



MEMORIAL SLOAN-KETTERING CANCER CENTER
IRB PROTOCOL

IRB#:12-079 A(10)

Phase 3 Trial of Intravenous Mannitol Use During Partial Nephrectomy Prior to Renal Ischemia and Impact on Renal Function Outcomes

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

We propose a placebo controlled randomized study on the use of mannitol as an agent to protect against the effects of transient renal ischemia and its impact on renal function during the surgical procedure of partial nephrectomy. Patients undergoing partial nephrectomy for the treatment of kidney tumors will be randomized 1:1 to receive either intravenous mannitol or saline during their procedure, administered prior to renal vascular clamping. Changes in renal function following surgery will be monitored using calculated glomerular filtration rate (eGFR) and renal scan data obtained pre- and post-operatively, as part of routine standard of care.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary endpoints:

- Difference in eGFR at 6 months after surgery.

Secondary endpoints:

- Difference in eGFR at 6 weeks after surgery.
- Difference in radionuclear scintigraphy renal scan at 6 months postoperatively.
- Difference in rate of grade 3-5 complications within 30 days of surgery.
- Difference in estimated blood loss.
- Difference in ischemia time.

3.0 BACKGROUND AND RATIONALE

The improved renal function outcomes that occur with nephron sparing surgery in patients with renal tumors amenable to partial nephrectomy has prompted a considerable increase in the number of partial nephrectomies performed for patients with small renal masses. Nationally, this trend has been notable, comprising less than 5% of cases in 1988, 15% of procedures by 2002 and roughly 25% of kidney surgery by 2008. Surgeons at Memorial Sloan Kettering have led the field in partial nephrectomy procedures consistently, publishing the initial papers describing the technique and now performing nephron sparing surgery in 95% of patients surgically treated for small renal masses and over 80% for larger tumors (4 - 7 cm) in contemporary experience.^{1, 2} With oncologic results that appear equivalent to radical nephrectomy, a fundamental goal of this procedure is to optimally preserve renal function. Several factors play a role in the loss of function which occurs as a result of surgery, some of which may be controlled for and studied in order to optimize the goals of oncologic surgical intent, minimize the risk of harm to the patient and ensure excellence in patient care while offering the best possible quality of life for our patients. Factors include cold and warm ischemia, limits of renal artery clamping time and the use of intraoperative mannitol as a renal protective medication prior to renal ischemia. Requirements of the surgery and patient variability limit the control that can be placed on many factors however, most would be evenly distributed in both arms of a randomized trial design which evaluates the factors that can be controlled. Our study aims to assess the significance of mannitol infusion prior to renal ischemia in partial nephrectomy in a randomized prospective manner.

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Mannitol's purported effects of increasing renal blood flow, decreasing intravascular cellular swelling, and increasing intravascular volume have been used as rationale for its use to ameliorate the damage to renal tissue caused by vascular insult to the kidney.³ During partial nephrectomy, renal ischemia occurs as a result of temporary renal artery occlusion to provide a bloodless field during the resection.⁴ Traditionally, mannitol has routinely been used during partial nephrectomy as a renal protective agent. Unfortunately, there is no level I or level II evidence supporting its use for this purpose in the surgical literature and, indeed, little evidence supporting its use in preventing the onset of renal dysfunction caused by other mechanisms of acute medical renal disease. Despite this, mannitol intravenously applied in this setting continues in contemporary surgical practice largely due to the legacy effect of its historic use based on limited preclinical data in animal models. There is mounting evidence, as the complex renal physiological milieu is elucidated, that mannitol may in fact be detrimental to kidney function.⁵

Mannitol is an osmotic diuretic with a number of physiologic effects on the kidney as studied in preclinical models. Zager et al. showed that mannitol increases renal blood flow (RBF) in rats compared to sham controls (2 fold) when rats were given an intravenous bolus after 25 minutes of renal artery occlusion.⁶ Corollary studies suggested that this increase in RBF was due possibly to prostaglandin mediated vasodilatory effect of mannitol⁷ and/or release of atrial natriuretic peptide.⁸ Physiologically, increased renal blood flow by mannitol in animal models can decrease intravascular hypoxic cell swelling^{9, 10} and increase intravascular volume with an associated decrease in hematocrit¹¹. Intratubular casts may be flushed out by an increase in tubule flow rate as shown in rat models of progressive aortic clamping.¹² Mannitol may also play a role in mitochondrial protection after ischemia. Schrier et al demonstrated in a dog renal ischemia model that mannitol preserved renal cortical mitochondrial function.¹³

