American Urological Association (AUA) Guideline

# FOLLOW-UP FOR CLINICALLY LOCALIZED RENAL NEOPLASMS: AUA GUIDELINE

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**Purpose:** The Panel sought to create evidence-based guidelines for the follow-up and surveillance of clinically localized renal cancers treated with surgery or renal ablative procedures, biopsy-proven untreated clinically localized renal cancers followed on surveillance, and radiographically suspicious but biopsy-unproven renal neoplasms either treated with renal ablative procedures or followed on active surveillance. These guidelines are not meant to address hereditary or pediatric kidney cancers, although they must take into account that a proportion of adult patients may harbor a yet unrecognized hereditary form of renal cancer.

**Methods:** A systematic review was conducted to identify published articles relevant to key questions specified by the Panel related to kidney neoplasms and their follow-up (imaging, renal function, markers, biopsy, prognosis). This search covered English-language articles published between January 1999 and 2011. An updated query was later conducted to include studies published through August 2012. These publications were used to inform the statements presented in the guideline as Standards, Recommendations or Options. When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate) or C (low). In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinion.

## GUIDELINE STATEMENTS

1. Patients undergoing follow-up for treated or observed renal masses should undergo a history and physical examination directed at detecting signs and symptoms of metastatic spread or local recurrence. (*Clinical Principle*)
2. Patients undergoing follow-up for treated or observed renal masses should undergo basic laboratory testing to include blood urea nitrogen (BUN)/ creatinine, urine analysis (UA) and estimated glomerular filtration rate (eGFR). Other laboratory evaluations, including complete blood count (CBC), lactate dehydrogenase (LDH), liver function tests (LFTs), alkaline phosphatase (ALP) and calcium level, may be used at the discretion of the clinician. (*Expert Opinion*)
3. Patients with progressive renal insufficiency on follow-up laboratory evaluation should be referred to nephrology. (*Expert Opinion*)
4. The Panel recommends a bone scan in patients with an elevated alkaline phosphatase (ALP), clinical symptoms such as bone pain, and/or if radiographic findings are suggestive of a bony neoplasm. (*Recommendation*; Evidence Strength: Grade C)
5. The Panel recommends against the performance of a bone scan in the absence of an elevated alkaline phosphatase (ALP) or clinical symptoms, such as bone pain, or radiographic findings suggestive of a bony neoplasm. (*Recommendation;* Evidence Strength: Grade C)
6. Patients with a history of a renal neoplasm presenting with acute neurological signs or symptoms must undergo prompt neurologic cross-sectional CT or MRI scanning of the head or spine based on localization of symptomatology. (*Standard;* Evidence Strength: Grade A)

7. The Panel recommends against the routine use of molecular markers, such Ki-67, p-53 and VEGF, as benefits remain unproven at this time. (*Recommendation*; Evidence Strength: Grade C)

**Surgery: *Low risk patients (pT1, N0, Nx):***

8. Patients should undergo a baseline abdominal scan (CT or MRI) for nephron sparing surgery and abdominal imaging (US, CT or MRI) for radical nephrectomy within three to twelve months following renal surgery. (*Expert Opinion*)

9. Additional abdominal imaging (US, CT or MRI) may be performed in patients with low risk (pT1, N0, Nx) disease following a radical nephrectomy if the initial postoperative baseline image is negative. (*Option;* Evidence Strength: Grade C)

10. Abdominal imaging (US, CT, or MRI) may be performed yearly for three years in patients with low risk (pT1, N0, Nx) disease following a partial nephrectomy based on individual risk factors if the initial postoperative scan is negative. (*Option;* Evidence Strength: Grade C)

11. The Panel recommends that patients with a history of low risk (pT1, N0, Nx) renal cell carcinoma undergo yearly chest x-ray (CXR) to assess for pulmonary metastases for three years and only as clinically indicated beyond that time period. (*Recommendation*; Evidence Strength: Grade C)

**Surgery: *Moderate to High Risk Patients (pT2-4N0 Nx or any stage N+):***

12. The Panel recommends that moderate to high risk patients undergo baseline chest and abdominal scan (CT or MRI) within three to six months following surgery with continued imaging (US, CXR, CT or MRI) every six months for at least three years and annually thereafter to year five. (*Recommendation;* Evidence Strength: Grade C)

13. The Panel recommends site-specific imaging as warranted by clinical symptoms suggestive of recurrence or metastatic spread. (*Recommendation;* Evidence Strength: Grade C)

14. Imaging (US, CXR, CT or MRI) beyond five years may be performed at the discretion of the clinician for moderate to high risk patients. (*Option;* Evidence Strength: Grade C)

15. Routine FDG-PET scan is not indicated in the follow-up for renal cancer. (*Expert Opinion*)

**Active Surveillance**

16. Percutaneous biopsy may be considered in patients planning to undergo active surveillance. (*Option;* Evidence Strength: Grade C)

17. The Panel recommends that patients undergo cross-sectional abdominal scanning (CT or MRI) within six months of active surveillance initiation to establish a growth rate. The Panel further recommends continued imaging (US, CT or MRI) at least annually thereafter. (*Recommendation;* Evidence Strength: Grade C)

18. The Panel recommends that patients on active surveillance with biopsy proven renal cell carcinoma or a tumor with oncocytic features undergo an annual chest x-ray (CXR) to assess for pulmonary metastases. (*Recommendation;* Evidence Strength: Grade C)

**Ablation**

19. A urologist should be involved in the clinical management of all patients undergoing renal ablative procedures including percutaneous ablation. (*Expert Opinion)*

20. The Panel recommends that all patients undergoing ablation procedures for a renal mass undergo a pretreatment diagnostic biopsy. (*Recommendation;* Evidence Strength: Grade C)

21. The standardized definition of "treatment failure or local recurrence" suggested in the Clinical T1 Guideline document should be adopted by clinicians. This should be further clarified to include a visually enlarging neoplasm or new nodularity in the same area of treatment whether determined by enhancement of the neoplasm on post-treatment contrast imaging, or failure of regression in size of the treated lesion over time, new satellite or port site soft tissue nodules, or biopsy proven recurrence. (*Clinical Principle*)

22. The Panel recommends that patients undergo cross-sectional scanning (CT or MRI) with and without intravenous (IV) contrast unless otherwise contraindicated at three and six months following ablative therapy to assess treatment success. This should be followed by annual abdominal scans (CT or MRI) thereafter for five years. (*Recommendation;* Evidence Strength: Grade C)

23. Patients may undergo further scanning (CT or MRI) beyond five years based on individual patient risk factors. (*Option;* Evidence Strength: Grade C)
24. Patients undergoing ablative procedures who have either biopsy proven low risk renal cell carcinoma, oncocytoma, a tumor with oncocytic features, nondiagnostic biopsies or no prior biopsy, should undergo annual chest x-ray (CXR) to assess for pulmonary metastases for five years. Imaging beyond five years is optional based on individual patient risk factors and the determination of treatment success. (*Expert Opinion*)
25. The Panel recommends against further radiologic scanning in patients who underwent an ablative procedure with pathological confirmation of benign histology at or before treatment and who have radiographic confirmation of treatment success and no evidence of treatment related complications requiring further imaging. (*Recommendation;* Evidence Strength: Grade C)
26. The alternatives of observation, repeat treatment and surgical intervention should be discussed, and repeat biopsy should be performed if there is radiographic evidence of treatment failure within six months if the patient is a treatment candidate. (*Expert Opinion)*
27. A progressive increase in size of an ablated neoplasm, with or without contrast enhancement, new nodularity in or around the treated zone, failure of the treated lesion to regress in size over time, satellite or port side lesions, should prompt lesion biopsy. (*Expert Opinion*)

## INTRODUCTION

Follow-up for adult cancer survivors has traditionally focused on the early detection of a cancer recurrence based on the presumption that treatment of a lower tumor burden would result in better patient outcomes, although the evidentiary data supporting this presumption is limited.[1] Adult cancer survivorship care is an evolving field initially borne out of the need for care of pediatric cancer survivors in their transition to adulthood and monitoring for the long term sequelae of cancer treatment. The recommended essential elements of adult cancer survivorship care now include not only monitoring for cancer recurrence, secondary cancers and treatment effects, but also the prevention of recurrences or new tumors, medical interventions for the consequences of cancer and its treatment effects and the coordination between specialists and primary care physicians to meet survivors' needs.[2] Treatment "effects" include those related to the sequelae of surgery, systemic therapies, ablative therapy and radiation.

Several recent concerns have made the development of this guideline document a high priority for the American Urological Association (AUA). There is now an increasing rate of detection and subsequent treatment of small renal masses of uncertain biological potential as well as a widening spectrum of contemporary treatment options with varied treatment related effects. Such options include observation/surveillance, ablative therapies and minimally-invasive as well as open approaches to partial and radical nephrectomy. The advent of a new generation of targeted systematic therapy now holds the promise of prolonged survival of patients with metastatic disease. Additionally, patients with renal cell cancer tend to be older and have a greater incidence of pre-existing kidney disease, which places them at an increased risk for either the development or progression of chronic kidney disease following therapy.[3-4] The negative impact of chronic kidney disease continues to be elucidated, with increased risks of osteoporosis, anemia, metabolic and cardiovascular disease, hospitalization and death now well established. Since effective treatment strategies are available to slow the progression of chronic kidney disease and reduce cardiovascular risks, it would seem prudent to include renal function monitoring in the follow-up of renal cancer patients to facilitate early interventions or referral to nephrology.[5] Lastly, concerns over the increased use of modern resource-intensive imaging techniques, are coupled with concerns as to the long-term adverse effects of repeated and cumulative radiation exposure.[6-7] Each of these factors impacts the management of renal masses and was considered in the deliberation of this panel, thereby making this a most timely document.

Keeping these issues in mind, the Panel sought to create evidence-based guidelines for the follow-up and surveillance of clinically localized renal cancers treated with surgery or renal ablative procedures, biopsy-proven untreated clinically localized renal cancers followed on surveillance and radiographically suspicious but biopsy-unproven renal neoplasms either treated with renal ablative procedures or followed on active surveillance. These guidelines are not meant to address hereditary or pediatric kidney cancers, although they must take into account that a proportion of adult patients may harbor a yet unrecognized hereditary form of renal cancer. These guideline recommendations have been systematically developed based on a comprehensive search of the English-language peer-reviewed and published literature, with a methodologically rigorous assessment of the quality of evidence for the prognosis, diagnosis and therapy of renal masses. The recommendations made in this document as to the extent to which the benefits of a given management strategy outweigh potential risks reflect the judgments of the multidisciplinary panel and are based on the currently available "best" evidence. These guidelines will provide an outline of judicious follow-up that balances patient risk and possible benefits of therapy. The following document details those evidence-based recommendations of the AUA, and a summary of the suggested follow-up protocols based on procedure are listed in Appendix A.

