Application of Laparoscopy in Upper Urinary Tract Surgery

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Doctoral (PhD) Thesis
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Pecs 2016
“Few procedures provide the urologist with more satisfaction than those that preserve renal function”
(Benjamin Abeshouse, 1950)

If we want to see into the future, we need only look to the past
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# ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>$^{99m}$Tc-DMSA</td>
<td>$^{99m}$Technetium-Dimercaptosuccinic Acid</td>
</tr>
<tr>
<td>AKI</td>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>AMP</td>
<td>Adenosine Monophosphate</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>ATN</td>
<td>Acute Tubular Necrosis</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine Triphosphate</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index (kg/m$^2$)</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>Chronic Kidney Disease Epidemiology Collaboration</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized Tomography</td>
</tr>
<tr>
<td>EAU</td>
<td>European Association of Urology</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>IR</td>
<td>Ischemia-Reperfusion</td>
</tr>
<tr>
<td>LN</td>
<td>Laparoscopic Nephrectomy</td>
</tr>
<tr>
<td>LPN</td>
<td>Laparoscopic Partial Nephrectomy</td>
</tr>
<tr>
<td>LRN</td>
<td>Laparoscopic Radical Nephrectomy</td>
</tr>
<tr>
<td>MAG 3</td>
<td>Mercapto-Acetyltriglycerine</td>
</tr>
<tr>
<td>NSS</td>
<td>Nephron-Sparing Surgery</td>
</tr>
<tr>
<td>OPN</td>
<td>Open Partial Nephrectomy</td>
</tr>
<tr>
<td>P-DRF</td>
<td>Partial Differential Renal Function</td>
</tr>
<tr>
<td>PN</td>
<td>Partial Nephrectomy</td>
</tr>
<tr>
<td>RCC</td>
<td>Renal Cell Carcinoma</td>
</tr>
<tr>
<td>RF</td>
<td>Renal Function</td>
</tr>
<tr>
<td>RN</td>
<td>Radical Nephrectomy</td>
</tr>
<tr>
<td>ROI</td>
<td>Region Of Interest</td>
</tr>
<tr>
<td>sCr</td>
<td>Serum Creatinine</td>
</tr>
<tr>
<td>T-DRF</td>
<td>Total Differential Renal Function</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>WI</td>
<td>Warm Ischemia</td>
</tr>
<tr>
<td>WIT</td>
<td>Warm Ischemia Time</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

1.1. THE CHANGING FACE OF RENAL CELL CARCINOMA

1.1.1. Epidemiology of renal cell cancer.

Renal cell carcinoma (RCC) makes up approximately 2-3% of all cancers and accounts for 90% of all malignancies of the kidney. It is the 9th most common cancer in men and 14th in women. However, the incidence of RCC varies worldwide (Ferlay J et al. 2012). It is more common in industrialized countries where it is ranked in both sexes as 11th most common tumor while in developing countries it is ranked as 21st place. Although the male-to-female ratio differs significantly for each type of renal cell tumor and in different age groups, generally there is a 2:1 predominance of men over women, with peak incidence occurring between 60 and 70 years of age (Hew MN et al. 2012).

Through the past decades there has been a steady increase in number of clinically recognized RCC in industrialized countries.

The growing number of incidentally detected RCC cannot be explained exclusively by extensive use of modern imaging techniques. Several other factors related to lifestyle of modern industrialized countries may also play a role in the increasing rate of RCC. The exact etiology of RCC, with exception of hereditary cases, is still unknown. It is estimated that smoking accounts for around one third of the RCC cases (Cumberbatch MG et al. 2016). In addition to smoking, which doubles the risk for RCC, obesity, hypertension and an unhealthy diet are also associated with the tumor development (Chow W-H et al. 2010).

Through the past decades the mortality rate has stabilized or even declined in most European countries.

In spite of the increasing number of clinically detected RCC, the mortality rate due to RCC has stabilized or even declined in European countries and the USA (Levi et al. 2008). The widespread use of imaging technique resulted in the detection of RCC that are smaller and of lower stage (Lightfoot et al. 2000). The number of incidentally detected T1a and also T1b tumours is increasing in operation statistics of most urological centers. These tumours metastasize less often compared with higher stage tumours.
1.1.2. New genetic classification system

RCC is not considered as a single pathological entity, but different types characterized by specific genetic alteration and natural history (Kovacs, 1993)\(^7\). The new knowledge was discussed at a conference held in Heidelberg and published as the Heidelberg Classification of Renal Cell Tumors (Kovacs et al. 1997)\(^8\). Each type of tumour displays a combination of chromosomal-genomic alterations of diagnostic impact (Table 1). The new classification system is now adapted by the WHO. The diagnosis of a specific type of RCC itself has a strong impact on the prognosis of tumors as the 5 years tumour specific survival indicates (Table 1).

**Table 1. Some pertinent genetic data on distinct types of renal cell tumours.**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Frequency (%)</th>
<th>Genomic alterations*</th>
<th>Gene mutations</th>
<th>5 years survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cRCC</td>
<td>65-70</td>
<td>-3p, +5q, -6q, -8p, -9p, -14q</td>
<td>VHL (50%) PBRM1 (35%)</td>
<td>~60</td>
</tr>
<tr>
<td>pRCC</td>
<td>10-15</td>
<td>+7, +17, +8, +12, +16, +20,</td>
<td>MET (5%)</td>
<td>~90</td>
</tr>
<tr>
<td>chRCC</td>
<td>5-7</td>
<td>-1, -2, -6, -10, -13, -17, -21</td>
<td>p53 (25%)</td>
<td>~95</td>
</tr>
<tr>
<td>RO</td>
<td>5-7</td>
<td>-1, -14q or t(11q:?) or none</td>
<td>?</td>
<td>100</td>
</tr>
<tr>
<td>ucRCC</td>
<td>5-7</td>
<td>?</td>
<td>?</td>
<td>~20</td>
</tr>
<tr>
<td>CDC</td>
<td>&lt;1</td>
<td>?</td>
<td>?</td>
<td>30</td>
</tr>
<tr>
<td>MTSCC</td>
<td>&lt;1</td>
<td>-1, -4, -6, -9, -13, -14, -15, -22</td>
<td>?</td>
<td>100</td>
</tr>
<tr>
<td>MA</td>
<td>&lt;1</td>
<td>none</td>
<td>?</td>
<td>100</td>
</tr>
</tbody>
</table>

*cRCC-conventional RCC, pRCC-papillary RCC, chRCC-chromophobe RCC, RO-renal oncocytoma, ucRCC-unclassified RCC, CDC-collecting duct carcinoma, MTSCC-mucinous tubular and spindle cell carcinoma, MA-metanephric adenoma.*

*Genomic alterations: “−”, = loss, “+” = gain, t = translocation; VHL – von Hippel Lindau gene; MET – Met tyrosin kinase receptor. (Table 1. is kindly provided by Professor Gyula Kovacs).*
Based on the characteristic cell morphology and growth pattern, 4 main types of renal cell tumours can be distinguished (Figure 1). The most common conventional RCC (also called clear cell RCC, which is a misleading name as every fourth of this genetically defined tumour does not display clear but eosinophilic cytoplasm). In spite of overlapping phenotype, the histological diagnosis can be made by experienced pathologist on haematoxilin-eosin stained slides in the vast majority of cases. However, in some cases a genetic analysis is necessary to detect the tumour type specific alterations and to achieve a correct diagnosis, especially for the differential diagnosis of benign renal oncocytoma and malignant chromophobe RCC (Table 1).

Figure 1. Characteristic histological picture of four main types of renal cell tumours. A, Conventional RCC composed of trabecular arranged clear cells with empty cytoplasm and picnotic nuclei. B, Papillary renal cell carcinoma composed of medium sized eosinophilic cells with foamy cells in papillary stalks. C, Chromophobe renal cell carcinoma with large pale cells, double nuclei arranged in large epithelial sheets. D, Renal oncocytoma showing large nests of strong eosinophilic cells embedded in oedematous stroma. (Haematoxylin and eosin staining, x400) (Kindly provided by Professzor Gyula Kovacs)
1.1.3. **TNM-G Classification and Staging: Estimating the outcome of the disease**

In 2012, 84,000 patients were diagnosed with renal cell carcinoma (RCC) and 35,000 patients died due to disease in European countries (Ferlay et al. 2013). Mortality of RCC correlates directly with the presence or postoperative development of metastasis. Approximately 20-25% of the most common conventional RCC are presented with advanced disease at the time of diagnosis and further 15-20% will develop metastasis within the next 5 years (Zisman et al. 2002).

When diagnosing cancer, the TNM Classification and stage of the tumor are important parameters which direct the management and used to estimate the outcome of disease (Table 2). The cancer specific survival rate is much higher in a cohort of patients with lower stage of RCC. There is a good correlation between the size of tumour and progression of disease. The latest classification divided T1 tumours into subgroup ≤ 4 cm (T1a) and another one > 4 cm and ≤ 7 cm in diameter (T1b), the former having a better prognosis. Moreover, T2 tumours have also been divided into two classes: T2a are tumours with a size > 7 and ≤ 10 cm, and T2b tumours > 10 cm, but confined to the kidney. This classification may be crucial by decision of carrying out a partial nephrectomy. The regional lymph node (N) positivity is another parameter having an influence on the outcome of the disease. The new classification system uses only one class. e.g. metastasis in one or more lymph nodes. The metastasis (M) is the ultimate sign of tumour malinancy, leading to patients’ death in the overwhelming majority of cases in spite of modern targeted therapy.

