Reduction of Warm Ischemia Time by Preoperative Three-Dimensional Visualisation in Robot-Assisted Laparoscopic Partial Nephrectomy

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ABSTRACT

Introduction: To investigate whether preoperative visualization of a renal tumor with a three-dimensional (3D) model results in a reduction of Warm Ischemia Time (WIT) during Robot-Assisted Laparoscopic Partial Nephrectomy (RALPN).

Materials and Methods: A total of 34 patients underwent RALPN between January 2016 and April 2018. For 12 of these patients, a Three-Dimensional Visualization (3DV) was performed preoperatively. No 3DV was undertaken in the remaining 22 patients. All RALPN procedures were performed by the same surgeon. All pre-, intra- and postoperative data was gathered and analyzed.

Results: There was no difference between the two groups in the preoperative demographics. In the intraoperative parameters, a statistically significant difference was shown in operation time between those undergoing 3DV and no-3DV (206.25 versus 152.05 minutes, p=0.0099), the presence of toxic fat (5 versus 0, absolute T-value=3.22) and Warm Ischemia Time (WIT) (17.75 versus 21.73 minutes, p=0.0419). Additionally, there was a statistically significant difference in the postoperative length of stay (4 days in 3DV versus 6 days in no-3DV, p=0.0218).

Conclusion: Preoperative visualization of the anatomy by means of 3DV can shorten WIT in RALPN. Care should be taken to avoid possible mismatches between 3DV and real anatomy.

ABBREVIATIONS

3D: Three-Dimensional; (RAL)PN: (Robot-Assisted Laparoscopic) Partial Nephrectomy; 3DV: Three-Dimensional Visualization; WIT: Warm Ischemia Time; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; RCC: Renal Cell Carcinoma; PDS: Polydioxanone; DICOM: Digital Imaging and Communications in Medicine; BMI: Body Mass Index; ASA: American Society of Anesthesiologists; eGFR: Estimated Glomerular Filtration Rate; PSM: Positive Surgical Margins

INTRODUCTION

Renal Cell Carcinoma [RCC] is diagnosed in approximately 208, 500 individuals worldwide annually (~2% of all cancers) [1-3]. This is undoubtedly linked to the increasing number of radiological examinations being performed for multiple non-tumor related indications, resulting in an incidental diagnosis of RCC. The standard treatment for organ-confined RCC was a radical nephrectomy, but technical innovations have resulted in a progressive shift towards both Minimally
Invasive Surgery (MIS) and organ-sparing treatments [4]. The advantages of MIS are well documented, and the oncological outcomes are comparable to those following conventional open, radical, non-organ-sparing surgery [5]. During organ-sparing tumor resection, the arterial blood flow to the kidney is temporarily interrupted. This results in little or no bleeding, allowing precise tumor resection and closure of the pelvicalyceal system (where opened), as well as closure of the parenchymal defect. The duration of this Warm Ischemia Time (WIT) has been the subject of much debate. Laboratory studies on porcine kidneys showed that a WIT of ≤60 minutes was well tolerated without irreversible damage to the renal parenchyma [6]. In humans, the time that a kidney can be devoid of its arterial blood supply without incurring irreversible renal parenchymal damage is significantly shorter compared to porcine kidneys. Particularly in patients with a solitary kidney, every minute of WIT counts if loss of renal function is to be minimized. According to some studies, every extra minute of WIT, above 20 minutes, results in a 5% increase in risk of developing chronic renal insufficiency (stage 4 chronic kidney disease) during follow-up and currently, a maximum WIT of 20-25 minutes is proposed as an appropriate target [7-9].

Traditionally, the surgeon relies on computed tomography or magnetic resonance imaging to formulate an assessment of the tumor and renal anatomy in order to decide whether a partial nephrectomy is feasible. A recent addition to these classic radiological imaging modalities is the creation of a 3D printed model. It has been demonstrated that 3D models can modify the chosen surgical approach during the pre-operative planning phase, in additional to their intrinsic educational value [10-12]. However, production of these 3D printed models requires additional effort, in terms of manual input during image processing and subsequent conversion into printable data. This results in an expensive and time-consuming process, which may limit the routine use of 3D printed models for preoperative planning. Since the production of a 3D model requires the initial fabrication of a 3D virtual model before it can be printed, it makes sense to use this 3D virtual model instead of the printed one, thus saving time, resources and money [12-16].

