Official Title: Evaluation of the Off-Clamp Robot-Assisted Partial Nephrectomy Technique in the Management of Renal Tumors

NCT Number: NCT01732120

Document date: 01 May 2015

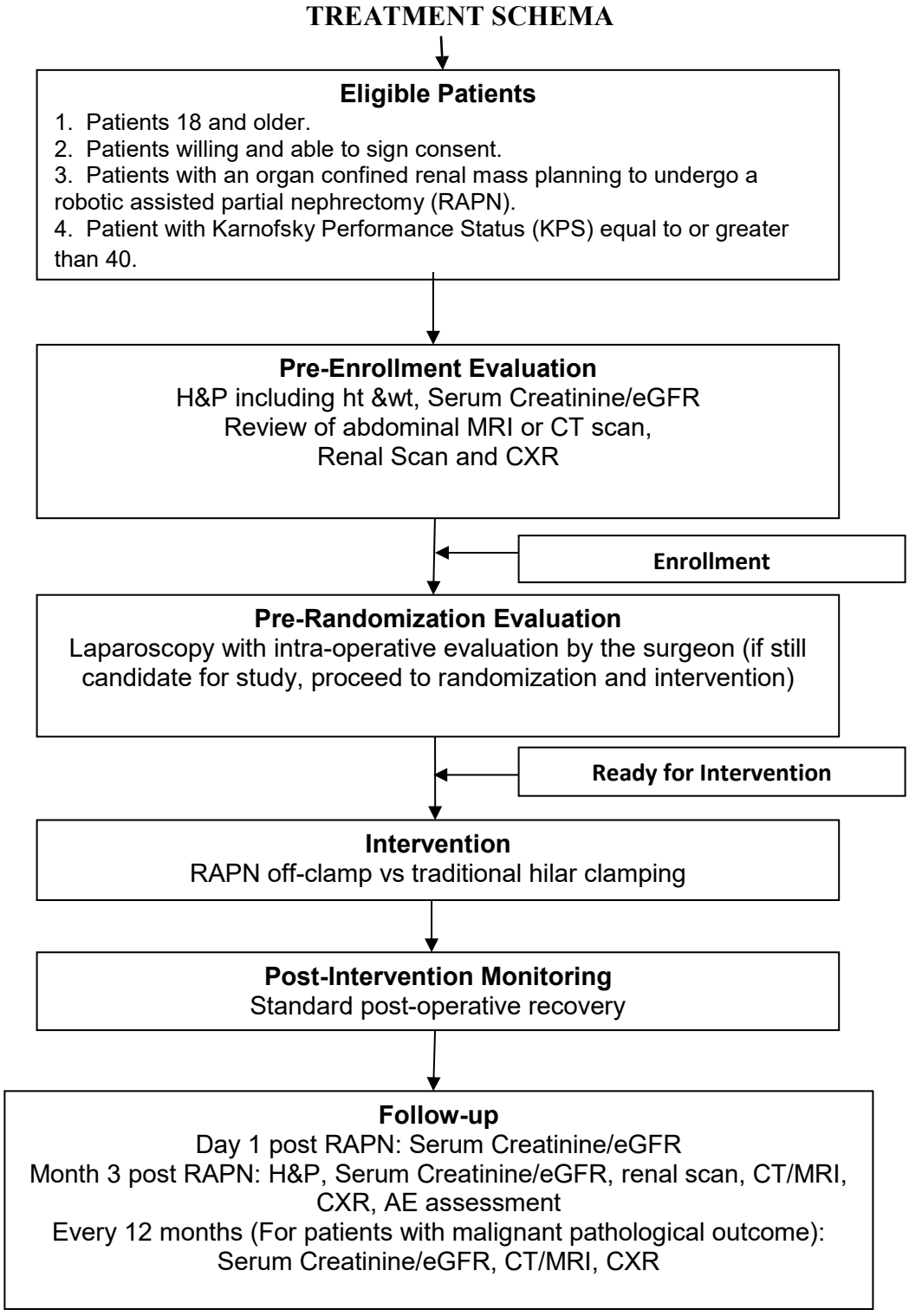
Evaluation of the Off-Clamp Robot-Assisted Partial Nephrectomy Technique in the Management of Renal Tumors

