Guideline for Management of the Clinical Stage 1 Renal Mass

Renal Mass Clinical Panel Members:

Andrew C. Novick, MD, Chair
Steven C. Campbell, MD, PhD, Co-Chair

Arie Belldegrun, MD
Michael L. Blute, MD
George Kuoche Chow, MD
Ithaar H. Derweesh, MD
Jihad H. Kaouk, MD
Raymond J. Leveillee, MD, FRCS-G
Surena F. Matin, MD
Paul Russo, MD
Robert Guy Uzzo, MD

Consultants:

Martha M. Faraday, PhD
Linda Whetter, DVM, PhD
Michael Marberger, MD

AUA Staff:

Heddy Hubbard, PhD, FAAN
Edith Budd
Michael Folmer
Katherine Moore
Kadiatu Kebe

American Urological Association
Education and Research, Inc.

Dedication to Andrew C. Novick, M.D.

Consensus is always difficult. Even in the setting of level I evidence, competing interpretations, experiences and interests present challenges to the best-intentioned analyses. Consensus requires commitment to the process, time, a spirit of collaboration and, above all, leadership.

For many, Andy Novick's career was both the quintessence of leadership and the embodiment of the best in academic urology. Andy's clinical and intellectual contributions in the fields of kidney transplantation and renovascular surgery provided the underpinning upon which surgical and functional renal preservation in cases of kidney cancer is based. He brought forward many of the concepts and techniques for nephron-sparing surgery. Perhaps most importantly, Andy facilitated the recognition that nephron-sparing surgery was safe, feasible and oncologically sound through the systematic study and publication of his work as well as thoughtful review of the work of colleagues. He moved the field forward by believing that technology could improve care, but insisting on responsible application and repetitive reassessment of the data as a means of doing so. Andy was an ardent supporter of basic and translational science in urology in both word and deed. He was a passionate educator and served our national organizations such as the American Board of Urology with pride and conviction. In the midst of all this, he mentored hundreds of students, residents and fellows, cared for thousands of patients and developed one of the premier urologic programs in the world.

Andy had an enormous set of expectations of himself and those around him, recognizing that great achievements are within each of our own capacities. People who knew Andy were most drawn to his profound dedication to the values of the medical profession. He understood that deserved admiration was a responsibility. Andy engendered loyalty not to himself, but to the best within one's self.

We therefore dedicate this document and our efforts herein to Andrew C. Novick. As a compendium of the data regarding the treatment of localized renal masses, it represents his passion, his high standards and a roadmap for future generations of caregivers and investigators interested in relieving suffering from kidney cancer. It reflects the best that Andy was so consistently able to bring forth in all of us.

Chapter 1: Management of the Clinical Stage 1 Renal Mass: Diagnosis and Treatment Recommendations

Contents

Mission Statement

Detection of clinical stage 1 (< 7.0 cm), solid, enhancing renal masses has increased in frequency and is now a common clinical scenario for the practicing urologist. The biology of these tumors is heterogeneous, and there are multiple management options available, ranging from observation to radical nephrectomy (RN). Approximately 20% of clinical stage 1 renal masses are benign, and only 20% to 30% of malignant tumors in this size range demonstrate potentially aggressive features, with substantial variance based on patient age, gender and tumor size.[1, 2] Current practice is divergent and, in some cases, potentially discordant with what the existing literature supports. The American Urological Association (AUA) commissioned this Panel to develop guidelines for the management of the clinical stage 1 renal mass that would be useful to physicians involved in the care of these patients.

Introduction

It is estimated that in 2008, approximately 54,390 new cases (33,130 men and 21,260 women) of kidney cancer will be diagnosed in the United States (U.S.), resulting in 13,010 deaths.[3] Renal parenchymal tumors (renal cell carcinoma, RCC) account for approximately 85% of kidney cancers diagnosed in the U.S., while most of the remainder (12%) are composed of upper tract urothelial cancers.[4]

Renal cell carcinoma, which represents 2% of all adult cancers, is the most lethal of common urologic cancers, with approximately 35% of patients dying from the disease at the 5-year mark.[4] Approximately 17.9 new cases per 100,000 of the population were diagnosed in 2008.[5]

Average age at diagnosis for renal cell carcinoma is in the early 60s.[4] Childhood RCC is uncommon, representing only 2.3% to 6.6% of all pediatric renal tumors.[6-10]

Background

Epidemiology

Renal cell carcinoma incidence rates have risen steadily each year during the last three decades in most of the world, with an average increase of 2% to 3% per year.[11] Most renal masses,

particularly clinical stage T1 tumors, are now discovered incidentally during imaging prompted by nonspecific or unrelated symptoms.

Etiology

Tobacco use and obesity are the most consistently identified risk factors for RCC, accounting for about 20% and 30% of cases, respectively.[4, 12] Hypertension has also been demonstrated to increase the risk of RCC development.[4, 13] Nonsteroidal anti-inflammatory agents and dietary factors have not been found to play significant etiologic roles in RCC development.[4, 14] Moderate alcohol,[15, 16] fruit and vegetable[17, 18] and fatty fish[19] consumption have been reported to reduce the risk of RCC development. No consistent data are available to support occupational risk factors for RCC development.[4] Family history is associated with increased risk for RCC development, with inherited forms of RCC accounting for approximately two to four percent of cases.[4]

Major Pathologic Subtypes

Renal tumors are subdivided based on cell of origin and morphologic appearance. Classification schemes have changed over time, and certain histologic subtypes have fallen out of favor. RCC subtypes now include clear cell, papillary, chromophobe, collecting duct and unclassified RCC[20] with granular cell and sarcomatoid RCC no longer considered distinct entities. Sarcomatoid features can be present in all histologic subtypes and portend a poor prognosis.[21, 22]

Clear cell RCC frequently presents with higher stage and grade than papillary and chromophobe subtypes, and therefore the disease-specific survival (DSS) is worse.[23, 24]

Presentation and Diagnosis

Presentation

Incidental detection accounts for more than 50% of RCC cases, and these tumors are more likely to be organ confined and associated with an improved prognosis.[25, 26]

Symptoms associated with RCC can be the result of local tumor growth, hemorrhage, paraneoplastic syndromes or metastatic disease. Flank pain is usually due to hemorrhage or

obstruction (ureteral, vascular or thromboembolic), although it also may occur with locally advanced or invasive disease. The classic triad of flank pain, gross hematuria and palpable abdominal mass is now uncommon[25] and invariably denotes advanced disease.

Physical exam has a limited role in diagnosing RCC, but may be valuable in detection of signs of advanced disease such as a palpable abdominal mass, lymphadenopathy, nonreducing varicocele or bilateral lower extremity edema. Paraneoplastic syndromes are found in about 20% of patients with RCC, the most common being hypertension, polycythemia and hypercalcemia.[27, 28]

Diagnosis

Imaging techniques

Discovery of a renal mass with ultrasound (US) or intravenous pyelography should be further investigated with a high-quality computed tomography (CT) scan both prior to and following intravenous contrast medium, presuming adequate renal function. Differential diagnosis of a renal mass includes: RCC, renal adenoma, oncocytoma, angiomyolipoma, urothelial carcinoma, metastatic tumor, abscess, infarct, vascular malformation or pseudotumor. Approximately 20% of small, solid, CT-enhancing renal masses with features suggestive of RCC prove to be benign oncocytoma or atypical, fat-poor angiomyolipoma after surgical excision.[29] The incidence of benign histology is higher in young women as well as in older patients.[2, 30] Tumors less than 3 cm may be more likely to be benign [2,31] and the aggressive potential of RCC increases dramatically beyond this size. [32] With the exception of fat-containing angiomyolipoma, no current scanning methods can distinguish between benign and malignant solid tumors or between indolent and aggressive tumor biology. Oral and intravenously based abdominal CT scanning characterizes the renal mass, provides information about contralateral renal morphology and function, assesses extrarenal tumor spread (venous and regional lymph node involvement) and determines the status of the adrenal glands and the liver.

Magnetic resonance imaging (MRI) may be reserved for the clinical settings of locally advanced malignancy, possible venous involvement, renal insufficiency or allergy to intravenous contrast. However, recent studies have raised concern about the routine use of MRI. The U.S. Food and Drug Administration (FDA) is currently investigating a potential link between nephrogenic systemic fibrosis (NSF) and gadolinium exposure. NSF is a condition characterized

by progressive fibrosis of the skin and other organs leading to significant disability and increased mortality. Initially reported most commonly in end-stage renal disease (ESRD) patients, it is also described in advanced chronic kidney disease (CKD) not requiring dialysis. No clearly effective therapies exist. Current FDA recommendations for utilization of gadolinium are to consider: (a) utilization only if clearly necessary in patients with advanced CKD and (b) institution of prompt dialysis in patients with advanced renal dysfunction who receive gadolinium contrast. MRI can be used selectively in the evaluation of patients with clinical stage 1 renal masses, primarily for patients at risk for contrast nephropathy or those who are allergic to conventional intravenous contrast. In these settings, a balanced discussion of the potential risks of NSF should be considered.

Routine metastatic evaluation should include liver function tests, abdominal/pelvic CT and chest radiography. Bone scan should be obtained for patients with elevated serum alkaline phosphatase, bone pain or decline in performance status,[33] and chest CT should be obtained for patients with pulmonary symptomatology or an abnormal chest radiograph.[34] Most brain and bone metastases are symptomatic at time of diagnosis, and therefore, routine imaging of these sites is generally not indicated.

Role of Renal Mass Biopsy

Percutaneous renal biopsy or fine needle aspiration (FNA) has traditionally served a limited role in the evaluation of renal masses because of the relatively high diagnostic accuracy of cross-sectional imaging such as CT or MRI and concern about a high false-negative rate and potential complications associated with renal mass biopsy.[35-38] Biopsy or aspiration was thus primarily reserved for patients suspected of having renal metastasis, abscess or lymphoma, or when needed to establish a pathologic diagnosis of RCC in occasional patients presenting with disseminated metastases or unresectable primary tumors.[35]

In recent years, the potential role of biopsy for localized renal tumors has been revisited, in part driven by the recognition that 20% clinical stage T1 renal masses may represent benign disease and could be considered for less aggressive management.[2,31,32,40] In addition, accuracy and safety of renal mass biopsy has improved substantially due to further refinements in CT- and MRI-guided techniques.[39-46] A review of studies since 2001 demonstrates that the false-negative rate with renal mass biopsy is now only 1%, and the incidence of symptomatic complications is relatively low, with only a very small percentage (< 2%) requiring any form of intervention.[40,48]

Needle-tract seeding also appears to be exceedingly rare, assuming appropriate patient selection. While another 10% to15% of renal mass biopsies are indeterminate, this is much less concerning than a false negative, which would lead to observation of a malignancy. Given the significant heterogeneity in the biological aggressiveness of clinical stage 1 renal masses and the wide range of treatment options now available, renal mass biopsy is now being used increasingly for patient counseling and clinical decision making. This approach is appropriate for patients in whom a wide range of management options are under consideration, ranging from surgery to observation. Renal mass biopsy is not indicated, however, for healthy patients who are unwilling to accept the uncertainty associated with this procedure or for older patients who will only consider conservative management options regardless of biopsy results. Incorporation of molecular analysis has shown great promise to further improve accuracy of renal mass biopsy/aspiration and remains a research priority.[41,43]

Tumor Characteristics

Staging

The 2002 tumor, nodes, metastasis (TNM) stage classification system proposed by the International Union Against Cancer, which defines the anatomic extent of disease more explicitly than previously, is recommended for clinical and scientific use.[49] T1 tumors are those that are confined to the kidney and ≤ 7 cm in greatest dimension. The T1 substratification (T1a: ≤ 4 cm in greatest dimension; T1b: > 4 cm but ≤ 7 cm in greatest dimension), introduced in 2002,[48] has been validated by a number of studies[49-51] with estimated five-year cancer-specific survival (CSS) rates by the 2002 tumor classification of 95.3% to 97% and 87% to 91.4% in patients with pT1a and pT1b RCC, respectively.[49, 50]

Grading

Over the past century, multiple grading systems for RCC have been proposed. In the early 1980s, Fuhrman and colleagues presented a landmark series of 100 patients after nephrectomy.[52] Four nuclear grades were defined based on increasing nuclear size and irregularity and nucleolar prominence. While concerns over interobserver variability persist, the Fuhrman grading system remains the most widely used system in the U.S. today.[53, 54] Higher Fuhrman grade is associated with larger tumor size and advanced stage.[55] Several large series have demonstrated that

Fuhrman grade is an independent predictor of survival for conventional clear cell RCC.[24, 56] For patients with pT1 clear cell lesions, the 5-year disease-specific survival (DSS) rate was 94.2% for patients with Grade 1-2 disease and 89.8% for patients with Grade 3-4 disease[179]. For cases of papillary tumors, type I and type II designation is more appropriate and for chromophobe[181] and other nonclear cell RCC, high or low grade (not Fuhrman) is appropriate.[180]

Other Prognostic Indicators

Tumor Size

The 2002 American Joint Committee on Cancer TNM system changed the classification system of T1 tumors to incorporate size, stratifying T1 tumors into T1a (≤ 4 cm) and T1b (> 4 cm and < 7 cm).[57] While this has been independently validated, the threshold cutpoints of 4 cm and 7 cm have generated controversy, and the current literature suggests that tumor size provides optimal prognostic information when used as a continuous rather than a dichotomous variable.[58-61]

Necrosis

Tumor necrosis in RCC can be microscopic or macroscopic. The majority of analyses deal with microscopic coagulative necrosis. This feature is associated with higher stage, grade and tumor size and is more common in papillary and clear cell subtypes.[62, 63] One recent analysis suggests that tumor necrosis is an independent predictor of poor outcomes in pT1 RCC.

Microvascular Invasion

Presence of microvascular invasion of neoplastic cells within an endothelial-lined vessel is associated with higher stage, grade and tumor size and has been shown to be an independent predictor of poor survival in clinically localized RCC. [64-66]

Sarcomatoid Features

While once considered a separate entity, sarcomatoid features can be found in all histologic subtypes.[20, 67] Sarcomatoid features represent an aggressive, de-differentiated component of the primary tumor.[68] Most tumors with sarcomatoid features present at an advanced stage, [182] and response to systemic therapy is poor.[21, 69-71]

Collecting System Invasion

Invasion into the collecting system occurs in less than 10% of T1 tumors. However, in this subgroup of patients, this finding indicates a poor prognosis.[72, 73]

Symptoms and Performance Status

Incidentally detected tumors are lower stage and grade.[74, 75] Patients with incidentally detected tumors have improved DSS; however, whether this association persists after controlling for larger size, stage and grade is unclear.[76-78] Performance status is a qualitative measure of the disease burden and functional status of a patient that has closely correlated with prognosis for patients with all stages of RCC.

