Review – Kidney Cancer

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

Francesco Greco, Riccardo Autorino, Vincenzo Altieri, Steven Campbell, Vincenzo Ficarra, Inderbir Gill, Alexander Kutikov, Alex Mottrie, Vincenzo Mirone, Hendrik van Poppel

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 (MEDLINE) 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 ml), 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 11.5% (95% CI: 7.7–12.2) of patients after cold, warm, and zero ischemia (p < 0.01), respectively. Positive surgical margins were recorded in 9.7% (95% CI: 7.7–12.2) of patients after cold, warm, and zero ischemia (p < 0.01), respectively. Local recurrence was recorded in 11.1% (95% CI: 6.7–27.4) of patients after cold, warm, and zero ischemia (p < 0.01), respectively. The log 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 of 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 assessed 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, 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 log₂ 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. 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).
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.

<table>
<thead>
<tr>
<th>Study</th>
<th>EBL loss No. of patients</th>
<th>Mean ± 95% CI</th>
<th>Weights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold ischemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(20) Palacios 2013</td>
<td>235.3 ± 235.3</td>
<td>23.5 ± 23.5</td>
<td>1.5%</td>
</tr>
<tr>
<td>(29) Ochsendorf 1995</td>
<td>428.10</td>
<td>428.10</td>
<td>1.5%</td>
</tr>
<tr>
<td>(57) Minervini 2013</td>
<td>221.5</td>
<td>221.5</td>
<td>1.5%</td>
</tr>
<tr>
<td>(79) Tatsugami 2008</td>
<td>110.12</td>
<td>110.12</td>
<td>1.5%</td>
</tr>
<tr>
<td>(79) Ibsen 2005</td>
<td>126.16</td>
<td>126.16</td>
<td>1.5%</td>
</tr>
<tr>
<td>(80) Katyal 2016</td>
<td>200.12</td>
<td>200.12</td>
<td>1.5%</td>
</tr>
<tr>
<td>(83) KC Koo 2015</td>
<td>220.22</td>
<td>220.22</td>
<td>1.5%</td>
</tr>
<tr>
<td>(104) Matsuda 2004</td>
<td>150.11</td>
<td>150.11</td>
<td>1.5%</td>
</tr>
<tr>
<td>(124) Parekh 2013</td>
<td>249.4</td>
<td>249.4</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

