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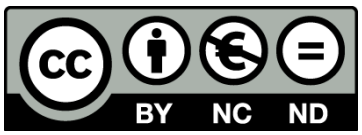
Assessing the use of a gelatine matrix thrombin tissue sealant to reduce warm ischemia time in laparoscopic partial nephrectomies. A randomised controlled trial

Carlos Toribio Vázquez



FINAL UNDERGRADUATE PROJECT (TFG)

Assessing the use of a gelatine matrix thrombin tissue sealant to reduce warm ischemia time in laparoscopic partial nephrectomies. A randomised controlled trial

Degree in medicine

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Index

Abstract

Introduction

The increase in diagnosis of small renal masses has forced a change in surgical treatment procedures. Conservative procedures diminish the risk of severe postoperative complications without increasing the rate of tumour recurrence. Haemostatic agents have the potential to facilitate suture-less laparoscopic partial nephrectomy reducing warm ischaemia time and improving postoperative kidney function.

Objective: To evaluate the reduction of warm ischaemia time using a gelatine matrix thrombin tissue sealant in patients with solid T1a renal tumours undergoing partial nephrectomy.

Methods

Design: A multicentre three-branch randomised controlled trial in the Spanish National Health System. Study population: patients aged 18-75 years diagnosed with exophytic solid small renal masses at any urological service in the Spanish National Health System between March 2019 and March 2020 that will undergo surgical management by laparoscopic partial nephrectomy. Intervention: patients will be randomly allocated, using a computer program, into one of the three groups according to the method of haemostasis that will be used after tumour excision: S + F) Sutures + gelatine matrix thrombin sealant (Floseal ®), S) Sutures and F) Gelatine matrix thrombin sealant (Floseal ®). Results variable: primary dependent variable is warm ischemia time and secondary dependent variables: time until complete haemostasis after tumour excision, presence of haemorrhagic complications, blood loss, change in renal function and tumour recurrence. Blinding: doctors (anaesthesiologist and the urologist team in charge of the patient) will be aware of patient allocation. Patients and data analysts will be blinded.

Ethical approval

Patients that meet inclusion criteria are informed of all aspects of the study including random allocation, potential complications. Ethical approval will be sought from the corresponding ethical committee. They will then be asked to sign informed consent forms ensuring care continuity regardless the study.

Expected results

Patients in group F (Floseal ®) will have the shortest warm ischemia time, less haemorrhagic complications, blood loss and improved postoperative kidney function. Postoperative renal

function will inversely correlate with warm ischemia time. Tumour recurrence rates will be the same between groups.

Resumen

Introducción

El aumento en el diagnóstico de pequeñas masas renales ha forzado una renovación en los métodos de manejo quirúrgico. Los procedimientos conservadores han mostrado disminuir el riesgo de complicaciones postoperatorias graves sin aumentar la tasa de recidiva tumoral. Los agentes hemostáticos tienen el potencial de permitir una nefrectomía parcial laparoscópica sin sutura, reduciendo el tiempo de isquemia caliente y mejorando la función renal postoperatoria. Objetivo: Evaluar la posible reducción del tiempo de isquemia caliente utilizando sellador de trombina con matriz de gelatina en pacientes con tumores renales sólidos con estadiaje T1a sometidos a nefrectomía parcial.

Métodos

Diseño: ensayo clínico aleatorizado multicéntrico de tres ramas en el Sistema Nacional de Salud Español. Población de estudio: pacientes entre 18 y 75 años diagnosticados de un tumor renal pequeño, sólido y de crecimiento exofítico en cualquier servicio de urología del Sistema Nacional de Salud Español entre marzo de 2019 y marzo de 2020 con indicación de manejo quirúrgico mediante nefrectomía parcial laparoscópica. Intervención: los pacientes serán aleatorizados utilizando un programa informático, a uno de los tres grupos: S + F) Suturas + sellador de trombina con matriz de gelatina (Floseal ®), S) Suturas y F) Sellador de trombina con matriz de gelatina (Floseal®). Variables de resultados: la variable dependiente primaria es el tiempo de isquemia caliente y las variables dependientes secundarias son: tiempo hasta la hemostasia completa tras la escisión tumoral, presencia de complicaciones hemorrágicas, pérdida de sangre, cambio en la función renal y recidiva tumoral. Enmascaramiento: los médicos (el anestesiólogo y el equipo de urólogos a cargo del paciente) tendrán conocimiento de la asignación del paciente a un grupo determinado. Los pacientes y los analistas estarán enmascarados.

Aprobación ética

Los pacientes que cumplen los criterios de inclusión y deseen participar serán informados de todos los aspectos del estudio, incluida la asignación aleatoria y las posibles complicaciones.

Se les pedirá que firmen formularios de consentimiento informado. Es importante que el paciente sepa que se mantendrá la continuidad asistencial, aunque quiera dejar el estudio.

Resultados esperados

Los pacientes en el grupo F (Floseal®) tendrán el tiempo de isquemia caliente más corto, menos complicaciones hemorrágicas, pérdida de sangre y una función renal postoperatoria mejorada. La función renal postoperatoria se correlacionará inversamente con el tiempo de isquemia caliente. Las tasas de recurrencia tumoral serán las mismas en todos los grupos.

Introduction

Renal tumours are associated with the clinical triad: haematuria, back pain and palpable mass. However, this clinical presentation is rare and currently most renal masses are asymptomatic at diagnosis. The last two decades have shown an increase in the diagnosis and treatment of these masses. Principally, due to a more widespread use of imaging techniques, primarily ultrasonography and computerised tomography scans. Most masses are diagnosed incidentally, with the size of the tumours found currently averaging 3.5cm (1). This has led to a renewal of the treatment options available for small renal masses (SRMs: localised tumours under 4cms (T1a)); including: surgical ablation, radical nephrectomy, partial nephrectomy and active surveillance.

Surgical ablation offers a less invasive approach for elderly and comorbid patients deemed higher risk. Nevertheless, recurrence rate remains too high for this technique to become standardised. Moreover, surgical intervention following ablative procedures can be technically complex. In addition to ablation, active surveillance acts as an extra tool for patients unsuitable for surgery. Surgery, however, has been the only technique proven effective for controlling tumour recurrence. Although traditionally gold standard, there is a recent shift away from Radical nephrectomy (RN) towards a more conservative approach. Partial nephrectomy (PN) offers clear benefits compared to radical surgery when managing SRMs. Reduced glomerular filtration rate acts as an independent risk factor for increased mortality risk, cardiovascular events and hospitalisation(2). Preserving renal parenchyma reduces the risk of long term chronic kidney disease (CKD), diminishing cardiovascular risk and all-cause mortality. Furthermore, PN shows similar tumour recurrence rates when compared to RN. American and European clinical guidelines recommend PN for accessible renal mases(3). These arguments have led to a more conservative approach as being widely accepted, making PN the new gold standard for treatment of SRMs (4)

PN was initially reserved for patients with high risk of developing CKD who would require dialysis after surgery, patients with one kidney or bilateral tumours. Recently, the indications for this surgery have broaden greatly. Yet, even if the number of partial nephrectomies has increased over the years, it continues to be underused. This is mostly due to its technical complexity and greater number of haemorrhagic and urinary complications, making radical

surgery a much more appealing setting for non-specialist surgeons in these types of procedures(5). Current research suggests that RN in young patients with SRMs reduces overall survival due to the decrease in renal function, further valuing PN as the standard of care(6). Simon P *et al*.'s work shows that PN achieves a 19%(HR 0.81, p<0.0001) reduction of all-cause mortality, 29% (HR 0.71, p = 0.0002) decrease in cancer specific mortality and a 61% (HR 0.39, p <0.0001) lower risk of developing severe CKD(7) when compared to RN. However, these results must be greeted with caution due to the retrospective nature of the study.