There has been suggestion, however, that mannitol's effects may not be entirely beneficial and the response of increased renal blood flow a reflection, or cause, of severe hypoxic injury. As described by Gelman and colleagues, the vascular anatomy of the human kidney is remarkable for the magnitude of the relative difference in arteriovenous oxygen tension between the cortex and the medulla, creating a region of hypoxia within the outer medulla that is sensitive to ischemia and metabolic changes.⁵ The cortex receives 94% of renal blood flow whereas the medulla only receives 6%, with the portion of the outer medulla receiving its vascular supply as venous blood from the inner medulla. Because of this, the partial pressure of oxygen in the medulla is normally around 10 mm Hg versus 50 mm Hg in the cortex. The medulla, therefore, exists in a state of relative hypoxia, even in the presence of adequate RBF, and the prime region of risk during states of ischemia. The thick ascending limb of Henle's loop is especially vulnerable to hypoxic injury.¹⁴ The decrease in RBF associated with oliguric renal failure and resultant reduction in GFR, has been postulated to act as a medullary protective mechanism by decreasing the metabolic demand required for solute reabsorption.¹⁰ Considering these physiologic findings, the adverse effects sometimes associated with mannitol use may be due to the selective increase in renal cortical RBF, filtration rate and resulting solute load, producing a shift in regional vascular flow while increasing the metabolic demand within the medulla and potentiating the effects of ischemia.⁵

In clinical practice, mannitol has been used and studied in a variety of settings involving acute renal dysfunction or the risk for progressive renal impairment. In vascular surgery, three randomized controlled trials have been performed to assess the use of mannitol in reducing the incidence of renal failure in patients undergoing abdominal aortic aneurysm (AAA) repair for infrarenal aortic aneurysms.¹⁵ There were no significant differences between the randomized groups when evaluating change in eGFR from 2 hrs to 7 days after surgery

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with the exception of one study (Wijnen et al) which identified evidence of improved outcomes in the mannitol treated cases on post operative day 2 ($p=0.047$).¹⁶⁻¹⁸ Early retrospective uncontrolled clinical studies of the effects of mannitol during interventional cardiology procedures suggested its renal protective effects against radiocontrast nephropathy.^{19, 20} Subsequent published RCT's have since demonstrated mannitol is not only ineffective in regard to renal protection, but also has potential for producing renal failure.^{21, 22} As a result of these trials mannitol is no longer used during interventional cardiology procedures. Other studies, including meta-analysis of renal protective agents for contrast induced nephropathy and Cochrane analysis of the use of perioperative renal protective agents have not identified a benefit to the use of mannitol for preserving renal function in these settings.^{23, 24}

The strongest arguments for the use of mannitol as a renal protective agent come from the transplant literature, although this model and the results of these studies may involve mechanisms dissimilar to those of partial nephrectomy patients. Collins and Green et al performed some of the early studies of unilateral normothermic renal ischemia in a rabbit model utilizing 1 hour of renal vascular occlusion.²⁵ The right kidney served as an internal control for the clamped left kidney. Renal function was assessed immediately after unclamping by measuring creatinine excretion at intervals acutely (within 1 hour) and chronically (up to 7 days). Mannitol conferred a significant benefit in both the acute and chronic measurements. The same investigators further characterized the timing and dose of mannitol in a subsequent study, and found that 0.25 mg/kg of IV mannitol given 15 minutes before the onset of warm renal ischemia provided the greatest benefit at day 3.²⁶ Shilliday and Allison provide a summary of the animal models supporting mannitol's beneficial role but conclude the "case for mannitol must remain, in the words of the Scottish legal verdict, 'Not proven'".³ Weimar et al subsequently reported results from a prospective randomized trial in which 50 patients receiving cadaveric donor transplant were provided either 50 g IV mannitol or saline infusion just prior to graft revascularization.²⁷ They found a significant decrease in the incidence of ATN in the early postoperative period in the mannitol group although no effect was demonstrated at 3 months when eGFR was compared.

In large part due to the results of mannitol use in the one-hour rabbit renal ischemia models by Collins and Green, intravenous mannitol at a dose of 12.5 gm has been provided as standard dosing during partial nephrectomy procedures as part of routine practice.²⁵ The origin of this dosing level is uncertain and the use of mannitol during surgery remains up to the surgeon's discretion. In a preliminary study, as yet unpublished, investigators at MSKCC performed a retrospective evaluation of the renal function outcomes in patients undergoing minimally invasive partial nephrectomy, segregating the cohort by use of mannitol (standard dosing regimen) during the procedure. In total, 164 patients received mannitol and 117 did not. Characteristics of the patients in each group are shown in Table 1 and were not notably favorable to the non-mannitol group. Statistically, those who received mannitol tended to have better preoperative eGFR (median 68 vs 61 ml/min/1.73m²), were more likely to undergo ischemia (98% vs 88%) and had fewer comorbidities (42% vs 53% had an ASA score of 3 or 4) than those who did not receive mannitol.