Random effects model: 218.5 (189.3; 247.7) 100.0% |

Warm ischemia |
| (32) McCallum 1998 | 217.9 | 217.9 | 1.5% |
| (54) Hoznek 2003 | 72.72 | 72.72 | 1.5% |
| (58) Hughey 2006 | 150.29 | 150.29 | 1.5% |
| (39) Porpiglia 2007 | 198.44 | 198.44 | 1.5% |
| (43) Hasek 2010 | 135.38 | 135.38 | 1.5% |
| (49) Sammon 2011 | 150.30 | 150.30 | 1.5% |
| (50) Bazzi 2012 | 147.31 | 147.31 | 1.5% |
| (58) Goldsmith 2010 | 255.19 | 255.19 | 1.5% |
| (57) Minervini 2013 | 192.25 | 192.25 | 1.5% |
| (61) Axia 2009 | 212.49 | 212.49 | 1.5% |
| (63) Benmamy 2008 | 143.50 | 143.50 | 1.5% |
| (64) Uoco 2014 | 250.74 | 250.74 | 1.5% |
| (66) Gon 2008 | 202.78 | 202.78 | 1.5% |
| (69) Porpiglia 2012 | 154.27 | 154.27 | 1.5% |
| (70) Bermejo 2003 | 200.19 | 200.19 | 1.5% |
| (72) LS Krane 2016 | 105.40 | 105.40 | 1.5% |
| (76) Tatsugami 2011 | 141.25 | 141.25 | 1.5% |
| (79) Ibsen 2005 | 194.16 | 194.16 | 1.5% |
| (80) Katyal 2016 | 200.25 | 200.25 | 1.5% |
| (83) KC Koo 2015 | 220.10 | 220.10 | 1.5% |
| (88) Papalia 2012 | 200.2 | 200.2 | 1.5% |
| (91) Bonali 2007 | 150.39 | 150.39 | 1.5% |
| (93) Petruzzi 2012 | 159.4 | 159.4 | 1.5% |
| (106) Springer 2013 | 165.14 | 165.14 | 1.5% |
| (108) Bahar 2015 | 100.15 | 100.15 | 1.5% |
| (110) Porpiglia 2014 | 152.44 | 152.44 | 1.5% |
| (117) Shah 2019 | 197.75 | 197.75 | 1.5% |
| (126) Weizet 2011 | 100.16 | 100.16 | 1.5% |
| (134) Pahmek 2013 | 249.13 | 249.13 | 1.5% |
| (141) Brown 2007 | 112.50 | 112.50 | 1.5% |
| (148) GS Gil 2003 | 200.10 | 200.10 | 1.5% |
| (151) Jan 2013 | 220.5 | 220.5 | 1.5% |
| (152) J H Zheng 2009 | 105.48 | 105.48 | 1.5% |
| (153) Kang 2013 | 273.18 | 273.18 | 1.5% |
| (158) Gidman 2001 | 125.12 | 125.12 | 1.5% |
| (159) Moinzadeh 2006 | 219.50 | 219.50 | 1.5% |
| (160) Nomura 2008 | 380.18 | 380.18 | 1.5% |
| (191) Jain 2013 | 220.22 | 220.22 | 1.5% |
| (170) Togucu 2018 | 196.80 | 196.80 | 1.5% |

Random effects model: 219.1 (175.2; 263.7) 61.8% |

Zero ischemia |
| (64) Uoco 2014 | 250.19 | 250.19 | 1.5% |
| (69) Porpiglia 2012 | 201.41 | 201.41 | 1.5% |
| (71) CP Hou 2016 | 100.19 | 100.19 | 1.5% |
| (76) GS Gil 2012 | 200.54 | 200.54 | 1.5% |
| (85) Pahmek 2011 | 800.3 | 800.3 | 1.5% |
| (86) Kobayashi 2008 | 500.5 | 500.5 | 1.5% |
| (87) Kim 2002 | 572.10 | 572.10 | 1.5% |
| (88) HC Koo 2010 | 165.11 | 165.11 | 1.5% |
| (89) Papalia 2012 | 200.40 | 200.40 | 1.5% |
| (93) Petruzzi 2012 | 135.13 | 135.13 | 1.5% |
| (95) Kazmak 2012 | 210.44 | 210.44 | 1.5% |
| (98) Colla 2013 | 75.11 | 75.11 | 1.5% |
| (107) TC Kim 2014 | 243.24 | 243.24 | 1.5% |
| (115) Porpiglia 2014 | 290.42 | 290.42 | 1.5% |
| (150) GS Gil 2010 | 150.15 | 150.15 | 1.5% |
| (154) Knoedler 2012 | 208.36 | 208.36 | 1.5% |

Random effects model: 261.2 (171.0; 351.3) 25.0% |

Mean ± 95% CI: 235.3 (235.3; 235.3) 1.5% |

Heterogeneity: I² = 100%, p = 0
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.
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 \( \geq 4 \) 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 \( \geq 25 \) 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).
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 (Supplementary Fig. 18).

Furthermore, analyses focusing on the effect of WIT on local recurrence showed that the proportion of patients with local recurrence was 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
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.

Author contributions: Francesco Greco had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Greco.

Acquisition of data: Greco, Autorino, Altieri.

Analysis and interpretation of data: Greco, Mottiri.

Drafting of the manuscript: Greco.

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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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EUROPEAN UROLOGY 75 (2019) 477–491


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