Nuclear grading refers to the appearance of the cancer cells under the microscope. The grade indicates how the cancer may behave, and is one of the important prognostic factor of RCC. The four grade nuclear grading system is the most used grading system for kidney cancer. However, recent studies showed by follow-up studies, that patients with grade 1 and grade 2 tumours have a similar survival and therefore can be evaluated together as a single grade. Doing so will result in the three grade system with better estimation of the outcome of the disease.
### Table 2. TNM Classification of kidney cancers

<table>
<thead>
<tr>
<th>T: Primary tumour</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tx</strong></td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td><strong>T0</strong></td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td><strong>T1</strong></td>
<td>Tumour ≤ 7 cm in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td><strong>T1a</strong></td>
<td>Tumour ≤ 4 cm in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td><strong>T1b</strong></td>
<td>Tumour &gt; 4 cm but ≤ 7 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td>Tumour &gt; 7 cm in greatest dimension, limited to the kidney</td>
</tr>
<tr>
<td><strong>T2a</strong></td>
<td>Tumour &gt; 7 cm but ≤ 10 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>T2b</strong></td>
<td>Tumours &gt; 10 cm limited to the kidney</td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td>Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland or beyond Gerota’s fascia</td>
</tr>
<tr>
<td><strong>T3a</strong></td>
<td>Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches, or invades perirenal and/or renal sinus fat (peripelvic), but not into the adrenal gland and not beyond Gerota’s fascia</td>
</tr>
<tr>
<td><strong>T3b</strong></td>
<td>Tumour grossly extends into the vena cava (VC) below the diaphragm</td>
</tr>
<tr>
<td><strong>T3c</strong></td>
<td>Tumour grossly extends into vena cava above the diaphragm or invades the wall of the VC</td>
</tr>
<tr>
<td><strong>T4</strong></td>
<td>Tumour invades beyond Gerota’s fascia (including contiguous extension into the ipsilateral adrenal gland)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N: Regional lymph nodes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NX</strong></td>
<td>Regional LNs cannot be assessed</td>
</tr>
<tr>
<td><strong>N0</strong></td>
<td>No regional LN metastasis</td>
</tr>
<tr>
<td><strong>N1</strong></td>
<td>Regional LN metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M: Distant metastasis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M0</strong></td>
<td>No distant metastasis</td>
</tr>
<tr>
<td><strong>M1</strong></td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

The results of TNM classification are grouped to determine the patient’s overall survival changes (Table 3). The four tumor stages (Stage I-IV) are a combination of local growth of tumor without or with invasive growth, the lymph node involvement and distant metastasis. The vast majority of tumors in Stage I and II have a high cancer specific survival, whereas stage IV tumors are in most cases fatal.
Table 3. TNM stage grouping of kidney cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1, T2, T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T4</td>
<td>Any</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>AnyT</td>
<td>AnyN</td>
<td>M1</td>
</tr>
</tbody>
</table>

Stage I tumours are the best candidates for laparoscopic partial nephrectomy (LPN), but larger tumours confined to the kidney (Stage II) may also be removed by laparoscopic radical nephrectomy (LRN). From the technical point of view, another scoring system, the PADUA score, is more important for a laparoscopic urologist.

1.1.4. Anatomic classification system: The PADUA and RENAL nephrometry scores

Because of the widespread use of imaging techniques such as ultrasonography and computed tomography, a large number of small localized renal cell tumours are detected incidentally. The vast majority of incidentally detected tumours are pT1a or pT1b and confined to the kidney, e.g. Stage I or Stage II tumours. For such patients, organ-sparing surgery is considered as the standard of care if applicable. There is no difference regarding tumour recurrence and cancer specific survival of patients with small renal tumours operated with open or laparoscopic radical or partial nephrectomy. Therefore, for decision making of the operation technique other parameters are necessary.

Objective anatomical classification systems, such as the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification system, and the Radius (tumor size as maximal diameter), Exophytic/endophytic properties of the tumor, Nearness of tumor deepest portion to the collecting system or sinus, Anterior/posterior descriptor and the Location relative to the polar line (R.E.N.A.L.) nephrometry score and the C-index have been proposed, to standardise the
description of renal tumours (Figure 2) (Kutikov and Uzzo, 2009). These systems are helpful as it allows objective prediction of potential morbidity of NSS and tumour ablation techniques. These tools provide information for treatment planning, patient counselling, and comparison of partial nephrectomy (PN) and tumour ablation series. However, when selecting the best treatment option, anatomic scores must always be considered together with patient features and surgeon experience.

<table>
<thead>
<tr>
<th>R (Radius) (maximal diameter in cm)</th>
<th>1pt</th>
<th>2pts</th>
<th>3 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>⪡≤4</td>
<td>&gt;4 but &lt; 7</td>
<td>≥ 7</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>E (Exophytic/Endophytic properties)</th>
<th>≥ 50%</th>
<th>&lt;50%</th>
<th>Entirely endophytic</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>N (Nearthness of the tumor to the collecting system or sinus (mm))</th>
<th>≥7</th>
<th>&gt;4 but &lt;7</th>
<th>≤4</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>A (Anterior/Posterior)</th>
<th>No points given. Mass assigned a descriptor of a, p, or x</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>L (Location relative to the polar lines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>* suffix “h” assigned if the tumor touches the main renal artery or vein</td>
</tr>
<tr>
<td>Entirely above the upper or below the lower polar line</td>
</tr>
</tbody>
</table>

**Figure 2. R.E.N.A.L. Nephrometry Score with scoring of (L)ocation component.** Polar lines (solid lines) and axial renal midline (broken line) are depicted on each sagittal view of kidney. Numbers 1 to 3 represent points attributed to each category of tumor (Kutikov and Uzzo, 2009)
The PADUA score is an important tool to predict possible risk of complications and the length of ischemia time. It is important for selection of patients for open, laparoscopic or robotic-assisted approaches. The size of tumour is one of the important parameters for the choice of surgical treatment, e.g. partial or radical nephrectomy. Small pT1a tumours are good candidates for NSS. However, in selected patients larger tumours can be removed by partial nephrectomy applying either open or laparoscopic surgery. Another important parameter of the scoring system is the tumour location. The localisation of tumour within the kidney plays a crucial role in the decision of the surgical treatment. Polar, rim or central location, the relationship with renal sinus and collecting duct system, the deep position are important parameters in the decision of total or partial nephrectomy. The preoperative PADUA score is an independent predictor of the occurrence of postoperative complications. A PADUA score of 10 or 8-9 means an approximately 30 and 15 fold risk for postoperative complications compared to PADUA score 6-7 which are reference scores of harad ratio (Figure 3) (Ficarra et al. 2009)
Figure 3. (a) Longitudinal classification of the tumours; (b) margin location of the tumours; (c) tumour relationship with renal sinus; (d) tumour relationship with urinary collecting system; (e) tumour deepening into the parenchyma; (f) tumour size classification.
1.2. OPEN OR LAPAROSCOPIC SURGERY FOR TREATMENT OF KIDNEY CANCER

Surgery remains the only curative treatment for RCC. The objective of surgical therapy is to excise the entire tumour with an adequate surgical margin. In 1969, Robson and colleagues\textsuperscript{13} established radical nephrectomy (RN) as the “gold standard” curative operation for localized RCC. In the past three decades, the increased use of imaging modalities such as ultrasound (US) and computerized tomography (CT) has led to increase the number of incidentally detected renal masses\textsuperscript{6}. Tumours detected by imaging techniques tend to be smaller, lower stage lesions that are typically amenable to partial nephrectomy (PN). The main aim of this surgical procedure is maximal preservation of unaffected renal parenchyma without sacrificing cancer control. During the last several years, refinements in the surgical technique of PN have made this procedure technically safe with acceptable complication rates. Long-term outcome data indicate that open partial nephrectomy (OPN) has cancer-free survival rates comparable to those of radical surgery with better preservation of renal function (RF), reduced frequency of cardiovascular events, and decreased overall mortality rate (Margreiter and Marbereger, 2010)\textsuperscript{14}.

According to European Association of Urology (EAU) guidelines 2016, with grade of recommendation “A”, for T1a tumours, NSS is recommended and for T1b tumours, NSS should be favoured over RN whenever feasible. RN is no longer the gold standard treatment in these cases (Delakas et al. 2002)\textsuperscript{15}. Standard indications for NSS are divided into the following categories: 1). Absolute – anatomical or functional solitary kidney, and bilateral renal tumours. 2). Relative – functioning opposite kidney is affected by a condition that might impair RF in the future, e.g.: hereditary forms of RCC, diabetes mellitus, hypertension, autoimmune diseases, stone formers, etc. 3). Elective – localized unilateral RCC with a healthy contralateral kidney. Recently, cases of elective indications for NSS of RCC have vastly increased. It has been proved that, in these cases, NSS for tumours limited in diameter to 4 cm (pT1a) provides recurrence-free and long-term survival rates similar to those observed after radical surgery (Becker et al. 2006)\textsuperscript{16}. For larger tumours (pT1b), PN has demonstrated feasibility and oncological safety in carefully selected patients (Patard et al. 2004)\textsuperscript{17}. 
The impact of laparoscopy has increased rapidly within the last two decades, and as a result, laparoscopic radical nephrectomy has become a recognized standard surgical approach by the 2006 European Association of Urology guidelines. Parallel to this evolution in technique, the indication for radical nephrectomy has also changed to a great extent. By means of imaging techniques such as ultrasonography and computed tomography scanning, an increasing number of small renal cancers are being detected incidentally. For the majority of these tumors nephrectomy is an over-treatment, and NSS has to be considered instead even if there is a normally functioning contralateral kidney because oncologic results are as good as with radical nephrectomy. Many surgeons are now confronted with the difficult situation that they can offer radical nephrectomy by means of laparoscopy to remove large tumors but are unable to perform laparoscopic NSS for the small ones. Thus, great effort has been directed towards the development of reliable and reproducible techniques for laparoscopic partial nephrectomy (LPN).

Open surgical partial nephrectomy is usually performed in ischemia to allow for precise tumor excision and reconstruction of the renal parenchyma in a bloodless field. Gill (Gill et al. 2002) was the first to show that these principles of open surgery can be duplicated by means of laparoscopy. Ischemia time, however, is critical for renal function which is traditionally restricted to a maximum of 30 minutes. Ischemia time can be increased substantially by cooling of the renal parenchyma, which is easily induced during open surgery. When comparing laparoscopy with open surgery, ischemia time is longer even in the most experienced hands and hypothermia for protection of the renal function is difficult to achieve.

Several attempts have been made to overcome the aforementioned problems in laparoscopic approaches. Direct excision of small and peripherally located tumors is feasible without ischemia. Haemostasis can be achieved by bipolar coagulation, ultrasonic scalpel, radiofrequency, microwave tissue coagulator and several other devices. A variety of tissue sealants have also been used for this purpose. The main problem with these techniques is not the haemostasis; however, because of ongoing burning and charring of the tissues and continuing bleeding, it becomes impossible to distinguish between normal parenchyma and tumor tissue so that a positive
surgical margin cannot be realized anymore. Therefore, this technique can be recommended for highly selected cases only.

Several technical modifications of laparoscopic partial nephrectomy have resulted in a substantial reduction of the time required for haemostasis and reconstruction of the parenchyma. Knotting is the most time-consuming part of laparoscopic reconstructive procedures. Therefore, all knots are replaced by clips. The large clips (Hem-o-lok®) used for the approximation of the parenchyma have the additional advantage that they avoid the suture cutting through the parenchyma when pressure is applied. Thereby efficient haemostasis can be achieved.

1.3. LAPAROSCOPIC SURGERY FOR TREATMENT OF T1 KIDNEY CANCER

Minimal invasive surgery, owing to its lower morbidity comparing to open surgery, has reformed urologic surgical approach particularly in kidney surgery. Since its introduction in 1990 by Clayman and colleagues (Clayman et al. 1991)\(^{19}\), laparoscopic nephrectomy (LN) for RCC has become an established surgical procedure worldwide. Whether done retro-peritoneally or trans-peritoneally, the laparoscopic approach must follow established open surgical oncological principles. Long-term outcome data indicate that LRN has equivalent cancer-free survival rates to those of open radical nephrectomy (Hemal et al. 2007)\(^{20}\). Consequently, LRN has become the standard of care for patients with T1 and T2 renal masses not treatable by NSS (Burgess et al. 2007; Rosoff et al. 2009)\(^{21-22}\).