Table 1. Patient characteristics, stratified by whether the patient received mannitol treatment. All values are median (IQR) or frequency (proportion).

	No Mannitol N=117	Mannitol N=164	P value* for difference between groups
Age at surgery (years)	60 (49, 68)	60 (51, 67)	1
Preoperative GFR	61 (54, 71)	68 (59, 75)	0.032
Male gender	75 (64%)	109 (66%)	0.7
Estimated blood loss	150 (50, 300)	200 (100, 350)	0.0017
White race	106 (91%)	143 (87%)	0.3
Ischemia	103 (88%)	161 (98%)	0.001
Ice slush	4 (4%)	6 (4%)	
Clamp time (in min)	32 (23, 39)	32 (25, 40)	
High grade	32 (41%)	38 (36%)	0.5
Pathologic Stage			0.8
T1	87 (83%)	130 (87%)	
T2A	4 (4%)	5 (3%)	
T2B+	14 (13%)	15 (10%)	
ASA Score			0.006
1	12 (10%)	6 (4%)	
2	43 (37%)	89 (55%)	
3	60 (51%)	65 (40%)	
4	2 (2%)	1 (1%)	
Year of surgery			<0.001
2005	3 (3%)	27 (16%)	
2006	5 (4%)	18 (11%)	
2007	5 (4%)	48 (29%)	
2008	30 (26%)	25 (15%)	
2009	49 (42%)	24 (15%)	
2010	25 (21%)	22 (13%)	

*Fisher's exact or Wilcoxon rank sum

Overall renal function appears to transiently decrease following nephron sparing surgery in a manner which suggests delayed recovery. As demonstrated in Figure 1, the profile of renal function, as assessed by eGFR, appears comparable for patients managed with and without mannitol based on retrospective data. Overall, the recovery of renal function was very similar in both groups ($p=0.8$ for effect of mannitol from GEE model). The predicted eGFR for a typical patient 2 months after surgery was 62 ml/min/1.73m² both for those given and not given mannitol; at 6 months the respective predicted GFR measurements were 63 and 64 ml/min/1.73m². It is notable that the mannitol group had a lower nadir and recovery of eGFR than the group who did not receive mannitol. In evaluating the open surgical experience in over 850 open partial procedures 34 did not receive mannitol, many of who did not require renal ischemia, limiting our evaluation of this cohort.