Clinical and Biological Indicators

A variety of clinical and biological indicators is associated with tumor progression and may influence survival in RCC. For instance, anemia, preoperative thrombocytosis and elevated erythrocyte sedimentation rate or C-reactive protein are all markers of poor prognosis in RCC.[79-83]

Molecular Studies

Molecular markers are the future to understanding RCC prognosis and response to therapy and will likely be incorporated into renal mass biopsy to improve patient counseling in the near future. Many important genes and proteins involved in key pathways are now known to be potential prognostic markers. Most prominent among these are various alterations in the *vhl* gene and altered expression of carbonic anhydrase IX (CAIX) or the B7H1 molecule, which is a costimulatory molecule involved in immune responses to RCC. Other potential molecular prognostic markers for RCC include cell cycle regulators such as p27, cyclin D1, pRb and p53 and markers of cellular proliferation such as Ki-67. Expression levels of important members of the hypoxia-inducible pathway such as HIF1α, VEGF and the VEGF receptors may also correlate with outcomes for RCC.[84, 85]

Overview of Treatment Alternatives

Surveillance

Patients diagnosed with a clinical T1 renal mass with radiologic characteristics consistent with RCC may be candidates for active surveillance (AS) with delayed or, alternatively, no treatment rendered. Indications for AS include elderly patients, those with decreased life expectancy or those with medical comorbidities that would be associated with increased risk if a therapeutic intervention were to be undertaken. Alternatively, a strategy of observation with delayed intervention as indicated may be elected in order to determine the growth rate or to obtain alternative diagnostic imaging. A judicious period of AS appears to be associated with a low risk of size or stage progression while maintaining most therapeutic options.[86]

Radical nephrectomy

For decades, RN has been the mainstay of treatment for all renal masses including clinical stage 1 tumors. This includes removal of the entire kidney including Gerota's/Zuckerkandel's fascia, regional lymph nodes and the adrenal gland. CSS, local tumor control and progression-free survival have been extremely high with this approach. The main concern with RN is the negative impact on renal function and association with CKD.[130] RN is currently greatly overutilized for the management of clinical stage T1 renal masses, particularly stage T1a.[87]

Open Radical Nephrectomy (ORN)

At one time, ORN was the gold standard for treatment of all renal masses. Currently, with the advent of minimally invasive approaches, the indications for ORN are diminishing, particularly in patients with clinical stage 1 renal masses. Urologic surgeons should still be skilled in ORN for situations where minimally invasive approaches may not be possible or if conversion to an open approach is required.

Laparoscopic Radical Nephrectomy (LRN)

In an effort to reduce patient morbidity, urologic surgeons adapted the minimally invasive technique of laparoscopy to perform kidney removal. First described in 1991,[88] there have been multiple adaptations of the operation, including entrapment with morcellation, intact extraction and hand-assisted laparoscopic nephrectomy. The literature includes many reports of the

advantages of these approaches with virtually unanimous agreement that there is reduced perioperative and postoperative morbidity while maintaining equivalent short- and long-term oncologic efficacy, particularly in patients with small, localized tumors.

Partial Nephrectomy (PN)

The understanding of increased risk of CKD with RN and recent data highlighting the association between CKD and cardiovascular morbidity and mortality has led to the desire to preserve as much normal renal parenchyma as possible.[130, 132] PN is now widely accepted as a treatment alternative which yields virtually identical oncologic outcomes as RN for appropriately selected patients. While PN was initially reserved for absolute indications such as patients with a solitary kidney, renal insufficiency whereby dialysis would likely ensue or in those with inheritable forms of renal cancer, PN is now considered the treatment of choice for most clinical T1 renal masses, even in those with a normal contralateral kidney.

Open Partial Nephrectomy (OPN)

Open partial nephrectomy is generally recognized as one of the standards of care for localized renal masses. Potential problems unique to PN include inadequate surgical margins, hemorrhage, warm ischemia and urine leak. Steps taken to avoid these complications include the use of frozen section of tumor base when indicated, hilar vessel clamping (artery alone or artery/vein), manual compression, use of diuretics and free radical scavengers, cold ischemia and meticulous closure of the collecting system and capsule. Multiple published series demonstrate OPN to be safe, effective and reproducible for the treatment of clinical T1 renal masses.

Laparoscopic Partial Nephrectomy (LPN)

Similar to the introduction of LRN with its equivalent oncologic outcomes and improved morbidity profile, LPN attempts to achieve equivalence with OPN. Initially reserved for superficial cortical tumors, with the advent of improved laparoscopic surgical instrumentation, LPN is now often performed utilizing the same surgical techniques as its open counterpart (vascular control, watertight closure of the collecting system and capsule, use of surgical bolsters, etc.). Shortcomings currently are the need for advanced laparoscopic techniques, such as suturing, and extensive experience. Although oncologically comparable to OPN for localized renal masses, most series demonstrate that LPN is associated with greater warm ischemia time

and an increased risk of postoperative hemorrhage when compared to OPN. Hence, LPN has largely been confined to centers of surgical excellence where high volume of cases is the rule. However, with further improvements in laparoscopic instrumentation and greater dissemination of expertise, more widespread application of LPN is anticipated in the future.

Robotic-Assisted Laparoscopic Partial Nephrectomy

Very recently, robotic-assisted LPN has been offered to patients at various practices. While robotic instrumentation has been used for treatment of prostate cancer for several years, its use for PN is a recent application. Currently, only a few small, single-institution reports offer limited information regarding this procedure, including whether robotic-assisted LPN offers any advantages over other forms of nephron-sparing surgery (NSS). At present there are insufficient data to evaluate outcomes. [89-91]

Ablative therapies

Renal ablative techniques were developed in an effort to improve patient procedural tolerance and reduce the potential for complications. A variety of generators, ablation probes and energy delivery systems are now commercially available. Energy-based tissue-ablative techniques include radiofrequency ablation (RFA) and cryoablation. Controversy exists about which technology is superior. The primary requirement for an ablative technology to be efficacious is that it must deliver a lethal treatment to the cancer cells, leaving no viable cancer cells within the treated zone. Of equal importance, the physician must be able to localize, control and predict the area of treatment while avoiding inadvertent ablation of surrounding healthy tissue. Renal tumor ablations can be performed through open incisions or via laparoscopic or percutaneous routes under image guidance (US, MRI, CT). Although ablative therapies show promise of efficacy, long-term oncologic follow-up is not yet available. Surrogate outcome measures such as radiographic demonstration of loss of contrast enhancement have come into question. Available data suggest that local control may be suboptimal when compared to surgical excision, and surgical salvage may be difficult. While it is likely that outcomes associated with ablative modalities will improve with further advances in technology and application, judicious patient selection remains of paramount importance.

Novel treatments

The literature reflects the evolution of novel treatment modalities which include high intensity focused ultrasound (HIFU), radiosurgery, microwave thermotherapy (MWT), laser interstitial thermal therapy (LITT), pulsed cavitational ultrasound (PCU), as well as other new technologies. Clinical outcomes are limited to a small number of patients with short-term follow-up, and these modalities remain investigational.

METHODOLOGY

The Panel's goals were to: conduct a systematic literature review of the relevant scientific evidence; identify descriptive information about samples and procedures relevant to interpreting existing evidence; identify outcomes relevant to patients, families, and practitioners; estimate outcome effect sizes for the most commonly used treatments and approaches; complement the available evidence with expert opinion; and determine what additional evidence is needed to further evidence-based management of the clinically localized renal mass. The Panel also carefully considered other important factors that may affect treatment options such as patient preferences and the availability of particular facilities or expertise.

The evidence review process included literature searches, extraction of descriptive information about samples and procedures and extraction of outcomes data. The management options evaluated were: AS; cryoablation (cryo in tables); RFA; LPN; OPN; LRN; and ORN.

The descriptive information considered included: patient age; tumor size; follow-up duration; and numbers of studies with/without pathological validation of tumor type. These data were used to describe the subpopulations treated with the different interventions and to interpret effect sizes across interventions when major patient variables (i.e., age, tumor size, follow-up duration) differed across interventions.

The outcomes examined were: major urological complications; major nonurological complications; perioperative events (conversions, transfusions and reinterventions); total recurrence-free survival (RFS); local RFS; metastatic RFS; CSS; and overall survival (OS).

Literature Searches and Article Selection

Literature searches on English-language publications were performed using the MEDLINE database from January 1, 1996 to September 30, 2007 using the terms "renal carcinoma" and "renal mass" in conjunction with the interventions evaluated. Pediatric studies, studies with sample size less than five, editorials and reviews were eliminated. Studies that focused primarily on surgical techniques without detailed outcomes information and studies in which more than 50% of patients were dialysis patients, solitary kidney patients, patients with recurrent RCC or patients with hereditary RCC syndromes were eliminated. Studies that reported descriptive or outcomes information collapsed across multiple interventions were also excluded. Multiple reports on the same patient group were carefully examined to ensure inclusion of only nonredundant outcomes data. For the survival analyses, studies had to meet the additional criteria that the diagnosis of RCC was validated pathologically and that survival outcomes for RCC patients were separable from outcomes for patients diagnosed with benign tumors. One exception was made to this rule: AS patients were included in metastatic RFS analyses. This exception was made because of the clinical importance of estimating the probability of metastases in patients for whom no intervention was undertaken.

All extracted articles used adult human subjects. A total of 114 articles met inclusion criteria and underwent data extraction.

All authors, consultants and the panel manager self-reported potential conflicts of interest (COI) in accordance with AUA policy. The panel chair and facilitator reviewed the COI disclosures, and the disclosures were made available to all panel members in hard copy prior to all meetings. Staff reviewed the AUA COI policy requiring recusal in the event of potential biases or conflicts prior to every meeting.

Data Extraction and Evidence Combination

Quantitative information about samples, procedures and outcomes was extracted by the methodologist into Excel spreadsheets. All entered data were double checked for accuracy.

Most studies examined one treatment group; some studies compared two treatment groups. All intervention groups were treated as single arms that estimated the outcome or other variable in the population of interest, regardless of the number of groups in a particular study. This approach maximized statistical power and the use of available information. Table 1 lists the

total number of arms for each intervention and the number of studies of each type used to generate descriptive information and used in the meta-analyses.

Table 1: Study Types for Descriptive Information and Meta-Analyses							
Total Number of Study Arms							
AS	**Cryo**	**RFA**	**LPN**	**OPN**	**LRN**	**ORN**	
12	16	21	26	29	17	17	
Single-Arm Observational Studies							
AS	**Cryo**	**RFA**	**LPN**	**OPN**	**LRN**	**ORN**	
12	13	18	20	13	10	2	
Two-Arm Observational Studies							
Cryo vs. RFA	**Cryo vs. LPN**	**RFA vs. OPN**	**LPN vs. OPN**	**LPN vs. LRN**	**OPN vs. LRN**	**OPN vs. ORN**	**LRN vs. ORN**
2	1	1	4	1	1	10	5

The effect size calculated was a point estimate with 95% confidence intervals. The point estimate for a given outcome includes all study arms that reported that particular outcome. Most of the data involved the occurrence of an event (i.e., a complication, a recurrence, a death), resulting in point estimates that are estimates of the event rate for a particular outcome in the population of interest bounded by 95% confidence intervals. In the tables, the event rates are expressed as percentages.

Statistical Model

A random effects model was used to calculate the effect size for each study and to generate the overall effect sizes for particular interventions.[a] This model assumes that the true effect could legitimately vary from study to study following a normal distribution and that some variability across studies is variability in true effect that is not error. This model produces conservative estimates of effect sizes and is the most appropriate given the type of data available.

Limitations of Available Data

***Limitations of study design*:** The overwhelming majority of studies available to the Panel were observational, retrospective, reported findings on samples of convenience that were not

[a] All effect size calculations and analyses were run using Comprehensive Meta-Analysis (CMA) software, version 2.0 (Biostat, Inc.).

randomized to treatments and involved only one treatment group. There are inherent, unknown and unquantifiable biases within each study because of the lack of randomization. The Panel weighed this issue carefully in its deliberations and concluded that meta-analysis was valuable to describe the existing literature and to determine what types of information are needed to further evidence-based management of the clinical stage 1 renal mass.

***Confounding variables*:** Interpreting statistically significant differences in outcomes across interventions requires thorough consideration of other variables that could account for differences. Three confounding variables that differed across interventions were focused on in detail: patient age, tumor size and follow-up duration. For most outcomes, the influence of confounding variables could not be separated from possible intervention effects, making interpretation of statistically significant differences difficult. For this reason, only comparisons for which confounding variables appear to exert minimal influence are presented. The possible impact of these factors is addressed in the sections that follow and must be weighed carefully in interpreting the point estimates.

RESULTS OF THE OUTCOMES ANALYSIS

This section summarizes the evidence evaluated by the Panel, including the descriptive information examined and results from meta-analyses.[b]

Descriptive Information

***Patient Age Varies Across Interventions*:** Table 2 presents the mean and median patient age for each intervention type. Patients treated with AS, cryoablation and RFA generally were older than those treated with OPN, LPN, ORN or LRN.

[b] Not all studies reported all descriptive information. The tables contain data from the study subsets that reported the variable of interest.

Table 2: Patient Age - Number of Studies and Patients			
Intervention Type	**# of Studies**	**# of Patients**	**Mean/Median Age (yrs)**
Active Surveillance	12	390	67.1 / 68.2
Cryoablation	15	644	66.9 / 66.3
Radiofrequency Ablation	19	745	68.5 / 70.0
Partial Nephrectomy – Lap	26	2245	60.5 / 60.1
Partial Nephrectomy – Open	28	6418	60.1 / 60.0
Radical Nephrectomy – Lap	17	1581	60.9 / 61.0
Radical Nephrectomy – Open	16	6235	62.5 / 63.0

***Tumor Size Varies Across Interventions*:** Table 3 presents the mean and median tumor size for each intervention type. AS, cryoablation, RFA, LPN and OPN were used to treat relatively small tumors. LRN and ORN were used to treat larger tumors.