Washington University School of Medicine
Department of Surgery
660 S. Euclid Ave., Campus Box 8109
St. Louis, MO 63110

Protocol v6
Version date: 05/01/15

Principal Investigator: R. Sherburne Figenshau, M.D.
Phone: (314) 454-2235
Email: figenshaur@wudosis.wustl.edu

Evaluation of the Off-Clamp Robot-Assisted Partial Nephrectomy Technique in the Management of Renal Tumors



Evaluation of the Off-Clamp Robot-Assisted Partial Nephrectomy Technique in the Management of Renal Tumors

1.0 BACKGROUND AND RATIONALE

1.1 Study Disease

Due in part to the widespread use of abdominal imaging procedures, the incidence of renal tumors has incremented exponentially over the last several decades [1]. The National Cancer Institute estimates the incidence of new cases of renal cell carcinoma in 2011 at 60,920 [2]. The increasing detection of incidental small renal masses on abdominal imaging has been accompanied by a clear downward stage migration, such that by 2007, close to 60% of renal tumors measured < 4 cm [3, 4]. Indeed, about 50% of the patients referred to urologists today for suspected renal malignancy have incidentally discovered asymptomatic small renal masses [5].

Importantly, the highest incidence of these tumors is seen in elderly patients, who usually present with a number of comorbidities[6]. In treating patients with renal masses, three competing factors have to be balanced: cancer control, patient morbidity, and preservation of renal function.

Preservation of renal function is a key factor in survival. With mounting evidence highlighting the importance of renal preservation [7-10] and documentation of the oncologic efficacy of partial nephrectomy [11], the American Urological Association's guidelines currently place partial nephrectomy as the standard of care for the management of T1a tumors (< 4 cm) and as an alternative treatment option for T1b tumors (4-7 cm) [12]. Reflecting this paradigm shift, the use of partial nephrectomy has risen substantially at many centers of excellence over the past decade, approaching 90% for T1a tumors [13].

With evidence demonstrating improved patient survival following partial rather than radical nephrectomy, nephron-sparing surgery (NSS) has become the standard of care for the management of T1a renal tumors and an accepted alternative for the management of T1b tumors [14, 15]. Furthermore, as the use of minimally invasive technology has advanced within the urologic community, laparoscopic partial nephrectomy and robot-assisted partial nephrectomy (RAPN) have been established as viable alternatives to open NSS [16, 17].

Open NSS traditionally involves clamping of the renal hilar vessels and an abundant use of ice to ensure tissue hypothermia. However, techniques of achieving kidney hypothermia have not been translated to minimally invasive NSS. Thus, renal hilar clamping during minimally invasive NSS is performed under warm ischemia. Increased duration of warm ischemia time (WIT) has been demonstrated to negatively impact short and long-term renal function [18]. As a result, many techniques for limiting WIT have been described, including segmental renal artery clamping, renal parenchymal clamping, early unclamping, and unclamped NSS following administration of hypotensive agents [19-22].

Several years ago, the Principal Investigator developed a technique where RAPN is performed without clamping of the renal hilar vessels and without systemic blood pressure manipulation. This technique is applicable to all renal tumors that are appropriate for partial nephrectomy.

In order to determine the efficacy of this procedure, a retrospective chart review, matched cohort study was performed at Washington University comparing 29 patients who underwent off-clamp RAPN for suspected renal cell carcinoma with a matched 29 patients that underwent RAPN with hilar clamping. The procedures were performed from 3/2008 to 9/2011, and the patients in each group were similar in nephrometry score and baseline renal function. The off-clamp patients experienced an estimated blood loss of 146.4cc, while the hilar clamped RAPN group had an estimated blood loss of 103.9cc (p=0.039). The complications were similar in the two groups with no complications seen in the off-clamp group and only one Clavien-2 complication in the hilar clamp group. The mean eGFR decline was 4.9 ml/min/1.73m2 in the off-clamp group and 11.7ml/min/1.73m2 in the hilar clamp group (p=0.033). In summary, the off-clamp RAPN patients experienced less decline in renal function while experiencing similar morbidity [23].