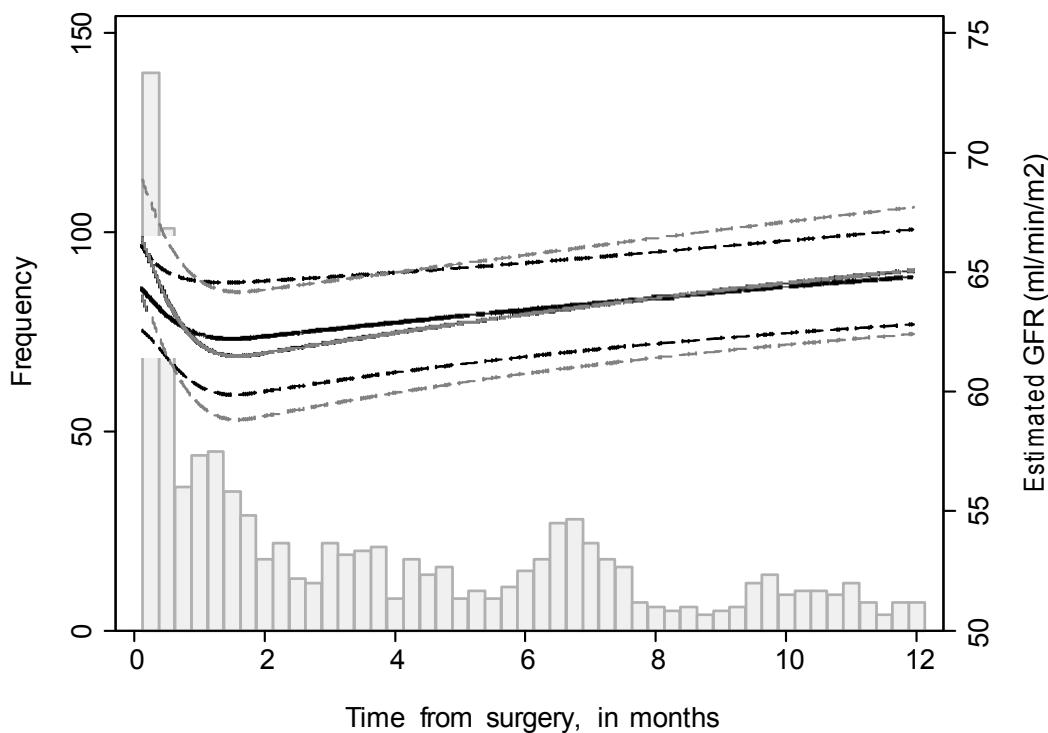


Figure 1. Population-averaged changes in GFR ($\text{mL}/\text{min}/1.73\text{m}^2$) after partial nephrectomy for patients given mannitol (grey line) and not given mannitol (black line), adjusted for differences in preoperative GFR, age, gender, ASA score, estimated blood loss, and ischemia time. Dashed lines indicate 95% confidence intervals. The histogram shows the number of GFR measurements over time, excluding postoperative measurements taken within two days of surgery that were recorded for all patients.

The clinical significance of 6 units of eGFR change is somewhat empiric though based on data considered clinically meaningful to prompt a change in clinical practice. For most clinicians informally questioned, detecting a 3 or 4 point difference between groups in post-operative eGFR was not felt clinically important. We further evaluated our retrospective dataset of 281 patients identifying an index patient as 60 yo, non-African American man with preoperative baseline eGFR of 65 cc/min/1.73m². Using the CKD Epi calculator, this would correlate to a serum creatinine of 1.2 mg/dL. For every 0.1 mg/dL change in serum creatinine, up or down from this baseline, there would be a roughly consistent 6 unit change in eGFR. Finally, we noted that a 6 unit decrease from the median value of 65 cc/min/1.73m² would place a patient below the threshold of stage 3 chronic kidney disease which is clinically meaningful. For these reasons we felt that detecting a difference in 6 units of eGFR between the groups was an appropriate level at which to power the study.

Other methods to describe the change in renal function by group would be to allow each patient to serve as their own control and use the change in eGFR experienced by the patient to serve as a metric. We will assess this outcome as a secondary endpoint and will also evaluate the relationship to the primary endpoint. This method will enable each patient's preoperative eGFR to be used as their own individual control. The percentage changes in each patient's postoperative eGFR compared to the preoperative baseline can then be used to compare the treatment and placebo arms of the trial.

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In summary, the practice of intravenous mannitol use during partial nephrectomy procedures as a renal protective agent has not been appropriately investigated to prove its effectiveness. Our preliminary retrospective data suggests mannitol does not demonstrate a benefit in attenuating the effects of ischemia or in the recovery of renal function following partial nephrectomy. We propose a randomized prospective study to evaluate its use for this purpose.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This study is a prospective randomized double blind placebo controlled trial comparing renal function outcomes in patients undergoing partial nephrectomy for renal tumors. Patients will be randomized in 1:1 fashion to receive mannitol or saline provided intravenously within 30 minutes prior to renal vascular clamping for performing partial nephrectomy.

Patient randomization will be accomplished by the Clinical Research Database (CRDB) once eligible patients have been consented and registered in the Protocol Participant Registration system. Pharmacy will be able to access the requisite information on the CRDB to ensure correct delivery of either mannitol or saline to the treatment or placebo arms respectively. The anesthesiologist, surgeon and patient will be blinded to the intervention.

To avoid any compromise in the blinding process, mannitol input into CASIS will be deferred until after the trial has finished. At this time it will be entered into CASIS by the research assistant.

An interim analysis half way through the trial when 88 patients have eGFR measurements at 6 months. The O'Brien-Fleming stopping boundaries will be used. The significance levels for the interim and final analyses are 0.0031 and 0.049, respectively.

4.2 Intervention

In patients undergoing partial nephrectomy, fluid management will be uniform and standardized for all operative techniques (open, laparoscopic or robot assisted) using the fluid management guidelines recommended by the Department of Anesthesia summarized herein. Upon arrival to the operating room patients will be placed supine on the operating room table and intravenous lines connected to allow initiation of IV hydration with Normosol or [Lactated Ringers](#). Before induction of general anesthesia, IV hydration may be provided by the anesthesia team as clinically indicated which should not exceed 500 cc, including IV antibiotics. Presurgical intravenous fluid use will be documented in the anesthesia operative record. Parameters for maintenance intravenous fluid rates will be according to standard institutional clinical practice as provided by the Department of Anesthesia. These guidelines are consistent with those recommended as standard hydration parameters for patients undergoing both open and laparoscopic surgical procedures²⁸. After induction of general anesthesia Normosol or [Lactated Ringers](#), at a target infusion rate of 10cc/kg (+/- 1cc/kg), will be administered over the first hour of surgery. After the first hour of surgery IV fluid will be administered at 6cc/kg (+/- 1cc/kg) intended to maintain a minimum systolic blood pressure of 90-100mmHg and a minimum urine output of 0.5cc/kg/hour.