Table 3: Tumor Size - Number of Studies and Patients			
Intervention Type	**# of Studies**	**# of Patients**	**Mean/Median Tumor Size (cm)**
Active Surveillance	12	390	2.7 / 2.2
Cryoablation	15	644	2.6 / 2.6
Radiofrequency Ablation	19	745	2.7 / 2.7
Partial Nephrectomy – Lap	26	2245	2.6 / 2.6
Partial Nephrectomy – Open	25	5596	3.2 / 3.0
Radical Nephrectomy – Lap	15	1391	4.8 / 5.1
Radical Nephrectomy – Open	14	5849	5.0 / 5.4

***Follow-Up Durations Vary Across Interventions*:** Table 4 presents the mean and median follow-up duration (mos) for each intervention type. AS, cryoablation, RFA, LPN and LRN had the shortest follow-up periods; OPN and ORN had the longest follow-up periods.

Table 4: Follow-Up Duration -- Number of Studies and Patients			
Intervention Type	**# of Studies**	**# of Patients**	**Mean/Median Follow-Up (mos)**
Active Surveillance	12	390	29.6 / 29.0
Cryoablation	10	463	19.5 / 16.7
Radiofrequency Ablation	10	528	22.9 / 19.4
Partial Nephrectomy – Lap	17	1639	20.8 / 15.0
Partial Nephrectomy – Open	22	5057	55.5 / 46.9
Radical Nephrectomy – Lap	8	795	30.2 / 17.7
Radical Nephrectomy – Open	13	5294	60.8 / 58.3

***Number of studies in which RCC was confirmed*:** Table 5 presents the number of studies in each intervention category with and without pathological validation of tumor type.

Table 5: Studies with and without RCC confirmation		
	Number of Studies	
Intervention Type	Patients with pathology-confirmed RCC identifiable; outcomes attributable to patients with RCC	No biopsy, no pathology, incomplete pathology, or outcomes not attributable to patients with RCC
Active Surveillance	3	9
Cryoablation	9	7
RFA	12	9
Partial Nephrectomy – Lap	23	3
Partial Nephrectomy – Open	29	2
Radical Nephrectomy – Lap	17	2
Radical Nephrectomy – Open	16	0

META-ANALYTIC FINDINGS

Interpretation Cautions: The findings presented below must be interpreted with full understanding of two issues. First, the data source was observational studies. The data are likely to contain, therefore, unknown and uncontrolled biases, including selection bias and other problems inherent in nonrandomized retrospective designs. Second, the descriptive data indicate that patient age, tumor size and follow-up durations varied widely across the interventions considered. Therefore, interpretation of the percentages presented in the tables (the point estimate effect sizes and confidence intervals) is limited by these issues. For most outcomes, the influence of confounding variables could not be separated from possible intervention effects, making interpretation of statistically significant differences difficult. For this reason, the only comparisons presented are those for which confounding variables appear to exert minimal influence. Overall, the findings presented below are best understood as accurately describing the available literature. Limited conclusions can be made regarding true differences among interventions. Differences that are most likely to be unconfounded are emphasized.

Tables and Sections: The tables summarize the meta-analyzed data by intervention type for all studies that reported extractable data in a particular category. The column labeled "Percent" is the point estimate effect size calculated using a random effects model, taking into account all studies that reported a particular outcome and met criteria for the analysis. The lower and upper limits represent 95% confidence intervals. Possible confounding variables are presented in

additional columns (i.e., patient age and tumor size for complications and perioperative events; age, tumor size and follow-up duration for survival). These numbers differ somewhat from the information presented in Tables 2, 3 and 4 because they are derived from the group of studies that met criteria for a particular analysis and the subset of these studies that provided descriptive information. The sections labeled "Interpretation" emphasize the potential role of confounding variables. Sections that include comparisons among interventions have an additional section labeled "Comparisons" that describes statistically significant differences with an accompanying table.

Major Urological Complications

Table 6a summarizes the major urological complications data. Major urologic complications include postoperative hemorrhage requiring transfusion or other intervention, urinary leak or fistula, abscess, unanticipated loss of renal function or other local complications potentially related to the procedure. Complication types are defined in Table 14. Conversions were not counted as complications.

Table 6a:
Major Urological Complications

Study Type	# of studies	Percent	Lower Limit	Upper Limit	Mean/Median Patient Age (yrs)	Mean/Median Tumor Size (cm)
Cryo	15	4.9	3.3	7.4	67.0 / 66.7	2.6 / 2.6
RFA	20	6.0	4.4	8.2	68.5 / 70.0	2.7 / 2.7
LPN	22	9.0	7.7	10.6	60.4 / 59.9	2.6 / 2.6
OPN	15	6.3	4.5	8.7	59.5 / 59.0	3.2 / 3.0
LRN	13	3.4	2.0	5.5	60.7 / 61.0	4.8 / 5.1
ORN	6	1.3	0.6	2.8	62.7 / 62.3	4.9 / 5.2

Table 6b:
Major Urological Complications: Significant Comparisons (p<0.05)

LPN			
OPN	OPN		
	Cryo	Cryo	
	RFA	RFA	
		LRN	
			ORN

Comparisons: Table 6b presents statistically significant differences among interventions.[c] Major urologic complication rates following laparoscopic partial nephrectomy were significantly higher ($p < 0.05$) than cryoablation, RFA, LRN and ORN rates, but statistically indistinguishable from

[c] Interventions in the same column have statistically similar rates; column order reflects relative magnitude with the highest values in the far left column and the lowest values in the far right column. Statistically significant differences are present when adjacent column and row entries do not overlap. ORN appears only in the last column; its rate is significantly lower than all other interventions. LPN appears only in the first column; its rate is significantly higher than all other interventions except for OPN, which also is present in the first column.

OPN rates. OPN rates were statistically indistinguishable from cryoablation and RFA rates but significantly higher ($p < 0.05$) than LRN and ORN rates. Cryoablation, RFA and LRN rates were statistically indistinguishable. ORN major urological complication rates, however, were significantly lower ($p < 0.05$) than rates for all other interventions.

Interpretation: Statistically significant differences must be interpreted in the context of patient age and tumor size differences. The higher LPN major urological complication rate may represent a valid finding because potential confounding variables would be expected to reduce the LPN complication rate. Specifically, among studies that treated smaller tumors (cryoablation, RFA, OPN, LPN), LPN major urological complication rates were significantly higher than ablation rates even though LPN patients were younger than ablation patients. Among studies that treated relatively young patients (LPN, OPN, LRN, ORN), LPN major urological complication rates were significantly higher than LRN and ORN rates despite the fact that LRN and ORN patients had larger tumors.

The relatively high major urological complication rate for OPN patients, though of less magnitude than the LPN rate, may also represent a valid finding because confounding variables would be expected to reduce the rate. OPN major urological complication rates were similar to ablation rates even though OPN patients were younger. OPN major urological complication rates were significantly higher than LRN and ORN rates even though LRN and ORN patients had larger tumors. In addition, a single randomized controlled trial compared OPN and ORN complication rates[92]and reported similar patterns. In 242 OPN patients, there was a 4.1% urinary fistula rate, and 12% of patients had a blood loss of 0.5 liters or greater. In comparison, in 287 ORN patients, there were no urinary fistulas and 5.2% of patients experienced a greater than 0.5 liter blood loss. These data were not included in the meta-analysis but lend validity to the higher urological complication rate for OPN compared to ORN suggested by the meta-analyzed data.[d]

The higher major urological complication rates for the ablation therapies compared to ORN are more difficult to interpret given that these patients were older than ORN patients and

[d] This study was the only randomized controlled trial (RCT) in the relevant literature. Conservative meta-analytic procedures stipulate that RCT data, because of the stronger study design, should be considered separate from and not combined with observational study data. Because this study reported complications in a way that did not fit the complications definitions used by the Panel, it was not possible to calculate a point estimate that would be comparable to those calculated for the observational studies. The RCT findings, however, are informative in that they parallel findings of the observational studies.

generally had comorbidities that may have increased the potential for complications. This difference should not be overinterpreted.

The higher major urological complication rate for LRN patients compared to ORN patients also may represent a valid finding. LRN major urological complication rates were significantly higher than ORN rates even though LRN and ORN were used to treat patients of similar ages and with similar tumor sizes.

Overall, the higher major urological complication rates for the PN and laparoscopic interventions may reflect the technical complexity of these procedures. A learning curve for laparoscopic procedures during this era may have contributed to these findings.

Major Nonurological Complications

Table 7a summarizes the major nonurological complications data.

Table 7a:
Major Nonurological Complications

Study Type	# of studies	Percent	Lower Limit	Upper Limit	Mean/Median Patient Age (yrs)	Mean/Median Tumor Size (cm)
Cryo	15	5.0	3.5	7.2	67.0 / 66.7	2.6 / 2.6
RFA	20	4.5	3.2	6.2	68.5 / 70.0	2.7 / 2.7
LPN	22	4.6	2.9	7.1	60.4 / 59.9	2.6 / 2.6
OPN	14	2.2	1.2	4.0	59.5 / 59.0	3.2 / 3.0
LRN	13	8.3	5.5	12.4	60.7 / 61.0	4.8 / 5.1
ORN	6	5.9	3.4	10.2	62.7 / 62.3	4.9 / 5.2

Interpretation: Given that the interventions treated patients of different ages and tumor sizes, meaningful comparisons were not possible. For example, although LRN and ORN had the highest rates, these patients had larger tumors than the other interventions.

Perioperative Events

***Conversions*:** Conversions were defined as any change from the planned renal surgical approach or procedure to a different renal surgical approach or procedure. Studies in which the authors specifically stated that no conversions were necessary were included in these analyses. Studies in which the authors did not address the occurrence of conversions were not included. Table 8a

summarizes the conversion data. ORN studies were not included because conversions were not relevant to this intervention.

Table 8a: Conversions

Study Type	# of Studies	Percent	Lower Limit	Upper Limit	Mean/Median Patient Age (yrs)	Mean/Median Tumor Size (cm)
Cryo	15	3.5	2.2	5.6	67.0 / 66/7	2.6 / 2.6
RFA	19	1.6	0.9	3.0	68.9 / 70.2	2.7 / 2.7
LPN	24	3.9	3.0	5.1	60.4 / 60.1	2.6 / 2.6
OPN	11	0.5	0.2	1.2	59.1 / 59.0	3.1 / 3.1
LRN	14	3.0	2.1	4.1	61.0 / 61.0	4.8 / 5.1

Table 8b: Conversions – Significant Comparisons ($p<0.05$)

LPN		
Cryo	Cryo	
LRN	LRN	
	RFA	
		OPN

Comparisons: Table 8b presents statistically significant comparisons.[e] OPN patients had the lowest conversion rate at less than 1%; this rate was significantly less ($p < 0.05$) than rates for all of the other interventions. RFA rates were significantly less ($p < 0.05$) than those for LPN. Rates for LPN, cryoablation and LRN were statistically similar; rates for cryoablation, LRN and RFA were statistically similar.

Interpretation: In the context of interventions used to treat small tumors in relatively young patients (LPN and OPN), the significantly higher conversion rate for LPN may reflect the greater technical challenge of laparoscopic procedures and may be a valid difference. It should be noted that an occasional and timely conversion from a laparoscopic to an open procedure should not necessarily be considered an adverse event. The higher conversion rates for the ablation therapies and LRN are more difficult to interpret because they may be influenced by the older patient population and larger tumor sizes treated, respectively, by these interventions. The very low rate for OPN also is difficult to interpret and may reflect the young patient population, the relatively small tumor sizes treated and/or the technical advantages of the open surgical approach.

[e] Interventions in the same column have statistically similar rates; column order reflects relative magnitude with the highest values in the far left column and the lowest values in the far right column. Statistically significant differences are present when adjacent column and row entries do not overlap. For example, OPN appears only in the last column; its rate is significantly lower than all other interventions. LPN appears in the first column with cryoablation and LRN; its rate is statistically similar to cryoablation and LRN rates but significantly higher than RFA and OPN rates.

Additional Information: The number of studies that reported the occurrence of conversions, the reason for conversion and the procedure to which the operation was converted are detailed in Tables 8c and 8d (e.g., of the 11 conversions reported in cryoablation studies, nine were converted to open cryoablation, and two were converted to ORN). Each column indicates the number of studies that reported the occurrence of a conversion, the total number of studies that addressed conversions, and the total number of procedures that were performed. Of 109 conversions, the most commonly reported conversion reason was bleeding (38 reports). In 23 instances, the reason for the conversion was not reported.

Table 8c: Reason for Conversion

Conversion Reason	**Cryoablation** (conversions occurred in 4 of 15 studies; total of 727 procedures)	**RFA** (conversions occurred in 1 of 19 studies; total of 837 procedures)	**LPN** (conversions occurred in 13 of 24 studies; total of 2067 procedures)	**OPN** (conversions occurred in 1 of 11 studies; total of 2216 procedures)	**LRN** (conversions occurred in 9 of 14 studies; total of 1387 procedures)
Bleeding	2	0	18	0	18
Perirenal fat, renal vessel or hilum involvement	1	0	4	0	1
Access or adhesions	6	0	11	0	3
Positive margins	0	0	12	1	0
Proximity to other intra-abdominal structure	0	1	2	0	0
Cutting into tumor or tumor fracture	0	0	1	0	0
Respiratory difficulty	2	0	0	0	0
Bowel injury	0	0	0	0	1
Multiple masses	0	0	1	0	0
Need to remove >50% of kidney	0	0	1	0	0
Not reported	0	0	12	0	11
TOTAL	**11 (1.5%)**	**1 (0.12%)**	**62 (3.0%)**	**1 (0.045%)**	**34 (2.45%)**

Table 8d: Original and Converted-To Procedures

	Original Procedure				
Converted to ⇩	**Cryoablation**	**RFA**	**LPN**	**OPN**	**LRN**
Open Cryo	9	n/a	n/a	n/a	n/a
Open RFA	n/a	1	n/a	n/a	n/a
LPN	0	0	n/a	n/a	n/a
OPN	0	0	38	n/a	n/a
LRN	0	0	22	0	n/a
ORN	2	0	2	1	34
TOTAL	**11 (of 727 procedures; 1.5%)**	**1 (of 837 procedures; 0.12%)**	**62 (of 2067 procedures; 3.0%)**	**1 (of 2216 procedures; 0.045%)**	**34 (of 1387 procedures; 2.45%)**

***Transfusions*:** Table 8e summarizes the transfusion data. ORN studies were not included in this analysis because these studies did not consistently report transfusion use.