These preliminary results have shown comparable perioperative outcomes to traditional clamped RAPN, while mitigating renal functional damage and providing excellent oncologic control. To date, we have submitted for publication: 1) video and detailed description of our off-clamp RAPN technique, 2) safety and efficacy of this technique in our initial 42 patient experience, 3) safety and efficacy of our technique for technically difficult renal tumors, and 4) a retrospective matched cohort study comparing off-clamp to clamped RAPN. We aim to prospectively compare renal functional, perioperative and oncologic outcomes between our off-clamp technique and traditional clamped RAPN.

1.2 Rationale

Randomizing patients to either traditional clamped RAPN or off-clamp technique will allow for prospective data in regards to the effect of hilar clamping on renal function. We hypothesize that the off-clamp RAPN technique will lead to decreased decline in renal function compared to the on-clamp RAPN.

2.0 OBJECTIVES

2.1 Primary Objective

1. To determine if off-clamp RAPN technique better preserves long-term renal function than the traditional clamped RAPN technique.

2.2 Secondary Objectives

1. To determine if oncologic outcomes are equivalent between off-clamp and traditional clamped RAPN.

2. To determine if the complication severity and rates are equivalent between off-clamp

technique and traditional clamped RAPN.

3. To determine if off-clamp RAPN technique requires longer operative times or prolongs hospital stay.

4. To determine if off-clamp RAPN technique causes greater blood loss during surgery.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Patients 18 and older.
2. Patients willing and able to sign consent.
3. Patients with an organ confined renal mass planning to undergo a robotic assisted partial nephrectomy (RAPN).
4. Patient with Karnofsky Performance Status (KPS) equal to or greater than 40.

3.2 Exclusion Criteria

1. Patients under 18.
2. Patients with Karnofsky Performance Status (KPS) less than 40.
3. Patients with non-organ confined renal masses (invading renal vein, inferior vena cava, peri-renal tissue, ipsilateral adrenal gland, or metastasis).
4. Patients with bilateral synchronous renal masses.
5. Patients who can not discontinue, Plavix, Coumadin or other anti-platelet or anti-coagulant medications.
6. Patients with renal lesions determined to be too complex to perform a RAPN without clamp by the surgeon. (The renal mass may be deemed too difficult based on pre-operatively radiological findings. The surgeon's decision to exclude a mass from a robotic assisted partial nephrectomy would be based on a higher risk of positive margin or complication if a RAPN was performed.)

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

The following information is required to confirm patient eligibility prior to registering patient:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Planned date of enrollment
6. Completed eligibility checklist, signed and dated by a member of the study team
7. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center Database

All patients must be registered through the Siteman Cancer Center database (SCCdb).

4.3 Assignment of UPN

For the purpose of this study, each patient will be identified with a unique patient number (UPN) which will be assigned consecutively at the time of registration in the SCCdb. All data will be recorded with this identification number on the appropriate CRFs. The UPN will not include the patient's initials as this is considered identifiable information per Siteman Cancer Center Guidelines.

5.0 TREATMENT PLAN

5.1 Preoperative Evaluation

Patients will be evaluated to determine whether they meet the criteria specified in Section 3.1. Patients meeting these criteria will continue to next step.

Patients will have standard of care blood work which will include serum creatinine, preoperatively. Tumor characteristics based on preoperative cross-sectional imaging will be recorded, particularly components of the nephrometry score.