## METHODOLOGY

***Process for Literature Selection.*** A systematic review was conducted to identify published articles relevant to key questions specified by the Panel (See Appendix B) related to kidney neoplasms and their follow-up (imaging, renal function, markers, biopsy, prognosis). This search covered articles in English published between January 1999 and 2011. An updated query was later conducted to include studies published through August 2012. Study designs consisting of clinical trials (randomized or not), observational studies (cohort, case-control, case series) and systematic reviews were included. All other study types were excluded. Studies with full-text publication available were included, but studies in abstract form only were excluded.

This literature included studies that focused on patients diagnosed with clinically localized, histologically proven renal cell carcinoma; clinically localized oncocytoma or cystic nephroma; radiographically suspicious, solid neoplasms or suspicious/complex cystic neoplasms without biopsy and neoplasms radiographically consistent with angiomyolipoma. Patients with metastatic renal cell carcinoma, transitional cell carcinoma and hereditary syndromes as well as those treated with radiation or systemic therapy were

excluded. Additionally, studies involving pediatric patients or those in which outcomes among qualifying index cases could not be separated from other cases or other malignancies were excluded as well. Management strategies considered include active surveillance, surgery (partial or radical nephrectomy) and ablative procedures (cryoablation or radiofrequency ablation). In terms of interventions, inclusion criteria incorporated studies involving follow-up regimens evaluating oncologic and functional outcomes using imaging and/ or lab measurements and/or physical examination and/ or biopsy. All other management strategies or treatment itself were excluded. Studies with less than 30 patients were excluded given the unreliability of the statistical estimates and conclusions that can be derived from them.

Articles with abstracts fulfilling the outlined inclusion criteria that addressed one or more of the posed questions were retrieved in full text for further review. Reason for exclusion of rejected articles was recorded. Studies reported within multiple publications were scrutinized in order to retrieve the most recent, non-redundant and inclusive data. Related references contained in each article were perused to ensure the inclusion of all pertinent material.

Accepted articles were extracted using customized forms. Given the pool size of eligible articles, independent double extraction was not possible for most articles. Instead, the methodologist reviewed the work of the extractors and searched for inconsistencies and missing information in the data extracted with emphasis on outcomes.

The methodological quality of the studies was evaluated using the QUADAS tool[8] for questions framed in the context of a "diagnostic" problem. Many studies included retrospective cohorts reporting on the follow-up of patients. For these studies, the framework proposed by Hayden et al.[9] was used to assess their methodological quality. This framework evaluates potential sources of bias within six domains: sample representativity, attrition, adequate measurement of prognostic factors, adequate measurement of outcomes, assessment and control of potential confounders and appropriate statistical analysis. This framework's implementation was adapted to the question context. Overall quality scores together with study design and consistency of estimates across studies were used to grade the strength of the evidence into three levels: A (strong), B (moderate) and C (weak).

Descriptive statistics of study characteristics were calculated to identify potential study outliers that could signal data extraction problems and/or influential studies. These were also used to identify factors that could explain heterogeneity of estimates, if found. Meta -analyses were performed on questions in which at least four studies were available. These estimates were based on DerSimonian-Laird random effects.[10] Meta-regression was performed when heterogeneity was encountered and enough studies were available to examine at least one predictor at a time. Heterogeneity was considered present if the inconsistency $I^2$ statistic[11] was above 25% or when the forest plot showed a potential mixture of outcomes if a small number of studies were available. Analyses were performed in the R platform version 2.12.0 for Windows and the code *meta*.

For most outcomes, a meta-analysis of proportions was performed. For these, raw counts for numerator and denominator were extracted from each study. The other meta-analyses were performed on the hazard rate (survival after surgery), hazard ratio (from multivariable Cox regression models) and area under the characteristic (AUC) curve and their corresponding standard error.

Hazard rates were obtained from survival rates at a minimum of five years, assuming that the curve exhibited an exponential distribution. The assumption of an exponential distribution could be confirmed graphically from a group of articles that provided corresponding survival curves. The resulting overall hazard rate was used to build a cumulative incidence function that covered five years of follow-up. The proportion of events in quarters for the first two years and biannually for the following three years were determined in order to guide the selection of an appropriate follow-up frequency for cases of clinically localized renal mass undergoing curative surgery without adjuvant or salvage treatment. Since partial and radical nephrectomy have been considered equivalent in terms of cancer control outcomes for T1 disease, these were included in the same analysis to increase the number of studies available.[12]

The standard error was estimated from available data when it was not provided directly by the individual studies. In the case of survival curves, Kaplan-Meier curves with number of individuals at risk were transformed to their corresponding standard error. In the case of the AUC, actual numbers of individuals diseased and non-diseased and numbers of individuals labeled as diseased and non-diseased by a threshold were used for determining the standard error as proposed by Hanley and McNeil.[13] AUC was used for assessing kidney function, and disease refers to patients with kidney insufficiency. When standard error was not available or could not be estimated the study was excluded from analysis.

***AUA Nomenclature: Linking Statement Type to***

***Evidence Strength*.** The AUA nomenclature system explicitly links statement type to body of evidence strength and the Panel's judgment regarding the balance between benefits and risks/burdens (see Table 1).[14] ***Standards*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A or Grade B evidence. ***Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade C evidence. ***Options*** are non-directive statements that leave the decision to take an action up to the individual clinician and patient because the balance between benefits and risks/ burdens appears relatively equal or appears unclear; ***Options*** may be supported by Grade A, B or C evidence. For some clinical issues, there was little or no evidence from which to construct evidence-based statements. Where gaps in the evidence existed, the Panel provides guidance in the form of *Clinical Principles* or *Expert Opinions* with consensus achieved using a modified Delphi technique if differences of opinion existed among Panel members.[15] A *Clinical Principle* is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. *Expert Opinion* refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge and judgment and for which there is no evidence. The completed evidence report may be requested through AUA.

***Panel Selection and Peer Review Process*.** The Panel was created by the American Urological Association Education and Research, Inc. (AUA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chair and Vice Chair who in turn appointed the additional panel members, all of whom have demonstrated a specific expertise with regard to the guideline subject. All panel members were subject to and remain subject to the AUA conflict of interest disclosure criteria for guideline panel members and chairs.

The AUA conducted an extensive peer review process. The initial draft of this Guideline was distributed to 67 peer reviewers; 39 responded with comments. The Panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the Guideline was submitted for approval to the PGC. It was then submitted to the AUA Board of Directors for final approval. Funding of the Panel was provided by the AUA. Panel members received no remuneration for their work.

**Table 1: AUA Nomenclature**

**Linking Statement Type to Evidence Strength**

| |
|---|
| **Standard:** Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/ burdens outweigh benefits) be taken based on Grade A or B evidence |
| **Recommendation:** Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C evidence |
| **Option:** Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/ burdens appears equal or appears uncertain based on Grade A, B, or C evidence |
| **Clinical Principle:** a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature |
| **Expert Opinion**: a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence |

**BACKGROUND**

***Radiologic Imaging Benefits and Risks.*** For follow-up of patients with treated or untreated renal carcinoma or patients with neoplasms suspected to represent renal carcinoma, radiologic imaging is a valuable tool and is, in fact, the mainstay of surveillance management of these patients. Radiologic imaging modalities that play an important role in detecting disease regression, progression, recurrence or metastasis include computed tomography (CT), magnetic resonance imaging (MRI), diagnostic ultrasound (US) and plain film chest x-ray (CXR). Positron emission tomography (PET) scanning with labeled antibody[16] is under evaluation for imaging of renal carcinoma and may play a role in the future but is currently not standard or recommended diagnostic measure. CT and MRI are used both for detection and characterization of neoplasms suspected to represent renal carcinoma; advantages of these two higher-resolution imaging modalities include their noninvasive nature and superior diagnostic accuracy.

Despite the advantages of CT and MRI, the potential adverse effects and cost should also be kept in mind. Recent attention has been paid to the cumulative radiation exposure of the population attributable to the widespread and increasing use of CT scanning. Indeed, the use of CT has markedly increased in recent decades. It is estimated that more than 62 million CT scans are currently obtained each year in the United States, as compared with about 3 million in 1980.[6] Much of the data confirming the carcinogenic potential of the relatively low dose (<100 mSv) radiation used for diagnostic imaging is extrapolated from analysis of mortality data of Japanese atomic bomb survivors exposed to intermediate (>100 mSv) radiation doses. An underlying assumption for these extrapolations is that the long term biological damage caused by ionizing radiation (essentially the cancer risk) is directly proportional to the dose regardless of how small the exposure (linear no-threshold (LNT) model).[17] The LNT model is not accepted by all organizations involved in establishing national and international recommendations on radiation protection. Nevertheless, there is some indirect evidence linking exposure to low-level ionizing radiation at doses used in CT to subsequent development of cancer. The National Academy of Sciences' National Research Council comprehensive review of biological and epidemiological data related to health risks from exposure to ionizing radiation was published in 2006 as the Biological Effects of Ionizing Radiation (BEIR) VII Phase 2 report. Epidemiologic data in the report includes a study of populations who had received low doses of radiation, including populations who received exposures from diagnostic radiation. Doses received by individuals in whom an increased risk of cancer was documented were similar to doses associated with commonly used CT studies.[18] Cancer risk decreases with lower dose, older age and male sex.[19] The recent attention to radiation dose in CT scanning has had the beneficial effect of stimulating development of new scanner technologies and protocols that limit radiation dose without compromising diagnostic image quality. Initiatives to better educate patients, referring physicians, radiologic technologists and radiology residents on radiation safety and patient dose have begun.[19-21] Although the true risk of cancer development from exposure to diagnostic radiation for a given individual from CT is not known, it is prudent to limit use of CT to those clinical indications in which the benefit is felt to outweigh the risk. In addition, risks related to administration of iodinated intravenous (IV) contrast for CT, including contrast hypersensitivity and contrast-induced renal failure, should also be kept in mind when considering the use of CT in the workup and follow-up of renal cancer. In designing follow-up imaging protocols for renal cancer, the Panel has kept these risks in mind.