PATIENTS AND METHODS

Patients

From January 2016 to April 2018, 34 patients underwent RALPN at the University Hospital Gasthuisberg in Leuven performed by one surgeon. In 22 of these, no additional preoperative 3DV was undertaken apart from the standard preoperative CT scan. In the other 12 patients, preoperative 3D visualization was performed. Whether preoperative 3D-visualization was performed or not depended solely on the availability of resources necessary to make these models. The patient or tumor characteristics were not considered in this process. Of the 12 models, the initial two visualizations were 3D prints (Materialize®) (Figure 1,2). The remaining 10 preoperative visualizations were not printed, but pure 3D visualizations (VisiblePatient®) (Figure 3).

RAPLN – Surgical technique

Under general anesthesia, patients were positioned in full flank position. A pneumoperitoneum (15 mmHg) was applied, trocars placed, and the robot docked. The renal artery (and branches) was located and isolated (Figure 4). The tumor was echo-located and dissected from surrounding tissue (Figure 5). At this stage, strongly adherent peri-renal fat ("toxic fat") can seriously complicate peri-renal dissection [17]. Mannitol was
applied. With bulldog clamps applied to the renal artery, WIT was commenced. The tumor was classically resected with a limited margin of surrounding healthy renal tissue (Figure 1,6). The pelvicalyceal system was closed and the resection bed sutured with polydioxanone [PDS] 2/0 for hemostasis. Floseal® hemostatic matrix was applied and the peri-renal capsule was approximated by means of Vicryl® 1 over bolster Surgicell®. The arterial clamps were loosened, and hemostasis monitored.

Gerota’s fascia was closed and the robot disconnected from the trocars. The retrieval bag with the specimen and all trocars were removed, a single intra-abdominal drain was secured in place. The surgical incisions were closed in layers. The patient was extubated and recovered normally.

Figure 3: 3DV (Visible Patient®) with tumor demonstrated in green.

Figure 4: Isolation and clamping of renal arterial blood flow.

Figure 5: Echo-location (top) and tumor marking (bottom).

Figure 6: Macroscopic image of removed kidney tumor with a margin of healthy kidney tissue.
3D Visualization

The first two models out of the 12 cases were 3D prints (Materialize®). All remaining models were 3DVs without print (VisiblePatient®). The models were created based on patient-specific preoperative cross-sectional CT or MRI scans. These scans images were anonymized and transferred according to the Digital Imaging and Communications in Medicine (DICOM) protocol. A technician trained in medical imaging then created the 3DVs using image processing software (VisiblePatient-Lab®). The resulting 3DV picture was verified by a second experienced technician to obtain the most accurate image. The final result of the 3DV image was viewable using a dedicated application on a computer, tablet or smartphone or on the control console of the Da Vinci robot® by means of the TilePro® function [18].

STATISTICAL ANALYSIS

To investigate whether there was a statistically significant difference between patients who had a preoperative 3DV model and those who did not, a classic Student’s t-test was used (Microsoft® Excel® for Mac, 2011 Version 14.7.7). For numerical data, a statistically significant difference was observed where the ‘p’ value was ≤0.05. For categorical data, the absolute t-value was calculated at 95% reliability interval. The result was considered statistically significant if the absolute t value was >1.96.

RESULTS

Preoperative data (Table 1), demonstrated no statistically significant difference between the two groups when age, sex, Body Mass Index (BMI), American Society of Anesthesiologists (ASA) score, tumor diameter, stage and complexity (calculated according to the RENAL nephrometry scoring system) were included in the analysis [19].

(Table 2) shows the intraoperative data. In contrast to the preoperative parameters, several statistically significant differences were noted between the two groups (marked in red). Firstly, operation time was longer in the group with preoperative 3DV (p= 0.0099), and warm ischemia time was shorter during tumor resection and reconstruction of the renal parenchyma (p= 0.041) compared to those who did not have 3DV. None of the patients had a WIT lasting longer than 30 minutes.