5.2 Operative Procedure

5.2.1. Randomization

Randomization will take place in the operating room, after feasibility of RAPN off clamp is confirmed. Patients will be randomized to either off-clamp RAPN or traditional clamped RAPN in a 1:1 ratio, for a total of 40 patients allocated to each group. To minimize selection bias, a randomization table will be developed before initiation of enrollment.

Envelopes containing randomization assignments will be created, sequentially numbered and sealed. Once enrollment is initiated, randomization envelopes will be opened for each subject after informed consent is granted and study eligibility is confirmed in the operating room.

5.2.2. Day of surgery

Standard preoperative and perioperative procedures for RAPN will be followed in both groups. For the control group (traditional clamped technique), RAPN will be performed in the standard fashion. For the treatment group (off-clamp technique), RAPN will be performed with our off-clamp technique. There is also a possible chance the procedure may be switched intraoperatively due to a variety of factors. For example, intraoperatively a patient undergoing a RAPN off-clamp may require emergent conversion to a traditional hilar clamped RAPN for excessive bleeding. Also, a patient undergoing either RAPN off-clamp or traditional hilar clamped RAPN could require conversion to either open partial nephrectomy, open radical nephrectomy, or laparoscopic radical nephrectomy given intraoperative conditions. A change in technique would only take place if required to maintain patient safety.

5.2.3. Description of the off-clamp RAPN technique

In the off-clamp RAPN technique, after surgical access is gained, kidney is mobilized and Gerota's fascia is incised. The perinephric fat is dissected away from the renal capsule to expose the tumor.

Intravenous mannitol (12.5 grams) is administered by anesthesia. Two robotic bulldog clamps are introduced to allow for expeditious clamping of the hilum if necessary. The margins of the mass are outlined circumferentially with monopolar electrocautery on the robotic scissors. This cautery is continued until an appropriate plane of dissection is found. Forceps are used to bluntly separate the tumor from the residual renal parenchyma with intervening tissue cauterized meticulously with the monopolar scissors. If a large vessel from the renal parenchyma is noted to be bleeding during tumor excision, the robotic bulldogs can be applied to the vessel in the resection bed. This controls the bleeding vessel(s) until suture ligation or clip application of the vessel(s) can be performed. Additionally, larger vessels that are directly supplying the tumor can be controlled with clips if hemostasis with cautery is not adequate. Mobilization of the tumor is continued circumferentially until complete excision of the tumor is achieved. The bedside assistant uses suction and applies countertraction as necessary during tumor excision. The specimen is then placed above the liver or spleen for later retrieval.

The base of the resection bed is cauterized. The insufflation pressure of the

pneumoperitoneum is decreased and the resection bed is examined for any ongoing bleeding.

Any patent venous sinuses or arteries at the base of the resection are oversewn. If the collecting system has been entered, it is similarly closed. The defect in the renal parenchyma is closed using a sliding clip renorrhaphy technique. Gerota's fascia is then similarly reapproximated.

The specimen is entrapped in a specimen bag and then the robot is undocked. The specimen is removed through a port site with extension of the incision as necessary.

The fascia for the ports is closed and skin is reapproximated.

5.3 Risks of RAPN

There are multiple potential risks associated with a RAPN. Complications include but are not limited to the following: hemorrhage requiring transfusion, urinary leak/fistula, abscess, loss of renal function, injury to surrounding organs, conversion to an open surgery, conversion to a radical nephrectomy, incisional hernia, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, and death.

A recent multi-institutional study reported complication rates for 450 RAPN procedures. The overall complication rate was 15.8% with 76.1% Clavien grade I-II and 23.9% Clavien grade III-IV. Hemorrhage requiring a transfusion occurred in 5.1% and arterial embolization to stop hemorrhage in 0.4%. A urine leak occurred in 1.6% with no patient requiring explorative operations for urinary leak. Intra-operative conversion to radical nephrectomy occurred in 1.6%. No deaths occurred in the 450 cases.

5.4 Postoperative Care

The postoperative management is standard of care for all patients who undergo RAPN.