PN can be performed laparoscopically, robotically or by open surgery. Recent research shows that minimally invasive techniques allow for quicker recovery and faster hospital discharge(8). Accordingly, laparoscopic and robotically assisted surgeries seem to offer best results, but due to high cost of robotically assisted interventions and its limited use to specific services, laparoscopic PN (LPN) continues to be the standard of care. This procedure has potential risk for complications, haemorrhage being one of the most important and feared by surgeons. Haemorrhage can occur at any point of the surgery, primarily due to ineffective renal clamping or upon revascularisation. Tumour size, location and amount of penetration to the renal parenchyma determines risk of haemorrhage. During laparoscopic nephrectomies there is a risk of severe bleeding and need for transfusion, meaning there is often need for open surgery or re-intervention. A combination of suturing techniques and haemostatic agents is recommended for adequate management of most masses(9).

Suturing is the most reliable method to achieve haemostasis, however it is time consuming and requires a certain level of expertise from the surgeon. Continuous suture and the use of clips eradicate the need for knot tying as an attempt to facilitate and decrease the time to haemostasis. However, Suturing can have negative effects, slicing through or de-vascularising tissue due to suture tension, contributing to a lower postoperative renal function(10). Furthermore, it does not provide rapid haemostasis. This has led to the development of many tissue sealants over the years.

Sealants differ greatly in composition and action. Floseal ® (Baxter Medical, Fremont, CA) is a gelatine matrix with bovine derived thrombin, which, when exposed to fibrinogen rapidly forms a clot by finishing the coagulation cascade. Thrombin is a key enzyme in the common rout of coagulation. The inclusion of haemostatic agents to assist haemostasis during surgery has been widely adopted, primarily the use of Floseal ®(11). Gill et al. performed 131

consecutive LPN and retrospectively classified their patients into two groups depending if Floseal ® was used or not. The initial 63 patients received only parenchymal suturing and the following 68 patients received Floseal ® as an additional haemostatic aid. It was seen that patients that did not receive Floseal ® had significantly greater blood loss ($p<0.006$). Furthermore, overall haemorrhagic complications were reduced from 11.8% (no Floseal ®) to 3.2% ($p=0.08$), allowing Gill and collaborators to suggest Floseal ® as a good haemostatic agent(12). Ozgor et al. recently published a review on the available knowledge regarding improved haemostasis by Floseal ®. They believe that this gelatine matrix has the power to enhance current LPN, but advocate for larger prospective randomised studies to further validate their finding(13).

Yucel *et al.* carried out a study evaluating the histopathological effect of sutures versus three haemostatic agents on rat kidneys. They performed a one-third lower pole renal PN on 32 rats that had been randomised into four groups. For the group that received suture, greater glomerular necrosis and calcification was observed ($p<0.001$). Comparing between haemostatic agents, no significant difference was observed ($p>0.005$). Yucel and his team also found that Floseal ® reduced blood loss and warm ischaemia time. Finally concluding, to their knowledge, the superiority of haemostatic agents in haemorrhage control during partial nephrectomies when compared to sutures(14). In a hypertensive pig model study conducted by Yannick *et al.*, even after deep one-third renal excision, haemostatic agents were capable of controlling bleeding without the need of sutures(15), suggesting the possibility of performing a suture-less LPN.

Another potential risk associated with LPN is warm ischaemia time (WIT). Clamping of the renal pedicle is vital, allowing tumour excision, without the risk of haemorrhage but at the cost of renal ischaemia. This creates a time window of 25 minutes over which nephron damage becomes extensive and there is risk of irreversible renal loss(16). Hung *et al.* describe their findings of decreasing WIT in PN's between 1999 and 2011. They retrospectively classified their patients into four groups; discovery era (mean WIT of 36 minutes), conventional clamping (mean WIT of 31 minutes), early unclamping (mean WIT of 14 minutes) and zero ischemia (no warm ischaemia). A clear benefit was observed with regards to serum creatine, estimated glomerular filtration rate (eGFR) ($p<0.0001$) and risk of acute kidney disease (50% increase of postoperative serum creatine of over baseline) ($p<0.05$) when decreasing WIT. Zero ischaemia by selective vessel occlusion showed the lowest renal function decay but a greater rate of

transfusion (intra and postoperatively) *(p=0.02)*, limiting the use of this technical procedure. Hung and collaborators also found that a WIT of 25 minutes was associated with a significant risk of stage IV CKD (HR 2.27, p=0.049). As postoperative renal volume and quality are unchangeable given correct surgical practice, WIT remains as the primary modifiable factor in PN(17).

Richter *et al*. proposed a technique for achieving haemostasis solely with the use of Floseal ®. They carried out 25 PN on tumours ranging from 2-5cms. They performed a double spread of sealant, the first after tumour excision and the second after unclamping of the renal vessels. There were no cases of bleeding after reperfusion, nor need for transfusion(18). Similarly, Bak *et al* carried out a small-scale study using Floseal ® for haemostasis. They performed 6 consecutive PN on patients with more than 50% of the tumour being exophytic and ranging from 2-3cm in size. They postulated that by avoiding the need to suture a potential reduction in WIT could be achieved (19). Recently, Minervini et al. performed a retrospective study evaluating the safety of suture-less LPN. They compared 68 patients that had received knot-tying suture, Floseal ® and Tabotamps bolster with 32 patients that only received bipolar cauterisation and Floseal ®. Minervini and collaborators concluded suture-less LPN to be a safe and effective procedure that allows for shorter periods of WIT. However, larger scale randomised studies are still required for this statement to become widely accepted(20).

In conclusion, available evidences suggest that in selected patients with exophytic renal tumours in which the collecting system is not affected, haemostatic control after partial nephrectomy can be performed solely with the use of haemostatic agents. Avoiding the need for sutures should potentially decrease WIT, improving current surgical management of SMRs. However, small sample sizes, retrospective designs, lack of randomisation or a direct evaluation of haemostatic agents on WIT, advocate for further investigation. In this sense, large scale randomised studies evaluating the potential benefit of this treatment procedure will contribute to fulfil the gap of knowledge.

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Hypothesis and Objectives

Hypothesis

Main hypothesis

Haemostatic agents have been proven sufficient for controlling bleeding after excision of small exophytic tumours in which closure of the collecting system is not required. Consequently, avoiding the need to suture will reduce time to haemostasis after tumour excision, meaning shorted periods of WIT.

Secondary hypothesis

- Shorter WIT will diminish the ischemic insult on the kidney during surgery and hence there will be an increased postoperative renal function (eGFR) when compared to longer WIT.
- Faster haemostasis will diminish blood loss during surgery therefore reducing overall number of transfusion, haemorrhagic related complications, need for reintervention or conversion to open surgery.
- The only variation between surgical procedures is the method of haemostasis used. Therefore, tumour recurrence rates should be similar between intervention groups.