Since the first laparoscopic partial nephrectomy (LPN) performed in 1992 by Winfield and colleagues (Winfield et al. 1993)\(^{23}\), in experienced hands and selected patients, it has become an alternative to open partial nephrectomy (OPN). Generally, during LPN, the renal ischemia time is longer than with OPN. Laparoscopic NSS has a higher complication rate compared to open surgery. However, the oncological outcome in available series with limited follow-up appears to be similar to the outcome achieved with open nephron sparing surgery (Gill et al. 2007; Porpiglia et al 2008)\(^{24-25}\). The optimal indication for laparoscopic nephron sparing surgery is a relatively small and peripheral renal tumour. With the ongoing advancements in minimal invasive surgery for renal tumours, it is now feasible to perform LPN for
larger and more complicated renal masses in experienced centres (Albqami et al. 2005; Porpiglia et al. 2010).  

According to EAU guideline (2010), OPN was considered as the standard of care for NSS and LPN was recommended to be performed by experienced surgeons. In EAU guidelines (2016), with level of evidence “2b”, it has been modified as follow: PN can be performed, either with an open, pure laparoscopic- or robot-assisted approach, based on surgeon’s expertise and skills. As familiarity with laparoscopic technique has grown in many centres, LPN application has also expanded worldwide. Modifications to standard techniques have helped improve perioperative characteristics and parameters, to levels comparable to open surgery (Eisenberg et al 2010). However, LPN has many technical difficulties when comparing with OPN. This is reflected in the learning curve. Operation of approximately 25 cases is necessary for OPN whereas to achieve a good experience in LPN around 200 operations should be carried out (Porpiglia et al. 2008).

Partial nephrectomy (PN) of either open or laparoscopic access can be divided into two main categories: PN without ischemia and PN with ischemia. The former is applicable in only selected cases of small peripheral tumors or with application of distinctive instrumentations for haemostasis (Knudsen et al. 2010; Thompson et al. 2010). Bloodless surgical field for optimal tumor excision can only be achieved by establishing renal ischemia, which can be applied by either cold ischemia or warm ischemia (WI). Renal ischemia can be global when the artery or the whole pedicle is clamped or regional when renal parenchymal compression is used. Cold ischemia is applied in cases where longer ischemic time is expected. Due to its safety and easiness of application, global renal WI is most widely used in most partial nephrectomies.

The interest in laparoscopic partial nephrectomy resulted in an urgent need for clear data describing ischemic renal damage in relation to time. Exact evaluation of the function of the operated kidney must be the basis of every study on that topic. This statement sounds very simple. However, when studying the literature on that topic one has to realize very quickly that not even this basic question has been answered so far. How to evaluate unilateral renal function? Split renal function determined by
mercapto-acetyltriglycine (MAG 3) isotope clearance is the minimal requirement. However, it cannot distinguish between loss of renal parenchymal volume due to excision of healthy tissue together with the tumor and permanent ischemic damage of the remaining tissue. Complete excision of a large tumor will result in a decrease of the split renal function of the involved kidney. Therefore, additional parameters are required to identify ischemic damage of the remaining tissue. Correlation of split renal function with the volume of the kidney could solve the problem.

1.4. THE EFFECT OF INTRAOPERATIVE ISCHEMIA ON KIDNEY FUNCTION

1.4.1. Mechanism of ischemia-reperfusion injury

During renal ischemia, hypoxia caused by cessation of renal blood flow, and finally reperfusion caused by instant release of blood flow, trigger a complex series of events that lead to tissue injury and acute tubular necrosis. The essential feature of injury caused by ischemia and reperfusion (IR) is that the initial damage caused by the ischemic insult is exacerbated by the reintroduction of blood flow to the relevant area (Wein et al. 2007)\textsuperscript{31}. The sentinel biochemical event in renal ischemia is the depletion of adenosine triphosphate (ATP), which is the major energy currency for cellular work. ATP is metabolized to adenosine monophosphate (AMP). During prolonged oxygen deprivation, AMP is further metabolized to the nucleosides adenosine, inosine, and hypoxanthine. These compounds diffuse from the cell, resulting in the loss of the substrate reservoir for ATP synthesis after reperfusion. Furthermore, hypoxanthine becomes an important substrate in the development of oxygen free radicals during the reperfusion period (Wein et al. 2007)\textsuperscript{31}. At the time of reperfusion, xanthine oxidase plays a role in conversion of hypoxanthine to xanthine. Xanthine is the major source of superoxide radical, which is ultimately metabolized to hydrogen peroxide and hydroxyl radical that produce cellular injury.

\textit{This reaction takes about 30 minutes in the kidney} (McCord ,1985)\textsuperscript{32}.
During prolonged ischemia, medullary hypoxia intensifies. Due to the high metabolic requirement of the nephron structures located in the outer medulla are most sensitive to injury. The straight portion of the proximal tubule sustains the most severe injury. Other structures that sustain injury in this region include the medullary thick ascending limb.

The arterial occlusion during surgery leads to a localized reduction in renal blood flow which disproportionately decreased in the outer medulla due to arteriolar vasoconstriction and local edema. IR leads to swelling of endothelial cells and enhanced leukocyte-endothelium interaction and some leukocytes migrate into the interstitial compartment. In rodent, endothelial cells loss their barrier function within two hours after reperfusion. The early innate and also later the adaptive immune responses contribute to the pathology of ischemic injury. During the early innate response neutrophils, macrophages, natural killer cells accumulate at the ischemic site and are active during the first days.

The reduced oxygen and nutrient delivery results in damage of epithelial cells especially in the pars recta of proximal tubules, which cannot convert from oxidative to glycolytic metabolism. Proximal tubular cells express toll-like receptors (TLR) such as TLR2 and TLR4, which initiates proinflammatory response by releasing cytokines and chemokines. Thus proximal tubular cells are not only victim the injury but actively participate in the inflammatory response to IR damage of the kidney. Kidney injury molecule-1 (KIM-1), a marker of proximal tubules injury accumulates in the urine after ischemia indication a strong proximal tubules injury (Han et al. 2002)33. Acute kidney injury also activates other genes including the neutrophil gelatinase-associated lipocalin (NGAL) (Mishra et al. 2005)34. Appearance of both genes in the urine indicates a significant injury of proximal tubules.

Cells of the distal tubules are more resistant to hypoxia, oxidative injury, e.g. ischemia-reperfusion. Cells of the distal nephron have greater capacity to shift from oxidative to glycolytic metabolism during reduced oxygen supply. These cells produce more anti apoptotic BCL-2 and also reparative growth factors than proximal tubules and therefore minimize the cell death and ischemic injury (Gobe et al.
Crosstalk between distal tubular cells and proximal tubules may contribute to the repair of the latter.

The interplay of these abnormalities forms the basis for the acute decrease in glomerular filtration rate (GFR), which is the result of intrarenal vasoconstriction, with a decrease in glomerular filtration pressure, tubular obstruction, transtubular back leakage of the filtrate, and interstitial inflammation (Lameire and Vanholder, 2001). Sublethal injury to tubular cells leads to irregularities in the cytoskeletal organization of the tubule cells. After sublethal injury, the kidney has a remarkable capacity for repair of normal structure and function.

1.4.2. Repair of the tubular system

*The kidney can completely recover from short lasting (<30 minutes) ischemia.*

Under normal circumstances human proximal tubular cells undergo a slow regeneration replacing some damaged cells (Nadasdy et al. 1994). The low rate of cell death and replacement by mitotic tubular cells dramatically changes after ischemia-reperfusion injury. Several cells loss the brush border and also the cell polarity, undergo necrosis and apoptosis and cause luminal obstruction. Viable cells with migration and stem cell like capacity replace the damaged cells, differentiate into polarized epithelial cells and finish the regeneration (Figure 4). During this time there is an increased mitotic activity in the kidney.
Figure. 4. Normal repair in ischemic acute kidney insufficiency. The current understanding of tubular injury and repair after ischemic acute kidney injury (AKI). With IR injury, the normally highly polar epithelial cell loses its polarity and brush border with proteins mislocated on the cell membrane. With increasing time/severity of ischemia, there is cell death by either necrosis or apoptosis. Some of the necrotic debris is released into the lumen. Viable epithelial cells migrate and cover denuded areas of the basement membrane. These cells undergo division and replace lost cells. Ultimately, the cells go on to differentiate and reestablish the normal polarity of the epithelium (from Yang et al. 2010)\textsuperscript{38}.

In conclusion, the kidney parenchyma has an enormous capacity for repair if the ischemic time remains below a limited time. This time frame should be kept in mind when carrying out open or laparoscopic partial nephrectomy.
2. AIM OF THE STUDY

1. To learn the upper urinary tract laparoscopy from international leading urologists in the field, to overcome the learning phase and develop modifications of standard laparoscopic techniques.

2. To design a study to answer some challenging questions in relation to the impairment of renal function after partial nephrectomy:

   a. What is the minimal renal ischemia time which can lead to kidney damage?
   b. What is the maximum ischemia time which can be tolerated by the majority of kidneys?
   c. Are there other factors which may worsen the damage?
   d. Are there renoprotective substances which can prolong ischemia time?
   e. What is the impact of volume reduction on renal function outcome after partial nephrectomy?

   In line with these questions, in patients with small renal mass (pT1a) operated with laparoscopic partial nephrectomy under warm ischemia, for determination of functional outcome, we designed a prospective randomized study to identify the role of renal parenchymal volume reduction distinguished from the ischemia-reperfusion injury.

3. OPERATIVE TECHNIQUES AND POSTOPERATIVE FUNCTIONAL EVALUATIONS

3.1. LAPAROSCOPIC PARTIAL NEPHRECTOMY IN COLD ISCHEMIA

3.1.1. Background

Within a short period of time, laparoscopic radical nephrectomy for renal cell carcinoma (RCC) became a standard of care (Chan et al. 2001). Because of the widespread use of imaging techniques such as ultrasonography and computed
tomography (CT), however, a large number of small localized renal tumors are detected incidentally (Lightfoot et al. 2000)

For such patients, organ-sparing surgery has to be considered as an alternative to radical nephrectomy even if the contralateral kidney functions normally (Herr, 1999).

In 2000, it was concluded by Fergany et al. that, owing to the encouraging reports about the tumor recurrence and cancer specific survival in cases of NSS, it’s not unlikely that partial nephrectomy may become more frequent than radical nephrectomy in the future. The first laparoscopic partial nephrectomy on a porcine model was reported in 1993 (McDougal et al. 1998).

Many centers have since developed their techniques to perform nephron sparing surgery by means of laparoscopy.