Table 8e: Transfusions

Study Type	# of Studies	Percent	Lower Limit	Upper Limit	Mean/Median Patient Age (yrs)	Mean/Median Tumor Size (cm)
Cryo	15	3.2	2.0	4.9	67.0 / 66.7	2.6 / 2.6
RFA	19	2.4	1.4	4.0	68.9 / 70.2	2.7 / 2.7
LPN	21	6.0	4.1	8.9	60.6 / 60.0	2.5 / 2.6
OPN	9	8.1	4.7	13.7	57.9 / 58.4	3.1 / 2.9
LRN	11	2.1	0.9	4.8	60.5 / 61.0	5.1 / 5.1

Table 8f: Transfusions – Significant Comparisons (p<0.05)

OPN	
LPN	
	Cryo
	LRN
	RFA

Comparisons: Table 8f presents statistically significant comparisons.[f] OPN and LPN patients had the highest transfusion rates; these rates were significantly higher ($p < 0.05$) than the rates for cryoablation, RFA and LRN patients.

Interpretation: Because OPN and LPN were used to treat younger patients with smaller tumors, the significantly higher transfusion rates may be valid differences and may reflect the technical challenges of PN procedures.

***Reinterventions*:** Reinterventions were defined as any unplanned operation that occurred during or after the planned renal surgery. Table 8g summarizes the reintervention data.

Table 8g: Reinterventions

Study Type	# of Studies	Percent	Lower Limit	Upper Limit	Mean/Median Patient Age (yrs)	Mean/Median Tumor Size (cm)
Cryo	15	2.6	1.5	4.3	67.0 / 66.7	2.8 / 2.6
RFA	20	3.2	1.9	5.1	68.5 / 70.0	2.7 / 2.7
LPN	22	3.4	2.7	4.4	60.4 / 60.0	2.6 / 2.6
OPN	14	1.6	1.0	2.7	59.0 / 59.5	3.0 / 2.9
LRN	13	2.0	1.2	3.2	60.7 / 61.0	4.8 / 5.1
ORN	6	1.1	0.6	2.1	62.0 / 62.3	5.0 / 5.4

Table 8h: Reinterventions – Significant Comparisons (p<0.05)

LPN		
RFA	RFA	
Cryo	Cryo	Cryo
	OPN	OPN
	LRN	LRN
		ORN

[f] Interventions in the same column have statistically similar rates; column order reflects relative magnitude with the highest values in the far left column and the lowest values in the far right column. Statistically significant differences are present when adjacent column and row entries do not overlap. For example, OPN and LPN have statistically similar rates that are significantly higher than rates for cryo, LRN, and RFA.

Comparisons: Table 8h presents statistically significant comparisons.[g] LPN patients had significantly higher ($p < 0.05$) rates than OPN, LRN and ORN patients. RFA patients had significantly higher ($p < 0.05$) rates than ORN patients. Rates for LPN and the ablation therapies were statistically similar. Rates for the ablation therapies, OPN and LRN were statistically similar. Rates for cryoablation, OPN, LRN and ORN were statistically similar.

Interpretation: The significantly higher reintervention rate for LPN may be a valid difference. LPN and OPN patients were similarly aged and had similar-sized tumors, suggesting that the higher LPN rate may be the result of the more technically difficult laparoscopic procedure. LPN patients had smaller tumors than LRN and ORN patients, which would tend to decrease the LPN reintervention rate if it were affected by tumor size. This difference may reflect the technical challenge of the LPN procedure. The higher rate for RFA patients compared to ORN patients should be interpreted with caution given that RFA patients were older than ORN patients but also had smaller tumors.

Survival

The survival analyses -- total RFS, local RFS, metastatic RFS, CSS and OS -- were conducted on the subset of studies that provided pathological confirmation of RCC and for which outcomes could be attributed to RCC patients. These criteria eliminated many studies that had incomplete pathological information or for which outcomes could not be attributed to RCC patients. One exception was made to this criterion: the AS studies were included in evaluation of metastatic RFS. The Panel made this exception because of the clinical priority to understand the probability of metastases in patients for whom no surgical intervention was undertaken.

[g] Interventions in the same column have statistically similar rates; column order reflects relative magnitude with the highest values in the far left column and the lowest values in the far right column. Statistically significant differences are present when adjacent column and row entries do not overlap. For example, LPN rates are statistically similar to ablation rates, but significantly higher than OPN, LRN, and ORN rates.

Total Recurrence-Free Survival

"Total recurrence" was defined as local recurrence plus metastatic or distant recurrence.[h] Table 9a summarizes the total RFS data. For the ablation studies, local recurrence was defined as any localized disease remaining in the treated kidney at any point after the first ablation treatment.

Table 9a: Total Recurrence-Free Survival

Study Type	# of studies	Survival Rate	Lower Limit	Upper Limit	Mean/Median Patient Age (yrs)	Mean/Median Tumor Size (cm)	Mean/Median Follow Up (mos)
Cryo	10	87.6	80.9	92.2	67.0 / 66.5	2.5 / 2.6	26.2 / 18.3
RFA	10	85.2	81.3	88.5	67.6 / 70.0	2.8 / 2.7	39.3 / 32.8
LPN	17	98.3	97.0	99.0	61.2 / 61.0	2.6 / 2.6	25.8 / 16.0
OPN	21	95.1	93.6	96.3	60.4 / 60.0	3.3 / 3.1	46.8 / 40.0
LRN	8	95.3	93.4	96.6	60.7 / 61.0	4.6 / 4.6	32.8 / 37.1
ORN	10	88.8	83.9	92.4	62.6 / 62.6	4.6 / 4.8	44.8 / 45.3

Interpretation: Given the existence of multiple confounding factors, particularly substantial differences in follow-up, meaningful comparisons among interventions were not possible. For example, although the LPN total RFS rate appears high, it may be accounted for by short follow-up duration, by younger patient age and/or by relatively small tumors. ORN has a relatively low total RFS rate, but the longest follow-up and treated some of the largest tumors. The low rates for cryoablation and RFA are noteworthy given the relatively short follow-up and smaller tumor size associated with these modalities. However, this finding must be interpreted in the context of the conservative definition used to define local recurrence (i.e., any disease remaining in the treated kidney after the first ablation; see Local RFS below).

Local Recurrence-Free Survival

"Local recurrence" was defined as any disease presence in the treated kidney or associated renal fossa posttreatment. For the ablation studies, local recurrence was defined as any localized disease remaining in the treated kidney at any point after the first ablation, in accordance with the recommendations of the Working Group of Image-guided Tumor Ablation.[93] Table 10a summarizes the local RFS data.

[h] Appearance of disease in the contralateral kidney was considered evidence of new disease and was not counted as recurrence.

Table 10a: Local Recurrence-Free Survival							
Study Type	**# of studies**	**Percent**	**Lower Limit**	**Upper Limit**	**Mean/Median Patient Age (yrs)**	**Mean/Median Tumor Size (cm)**	**Mean/Median Follow-Up (mos)**
Cryo	10	90.6	83.8	94.7	67.0 / 67.0	2.5 / 2.6	19.5 / 18.2
RFA	10	87.0	83.2	90.0	67.6 / 70.0	2.8 / 2.7	22.9 / 19.4
LPN	17	98.4	97.1	99.1	61.2 / 61.0	2.6 / 2.6	20.8 / 15.0
OPN	21	98.0	97.4	98.5	60.5 / 60.0	3.3 / 3.1	55.5 / 46.9
LRN	8	99.2	98.2	99.7	60.7 / 61.0	4.6 / 4.6	30.2 / 17.7
ORN	10	98.1	97.3	98.6	62.6 / 63.0	4.6 / 4.8	59.3 / 58.3

Table 10b: Local RFS – Significant Comparisons (p<0.05)	
LPN	
OPN	
LRN	
ORN	
	Cryo
	RFA

Comparisons: Table 10b presents statistically significant comparisons.[i] LPN, OPN, LRN and ORN local RFS rates were statistically similar and were all significantly higher ($p < 0.05$) than local RFS rates for cryoablation and RFA.

Interpretation: The most striking finding with regard to local RFS is the significantly lower rates for the ablation therapies despite their short follow-up durations. These low local RFS rates should be interpreted in the context of the definition for local recurrence used for this analysis, which categorized re-ablation for remaining disease as a treatment failure. The high local RFS rates of the other four interventions (which treated relatively young patients) are noteworthy given the generally long follow-up durations and larger tumor sizes with the exception of LPN. The consistency of local RFS rates for surgical excisional procedures despite differences in follow-up and tumor size suggests that local recurrence may be minimally influenced by these factors as long as complete surgical excision has been performed, but there is a need for long term data on laparoscopic procedures to state this conclusion firmly.

Metastatic Recurrence-Free Survival

"Metastatic recurrence" was defined as any disease presence in the body other than in the treated kidney or associated renal fossa posttreatment.[j] AS patients were included in this analysis

[i] Interventions in the same column have statistically similar rates; column order reflects relative magnitude with the highest values in the far left column and the lowest values in the far right column. Statistically significant differences are present when adjacent column and row entries do not overlap. LPN, OPN, LRN, and ORN have statistically similar rates that are significantly higher than rates for the ablation therapies.

[j] A small number of patients had local and metastatic recurrence detected simultaneously; there were not enough cases to analyze separately. These patients are contained in the Total Recurrence analyses; they are not included here or in the local recurrence analyses.

despite incomplete information about tumor pathology because of the clinical importance of estimating the probability of metastases in patients for whom no intervention was undertaken. Table 11a summarizes the metastatic RFS data.

Table 11a: Metastatic Recurrence-Free Survival							
Study Type	**# of studies**	**Percent**	**Lower Limit**	**Upper Limit**	**Mean/Median Patient Age (yrs)**	**Mean/Median Tumor Size (cm)**	**Mean/Median Follow-Up (mos)**
AS	12	97.7	95.5	98.9	67.1 / 68.2	2.7 / 2.2	29.6 / 29.0
Cryo	10	95.3	91.1	97.5	67.0 / 66.5	2.5 / 2.6	19.5 / 16.7
RFA	10	97.8	95.5	98.9	67.6 / 70.0	2.8 / 2.7	22.9 / 19.4
LPN	17	98.8	97.8	99.4	61.2 / 61.0	2.6 / 2.6	20.8 / 15.0
OPN	21	96.7	95.6	97.5	60.4 / 60.0	3.3 / 3.1	56.0 / 47.0
LRN	8	95.7	93.9	97.0	60.7 / 61.0	4.6 / 4.6	30.2 / 17.7
ORN	10	89.8	85.3	93.1	62.6 / 62.6	4.6 / 4.8	69.1 / 56.7

Interpretation: Overall, it is noteworthy that metastatic RFS rates are relatively high regardless of intervention type, likely reflecting the indolent nature of many clinical stage T1 renal masses. However, the presence of confounding factors precludes meaningful comparisons. The interventions with the highest rates have short follow-up durations and treated relatively small tumors. ORN rates are the lowest, but ORN patients had the largest tumors and the longest follow-up durations. Until long-term follow-up data are available on all interventions, it is not possible to draw conclusions about differences in metastatic RFS. As with all these data, the AS data should be interpreted with caution due to concerns about patient selection. In addition, a proportion of patients undergoing initial AS eventually underwent surgical intervention for tumors that were increasing in size, and some tumors in the AS series were likely benign.

Cancer-Specific Survival

"Cancer-specific survival" was defined as the proportion of patients that did not die from RCC during the follow-up period. Only studies in which survival could be attributed to patients with RCC were included in this analysis. Table 12a summarizes the CSS data.

Table 12a: Cancer-Specific Survival							
Study Type	**# of studies**	**Percent**	**Lower Limit**	**Upper Limit**	**Mean/Median Patient Age (yrs)**	**Mean/Median Tumor Size (cm)**	**Mean/Median Follow-Up (mos)**
Cryo	6	95.2	89.2	97.9	67.6 / 66.1	2.6 / 2.6	20.5 / 16.4
RFA	8	98.1	95.2	99.2	67.8 / 70.0	2.8 / 2.7	23.4 / 19.4
LPN	17	98.8	97.6	99.4	61.2 / 61.0	2.6 / 2.6	20.8 / 15.0
OPN	21	97.2	96.0	98.0	60.4 / 60.0	3.3 / 3.1	56.0 / 47.0
LRN	8	98.2	96.7	99.0	60.7 / 61.0	4.6 / 4.6	30.2 / 17.7
ORN	12	89.1	84.0	92.8	62.5 / 62.6	4.8 / 5.2	60.8 / 56.7

Interpretation: Overall, CSS rates are relatively high regardless of intervention type, again possibly reflecting the indolent nature of many clinical stage T1 renal masses. However, the presence of confounding factors precludes meaningful comparisons. The interventions with the highest rates have short follow-up durations and treated younger patients and/or small tumor sizes. ORN had the lowest rate, but has the longest follow-up and treated the largest tumors. Until longer-term follow-up data are available on all interventions, it is not possible to draw conclusions about differences in CSS.

Overall Survival

"Overall survival" was defined as the proportion of patients that did not die from any cause, including RCC. Only patients known to have RCC were included in these analyses. Table 13a summarizes the OS data.

Table 13a: Overall Survival							
Study Type	**# of studies**	**Percent**	**Lower Limit**	**Upper Limit**	**Mean/Median Patient Age (yrs)**	**Mean/Median Tumor Size (cm)**	**Mean/Median Follow-Up (mos)**
Cryo	5	96.5	85.5	99.2	65.9 / 65.2	2.4 / 2.6	23.0 / 20.5
RFA	8	93.2	82.2	97.6	67.8 / 70.0	2.8 / 2.7	23.4 / 19.4
LPN	12	98.0	96.1	99.0	60.6 / 60.2	2.5 / 2.5	16.4 / 13.5
OPN	17	89.0	85.3	91.8	60.0 / 59.1	3.0 / 3.0	55.5 / 47.0
LRN	7	92.8	86.4	96.3	60.7 / 61.1	4.6 / 4.6	31.8 / 16.1
ORN	9	81.9	65.5	91.5	62.7 / 64.0	4.6 / 4.8	58.4 / 58.3

Interpretation: As with the other survival analyses, the presence of confounding factors precludes meaningful comparisons. Similar to the CSS data, the interventions with the highest rates had short follow-up durations and treated younger patients and/or small tumors. ORN had the lowest rate, but has the longest follow-up and treated the largest tumors. Until long-term

follow-up data are available on all interventions, it is not possible to draw conclusions about differences in OS. Some have hypothesized that the better overall survival for OPN compared to ORN (the interventions with the longest follow-up) is related to a deleterious effect of CKD associated with ORN, but selection bias may be a confounding factor. Studies that focus specifically on post-procedure CKD are needed to definitively answer this question.

