Zero ischemia partial nephrectomy: Techniques and outcomes

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Abstract

Nephron sparing techniques nowadays have replaced radical nephrectomy as the gold standard management for T1a tumors. Even though the basic step of this technique was hilar clamping in order to achieve a bloodless surgical field and ease tumor excision and renorrhaphy, many surgeons have moved one step further and developed minimal or no vessel clamping.

These techniques were grouped under the title of zero ischemia partial nephrectomy. Nevertheless there is a great heterogeneity in the literature concerning every aspect of this term including surgical steps, oncological outcomes and functional results. The purpose of this paper is to review the literature about this interesting topic and to clarify the different aspects of this challenging procedure.

Introduction

Radical nephrectomy for T1 renal tumors has been the gold standard technique for many decades until nephron sparing techniques have emerged with similar if not better oncological and safety outcomes and replaced it in everyday clinical practice¹. Furthermore minimal invasive techniques like laparoscopy or robot assisted laparoscopy with their unique characteristics provided a significant aid in optimizing this challenging procedure. The body of the literature that proves their superiority in terms of functional outcomes is growing every day². From the dawn of partial nephrectomy its basic step was hilar clamping in order to achieve a bloodless surgical field and ease tumor excision and renorrhaphy³⁴. The time that the hilar vessels remain clamped is called warm ischemia time (WIT) and its length is the topic of argument for many experts, who set it to 30 mins or more recently to 20

Key words

zero ischemia; partial nephrectomy; renal cell carcinoma; clampless

Citation


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mins. They believed that if WIT didn’t pass this limit the impairment of renal function would be reversible and no long term renal functional loss was going to be established. This assumption prevailed until Thompson et al published their study suggesting that every minute of hilar clamping counts and their result confirmed by Gill et al who provided data that implied that this impairment in some categories of patients can be detrimental in the long term. Under these suspicions a novel technique of “Zero” ischemia emerged, utilizing no renal artery occlusion. We reviewed the literature for this novel technique and report the different aspects of surgical steps and their outcomes and at the same time we try to shed light into the heterogeneity of the terminology and reporting of functional outcomes.

Material and Methods

We reviewed the literature for articles concerning zero ischemia partial nephrectomy for the management of renal cell carcinoma. The search was limited in articles which had at least an abstract written in English and were indexed in PubMed from 2000-2017. The keywords that were used in our search were renal cell carcinoma, zero ischemia, clampless. We studied all the relevant articles and we analyzed the ones with the biggest series. We excluded only the articles that weren’t written in English and the case reports or case series with low number of patients (<10 patients).

Variations of techniques under the term zero ischemia

Reviewing literature ended up with a very interesting finding: the term “zero ischemia” is used to describe very different techniques including, “pure” off clamp techniques (with a variety of sub categories) but also “on clamp” techniques like high order arterial clamping, controlled hypotension and renal artery microdissection. Furthermore several techniques, which were described as zero ischemia, in fact involve the placement of a clamp on a primary, secondary, tertiary or higher-order artery. On the other hand, other techniques that were described as ‘off clamp’ or clampless did not use the term zero ischemia. Great diversity also exists in reporting results of nearly every aspect of nephron sparing surgery and Table 1.

One of the most popular techniques in nephron sparing surgery described as zero ischemia is arterial microdissection combined with pharmacological controlled hypotension. It consists of microdissection and clip ligation of high order arterial branches during a short hypotension period induced by inhaled isoflurane and nitroglycerin. Gill et al first reported this technique which resulted in no eGFR and serum creatinine change between pre and post-operative values, possible due to continuous intrarenal arterial perfusion during nadir hypotensive period. On the other hand low pressure for a significant period of time cannot be tolerated from patients with cardi or cerebrovascular comorbidities and controlled hypotension can be utilized only in selected patients. Other disadvantages include a more difficult (due to hemorrhage) suturing field, and the fact that it includes clamping even though it is on a small arterial branch. In pursuit of optimizing this technique Borofsky et al reported a possible aiding factor when performing this procedure robotically. The authors utilized the near infrared fluorescence imaging utility (NIRF) of the robotic platform after intravenous administration of 7.5 mg indocyanine green (ICG) and after placement of a microsurgical bulldog on the high end artery feeding the tumor. With this maneuver the tumor remains dark whereas the rest parenchyma turns into vivid green. The technique was successful on 93% of the patients and their matched pair analysis yielded statistical difference in terms of operation time in favor or the main artery clamping whereas the functional preservation outcomes were in favor of the NIRF group (-1.8% vs. 14.9% $p = 0.03$). Even though this technique seem promising the short follow up period does not permit safe conclusions and require validation from bigger studies with longer follow up.