For MRI, which does not involve the use of ionizing radiation, the prime adverse effect to consider is the development of nephrogenic systemic fibrosis (NSF) due to IV gadolinium administration. NSF is a rare but potentially debilitating or even fatal fibrosing condition that most often affects the skin but can involve multiple organs. There is currently no effective treatment for this condition,[22] which was first reported in 1997. In a 2006 study, five of nine patients with end-stage renal disease who underwent gadolinium-enhanced magnetic resonance (MR) angiography developed NSF, and since then additional studies have supported the causative role of gadolinium contrast agent in the development of NSF. Gadolinium has been found in the skin biopsies of affected patients.[23] A study by Broome[24] investigated risk factors for the development of NSF in 168 dialysis patients who underwent 559 MR imaging examinations from January 2000 to August 2006. In this study, 12 patients developed NSF, all of whom had undergone gadolinium contrast-enhanced MR imaging using a double dose of IV contrast. Four of the 12 patients developed acute renal failure related to hepatorenal syndrome; all four patients underwent liver transplantation within 17 days of MR imaging. One patient had renal transplant failure two weeks prior to undergoing MR imaging. The remaining seven patients had chronic renal failure from a variety of causes. Eight of the 12 patients had undergone vascular surgery, had deep venous thrombosis or had coagulopathies in the interval between contrast agent injection and the development of NSF. Risk factors for development of NSF include high doses of gadolinium-based contrast agents, both acute and chronic renal failure and vascular injury.

Unless the diagnostic information is essential and not available with MRI performed without IV contrast, the U.S. Food and Drug Administration (FDA) currently recommends against the use of gadolinium-based contrast agents in patients with acute or chronic renal insufficiency, with a glomerular filtration rate (GFR) less than 30 mL per minute per 1.73 $m^2$ or with any acute renal failure caused by the hepatorenal syndrome or perioperative liver transplantation.[22] Radiology departments have developed institutional policies regarding identification of at-risk patients and alternative MR imaging strategies, including use of non-contrast MR imaging protocols, use of lower doses of gadolinium IV contrast and use of higher field strength magnets that magnify the relative T1 shortening effects of gadolinium, thus allowing for the use of lower doses of gadolinium.[25] Patients who require radiologic studies for detection or follow-up of renal carcinoma who fall into high risk categories for development of gadolinium contrast-related NSF should undergo radiologic imaging using alternative imaging strategies, including MR strategies outlined above, CT (without IV contrast for patients with renal failure) or ultrasound with Doppler interrogation.

Although US is an attractive modality for imaging renal masses owing to its less invasive nature and availability as compared to CT and MRI, the use of US as a tool for de novo detection of renal mass lesions is limited by its lower sensitivity, especially for detection of small mass lesions, lesions that are similar in echogenicity to the renal parenchyma, and lesions that do not deform the renal contour. The sensitivity of CT and ultrasonography for detection of lesions 3 cm and less is 94% and 79%, respectively.[26] US can be useful in characterizing some indeterminate renal mass lesions seen on CT or MRI, such as atypical cystic lesions or solid hypovascular lesions.[27] The role of US for monitoring the size of a known renal mass lesion, in order to demonstrate tumor growth during surveillance, appears promising. In a recent study of a group of patients who all underwent US evaluation of their renal mass as well as contemporary CT, MRI or both prior to treatment of the mass, as compared with MRI and CT, ultrasound measurements of tumor size were well correlated ($P = .001$ and $P = .001$).[28] For detection of residual or recurrent disease in the remaining kidney after partial nephrectomy or tumor ablation, CT and MRI remain the mainstay imaging modalities, although the use of contrast-enhanced US (CUS) has been recently investigated after percutaneous cryoablation in a small series.[29] CT or MRI is used for detection of recurrent tumor in the renal fossa following radical nephrectomy; US has not been demonstrated to play a significant role for this purpose.

***Renal Function Assessment.*** Preservation of renal function in patients with renal neoplasms is a key clinical consideration that factors heavily in management decisions and, therefore, deserves appropriate assessment during follow-up. Pre-existing renal dysfunction has been identified in over 25% of surgically managed patients with small renal masses,[3] while the prevalence of chronic kidney disease in the general population has been estimated between 10% and 15%, suggesting that patients with renal tumors may have risk factors contributing to functional renal loss.[30] Though the true impact of iatrogenic renal dysfunction related to surgical or other therapeutic intervention is still being elucidated, the timely identification of renal dysfunction or progressive deterioration can provide opportunity for medical intervention when indicated. Table 2 provides data reviewed on the incidence of renal function impairment among patients undergoing either partial or radical nephrectomy indicating the large proportion of patients meeting criteria for chronic kidney disease following renal surgery and relative insensitivity of isolated serum creatinine measurements in assessing this impact.

Renal function may be estimated by a variety of methodologies including timed voided creatinine collections, inulin clearance, nuclear renal scan or standardized mathematical formulas, though none are currently validated for use in the follow-up of patients covered by this guideline. Recognition of the variability in nephrologic outcomes associated with aspects of treatment and the central role of renal physiology has refocused efforts in quantifying dynamic changes in functional renal outcomes. Functional renal imaging studies including MRI and radioscintigraphy are used with increasing regularity throughout the course of management to evaluate differential contribution of renal function, the impact of therapy and factors that may influence the effects of treatment on global renal function. Serum creatinine is commonly used as a benchmark of renal function; however, as a byproduct of creatine phosphate metabolism in muscle, it is predominantly cleared by the glomerulus, with serum levels subject to influence by a number of factors, including gender, age and genetic variations, among others. Therefore, it is more clinically relevant and appropriate to utilize serum creatinine to calculate an individual's estimated glomerular filtration rate (eGFR) using a mathematical formula that can correct for these main variables.

The two formulas for eGFR commonly used and reported upon in the contemporary literature at the time of this guideline are the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) equations. While both formulas utilize the same four variables (serum creatinine, age, gender, ethnicity), sufficient differences in their performance characteristics suggest that they

Table 2: Incidence of renal function impairment among patients undergoing nephron-sparing or radical nephrectomy

| Preop CRI | Type | Abnormal sCr | sCr>2 | CKD 3-5 | ESRD or dialysis |
|---|---|---|---|---|---|
| ALL* | ALL | 17.8 (11.1, 25.6) | 3.7 (1.1, 7.8) | 26.4 (18.1, 35.6) | 1.6 (0.7, 2.9) |
| No | NS | 9.9 (2.9, 20.4) | 2.2 (0.1, 6.9) | 11.4 (8.3, 14.8) | 1.1 (0.1, 5.6) |
| No | RN | 17.3 (6.9, 31.1) | 6.0 (2.8, 10.1) | 48.2 (28.2, 68.5) | - |
| Yes | NS | 32.4 (10.5, 59.5) | - | 19.0 (9.5, 30.8) | 2.5 (1.0, 4.5) |
| Yes | RN | 18.0 (7.5, 31.9) | - | 51.0 (39.3, 62.7) | 0.5 (0.0, 2.5) |
| p-v± | - | 0.3181 | 0.1709 | <0.0001 | 0.2465 |

Cases were divided into four strata based on presence of preoperative chronic renal insufficiency (Preop CRI = eGFR ≤ 60) and procedure type (NS= nephron sparing, RN= radical nephrectomy). sCr= serum creatinine, CKD= chronic kidney disease, ESRD = End Stage Renal Disease.

*First row corresponds to overall estimates

±Statistical significance for the test of difference in estimates of incidence of the renal impairment outcome among the four strata.

are not interchangeable.[31] Developed for use in patients with risk factors for renal dysfunction, the MDRD equation is of limited application in healthier individuals, particularly those with low/normal serum creatinine levels and tends to provide an underestimate GFR in normal and older patient populations. The CKD-EPI formula was devised and validated to address this and is based on an isotope dilution mass spectrometry standard that must be utilized by the clinical testing laboratory.

In clinical practice, assessment of renal function should be used to identify patients who may benefit from medical management strategies which may prevent or delay the progression of chronic kidney disease. Threshold values of renal dysfunction have been identified with guidelines for management established by the National Kidney Foundation.[5] These guidelines classify Stage 3 chronic kidney disease as a moderate reduction in GFR (30 - 59 mL/min/1.73m$^2$) and Stage 4 chronic kidney disease as a severe reduction in GFR ( 15 – 29 mL/min/1.73m$^2$. Early detection and effective treatment may prevent or delay the progression of renal dysfunction in patients with risk factors. Many of these underlying risk factors are well-known, including hypertension and diabetes, requiring chronic management for which referral may be made to an appropriate medical physician.

***Secondary Malignancies.*** Several articles that deal with the incidence of secondary malignancies after the diagnosis of renal cell carcinoma were identified from the general query. These results include the following: Chakraborty et al. (2012)[32] used the 9th and 17th editions of the SEER registry to identify secondary malignancies among renal cell carcinoma cases. They identified 3,795 cases for a slightly increased standardized incidence ratio (SIR)[i] of 1.18 (95%CI 1.15 -1.22). Solid tumors accounted for more than 90% of the secondary malignancies. The most common sites were the male genital system (n=896, 23.6%), the digestive system (n=718, 19%), and the respiratory system (n=562, 15%). Race, age and sex were associated with particular sites. Interestingly, they found that the risk of a secondary malignancy was slightly higher in patients who did not receive radiation therapy compared to those who did (SIR 1.18 vs. 1.11). Among those who received radiation therapy, the adrenal glands and the thyroid were the most likely sites of secondary malignancy, and the risk was significantly increased only between 6-12 months after the renal cell carcinoma diagnosis, suggesting an observer bias. Leukemias were also increased in the radiation treated group. Skin and urinary bladder were the more likely sites among those who did not receive radiation. In multivariable analysis, age younger than 60, lack of history of radiation treatment and 12 or more months between the diagnosis of renal cell carcinoma and the identification of a secondary malignancy were associated with increased overall

survival. It is important to highlight that this study included children, and thus a genetic component cannot be discarded in the younger group since this information is not available in the SEER registry.

Liu et al. (2011)[33] reported on 8,667 patients with cancer of the kidney parenchyma diagnosed after January 1993 in the Swedish Cancer Registry and who were followed-up until December 2006. Of these 8,030 individuals (93%) had renal cell carcinoma (2,303 clear cell, 130 papillary, and the remainder not specified. Among the patients with renal cell carcinoma, 677 (8.4%) experienced a second malignancy. The SIR for a second metachronous renal cell carcinoma beyond one year after the first diagnosis was 5.5 (3.6-8.1). The SIR for other second malignancies among the renal cell carcinoma cases was 1.5 (1.2-2.0, 60 cases) colorectal, 2.0 (1.5-2.7, 49 cases) lung, 1.5 (1.1-2.0, 44 cases) breast, 1.7 (1.4-2.0, 135 cases) prostate, 2.5 (1.9-2.4, 45 cases) bladder, 3.9 (2.5-5.9, 23 cases) nervous system, 5.0 (1.8-10.9, 6 cases) thyroid, 42.2 (21.1-75.4, 11 cases) adrenal gland, 1.8 (1.0-2.8, 17 cases) melanoma and 2.1 (1.3-3.2, 21 cases) non-Hodgkin lymphoma. Eighty-four second parenchymal kidney cancers occurred during the first year after diagnosis (20 clear cell) and 28 at one year or beyond (3 clear cell). In this study, cases with a secondary within one year were considered synchronous.