Objectives

Main objective

To evaluate the reduction of warm ischaemia time using a gelatine matrix thrombin tissue sealant in patients with solid T1a renal tumours undergoing laparoscopic partial nephrectomy.

Secondary objectives

- To compare the time taken by each intervention to achieve complete haemostasis after tumour excision.
- To evaluate the risk of haemorrhagic related complications associated to each procedure.
- To compare blood loss between interventions.
- To compare change in eGFR depending on method of haemostasis used.
- To determine if reduction in WIT contributes to a greater postoperative eGFR.
- To ensure method of haemostasis does not affect rate of tumour recurrence.

Methods

Study design

A multicentre three-branch randomised controlled trial in the Spanish National Health System (NHS). Patients with diagnosed exophytic solid SRMs at any urological service of the Spanish NHS with an indication to undergo laparoscopic partial nephrectomy between March 2019 and March 2020, will be offered to participate in the study. If inclusion criteria are met and informed consent is understood, accepted and signed, patients will be randomly allocated using a computer program into one of the three intervention groups:

S+F) Sutures + gelatine matrix thrombin sealant (Floseal®)

S) Sutures only

F) Gelatine matrix thrombin sealant (Floseal®) only

Blinding. Single blinded, doctors (anaesthesiologist and the urologist team in charge of the patient) will be aware of patient allocation. Patients and data analysts will be blinded.

Study population. Patients of both sexes aged between 18-75 years who have been diagnosed with a SRM at any urological service in the Spanish NHS where LPNs are performed who meet the inclusion criteria.

Inclusion and exclusion criteria

Inclusion criteria

Patients aged between 18-75, diagnosed with a solitary, solid, sporadic T1a renal tumour, with a contrast-enhanced computed tomography confirming low complexity (4-6 R.E.N.A.L. nephrometry score) with an exophytic growth pattern (>50% of tumour volume) that does not affect the collecting system or renal hilum and is recommended for surgery by transperitoneal LPN. Patients who have accepted and signed informed consent forms to participate in the study.

Exclusion criteria

Patients with age under 18 or over 75.

Multifocal tumours, cystic tumours, patients with tumour staging greater than T1a, high complexity tumours (nephrometry score greater than 6), non exophytic growth pattern, tumour

that affects the collecting system, tumour proximity to major blood vessel <5mm, tumours not recommended for surgery by transperitoneal LPN.

Patients unfit for surgery

Underlying diagnosed coagulopathy

Uncontrolled hypertension

Patients with obstructive kidney stones

Documented previous hypersensitivity to bovine derived products

Patients that refuse to sign the informed consent

Patient recruitment

Any member of the urologist team at the hospitals participating in the study will be involved in patient recruitment. Before the patient reads and signs the informed consent document, all possible complications related to the surgery should be explained and ensured they are understood by the patient. The patient should also be reminded that medical care will be assured, regardless of the study.

Sample recruitment estimation

PNs are performed at high-volume hospitals (over 1000 beds). There are currently 17 hospitals with these characteristics in Spain. According to a member of the Urological team(21) of the Carlos Haya Hospital in Malaga, an average of 35 PNs are performed each year. Around 16 of these are done laparoscopically by a transperitoneal approach. Extrapolating from this figure we can hypothesise a similar number of interventions at other high-volume hospitals in Spain. This would mean an approximated average of 272 LPNs performed each year in the Spanish NHS. We hypothesise a total of 25% of the population will not meet the inclusion criteria or will refuse to participate. Similarly, population drop out has been estimated at 10% during follow up. The following flowchart is an estimation of population distribution during the study.

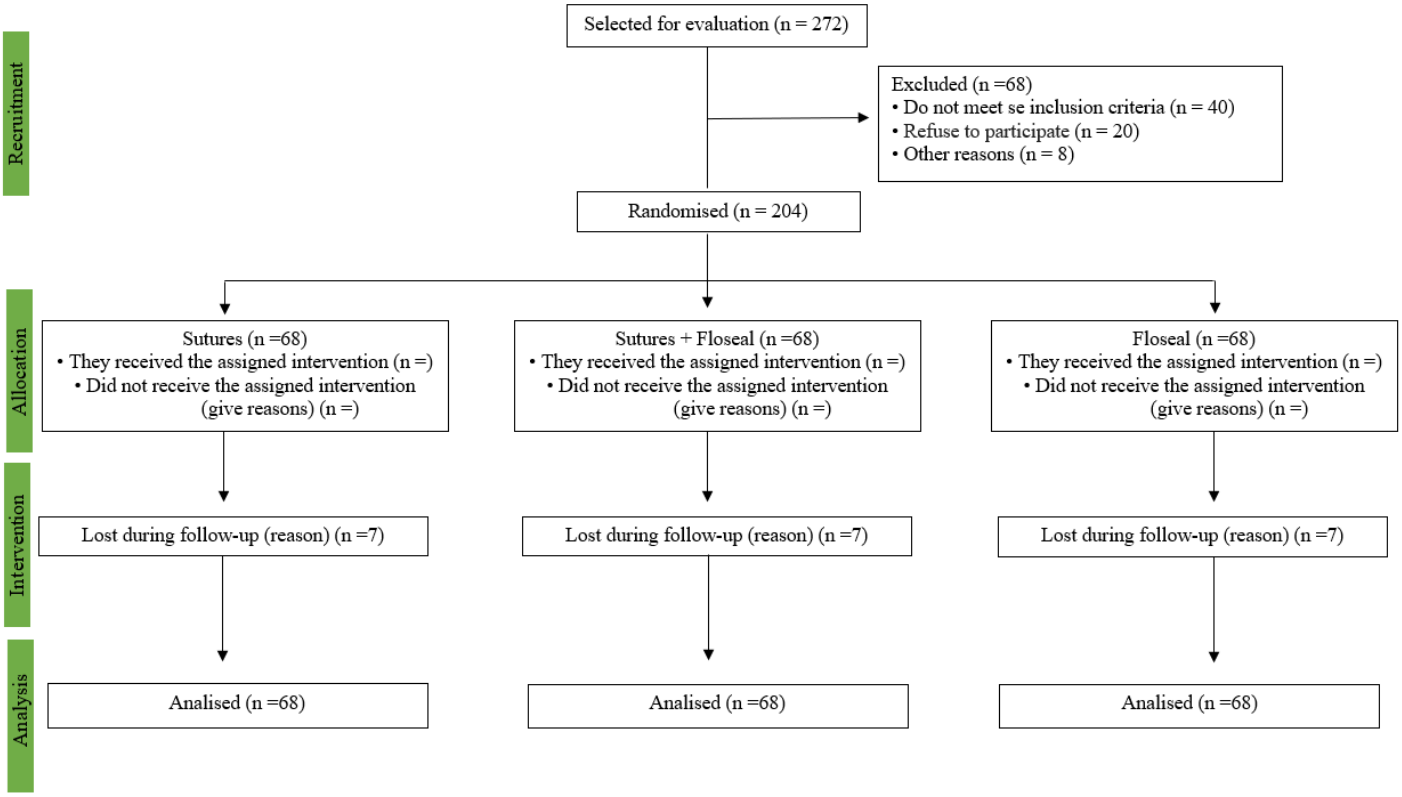

Figure 1. Study flowchart

Study variables

Dependent variables

Primary dependent variable. Warm ischemia time (WIT) (minutes).