Secondly, the number of patients with demonstrable peri-renal adherent fat (“toxic fat”) was significantly higher in the group with 3DV (t-value=3.22). Finally, there was one complication in the group without 3DV where limited bleeding was encountered due to an inadvertently severed arterial branch, with subsequent clipping of this branch. There were no intraoperative complications in the group with 3DV.

Table 1: Preoperative patient and tumor characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3D visualization (n=12)</th>
<th>No 3D visualization (n=22)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.08 ± 8.97</td>
<td>57 ± 12.39</td>
<td>0.0640</td>
</tr>
<tr>
<td>BMI</td>
<td>29.3 ± 6.06</td>
<td>27.6 ± 3.77</td>
<td>0.2000</td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>17</td>
<td>0.1573</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>5</td>
<td>0.5031</td>
</tr>
<tr>
<td>ASA score</td>
<td>3 ± 0.71</td>
<td>3 ± 0.71</td>
<td>0.3835</td>
</tr>
<tr>
<td>Tumor diameter (cm)</td>
<td>2.64 ± 0.79</td>
<td>3.02 ± 1.01</td>
<td>0.1594</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1a</td>
<td>12</td>
<td>19</td>
<td>0.0917</td>
</tr>
<tr>
<td>pT1b</td>
<td>0</td>
<td>3</td>
<td>0.9083</td>
</tr>
<tr>
<td>RENAL nephrometry score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low complexity (4-6)</td>
<td>7</td>
<td>14</td>
<td>0.6132</td>
</tr>
<tr>
<td>intermediate (7-9)</td>
<td>5</td>
<td>7</td>
<td>0.2830</td>
</tr>
<tr>
<td>high complexity (10-12)</td>
<td>0</td>
<td>1</td>
<td>0.7706</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>8</td>
<td>9</td>
<td>0.0784</td>
</tr>
<tr>
<td>right</td>
<td>4</td>
<td>13</td>
<td>0.9216</td>
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Table 2: Intra-operative data.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>3D visualization (n=12)</th>
<th>No 3D visualization (n=22)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR time (min)</td>
<td>206.25 ± 67.18</td>
<td>152.05 ± 32.9</td>
<td>0.0099</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>135 ± 117.79</td>
<td>171.82 ± 180.14</td>
<td>0.2703</td>
</tr>
<tr>
<td>WIT (min)</td>
<td>18.25 ± 4.04</td>
<td>21.72 ± 5.79</td>
<td>0.0010</td>
</tr>
<tr>
<td>Toxic fat present</td>
<td>5</td>
<td>0</td>
<td>0.0002</td>
</tr>
<tr>
<td>Complications</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
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</table>

Postoperative data (Table 3) showed two statistically significant differences. The length of hospital stay in the group without preoperative 3DV was higher compared to patients who underwent 3DV (6±3.72 versus 4±1.34 days; p=0.0438), as well as the total number of complications recorded in the postoperative period (6 versus 2; t value=3.07).

In the group without 3DV (n=22), there were two post-surgical renal infarctions (managed conservatively), two patients experienced ongoing postoperative hemorrhage requiring selective renal artery embolization and transfusion with two units of packed cells each. Two patients developed a pyrexia, which was resolved following intravenous antibiotics administration. In the group with 3DV (n=12), one patient had a prolonged chyle leakage, which was successfully treated with


The histopathological analysis results of resected tissue are found in (Table 4). There were no statistically significant differences between the two groups, neither in the final histological diagnosis or RCC tumor type, nor in resection margin status.

**DISCUSSION**

Frequent use of medical imaging has led to an increased diagnosis of small renal masses (‘incidentalomas’). The time when incidentalomas routinely resulted in radical nephrectomy is thankfully behind us, as unnecessary removal of surrounding non-tumor renal tissue leads to a higher risk of renal failure and renal replacement therapy, but also a higher incidence of subsequent cardiovascular events which have a negative impact on the patient’s quality of life and life expectancy [21]. For these reasons, Nephron-Sparing Surgery (NSS) has gained popularity.

