within those studies. Indeed, each technique has a proper indication and use in current clinical practice. For instance, cold ischemia is generally used for the most difficult cases that are characterized by a larger parenchymal loss due to surgical complexity.

It is of note that the ischemia effect itself on renal parenchyma is still debated [111]. In a recent analysis, Dong et al. [27] showed that cold ischemia was associated with a functional recovery of 99% versus 92% recorded after warm ischemia. Moreover, the authors also showed that for each 10 min of warm ischemia, the average renal function loss was about 2.5%. The authors adjusted for the parenchymal mass saved in their analyses. These results suggest a role of ischemia type on renal function preservation, although the impact of functional loss was marginal when compared with the impact of parenchymal mass loss, which is the main determinant of functional outcomes after PN. However, other authors showed different findings. For example, Lee et al. [137] corroborates our findings on a similar detrimental effect of warm ischemia regardless of the WIT. Indeed, the authors showed no significant difference in incidence of chronic kidney disease after PN between two groups defined according to WIT <30 or ≥30 min.

Parekh et al. [134] prospectively addressed the effect of ischemia on human kidney. The authors performed renal biopsies before, during, and after surgically induced renal clamp ischemia in 40 patients undergoing PN. Results showed a mild transient increase in serum creatinine with a stable level of serum cystatin C. Renal functional changes did not correlate with ischemia duration, while renal structural changes were less severe than in animal models. The authors concluded that human kidney may safety tolerate 30–60 min of controlled clamp ischemia [134]. Authors emphasize the differences with previous reports, which suggested a deleterious effect of ischemia time of >20–30 min, and justified these differences with other concurrent causes of renal function deterioration, such as tissue damage, sepsis, nephrotoxins, and/or shock [134].

More recently, Zhang et al. [111] evaluated the parenchymal atrophy after clamped PN on 164 patients. The authors evaluated the volume of the renal pole opposite to surgery site before and 4–12 mo after surgery. Their findings showed that median opposite pole volumes were 63.2 and 62.5 cm^3, respectively, before and after surgery, with a resulting ratio of 0.99. The authors also did not find any differences between warm and cold ischemia. The percent of parenchyma preserved may be more important for renal function preservation. Indeed, the percent of parenchymal mass saved during PN seems to strongly correlate with the renal function preservation [28]. Moreover, another source of parenchymal loss is the parenchyma devascularization secondary to the renal reconstruction and renorrhaphy [135,185].

Simmons et al. [105] showed after multivariable adjustment that ischemia time correlated with the nadir of postoperative eGFR but not with the late eGFR. Conversely, preoperative eGFR and the percent functional volume preservation were correlated with late eGFR. These findings were confirmed in a more contemporary analysis by Ginzburg et al. [127]. These investigators also showed a correlation of preoperative eGFR and percent functional volume preservation with eGFR at 6 mo after PN. In the same analysis, the authors also showed the absence of a correlation between eGFR 6 mo after PN and WIT [127].

In summary, current literature evidences are not of enough quality to suggest any clinically meaningful difference between the available ischemia techniques. In consequence, none of the different ischemia techniques seems to outperform the others in regard to any of the examined outcomes. Thus, we are not able to suggest one approach over another. Indeed, several confounders may have affected this result. In particular, postoperative kidney function may be influenced more by the presence of a contralateral functional kidney. Indeed, eGFR evaluates global renal function, while other methodologies such as nuclear renal scan should be adopted when evaluating the single kidney function [186]. In addition, the resection type and the percent of functional parenchyma preserved may have a stronger effect on renal function preservation. Nonetheless, the ischemia technique used may influence both these variables. This consideration may justify the differences in positive surgical margin rates across the different ischemia techniques that may be related to difficulties occurring when surgery is performed without the main artery clamp [15]. Unfortunately, our analysis, as mentioned above, was limited by the small number of studies that relied on resection technique standardization (pure enucleation, enucleoresection, or resection) [180] and/or reported the percent of functional volume preservation.

Other limitations should also be acknowledged. The generalizability of our findings could be limited by the impossibility to perform analyses in a specific subset defined according to the tumor size and some of the outcomes of interest. Despite the efforts of the authors to reduce the variability in the definitions of different ischemia types and make the definitions homogenous during the selection of study phase, a standardized nomenclature of "zero ischemia" is still an unmet need [181]. Moreover, the

follow-up time when postoperative eGFR was collected varies throughout the included studies. To minimize this variability, we included the first postoperative control when more than one control was reported. Thus, our findings mainly relate to the early postoperative renal function preservation or damage. The reported difference will be even lower and eventually disappear with longer follow-up.

Clinically actionable conclusions from such data can only be reached cautiously, given the marked selection biases inherent to retrospective cohorts. For instance, in some of the analyses, a direct comparison between different ischemia techniques was not possible due to the limited number of studies. Furthermore, differences may be related to a selection bias. Indeed, a high risk of selection bias within retrospective series is possible [179], and in our analyses, we were not able to adjust for all the possible confounders. Moreover, the high heterogeneity existing within the included studies should be taken into consideration before taking making definitive conclusion based on our analyses. Several sources of heterogeneity could be identified; in particular, only a part of the included studies directly addressed the hypothesis that differences may exist in terms of surgical, oncological, or functional outcomes according to the ischemia technique used at PN. In consequence, only a small part of the included studies represent a direct comparison of the three ischemia types. In addition, when this hypothesis was tested, only few of the included studies adjusted for confounding such as the percent of functional parenchyma spared. In summary, the overall quality is biased by the lack of a robust comparative cohort neither prospective nor retrospective. Furthermore, the complications of recording and the time frame of records varied across different studies. Such variability did not allow any standardization and may be a source of bias.

Now, the literature lacks robust randomized clinical trials testing differences between ischemia techniques; thus, none of the included studies is a randomized clinical trial. The latter is a further limitation to the overall quality of our results. In the future, standardized and robust prospective studies are necessary to reach clinically meaningful conclusions. Several ongoing or recently completed randomized clinical trials will analyze the effect of different ischemia types on PN outcomes [187–190]. Hopefully, these studies will answer many other questions that are still open.

4.   Conclusions

The effect of ischemia technique at PN is still debatable and subject to confounding by several factors, namely, patients' selection criteria, surgical technique used, and percentage of functional parenchyma spared during surgery. These confounders bias available evidence and were addressed by only a small part of the available studies. Unfortunately, the overall quality of literature evidence and the high risk of selection bias limit the possibility of any causal interpretation about the relationship between the ischemia technique used and surgical, oncological, or functional outcomes. Thus, none of the available ischemia techniques could be recommended over the other.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.10.005.

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