Ojha et al. (2010)[34] reported on the potential relationship between renal cell carcinoma and secondary multiple myeloma using the SEER registry covering primary malignancies detected between January 1973 and December 2006. Within the renal cell carcinoma cohort (n=57,190), 88 cases of multiple myeloma were identified during over 293 thousand person-years of follow-up. Patients with renal cell carcinoma had a higher relative risk of multiple myeloma than the general population (SIR=1.51, 95% CI 1.21-1.85). Estimates of SIR by age groups revealed no trend with age, and the 50-59 year age group and the >80 year age group were the only ones in which the SIR was increased with respect to the general population. For the 50-59 year age the SIR was 3.19 (1.83-5.19) and for the >80 year group it was 1.88 (1.24-2.73). The highest risk for this secondary malignancy was within one year of the renal cell carcinoma diagnosis. Thirty-one of the 88 cases (35%) were identified within this time frame. Between 1-5 years, 22 (25%) cases were identified, 21 (24%) cases between 5 and 10 years, and the remaining 14 (16%) cases were identified after 10 years.

***Needle Biopsy Considerations.*** Advances in our knowledge of the molecular characteristics of most renal epithelial neoplasms have led to a better and more clinically relevant morphological classification system. While the incidence of newly diagnosed tumors has surpassed 60,000 cases per year in the United States, over 70% of these tumors are found incidentally and at a smaller size. Similarly, the percentage of clear cell carcinoma, the most common of renal cortical neoplasms, is now reported to be 60% to 65%, which is significantly lower that what was seen two decades ago. With the increase of incidentally detected and smaller tumors, the number of benign or low-grade neoplasms has increased. In a recent study by Thompson et al, 13% of tumors measuring 4cm or less and 16.5% of tumors measuring 3cm or less were benign.[35] In addition, some tumors known to be malignant but resected at a smaller size are more likely to behave in an indolent manner. For example, in a recent study by Przybycin et al, only 1 of 74 Chromophobe carcinomas resected with a size of 4 cm or less developed metastatic disease, with a median clinical follow-up period of over six years.[36] Thus, it is logical that attempts should be made to establish the type of tumor present prior to deciding on either active surveillance or therapy, whether surgery or ablation. This approach is particularly appropriate in older patients and those with significant comorbidities, whether this is appropriate in young patients is debatable. See Table 3 below for a complete list of the incidence of benign cases from biopsy reviewed in this guideline.

The accuracy of percutaneous biopsy has improved substantially over the past several years due to further refinements in CT- and MRI-guided techniques, and several systematic reviews have addressed this specific diagnostic procedure,[58,59] focusing on several key issues. First, the specificity is 100% in nearly all reported series while the sensitivity ranges from 90% to 100% if small studies are removed from analysis. Approximately 10% to 15% of renal mass biopsies are non-diagnostic or indeterminate, although these are not as concerning as false negative biopsies, which may lead to altered follow-up protocols. Furthermore, by removing the indeterminate biopsies from analyses, the overall sensitivity increases to nearly 100%. Lastly, the incidence of symptomatic complications is relatively low, with only a very small percentage requiring any form of intervention. In most studies only a fraction of patients who underwent percutaneous aspiration or needle core biopsy went on to nephrectomy, making the assessment of sensitivity and specificity of the diagnostic procedures less reliable. Whether the size of the tumor affects diagnostic accuracy has not been

[i]Standardized incidence ratio: incidence estimate (i.e. number of new cases in period of observation) in which the number of events (numerator) and the number of individuals at risk during the period of observation (denominator) are summarized across strata formed by the combination of adjustment variables (e.g. age groups, sex, race). (For more information the reader could be directed to: http://seer.cancer.gov/seerstat/WebHelp/Standardized_Incidence_Ratio_and_Confidence_Limits.htm

studied well, a potentially important issue given the inherent heterogeneity seen in renal neoplasms. Needle -tract seeding, once a common fear of renal biopsy, also appears to be exceedingly rare.[58] According to a Volpe et al. study, the overall estimated risk of needle tract seeding is less than 0.01%.[60]

The overall accuracy of renal biopsy varied slightly according to biopsy technique, specifically core biopsy technique versus fine needle aspiration (FNA). The variance was primarily attributed to the difference in non-diagnostic biopsy rate. Importantly, when non-diagnostic biopsies are discarded from analyses, sensitivity for core v. FNA is 99.5% v. 96.5% and specificity is 99.9% v. 98.9%, respectively. When both diagnostic and non-diagnostic samples are considered, core biopsies are more sensitive but less specific than FNA, although not statistically significantly different for either parameter. Attempts to improve the accuracy of biopsy such as incorporation of molecular analysis have shown promise and remain a future research priority.

Early studies that investigated the utility of percutaneous needle biopsy of renal masses were disappointing. However, more recent studies are more promising because of improvements in biopsy techniques, familiarity among pathologists with this type of specimen and the ability to apply ancillary tools, such as immunohistochemistry and fluorescent *in situ* hybridization to aid in the diagnosis.[61] A significant advantage of tissue core biopsies over FNA cytology rests in the sample size and the ability to utilize these ancillary diagnostic tools more readily in order to classify the tumor more precisely.

Fuhrman nuclear grade, particularly in clear cell carcinoma, has been shown to be an important predictor of progression and may influence subsequent treatment decisions. Given the heterogeneity seen in any given tumor, it is unlikely that grading a tumor on an aspirate or core biopsy will be reliable, nor has it shown to be reliable in studies.

***Needle Biopsy Post-Ablation.*** Percutaneous needle core biopsy or FNA cytology after ablation is done when there is clinical suspicion that there is residual viable disease. In this setting interpretation of pathologic material is difficult because it is likely that the number

**Table 3:** Biopsy-proven benign tumors

| Type | Biopsies[37-47] | Benign[±] | Type | Biopsies[48-57] | Benign |
|---|---|---|---|---|---|
| Bench[*] | 77 | 17 (22%) | Core | 100 | 42 (42%) |
| Bench | 62 | 5 (8%) | Core | 119 | 24 (20%) |
| FNA | 41 | 35 (85%) | Core | 152 | 65 (43%) |
| FNA | 180 | 98 (54%) | Core | 30 | 7 (23%) |
| FNA | 58 | 20 (34%) | Core | 70 | 22 (31%) |
| FNA | 31 | 2 (6%) | Core | 138 | 43 (31%) |
| FNA | 31 | 3 (10%) | Core | 78 | 13 (17%) |
| Core | 73 | 17 (23%) | Core | 235 | 78 (33%) |
| Core | 100 | 15 (15%) | Core | 100 | 33 (33%) |
| Core | 115 | 12 (10%) | Core | 110 | 43 (39%) |
| Core | 88 | 17 (19%) | **TOTAL** | **1988** | **611** |

[*]Bench tissue samples taken directly from *ex vivo* surgical specimens

The average proportion (prevalence) of benign cases is 0.28 95% CI (0.21, 0.35). This estimate carries considerable heterogeneity ($p<0.0001$) reflecting the variations in patient selection criteria and methodologies among the studies. Further, two studies of FNA conducted in 1999 had a proportion of benign cases that was considerably large (0.54, 0.85) with respect to all the others in the table. Re-estimating the proportion of benign cases excluding these two FNA studies results 0.24 95% CI (0.19, 0.29), and still substantial heterogeneity remains, indicating the impact of other confounding sources responsible for this large variation. Benign cases ranged between 0.06 and 0.42 in all the other studies.

of tumor cells present is small and the growth pattern distorted by the prior ablative procedure. For this reason it is particularly important for the biopsy to be taken from an enhancing area of the neoplasm, avoiding the center of the mass that is commonly fibrotic. Evaluation of specimen adequacy at the time of biopsy is essential, assuring that sufficient diagnostic material remains for subsequent tumor characterization. In the post ablation setting it may be more important to perform ancillary studies, such as immunohistochemistry or fluorescent *in situ* hybridization, to arrive at the correct diagnosis. It is also helpful to review the pathology of the biopsy material performed prior to the initial ablation as a means of comparison.

***Laboratory Data and Biomarkers.*** While no prospective validation currently exists for the use of common laboratory parameters in the early detection of metastases, following established practice provides an overall assessment of biochemical parameters, which in combination with a history and clinical exam provide the clinician a good estimate of a patient's overall condition and renal function. There are several laboratory values that have been utilized both in the staging and monitoring of patients with renal cell carcinoma following treatment for recurrence.

The identification of non-metastatic patients at high risk for relapse and those who are likely to benefit from adjuvant therapy with specific molecularly targeted agents is a long-term goal to optimize post-operative follow-up and management.

**GUIDELINE STATEMENTS**

Many of the following guidelines are clinical principle or expert opinion only and cannot be substantiated due to the limited clinical evidence:

***Guideline Statement 1.***

***Patients undergoing follow-up for treated or observed renal masses should undergo a history and physical examination directed at detecting signs and symptoms of metastatic spread or local recurrence. (Clinical Principle)***

**Discussion:** Interval patient history and physical examination are an integral part of medical care, offering the opportunity to yield critical information regarding the presence of disease recurrence or adverse events related to treatment effects. A myriad signs and symptoms including weight loss, night sweats, shortness of breath, dermatologic involvement, musculoskeletal pain or weakness may herald disease progression or developing complication and serve as an indication for further investigation.

***Guideline Statement 2.***

***Patients undergoing follow-up for treated or observed renal masses should undergo basic laboratory testing to include blood urea nitrogen (BUN)/creatinine, urine analysis (UA) and estimated glomerular filtration rate (eGFR). Other laboratory evaluations, including complete blood count (CBC), lactate dehydrogenase (LDH), liver function tests (LFTs), alkaline phosphatase (ALP) and calcium level, may be used at the discretion of the clinician. (Expert Opinion)***

**Discussion:** Please see the renal assessment background section for a discussion of the benefits of monitoring renal function and referral to nephrology.