Furthermore, NSS is increasingly undertaken using MIS techniques which have numerous well recognized advantages, including avoiding a large flank incision, reduced pain, fewer and faster recovery. Additionally, robot-assisted laparoscopic surgery provides the additional benefits of a 3D image system and higher degrees of freedom of movement afforded by extra distal articulation.

Preservation of postoperative renal function in patients undergoing nephron-sparing surgery is aided significantly by reducing the duration of warm ischemia time during tumor excision and reconstruction of the collecting system. Conventionally, the WIT is set at a maximum limit of 25 minutes, though the shorter the WIT, the better the probability of renal function preservation. Several techniques to reduce WIT during laparoscopic and robot-assisted surgery have already been described, such as early unclamping and (super) selective clamping [22].

To make the decision whether a partial nephrectomy is feasible, the surgeon relies on classical medical imaging including computed tomography and magnetic resonance imaging. Due to the development of image segmentation, it is possible to split these digital images up into super-pixels, which allows for the anatomical structures to be reconstructed and printed, creating a 3D model of the tumor, kidney and surrounding structures. This has an added educational and surgical value, but the time and resource implications hamper the routine use of this imaging modality in most centers. A potential helpful step to mitigate the costliness of the process is to simply use the 3D virtual model only, which is an obligatory step prior to printing, and skip the physical printing process itself.

The current study demonstrates the importance of preoperative imaging and its impact on reducing WIT. Preoperative 3DV of the kidney with the location of the renal tumor, the associated arterial and venous configuration and anatomy of the

collecting system, appears to facilitate a reduction in the WIT. There was a statistically significant reduction in the WIT in the group who underwent preoperative 3DV. Interestingly, however, we also observed significant longer operation times and a greater proportion of patients with strongly adhesive perinephric fat in the 3DV group. This so-called “toxic fat” adds to the complexity of the procedure by making it substantially more difficult to mobilize the kidney, locate the tumor and undertake meticulous dissection of tumor and renal cortex. A higher incidence of adherent perinephric toxic fat is associated with longer operation times and we assume that that explains the long operation time in the 3DV group [17]. With regards to intra-operative complications, a single case of bleeding was encountered in the group without 3DV, but the low absolute number (0 vs 1 complication) does not allow for any firm conclusions to be drawn from this study.

With regards to postoperative parameters, the no-3DV group had a longer stay in hospital. In this group, one patient stayed in hospital for 21 days post procedure, but even if this patient is excluded from the analysis, the statistically significant difference remains in favor of the 3DV group having a shorter hospital stay. The authors speculate that this may be related to the learning curve associated with RALPN [23]. In the no-3DV group with a longer length of hospital stay, 17 patients underwent surgery in 2016 with the five remaining patients undergoing a RALPN in 2017. In the other group with 3DV, two patients were operated on in 2016, six in 2017 and four in 2018. This distribution could help explain why the group with 3DV had a shorter length of stay as they generally underwent their procedure when the operating surgeon had already gained more experience and was further along his learning curve.

The total number of postoperative complications (Table 3) is higher in the no-3DV group, but when classified according to severity no statistically significant difference is observed. Final histopathological findings and proportion of positive surgical resection margins (PSM) were comparable in both groups. The total number of patients with a PSM on specimen analysis following RALPN was 6/34 (17.6%). This is higher than PSM rates reported in literature which range from 5.5 to 6.4% [24,25]. When the data from the total cohort of 34 patients is taken into account, some additional factors could potentially have had an influence on the PSM rate. The presence of perinephric toxic fat in three of the six patients and a BMI >30 in four out of six patients (one of whom had a BMI >40) with a PSM, may suggest both of these to be possible contributory factors which could make surgical dissection more difficult. Additionally, two of the six patients with a PSM were categorized as moderate complexity and a third patient as high complexity according to the RENAL nephrometry score. These factors may play a role in the higher number of PSM in the present study, though a definite conclusion cannot be reached from the current sample. It is undoubtedly desirable to reduce the PSM rate to as low as possible, but current evidence demonstrates that a PSM does not necessarily result in a negative prognostic factor for patients undergoing RALPN [26]. Recurrence-free survival, cancer-specific survival and overall survival do not appear to differ in patients with positive and negative surgical resection margins after partial nephrectomy [26]. Therefore, even those with a PSM can be followed up by means of radiographic imaging and do not need immediate additional treatment postoperatively.