Grading the recommendations

The present statements are graded with respect to the degree of flexibility in application. A "standard" is the most rigid treatment policy. A "recommendation" has significantly less rigidity, and an "option" has the largest amount of flexibility. These terms are defined as follows:

1. **Standard**: A guideline statement is a standard if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions, and (2) there is virtual unanimity about which intervention is preferred.
2. **Recommendation**: A guideline statement is a recommendation if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions, and (2) an appreciable, but not unanimous majority agrees on which intervention is preferred.
3. **Option**: A guideline statement is an option if: (1) the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions, or (2) preferences are unknown or equivocal.

The draft was sent to 69 peer reviewers of whom 35 provided comments; the Panel revised the document based on the comments received. The guideline was submitted first for approval to the Practice Guidelines Committee of the AUA and then forwarded to the AUA Board of Directors for final approval.

Summary of the Treatment Options for the Clinical Stage 1 Renal Mass

Active Surveillance

Surveillance of localized renal tumors is now performed increasingly in carefully selected patients with a growing literature to support this management option.[32, 39, 48, 94-102] A meta-

analysis of this literature demonstrated an average growth rate of only 0.28 cm per year,[48] and the Panel's review of the literature indicated that progression to metastasis was reported in only about 1% (4/390) of patients. Meta-analysis of these data yielded a point estimate based on the random effects model of about 2.3%. These favorable results are consistent with data about the biological aggressiveness of clinical stage T1 renal masses -- many are benign (20%) or indolent. Only about 20% to 30% of these tumors have potentially aggressive features.[2, 32, 103] The favorable results in AS series also likely reflect a selection bias for small tumors and favorable radiographic characteristics. In addition, there is limited follow-up in most series (30 months mean).[48, 94] More adverse events and thus reduced RFS are expected with extended follow-up. For incidental stage T1 renal masses, prolonged follow-up will be necessary, similar to low-risk prostate cancer. Other important considerations in interpreting this literature are that some patients eventually underwent surgery for increasing tumor size, and many tumors were not biopsied, raising the possibility that a substantial portion may have been benign. In the meta-analysis by Chawla and colleagues,[48] only 46% of tumors had pathologic confirmation of RCC. These issues tend to bias results positively. It is also important to recognize that there are no established protocols for AS for renal tumors. The current literature reports a wide variety of surveillance protocols, none of which has been adequately substantiated.

Operational considerations can affect AS of localized renal masses and must be recognized. First, estimation of tumor volume will more accurately reflect true tumor kinetics and hence biological aggressiveness and should be considered for surveillance.[101] Unfortunately, tumor diameter rather than tumor volume is reported in most studies.[48] In addition, for measurements of tumor size, differences of < 3.1 mm for interobserver or < 2.3 mm for intraobserver evaluations lie within the variability of measurement and should thus not be attributed to tumor growth.[104]

There are many ongoing concerns about AS that should be conveyed during patient counseling and the decision-making process. First, the growth rate of a renal mass does not predict malignancy, as even tumors with zero growth rates have proven to be malignant.[98] At present there is no truly reliable way to distinguish benign vs. malignant or indolent vs. potentially aggressive tumors based on clinical or radiographic features.[2, 31, 48, 105, 106] One must also recognize that a small subgroup of patients may demonstrate rapid growth and aggressive behavior with AS. In the Volpe study,[47] 25% of the tumors doubled in volume in 12 months, and

one patient developed metastatic disease. Clinical T1b tumors (> 4.0 cm and < 7.0 cm) in particular may be at higher risk with AS. In the study by Sowery and colleagues,[101] such tumors demonstrated a rapid growth rate of 1.43 cm per year, and 1/9 patients developed metastasis. This is consistent with our knowledge about the natural history and biological aggressiveness of larger tumors.[31, 32, 103] Several studies have shown increased biological potential for tumors > 3.0 cm,[31, 32, 103] and Kunkle et al. [99] showed that the risk of synchronous metastasis goes up 22% with each one centimeter increase in tumor size.

The other important concern is that AS could be associated with the loss of the window of opportunity for NSS. There is only limited data about this issue in the current literature, and it remains a valid concern.[48, 86] Clearly, enhanced renal mass biopsy incorporating molecular analyses holds promise for assessing aggressive potential and guiding decision making about AS; however, further research will be required to define the utility and limitations of this approach.[106] Until this field is more firmly established, AS remains a calculated risk that the patient must be willing to accept.

Active surveillance is a reasonable option for patients with limited life expectancy or for those who are unfit for or do not desire intervention. The patient should be counseled about the small but real risk of cancer progression, possible loss of window of opportunity for NSS, lack of curative salvage therapies if metastases develop, limitations of renal mass biopsy and deficiencies of the current literature. Larger tumors and those with aggressive appearance, such as substantial heterogeneity or infiltrative growth pattern, may be at higher risk and should be treated proactively if the patient is a reasonable surgical candidate.

Radical Nephrectomy

Radical nephrectomy is still an appropriate treatment option for select clinical T1 renal tumors not amenable to PN. ORN can be performed by a variety of surgical approaches, most commonly the 11th or 12th rib resection flank or mini-flank (6-8 cm, without rib resection) incisions.[107, 108] The component parts of the traditional ORN (e.g., regional lymphadenectomy or ipsilateral adrenalectomy) are usually recommended at the time of RN, but their oncological efficacy has never been tested in prospective trials. In today's era of modern CT and MRI, it is extremely uncommon that unsuspected regional nodal or ipsilateral adrenal metastases will be encountered in patients with localized renal masses. LRN can be performed by intraperitoneal,

extraperitoneal, and hand-assisted approaches.[88, 109-117] The choice of ORN or LRN is largely made by surgeon discretion and training background along with careful consideration of many patient factors including body habitus; tumor size and location; comorbidities; and history of prior abdominal or retroperitoneal operations. Given that oncologic efficacy appears to be equivalent, a minimally invasive approach is preferred whenever feasible, given sensible patient selection and adequate expertise.

Major urological complications and major nonurological complications related to ORN occur in 1.3% and 5.9% of cases, respectively. Complications unique to LRN in particular and laparoscopy in general have been reported from individual centers and are more likely to occur earlier in a center's experience.[118] Open conversion occurs in approximately 2.9 - 5.9% of cases.[119-124, 144]

Over the last 10 years, several important factors have led many urologic oncologists to reconsider the routine use of RN for the management of localized renal masses. These factors include: a) oncological outcomes are the same whether RN or PN is performed for renal cortical tumors of less than 4 cm[125, 126] and less than 7 cm[127, 128] across all tumor histological subtypes; b) in most contemporary series, despite state of the art imaging, approximately 20% of clinical T1 renal tumors are benign neoplasms (i.e., renal oncocytoma, fat-poor angiomyolipoma) and 60% to 70% are indolent tumors with limited metastatic potential; c) concerns about late contralateral recurrence following cure of the index tumor; and d) emerging evidence that RN is an independent risk factor for the development of CKD.

The final item requires careful consideration as it underlies an overriding principle in the management of clinical T1 renal masses -- nephron-sparing approaches should be used whenever feasible. Reports comparing renal functional outcomes between patients undergoing PN or RN for clinical T1 renal masses revealed that closely-matched patients undergoing RN were more likely to have proteinuria and a serum creatinine > 2.0 mg/dl,[126, 129] a finding that was later confirmed using the calculation of estimated glomerular filtration rate (eGFR) obtained from the Modification of Diet in Renal Disease formula.[130] In addition, prior to tumor resection in apparently healthy patients with an apparently normal contralateral kidney, it was reported that 26% of clinical T1a renal tumor patients had pre-existing CKD as defined by an eGFR of < 60 ml/min/1.73m^2.[130] After surgery, the three-year probability of mild CKD (GFR < 60 ml/min/1.73m^2) was 20% after PN, but 65% after RN. Corresponding values for three-year

probability of moderate CKD (GFR < 45 ml/min/1.73m^2) were 5% for PN and 36% for RN. Multivariate analysis indicated that RN remained an independent risk factor for the development of new-onset CKD even after controlling for a variety of potential confounding factors. [130, 131]

Even in the absence of end stage renal failure, it is now established that CKD (eGFR 15-60 ml/min/1.73m^2) is associated with increasing risks of cardiovascular events, hospitalization and death, the likelihood of which increases as the eGFR decreases.[132] Unlike the carefully selected and much younger kidney transplant donors, renal tumor patients have a median age of more than 60 years and often have comorbid medical conditions such as diabetes, hypertension and peripheral vascular disease that can affect baseline kidney function. Recent data demonstrates that RN is an independent risk factor for worse OS compared to PN when utilized in matched patients undergoing resection of a clinical T1 renal tumor with a normal contralateral kidney.[133] In addition to the interplay between cardiovascular diseases and CKD, there are quality of life data suggesting that patients undergoing elective NSS have a better overall health-related quality of life than those undergoing radical nephrectomy with no significant difference in hospital costs.[134]

Despite these compelling data, evidence from large cross-sectional national databases indicates that RN is overutilized in the U.S. and abroad and still accounts for 80% to 90% of operations for clinical T1 renal tumors.[135-137] Overutilization of RN is an important quality of care issue that must be carefully addressed through educational programs, and increased training in both open and laparoscopic nephron-sparing operations, and referrals to surgeons with these advanced nephron-sparing techniques.

Open Partial Nephrectomy

Open partial nephrectomy remains the nephron-sparing modality with the most substantial supporting body of data and the most extensive clinical experience. The number of patients who have undergone OPN reported in the literature exceeds the number of patients who have undergone all other forms of treatment combined (excluding ORN) for the treatment of localized RCC. OPN remains a standard of care in the treatment of localized RCC given its wide application over the last two decades and the robustness of its operative and oncologic data.

The indications for OPN have been well described previously[138] and include absolute, relative and elective indications. As a surgical technique, OPN is versatile and reproducible.

Moreover, the required skill set has traditionally been more easily transferred to trainees than minimally invasive nephron-sparing techniques. Key concepts include excellent exposure, early vascular control, wide excision with a negative surgical margin and reconstruction of the renal remnant to minimize the risk of postoperative hemorrhage or urinary fistula. Ischemic times can be kept acceptably low, and much of the uninvolved kidney can often be kept on ice during the entire procedure. In addition, in many cases, manual compression may obviate the need for vascular clamping. For more complex cases requiring difficult excisions and/or reconstructions, longer periods of cold ischemia are readily achieved with excellent functional results.[139] The use of smaller incisions, perioperative epidurals, intercostal nerve blocks and patient-controlled analgesia and/or potent anti-inflammatory agents (i.e., ketorolac) have all served to reduce postoperative pain and hasten recovery following OPN.[138]

Postoperative serious adverse events with OPN are among the lowest of all nephron-sparing options. Despite the higher risk profile of most demographic variables in OPN series (older patients, larger mean tumor size, more centrally placed lesions),[141] the risk of serious adverse events remains acceptably low and comparable to all other treatment options. The Panel's meta-analysis indicated that total major urological complication rates for OPN were 6.3%, statistically similar to other forms of NSS such as LPN (9.0%), cryotherapy (4.9%) and RFA (6.0%). Major nonurological complication rates for OPN were 2.2%, the lowest of all interventions considered. OPN is associated with a very low reintervention rate (1.6%) and/or retreatment rate. A randomized study by the EORTC comparing RN to OPN for small (< 5 cm) renal tumors found a slightly higher rate of severe hemorrhage after NSS (3.1% vs. 1.2%) in addition to a 4.4% rate of urinary fistulas.[92]However, the overall complication differences were minimal in the context of the benefits of renal preservation in this study.

Physiologically, OPN is associated with the most robust data regarding preservation of filtration function and the lowest risk of CKD, even in the elective setting.[130] Moreover, unlike minimally invasive and/or ablative treatment options, OPN allows definitive pathological identification (i.e., stage, grade and histology) of the treated renal mass.[140] Oncologically, OPN produces very low rates of local and metastatic recurrence and high rates of CSS. In fact, as measured by nearly all oncologic endpoints, OPN stands out as among the most effective means of therapy for localized RCC, even when compared with RN. Given emerging data which suggest that localized RCC has a prolonged natural history,[48] the finding that OPN has three to

five times longer mean follow-up than any other nephron-sparing treatment modality is also noteworthy.

Open partial nephrectomy is considered a standard of care for the treatment of the clinical T1 renal mass, particularly in patients with compromised renal function but now also including those with a normal opposite kidney.

Laparoscopic Partial Nephrectomy

Among nephron-sparing approaches, the Panel's review indicated that LPN was primarily utilized for the treatment of small cortical tumors (mean tumor size 2.6 cm, similar to those treated by cryoablation). This would suggest that tumors treated by LPN were more likely to be of lower pathologic stage than those treated by most other means.

In addition, LPN is associated with the second shortest mean duration of follow-up (20.8 months) with only cryoablation associated with shorter follow-up. There are limited studies[143] addressing follow-up of at least five years. Pathological confirmation was available in all but a small percentage of patients (< 2%) undergoing LPN

LPN is typically associated with longer warm ischemia times than other nephron-sparing techniques. General conclusions about ischemia time cannot be offered based on the meta-analysis since few studies reported this information; however, in a combined study from major centers with the greatest expertise, warm ischemic time was significantly shorter (20 min) for OPN compared to LPN (31 min).[141] Some studies suggest an advantage to routine hilar clamping as a means to reduce blood loss, positive margins and operative time during LPN.[145, 146] The main concern is that increased warm ischemic times appear to be an independent predictor of reduced renal function after PN.

LPN was associated with a statistically significant higher major urological complication rate (9.0%) than any of the other treatment modalities except for OPN (6.3%). The LPN major nonurological complication rate (4.6%) did not differ from other intervention types, however. Conversion rates were highest for LPN at 3.9%, but these rates were statistically similar to those for cryoablation (3.5%) and LRN (3.0%). In addition, Breda et al.[147] reported the results of 855 LPNs from 17 centers and identified a 2.4% positive margin rate. These sobering statistics emphasize the fact that LPN belongs in the hands of an experienced surgeon.