Secondary dependent variables:

- Time until complete haemostasis after tumour excision (seconds).
- Presence of haemorrhagic related complications (Yes: severity of complications evaluated using the Clavien-Dindo scale (CDS), (full table in Appendix 3), if transfusions required (number) if re-intervention is required (reason) or no).
- Blood loss calculated by change in haemoglobin level (Hb (gr/dL): (Hb = preoperative Hb – postoperative Hb).
- Kidney function loss, calculated as the difference between theoretical postoperative eGFR and the actual postoperative eGFR (kidney function loss = theoretical – actual). This will differentiate between surgical related renal function loss from that due to volume reduction. The eGFR (mL/min/1.73 m^2) will be obtained from serum creatine levels (Scr) (mg/dL) with the IDMS-traceable MDRD study equation (GFR (mL/min/1.73 m2) = 175 × (Scr)-

1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American).). Conversely, theoretical postoperative renal function will be calculated by: theoretical postoperative renal function = preoperative eGFR x ((percentage of residual kidney after tumour extraction + 100)/2).

- Presence of tumour recurrence (yes or no)

Independent variables

Primary independent variable. Method of haemostasis used: S+F, S or F

- Group S+F (Suture + Floseal). Bipolar coagulation of the excised tumour bed, followed by renal defect closure using continuous vicryl 2/0 associated with two hemo-locks placed on the proximal edge of the suture. After the continuous suture is completed tension should be maintained by addition of two hemo-locks. Once suturing of the renal defect is completed 10ml of Floseal® shall be placed over the sutures.
- Group S (Suture). Bipolar coagulation of the excised tumour bed followed by renal defect closure using continuous vicryl 2/0 associated with two hemo-locks placed on the proximal edge of the suture. After the continuous suture is completed tension should be maintained by addition of two hemo-locks.
- Group F (Floseal). Bipolar coagulation of the excised tumour bed followed by renal defect coating with 5ml of Floseal®. Following renal reperfusion, a second layer of 5ml of Floseal® shall be placed.

Secondary independent variables. Factors related to the patient (demographic characteristics, previous medical history and baseline blood results), tumour characteristics, surgical procedure related variables and hospital characteristics will be analysed to assess their potential influence on the dependent variables (Table 1).

Table 1. Secondary independent variables

Secondary independent variable categorization	Secondary independent variables	Categories or Units
Demographic characteristics	Age	Years
	Sex	Male / female
Previous medical history	BMI	kg/m^2
	Eastern Cooperative Oncology Group (ECOG) score. (Full table in appendix 1)	0/1/2/3/4
	Hypertension	Yes / no
	Charleson comorbidity index score (CCI) (Full table in appendix 2)	0/1-2/3-5/>5
Baseline blood results	Blood Haemoglobin	g/dL
	Kidney function: Serum Cr eGFR	 mg/dL mL/min/1.73 m^2
	Coagulation: Platelet count Prothrombin time Activated partial thromboplastin time	 plaq/ uL Seconds Seconds
Tumour characteristics	Tumour size	Centimetres
	Tumour site	Upper pole / Mid pole / Lower pole
	Tumour location	Perihilar / Anterior surface / Posterior surface / Medial margin / Lateral margin
	Tumour R.E.N.A.L. nephrometry score (Full table in appendix 4)	4-12 nephrometry score
	Tumour staging by TNM classification (Full table in appendix 5)	Low grade (1-2) High grade (3-4)
Surgical complications	Lumbar vessels rupture	Yes / no
	Closure of collecting system required	Yes / no
	Percentage of residual kidney after tumour extraction	Percentage (%)
	Re-intervention due to positive margins	Yes / no
Hospital characteristics	Number of partial nephrectomies performed at the Hospital each year	>30 high volume centre <30 low volume

Data collection

Data will be collected by the urologist and anaesthesiologist in charge of the patient using the specifically designed online forms at different stages of the study (see table 2 and 3). The anaesthesiologist will fill in a preoperative form while all other information will be registered by the urologist. All information registered online will automatically be download to the database in the central office in Barcelona.

Two weeks before surgery (preoperative)

The urologist will use the radiologist's report to describe tumour characteristics and hospital records to define the hospital characteristics. A signed copy of the informed consent will also be included when completing the online preoperative form. In the anaesthesiologist's preoperative form, information from: physical examination, blood test results and patient's medical history will be registered online. Any missing information that cannot be retrieved from the patient's medical history should be obtained during the preoperative visit. After both preoperative forms have been filled in the patient will be randomly allocated into an intervention group. Random allocation is computer generated.

Table 2. Blood test and imaging techniques performed at each stage of the study

Time:	1 week before preoperative visit	Postoperative (48h after surgery)	1 month follow up	3 month follow up	6 month follow up	12 month follow up	18 month follow up
Coagulation parameters	X						
Blood haemoglobin	X	X	X	X			
Kidney function	X	X	X	X	X		
Extensive blood test (CBC, SCh, LFT)						X	X
Abdominal US		X	X	X		X	X
Chest X-ray							X
Abdominal contrast-enhanced CT	X					*	*

eGFR: Estimated glomerular filtration rate / US: Ultrasound / CT: Computerised tomography / CBC: Complete blood count / SCh: Serum chemistry / LFT: Liver function tests / * Performed only when tumour recurrence is suspected

Blood tests
Imaging techniques

During/after surgery (perioperative)

All surgical times will be recorded by a theatre nurse in close communication with the surgeon. Arterial clamping time (WIT) will be recorded from the moment the bulldog clamp is placed and until it is removed. Recording of time until complete haemostasis after tumour excision will be done using a stopwatch. The stopwatch should be started the moment bipolar coagulation of the excised tumour bed begins. Once the surgeon believes complete haemostasis has been achieved, the theatre nurse should be asked to pause the stopwatch. If further haemostasis is necessary after clamp removal, the surgeon will inform the theatre nurse to restart the stopwatch until haemostasis of the tumour bed has been fully achieved. Percentage of residual kidney after tumour extraction will be estimated by the surgeon and two operating

room assistants following previous study practice performed by Hung et al (17). After the operation, the surgeon will input all data into the perioperative online form.

Until hospital discharge (postoperative), 1 and 3 month follow up

Blood results will be registered to monitor patient recuperation along with a clinical evaluation aided with the use of an abdominal ultrasound to determine if there is presence of haemorrhagic complications. When complications are present, scoring according to the CDS should be performed and registered online. The preoperative form will also include the pathologist report describing anatomopathological tumour required information.

** If the patient returns to hospital before one month, an extra follow up form will be filled in online. If reintervention is required, extra preoperative, perioperative and postoperative forms should also be filled in.*

6 month follow up

Only blood results regarding kidney function will be registered.