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The treatment arm will receive a standard dose of 12.5 grams of mannitol (200 cc of a 6.25% mannitol solution) intravenously completely infused through an existing intravenous access catheter within 30 minutes prior to renal artery clamping. The placebo arm will receive 200cc of normal saline completely infused within 30 minutes prior to renal artery clamping. The perioperative team, investigator and patient will be blinded to the intervention

Intraoperative events related to fluid resuscitation will be documented in the record. Hypotension (systolic blood pressure less than 90 mm Hg) or low urine output will be treated with 250cc intravenous boluses of Normosol or [Lactated Ringers](#) solution. Episodes of hypotension not responsive to intravenous fluids may be treated with small doses of intravenous vasopressors (phenylephrine or ephedrine) as per current practice at MSKCC. Surgical blood loss may be replaced on a volume basis cc per cc with colloids, including albumin or 6% hetastarch solution. Blood transfusion will be performed as per MSKCC Blood Bank guidelines.

At the end of the procedure, all intravenous fluid provided during the surgery will be summarized and documented in the operative record as per Anesthesia institutional standards. Any events of total intravenous fluid volume outside of the ranges defined by the maintenance parameters above will be recorded as events. The randomized design would lead to the expectation that these events would be similarly distributed between the stratified arms of the study.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Mannitol (US Brand Name: Osmotrol) is in the osmotic diuretic pharmacologic category according to the American Hospital Formulary Service (AHFS) database.²⁹ MSKCC OR pharmacy prepares a 6.25% mannitol solution by combining a 50 ml vial (12.5 grams) of mannitol with 150 ml of normal saline. .

Mannitol solutions $\geq 15\%$ concentrations may crystallize when exposed to low temperatures therefore the solution is stored at room temperature (15-30 degrees Celsius).²⁹

Mannitol is injected by intravenous infusion using an administration set with a filter and infused over 5-10 minutes as a 6.25% solution. As per current institutional practice, a volume of 200 cc will be infused.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

Describe the characteristics of the patient/subject population.

6.1 Subject Inclusion Criteria

- Age ≥ 18 years
- Scheduled for partial nephrectomy at MSKCC (open or minimally invasive technique) during which renal ischemia is anticipated
- Preoperative eGFR ≥ 45 cc/min/1.73m² as measured by the CKD-EPI study equation

6.2 Subject Exclusion Criteria

- Allergy to mannitol

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- Severe renal impairment (stage 3B) defined as eGFR < 45 cc/min/1.73m² as measured by the CKD-EPI calculation.
- Combined major surgical cases that include a partial nephrectomy.

7.0 RECRUITMENT PLAN

Patients will be recruited from the practices of the Division of Urology, Department of Surgery. The study will be introduced to every patient scheduled for partial nephrectomy by the participating consenting physicians from the Department of Surgery and consent obtained prior to surgery. Candidate patients will be provided time to consider the study, to read the informed consent document at their convenience, and discuss with family and others, as desired. Once the participant is ready to provide informed consent, this will occur in-person with written informed consent.

Estimated Breakdown of target population by race/ethnicity (derived from CAISIS generated data for numbers of partial nephrectomies performed from 2002-2010 at MSKCC, N=1426 patients):

• Male	64%
• Female	36%
<hr/>	
• Native American/Alaskan	0.1%
• Asian/Pacific Islander	2.5%
• Black Non-Hispanic	4.0%
• Hispanic	0.9%
• White Non-Hispanic	91%
• Other	1.5%

8.0 PRETREATMENT EVALUATION

This protocol does not require any additional pretreatment evaluations other than those which are part of current clinical care standards for a patient undergoing a partial nephrectomy at MSKCC. These include:

- Baseline radionuclear scintigraphy renal scan within 6 months of surgery
- Routine history and physical examination to include documentation of any comorbidities, medications (including complementary and alternative medications), family history, social history (alcohol and tobacco usage), height, body weight, Karnofsky performance status within 30 days of surgery
- Abdominal and pelvic CT scan and/or renal ultrasound within 3 months of surgery
- Chest X-ray or Chest CT scan within 3 months of surgery
- Preoperative laboratory investigations: CBC, basic chemistry panel, urinalysis (dipstick, microalbumin, creatinine, microscopic evaluation if indicated), urine culture if indicated within 30 days of surgery
- Baseline creatinine values will be converted to eGFR using the CKD-EPI equation.
 - This value will be recorded from the MSKCC pre-surgical testing blood work mandatory for all patients undergoing surgery at MSKCC

9.0 TREATMENT/INTERVENTION PLAN

Patients will be randomized to receiving 12.5 g of mannitol versus placebo as an intravenous infusion to be initiated and be completely infused within 30 minutes prior to vascular occlusion of the renal artery in patients undergoing partial nephrectomy for a renal mass.