Günter Janetschek was one of the pioneers in performing and developing the techniques of wedge resection for RCC by means of laparoscopy about two decades ago (Janetschek et al. 1998). However this technique was restricted to tumors 2 cm or less as it was performed without renal ischemia. To duplicate all principles of open surgery by means of laparoscopy, the technique was changed by introducing renal ischemia and suture repair of the collecting system and renal parenchyma as was described by Gill and colleagues (Gill et al. 2002). Ischemia can be achieved by temporary occluding the renal artery or artery and vein (en-bloc), the so-called warm ischemia. The time available to do wedge resection and repair of collecting system and parenchyma during warm ischemia is limited and the surgeon has to race against the clock. Renal cooling during ischemia protects the kidney and offers the surgeon extra time. The problem of renal cooling during ischemia when performing laparoscopic wedge resection has not been solved yet. In 2003, we presented our first experience with renal cooling during laparoscopic surgery for small RCC by means of cold arterial perfusion.

3.1.2. Patients and laparoscopic approach

Between November 2001 and March 2003, laparoscopic partial nephrectomy in cold ischemia was performed in 17 patients. During this period, no open NSS was done. The indication was suspected RCC in 15 patients with a mean tumor size of 2.71 cm (range: 1.5 - 4 cm), and a pyelonephretic lower pole due to recurrent stone disease in 2 patients. The metastatic work up was negative and all tumors were clinically T1a,
N0, M0. In all patients, preoperative angio-MRI was performed to visualize the renal artery(s). Preoperative renal scintigraphy (DMSA) was done to have a baseline data about the renal function for follow-up. Patients were consented for conversion to laparoscopic radical nephrectomy or open partial nephrectomy if needed.

Preoperative preparation and anesthesia induction were done as usual. Placement of an open tip ureteric catheter (usually a single pigtail catheter) was done under fluoroscopy to be used later to check the integrity of the collecting system. Next, an angiocatheter was passed into the main renal artery through a femoral puncture on the ipsilateral side. This procedure was carried out by one of our interventional radiologists. Then the patient was brought to 45-degree lateral decubitus position. In this final position for laparoscopic surgery the angiocatheter was checked again and advanced in the renal artery close to the origin of the segmental arteries if needed. Port placement varied according to the tumor location.

The approach to the kidney was transperitoneal in 16 patients and retroperitoneal in 1 patient. In the first 2 patients the renal hilum was not dissected, and the renal artery was occluded by a balloon integrated in the angiocatheter. However, since some arterial bleeding occurred in the second patient, we shifted to use a tourniquet for artery occlusion in the following 15 patients, which proved to be much safer. The renal artery was secured and later on occluded using a tourniquet (5mm umbilical tape and 10 Fr. silicon tube), which was placed as close to the origin of the artery as possible. This tourniquet was handled through a separate 10 mm trocar in the lower abdomen. We were prepared to occlude additional smaller arteries with laparoscopic bulldog clamps, but this was never required. The renal vein was secured (distal to the gonadal, lumbar and adrenal veins) but not occluded in 13 patients, using also the umbilical tape. We stopped securing the renal vein as we found it was never necessary.

Intravenous infusion of 200 cc of 20% mannitol was given 15 minutes before arterial occlusion. After approaching the tumor, the fat overlying it was dissected and the renal capsule around the tumor was incised by monopolar hook. Then cold ischemia was started. This was achieved by occluding the renal artery, and perfusion of 1000 ml iced ringer lactate at 4°C at a rate of 50 ml/min through the angiocatheter. 100 ml
of 20% mannitol was added to each 1000 ml ringer lactate to achieve osmolality of 430 mOsm/ml to avoid parenchymal oedema. Renal temperature was continuously monitored with a thermo probe residing in the parenchyma. When a parenchymal temperature of 25°C was reached, perfusion was reduced to maintain a steady state. The patient was warmed with warm air blanket (Bair Hugger, Augustine Medical Inc. Eden Prairie, USA), and his temperature was continuously monitored. Tumor excision was performed in a bloodless field using scissors with no diathermy (Figure. 5). A biopsy was taken from the tumor bed. The tumor and the overlying fat were placed in separate organ bag, which were removed later. The integrity of the collecting system was checked by injection of methylene blue through the preplaced ureteric catheter. Occasionally injured large vessels in the tumor bed were clearly observed by jet of perfusate. Therefore, both the collecting system and the injured vessels could be precisely repaired by a figure of 8 sutures using 4-0 vicryl (17 mm needle, 1/2 C) (Figure. 6-7). The cut edges of the parenchyma were approximated by 2-3 figure of 8 sutures over a haemostatic bolster (TapoTamb: Ethicon Sarl, Neuchatel, Switzerland) using 0 vicryl (36.4 mm needle) (Figure. 8). Fibrin glue (Baxter AG, Vienna, Austria) or a strip of a Tachocomb (Nycomed, Linz, Austria) was applied on the cut surface to avoid delayed bleeding. A tube drain was always left in place.

**Figure 5:** Left kidney: Tumor resection in a bloodless field during cold ischemia. In the background thermoprobe is seen residing in the renal parenchyma
Figure 6. Left kidney. A, entry to collecting system is evidenced by methylene blue leakage. B, suture repair of collecting system with jet of perfusate issuing from cut vessel on tumor bed.

Figure 7. Suture repair of left kidney (K) renal vein (V) in complete bloodless field after resection of centrally located tumor. R, renal parenchyma resection margin.
Figure 8. Left kidney after complete parenchymal repair with sutures over hemostatic bolster.

3.1.3. Discussion

Laparoscopic partial nephrectomy with our technique could be performed successfully in all patients with no conversion. The mean intraoperative blood loss was 145 ml (30 – 650). In 2 patients we had high blood loss. In one of them it was due to insufficient balloon occlusion and in the other one because of intermittent failure of the perfusion pump, which resulted in venous backflow from the injured renal vein. Only one patient required intraoperative blood transfusion. Mean total ischemia time was 41 minutes. (27 - 101 min.). Entry to the collecting system happened in 7 patients and was repaired intraoperatively. Repair of the renal vein, segmental vein and artery was done in 2 patients, in whom the tumors were centrally located very close to the hilum. Mean amount of perfusate was 1,600 ml (1,150-2,800). Mean decrease of body temperature during cold perfusion was 0.66°C (0.5-1.1). Mean operative time was 176 minutes (135-220). Urethral and ureteric catheters were removed on the second postoperative day. Drainage was removed when its output was less than 50ml/24hours. Mean hospital stay was 9.4 days (7-14 days). Bleeding occurred in one case in the first postoperative day due to
parenchymal tear from the sutures. This was managed laparoscopically by bipolar coagulation and application of a strip of Tachocomb (Nycomed, Linz, Austria). No urinary fistula or urinoma were encountered. The histopathological examination revealed RCC in 13 patients, angiomyolipoma in 2, and pyelonephretic renal tissue in another 2. The resection margins were negative in 14 patients. In one patient, negative margin was not described where the tumor was in direct contact with the renal vein. During resection the vein was entered and repaired.

Postoperative renal function was evaluated in 8 patients. In 5 patients the reduction in renal function was 1%, 1%, 2%, 3%, and 8%, respectively by renal scintigraphy (DMSA). In the other 3 patients, CT scan showed undisturbed perfusion of the renal parenchyma. We concluded that the reduction in renal function was most probably attributed to reduction in the total renal volume after wedge resection.

Cold arterial perfusion is an old method, which however is not remembered anymore nowadays. It was developed for open renal stone surgery by Marberger and colleagues in 1978 (Marberger et al. 1978) and it is still used by vascular surgeons to protect the kidney during the repair of complicated thoracoabdominal aneurysms (Morishita et al. 1999). For these purposes, it has been proved to be effective and safe. Since external renal cooling by slushed ice is easier to apply, this technique is not used anymore for open kidney surgery.

Laparoscopic NSS without renal ischemia is feasible and can be achieved by step-by-step resection and hemostasis without ischemia (Janethschek et al. 1998; Jeschke et al. 2001). However, this technique has its drawbacks. It is restricted to small tumors (2cm or less) in a favorable peripheral location. Hemostasis is slow and tedious. The cut surface is continuously covered with blood and burned by the extensive use of monopolar and bipolar coagulation, therefore distinction between tumor and normal renal tissue is very difficult. This may compromise complete tumor resection. Necrosis urinary fistula from the use of diathermy close to the collecting system was also encountered. These were the reasons for us to replace this technique by partial nephrectomy in ischemia.
During ischemia, the tissue is cut sharply in a bloodless field, avoiding the use of diathermy. Normal renal tissue and tumor can be discriminated very precisely, so that complete tumor resection can be continuously monitored. As in open surgery, hemostasis relies on suturing the cut edges of the parenchyma on bolsters of haemostatic materials (Gill et al. 2002). A major restriction for this technique is the time, as renal damage is expected if the ischemia time is longer than 30 minutes. Therefore cooling of the kidney as in open surgery is required if ischemia time is anticipated to last more than 30 minutes as in larger tumors and tumors in unfavorable sites. In addition unexpected problems during surgery may extend the time of operation.

In animal model, cooling has been performed by injecting cold fluid in the collecting system (Landman et al. 2002). Because of the relatively small surface of the collecting system and its central location within the kidney, parenchymal cooling may be insufficient. Contrary, cold arterial perfusion will directly cool the parenchyma, which is well perfused. Because of the large surface area of the arterio-venous system in the kidney, efficient heat exchange can be achieved. External renal cooling with slushed ice during laparoscopic wedge resection has been described in one patient (Gill et al. 2002). This may become an alternative method for cold ischemia in NSS.

During laparoscopic wedge resection, cold arterial perfusion has the advantage that the laparoscopic procedure itself is not rendered more complicated than resection without ischemia since all necessary maneuvers are performed prior to surgery. Resection of the tumor and parenchymal repair can be done in a clear bloodless field at leisure of time. During our initial experience we realized another advantage of our technique. Since the whole renal vasculature from the renal artery to the vein is completely filled with perfusate, repair of arterial and venous lesions becomes feasible in a completely bloodless field. In addition jets of perfusate will help in recognition of the exact site of the vascular injury. In two complicated centrally located tumors, vascular lesions had to be repaired after removal of the tumor. These procedures would certainly not have been possible without ischemia and cooling.
In our series we didn’t encounter any problem regarding the renal function or the amount of perfusate used. This is probably because all the patients were with a normal contralateral kidney and diuresis was induced prior, during and after ischemia. However in a solitary kidney, one should be aware of the risk of volume overload resulting from the non-excretion of the perfusate during temporary renal ischemia. In this case excretion of the perfusate will depend on the fast recovery of the kidney after ischemia.

3.1.4. Conclusion

Our initial experience of incorporating cold ischemia via arterial perfusion to laparoscopic partial nephrectomy shows the feasibility and safety of this technique. Injury to the arterial system has been observed neither in the literature nor in our limited experience. This approach allows the duplication of the principles of the open surgery and makes laparoscopic NSS for RCC and complex renal pathology safe and reliable. It also allows for vascular repair during surgery of difficult central tumors. We believe that our technique will make laparoscopic NSS safer for the less experienced laparoscopist and will also increase the scope of indications for the experienced one.