Oncologic outcomes and survival rates reported with LPN performed for malignancy are encouraging but very preliminary. More extended follow-up and more sophisticated analysis to control for confounding factors will be required.

Patients with small peripheral lesions who meet criteria for OPN should be considered for LPN. The potential benefits of minimally invasive surgery must be weighed against the higher risk of complications and the possibility of longer periods of ischemia. However, with further advances in laparoscopic instrumentation and greater dissemination of expertise, improved outcomes and more widespread application of LPN is anticipated in the future.

Thermal Ablation

Probe-based thermal ablative modalities offer a proactive treatment approach associated with a minimally invasive recovery profile. Ongoing concerns include increased local recurrence rates when compared to surgical excision, controversy about radiographic parameters of success[148] and difficulty with surgical salvage if required.[149, 150] It is possible that outcomes associated with ablative modalities will improve with further advances in technology and application and that some of these concerns will be answered with more prolonged and informative outcomes data. Nevertheless, even in their current iteration, cryoablation and RFA represent valid treatment alternatives for many older patients or those with substantial comorbidities, presuming judicious patient selection and thorough patient counseling. Given these concerns and the complexity of the decision-making process, a primary role of the urologist in counseling and the informed consent process is recommended.

Cryoablation

The clinical use of cryoablation for treatment of localized renal masses was initially developed primarily by one institution using a stable technology platform via a laparoscopic approach and applying standard patient selection criteria and follow-up regimens. Subsequent data on cryoablation are largely from laparoscopic series (8 studies), but also include percutaneous MRI-guided (2), percutaneous CT-guided (2 reports from the same institution), percutaneous US-guided (1), open and laparoscopic (2 reports from the same institution), and 1 multi-institutional study looking at all types of ablative therapy. Most reports are from the U.S., with only one from

Europe (Italy).[151] There are no well-designed prospective studies comparing cryoablation to RFA or to other forms of NSS. With one exception, no QOL measures are provided in these studies. Overall, there is substantial variability in reported outcomes, treatment strategies and follow-up methodologies. Some investigators did not routinely perform preoperative biopsy. Most investigators did not perform routine postablation biopsies; however some investigators report selective use of postablation biopsies to confirm recurrence[152].

The major urological complication rate for cryoablation was 4.9%; this rate is similar to rates for RFA, OPN and ORN and significantly lower than for LPN. The most common complication reported with cryoablation is hemorrhage, usually due to renal fracture, [153,155] but studies also report pancreatic injury and ureteral obstruction.[154, 155] Cryoablation is associated with good renal function preservation in the absence of complications, but renal loss has been reported in the presence of complications. Interestingly, conversion rates for cryoablation (3.5%) are similar to LPN rates (3.9%) and nearly twice as high as RFA rates (1.6%).

For the purpose of the Panel's meta-analysis, a tumor was defined as incompletely ablated if it required more than one ablation session to achieve elimination by radiographic criteria in accordance with the recommendations of the Working Group on Image-Guided Tumor Ablation.[93] This is a point that is key to interpreting these data. Cryoablation was associated with a significantly lower rate of incomplete ablation (4.8%) than RFA (14.2%). It is important to note, however, that the laparoscopic vs. percutaneous techniques may be relevant variables to consider. Specifically, most cryoablation studies were performed laparoscopically, and most RFA studies were performed percutaneously. When ablation studies were compared based only on technique, percutaneous studies had significantly higher incomplete ablation rates than laparoscopic studies (13.9% vs. 2.1%). This pattern remained when percutaneous cryoablation studies were compared to laparoscopic cryoablation studies (10.5% vs. 2.2%). While it is tempting to conclude that technique or approach may impact outcomes, this information is based on limited reports in the percutaneous cryoablation and laparoscopic RFA literature. In addition, the influence of selection, technique and reporting biases may play a role in these differences.

Survival outcomes for cryoablation must be interpreted in the context of small sample sizes, short follow-up duration and a limited number of studies. The longest published follow-up of three years is based on two studies (Gill et al.[152], Davol et al.[153]) which had similar CSS rates. Overall, cryoablation total RFS rates were lower than rates for LPN, OPN and LRN, and

relatively similar to RFA and ORN rates. This lower rate may reflect, in part, the definition used for local recurrence as any disease remaining in the treated kidney after the first ablation. Local RFS cryoablation rates were significantly lower than any other intervention except for RFA. Metastatic RFS and CSS also were lower for cryoablation than for LPN; this difference may be related to older patient age or other selection biases. Metastases are rare in this population, but a few patients with small localized tumors went on to develop metastasis. This seemed to occur primarily in those with untreated residual disease, substantiating an ongoing concern about this type of clinical event.

Renal cryoablation may be a treatment option for the patient at high surgical risk who is not a candidate for observation or who wants proactive treatment, and who accepts with full understanding the need for lifelong radiographic surveillance and repeat biopsy after treatment. This treatment option needs to be considered in light of the reduced RFS rates compared to surgical excision. Biopsies (multiple cores in addition to FNA) are strongly encouraged prior to therapy and also after therapy when recurrence or incomplete ablation is suspected (at the very least) or as a routine in all cases.[148] Recent data suggest that surgical salvage of cryoablation failures can be difficult due to fibrotic reaction within the perinephric space and can be associated with significant complications. [149]

Radiofrequency Ablation

Radiofrequency ablation is one of the most recently developed treatment modalities for localized renal tumors. Reflecting this, the RFA literature reviewed by the panel reported a mean follow-up of only 22.9 months. Nevertheless, published series emerging since 2002 have accumulated more than 700 patients treated with RFA so far. The majority of RFAs are performed percutaneously under CT-scan guidance with only a few centers using a laparoscopic approach. Patients treated with RFA and cryoablation share similar demographics and selection criteria, mainly for high surgical risk patients and renal tumor size of < 3 cm. The population treated with ablation is older (mean, 68.5 years) and includes more solitary kidneys than any other treatment modality. Moreover, RFA is now commonly utilized for salvage treatment of patients with hereditary RCC because it can be performed percutaneously. To date, there are no randomized studies to compare the laparoscopic and percutaneous approaches or to compare RFA and cryoablation. All published series are retrospective observational studies.

Radiofrequency ablation results in fewer conversions than other procedures with the exception of OPN; however, patients may require reintervention more frequently than with other treatment options. Complications associated with RFA are similar to those reported with other treatment modalities. A large proportion of tumor pathology in the RFA group was undetermined, most likely due to the common use of FNA rather than tissue core biopsy prior to ablation.

Efficacy outcomes for RFA are 85.2% total and 87% local RFS, but this must be interpreted within the context of a variety of confounding factors. Although CSS and metastatic RFS after RFA did show favorable initial results, follow-up was too short in most reported series to support definitive conclusions and comparisons. In accordance with the recommendations of the Working Group on Image-Guided Tumor Ablation,[93] RFA was defined as resulting in local recurrence in our analysis if the original tumor was incompletely ablated at the initial ablation session. This definition may have contributed to the high local recurrence rates associated with RFA. As noted in the cryoablation section above, the percutaneous surgical approach produced higher incomplete ablation rates than the laparoscopic approach. Moreover, rates of local RFS and total RFS were significantly higher in the laparoscopic compared to the percutaneous approach, respectively, when ablation studies were evaluated together.

In summary, RFA is a minimally invasive treatment option for localized renal masses, especially for patients who represent a high surgical risk. Standard technique is lacking in the current literature, and follow-up criteria are not well defined. Percutaneous renal core biopsy with or without FNA are strongly encouraged in patients undergoing thermal ablation. The percutaneous approach, although less invasive, has a higher incomplete ablation rate compared to the laparoscopic approach, a phenomenon that may also be influenced by technique bias (see Limitations of Literature). Recent data suggest that surgical salvage of RFA failures can also be challenging and subject to significant complications. [150]

Novel Treatment Modalities of the Clinical Stage 1 Renal Mass

Overview

The literature reflects the evolution of novel treatment modalities which include HIFU, radiosurgery, MWT, LITT, PCU, as well as other new technologies. Clinical outcomes are

limited to a small number of patients and short-term follow-up, and these modalities are best considered developmental.

High intensity focused ultrasound

Although attractive as a noninvasive therapy of malignancies, transcutaneous HIFU has limitations. Vallancien et al. reported the first feasibility study of HIFU involving eight patients with renal tumors.[156] They noted evidence of ablation in the treated areas after the specimens were excised, but encountered skin burns in 10% of patients. Others have attempted HIFU for palliative treatment with mixed results.[157, 158] All studies have shown incomplete eradication of tumor, i.e., viable tumor on excision or on follow-up imaging.[159, 160] Since HIFU is ultrasound based, artifacts (acoustic shadowing, reverberation and refraction) may affect its utility. Additional disadvantages include the inability to monitor treatment progression in real time, limited focal zone depth, risk of injury to or obstruction by air-filled viscera (colon) and difficulty in synchronizing targeting with respiratory movements. Extracorporeal HIFU ablation faces substantial technical challenges. Long treatment times (5.4 hours; range 1.5 to 9 hours), small ablation zones (less than 10 mm) and side effects (treatment site discomfort/fevers, skin burns) hamper its utility. HIFU technology is still being modified, the number of patients treated and reported remains small (less than 100 treated), and it does not produce complete tumor ablation reproducibly, therefore, there is insufficient evidence available to support HIFU beyond experimental use at this point.

Radiosurgery ("Cyberknife")

The literature review identified only one human Phase 1 study of radiosurgery involving three patients who were treated with a radiation dose of 4 Gy/fraction x 4 fractions, followed eight weeks later by RN or PN.[161] No adverse events or toxicities were noted, with a mean follow-up of 12 months. Results showed one patient with necrotic tumor while the other two had pathologic evidence of viable cancer cells. These results were certainly encouraging considering that in animal models, ablation was not noted until a target of 40 Gy was obtained. Other preclinical data found that 16 porcine kidneys with sequential histological evaluation demonstrated complete fibrosis at the eight week mark. [162]

In a retrospective study,[163] the safety and local efficacy of radiosurgery in metastatic or inoperable primary RCC was evaluated. Thirty patients with metastatic RCC or inoperable primary RCC received high-dose fraction stereotactic radiation; 82 lesions were treated with

varied dose/fractionation schedules (8 Gy x 4, 10 Gy x 4, 15 Gy x 2 or 15 Gy x 3) according to target location and size. Local control, defined as radiologically stable disease or partial/complete response, was obtained in 98% of treated lesions, although 19% of lesions had a follow-up time of less than six months. A complete response was obtained in 21% of treated lesions, with stable disease/partial response in 58% at a median 52 months (range 11 to 66) for living patients and 18 months (range 4 to 57) for deceased patients. Side effects were low grade and easily manageable in 90% of cases, and OS was 32 months.

In conclusion, radiosurgery in renal surgery is an experimental modality, and human trials in patients with localized disease are just beginning. It is extracorporeal; multiple treatment sessions are required; and it appears to be safe, with no acute toxicities reported. It is minimally invasive but still requires a biopsy and placement of fiducial markers. The status of radiosurgery for localized renal tumors remains experimental at this time.

Other modalities

Other energy ablative technologies such as MWT, LITT, and PCU are still in the developmental stage.

Microwave thermotherapy. In MWT, energy is delivered through an antenna placed directly into the lesion, generating an electromagnetic field that causes rapid ion oscillation and produces frictional heat. MWT is similar in principle to RFA, but can generate heat 100 times faster and may be less susceptible to heat sinks. In one *in vivo* rabbit model of RCC, MWT did not appear to be effective. Carcinomatosis occurred most frequently after microwave therapy using this model. [164] Microwave ablation followed by nephrectomy has been evaluated in a single Phase 1 study in which no skip areas were noted in the ablated zones. [165]

Laser Interstitial Thermal Therapy. LITT delivers energy through the placement of a specialized laser fiber directly into the lesion. Laser light is converted into heat > 55°C and causes tissue necrosis. In one study by Deane and colleagues,[166] LITT showed a reduction in enhancement volume (percent of approximate tumor volume that is 'viable') from 73.7% to 29.5%, but the clinical implications of this finding are not clear. [166]

Pulsed Cavitational Ultrasound. The transcutaneous, nonthermal, mechanical effects of US waves are thought to have an advantage over temperature-based ablation systems for which precise targeting of the lesion is more dependent on local factors. PCU utilizes cavitational effects to damage target tissues by varying acoustic parameters. No thermal collateral damage to surrounding

tissue and skin or collecting system has been noted. A potential theoretical complication is the dissemination of malignant cells from the shear forces generated by the procedure. Data about PCU are limited to two preclinical studies involving an *in vitro* porcine model[167] and an *in vivo* study in rabbits. [168]

Limitations of the Literature

The Panel identified major limitations of the available literature. Suboptimal study design was the predominant limitation across all studies, with a near absence of prospective or randomized data. Selection bias (e.g., differences in patient ages and tumor sizes) is evident across all interventions. Widely divergent duration of follow-up for the various modalities is another major confounding factor. Additional weaknesses include lack of standardized reporting and substantial variability in applied techniques, definitions of success, reporting of complications and other related outcomes. Complications were reported in variable ways or sometimes were completely omitted. Renal function was typically reported as pre and posttreatment serum creatinine values as opposed to eGFR or creatinine clearance as determined by a 24-hour urinary collection. Many of the AS and ablative studies lacked pathologic data as did some surgical studies.

The nomenclature for renal mass anatomy is also highly variable among studies, limiting the ability to compare outcomes among different institutions. Reporting and publication biases probably also exist; studies with higher complication rates, recurrences or other inferior outcomes tend not to be published. For example, few data regarding the morbidity of RN were published until the advent of LRN. Limited clinical follow-up is available for many of the studies, particularly for ablative therapies, LPN and AS, making their oncologic outcomes subject to follow-up bias.

Finally, there is the problem of technique bias. This issue is most obvious for the literature on ablative therapies, but is applicable to other interventions which lack standardization. For example, percutaneous therapy is easily repeated whereas laparoscopic therapy is not. This undoubtedly influences the behavior of the treating physician at the time of therapy. In particular, because the percutaneous technique allows relatively straightforward retreatment, the physician may use a more conservative approach. In contrast, because retreatment is more difficult laparoscopically, the physician may be more aggressive and thorough on the first procedure.

As emphasized, there are multiple confounding factors that affect interpretation of the meta-analytic results. The findings reported here must be appreciated within the context of these limitations. In particular, the meta-analysis cannot account for or correct biases inherent in weak study designs and lack of randomization. Future research endeavors must minimize the limitations outlined above with prospective, randomized designs, homogeneous and transparent selection criteria, standardized technical application and methodical reporting of outcomes.