Three month post op visit:

- CR/eGFR
- Renal Scan
- CT/MRI of abdomen
- Chest x-ray (CXR)

5.5 Duration of Follow-Up

The follow up management is standard of care but uniquely different for patients based on pathologic outcome. Patients with a malignant (cancerous) surgical pathology will be followed for a period of 3 years. Patients with a benign (non-cancerous) surgical pathology will only be followed through a period of 3 months postoperatively. Patients removed from

this study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Yearly follow up visits:

- CR/eGFR
- CT/MRI of abdomen
- Chest x-ray (CXR)

5.6 Criteria for Removal from Study

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to proceed with the protocol intervention, the patient should be removed from the study and the reason(s) for discontinuation documented in the case report forms.

Otherwise, the patient will receive the intervention and be followed as described.

6.0 ADVERSE EVENT REPORTING

6.1 Adverse Events

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

All HRPO guidelines for reporting unanticipated problems will be followed.

6.2 Measurement of Post-Operative Complications

In addition to reporting AEs according to the CTCAE (as described in Section 6.1), postoperative complications will be reported using the Clavien-Dindo Classification of Surgical Complications Appendix B. Adverse Events and Complications will be assessed from time of study intervention to the three month post visit.

The principal investigator will also determine complications based on normal standards.

Complication Examples:

1. Intra-operative complications for a RAPN include but are not limited to injury to the surrounding organs and vessels, excessive blood loss requiring blood transfusions, and conversion to radical nephrectomy or open surgery.

2. Postoperative complications for RAPN include but are not limited to urine leak, urinoma, abscess, pseudoaneurysm, ileus, blood transfusion requirements, incisional hernias, wound infection, blood transfusion requirements, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, and death.

7.0 DATA SUBMISSION SCHEDULE

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Eligibility Checklist	Prior to starting treatment
Baseline Data Sheet	Following receipt of pathology report
Adverse Event/Complication Assessment	Baseline, and 3 months after surgery and at the time of any complication
Follow-Up Data Sheet	3 months after surgery then annually thereafter
SAE Reporting Form	At the time of any SAE

8.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data on an ongoing basis and provide a semi- annual report to the Quality Assurance and Safety Monitoring (QASM) Committee. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study

- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and research patient coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or research patient coordinator becomes aware of a serious adverse event, the SAE will be reported to the HRPO and QASM Committee according to institutional guidelines.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Objectives and Endpoints

Primary Outcome:

Evaluation of renal function following RAPN with or without hilar clamping using:

1. Decline in estimated glomerular filtration rate (eGFR). eGFR is calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration formula [11]. Decline in eGFR = Postoperative eGFR – Preoperative eGFR.
2. Decline in split renal function (SRF). SRF is a percentage of the total renal function supplied by one kidney. Ideally each kidney has a SFR of 50%. SRF is measured during renal scintigraphy (renal scan). Decline is SRF =preoperative SRF- postoperative SRF (3 month).

Secondary Outcomes:

1. Oncological outcomes:
    a. Pathological results
        1. Pathologic margin status
        2. Tumor histology, including Fuhrman grade if applicable
        3. Distance between tumor margin and surgical margin

b. Evidence of disease recurrence or metastasis on follow-up imaging
1. Recurrence free survival

2. Perioperative outcomes
   a. Estimated blood loss
   b. Operative time and warm ischemia time
   c. Intra-operative complications, including but not limited to injury to the surrounding organs and vessels, excessive blood loss requiring blood transfusions, and conversion to radical nephrectomy or open surgery.
   d. Length of postoperative hospital stay
   e. Postoperative complications, including but not limited to urine leak, urinoma, abscess, pseudoaneurysm, ileus, blood transfusion requirements, incisional hernias, wound infection, blood transfusion requirements, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, and death.

9.2 Study Design

This is a single institution, prospective, randomized, controlled study to evaluate the off-clamp RAPN technique. Parallel group design with randomization allocation ratio of 1:1 to off-clamp RAPN technique (study treatment) and traditional clamped RAPN technique (control) will be utilized. Study will be conducted at Washington University and will enroll approximately 80 participants over the course of the study.