3.2. LAPAROSCOPIC PARTIAL NEPHRECTOMY IN WARM ISCHEMIA

3.2.1. Introduction

Partial nephrectomy (PN) has become a standard of care for treatment of small renal masses. Hilar occlusion is commonly performed for a precise tumour resection and renal reconstruction. The above surgical manoeuvre results in warm ischemia (WI) of the remaining renal tissue and has been associated with ischemic-reperfusion injury (RI) to the organ. Current evidence showed that the length of the warm ischemia time (WIT) and the subsequent reperfusion injury may result in permanent renal damage (Becker et al 2009; Simmons et al 2008). Moreover, the resection of the renal tumour and the suturing of the parenchyma resulted in additional reduction of the functional renal tissue (Simmons et al 2012; Song et al 2011).
Thus, two mechanisms of renal function damage during PN could be proposed. Nevertheless, the importance of the mechanisms for the decline of the postoperative renal function has not been investigated. The current prospective study evaluated the split renal function and elucidated the role of renal parenchymal loss in patients with small renal mass who were treated by LPN with WI.

3.2.2. Patients and methods

Small renal masses have been treated by LPN at our institutions since 2005. Thirty five patients were enrolled in a prospective pilot study. Regional research ethics committee approval was received and informed consent was obtained from all patients. The procedures were performed by two experienced laparoscopists. The exact location and dimensions of the tumour was identified by three-dimensional CT scan prior to the operation. Only patients with a single exophytic mass of ≤ 4 cm in diameter located in either lower or upper pole of the kidney with normal contralateral kidney were enrolled.

All operations were performed by laparoscopic transperitoneal approach with en-bloc hilar occlusion using a Rumel tourniquet. Two minutes before hilar occlusion, 0.5 gr/kg of 20% mannitol was infused. The surgical technique has been previously described (Spaliviero and Gill, 2007). Cold scissors were used for tumour resection. Running sutures of 3/0 Vicryl were applied for collecting system closure and haemostasis. In all cases, the parenchymal defect was filled with one or two rolled Surgicel bolsters. Parenchymal reconstruction was achieved by running 0 Vicryl sutures secured at each parenchymal exit by a Hem-o-lok clip. The renal pedicle was released only after tumour excision and completion of renorrhaphy. At the time of hilar tourniquet release, 0.5 mg/kg of Furosemide injection was administered.

After extraction of the specimen, the surrounding fat tissues were detached and weight of the remaining resected mass was measured. The kidney was placed in its anatomic position and the Gerota's fascia was closed.

The recorded parameters included the time for tumour resection, calyceal closure, haemostatic sutures and the total WIT.
Serum creatinine (sCr) was recorded and estimated glomerular filtration rate (eGFR) was calculated using chronic kidney disease epidemiology collaboration (CKD-EPI) equation (Levey et al. 2009). The above measurements were performed preoperatively (baseline), 5-6 hours after the surgery, on the 1st, 3rd and 7th postoperative days and at the end of 1st, 3rd, 6th, and 12th postoperative months.

In this study, in addition, 15 randomized patients treated with laparoscopic radical nephrectomy (LRN) were examined as a control group for our laboratory outcomes and all the above parameters were registered in this group.

3.2.3. Renal scintigraphy

In order to distinguish the impact of parenchymal loss from WI effect on the operated kidney, we planned a novel method of investigation with renal scan as follow. All patients in LPN group underwent 99m Technetium-Dimercaptosuccinic Acid (99mTc-DMSA) renal scintigraphy for the determination of split renal function preoperatively and at the end of 1st, 3rd, 6th, and 12th postoperative months. 99mTc-DMSA isotope is a static renal agent and allows accurate calculation of differential renal function (DRF) (Kibar et al. 2003). Since 99mTc-DMSA scan provides relative functional percentage of the two kidneys and the contralateral kidney served as a control for comparison after LPN, we selected patients with solitary small polar mass (T1a), otherwise normal ipsilateral kidney, and normal contralateral kidney. Such selections have resulted in a young cohort of patients with mean age of 50.5 ± 11.9 years old in our study.

3.2.4. Assessment of total and partial differential renal function: A novel approach.

Before the operation, all patients underwent radionuclide isotope examination performed by 99mTc-DMSA. Renal scans were performed in supine position. Individual kidney uptake and differential renal function (DRF) percentage of left-to-right kidneys were determined by the Patlak-Rutland method (Rutland, 1996). The region of interest (ROI) of each kidney was determined with the use of an automated
computer program drawing the ROI around the whole kidney. For processing purposes, all isotope results were saved in a computer program. This assessment which is a customary method of evaluating a static renal scan was called a “Total-DRF” (T-DRF) in our study (Figure 9A).

By this means, in the tumorous kidney, the postoperative decline in percentage ratio, reflecting decrease in renal function, was considered as a consequence of both factors: 1). IR injury caused by length of WIT. 2). The kidney parenchymal volume reduction caused by removal of the tumour, and excision and suturing of the surrounding healthy tissues.

In an attempt to distinguish the impact of each of these two factors, we introduced a novel method which is referred as “Partial-DRF” (P-DRF). For this reason, in the preoperative renal scans, the exact location of the tumour was determined and only small polar masses (either upper or lower pole mass) were selected for the study. In the tumorous kidney, a region in the tumour-free pole was selected and manually a ROI was drawn in that pole. Identical ROI was selected in the same pole of the contralateral kidney (Figure 9B). The same ROI drawing was used in all follow-up studies of a given patient. Accordingly, P-DRF which reflects DRF of the intact pole of the operated kidney, which is affected only by the IR injury, was compared with the same pole on the contralateral kidney. The same processing was applied for all patients in all isotope scan examinations. As a result, in the postoperative isotope scans, with the P-DRF, we could compare an intact part of the operated kidney which was impacted by WI but not affected by parenchymal volume reduction with an identical segment of the normal contralateral kidney.

Any postoperative decline in the P-DRF of the operated kidney was considered as the renal functional loss resulted from IR injury only.

All renal isotope tests were evaluated and reported by same specialist doctor in nuclear medicine.
Figure 9: Renal scintigraphy is shown with an imaginary tumour in the lower pole of one kidney (red circle). A: The ROI is selected (purple line) to demonstrate and compare the T-DRF of both kidneys. B: The ROI is selected in the nontumorous pole of the involved kidney and compared with the same ROI in the contralateral kidney.

3.2.5. Patient selection and statistical evaluations.

Any factor which could unpredictably influence on the WI consequence or the renal function outcome was excluded from the statistical assessments. Accordingly, one patient was excluded due to conversion to open partial nephrectomy assuming that absence of pneumopreperitoneum may give diverse renal functional outcome. One patient was excluded due to continuous moderate bleeding from the resected site during WI time. In this patient, we presume that WI was insufficient due to incessant blood supply to the kidney. In one patient with two accessory renal arteries, we had to clip one of the arteries for safe resection. In this case, we suppose that some renal function deterioration may be as a result of arterial clipping so this patient was not included for evaluation. In one case, five days after the operation, selective segmental arterial embolization of the operated kidney was applied due to arteriovenous shunt. This patient was also excluded owing to impact of embolization on the renal function outcome. Three patients were disqualified for statistical analysis since they missed more than one cycle of post operative follow-ups. Consequently, 28 patients were enrolled in the final statistical analysis. Demographics of the 28 patients which were included for analysis, and results of the operations are described in Table 4.
### Table 4 – Patient’s demographics and operation results of LPN

<table>
<thead>
<tr>
<th><strong>Number of enrolled patients</strong></th>
<th><strong>35</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reasons for patient exclusion (number of patients):</strong></td>
<td></td>
</tr>
<tr>
<td>- Conversion to open partial nephrectomy</td>
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</tr>
<tr>
<td>- Continuous moderate bleeding from the resected site during WIT</td>
<td>1</td>
</tr>
<tr>
<td>- One of two accessory arteries were clipped for safe resection</td>
<td>1</td>
</tr>
<tr>
<td>- Early postoperative bleeding and selective arterial embolization</td>
<td>1</td>
</tr>
<tr>
<td>- Missed more than one follow-up appointment</td>
<td>3</td>
</tr>
<tr>
<td><strong>Number of patients included in statistical analysis</strong></td>
<td><strong>28</strong></td>
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<tr>
<td><strong>Male / female ratio</strong></td>
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<tr>
<td><strong>Patient’s age (years)</strong></td>
<td><strong>50.5 ± 11.9 (range: 23-74)</strong></td>
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<td><strong>Body mass index</strong></td>
<td><strong>27.6 ± 4.3 (range: 19.7-39)</strong></td>
</tr>
<tr>
<td><strong>Right / left ratio</strong></td>
<td><strong>12 / 16</strong></td>
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<tr>
<td><strong>Tumor greatest dimension (mm) by CT Scan</strong></td>
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<tr>
<td><strong>Surgery indication:</strong></td>
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</tr>
<tr>
<td>- Relative</td>
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<td>- Elective</td>
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</tr>
<tr>
<td>- Absolute</td>
<td>0</td>
</tr>
<tr>
<td><strong>Operative time (min)</strong></td>
<td><strong>145 ± 35 (range: 95-245)</strong></td>
</tr>
<tr>
<td><strong>Time used for tumor resection (min)</strong></td>
<td><strong>4.8 ± 1.5 (range: 2.5-10)</strong></td>
</tr>
<tr>
<td><strong>Time used for internal sutures (min)</strong></td>
<td><strong>9.6 ± 3.5 (range: 5-18)</strong></td>
</tr>
<tr>
<td><strong>Warm ischemia time (min)</strong></td>
<td><strong>22 ± 5.3 (range: 12-32)</strong></td>
</tr>
<tr>
<td><strong>Weight of the resected specimen (gm)</strong></td>
<td><strong>18 ± 9.1 (range: 6-40)</strong></td>
</tr>
<tr>
<td><strong>Histopathology results:</strong></td>
<td></td>
</tr>
<tr>
<td>- RCC, Conventional type</td>
<td><strong>19 (68%)</strong></td>
</tr>
<tr>
<td>- RCC, Chromophobe type</td>
<td><strong>2 (7%)</strong></td>
</tr>
<tr>
<td>- RCC, Papillary type</td>
<td><strong>4 (14%)</strong></td>
</tr>
<tr>
<td>- Oncocytoma</td>
<td><strong>2 (7%)</strong></td>
</tr>
<tr>
<td>- Angiomyolipoma</td>
<td><strong>1 (4%)</strong></td>
</tr>
<tr>
<td><strong>Positive Surgical Margins</strong></td>
<td><strong>None</strong></td>
</tr>
</tbody>
</table>

*PADUA: Preoperative aspects and dimensions used for an anatomical classification of renal tumours; RCC: Renal cell carcinoma; WIT: Warm ischemia time*

**Statistical evaluations:** The IBM SPSS version 20 (IBM Corp., Armonk, NY, USA) was used for the calculations and statistical analysis. ANOVA and Pearson product-moment correlation were calculated as deemed necessary. A p-value < 0.05 was considered statistically significant.