LDH is included in several nomograms where it provides prognostic information, in particular for patients with advanced disease.[62,63] However, there are no data that demonstrate that regular LDH measurements in the non-metastatic setting improve detection of metastatic disease. Although no strong evidence exists for the use of these laboratory tests in the follow-up of patients with clinically localized renal cancers, a common sense approach dictates that measures of general organ function are part of routine follow-up for patients who are diagnosed with cancer.

While elevated pre-operative ALP is a potential prognostic marker for renal cell carcinoma,[64] additional retrospective reviews do not demonstrate utility of either bone scan or ALP in the initial evaluation or follow-up of asymptomatic patients with of renal cell carcinoma.[65,66]

***Guideline Statement 3.***

***Patients with progressive renal insufficiency on follow-up laboratory evaluation should be referred to nephrology. (Expert Opinion)***

**Discussion:** The long term impact of renal dysfunction increases risks of osteoporosis, anemia, metabolic and cardiovascular disease, hospitalization and death. Effective treatment strategies are available to slow the progression of chronic kidney disease and reduce cardiovascular risks, and therefore timely identification of progressive renal dysfunction can provide opportunity for medical intervention when indicated. The two formulas for monitoring eGFR commonly reported upon in the contemporary literature at the time of this guideline are the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) equations. Please refer to the Renal Assessment section for additional information.

***Guideline Statement 4.***

***The Panel recommends a bone scan in patients with an elevated alkaline phosphatase (ALP), clinical symptoms such as bone pain, and/ or if radiographic findings are suggestive of a bony neoplasm. (Recommendation; Evidence Strength: Grade C)***

**Discussion:** Studies that address the utility of an initial bone scan in the work up of patients with of renal cell carcinoma[67-69] show that, although bone scan has a reasonable sensitivity and specificity, the probability of finding bony neoplasms in the absence of elevated ALP or bone pain is low. As such, the routine use of bone scan in the absence of bone pain or elevated ALP may be unnecessary. However, with the presence of symptoms and/or elevated markers, radionuclide bone scan is a useful test.

This recommendation is based on studies indicating that an elevated ALP or the presence of clinical symptoms, such as bone pain, raises the probability of metastatic spread to a level >5%-10%. Assuming a sensitivity of 94% and a specificity of 86%[70] with a pre-test probability of 5%, a negative bone scan would drop the post-test probability below 1%, whereas a positive test would raise the post-test probability to 26%, likely necessitating further diagnostic evaluation. In this setting, the Panel judged the benefit to risk/burden ratio to favor the performance of a bone scan.

***Guideline Statement 5.***

***The Panel recommends against the performance of a bone scan in the absence of an elevated alkaline phosphatase (ALP) or clinical symptoms, such as bone pain, or radiographic findings suggestive of a bony neoplasm. (Recommendation; Evidence Strength: Grade C)***

**Discussion:** There are no compelling data in the literature supporting the use of bone scan in the follow-up of patients with non-metastatic disease. This recommendation is based on studies indicating that in the absence of an elevated ALP or clinical symptoms, such as bone pain, the prevalence of bony metastases is very low (<1%). Routine imaging of these patients would result in a high rate of false-positive findings necessitating further burdensome, potentially invasive and resource intensive studies. As such, the routine use of bone scan in the absence of bone pain or elevated ALP is not required.

***Guideline Statement 6.***

***Patients with a history of a renal neoplasm presenting with acute neurological signs or symptoms must undergo prompt neurologic cross -sectional CT or MRI scanning of the head or spine based on localization of symptomatology. (Standard; Evidence Strength: Grade A)***

**Discussion:** This recommendation is based a high diagnostic accuracy of neurologic cross-sectional (CT or MRI) imaging to rule in or rule out metastases to the brain and/or spine, in addition to a high prevalence of underlying management-altering pathology in patients with these symptoms, including but not limited to metastatic disease. MRI may be more sensitive than CT scan for the detection of small CNS neoplasms. CT may be used in the setting of acute neurological signs or symptoms to diagnose abnormalities that require emergent treatment,[71] but MRI is the most sensitive and specific imaging test for detection of metastatic neoplasms to the brain.

***Guideline Statement 7.***

***The Panel recommends against the routine use of molecular markers, such Ki-67, p-53 and VEGF, as benefits remain unproven at this time. (Recommendation; Evidence Strength: Grade C)***

**Discussion:** The Panel's recommendation is based on the lack of evidence supporting the value of these markers as well as a perceived unfavorable benefit to risk/burden ratio. Although there is some data indicating that an increase in molecular pathological markers, such Ki-67, p-53 and VEGF, may be associated with a worse prognosis, none of the molecular markers have been prospectively validated in large series of patients; therefore, their utility in the current follow-up of patients is unknown.

At the time these guidelines were published, no prospectively validated biomarkers were available for use in either pre-treatment staging or post-treatment risk of recurrence for patients with of renal cell carcinoma, nor had any agents shown benefit in the adjuvant setting. However, as part of the analysis performed for the Guideline, molecular markers were assessed for their accuracy in predicting the risk of local recurrence, secondary tumors, metastases and cancer-specific deaths from of renal cell carcinoma in general and at one, two, three and five years. No meta-analyses assessing the predictive role of markers on of renal cell carcinoma were found in the literature. A recent review of the literature[72] qualitatively summarizes the evidence for the different markers and their prognostic relevance and identifies the need for clinical trials that test candidate biomarkers prospectively.

Our literature search gave 514 articles dealing with biomarkers, cancer-control outcomes and characterization of subtypes. Of these, 87 articles were deemed relevant for further examination and covered a set of 14 different markers (VEGF, Ki67, p53, MMP, p27, e-cadherin, MUC1, COX2, IL-6, survivin, VHL, HIF-

1, CA-IX, cyclin).

After the review of these 87 articles, 30 did not have data linking the marker with a cancer control outcome, 26 had metastatic cases at baseline ranging from 9% to 50%, and six could be used in a qualitative manner since they provided a significance value but not a quantitative measure of the strength of the association. There were four articles reporting the same cohort from UCLA. The most recent article, which was also more comprehensive in terms of number of markers assessed, was selected. These exclusions led to only 15 articles with potential data for meta-analysis. This final set only covered three markers Ki67, p53 and VEGF.

All but one study was based on renal cell carcinoma tissue from radical or partial nephrectomy specimens, rather than biopsy or FNA. The quality of the potential conclusions derived from tumor tissue with a more accurate characterization than that observed in the reports for ablation or observation and a moderate sample size was somewhat diminished by the retrospective design used by all but one study. These studies were conducted before 2000.

Most outcomes were represented by only two studies. Since at least five studies of 30+ patients each are required for meta-analysis, proper analysis could not be performed for these outcomes. For all outcomes and markers, an increase in the putative marker translated into a worse prognosis. For the proliferation marker Ki-67, a cutoff of 6% is strongly associated with recurrence and cancer-specific mortality in univariate analysis. In multivariable analysis, considering stage and grade and other covariates, a cutoff of 10% is moderately associated with recurrence and overall death but not necessarily with statistical significance. For p53, a cutoff of 10% provides an independent moderate and statistically significant association with cancer-specific mortality even in the presence of stage and grade. Finally, for the angiogenic marker VEGF a cutoff of 25% confers a slight increase in the likelihood of cancer-specific mortality, but this was not statistically significant.

**Surgery**

Surgical management with resection of the primary tumor provides for immediate local control of renal tumors and valuable pathologic data that may aid in understanding prognosis and guide patient follow-up. Post-operative follow-up seeks to satisfy several goals: the assessment of disease-specific outcomes; local, regional or distant recurrence; the adequacy of resection; evidence of residual disease and evaluation of ongoing or potential post-operative complications, such as loss of renal function or post-operative sequelae that may influence or require subsequent intervention. Though the predictability of these outcomes may be partly quantified based on patient- and pathology-derived factors, standardized follow-up paradigms will ideally optimize post-operative care by providing opportunity for timely intervention of detected abnormalities with the expectation of patient benefit.

The presumption, thus far untested, is that earlier detection of recurrent or metastatic disease will lead to earlier treatment and better outcomes for patients. However, with the advent of a new generation of targeted systematic therapy, adjuvant therapy in patients identified with metastatic disease may hold the promise of a prolonged survival. Post-operative clinically-accepted standards for routine medical evaluation include thorough patient history and physical examination and laboratory studies as well as directed imaging procedures that focus primarily on the likely sites of local recurrence or metastatic progression. The frequency and timing of these evaluations are influenced by a variety of factors in an individual patient. These include the stage and grade of the primary tumor, tumor histology and margin status as well as method of tumor extirpation (e.g., partial v. radical nephrectomy). In reviewing the literature, other factors appear to demonstrate prognostic significance including patient performance status,[73,74] the presence of sarcomatoid histology,[75,76] tumor grade, the presence of histologic tumor necrosis[77,78] and patient age.[79]

There are a variety of nomograms or scoring systems described in the literature that combine various clinical, pathologic and even molecular markers purported to be prognostic in localized, locally advanced and metastatic renal cell carcinoma. These include the University of California Integrated Staging System (UISS); the Mayo Clinic Stage, Size, Grade and Necrosis (SSIGN) Score and the Memorial Sloan Kettering (MSKCC) Renal Cell Carcinoma Nomogram.[80,81] These models have clinical utility, particularly in the design of prospective trials, yet they have not gained universal acceptance in general urologic practice to the level necessary to warrant endorsement. Instead, the TNM pathologic stage, grade, nodal involvement and margin status remain the primary utilized factors to assess risk of local and distant recurrence following curative surgery.

In regards to the timing of failure, most studies note that the majority of disease relapses occur within the first three years following surgery. After that, additional failures are less common but have been reported to occur as late as 20 years following surgery. Therefore, surveillance guidelines are tailored to account for this disease biology, with more rigorous follow-up during the first three years following surgery and then decreasing the frequency of surveillance in subsequent

years to reflect the decrease in recurrence risk over time following surgical resection.

Although the aforementioned algorithms assess prognosis using more clinical features, the current and past literature that provide guidance on surveillance regimens primarily depend on stage; however, grade is included in some risk stratification tools, such as UISS, SSIGN and MSKCC.[80,82,83] For the purposes of post-operative surveillance guidelines, patients with localized renal cancers may be grouped into strata of low and moderate to high risk for disease recurrence based on pathologic features reflecting tumor biology. Although grade is a risk factor considered in existing stratification tools, based on the meta-analysis conducted, including only cohorts of patients with localized disease, a consistent overall estimate was not feasible at this point using these prognostic factors. Only stage was consistently analyzed in the recurrence data and thus serves as the key risk stratifier. See Appendix C for corresponding forest plots.