CAISIS fields will be added to the standardized kidney surgery reporting form, currently used for all such cases, to record the binary variables of: Mannitol (or placebo) infusion prior to clamping (Y/N), Clamping of renal vessels within 30 minutes of mannitol infusion completion (Y/N). If negative responses are recorded, details will be required. Currently, CAISIS fields for details of nephrectomy are extensive and include duration of ischemia time and proportion of kidney tissue preserved during surgery.

The technique of surgery (open, laparoscopic, robot assisted laparoscopic) will be at the discretion of the surgeon and patient. None of the techniques utilized in the study are considered experimental and all are considered standard therapeutic options for a patient with a renal mass amenable to partial nephrectomy. Since patients will be randomized as stratified by approach (laparoscopic or open) any impact from physiologic differences between the 2 approaches are expected to be equally distributed between the 2 arms. The decision for renal hypothermia during surgery will be at the discretion of the surgeon and patient. Patient medications will be recorded from the home medications list and managed perioperatively per institutional standards.

The operating team will consist of surgeons on faculty at the MSKCC Department of Surgery, Urology Service. The procedures are performed under general anesthesia with standard intraoperative vital sign monitoring. This will include blood pressure, 4-lead ECG, heart rate, pulse oximetry, temperature and urine output. Intravenous fluid use during surgery will be provided by the anesthesiology team as clinically indicated. Total volume of fluids provided as well as estimated blood loss will be recorded.

Mannitol solution of 12.5 gm in 200 cc of saline or placebo will be available in the OR at the time of surgery initiation. It will be administered intravenously and will be completely infused within 30 minutes prior to renal artery clamping. During the surgery, vascular occlusion will be provided using vascular bulldog or Satinsky clamp of the renal artery. If multiple primary renal vessels are encountered, selective occlusion of the vessels can be provided at the surgeon's discretion and the details regarding number of arterial vessels and number of clamped vessels recorded. Clamping or non-clamping of the renal vein will also be recorded. Patients who do not undergo clamping of the renal artery will still receive either the mannitol or placebo since kidney surgery for partial nephrectomy is intrinsically damaging to the kidney and the effects of dissection of the kidney have unknown effects on renal perfusion for which mannitol may have potential benefit.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

This protocol does not require any additional evaluations after the patient is admitted for surgery other than those routinely part of clinical care for a patient undergoing a partial nephrectomy. These will include:

- ASA classification, assigned by the anesthesiologist
- Deep venous thrombosis prophylaxis per standardized pathway

- Type of anesthesia: general, epidural, combination
- Duration of anesthesia and of surgery
- Duration of warm or cold ischemia time
- Estimated blood loss
- Use of intraoperative fluids (crystalloid, colloid, blood products)
- Postoperative day 1 and postoperative day 2 serum creatinine measurement. For patients discharged before post-operative day 2, serum blood testing will be ordered as an outpatient test.
- Follow up visit serum creatinine measurements (6 weeks +/- 4 weeks and 6 months +/- 2 months)
- 6 month +/- 2 months follow up radio nuclear scintigraphy renal scan, which is a routine postoperative investigation for patients who have undergone a partial nephrectomy.
- Patients may be concurrently enrolled on protocol 89-076 for collection of tissue and blood for tissue banking.

11.0 TOXICITIES/SIDE EFFECTS

There are minimal side effects to the use of mannitol in the dosages prescribed for this study. The AHFS warnings/ precautions relate to excess amounts (>100 g of intravenous mannitol in a 24 hour period).²⁹ 12.5 g of mannitol is considered the “test dose” in adult populations when mannitol is used for other therapeutic effects. Nonetheless, concerns related to adverse effects listed are:

- Fluid/electrolyte loss: excess mannitol infusion can lead to profound diuresis with fluid and electrolyte loss; close medical supervision is required
 - The anesthesia and PACU teams routinely monitor urine output, vitals and volume status and therefore this concern is minimal.
- Nephrotoxicity: may cause renal dysfunction especially in high doses therefore caution is required in patients taking nephrotoxic agents or have pre-existing renal disease
 - Patients are excluded from participating if their eGFR identifies them as having pre-existing Stage 3b or greater chronic kidney disease. All nephrotoxic agents are closely monitored/discontinued routinely in all partial nephrectomy patients.
 - Severe clinical complications from mannitol use in the literature are exceedingly rare and only follow massive doses of mannitol, in the range of 400-900 g/day.³⁰
- Cardiovascular: may lead to chest pain, tachycardia, hypotension, hypertension, dyspnea due to congestive heart failure or overload
- Respiratory: Pulmonary edema
- Central Nervous System: Pyrexia, headache, confusion, vertigo
- Dermatological: Urticaria
- Gastrointestinal: Nausea, emesis, xerostomia