Table 3. Monitoring of variables at each stage of the study

Time: / Variables:	Preoperative	Perioperative	Postoperative (48h after surgery)	1 month follow up	3 month follow up	6 month follow up	12 month follow up	18 month follow up
Patient, tumour and hospital characteristics	X							
Surgical independent variables		X						
WIT		X						
Time until complete haemostasis after tumour excision		X						
Presence of haemorrhagic complications		X	X	X	X			
Blood loss			X	X	X			
Kidney function			X	X	X	X		
Tumour Recurrence							X	X

WIT: Warm ischemia time / Patient characteristics includes (demographic, previous medical history and baseline blood results)

Secondary independent variables
Dependant variables

12 and 18 month follow up

To facilitate tumour recurrence evaluation, blood tests performed during the 12 and 18 month follow up visits should be more extensive, including complete blood count, serum chemistry and liver function. Blood results along with an abdominal ultrasound will be used to determine tumour recurrence; if suspected, a high resolution contrast-enhanced computed tomography

should be performed. During the 18 month follow up, following standard follow up recommendations regarding tumour recurrence evaluation (22), a chest-X-ray report will also be registered. Standard recommendations require image evaluation 24 months after surgery, however, due to time limitations, such control will be performed at 18 months. After this point, patients will be discharged from the study and sent to their primary doctor for posterior follow up.

Instruments for data collection

The following forms will be used for data collection at the different stages of the study:

- Urologist preoperative form includes:
    - Signed informed consent
    - Tumour characteristics
    - Hospital characteristics
- Anaesthesiologist preoperative form includes:
    - Patient demographic characteristic
    - Previous medical history
    - Baseline blood results, ensuring correct control of coagulation and blood tension.
- Urologist perioperative form includes:
    - Method of haemostasis used
    - WIT
    - Time until complete haemostasis after tumour excision
    - Presence of haemorrhagic related complications evaluated using the CDS
    - Surgical complications independent variables
- Urologist postoperative form includes:
    - Blood loss evaluation
    - Kidney function evaluation
    - Presence of haemorrhagic related complications evaluated using the CDS
    - Anatomopathological tumour analysis

- 1 and 3 month follow up forms includes:
    - Blood loss evaluation
    - Kidney function evaluation
    - Presence of haemorrhagic related complications evaluated using the CDS

** If patient returns to hospital before one month, an extra follow up form will be submitted, evaluating: blood loss, kidney function and presence of haemorrhagic complications. If reintervention is required, extra: preoperative, perioperative and postoperative forms should also be submitted.*

- 6 month follow up form:
    - Kidney function evaluation
- 12 and 18 month follow up form:
    - Tumour recurrence

Sources of data

- Contrast-enhanced computerised tomography (CT)
- Radiologist report
- Patient medical history
- Blood tests
- Sphygmomanometer
- Stopwatch
- Abdominal ultrasound
- Histopathological analysis by pathologist
- Chest X ray

Data analysis

Data analysis will be performed by intention to treat (ITT). Patient group allocation will be maintained even if changes in treatment procedures or during follow up occur. Three groups will be analysed according to the intervention: S+F) sutures+ Floseal®, S) suture, F) Floseal®. Statistical analysis will be performed using IBM SPSS 22.12 (New York, USA).

Firstly, a descriptive analysis of all variables will be performed. Continuous variables will be expressed as mean and standard deviation and categorical variables as frequencies and percentages.

To answer study objectives, the main analysis will be first to determine differences in WIT between interventions evaluating significance using an analysis of variance (ANOVA) test. Secondly, mean values for continuous dependent variables (time until complete haemostasis after tumour excision, change in blood haemoglobin level and actual postoperative kidney function in relation to the theoretical postoperative value) will also be compared between intervention groups using the same test.

Frequency of haemorrhagic complications classified by the CDS and tumour recurrence in each intervention group will be evaluated using the chi^2 (X^2). We hypothesise that >25% of calculations will include less than five individuals (tumour recurrence and haemorrhagic complications are low) therefore a Fisher's exact test will also be implemented(23).

To analyse which factors have potentially influenced results, a logistic regression assessing the relationship with each dependant variable will be performed for categorical variables (patient demographic characteristics, previous medical history, tumour characteristics aside from size and nephrometry score, hospital characteristics and surgical complications). While a linear regression will be used to analyse the effect of continuous variables (baseline blood results, tumour size and nephrometry score). Results obtained will be expressed as odds ratio and a 95% confidence interval.

Activity timeline

Study preparation (1st month)

The research team will elaborate on the informed consent and online data collection forms under supervision by project investigator. The IT technician will finalise the online data collection program and verify access restrictions. The project manager will manage the formation of a data quality control board. The board will be consisted of researchers and urologists with no direct relation with the study. Following this, selection of the hospitals participating in the study will be performed. Informed consent and follow up

forms should be validated by the head of urology, anaesthesiology and the ethical committee at each hospital. During hospital inclusion a detailed explanation of the surgical procedure and methods for data collection will be done using an online video for all members participating in the study. Any desired variations by the selected hospitals with the coordinator will be discussed during this time allowing for a finalisation of the informed consent, follow up forms and surgical materials.

Data collection (2nd – 32nd month)

Patient recruitment (2nd- 14th month)

There will be a twelve-month patient recruitment period. Urologist teams at each hospital included in the study will offer study participation to those patients suited to the inclusion and exclusion criteria. A detailed verbal explanation will be given to those patients who wish to join the study ensuring their understanding of the process along with a written copy. Each patient recruit will be finalised with a signing of the informed consent.

Intervention (2nd- 14th month)

There will be a preoperative visit with anaesthesiologist two weeks prior to surgery. Patients will then be randomly allocated into one of the three interventions (S+F, S or F). During surgery post-excisional haemostasis will be done according to the assigned intervention group. All postoperative data will be recollected before the patient is discharged from the hospital.

Follow up (3rd - 32nd month)

- 1, 3, 6, 12, 18 month follow up tests will be performed.

º See data collection section (page 17) for a description of required data during each follow-up stage

Data analysis (3rd - 35th month)

Research team will begin the data analysis. Periodical reports (every two months) will be sent to the data quality board.

Data quality monitoring

The data quality board will analyse the reports and determine the continuity of the study evaluating the risk/benefit ratio of each intervention.

Data discussion

Teleconferences will take place between the head of urology at each hospital and the coordinator for observations and data discussion. Initial presentation of results will be sent out

to the hospitals to allow for feedback. Final research document with conclusions will be prepared. There will then be a final meeting inviting heads of department at each centre to discuss results and finalise the publishing proposal.

Results dissemination (35th – 36th month)

Study results will be shared through publications and presentations at meetings and conference