**Low risk** is defined as organ-confined tumors (pT1, N0 or Nx) with negative or radiographically normal lymph nodes. These tumors have a risk of metastasis of less than 15% and an extremely low risk of local recurrence (less than 5%) in the absence of a positive surgical margin.

**Moderate to high risk** is defined as organ confined tumors greater than 7cm (pT2 N0 or Nx), non-organ confined tumors (pT3-4 N0 or Nx) with evidence of extension beyond the renal capsule, into the perinephric fat, renal sinus, renal vein or inferior vena cava, adjacent organ invasion including the ipsilateral adrenal gland and/or any stage tumor with positive regional nodes (N+). Patients with these tumors have a higher risk of both local and metastatic recurrence in the range of 30% to 70% and, therefore, are recommended to have an increased frequency of examinations due to a higher likelihood of primary treatment failure.

***Low risk patients (pT1, N0, Nx):***

***Guideline Statement 8.***

***Patients should undergo a baseline abdominal scan (CT or MRI) for nephron sparing surgery and abdominal imaging (US, CT or MRI) for radical nephrectomy within three to twelve months following renal surgery. (Expert Opinion)***

**Discussion:** A baseline abdominal scanning (CT or MRI) rather than US within three to twelve months after nephron-sparing surgery is useful for several reasons. Following a partial nephrectomy and alteration of the kidney architecture, this imaging serves as a comparison point for possible future evaluations. In addition, imaging may be clinically indicated to monitor for post-operative complications and for patient symptomatology. For those undergoing a radical nephrectomy for low risk cT1 tumors a baseline postoperative US may suffice.

Although during this time frame the risk of metastasis and metachronous cancer is low, this imaging does allow monitoring of the contralateral kidney as well. In patients at higher risk for local recurrence related to aberrant histology or positive margins, or those with bilateral or multifocal disease, such as the case of heredity or papillary cancer types, more frequent imaging may be indicated. Please refer to radiographic imaging background for limitations/advantages of the various imaging modalities following partial nephrectomy.

***Guideline Statement 9.***

***Additional abdominal imaging (US, CT or MRI) may be performed in patients with low risk (pT1, N0, Nx) disease following a radical nephrectomy if the initial postoperative baseline image is negative. (Option; Evidence Strength: Grade C)***

**Discussion:** Abdominal imaging (US, CT or MRI) beyond the baseline post-operative evaluation is optional, as the risk of local recurrence (in the renal remnant or the renal fossa) and visceral or nodal metastatic progression is low. Patients should be made aware that there is a 2-4% risk for a metachronous, contralateral tumor in the setting of sporadic, non-familial renal cell carcinoma. Patients with familial renal cell carcinoma syndromes represent a unique clinical situation that warrants more intensive and serial monitoring for the development of future renal tumors.[84-88]

***Guideline Statement 10.***

***Abdominal imaging (US, CT, or MRI) may be performed yearly for three years in patients with low risk (pT1, N0, Nx) disease following a partial nephrectomy based on individual risk factors if the initial postoperative scan is negative. (Option; Evidence Strength: Grade C)***

**Discussion**: Abdominal imaging (US, CT or MRI) beyond this baseline post-operative evaluation for low risk patients (pT1, N0, Nx) is optional as the risk of local recurrence (in the renal remnant or the renal fossa) and visceral or nodal metastatic progression is low. Early series of partial nephrectomy for imperative indications and for larger masses demonstrated a local recurrence rate of up to 6-10%, with recommendation for close follow-up indefinitely.[89,90] With increasing utilization of CT and MRI imaging and an increasing utilization of nephron sparing surgery for smaller,

incidentally discovered tumors local recurrence rates of 1.4- 2% are now reported.[91,92] These more recent data, however, are derived from mostly Clinical T1a renal masses. With increasing awareness of the consequences of chronic kidney disease,[93] there has been an expanded utilization of partial nephrectomy for Clinical T1b and higher renal masses, which may be associated with a higher recurrence rate; therefore, careful attention and close follow-up should be conducted in patients with higher risk characteristics for recurrence (imperative indications, clinical T1b and above, positive margins, higher tumor grade or aberrant histology) or in patients who have perioperative adverse events such as a urinary leak, urinary fistula, AV fistula or ureteral stricture, and may warrant further imaging until the issue(s) is (are) resolved. Additionally, multicentricity is found in as many as 10-20% of tumors with higher prevalence in papillary renal cell carcinoma and familial renal cell carcinomas; consideration for more frequent monitoring after partial nephrectomy may be considered in these situations[94]

***Guideline Statement 11.***

***The Panel recommends that patients with a history of low risk (pT1, N0, Nx) renal cell carcinoma undergo yearly chest x-ray (CXR) to assess for pulmonary metastases for three years and only as clinically indicated beyond that time period. (Recommendation; Evidence Strength: Grade C)***

**Discussion**: Pulmonary metastases are the most common site of renal cancer recurrence and are associated with more favorable outcome with appropriate treatment when identified as the sole site of recurrence. Based on the projected risk of progression, rates and sites of recurrence, thoracic imaging for the purpose of detecting pulmonary metastasis at least annually for three years is recommended. CXR may be preferable to CT scan of the chest given the propensity of false positive CT imaging in the detection of benign radiographic findings that may then mandate invasive workups, such as intrapulmonary lymph nodes and granulomas. The choice of imaging modality should be weighed against the level of clinical suspicion. In the patient with low risk (pT1, N0, Nx) disease, it is reasonable to perform a CXR annually for at least three years. If chest imaging is negative for three years post-surgery, then imaging beyond that point should only be done as clinically indicated.

***Moderate to High Risk Patients (pT2-4N0 Nx or any stage N+):***

***Guideline Statement 12.***

***The Panel recommends that moderate to high risk patients undergo baseline chest and abdominal scan (CT or MRI) within three to six months following surgery with continued imaging (US, CXR, CT or MRI) every six months for at least three years and annually thereafter to year five. (Recommendation; Evidence Strength: Grade C)***

**Discussion:** Patients with moderate to high risk tumors have a substantially higher risk of both local and metastatic recurrence (approximately 30-70%) when compared to low risk patients. Therefore, for patients who are candidates for further therapy to treat a local or metastatic disease recurrence, an increased frequency of examinations is recommended. Based on the known rates and sites of recurrence, both chest (CXR or chest CT) and abdominal imaging (US, CT or MRI) is recommended every six months for at least three years and annually to year five following baseline imaging. As pulmonary metastases are the most common site of renal cancer recurrence, timely detection of recurrent disease in the chest is optimized by a chest CT, which can be performed at the same time as the abdominal imaging.

***Guideline Statement 13.***

***The Panel recommends site-specific imaging as warranted by clinical symptoms suggestive of recurrence or metastatic spread. (Recommendation; Evidence Strength: Grade C)***

**Discussion:** Occasionally, patients will present with symptoms that could be attributed to metastatic disease. These symptoms may include, but are not limited to, new onset bone pain, weight loss, anorexia, abdominal discomfort, asthenia, fatigue, gross hematuria and lower extremity edema. When patients present with symptoms that could be attributed to disease recurrence or metastasis, site-specific imaging should be obtained, and the modality of imaging (CT, MRI, US, bone scan, plain films) should be tailored to the specific presenting symptom.

***Guideline Statement 14.***

***Imaging (US, CXR, CT or MRI) beyond five years may be performed at the discretion of the clinician for moderate to high risk patients. (Option; Evidence Strength: Grade C)***

**Discussion:** The frequency of abdominal imaging (US, CT or MRI) can be increased for patients presenting with symptoms that could be attributable to local and/ or metastatic progression. The type of abdominal imaging utilized should be based on clinical factors and physician discretion keeping in mind the limitations of US over cross-sectional imaging with MRI or CT in visualizing a recurrence, the radiation exposures over

time and the limitations based on contrast allergies or renal function. Please refer to the radiologic imaging benefits and risks section for additional details. Cross-sectional imaging seems prudent for the first postoperative baseline scan due to the higher accuracy and detail provided over ultrasound.

Most studies with five years of follow-up note that disease relapse usually occurs within the first three years with additional failures decreasing in frequency after three years. Therefore, surveillance guidelines are tailored to account for disease biology with more rigorous follow-up during the first three years following surgery and then decreasing the frequency of surveillance in subsequent years to reflect the decreased risk of recurrence over time following surgical resection. The frequency can be increased for patients presenting with symptoms that could be attributable to local and/or metastatic progression.

Studies in the literature support continued imaging up to five years from the date of surgery;[95] however, there is a paucity of data to direct the frequency of imaging (US, CT or MRI) beyond five years. Articles providing rates for 10 years,[80,96-100] mainly for cancer-specific survival, do it for stages or risk groups from the available tools in a non-overlapping manner, so overall estimates as those obtained for five years cannot be calculated at this point. Still, these studies and those that enumerate the occurrence of metastases in terms of their location and timing show that (1) metastases to the lung are the most common ones and can occur at any time during follow-up between 10 and 20 years after surgery,[101,102] either solitary or in combination with other sites,[103] (2) the contralateral kidney, bones and brain are other common metastatic sites during the period between 10 and 15 years after surgery,[102] (3) even individuals with pT1a disease can experience distant metastases beyond 5 years,[79,101] and (4) metastases have been reported to occur beyond 30-40 years after nephrectomy.[104,105] Thus patients with recurrent disease beyond five years may still benefit from imaging.

***Guideline Statement 15.***

***Routine FDG-PET scan is not indicated in the follow-up for renal cancer. (Expert Opinion)***

**Discussion:** This statement is based on a review of the evidence, which failed to identify studies to support a role for FDG-PET. There are no data in the literature to support the use of PET scanning in the evaluation or surveillance of patients with renal tumors due to the lack of data on the specificity and sensitivity. Its use is discouraged in these circumstances. Future roles may exist for PET with newer imaging agents, such as G-250, which are currently being studied.[16]

**Active Surveillance**

The follow-up protocol for patients who have been selected for active surveillance[ii] is based on the AUA small renal mass treatment guidelines criteria, where definitive treatment has been deferred, and involves unique considerations. It is assumed that the patient who has been chosen for active surveillance is one who would undergo intervention if, in the course of active surveillance, changes occur in the primary tumor for which intervention would normally be indicated. In the patient for whom no surgical or minimally invasive intervention (i.e., surgery or percutaneous ablative procedure) would ever be considered due to comorbidities, no imaging is necessary. For a complete definition of the patient criteria for whom active surveillance is indicated, please refer to Appendix D.