For further confirmation, a linear correlation coefficient was calculated for the assessment of a possible correlation of the T-DRF decline to the WIT in the operated kidney and to the mass of the resected specimen.
3.2.6. Patients operated with laparoscopic radical nephrectomy

In 15 patients with LRN selected for control group, the mean age was 61 ± 12 years (range: 41-78). The male to female ratio was 11/4, and right to left involved kidney ratio was 12/3. Their mean BMI was 29.7 ± 5.4 (range: 21.6-38.6), and the mean operative time was 153 minutes (range: 100-220). The mean age, BMI and the mean operative time were slightly higher than in the group of LPN.

3.2.7. Results

Twenty eight patients with small renal mass successfully underwent LPN and completed one year follow up according to our protocol. Operation data and histopathology results are summarized in Table 4. During operation, after hilar unclamping, in six patients we observed mild bleeding from the resected margin, which were resolved within 2-3 minutes by increasing pneumopreitoneum or application of Surgicel. We didn’t have any significant bleeding, necessitate hilar re-oclusion. In our selected patients for statistical evaluations, major intra- or postoperative complication was not observed.

In the LPN group, the mean results of preoperative and postoperative renal function measured by serum creatini (sCr), estimated glomerular filtration rate (eGFR, CKD-EPI equation) as described by Levey and colegaues (Levey et al. 2009) and total differential renal function (T-DRF) as well as partial differential renal function (P-DRF) are summarized in Table 5.
Table 5. Mean estimations of kidney function before and after LPN surgery

<table>
<thead>
<tr>
<th>Investigated parameter and normal ranges</th>
<th>Pre- op (baseline)</th>
<th>1 day post-op</th>
<th>3 days post-op</th>
<th>7 days post-op</th>
<th>1 month post-op</th>
<th>3 months post-op</th>
<th>6 months post-op</th>
<th>12 months post-op</th>
<th>Mean of all post-op results after day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine (62-106 μmol/l)</td>
<td>71 ± 14 (44-94)</td>
<td>86 ± 22 (43-120)</td>
<td>82 ± 20 (42-124)</td>
<td>82 ± 16 (50-112)</td>
<td>80 ± 16 (43-103)</td>
<td>79 ± 17 (47-108)</td>
<td>80 ± 17 (40-98)</td>
<td>82 ± 16 (50-111)</td>
<td>81 (14% ↑)</td>
</tr>
<tr>
<td>eGFR (CKD-EPI) (&gt; 90 mL/min/1.73m²)</td>
<td>97 ± 17 (55-122)</td>
<td>81 ± 21 (44-114)</td>
<td>87 ± 20 (55-117)</td>
<td>85 ± 18 (60-106)</td>
<td>87 ± 18 (49-114)</td>
<td>90 ± 21 (48-124)</td>
<td>87 ± 20 (54-120)</td>
<td>86 ± 20 (48-116)</td>
<td>87 (10% ↓)</td>
</tr>
<tr>
<td>T-DRF of the involved kidney (%)</td>
<td>49 ± 4 (43-58)</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>42 ± 7 (24-52)</td>
<td>42 ± 7 (25-54)</td>
<td>41 ± 7 (25-52)</td>
<td>41 ± 7 (24-51)</td>
<td>42 (7% ↓)</td>
</tr>
<tr>
<td>P-DRF of non-tumorous pole of involved kidney (%)</td>
<td>50 ± 4 (44-59)</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>47 ± 6 (37-57)</td>
<td>48 ± 5 (37-55)</td>
<td>46 ± 4 (35-52)</td>
<td>47 ± 4 (38-54)</td>
<td>47 (3% ↓)</td>
</tr>
</tbody>
</table>

Pre-Op: Preoperative; Post- op: Postoperative; eGFR: Estimated glomerular filtration rate; CKD-EPI: Chronic kidney disease epidemiology collaboration; T-DRF: Total differential renal function; P-DRF: Partial differential renal function
3.2.8. Evaluation of the renal function based on serum creatinine.

The detailed mean values of these tests are shown in Table 5 for LPN and Figure 10 for both LPN and LRN patients. In Figure 10, the preoperative (time point 1) mean values of serum creatinine as well as the mean values at the eight postoperative check points is shown for both LPN and LRN groups. The two groups were compared taking into consideration that in LRN group we had elder population (61 ± 12 years vs. 50.5 ± 11.9 years, p-value = 0.008), more male to female ratio (73% vs. 57%) and higher body mass index (BMI) (29.7 ± 5.4 vs. 27.6 ± 4.3, p-value = 0.18). These data may explain the higher baseline (84 umol/l) serum creatinine in the LRN group. It was a strong increase of serum creatinine level immediately after LRN with a peak on the 3rd post-op day. It declined slightly and remained constantly high (123 umol/l) until the end of first postoperative year. This reflects ~ 46% rise in sCr level compared to the baseline in LRN patients. In contrary, in the LPN group, the serum creatinine level was only slightly increased from 71 umol/l to 82 umol/l (~16% increase) during the first three postoperative days and remained constant until the end of observation.

Figure 10: The curves show the mean preoperative (time point 1) serum creatinine and mean results of postoperative serum creatinin measured in patients with LRN.
and LPN at different time intervals (point 2: 5-6 hours post-op; point 3: 1st post-op day; point 4: 3rd post-op day; point 5: 7th post-op day; point 6: 1st post-op month; point 7: 3rd post-op month; point 8: 6th post-op month; point 9: 12th post-op month)

3.2.9. Evaluation of the renal function based on estimated GFR.

As shown in Table 5 and Figure 11, the mean preoperative or baseline eGFR of patients treated with LPN was 97 ± 17 (range: 55-122) which decreased to 81 ± 21 (range: 44-114) in the 1st postoperative day (p-value = 0.0069). This shows a 16% decline in average eGFR which was the largest postoperative drop within one year of follow up. Conventionally, we call it “transient-state” of kidney function deterioration. In the 3rd postoperative day, we observed a 7% recovery in the average eGFR comparing to the 1st day. Although, due to the large deviations in the values, this tendency toward recovery was statistically insignificant (p-value = 0.3821). From the 3rd postoperative day to end of the study in 12th month, the average eGFR remained roughly the same in both groups. In these time points of LPN group, comparing the lowest with the highest values, which were in the 7th postoperative day and 3rd month respectively, showed insignificant alteration in the eGFR (p-value = 0.4483) (Figure 12). Accordingly, for simplicity, average of all postoperative eGFR mean values after the transient-state (after the 1st day) were calculated and considered as the “steady-state” of renal function deterioration. This was 87 ml/min/1.73 m² in LPN patients which demonstrates ~10% decrease in renal function comparing to the baseline (p-value = 0.0757).

As shown in figure 13, the eGFR was lower for patients treated with LRN and showed a decrease during the first three postoperative days and thereafter remained at the same level. By this comparison, the difference in clinical parameter between the two groups as indicated above also should be taken into account.

It is worth to highlight that in the LRN control group, the average decline in the “steady state” of the kidney function was ~ 40% (81.34 declined to 48.36 ml/min/1.73 m²).

In a simple explanation, we can conclude that, by removal of one whole kidney, nearly 40% of global kidney function declines, and by removal (resection) of one part of a kidney, nearly 10% of the global kidney function decreases. Accordingly,
Parenchymal volume reduction after partial nephrectomy has a very important impact on outcome of kidney function and this should be certainly distinguished from the impact of the IR injury caused by WI.

Figure 11. The graph shows the mean preoperative and postoperative eGFR values in the studied time intervals for the LPN patients enrolled in the statistic evaluation.

Figure 12. This graph shows same parameters as the previous graph (figure 11) excluding the baseline and the 1st post-op values. It remarks the so called “steady-state” of renal function after partial nephrectomy.
Figure 13. The curves show mean preoperative (time point 1) eGFR and mean results of postoperative eGFR measured in patients with LPN and LRN at different time intervals (point 2: 5-6 hours post-op; point 3: 1st post-op day; point 4: 3rd post-op day; point 5: 7th post-op day; point 6: 1st post-op month; point 7: 3rd post-op month; point 8: 6th post-op month; point 9: 12th post-op month)

3.2.10. Impact of parenchymal volume reduction on the kidney function

As seen in Table 5 and Figure 14, in the LPN study group, the mean preoperative or baseline T-DRF of the operated kidneys was 49% which is decreased to 42% on the 1st postoperative month ($p$-value = 0.001). This value remained almost the same in the following time points. Repeated ANOVA measurements of all postoperative T-DRF did not show any significant alteration among them ($p$-value > 0.6). Accordingly, average of all postoperative T-DRF which was 42% was considered as the final postoperative result. On the other hand, the mean preoperative P-DRF of the intact pole of the operated kidney was 50% which decreased to 47% on the 1st postoperative month ($p$-value = 0.0727). Average of all postoperative P-DRF was also 47% without any significant alteration among the time periods ($p$-value = > 0.1).
Figure 14. The graph shows the mean decline of both P-DRF and T-DRF of the operated kidney (LPN) in the studied time intervals.

Linear correlation coefficient was used to compare relationship of the T-DRF decline in the operated kidney to the mass of the resected specimen (Figure 15).

We have also used linear correlation coefficient to compare relationship of the T-DRF decline in the operated kidney to WIT (Figure 16). This showed a much stronger correlation between T-DRF decline and the resected mass comparing to the WI time (R2 = 0.7241 and p<0.0837 respectively).
Figure 15. Comparing correlation of the T-DRF decline in the operated kidney to the mass of the resected specimen.

Figure 16. Comparing correlation of the T-DRF decline in the operated kidney to WI time.
3.2.11. Discussion

In 1950, Benjamin Abeshouse wrote “Few procedures provide the urologist with more satisfaction than those that preserve renal function”\(^{56}\). While Dr. Abeshouse may have practiced urology prior to the availability of the strong data we now possess, his statement rings true to this day. On this principle, NSS has taken a prominent position at the helm of the treatment of renal tumours. Likewise, there has been continual progress toward resecting less and less renal parenchyma to preserve more renal function without sacrificing any of oncological rules.

There are several factors determining the postoperative renal function: A. the preoperative quality of renal function (underlying renal disease, limited glomerular function, etc.); B. the quantity of renal parenchyma remained after operation; and C. the warm ischemia time. The first factor can’t be modified by surgical technique; the second is determined by the anatomical size and location of the tumour. The warm ischemia time is influenced by the experience of the surgeon and the operation technique applied.