Panel Consensus Regarding Treatment Modalities

Despite the above described limitations of the literature, the Panel was able to reach the following consensus about the various treatment modalities:

- Nephron-sparing surgery should be considered in all patients with a clinical T1 renal mass as an overriding principle, presuming adequate oncologic control can be achieved, based on compelling data demonstrating an increased risk of CKD associated with RN and a direct correlation between CKD and morbid cardiovascular events and mortality on a longitudinal basis. RN is still a viable option when necessary based on tumor size, location or radiographic appearance if the surgeon judges that NSS is not feasible or advisable. A laparoscopic approach to RN is now an established standard and should be considered if this procedure is required as it is associated with a more rapid recovery.

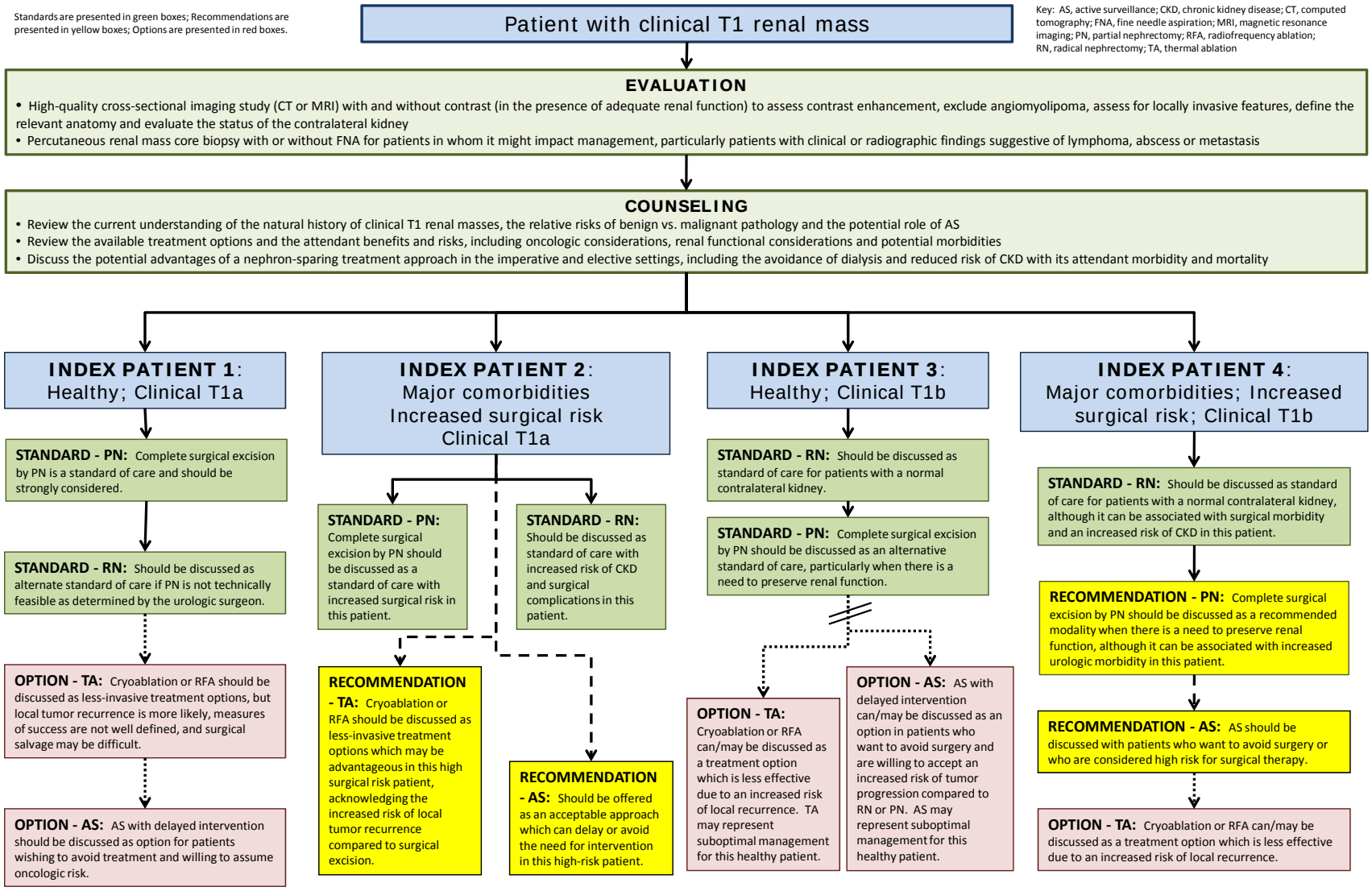
- Active surveillance is a reasonable option for the management of localized renal masses that should be discussed with all patients and should be a primary consideration for patients with decreased life expectancy or extensive comorbidities that would make them high risk for intervention. For patients who are candidates for intervention, counseling about AS should include a balanced discussion of the small but real risk of cancer progression, lack of curative salvage therapies if metastases develop, possible loss of window of opportunity for NSS and substantial limitations of the current AS literature. Larger tumors (> 3 to 4 cm) and those with aggressive appearance, such as infiltrative growth pattern, may be associated with increased risk and should be managed in a proactive manner, if possible.

- Thermal ablation (cryoablation or RFA), either percutaneous or laparoscopic, is an available treatment option for the patient at high surgical risk who wants active treatment and accepts the

need for long-term radiographic surveillance after treatment.[169] Tumor biopsy (core biopsy is recommended for better diagnostic accuracy) should always be performed prior to treatment to define histology and should also be considered after treatment, particularly if there is any suspicion of recurrence. Counseling about thermal ablation should include a balanced discussion of the increased risk of local recurrence when compared to surgical excision, potential need for reintervention, lack of well-proven radiographic parameters for success, potential for difficult surgical salvage if tumor progression is found and the substantial limitations of the current thermal ablation literature. Larger tumors (> 3.5 cm) and those with irregular shape or infiltrative appearance may be associated with increased risk of recurrence when managed with thermal ablation.

- Surgical excision by PN is a reference standard for the management of clinical T1 renal masses, whether for imperative or elective indications, given the importance of preservation of renal parenchyma and avoidance of CKD. This treatment modality is greatly underutilized. PN has well established longitudinal oncologic outcomes data comparable to RN. Adequate expertise and careful patient selection are important. A laparoscopic approach can provide more rapid convalescence, but has been associated with an increased risk of major urologic complications and longer warm ischemia times when compared to traditional OPN. In general, OPN is preferred for complex cases such as tumor in the renal hilum, tumor in a solitary kidney or multiple tumors.

Treatment Algorithm



Treatment Guideline Statements

The Panel developed the following guideline statements from a careful assessment of the meta-analysis, the use of expert opinion when data were lacking or incomplete, and panel consensus. These statements apply to the treatment of patients with clinical T1 renal masses. Inherent in these guideline statements is the importance of individualizing patient diagnostic evaluation and therapy. In an attempt to recognize commonly encountered clinical variations, each guideline statement addresses a specific patient.

For All Index Patients

> **Standard: Physicians should obtain a high-quality cross-sectional imaging study (CT or MRI) with and without contrast (in the presence of adequate renal function) to assess contrast enhancement, exclude angiomyolipoma, assess for locally invasive features, define the relevant anatomy and evaluate the status of the contralateral kidney and its vasculature.**
> [Based on Panel consensus.]

> **Standard**: **Physicians should discuss with the patient the current understanding of the natural history of clinical stage 1 renal masses, the relative risks of benign vs. malignant pathology and the potential role of active surveillance.**
> [Based on Panel consensus.]

Overall, about 20% of clinical stage T1 enhancing renal masses are benign. In addition, a potentially aggressive variant is only observed in 20% to 25% of all RCCs in this size range. Tumor size and gender are important determinants of the risk of benign vs. malignant pathology.

> **Standard**: **Percutaneous renal mass core biopsy with or without fine needle aspiration should be performed in all patients undergoing thermal ablation and in patients for whom it might impact management, particularly patients with clinical or radiographic findings suggestive of lymphoma, abscess or metastasis.**
> [Based on Panel consensus.]

Standard: Physicians should review with the patient the available treatment options and the attendant benefits and risks, including oncologic considerations, renal functional considerations and potential morbidities.

[Based on Panel consensus.]

Standard: **Physicians should counsel the patient about the potential advantages of a nephron-sparing treatment approach in the imperative and elective settings. These advantages include avoidance of the need for dialysis and a reduced risk of developing chronic kidney disease with the attendant morbidity and mortality.**

[Based on Panel consensus.]

Radical nephrectomy can lead to an increased risk of CKD, which is associated with increased risk of morbid cardiac events and death according to population-based studies. Management should focus on optimizing renal function rather than merely precluding the need for dialysis.

For Index Patient No. 1: *A healthy patient with a clinical T1a (≤ 4.0 cm) enhancing renal mass*

Standard: **Complete surgical excision by partial nephrectomy is a standard of care and should be strongly considered.**

[Based on review of the data and Panel consensus.]

Both open and laparoscopic approaches to PN can be considered, dependent on tumor size, location and the surgeon's expertise. LPN can provide more rapid recovery, although this approach has been associated with increased warm ischemic times and an increased risk of urological complications including postoperative hemorrhage and urinary fistula. Most patients with a solitary kidney, preexisting renal dysfunction, hilar tumor, multiple tumors or predominantly cystic tumor are best managed with on open surgical technique. With improved laparoscopic instrumentation and greater dissemination of expertise, improved outcomes and more widespread application of LPN is anticipated in the future.

Standard: **Radical nephrectomy should be discussed as an alternate standard of care which can be performed if a partial nephrectomy is not technically feasible as determined by the urologic surgeon.**

[Based on review of the data and Panel consensus.]

Radical nephrectomy can lead to an increased risk of CKD, which is associated with increased risks of morbid cardiac events and death according to population-based studies. Management should focus on optimizing renal function rather than merely precluding the need for dialysis. PN is a greatly underutilized procedure that is often feasible even for central or hilar tumors, given adequate surgeon expertise. Nevertheless, occasional localized renal tumors in this size range are not amenable to PN, and RN should be considered an alternative standard of care. A laparoscopic approach can provide reduced blood loss and more rapid recovery and should be considered, presuming adequate surgeon expertise.

> **Option**: **Thermal ablation, such as cryoablation or radiofrequency ablation, should be discussed as a less-invasive treatment option, but local tumor recurrence is more likely than with surgical excision, measures of success are not well defined, and surgical salvage may be difficult.**
>
> [Based on review of the data and Panel consensus.]

Thermal ablation is associated with a substantially increased risk of local recurrence, the majority of which can be managed with a second attempt at thermal ablation. However, some local recurrences are not amenable to this approach and require surgical salvage. In this setting laparoscopic surgery and PN are often not possible due to extensive reactive fibrosis within the perinephric space. In addition, measures of success for thermal ablation have come into question with some studies demonstrating apparently viable cancer cells despite loss of contrast enhancement. It is possible that outcomes associated with ablative modalities will improve with further advances in technology and application; however, judicious patient selection and counseling remain of paramount importance for these less-invasive technologies.

> **Option**: **Active surveillance with delayed intervention should be discussed as an option for patients wishing to avoid treatment and willing to assume oncologic risk.**
>
> [Based on review of the data and Panel consensus.]

Approximately 80% of all clinical T1a renal masses are malignant, and of these, about 20% to 30% demonstrate potentially aggressive histologic features. The risk of tumor progression that could preclude NSS or lead to unsalvageable systemic metastases is not well defined in the current literature. Enhanced renal mass biopsy (incorporating molecular analyses) holds promise

for assessing aggressive potential; however, further research will be required to define the utility and limitations of this approach. Healthy patients considering AS must be willing to assume a calculated risk of tumor progression.

For Index Patient No. 2: *A patient with major comorbidities/increased surgical risk and a clinical T1a (≤ 4.0 cm) enhancing renal mass*

> **Standard**: **Complete surgical excision by partial nephrectomy should be discussed as a standard of care with increased surgical risk in this patient.**
>
> [Based on review of the data and Panel consensus.]

Partial nephrectomy is associated with an increased risk of perioperative morbidity when compared to RN, a relevant consideration for this patient with increased risk for surgical intervention. Nevertheless, PN or other nephron-sparing approaches should be considered whenever preservation of renal function is a primary issue. Both open and laparoscopic approaches to PN can be considered, dependent on tumor size, location and the surgeon's expertise.

> **Standard**: **Radical nephrectomy should be discussed as a standard of care with an increased risk of surgical complications and chronic kidney disease in this patient.**
>
> [Based on review of the data and Panel consensus.]

Radical nephrectomy is another standard of care in this high-risk patient population with substantial comorbidities. However, RN can lead to an increased incidence of CKD with its attendant risks, and some patients may have relative or imperative indications to avoid RN. A laparoscopic approach to RN can provide reduced blood loss and more rapid recovery and should be considered, presuming adequate surgeon expertise.

> **Recommendation**: **Thermal ablation should be discussed as a less-invasive treatment option which may be advantageous in this high surgical risk patient, acknowledging the increased risk of local tumor recurrence compared to surgical excision.**
>
> [Based on review of the data and Panel consensus.]

Thermal ablation is a reasonable option for this high surgical risk patient that allows for proactive treatment without the risks associated with major surgical intervention. However, an increased risk of local recurrence should be discussed during counseling

Recommendation: **Active surveillance should be offered as an acceptable approach which can delay or avoid the need for intervention in this high-risk patient.**

[Based on review of the data and Panel consensus.]

Active surveillance has been associated with relatively low rates of tumor growth and metastatic progression during short-term (2 to 3 year) follow-up. Overall, about 20% of clinical T1a renal masses are benign, and a potentially aggressive variant is only observed in 20%-30% of all RCCs in this size range. AS should be a primary consideration in patients with decreased life expectancy or those who are particularly high risk for proactive intervention.

For Index Patient No. 3: *A healthy patient with a clinical T1b (> 4.0 cm to < 7.0 cm), enhancing renal mass*

Standard: **Radical nephrectomy should be discussed as a standard of care for patients with a normal contralateral kidney.**

[Based on review of data and Panel consensus.]

Radical nephrectomy is associated with less perioperative morbidity than PN and remains a standard of care for clinical T1b tumors, presuming a normal contralateral kidney. A laparoscopic approach can provide reduced blood loss and more rapid recovery and should be considered, presuming adequate surgeon expertise.