Follow-up protocols may vary depending on whether the patient has undergone a biopsy of the renal mass. The Panel considered clinical scenarios including biopsy-proven, untreated, clinically localized renal cancers; biopsies yielding low-malignant potential neoplasms or normal renal parenchyma; and renal lesions radiographically suspicious for neoplasm that either have not been biopsied or have indeterminate biopsy results.

Physicians should counsel patients on their other therapeutic options, as addressed in the AUA Treatment of T1 Renal Mass Guidelines.[106] Specifically, the patient should be counseled about the small but potential risk of cancer progression while on active surveillance, the potential loss of a window of opportunity for nephron-sparing surgery, the lack of curative salvage therapies if metastases develop and the deficiencies of the current data used to support this approach.

Potential triggers for intervention while on active surveillance primarily involve absolute tumor size, tumor growth rate or a change in patient preference. The meta-analysis by Chawla and colleagues focused on estimating the yearly tumor growth rate of enhancing renal masses among multiple small series.[107] Among 234 individuals who presented with mean neoplasm size of 2.6 cm and who were followed for an average of 34 months, the mean growth rate was 0.28 cm/yr. The series evaluated a total of 286 neoplasms, and pathologic findings were available in 131 (46%) of

[ii]Indications for active surveillance 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.

them, 92% with malignant histology. Metastasis developed in 3 of 286 (1%) cases. The development of these metastases could not be associated with tumor growth or neoplasm size at presentation. The more recent meta-analysis for the AUA Renal Mass Guidelines extended the information gathered by Chawla et al. to include 12 studies evaluating 390 renal masses.[106,107] Among these 390 cases, the mean tumor size was 2.7 cm, and mean duration of follow-up was 29.6 months. Among these studies, the mean metastasis-free survival rate was 97.7% (95% confidence interval = 95.5 to 98.9).

The current meta-analysis includes 10 retrospective studies with a sample size of 30 patients or more, assessing a total of 852 patients. Tumor growth was evaluated on 538 neoplasms, while metastasis and deaths were evaluated on 804 patients. The mean tumor size was 3.7 cm, and the first assessment after diagnosis occurred at either three or six months and were equally distributed among the 10 studies. Of the nine studies that provided follow-up times, the average follow-up was 29 months with a minimum of 16 months and a maximum of 47.6 months.[108-116] While the overall cohorts are comparable in terms of average age (72 years), average tumor size (3 cm) and proportion of men to women (2 to 1), some studies differed somewhat from this average. Two studies had an average age of 56 and 81, respectively. Additionally, two studies showed an average tumor size of 7 cm or more. Three studies had a male to female ratio of 1.5 instead of 2. The radiographic diagnostic study most frequently utilized was CT. Similar to previous meta-analyses, the proportion of metastasis was 1 per 100 patients, whereas the overall mortality was 16 per 100 patients, further verifying the heterogeneity of this population.

The meta-analysis for Table 4 is the product of the data summarized in Appendix E. All are retrospective cohorts.

The rate of metastasis is 1 per 100 patients followed. The overall mortality, or death from any cause, is 16 per 100 patients; however, there was significant heterogeneity noted in the estimates depending on whether the interval between subsequent imaging evaluations was three or six months as per study design. When the interval is three months only one death was reported, but when imaging scans were six months apart, the mortality rate raises to an average of 34 per 100 patients. Since the deaths averted by a more intense follow-up were not kidney-related, it is unclear whether it was the imaging itself, or just the more frequent contact with a health care provider that led to a reduction of death by detecting other life-threatening issues, thus allowing corresponding life-preserving measures to be taken.

Of note, the rate of tumor growth in the current meta-analysis is similar to that reported by Chawla et al.'s study; however, it is important to highlight that only one study from that meta-analysis is included in the current meta-analysis. This indicates that the newer studies examining active surveillance have similar findings to those performed in the late 1990s. Corresponding Forest plots are displayed in Appendix F. In addition, none of the studies reported the intra-observer variability or intra-observer evaluations in tumor measurements and how that might impact observed growth rates.

The quality score (Appendix G) implemented for this question has a maximum of 11 points. All items were scored between 0 (desirable property not present) and 1 point (desirable property present). One property was given an additional point to studies that satisfied the particular item beyond the minimum requirement (i.e. more than the minimum sample size, this increases the precision of estimates obtained). The average quality was 4.5, indicating the generally low quality of studies. The main deficiencies in methodological quality were noted in the study design component (retrospective, small sizes, not clear whether individuals were included consecutively), follow-up, and handling of potential confounding factors. The latter is probably motivated by the small number of individuals that makes difficult any multivariable modeling approach.

The precise growth rate or absolute tumor size that would trigger intervention is controversial given the limited available data. Some would propose that because the normal growth rate is approximately 0.3 cm/year, a persistent tumor growth rate of greater than 0.3- 0.5 cm per year, and/or an absolute tumor size of greater than 3cm would justify intervention. The intervention would primarily involve local treatment as outlined in the AUA Renal Mass Guideline, although a biopsy (in the case of biopsy-unproven renal masses) or a change to more frequent imaging could also be incorporated.

Groups appropriate for active surveillance have already been defined in The Renal Mass Guideline.[106] In the event that the index patient has chosen active surveillance, and it is assumed that the patient is a candidate for surgical/ablative intervention at a later time, a judicious period of active surveillance appears to be associated with a low risk of size or stage progression while maintaining the viability of most therapeutic options.

***Guideline Statement 16.***

***Percutaneous biopsy may be considered in patients planning to undergo active surveillance. (Option; Evidence Strength: Grade C)***

**Table 4.** Overall estimates (proportion) of cancer control outcomes and corresponding 95% confidence interval for localized enhancing renal masses followed with active surveillance

| Outcome measure | Studies[108-118] | Size* | Overall (CI) | Heterogeneity (p-value) |
|---|---|---|---|---|
| Metastases (p) | 6 | 423 | 0.01 (0.00, 0.02) | 0.5998 |
| All-cause deaths (p) | 6 | 423 | 0.16 (0.07, 0.26) | <0.0001 |
| All-cause deaths (p): studies with imaging intervals at least e/3 mo. | 3 | 220 | 0.00 (0.00, 0.01) | 0.5860 |
| All cause deaths (p): studies with imaging intervals at least e/6 mo. | 3 | 203 | 0.34 (0.28, 0.41) | 0.8589 |
| Tumor growth cm/yr (t) | 8 | 538 | 0.30 (0.24, 0.37) | 0.5323 |

*Size: number of patients

**Discussion:** The accuracy of percutaneous biopsy has improved substantially over the past several years due to further refinements in CT- and MRI-guided techniques. Several systematic reviews have addressed this specific diagnostic procedure,[58,59] focusing on several key issues. Renal mass biopsy is not indicated, however, for comorbid patients who may consider only conservative management options regardless of biopsy results or who have higher risks of biopsy related complications due to comorbid conditions. Clinical characteristics of the renal neoplasm, such as location, cystic nature and hemorrhagic necrosis, may diminish the possible contribution of renal biopsy and should be considered as well.

***Guideline Statement 17.***

***The Panel recommends that patients undergo cross-sectional abdominal scanning (CT or MRI) within six months of active surveillance initiation to establish a growth rate. The Panel further recommends continued imaging (US, CT or MRI) at least annually thereafter. (Recommendation; Evidence Strength: Grade C)***

**Discussion:** Only a limited number of studies have specifically examined long-term growth patterns; however, the published studies do not suggest logarithmic growth but rather linear growth patterns.[107] As such, obtaining an abdominal scan (CT or MRI) as early as six months from initiation of surveillance will establish the expected growth pattern. Subsequent imaging (US, CT or MRI) can then be performed yearly unless the pace or characteristics of growth are concerning. This would include patients with indeterminate renal biopsy with a radiographically identifiable neoplasm, due to the risk of a false negative biopsy. For benign or negative neoplasms on biopsy, at this point without 100% accuracy, we recommend follow-up in the patient as if the patient did not undergo a biopsy. A physician may choose to discontinue chest imaging and only proceed with yearly ultrasounds to watch for growth that may require intervention.

CT and MRI tend to be used more often for surveillance because they provides higher quality information over US, especially for neoplasms under 3cm; however, there may be benefits in reducing the risks of contrast and radiation exposure by employing alternative imaging. Alternative methods for limiting the amount of radiation and contrast exposure, include limiting CT use to once yearly unless otherwise clinically indicated, using a low dose radiation CT protocol for imaging, using MRI, and/or alternating the use of CT or MRI with US for surveillance. **Importantly, with respect to tumor size measurements, differences of < 3.1 mm for inter-observer or < 2.3 mm for intra-observer evaluations are within the variability of measurement and should, therefore, not be attributed to tumor growth,[106] unless in the case where there are persistent increases over two or more interval exams.** Although it has been shown that the growth rate of a renal mass does not necessarily predict the presence of cancer and no robust method exists for distinguishing benign/indolent v. malignant/aggressive tumors based purely on radiologic features, more rapid rates and larger size trend towards association with true cancer and aggressive disease.

Once the neoplasm is characterized with CT or MRI and confirmed to be visible on US, the alternative of low-radiation CT or MRI may be used to monitor the size of the neoplasm over time. Few studies have examined the correlation between the different imaging modalities, but one study by Mucksavage and colleagues, retrospectively reviewed the clinicopathological data of 776 patients who underwent radical or partial nephrectomy and correlated the ability of CT, MRI and US to predict pathologic maximum tumor diameter.[119] They found no significant differences between the estimated pre-operative tumor size and pathological tumor size between all modalities, and all three standard renal imaging modalities appear to accurately predict pathological tumor size. One limitation of this study was that the mean tumor diameter was approximately 4.5 cm with evidence of slightly greater differences in measurements in patients with smaller masses, perhaps with tumor sizes more similar to patients who might opt for active surveillance. The lack of inferiority of ultrasonography in predicting pathological tumor size affords opportunities for the reduction of ionizing radiation exposure, reduced need for IV contrast and reduced dependence on adequate renal function to administer contrasts.[119,120] These benefits should be weighed against the superiority of CT and MRI to evaluate for invasion of the perirenal or sinus fat and lymph node involvement, although the majority of patients on active surveillance harbor smaller renal masses with likely decreased need to evaluate for local and regional disease.