Renal function was well maintained with no difference noted in the pre- and postoperative estimated glomerular filtration rate (eGFR) in both groups (Table 3). Factors which may have been crucial in the renal function preservation include the WIT not exceeding 30 minutes in any of the procedures, as well as a normal preoperative kidney function with a normal contralateral kidney in most cases.

Preoperative 3DV also allows easier detection of variations in renal tumor and vascular anatomy, which can then be anticipated during surgery. An example of this is the preoperative visualization of a left renal artery, which may originate cranially in relation to the renal vein (instead of its more conventional position posterior to the vein) and thus needs to be anticipated and located in a more cranial position. A second example is the presence of two renal arteries (Figure 7a). This preoperative visualization allows the surgeon to consider the possibility of selective arterial clamping, which could theoretically result in better preservation of renal function. However, convincing data to support the benefits of selective arterial clamping is currently still lacking [13,22]. (Figure 7b) shows how selective clamping of the upper pole...
artery is possible to acquire selective ischemia of the upper pole. Intraoperatively, this can be monitored by using the FireFly® module on the robot.

It is important to remember that neither computer algorithms nor humans are perfect, which allows the potential for a mismatch between 3DV and real anatomy [27]. The quality of the preoperative CT is crucially important and ideally necessitates a triphasic CT scan with excretory series to visualize the anatomy, with a slice thickness of between 0.8 and 1.5 mm. The upper limit of the slice thickness is 3 mm, but this results in a less detailed, coarse-grained model which is less than ideal (Figure 8). In one case, two models were made to derive from the preoperative CT scan images; one was obtained using by the VisiblePatient-Lab® software while the second model was obtained using standard software used by the Department of Radiology at the hospital (Figure 9). In the latter model, the visualization of a separate blood vessel of the tumor was missing, which is obviously essential information during the operation. In another case (Figure 10), two tumors appeared to be shown on the 3DV model, although, in reality, there was only one tumor and one complicated cyst. We thus acknowledge that 3DV software is not without its flaws, and meticulous attention to details is mandatory to corroborate all available information.

We acknowledge the limitations of our study, which include a smaller sample size and the retrospective nature of the study. A smaller sample size is a well-recognized problem when investigating newer techniques. We have sought to reduce the impact of the sample size by avoiding multivariate statistical analysis of the results obtained. The above mentioned findings should be confirmed in larger studies with higher numbers. Nevertheless, our study allows a glimpse of the possibilities offered by this technology which is expanding rapidly. In the
future, due to the ability to easily incorporate augmented reality models directly into the operators' console, preoperative 3DV could be used to overlay and superimpose images over the live images, which facilitates quicker and improved identification of important structures intraoperatively. Ultimately, procedures would be faster— and possibly with a shorter WIT – which may result in a reduction in procedure-related complications. Prolonged surgical times have been demonstrated to have a negative impact on the rates of surgical complications [28]. Furthermore, in time, increased utilization of 3DV technology may help provide a clearer definition of tumor anatomy, precise tumor penetration depth and tumor relation to renal parenchyma which may help reduce the PSM rates.

**Figure 9:** (a) Lack of tumor-supplying artery (left)using standard software and (b) model obtained using the VisiblePatient-Lab® tool demonstrating the correct arterial anatomy (right).

**Figure 10:** Marking of two lesions as tumor(bright green), one of which is not anRCC but a complex cyst.
To alleviate the bottleneck created by the costs and resources involved in 3DV creation, largely due to the necessity for time consuming manual input, the use of convolutional neural networks (a deep learning algorithm which receives and stratifies image component data enabling enhanced image manipulation) can be beneficial, once this technique has been refined and tested. This would allow the routine use of 3DV in RALPN [29-30].

CONCLUSION
The use of 3DV in the preoperative planning of RALPN is a viable tool for the surgeon to reduce WIT. The current available technology to obtain 3DV for use intra- and preoperatively still requires refinement and scrutiny of the resulting model is necessary to avoid mismatch between the 3DV model and real anatomy.

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