Surgical complications will be assessed prospectively and retrospectively reviewed using the institutional standard for complications reporting for all surgical patients as followed by the Department of Surgery. Standardized graded complications and adverse events at MSKCC utilize the five point modified Clavien system. Grade I include complications requiring

monitoring but no intervention, Grade II requires bedside or medical treatment; grade III constitutes adverse events require surgical or procedural intervention with return to normal functioning; grade IV includes disabling, life-threatening complications with resulting functional loss and grade V is the death of the patient. This is a modification of the Clavien system for reporting complications with defined, categorized, and classified events that will be segregated into time periods of ≤ 30 days, 31 - 90 days and > 90 days after surgery and includes medication related complications following NCI CTCAE version 3 guidelines.³¹

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

As an intent-to-treat study, patients will be evaluated for the primary endpoint if they are registered on study, brought to the operating room for surgery, and begin anesthesia for the procedure. Because the role of mannitol as a protective agent in regard to kidney function is not entirely clear and its mechanism of action may be mediated through its effects on the contralateral kidney, all patients will be evaluated for the primary endpoint even if the ipsilateral kidney is not clamped during the procedure. If the surgery is aborted for any reason before attempted excision of the mass or if intravenous infusion fails for any reason the patient will be dropped from the study and replaced. Based on past experience these issues are rare events.

Estimated glomerular filtration rate (eGFR) will be estimated according to the CKD-EPI formula.

Perioperative complications are defined as any complication graded in the MSKCC grading system occurring during the intraoperative and postoperative period up to 30 days.

Immediate perioperative morbidity is defined as any complication graded in the MSKCC grading system occurring during the initial hospital stay.

The intraoperative period is defined as the period from anesthesia induction to final skin closure.

The postoperative period is defined as the period from final skin closure to the study endpoint at 6 months \pm 2 months.

Renal hypothermia will be defined as induced cooling of the kidney by externally applied ice-slush or cold crystalloid infusion via catheter of the renal pelvis or intravascularly.

Warm ischemia will be defined as no kidney cooling during renal artery occlusion.

Ischemia time will be defined as the time elapsed from renal artery occlusion by a vascular clamp to removal of the vascular clamp. Re-clamping of the vessels will be recorded as an event and total duration of ischemia recorded as the sum duration of occlusion.

Blood loss is defined as the estimate accounted from the suction device and absorptive sponges during the surgical procedure, and will be noted in the anesthesia record per institutional standard.

Intraoperative complications are defined as any complications related to either surgical or clinical aspects during the procedure, as described by the surgeon and covered by the institutional guidelines.

Any patient who does not undergo renal ischemia by vascular clamping will during their procedure will be recorded as a zero ischemia time.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be withdrawn from the study if they express a desire to do so, if it is determined to be in the patient's best interest to do so, or if they do not undergo initiation of their surgical procedure as stipulated in section 12.0. Patients who are not evaluable for the study primary endpoint by failure to obtain data for the primary endpoint will be excluded from the analysis and replaced.

14.0 BIOSTATISTICS

14.1 Primary Aim

The primary aim is to establish the difference in eGFR 6 months after surgery between the mannitol group and the placebo group. The difference will be assessed with an ANCOVA model with eGFR 6 months after surgery (+/- 2 months) as the outcome and treatment group, surgical technique, and preoperative eGFR as covariates. We will report a two-tailed p-value and a 95% confidence interval for the difference between groups. If a patient does not have an eGFR measurement between 5-7 months after surgery and has both a measurement between 3-5 months and 7-12 months after surgery, then the 6 month eGFR measurement will be linearly interpolated.

Based on historical data, patients not receiving mannitol have a mean eGFR of 60 cc/min/1.73m² 6 months after surgery. The observed correlation between the preoperative eGFR and eGFR 6 months was 0.6. The standard deviation is 14.4. Using bootstrap methods, the 75th percentile of the standard deviation was estimated to be 14.9. This inflated standard deviation was used in the sample size calculation. To detect the minimal clinical significant difference of 6 units of eGFR, a trial with 90% power and 5% alpha requires 83 patients per treatment arm. Because of the loss of power in the interim analysis, a total of 88 patients are required per treatment arm. The trial will accrue until it is anticipated that 88 patients per treatment arm will have evaluable eGFRs at 6 months. We expect that, due to drop out, this will involve accruing approximately 105 patients per treatment arm. Sensitivity analyses will be performed to assess the effect of patient withdrawal on the primary analysis.