The above mentioned techniques required clamping somewhere in the renal artery tree. As experience with nephron sparing procedures increase, surgeons developed “clampless” techniques. All these procedures have a lot of differences but one common: they do not include clamping of any sort. Data in the literature generally agree that off clamp techniques provide better short term functional results but longer operation times and increased median estimated blood loss (EBL) when compared to on clamp techniques. The main disadvantage of these studies was the short follow up which can potentially be misleading since any advantage on eGFR values usually disappears in time. In pursuit of minimizing bleeding which is the main...
factor that can implicate off clamp partial nephrectomy several minimally ischemic procedure were introduced including preoperative superselective transarterial embolization (P-STE) of the feeding artery of the tumor in a hybrid operation room which contains specialized equipment. Even though this idea seemed promising because of the favorable functional outcomes there are several risks including post embolization syndrome and positive surgical margins due to edema and the need of high tech equipment or straight access to operating room immediately after angiographic procedure. In the same pace smaller reports in the literature utilized different techniques in order to minimize hemorrhage during operation like harmonic scalpel, running sutures before or/and during tumor resection and hemostatic agents with controversial results.

Functional outcomes: Do we speak the same language?
The major endpoint of all the studies concerning nephron sparing techniques is their functional outcomes. Nevertheless reporting on this important issue lacks of consensus throughout literature. The great heterogeneity on functional outcomes is shown in Table 2. The first and more crucial factor that may influence functional outcomes is follow up period. Many studies report better functional results after zero ischemia partial nephrectomy in the short term, results that are significantly diminished in other major studies that are reporting a longer follow up. Follow up period varies from 3 months to 24 months or more making comparison with other techniques extremely difficult. Another important issue is the strength of the factors that are utilized in order to measure the loss of renal function. Even the most easy to access and most widely adopted, the estimated glomerular filtration rate (eGFR), has major disadvantages include, ignoring patient BMI, its approximation nature and its low sensitivity on detecting changes in unilateral renal function due to opposite kidney increased function. The need for accurate detection of renal failure has lead researchers utilize renal scintigraphy or novel biomarkers that are more sensitive to kidney injury (Cystatic C, Kidney injury mol-

### Table 1

<table>
<thead>
<tr>
<th>Tumor Location</th>
<th>Anatomical Control</th>
<th>Type of Ischemia</th>
<th>Duration of Ischemia</th>
<th>Intraoperative Assessment of Renal Surgical Ischemia</th>
<th>Physiological Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>PADUA score</td>
<td>Global renal ischemia</td>
<td>Warm</td>
<td>Warm ischemia time</td>
<td>Visual inspection of renal parenchyma</td>
<td>Pneumoperitoneal pressure</td>
</tr>
<tr>
<td>Nephrometry score</td>
<td>Selective minimal renal ischemia</td>
<td>Cold</td>
<td></td>
<td>Doppler probe studies</td>
<td>Pharmacologically induced hypotension</td>
</tr>
<tr>
<td>Kidney segmentation system</td>
<td>Zero renal ischemia</td>
<td></td>
<td></td>
<td>Colour flow Dopple imaging</td>
<td>Indocyanine green fluorescence</td>
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</table>