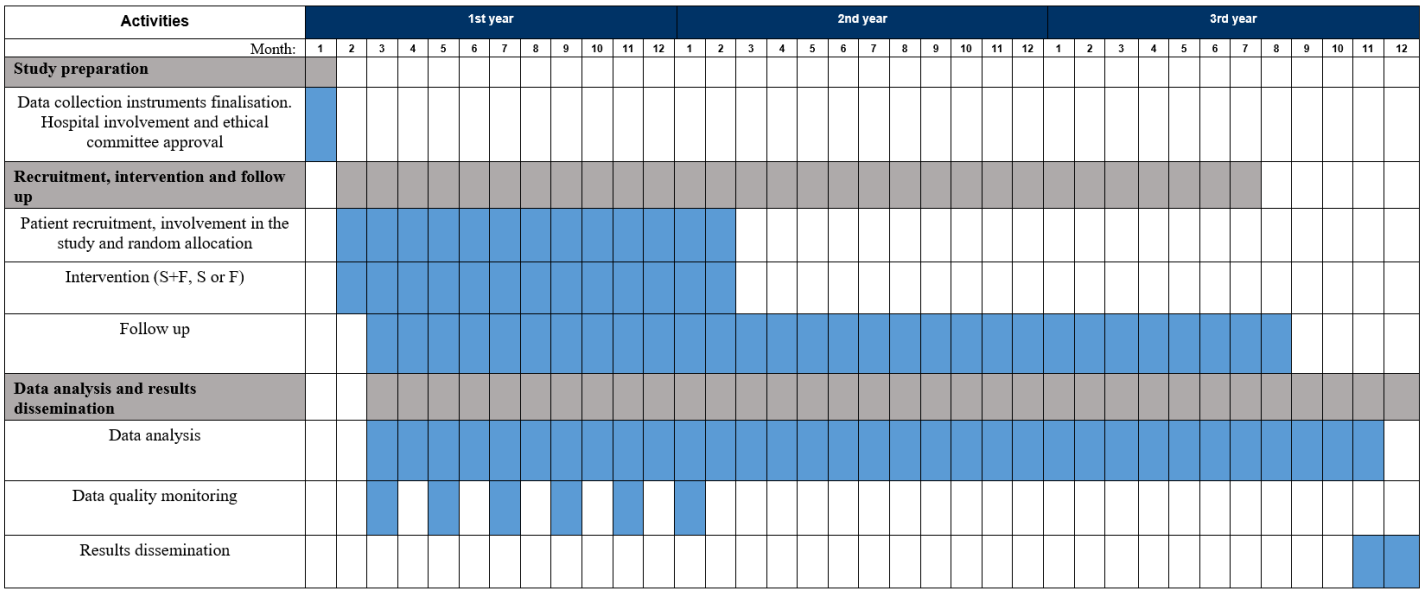

Figure 2. Timeline of activities.

References

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Study limitations

The primary limitation of the study will be to obtain sufficient population to make data comparison between groups significant since LPNs are only performed in specialised hospitals. For this reason, it is considered that a 5-year study could allow for a longer recruitment period and therefore increase the study population number. Furthermore, it could be possible that patient recruitment is lower or loss at follow up is greater than initially estimated. This would further diminish the statistical power of the results. Even so, to our knowledge there is no other study with these characteristics, thus maintaining the potential to act as a pilot study to continue investigations for suture-less LPN.

Another limitation regarding the multicentre approach is the difficulty of maintaining equal conditions between all interventions. Although the figure of the coordinator and the detailed description of the procedure is intended to diminish such risk, it is still present.

Economic standpoint has not been taken into consideration, it is understandable that the standardised use of a haemostatic agent may be frowned upon by hospital managers, however, we believe that costs will be counteracted by reducing surgical times, patient benefit or even hospital stay. A follow up study evaluating cost-effectivity would contribute to obtaining a greater impact of the study results. We also believe that by increasing the use and demand for these products, manufacturing costs will lower and therefore, increment availability.

On the other hand, we are aware that there are several haemostatic agents available on the market. It may be possible that a product with similar characteristics but with a lower price is available. If the results of our study were confirmed, we believe a follow up study comparing different sealants would further power the results of our study. This would ensure a wider acceptance of this new treatment procedure.

With regards to tumour recurrence, the median appearance is around thirty-nine months (22). As the follow up protocol of this study only reaches eighteen months it is likely that results will not be able to confirm that the method of haemostasis does not interfere with tumour recurrence. Although no previous study specifies that this risk exists, we believe that any study involving malignant growths should verify safety with regards to this aspect(17).

Finally, LPN is a complex surgery currently only available at high volume hospitals. This has a slight limit on the potential impact of our findings, as direct implementation on small services is unlikely. However, we must take into consideration that if suture less-LPN for SMRs is proven to obtain better results, this will slowly increase its availability, by decreasing the learning curve for the procedure.

Ethical implications

This study will be performed according to the primary ethical considerations written in the Helsinki declaration along with the revised and accepted procedures for good medical practice. Like any randomised controlled trial in Spain, the trial will begin once acceptance on behalf of the Spanish drug agency has been granted. The study will be evaluated by the ethical committee at each urological service included in the study allowing for any queries or doubts to be discussed with the coordinator.

Patients diagnosed with SMRs at any urological services that perform LPNs will be explained the existence of the study, offering the possibility to participate. Patients interested in joining the study will receive a verbal explanation of the aim and process of the study. This should include an explanation of the possible side effects, ensuring that these are understood by the patient. Patients will be allowed to enter and leave the study at their own free will without being sanctioned in any way and this should be clearly stated on the informed consent form. It should also be clear to the patient that even if study drop out occurs, medical assistance will be maintained.

After all information has been verbally transmitted to the patient, they will be asked to read and sign the informed consent form. The form will include all aspects previously explained to the patient. Informed consent forms will be written according to standardised norms written in the Helsinki declaration as well as current legislations.

Regarding patient data confidentiality, only doctors responsible for each patient and final investigators will have access to the information. Doctors will be allowed to access information regarding their own patients but not the whole study database. All workers who will at some point access the database or be part of the study will be asked to sign a collaboration agreement.

In this form, investigators agree to obey the standard ethical and good medical practice norms of the study, along with a confidentiality agreement according to established European Union laws.

Research team

This study requires an experienced multidisciplinary team composed of health care professionals, researchers, lab workers, IT technicians, and administrators. The principal investigator will ensure every member of the study team has correct and clear understanding of their task. The coordinator will oversee all urological services involved in the study, ensuring investigation is performed according to study protocol.

The IT technician will create and manage the online database. Informed consent along with follow up forms will be drafted by the study coordinator and sent out to the various services for analysis and validation by the urologist and anaesthesiologist participating in the study. Administrators will maintain communication between hospitals and the coordinator.

The urologist and anaesthesiologist will obtain blood analysis results from lab workers. Hospital radiologists will stratify patient cTNM. WIT and time until complete haemostasis of the renal bed will be recorded by the theatre nurse in communication with the operating surgeon. The theatre nurse should be specialised in surgery and understand how the stopwatch functions. All other operative data will be obtained by the surgeon.

Patient postoperative data will be collected from patient medical history, image analysis and blood results. Tumour analysis will be done by the hospital pathologist. All required patient data will be used to fill in the online forms.

The research team and quality monitoring board will include doctors, nurses, epidemiologist and statisticians. Data analysis, quality confirmation and result description will be performed in collective meetings with the aid of the project investigator. Final study writing will be performed by the research team, coordinator and project investigator at the head offices in Barcelona. All doctors involved in the study will be asked to attend a final evaluation session to expand on the results of the study.

Results and potential impact

Result. One method of haemostasis will obtain a reduction in WIT during partial nephrectomy. If the study proves the improvement of one intervention over the others, this will influence standard practice when approaching haemostasis after excision of SMRs.