We expect to reach our target sample size within 2 years, given that nearly 200 patients per year are eligible to enroll. We expect to enroll 8 patients per month to reach accrual in 2 years.

14.2 Secondary Aims

An ANCOVA model will be used to compare the difference in eGFR between treatment groups at 6 weeks (+/- 4 weeks) after surgery with postoperative eGFR as the outcome, and treatment group, surgical technique, and preoperative eGFR as covariates.

We will also use the ANCOVA on the absolute level of eGFR because this has the greatest statistical power. However, the estimate produced by ANCOVA – a mean difference in eGFR levels – is of incomplete clinical interpretability. We will therefore present estimates in two other ways for the purposes of illustrating the results in clinical terms. We will first give percentage change separately by group, along with a difference between groups. We will also report the percentage of patients in each treatment group that have postoperative eGFR less than 60 ml/min/1.73 m², as this is generally considered to represent a clinical level of kidney dysfunction.

ANCOVA will be used to compare 6 month (+/- 2 months) postoperative radionuclear scintigraphy renal scan with treatment group, baseline postoperative radionuclear scintigraphy renal scan, and randomization stratum as covariates. ANCOVA will also be used to compare estimated blood loss and ischemia time with treatment group and randomization stratum as covariates.

Multivariable logistic regression will be used to assess the difference in the rate of grade 3-5 complications between treatment groups. The multivariable model will include treatment group and randomization stratum as covariates.

We will report a two-tailed p-value and a 95% confidence interval for the difference between groups for all secondary outcomes. Summary statistics will be calculated by group for age, sex, race, BMI, serum hemoglobin, serum albumin, ASA, and Karnofsky Performance Scale.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (<http://ppr/>). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

Randomization will be accomplished by the method of random permuted block, and patients will be stratified by preoperative eGFR (<60 v. ≥ 60 ml/min/1.73 m²) and surgical technique (open versus minimally invasive). This ensures adequate numbers of patients above and below the K/DOQI chronic kidney disease classification (i.e. <60 ml/min/1.73 m²) in the final study patient population. Also, we do not believe that surgical approach plays a role in the putative mechanism of action. To control for any such effects, randomization of cases will be stratified by minimally invasive or open surgical approach. Since this is a double blind study, the patients' treatment assignments can be viewed in the CRDB only by the hospital pharmacists who are dispensing the study drugs.

After eligibility is established and immediately after consent is obtained, patients will be registered in the Protocol Participant Registration (PPR) system and randomized using the Clinical Research Database (CRDB), by calling the MSKCC PPR Office at 646-735-8000 between the hours of 8:30 am and 5:30 pm, Monday - Friday.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study who will provide 15% of data management support. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the protocol study team activities. The data collected for this study will be entered into a secure departmental database. A minimal data set will be added to CRDB.

16.1 Quality Assurance

Monthly registration reports will be generated to monitor patient accrual and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, and extent and accuracy of evaluations will be monitored throughout the study period. Potential problems will be brought to the attention of the study team for discussion and action.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at:

<http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:
<http://mskweb2.mskcc.org/irb/index.htm>.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our



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clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk, and degree of monitoring required. Each type of protocol (e.g. NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Benefits and risks: The experimental intervention (mannitol) is preferentially omitted by certain oncological surgeons and is inconsistent in daily clinical practice at MSKCC. A previous study has suggested there is no benefit and there are theoretical arguments that it may do harm. Therefore we do not believe that the therapeutic aspects of this trial pose any risks different from those faced for patients undergoing a partial nephrectomy off-study.

Toxicities/side effects: Adverse outcomes have not been associated with the doses of mannitol being used in the protocol.

Alternatives/options for treatment: The alternative to participation in the trial would be to undergo a partial nephrectomy according to the surgeon's standard practice rather than be randomized. No other aspect of patient care would differ.

Financial costs/burdens: The subjects will not be compensated for their participation and there are no costs involved in participation.

Privacy and confidentiality: Every effort will be made to keep the study records private. No identifiers will be used in any reports or publications resulting from the study, however, the data will be used in the interests of ongoing research.

Voluntary nature of the study: Participation is entirely voluntary. All aspects of patient's care and monitoring will be unaffected by whether the patient chooses to consent for the study.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

IRB
PB

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- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
 - A explanation of how the AE was handled
 - A description of the subject's condition
 - Indication if the subject remains on the study
 - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:

The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1

This protocol is not an Industry or Cooperative group protocol.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

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Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

No appendices.