Standard: **Complete surgical excision by partial nephrectomy should be discussed as an alternative standard of care, particularly when there is a need to preserve renal function.**

[Based on review of data and panel consensus.]

Even in patients with a normal contralateral kidney, RN can lead to an increased risk of CKD, which is associated with increased risks of morbid cardiac events and death based on population-based studies. PN is an alternative standard of care for this patient, presuming favorable tumor location and adequate surgeon expertise.

Option: **Thermal ablation can/may be discussed as a treatment option which is less effective due to an increased risk of local recurrence.**

[Based on Panel consensus.]

Tumors that are 4 cm to 7 cm in diameter are difficult to adequately treat with thermal ablation, and the risks of local recurrence and complications are high in this patient population. Thermal ablation may represent suboptimal management for this healthy patient, and this should be emphasized during patient counseling.

Option: **Active surveillance with delayed intervention can/may be discussed as an option in patients who want to avoid surgery and are willing to accept an increased risk of tumor progression compared to partial nephrectomy or radical nephrectomy.**

[Based on review of the data and Panel consensus.]

The risk of malignancy and potentially aggressive histologic features is substantially increased for clinical T1b tumors. Hence, the risk of tumor progression that could preclude nephron-sparing approaches or lead to unsalvageable systemic metastases is also increased. AS may represent suboptimal management in this scenario and should only be considered in patients that are willing to assume a high risk of adverse oncologic outcomes related to delayed intervention.

For Index Patient No. 4: *A patient with major comorbidities/increased surgical risk and a clinical T1b (> 4.0 cm to < 7.0 cm), enhancing renal mass*

Standard: **Radical nephrectomy should be discussed as a standard of care for patients with a normal contralateral kidney, although it can be associated with surgical morbidity and an increased risk of chronic kidney disease.**

[Based on review of the data and Panel consensus.]

Radical nephrectomy is associated with less perioperative morbidity than PN, a relevant consideration for this patient with increased risk for surgical intervention. RN thus remains a standard of care, presuming a normal contralateral kidney. However, RN can lead to an increased risk of CKD with its attendant risks, and some patients may have relative or imperative

indications to avoid RN. A laparoscopic approach to RN can provide a more rapid recovery and should be considered, presuming adequate surgeon expertise.

Recommendation: **Complete surgical excision by partial nephrectomy should be discussed as a recommended modality when there is a need to preserve renal function, although it can be associated with increased urologic morbidity.** [Based on review of the data and Panel consensus.]

Partial nephrectomy can be associated with an increased risk of urologic morbidity, an important consideration in this high-risk patient. Nevertheless, PN or other nephron-sparing approaches should be considered whenever preservation of renal function is a primary issue.

Recommendation: **Active surveillance should be discussed with patients who want to avoid surgery or who are considered high risk for surgical therapy.**

[Based on review of the data and Panel consensus.]

The risk of tumor progression that could preclude nephron-sparing approaches or lead to unsalvageable systemic metastases may be increased in this patient. Nevertheless, AS should be a primary consideration in patients with limited life expectancy or those who are particularly high risk for proactive intervention.

Option: **Thermal ablation can/may be discussed as treatment option which is less effective due to an increased risk of local recurrence.**

[Based on Panel consensus.]

Clinical T1b tumors are difficult to adequately treat with thermal ablation, and the risks of local recurrence and complications are high in this patient population.

New Research/Future Directions

Application of evidence-based medicine: In general, future studies attempting to compare different treatment modalities and their outcomes should be prospectively designed, have uniform selection criteria, standardized treatment protocols and consistent follow-up strategies using tissue-based markers of success and ideally be performed in randomized fashion.[170]

Markers of clinical success that could be used to supplement radiographic findings are needed. As newer ablative and noninvasive modalities become available, it will become increasingly unacceptable to await the long-term results of radiographic evaluations. QOL outcomes should be incorporated in the evaluation of treatments of localized renal masses.[171]

Oncological outcomes/translational research: The classification of RCC into separate types with differing morphology, genotype and probable clinical outcome has led to a re-evaluation of prognostic parameters. Further refinements of staging and prognostication await the discovery of new molecular markers for the various RCC morphotypes.[172] The indications for AS should be defined for each patient, and their age and comorbidity index should be reported. Additional studies of AS with long-term follow-up are needed to define the true risks associated with this approach. Research into the role of renal mass biopsy enhanced by molecular profiling, with correlation with pathologic findings and long-term outcomes, should be a top priority in this field.[173]

Further efforts to elucidate the long-term metabolic side effects of decreased functioning nephron mass as a consequence of RN for RCC may not only enhance the understanding of the plieotrophic effects of progressive renal disease in the setting of RN, but may provide a further rationale for the adoption of nephron-sparing strategies for treatment of RCC. Such studies will expand our understanding of risk factors and consequences of precipitous declines in functional nephron mass.[133] In addition, novel forms of ischemic protection (pharmacologic, immunologic) should be further investigated as a way to minimize renal damage and thus potentially enhance the feasibility and safety of NSS.[174]

Surgical technology: Use of the DaVinci Robot for robotic-assisted LPN is being currently evaluated at centers of excellence,[158, 175] with the emergence of the robot as a platform for image-guided therapies as well. Furthermore, promising new developments such as single-port access surgery and natural-orifice translumenal endoscopic surgery might add to the surgical armamentarium for minimally invasive renal surgery.[176, 177]

Targeted molecular therapy: Improved understanding of the biology of RCC has resulted in the development of novel targeted therapeutic agents that have altered the natural history of this disease. In particular, the hypoxia-inducible factor/vascular endothelial growth factor pathway and the mammalian target of rapamycin signal transduction pathways have been exploited. Sunitinib malate, sorafenib tosylate, bevacizumab /interferon alfa and temsirolimus have improved clinical outcomes in randomized trials of patients with metastatic RCC by inhibiting tumerigenic pathways, ushering in a new age for systemic treatment.[178] Recently reported and ongoing clinical trials will help further define the role of these agents as therapy for RCC. Currently, these and other emerging agents are being investigated as adjunctive agents for higher-risk localized or locally-advanced disease, and these agents could potentially facilitate nephron-sparing approaches by downsizing localized RCC. However, there currently is no role for targeted molecular therapy in the treatment of localized disease outside of a clinical trial.

Table 14. Classification of Complications Listed in the Literature*

Urologic Complications		Nonurologic Complications		
Major	**Minor**	**Major**		**Minor**
Chronic renal failure requiring dialysis	Bladder outlet obstruction	Abscess	Intra-abdominal complications	Abnormal labs - transient
Dialysis - temporary	Hematuria	Arrythmia/dysrrhythmia	Intraoperative transfusion	Anterior abdominal wall paresthesia - transient
Hemorrhage-major	Perinephric hematoma - no transfusion	Atrial fibrillation	Ischemic colitis	Anterior abdominal wall weakness - persistent
Hemorrhage-minor	Perirenal fluid	Atrial flutter	Liver infarct	Atelectasis
Hydrocalicosis	Renal thermal injury	Bowel abrasion	Myocardial infarction	Bowel serosal tear
Hydronephrosis	UTI	Bowel obstruction	Needle or electrode track seeding	Dermatitis
Interstitial nephritis		Cardiovascular complications	Neurological complication	Elevated myoglobin - transient
Kidney infarct		Chronic respiratory failure	Neuropathy	Esophagitis
Kidney loss		Coagulopathy	Nonrenal vascular injury	Fatigue
Parietal abscess		Colitis	Pancreatic injury	Genitourinary complication
Perinephric hematoma - requiring transfusion		Colonephric fistula	Pancreatitis	Gout
Renal fracture		Colonic ischemia	Persistent pain	Hypertension - transient
Renal hemorrhage		Colonic perforation	Pneumonia	Narcotic or sedative reaction
Renal insufficiency		Death	Pneumothorax	Nonspecific EKG changes
Renal - other		Duodenal perforation	Pseudoaneurysm	Pain during procedure
Renal vascular injury		Duodenal ulcer	Psoas muscle laceration	Pleural effusion
Ureter injury		DVT	Pulmonary complications	Rash associated with contrast
Ureteral obstruction		Elevated creatinine - persistent	Pulmonary embolism	Subcutaneous emphysema
Ureteropelvic junction injury		Elevated myoglobin requiring treatment	Rehospitalization	Transient hyperthermia
Urine leak		Embolus	Retained vessel loop	Transient pain
Urinoma		Fistula	Retroperitoneal fibrosis	
		GI complication	Retroperitoneal hematoma	
		GI hemorrhage	Splenic hematoma	
		Gluteal compartment syndrome	Splenic injury	
		Gluteal fasciotomy	Stroke	
		Heart failure	Thermal injury - other	
		Hernia	Thrombus	
		Infection	Transfusion	
		Ileus	Trochar site infection	
		Injury to diaphragm	Wound complications	
		Injury to nonrenal intra-abdominal structures		

*The complications presented in this table were drawn directly from the articles included in the meta-analysis; the terms listed are the terms chosen by the authors to describe particular adverse events. These terms were sorted by the Panel into the categories of major and minor urological and nonurological complications. The variety of terms presented here highlights the lack of standardized complications reporting in this literature and demonstrates the difficulty inherent in synthesizing evidence across studies that used different terminologies.

Conflict of Interest Disclosures

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Acknowledgements and Disclaimers: Guideline for Management of the Clinical Stage 1 Renal Mass: Diagnosis and Treatment Recommendations

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The final report is intended to provide medical practitioners with a current understanding of the principles and strategies for the management of the clinical stage 1 renal mass. The report is based on an extensive review of available professional literature, as well as on clinical experience and expert opinion.

This document provides guidance only, and does not establish a fixed set of rules or define the legal standard of care. As medical knowledge expands and technology advances, the guideline will change. Today the guideline statements represent not absolute mandates but provisional proposals or recommendations for treatment under the specific conditions described. For all these reasons, the guideline does not preempt physician judgment in individual cases. Also, treating physicians must take into account variations in resources, and in patient tolerances, needs and preferences. Conformance with the guideline reflected in this document cannot guarantee a successful outcome.

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Appendix 1: Small Renal Mass Guideline Panel Members and Consultants (2008)

Members:

Andrew C. Novick, M.D., Chair
Cleveland Clinic Foundation
Cleveland, Ohio

Steven Charles Campbell, M.D., Ph.D., Co-Chair
Cleveland Clinic Foundation
Cleveland, Ohio

Raymond J. Leveillee, M.D., FRCS-G
PGC Representative
University of Miami School of Medicine
Miami, Florida

Arie Belldegrun, M.D.
UCLA School of Medicine
Los Angeles, California

Michael L. Blute, M.D.
Mayo Clinic
Rochester, Minnesota

George Kuoche Chow, M.D.
Mayo Clinic
Rochester, Minnesota

Ithaar H. Derweesh, M.D.
University of Tennessee
Memphis, Tennessee

Jihad H. Kaouk, M.D.
Cleveland Clinic Foundation
Cleveland, Ohio

Surena Fazeli Matin, M.D.
MD Anderson Cancer Center
Houston, Texas

Paul Russo, M.D.
Memorial Sloan-Kettering Cancer Center
New York, New York

Robert G. Uzzo, M.D.
Fox Chase Cancer Center
Philadelphia, Pennsylvania

Consultants:

Martha M. Faraday, Ph.D.
Linda E. Whetter, Ph.D., D.V.M.
Michael Marberger, M.D.

Abbreviations and Acronyms

AS	=	active surveillance
AUA	=	American Urological Association
CAIX	=	carbonic anhydrase IX
CKD	=	chronic kidney disease
cm	=	centimeter
COI	=	conflict of interest
cryo	=	cryoablation
CSS	=	cancer-specific survival
CT	=	computed tomography
dl	=	deciliter
e.g.	=	for example
eGFR	=	estimated glomerular filtration rate
et al.	=	and others
etc.	=	et cetera; and the rest
FNA	=	fine needle aspiration
GFR	=	glomerular filtration rate
Gy	=	Gray
HIFU	=	high intensity focused ultrasound
i.e.	=	that is
lap	=	laparoscopic
LITT	=	laser interstitial thermal therapy
LPN	=	laparoscopic partial nephrectomy

LRN	=	laparoscopic radical nephrectomy
m^2	=	meters squared
mg	=	milligrams
min	=	minute
ml	=	milliliter
mm	=	millimeter
mos	=	months
MRI	=	magnetic resonance imaging
MWT	=	microwave thermotherapy
N/A	=	not applicable
NSS	=	nephron-sparing surgery
OPN	=	open partial nephrectomy
ORN	=	open radical nephrectomy
OS	=	overall survival
p	=	*p*-value
PCU	=	pulsed cavitational ultrasound
PN	=	partial nephrectomy
QOL	=	quality of life
RCC	=	renal cell carcinoma
RFA	=	radiofrequency ablation
RFS	=	recurrence-free survival
RN	=	radical nephrectomy
SRM	=	sorenal mass(es)

TNM	=	tumor, nodes, metastasis cancer stage classification system
U.S.	=	United States
US	=	ultrasound
vhl	=	von Hippel-Lindau gene
vs.	=	versus
°C	=	Celsius

Glossary

Cancer-specific survival – the proportion of patients diagnosed with renal cell carcinoma that did not die from renal cell carcinoma within a specified follow-up period

Conversion – any change from the planned renal surgical approach or procedure to a different renal surgical approach or procedure

Local recurrence – any disease presence in the treated kidney or associated renal fossa at any point after the initial procedure; for ablation studies, local recurrence would include any disease remaining in the treated kidney at any point after the first ablation.

Local recurrence-free survival – the proportion of patients diagnosed with renal cell carcinoma that did not experience a local recurrence within a specified follow-up period.

Metastatic recurrence – any disease presence in the body other than in the treated kidney or associated renal fossa post-treatment

Metastatic recurrence-free survival - the proportion of patients diagnosed with renal cell carcinoma that did not experience a metastatic recurrence within a specified follow-up period

Overall survival - the proportion of patients diagnosed with renal cell carcinoma that did not die from any cause within a specified follow-up period

Reintervention – any unplanned procedure or operation that occurred during or after the planned renal surgery.

Total recurrence - the sum of local recurrence events plus metastatic recurrence events

Total recurrence-free survival – the proportion of patients diagnosed with renal cell carcinoma that did not experience a local or metastatic recurrence within a specified follow-up period