Indicator. Primarily WIT and secondly: time until complete haemostasis after tumour excision, presence of haemorrhagic complications, blood loss and change in renal function and tumour recurrence

Benefit:

- ***For the patient***: Reducing WIT will diminish ischemic insult on the kidney during the surgery. This would correlate with a faster recovery after the operation, reduce the risk of severe acute kidney disease and improve overall well-being of the patient. For patients with pre-established medical renal function loss there would be an even greater benefit, as in these cases the risk of postoperative kidney disease is much higher. It can also be hypothesised that by using a faster method of haemostasis, less blood loss will occur, decreasing the number of haemorrhagic related complications and the need for transfusions. Furthermore, as it has been stated that haemostatic agents maintain tissue anatomy better than sutures, decreasing the overall impact of the surgery on the patient.
- ***For the surgeon***: By avoiding the need to suture, LPN will become more available to less experienced surgeons, as this will shorten the learning curve of the procedure. Another worry for the surgeon performing PN is WIT. Doctors are aware of the risk that WIT can have for the kidney. Therefore, if the feasibility of using Floseal® as the sole method of haemostasis increases, this will also allow the surgeon to approach the surgery with more confidence. Finally, it has been proven that PN continues to be an underused technique, consequently, we believe it is of vital importance to investigate into potential interventions that will increase its use.
- ***For the hospital***: If postoperative complications are diminished, patient hospital discharge will be faster and less patients will return to hospital contributing to a reduction cost. We are aware of the cost of Floseal®, but we believe this will be counteracted by reducing cost in other areas. By increasing the availability of the surgery, the urologist teams will be able to reduce the number of radical nephrectomies and therefore improve their standards of care.

Abbreviations

BMI: body mass index

CCI: Charlson comorbidity index

CDS: Clavien-Dindo scale

CKD: Chronic renal disease

CT: Computerised tomography

ECOG: Eastern Cooperative Oncology Group

eGFR: Estimated glomerular filtration rate

F: Floseal®

Hb: Haemoglobin

LPN: Laparoscopic partial nephrectomy

MDRD: Modification of Diet in Renal Disease

NHS: National Health System

PN: Partial nephrectomy

RN: Radical nephrectomy

S + F: Suture plus Floseal®

S: Suture

Scr: Serum creatine

SMRs: Small renal mases

WIT: Warm ischemia time

Appendix 1: ECOG performance status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Table developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair, Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group.*Am J Clin Oncol.* 1982;5:649-655.

Appendix 2: Charlson commodity index

Assigned weights to each relative risk of death for each chronic condition (Cohesca Study, 1994–1998)

RR	Assigned weight	Men	Women
<1.1	0	Hypertension	Hypertension
		Arthrosis	Varicose veins
		Allergy	Arthrosis
		Peptic ulcer	Allergy
		Urinary diseases	Asthma
		Skin conditions	High cholesterol
		Constipation	Cataracts
			Depression
1.1–1.49	1	Hearth diseases	Hearth diseases
		Varicose veins	Bronchitis
		Asthma	Peptic ulcer
		Bronchitis	Skin conditions
		Diabetes	Constipation
		High cholesterol	
		Depression	
1.50–2.49	2	Cataracts	Diabetes
		Stroke	Urinary diseases
2.50–3.49	3		Stroke

Mortality according to comorbidity index categories. [Relative Risks (RR) and 95% Confidence interval (95% CI); Cohesca study, 1994–1998]

	Men (n = 3105)		Women (n = 3536)	
	RR[a,b]	95% CI	RR[a,b]	95% CI
Comorbidity Index				
0	1.0		1.0	
1–2	1.02	0.74–1.41	0.83	0.56–1.24
3–4	1.51	1.0–2.30	1.72	1.08–2.72
>=5	2.65	1.43–4.89	2.65	1.48–4.77

[a] RR Adjusted by social class, smoking habit, alcohol consumption, physical activity, and self-perceived health.

[b] Likelihood ratio test, $\chi^2_{men} = 11.835$, $df = 1$, $P < .0001$; $\chi^2_{women} = 17.557$, $df = 1$, $P < .00001$.

Both tables have been obtained from: Rius C, Pérez G, Martínez JM, Bares M, Schiaffino A, Gispert R, et al. An adaptation of Charlson comorbidity index predicted subsequent mortality in a health survey. J Clin Epidemiol. 2004;57(4):403–8.

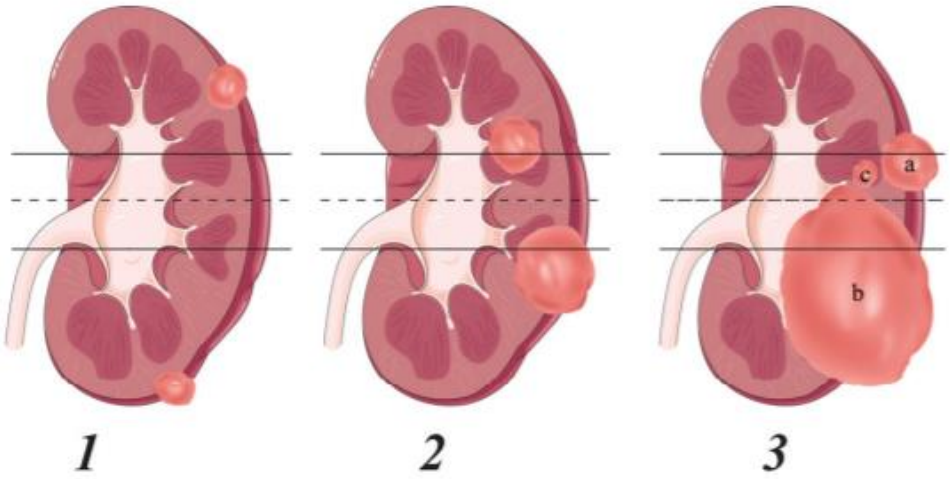
Appendix 3: Clavien-Dindo complication severity classification

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade IIIa	Surgical, endoscopic, or radiological intervention that is not under general anesthesia
Grade IIIb	Surgical, endoscopic, or radiological intervention that is under general anesthesia
Grade IVa	Life-threatening complication requiring intermediate care or intensive care unit management, single organ dysfunction (including dialysis, brain hemorrhage, ischemic stroke, and subarrachnoidal bleeding)
Grade IVb	Life-threatening complication requiring intermediate care or intensive care unit management, multi-organ dysfunction (including dialysis)
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication

This table has been obtained from: Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–213

Appendix 4: R.E.N.A.L. nephrometry score

	1pt	2pts	3 pts
(R)adius (maximal diameter in cm)	≤4	>4 but < 7	≥ 7
(E)xophytic/endophytic properties	≥ 50%	<50%	Entirely endophytic
(N)earness of the tumor to the collecting system or sinus (mm)	≥7	>4 but <7	≤4
(A)nterior/Posterior	No points given. Mass assigned a descriptor of a, p, or x		
(L)ocation relative to the polar lines* * suffix "h" assigned if the tumor touches the main renal artery or vein	Entirely above the upper or below the lower polar line	Lesion crosses polar line	>50% of mass is across polar line (a) or mass crosses the axial renal midline (b) or mass is entirely between the polar lines (c)



The tables have been obtained from: Kutikov A, Uzzo RG. The R.E.N.A.L. Nephrometry Score: A Comprehensive Standardized System for Quantitating Renal Tumor Size, Location and Depth. J Urol [Internet]. 2009;182(3):844–53. Available from: http://dx.doi.org/10.1016/j.juro.2009.05.035