We planned a prospective study in order to distinguish the impact of parenchymal loss and effect of warm ischemia on the function of operated kidney. In our study, \(^{99m}\)Tc-DMSA isotope was used which is a static renal agent and allows accurate calculation of DRF (Kibar et al 2003)\(^{54}\). This was measured preoperatively and completed in different postoperative intervals in 28 patients with solitary small polar renal mass and no any other abnormality in that kidney. Since \(^{99m}\)Tc-DMSA scan provides relative functional percentage of the two kidneys and the contralateral kidney served as a control for comparison after LPN, we selected patients with normal contralateral kidney. Such selections have resulted in a young cohort of patients with mean age of 50.5 ± 11.9 years old in our study. The T-DRF was measured in all isotope studies. Any postoperative decline in T-DRF in the operated kidney was considered as a result of warm ischemia and ischemia-reperfusion injury combined with parenchymal loss. In nearly all postoperative studies, mean decline of T-DRF in the operated kidney was 7%. In order to distinguish the effect of warm ischemia from the parenchymal loss, we introduced the so-called P-DRF in which a region of interest was selected on nontumorous pole of the involved kidney and it was compared with the same region in the contralateral kidney.
For this reason, we selected only patients with tumor mass of ≤ 4 cm in diameter which were located on either upper or lower pole of the kidney so that the region selected in the intact nontumorous pole of the operated kidney was not affected by parenchymal loss and suturing. Any postoperative functional decline in this intact pole of the operated kidney was considered to be as a result of warm ischemia and ischemia-reperfusion injury only. In our study, mean postoperative decline in the P-DRF of the operated kidney was only 3% which was found to be statistically insignificant (p-value = 0.0727). In agreement with the previous studies, we believe that within certain time limits of warm ischemia, which was 22 ± 5.3 minutes in our study, the ischemia-reperfusion insult may be negligible or reversible. On the other hand, deliberate parenchymal loss plays a major role in kidney function deterioration.

Warm ischemia and the IR injury to the kidney have been considered for a long time as the main factor related with postoperative renal function deterioration in patients undergoing PN under WI\textsuperscript{30,48,57,59,60}. Several technically challenging techniques have been introduced for the reduction of WI\textsuperscript{61,62}. Nevertheless, the impact of renal parenchymal mass reduction was not distinguished from the effects of WI and IR in the above literature. Parenchymal loss after PN occurs as a result of intentional tumor excision, some normal parenchyma resection and suturing. Thus, the mass or volume of the parenchymal loss should be considered and differentiated from IR injury when evaluating the renal functional outcome after PN.

Few authors have studied the impact of parenchymal volume reduction on renal function. In a large multicenter study cohort Shikanov and colleagues (Shikanov et al. 2010)\textsuperscript{63} assessed the influence of renal ischemia on long-term global renal function after LPN in patients with 2 functioning kidneys. They retrospectively evaluated eGFR of 401 patients with median tumor size of 25 mm and normal contralateral kidney who underwent LPN with median warm ischemia time of 29 minutes. Changes in early postoperative and nearly one year follow-up eGFR were \(-16\%\) and \(-11\%\), respectively. This result is nearly identical to our findings. The percent change in last eGFR was worse in patients with larger tumors suggesting that excising a larger lesion would result in more loss of renal parenchyma. Mir and colleagues (Mir et al 2015)\textsuperscript{64} also reported that the preservation of the total renal
function after PN ranged between 88% and 91% which reflects approximately 10% loss of the renal function (similar to our finding). Mir et al also showed that a higher reduction of the eGFR in patients with larger tumors which could be attributed to the excision of a larger lesions and the consequent greater loss of renal parenchyma. This was documented also by Sharma and colleagues (Sharma et al 2008) in 21 patients with solitary kidney who underwent partial nephrectomy due to small renal mass. Volume of the kidney was measured preoperatively and postoperatively by CT scan and software with an automated segmentation algorithm. An average of 15% parenchymal volume loss and 19.7% deterioration in kidney function were documented in mid-term postoperative period. They concluded that the percent of renal parenchymal volume loss was correlated with the percent loss in eGFR. It was shown that volume loss had a more direct, predictable effect on ultimate eGFR than ischemia time. A similar result was concluded by Simmons and colleagues (Simmons et al. 2012) and also Song and colleagues (Song et al. 2009). In the later study, Diethylenetetramine pentaacetic acid ($^{99m}$Tc-DTPA) was used for accurately estimating renal clearance and measuring eGFR by the kidney. They measured changes in individual renal function and investigated factors determining the degree of functional reduction in 65 patients who underwent LPN and 52 patients with open partial nephrectomy. In the entire cohort, renal volume reduction was the most significant, independent prognosticator for eGFR reduction after partial nephrectomy. Mir and colleagues (Mir et al. 2013) evaluated the role of volume preservation by introducing computed tomography volumetric analysis using free-hand scripting. The eGFR was measured by MAG3 in 92 patients who underwent partial nephrectomy. The authors revealed that the ultimate renal function after partial nephrectomy was primarily driven by parenchymal preservation with ischemia playing a secondary role as long as it was within a limited time period.

Current literature has not concluded to the most important factor for the renal function decline after PN and the contribution of WI to the postoperative renal function has not been well documented. Some investigators advocated that the parenchymal mass preservation was stronger correlated to the functional recovery in comparison to the WI. The current prospective study aimed in distinguishing the impact of parenchymal loss from the WI effect on the operated kidney. The $^{99m}$Tc-DMSA isotope was used
for the purpose due to the fact that it allows accurate calculation of DRF. The latter parameter was measured preoperatively and in different postoperative intervals in 28 patients with solitary small polar tumours. Since 99mTc-DMSA scan provided relative functional percentage of the two kidneys, the contralateral kidney served as the control for the comparison after LPN. Consequently, only patients with normal contralateral kidney were selected and a young patient population with mean age of 50.5 ± 11.9 years was eventually included in the study. Any postoperative decline in the T-DRF of the operated kidney was considered as a result of WI and WI combined with parenchymal loss. In nearly all postoperative studies, a mean decline of 7% in the T-DRF was noted. In an attempt to distinguish the effect of WI from the parenchymal loss, the P-DRF was introduced. A ROI was selected on the non-tumorous pole of the involved kidney and was compared with the same ROI on the contralateral kidney. Any interference of the excision area to the ROI was prevented by including only patients with tumour mass of ≤ 4 cm in diameter located on either upper or lower pole of the kidney. Any postoperative functional decline in this intact pole of the operated kidney was considered to be as a result of WI only. The mean postoperative decline in the P-DRF of the operated kidney was only 3% which was found to be statistically insignificant (p-value = 0.072). In agreement with the previous studies, it could be suggested that WI may result in negligible or reversible renal damage within certain time limits of WIT such as a mean WIT of the current study. In addition, the parenchymal loss seemed to play a more important role in kidney function deterioration than WI. Considering the above, it could be advocated that the LPN surgical technique could probably focus on the precise tumour excision and suturing rather than to the minimization of WIT. Nevertheless, additional studies are necessary for the confirmation of the above hypothesis.

Limitations of this study include the reliance on DRF and the use of the non-operated kidney as a stable reference unit before and after the surgery. Any postoperative compensatory hypertrophy of the contralateral kidney may result in a false outcome of DRF. Takagi et al. showed that the compensatory hypertrophy of the contralateral kidney after PN remained rather limited and less than 2.3% in most cases. They concluded that the larger the excised volume of the kidney, the more hypertrophy of the contralateral kidney was expected. The median tumour diameter of the latter study was 3.5 cm and probably resulted in higher volume loss in
comparison to our series (median of 2.6 cm). Hence, we assume that the compensatory hypertrophy may have been negligible in our study. Another limitation of our study was the lack of stratification of the results according to the length of the WIT or the tumour size. The parenchymal volume was never measured and the current study could not provide information regarding the pre-and postoperative changes in the volume of the renal parenchyma. Nevertheless, the changes in the contour of the operated kidney may influence measurements of the renal volume and the selection of ROIs out of the excision field for measurements probably allowed for more reliable results. Moreover, the use of CT scans for the evaluation of renal volume would expose the patient in additional radiation without providing evidence that would significantly influence the results of the study.

3.2.12. Conclusion

In LPN, the parenchymal loss caused by the resection of the tumor and the suturing of the surrounding normal tissues resulted in kidney function deterioration which should be distinguished from WI effects. An average WIT of 22 minutes for a mean tumor diameter of 2.6 cm resulted in a 7% kidney function decline. 4% could be attributed to the parenchymal loss and 3% to WI.

The ultimate renal function after partial nephrectomy is primarily driven by parenchymal preservation with ischemia playing a secondary role as long as it is within a limited time period. One of the major implications of our study is that creating a bloodless filed by clamping the renal pedicle within certain time limits, and consequently precision of excision and renorrhaphy, should be a primary objective during any partial nephrectomy. This may result in more kidney function preservation than putting all efforts to decrease WI time to zero while accepting all potential complications.
3.3. TECHNICAL MODIFICATIONS OF LAPAROSCOPIC SURGERY

3.3.1. Laparoscopic partial adrenalectomy for recurrent pheochromocytoma

In 1998, we performed a transperitoneal laparoscopic bilateral partial adrenalectomy in an 8-year-old boy with symptomatic familial pheochromocytoma, as a manifestation of von Hippel-Lindau disease (VHL) (Radmayr et al. 2000). The symptoms recurred 53 months later, starting with hypertension, tachycardia and headache. The 24-hour urinary excretion of catecholamines was elevated. MRI revealed a 2.5 cm mass on the right adrenal remnant. After preoperative medications with phenoxybenzamine and propranolol, we performed the second laparoscopic transperitoneal partial adrenalectomy (Nambirijan et al. 2004). The previous port sites were used for placement of 3 trocars. Only the fourth trocar (5 mm) was inserted through an additional incision. The only observed intraperitoneal adhesion was at the inferior surface of the liver, which was fixed to the site of adrenal gland. These adhesions were removed easily to approach the tumor. Intraoperative color Doppler ultrasound was used to delineate the tumor. Considering that the tumor was embedded to a great extent in the adrenal gland, the procedure proved to be challenging. Dissection and hemostasis were achieved using monopolar scissors and bipolar coagulation forceps. The vein from the tumour could be isolated and transected preserving the adrenal vein. The tumour was removed completely sparing the normal adrenal tissue. To avoid delayed bleeding, the cut surface was sealed with fibrin glue. Operative time was 120 minutes. The blood loss was minimal and drainage wasn’t needed. Postoperative course was uneventful. Histopathological examination confirmed the diagnosis of pheochromocytoma. During follow-up, blood pressure and catecholamine values returned to normal and no residual tumor was observed.

Patients with VHL, as well as multiple endocrine neoplasia (MEN) type 2 disease, are predisposed to recurrent bilateral adrenal pheochromocytoma. Partial adrenalectomy is considered to be the first choice of treatment in these patients in order to avoid a life-long steroid replacement therapy. In addition, in children preserving the adrenocortical function is essential for normal child growth. The high possibility of recurrence and also predisposition to other intraabdominal pathologies, such as renal cell carcinoma and pancreatic islet cell tumors in VHL may necessitate
repeat surgical procedures. Therefore, any surgical procedure performed in these patients should be as minimal as possible. Our experience with laparoscopy has given rise to strong arguments over open surgery in dealing with the above-mentioned diseases. These arguments are based on advantages, which could be summarized as follows: 1. Minimal procedure, 2. Lower morbidity, 3. Less adhesion formation, 4. Much easier repeat operation for recurrence(s). By this technique, not only the recurrent tumour could be removed successfully but also the unaffected adrenal gland was preserved for the second time.