9.3 Data Analysis

Data analysis for this study will be descriptive in nature. Demographic and clinical characteristics of the sample, as well as local recurrence and post-surgery complications will be summarized using descriptive statistics. Kaplan-Meier product limit method will be used to estimate the 2-year overall and disease-free survival. The median disease-free survival, overall survival and their 95% confidence interval will also be estimated.

10.0 REFERENCES

1. Chow WH, Deresa SS, Warren JL, et al: Rising incidence of renal cell cancer in the United States. JAMA 1999; 281: 1628-1631.
2. National Cancer Institute at the National Institute of Health. Kidney Cancer- Estimated new cases and deaths. (http://www.cancer.gov/cancertopics/types/kidney)
3. Kane CJ, Mallin K, Ritchey J, et al: Renal cell cancer stage migration: analysis of the National Cancer Data Base. Cancer 2008; 113: 78.
4. Cooperberg MR, Mallin K, Kane CJ, et al: Treatment trends for stage I renal cell carcinoma. J Urol 2011; 186(2): 394-9.
5. Miller DC, Ruterbusch J, Colt JS, et al: Contemporary clinical epidemiology of renal cell carcinoma: insight from a population based case-control study. J Urol 2010; 184: 2254-8.
6. Jewett MAS, Mattar K, Basiuk J, et al: Active surveillance of small renal masses: progression patterns of early stage kidney cancer. Eur Urol 2011; 60: 39-44.
7. Go AS, Chertow GM, Fan D, et al: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. NEJM 2004; 351: 1296-1305.
8. Huang WC, Levey AS, Serio AM, et al: Chronic kidney disease after nephrectomy in patients with renal cortical tumors: a retrospective cohort study. Lancet Oncol 2006; 7: 735-740.
9. Thompson RH, Boorjian SA, Lohse CM, et al: Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. Cancer 2008; 112: 511-520.
10. Weight CJ, Lieser G, Larson BT, et al: Partial nephrectomy is associated with improved overall survival compared to radical nephrectomy in patients with unanticipated benign renal tumors. Eur Urol 2010; 58(2): 293-8.
11. Fergany A.F, Hafez KS, and Novick AC: Long-term results of nephron sparing surgery for localized renal cell carcinoma: 10-year followup. J Urol 2000; 163: 442.
12. Campbell SC, Novick AC, Belldegrun A, et al: Practice Guidelines Committee of the American Urological Association. Guidelines for management of the clinical T1 renal mass. J Urol 2009; 182:1271-9.
13. Clark PE, Schover LR, Uzzo RG, et al: Quality of life and psychological adaptation after surgical treatment for localized renal cell carcinoma: impact of the amount of remaining renal tissue. Urology 2001; 57: 252.
14. Thompson RH, Boorjian SA, Lohse CM, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. Cancer 2008; **122**: 511-520.
15. American Urological Association Education and Research (AUA) Guidelines: "Guidelines for Management of the Clinical Stage I Renal Mass." Renal Mass Clinical