Appendix 5: TNM renal tumour classification

Primary tumor			
TX: Primary tumor cannot be assessed			
T0: No evidence of primary tumor			
T1a: Tumor ≤4.0 cm and confined to the kidney			
T1b: Tumor >4.0 cm and ≤7.0 cm and confined to the kidney			
T2: Tumor >7.0 cm and confined to the kidney			
T3a: Tumor invading adrenal gland or perinephric fat but not beyond Gerota's fascia			
T3b: Tumor extends into the renal vein (or its segmental branches) or vena cava below diaphragm			
T3c: Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava			
T4: Tumor invades beyond Gerota's fascia			
N: Regional lymph nodes			
NX: Regional lymph nodes cannot be assessed			
N0: No regional lymph node metastasis			
N1: Metastasis in a single regional lymph node			
N2: Metastases in more than one regional lymph node			
M: Distant metastases			
MX: Distant metastasis cannot be assessed			
M0: No distant metastasis			
M1: Distant metastasis present			
Stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2 T3	N1 N0 or N1	M0 M0
Stage IV	T4 Any T Any T	Any N N2 Any N	M0 M0 M1

This table has been obtained from: Heldwein F, McCullough T, Souto C, Galiano M, Barret E. Localized renal cell carcinoma management: an update. Int Braz J Urol 2008; 34(6):676-90

Appendix 6: Study procedure specifications

Preoperative procedure

Anaesthesiologist should book all blood tests a week before preoperative consultation. This will ensure availability of all results during the visit. Patients with altered coagulation will be sent to the haematologist for management. Patients with anticoagulant or anti-aggregation treatments these will be stopped 7 days prior to surgery, blood controls must be performed to ensure normalised coagulation parameters. Patients with anticoagulation will be changed to low molecular weight heparin. With regards to hypertension, it is important to perform treatment modifications to ensure correct levels, patients with uncontrolled comorbidities will not undergo surgery

Both the urologist and the anaesthesiologist should remind patients that they must remove hair over surgical area, use evacuation enemas prior to surgery, and receive antibiotic and antithrombotic prophylaxis.

Surgical technique

All selected patients will undergo surgery by a laparoscopic transperitoneal approach. Only study approved surgical equipment will be used during interventions. Prior to starting, a renal catheter will be placed so that any collecting system leakages can be identified after tumour excision. All patients shall be placed in lateral decubitus, opposite to that of the affected kidney.

Initial mini-laparotomy will be performed, followed by laparoscopic port placement under camera vision. Total operation time shall be recorded by a theatre nurse from the moment the camera is introduced into the peritoneum. Pneumoperitoneum should be at a 15mmhg with a recap pressure of 30mmhg. Four ports will be placed, one 10-12mm camera port, one 15mm, and two 5mm ports. Laparoscopic port modifications are permitted if required by patient characteristics. When performing right sided access it is recommended to use an accessory port for hepatic displacement.

Upon access, it is recommended to detach any intestinal adhesions present. Organ shifting must be performed for correct access to retroperitoneum. For right sided approach, Kocher duodenum separation should be implemented. Initial kidney dissection should be performed before attempting to reach the hilum. It is essential to avoid damaging any lumbar vessels to

ensure correct visibility during dissection and minimise blood loss, rupture of these should be noted. Gerota's fascia is then dissected from the renal surface, peri-tumour fat should be maintained to ensure all tumorous cells are removed. We recommend dissection of the renal hilum with the suction canula, this allows for an atraumatic approach, diminishing the risk of bleeding. Once the hilum is fully dissected and the renal artery is located, an assistant should begin the preparation of the Floseal® matrix if needed.

Prior to clamping, 20mg of mannitol will be infused into the patient. Selective arterial clamping is done by use of bulldog clamp (Aesculap-Braun, Tuttlingen, Germany) introduced through laparoscopic 15mm port. Arterial clamping time (WIT) will be recorded by the same theatre nurse from the moment the bulldog clamp is released. Following arterial clamping, tumour excision using scissors should performed, ensuring a 0.5cm margin between the tumour and healthy renal tissue. Intraoperative samples are sent to the pathologist to ensure negative margins.

Tumour will be collected using an Endocatch II bag (U.S. Surgical, Norwalk, Connecticut) for posterior extraction. Blue dye should then be injected thorough the renal catheter to ensure collecting system is still intact. If collecting system is accessed, suturing must be performed to ensure closure using 3/0 polyglactin continuous running suture. Once collecting system closure is ensured, haemostasis of excised tumour bed can commence.

Before starting, the surgeon must indicate to the theatre nurse when haemostasis of the renal bed will begin. The theatre nurse will use a stopwatch to record the time until complete haemostasis after tumour excision. The stopwatch should be started the moment bipolar coagulation of the excised tumour bed begins. Tumour bed haemostasis will be done according to patient group allocation: S+F, S, or F. This is the only step that should vary between patients. Once the surgeon believes complete haemostasis has been achieved, the theatre nurse should be informed to pause the stopwatch.

Removal of the bulldog clamp should be done under close supervision of the surgical bed to ensure there are no areas of bleeding that requiring further haemostasis. The theatre nurse should record WIT from the moment the bulldog clamp is released. If further haemostasis is necessary, the surgeon will inform the theatre nurse to restart the stop watch. Once bleeding is

controlled, the theatre nurse should make a note of the total time until complete haemostasis after tumour excision.

Once correct haemostasis is ensured Endocatch II bag can be extracted through a 2-3cm amplified port. At this point total surgical time can be recorded. It is important that there is close communication between surgeon and theatre nurse, this will ensure precision when recording WIT, time until complete haemostasis after tumour excision and total surgical time. When pathologist has confirmed negative margins, laparoscopic exit can begin, drainage pumps placed and skin closure with sutures and staples.

After the operation, the surgeon will fill in all required information to the perioperative online form. It is important to identify and notify investigators regarding patients in which there has been a need for reintervention making a note of the reason for this.

Specifications created by the project investigator based on current recommended LPN procedures: 1. GILL I, DESAI M, KAOUK J, MERANEY A, MURPHY D, SUNG G, et al. Laparoscopic Partial Nephrectomy for Renal Tumor: Duplicating Open Surgical Techniques. J Urol [Internet]. 2002;167(2):469–76. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0022534701690669

Appendix 7: Patient follow up checklist

- 1 and 3 month follow up:
    - Physical examination
    - Recording of any complications the patient may have encountered in the first month after surgery
    - Blood test
        - Haemoglobin levels
        - Creatine levels
        - eGFR
    - Renal ultrasonography to evaluate presence of:
        - renal haematoma
        - pseudoaneurysms

* SPECIAL NOTE: if patient returns to the hospital before the one-month follow-up, a second postoperative sheet must be filled in completing all previous parameters except for tumour characteristics.

- 6 month follow up:
    - Physical examination
    - Blood test
        - Creatine levels
        - eGFR

- 12 month follow up:
    - Physical examination
    - Extended blood test including:
        - Complete blood count
        - Serum chemistry
        - Liver function test
    - Renal ultrasonography to evaluate presence of:
        - Tumour recurrence
            - If suspected: high definition CT scan must be performed

- 18 month follow up:
    - Physical examination
    - Extended blood test including:
        - Complete blood count
        - Serum chemistry
        - Liver function test
    - Renal ultrasonography to evaluate presence of:
        - Tumour recurrence
            - If suspected: high definition CT scan must be performed
    - Chest X ray

Protocol created by study coordinator based on follow-up guideline for renal tumours after PN: Kassouf W, Siemens R, Morash C, Lacombe L, Jewett M, Goldenberg L, et al. Follow-up guidelines after radical or partial nephrectomy for localised and locally advanced renal cell carcinoma. 2009;3(1):1–4.