3.3.2. New tool for laparoscopic antegrade ureteral stenting in repair of circumcaval ureter and pyeloplasty operations.

Circumcaval ureter (CU) is a rare congenital anomaly of the inferior vena cava (IVC). It forms as a result of posterior cardinal vein persisting as the renal segment of the IVC during development. Because the posterior cardinal vein is located ventral to the ureter, the ureter will become entrapped behind the vein. Extrinsic compression or functional loss of the retrocaval ureteral segment may lead to ureteral obstruction and hydronephrosis and subsequently to deterioration of kidney function. Correction of such anomaly is recommended in specific cases. The pathogenesis of the disease and also the indication of the operation are nearly similar to that of uretero-pelvic junction (UPJ) stenosis. By development and progress of laparoscopic technology, laparoscopic approach is considered as the standard of care for such operation. One of the challenging and time-consuming parts of the laparoscopic approach is intraoperative antegrade ureteral stenting. Accordingly, several different methods have been studied and recommended for this purpose.

We have developed a new method for intraoperative antegrade ureteral stenting (Bagheri et al. 2009). The same instrument can be used in any type of laparoscopic ureteric operations necessitating ureteral stenting. We have applied the new technique for laparoscopic transperitoneal repair with transection and reanastomosis of the ureter anterior to the IVC in patients with circumcaval ureters and in several laparoscopic pyeloplasty and ureterotomy cases. In one of the patients with circumcaval ureter, only a mild pelvic dilatation with relatively slight ureteric narrowing was noticed. Therefore, the retrocaval ureteral
segment was preserved and the ureter was transected at its distal dilated part lateral to the IVC. The lower ureteral segment, together with the double coil stent, was transpositioned to the front and lateral of the IVC. The ureteral stump had a normal appearance and the patency of its lumen was confirmed by easy passage of an 8F ureteral catheter. Spatulated end-to-end uretero-ureteral anastomosis was performed using interrupted 4-0 Vicryl sutures.

In two patients, the rectrocaval segment especially the ascending course appeared to be narrowed and aperistaltic. In these cases the ureter was transected medially to the IVC to access the retrocaval segment. The upper stump had a tortuous appearance with very narrow lumen. With peristaltic movements of the pelvis, urine jet was not seen. Therefore that ureteral segment was resected until a normal ureteric lumen and urine flow were visible.

For stenting, we attempted to avoid any retrograde procedure. We applied antegrade stenting using a ureteral stenting cannula, which was developed by our group and used routinely in laparoscopic pyeloplasty operation in our institute (Figure 17).

We developed two sets of ureteric stenting cannula which can be used for intraoperative antegrade ureteric stenting. Each cannula has a length of 28cm to be long enough to pass through the standard laparoscopic trocars and easily reach to the ureteric stump. It is 3mm in diameter so can be easily inserted into any standard trocar or directly into the abdomen by a small percutaneous puncture. The lumen of the cannulas can easily accept stents of up to 7 French.

The cannula in the upper portion of the picture has a mild curvature at the tip. This can be inserted through any standard laparoscopic trocar. The tip of the cannula can be directed to the lower ureteric stump to facilitate insertion of the stent or guidewire into the ureter. The other two parts form a separate kit. The one with a sharp straight tip works as a trocar. It is inserted into the straight cannula for percutaneous puncture from any site of the abdomen. After insertion into the abdomen, the inner trocar can be removed and the cannula can be used for stenting. At the top of each cannula, appropriate sealing cap can be used for insertion of stent and pusher or a guidewire without any leakage of CO2. After insertion of the stent into the distal ureteric stump, the cannula can be removed. After the first few anastomotic sutures, the upper part of the stent can be pushed into the upper ureteric stump or renal pelvis.
Based on our experience, we recommend intraoperative antegrade ureteral stenting, using the stenting cannula, which is fast, safe and easy to apply and additional transureteral retrograde procedure can be avoided. Using antegrade ureteral stenting has the advantage of having a dilated renal pelvis and intact upper ureter during the surgery. These would provide a better preparation of the ureter and renal pelvis and also gives a more accurate evaluation of the narrowed ureteral segment.

**Figure 17.** Two types of ureteral stenting cannula (28 cm long with 3-mm diameter) were used for intraoperative ante-grade ureteral stenting. Cannula with mild curvature at tip, which can be inserted through any trocar with diameter 10 mm (upper). Ureteral stenting cannula formed of sharp, straight-tip trocar and cannula, which can be inserted into abdomen from any direction (lower). At top of each cannula is appropriate sealing cap used for insertion of double coil stent and its pusher.
3.3.3. Ligation of a wide renal vein during laparoscopic nephrectomy: an effective method

Laparoscopic nephrectomy has been refined to a point that is now considered as a first option for radical nephrectomy with excellent results. The crucial step during laparoscopic nephrectomy is the dissection and control of renal pedicle. Application of the endovascular gastrointestinal anastomosis (GIA) stapler has been a standard procedure to control renal vein during laparoscopic nephrectomy. The significant complication due to device malfunction has led several surgeons to find another secure method for renal vein ligation. Accordingly, the so-called Hem-o-lok clips were introduced. However, some renal veins may be so wide that cannot be occluded safely by even the largest available clip. This fact inspired us to find a simple, secure and cost-effective technique to ligate wide renal veins.

After renal pedicle dissection, the renal artery is occluded with Hem-o-lok clips and divided when appropriate. A right angle dissector is passed posterior to the renal vein. A 2-zero 70 cm monofilament suture is fed to the dissector, which is withdrawn and pulled out. The other end of the suture is also grasped and drawn out through the same trocar, so that the suture is placed around the vein. Extracorporally one end of the suture is inserted into the convex side of a specially designed, round eyed knot pusher (Figure 18). It is then grasped by a mosquito and fixed under minimal tension by the assistant in the line of the trocar, while ensuring that there is no kinking or twisting in whole length of the thread. The knot pusher is held by one hand and the free end of the suture is held with the other hand to form a loop around the fixed part, as in open surgery. By maintaining minimal tension on each end of the thread, the loop is gently pushed down by the knot pusher to the level of the renal vein and then slightly tightened. This maneuver can be repeated 3 to 5 times to shrivel the vein. The whole procedure requires about 2 minutes and it can be easily mastered even by an inexperienced laparoscopist.
This rapid and simple maneuver is important to shrink a vein of any diameter to allow the safe application of clips. We preferred to use Hem-o-lok clips with a locking mechanism, which provides a strong hold on the tissue and prevents clip dislodgement. Although we have not experienced any dislodgement, we placed two 10 mm clips on the central side in addition to the ligature and 1 on the peripheral side of the vein (Figure 19). This approach can be used to ligate the renal vein without any morbidity or significant increase of operative time. The combined use of suture tied extracorporally and clips with locking mechanism allows a safe, rapid secure ligation and transection of a vein of any size and may replace the endovascular GIA stapler, which may lead to complications.

**Figure 18.** Knot pusher with closed eye and curved tip used to push down standard surgical knot through a 10 mm trocar.
Figure 19. A. right angle clamp is passed behind renal vein and fed with suture. B. renal vein is shriveled by knots tied extracorporeally. C. vein is clipped with Hem-o-lok clips. D. renal artery and vein after clipping is completed.
4. THESIS RELATED NEW OBSERVATIONS

In the past two decades, laparoscopic procedures have gained popularity among urologists. However, many of the laparoscopic procedures require standardization so all urologists can perform them safely and relatively easily. In our studies, we have tried to standardize some of the upper urinary tract laparoscopic techniques such as repair of circumcaval ureter, pyeloplasty, application of cold ischemia in partial nephrectomy and concerns related to warm ischemia time in nephron-sparing surgeries.

We have observed that in pyeloplasty and any type of upper urinary tract reconstructive laparoscopic procedures, antegrade ureteral stenting with the ureteral stenting cannula which is developed by our team facilitates the antegrade stenting and its application is safe, easy and quick.

We have proved in a prospective study that in partial nephrectomy operations, loss of renal parenchymal mass has an important impact on renal functional outcome. In nephron-sparing laparoscopic surgeries with an average warm ischemia time of 22 minutes, we observed a 7% kidney function decline of which, 4% contributed to the parenchymal loss and only 3% to the ischemia. This research and findings can be of beneficial in future studies to consider the following points:

1. In any partial nephrectomy surgery, intentional resection and suturing of the renal parenchyma which results in loss of some renal mass, has a significant impact on kidney function. This fact should be taken into consideration and it should be distinguished from effects of warm ischemia time in future studies.

2. Probably, potentially unsafe and challenging techniques which advocate zero ischemia time in partial nephrectomy should not be promoted among urologists.
5. REFERENCES


6. PUBLICATIONS AND PRESENTATIONS

Foreign language publications related to the thesis


**IF:** 3.297  
**cit:** 37


**IF:** 3.713  
**cit:** 141


**IF:** 0.862  
**cit:** 9


**IF:** 2.247  
**cit:** 19


**IF:** 2.365  
**cit:** 11


**IF:** 2.666  
**cit:** 0
Publications in Hungarian related to the thesis


IF: 0

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IF: 0

Thesis related IF: 15.150

Thesis related citations: 217

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IF: 2.486 cit: 1


IF: 2.285 cit: 32

IF: 2.286  cit: 10


IF: 1.479  cit: 2

Other presentations


Information Booklet: The Prostate and Its Related Diseases. The First Dubai Prostate Disease Awreness Day, Dubai, 21, September 2011

Total number of publications: 12
Cumulative Impact Factor: 23.962
Citation: 263.
7. ACKNOWLEDGEMENTS

I wish to express sincere gratitude to Prof. Dr. Farkas László, my advisor and head of Urology Department in Pécs at the time of my research, who assigned to me and greatly supported me to implement laparoscopic techniques and accomplish my PhD work in his department.

Many thanks to current acting head of Pécs Urology Department, Dr. Szántó Árpád and all my colleagues and friends in the Department – doctors, operating theater staff, anesthesiology team, nurses, administrative personnel, and lab members – for their continuous help, patience, and availability in my operations and patients’ work up.

Special thanks to head of the departments and colleagues in the following institutes who were directly involved and maximally supportive in my work: Department of Nuclear Medicine, Department of Research and Techniques, Diagnostic Center of Pécs, Institute of Bioanalysis.

I would like to acknowledge the medical staff of University of Pécs, who gave me the opportunity to complete my thesis in this University.

I am indebted to many of my colleagues and friends for their continued encouragement, support, optimism and confidence in me in my whole urology career and the PhD work.

Last, but not least, many thanks to my parents, my wife, my children, and Gabi mama for their unconditional support and encouragement to pursue my interests, even when the interests went beyond boundaries of language, field, and geography. Thanks to God for everything.