Panel Chairs: Novick AC (Chair), Campbell SC (Co-Chair): www.auanet.org/content/media/renalmass09.pdf
16. Gill IS, Kavoussi LR, Lane BR, et al. Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumors. J Urol 2007; **178**: 41-46.
17. Benway BM, Bhayani SB, Rogers CG, et al. Robot assisted partial nephrectomy versus laparoscopic partial nephrectomy for renal tumors: a multi-institutional analysis of perioperative outcomes. J Urol 2009; **182**: 866-873.
18. Every minute counts when the renal hilum is clamped during partial nephrectomy. Thompson RH, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, Gill IS, Blute ML, Campbell SC. Eur Urol. 2010 Sep;58(3):340-5.
19. Figenshau RS. Laparoscopic partial nephrectomy with segmental renal vascular control. J Endourol 2005; **19** (supplement 1): A257.
20. Viprakasit DP, Altamar HO, Miller NL, and Herrell SD. Selective renal parenchymal clamping in robotic partial nephrectomy: initial experience. Urology 2010; **76**: 750-753.
21. San Francisco IF, Sweeney MC and Wagner AA. Robot-assisted partial nephrectomy: early unclamping technique. J Endourol 2011; **25**: 305-308.
22. Gill IS, Eisenberg MS, Aron M et al. 'Zero ischemia' partial nephrectomy: novel laparoscopic and robotic technique. Eur Urol 2011; **59**: 128-134.
23. Tanagho Y, Bhayani S, Sandhu G, Vaughn N, Nepple K, Figenshau R. Renal Functional and Perioperative Outcomes of Off-Clamp vs. Clamped Robot-Assisted Partial nephrectomy: Matched Cohort Study. (Accepted for publication in Urology)
24. Kutikov A and Uzzo RG. The RENAL nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol 2009; **182**: 844-853.
25. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; **150**: 604-612.
26. Spana G, Haber G, Dulabon L, Petros F, Rogers C, Bhayani S, Stifelman M, and Kaouk J. Complications after robotic partial nephrectomy at centers of excellence: a multi-institutional analysis of 450 cases. *J Urol.* 186: 417-422.

APPENDIX A: Karnofsky Performance Scale

Description	Percent (%)
Normal; no complaints; no evidence of disease	100
Able to carry on normal activity; minor signs and symptoms of disease	90
Normal activity with effort; some signs and symptoms of Disease	80
Cares for self; unable to carry on normal activity or do Work	70
Requires occasional assistance, but is able to care for most personal needs	60
Requires considerable assistance and frequent medical Care	50
Disabled; requires special care and assistance	40
Severely disabled; hospitalization indicated although death not imminent	30
Very sick; hospitalization necessary; requires active support treatment	20
Moribund; fatal processes progressing rapidly	10
Dead	0

APPENDIX B: The Clavien-Dindo Classification of Surgical Complications

Full Scale			Contracted Form	
Grades	Definition		Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.		**Grade I:**	Same as for Full Scale
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.			
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.		**Grade II:**	Same as for Full Scale
Grade III:	Requiring surgical, endoscopic or radiological intervention		**Grade III:**	Grades IIIa & IIIb
Grade III-a:	intervention not under general anesthesia			
Grade III-b:	intervention under general anesthesia			
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management		**Grade IV:**	Grades IVa & IVb
Grade IV-a:	single organ dysfunction (including dialysis)			
Grade IV-b:	multi organ dysfunction			
Grade V:	Death of a patient		**Grade V:**	Same as for Full Scale
Suffix 'd':	If the patients 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.			

‡ brain hemorrhage, ischemic stroke, subarrachnoidal bleeding,but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit.

Dindo D., Demartines N., Clavien P.A.; Ann Surg. 2004; 244: 931-937

APPENDIX C: Study Schedule of Events

	Pre-Operative Assessments	Surgery	Post-Operative Assessments		
	Baseline[1]	RAPN	1 day Post RAPN	3 months Post RAPN	Every 12 months[2]
Informed Consent	X				
Demographics	X				
Medical & Surgical History	X				
Height & Weight	X				
Serum Creatinine/eGFR	X		X	X	X
Renal Scan	X[1]			X	
CT/MRI of abdomen	X[1]			X	X
CXR	X[1]			X	X
Incl./Excl. Criteria Confirmation	X				
Randomization		X			
Perioperative Outcomes		X			
Pathology results		X			
Adverse Event Assessment				X	
Assessment of Evidence of Disease Recurrence				X	X

[1] Scans (Renal Scan, CT/MRI of abdomen and Chest Xray (CXR)) performed prior to or at time of baseline assessments per standard of care

[2] From the date of 3-mo follow up for total of 3 years only for patients with malignant pathological outcome