### Table 2

<table>
<thead>
<tr>
<th>Duration of follow up</th>
<th>Biochemical parameters</th>
<th>Differential renal function with imaging scintigraphy</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to 24 months</td>
<td>eGFR</td>
<td>Tc–DTPA 99m</td>
<td>CKD</td>
</tr>
<tr>
<td>&gt;24 months</td>
<td>eGFR or renal clearance normalized for BMI</td>
<td>Tc–DMSA 99m</td>
<td>DMSA</td>
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<tr>
<td></td>
<td></td>
<td>99m Tc–MAG3</td>
<td>EDTA</td>
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Even though it seems logical that lesser or no ischemia during nephron sparing surgery leads to lesser renal function loss this assumption is not reinforced from most published papers in the literature. Big studies reveal a small advantage of zero ischemia techniques in terms of functional outcomes on the short term (3 months 8% vs. 1.5% \( p =0.04 \)) but this advantage disappears during longer follow up period (>1 year)\(^2\). On the other hand meta-analysis that demonstrate an advantage of off clamp techniques versus hilar clamp techniques must be interpreted with caution since there is significant bias regarding patient selection\(^2\) and quality of included studies\(^2\). Finally one important question in the minimal invasive urology era is if minimal invasive techniques (laparoscopic or robotic) provide any advantage in the final functional outcomes compared with open partial approach. In this question Mearini et al answered with a study of over 150 patients that didn’t find any statistical significant difference when comparing open, laparoscopic and robotic approaches in terms of pre and post-operative eGFR changes\(^2\).

**Conclusion**

In pursuit of better functional outcomes after partial nephrectomy, many surgeons utilized different zero or minimal ischemia techniques with promising results, despite the fact that there is no consensus in post-operative outcomes reporting. Zero ischemia doesn’t seem to provide any significant advantage over hilar clamping nevertheless increasing surgical experience and novel markers may change this conclusion in the near future.

**Conflicts of interest**

The author declared no conflict of interest.

**TABLE 3**

<table>
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<tr>
<th>Studies included with their basic characteristics and reported results</th>
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<tr>
<td><strong>Type of procedure</strong></td>
</tr>
<tr>
<td>Gill et al.(^4)</td>
</tr>
<tr>
<td>Borofsky et al.(^4)</td>
</tr>
<tr>
<td>Bigot P et al.(^1)</td>
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<td>Hou CP et al.(^1)</td>
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<tr>
<td>Rizkala et al.(^1)</td>
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VMD= vascular microdissection, Lap=Laparoscopic, Rob=Robotic, WIT= warm ischemia time, EBL= estimated blood loss. PSM= positive surgical margines, MC= Major complications, eGFR= estimated glomerular filtration rate (at 2 months), SSAC= superselective arterial clamping, P-STE = preoperative superselective transarterial embolization, HS=Harmonic Scalpel, PSR = replaced suture renorrhaphy.

## Περίληψη

Η μερική νεφρεκτομία πλέον έχει αντικαταστήσει την ριζική νεφρεκτομία στην αντιμετώπιση του νεφροκυτταρικού καρκίνου στάδιο Τ1α. Βασικό χειρουργικό βήμα στην μερική νεφρεκτομία είναι το clamping της νεφρικής αρτηρίας με στόχο την διατήρηση ενός μη αιμορραγικού χειρουργικού πεδίου το οποίο βοηθά στην καλύτερη εκτομή του όγκου αλλά και συρραφή του νεφρικού παρεγχύματος. Ωστόσο πολλοί χειρουργοί θέλουν να βελτιώσουν την μέθοδο αυτή μειώνοντας όσο το δυνατόν το χρόνο νεφρικής ισχαιμίας ανεπτύσανελάχιστα ή και καθόλου ισχαιμικές τεχνικές. Οι τεχνικές αυτές παρότι ομα-
Περίληψη (συνέχεια)

δοποιήθηκαν κάτω από τον τίτλο μερική νεφρεκτομή μηδενικής ισχαιμίας, παρουσιάζουν μεγάλη ετερογένεια τόσο στα χειρουργικά βήματα όσο και στην παρουσίαση των ογκολογικών και λειτουργικών αποτελεσμάτων τους. Ο σκοπός της παρούσας μελέτης είναι η ανασκόπηση της βιβλιογραφίας για το ενδιαφέρον αυτό θέμα αλλά και η αποσαφήνιση των διαφορετικών πτυχών της απαιτητικής αυτής χειρουργικής προσέγγισης.

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