If a biopsy is performed, the findings of the biopsy and subsequent neoplasm growth rate should dictate follow-up. Patients with renal carcinoma, oncocytoma or oncocytic neoplasms and indeterminate histology should be followed with the same imaging protocols for untreated, low risk (cT1, N0, Nx) renal cancer patients for two primary reasons. First, oncocytomas, while benign, can exhibit substantial growth patterns over time that may threaten the renal unit. As sparing of the nephron is the goal in patients with small renal masses, it is recommended that even benign neoplasms undergo vigilant surveillance to assess for local growth and to avoid the compression/invasion of surrounding parenchyma and vascular structures that may hamper nephron-sparing surgery. As such, routine imaging of these neoplasms aims to capture undue tumor growth on follow-up and thus allows for expedient surgical/ ablative intervention and avoidance of radical nephrectomy.

Second, while the accuracy of percutaneous biopsy has improved substantially in the past several years, as previously mentioned (see renal biopsy background section), the differentiation between oncocytoma and oncocytic neoplasms (e.g., chromophobe renal cell carcinoma) can present a diagnostic dilemma. The chromophobe renal cell carcinoma entity is generally associated with more indolent natural history, although it falls within the spectrum of low-risk renal cell carcinoma, and, as such, most investigators have correspondingly adjusted the associated surveillance protocol.[80, 82,83] In most cases, investigators recommend to follow these oncocytic neoplasms with abdominal imaging in the same manner as any low-risk renal tumor.

***Guideline Statement 18.***

***The Panel recommends that patients on active surveillance with biopsy proven renal cell carcinoma or a tumor with oncocytic features undergo an annual chest x-ray (CXR) to assess for pulmonary metastases. (Recommendation; Evidence Strength: Grade C)***

**Discussion:** The available literature on tumors followed by active surveillance reveal a low metastatic rate (1-2%) during the first few years of surveillance.[106,107] These favorable results are consistent with well-established data regarding the biological aggressiveness of clinical stage T1 renal masses followed by active surveillance: many are benign or indolent, while approximately 20-30% have potentially aggressive features.[107] These favorable data likely reflect a selection bias of active surveillance series for small tumors with favorable radiographic characteristics.

However, the Panel believes that these findings need to be considered carefully. There is very likely an ascertainment bias introduced by lack of chest imaging, not only in the surveillance series, but also in the surgical series of T1 disease. For example, CT imaging was abdominal only in the early surveillance series, except in four studies where the type of CT imaging was not specified. Similarly, the surgical series was dominated by either abdominal only CT imaging or with the addition of imaging at the pelvic or unspecified site. Only one report specifically noted chest imaging. As early distant disease is often asymptomatic, and most series had limited follow-up duration, one potential explanation for the low metastatic rate lies in the lack of chest imaging to capture these metastases.

Historically, chest imaging has been recommended in surveillance series, although the ideal recommended frequency is unknown and should thus be individualized depending on clinical and radiologic characteristics. Of 11 studies, only three explicitly indicated chest imaging, all with CXR and one with CT as well.[108,111,113] Specifically, if the tumor is biopsy-proven high grade renal cell carcinoma and/or displays rapid interval growth patterns, chest imaging may be performed

annually or more frequently based on clinical behavior of the tumor. Conversely, if the tumor is biopsy-proven benign parenchyma,[121,122] chest imaging may be omitted**.** As outlined previously, patients with biopsy-proven oncocytoma or tumor with oncocytic features should be followed like patients with low risk (clinical T1, N0, Nx) renal cell carcinoma.

**Ablation**

Thermal ablative modalities, specifically cryoablation and radiofrequency ablation (RFA), currently represent accepted minimally invasive treatment options for clinical T1a renal masses in select patients with appropriate informed consent and counseling.[123] Ablative techniques may be performed by a variety of approaches (open/laparoscopic/percutaneous) and operators (urologic surgeons/interventional radiologists). The majority of neoplasms selected for ablative procedures are less than 4 cm and exophytic, as markedly higher incomplete ablation rates have been noted for endophytic, central and larger neoplasms.[124-126]

Thermal ablative techniques are associated with an increased risk of local recurrence compared to extirpritive surgery in the early clinical experience literature and current meta-analysis of the available literature.[106] In addition, the risk assessment for a local recurrence of renal cell carcinoma and/or the development of metastatic disease and death from clinical stage T1 renal cell carcinoma after ablative procedures is difficult to ascertain with certainty from the current literature due to the evolving ablative techniques and criteria for ablation, the lack of pretreatment biopsy confirmation of tumor, the lack of long term follow up, the difficulty in assessing recurrent/residual tumor on biopsy or radiographic imaging, poor quality of reporting and the lack of uniformity in the definition of a local recurrence. For the purposes of this document and to maintain consistency with the AUA Guidelines on Management of the Clinical T1 Renal Mass, and the recommendations of the Working Group of Image-guided Tumor Ablation, **"local recurrence" was defined as any localized disease remaining in the treated kidney at any point after the first ablation, as determined by a tumor with contrast enhancement after ablation or a visually enlarging lesion in the same area of treatment with or without the presence of contrast enhancement**.[127] This definition was promulgated in 2005, when there was little long term data available on local recurrence or the reliability of imaging and post treatment biopsies following ablative procedures to determine the presence of a recurrence. Now that there are more intermediate data available on risks of local recurrence following ablative procedures we are taking this further step in defining the term "local recurrence" to include **"the failure of an ablated lesion to regress in size over time, and or the development of new satellite or port site soft tissue nodules."** This is with the knowledge that ablative modalities have higher rates of local recurrence and treatment failure compared to extirpative surgery, and that the presence or lack of contrast enhancement or post treatment biopsies may not be reliable in detecting all local recurrences.

***Cryoablation.*** Modern cryoablative technology involves small and medium caliber needle(s) systems. Current systems use argon gas to create rapid freezing with temperatures of less than -40°C within the ice ball. Post -procedurally, the cryoablation zone is largest on imaging post-operative day one, but then typically steadily decreases.[128] Various appearances of post-operative radiographic imaging have been noted in the literature including that of persistent non-enhancing mass/scar, fibrosis, cyst or cortical defect. Failure is typically defined as persistence or development of enhancement within the ablated region. However, at least one study has noted that persistent contrast enhancement may continue for up to nine months after the procedure.[129]

A recent meta-analysis summarized 47 studies assessing the efficacy of ablative interventions in 1,375 kidney neoplasms. Studies were similar in patient demographics and tumor size, and the majority exhibited short-term follow-up for the two ablative modalities. The majority of studies were non-comparative, retrospective, and of small cohort size.[130] A second follow-up meta-analysis compared partial nephrectomy, ablation and surveillance, and this has been summarized extensively in the literature and as part of the 2009 AUA Clinical T1 Renal Mass Guidelines.[106]

Similar to the overall ablative cohorts, cryoablation series have tended to intervene on smaller neoplasms and have had a shorter length of follow-up compared to surgical series. Additionally, many of these series have significant numbers of neoplasms with either no pathologic biopsy or a non-diagnostic biopsy.[131] Given the approximate 20% rate of benign renal masses found in most series of small renal masses, a significant number of unidentified/non-biopsied neoplasms may have been benign. Lack of definitive ability to assess benign pathology should result in a reduced rate of development of metastatic disease and increased cancer specific survival compared with studies looking at surgical extirpative procedures where definitive pathology is obtained. However, the impact of staging inaccuracy, which is inherent to non-extirpative procedures, may produce the opposite bias resulting in higher levels of development of metastatic disease and reduced cancer specific survival. At present, there is no

imaging, molecular marker or methodology to eliminate this inaccuracy.

***Radiofrequency Ablation.*** RFA ablation involves *in situ* needle placement and treatment of a tumor to 105°C, according to the size of the neoplasms, with the goal of creating an ablation zone of approximately 5 mm to 10 mm beyond the tumor margin. Larger tumors are treated for longer periods of time, and two treatment/cool-down cycles are involved with monitoring by CT for percutaneous approaches and ultrasound for laparoscopic approach.

The meta-analysis conducted as part of the AUA Clinical T1 Renal Mass Guideline Panel[106] demonstrated similar limitations with respect to the quality of the literature, lack of histologic confirmation and short-term follow-up as cryoablation. Furthermore, patients treated with RFA and cryoablation share similar demographics and selection criteria, mainly being of high surgical risk and having a 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. As summarized in the Clinical T1 Renal Mass Guideline document,[106] RFA resulted in a 85.2% and 87% recurrence free survival.

***Post Ablation Imaging.*** Patients who have undergone ablative treatment of renal tumors are subsequently followed with radiologic imaging, using CT or MRI. Immediate post-procedural imaging of the ablated tumor generally shows the tumor to be larger than its pre-treatment size for RFA due to ablation of a peripheral margin of normal tissue, and for cryoablation due to extension of the iceball beyond the original tumor margin. Radiological evolution of cryoablated tumors is characterized by significant decrease in size and loss of contrast enhancement on CT. Tumors successfully treated with RFA demonstrate no IV contrast enhancement but with minimal involution on CT.[123] On MRI, the imaging hallmark of successful renal tumor ablation is lack of tumor enhancement at gadolinium-enhanced imaging. Rim enhancement, believed to represent reactive change, may occasionally be seen at early postprocedural MR imaging after RFA or cryoablation, which later resolves and is not considered ablation failure. Cryoablated or RF-ablated renal tumors generally appear relatively hypointense on T2-weighted images as compared to the intermediate or high signal intensity tumor seen on pre-ablation images. Ablation zones exhibit somewhat varied signal intensity on T1-weighted images following RFA or cryoablation. Renal tumors that have been successfully treated with cryoablation demonstrate reduction in size, complete resolution or scar formation.[131] After successful RFA, gradual involution of the ablation zone is typically observed during the remainder of the MRI imaging follow-up period.[131]

Several reports have questioned whether the absence of contrast enhancement in the ablated tumor is a reliable indicator of successful tumor ablation after RFA, although the reliability of the histopathologic "gold standard" used to determine presence of viable tumor in these studies has been subject to criticism.

A study by Weight et al.[128] also questioned the ability of post ablation MRI or CT to predict absence of tumor after RFA. The study included a total of 109 renal neoplasms in 88 patients treated with percutaneous RFA and a total of 192 renal neoplasms in 176 patients treated with laparoscopic cryoablation. All patients scheduled for ablative therapy underwent initial biopsy. The post-ablation protocol included radiographic imaging with CT or MRI on post-operative day 1, at 3, 6 and 12 months and then annually. Biopsy of the ablated site was performed immediately after the six-month abdominal imaging. The rate of radiographic success, defined as a lack of central or nodular enhancement, on post-contrast CT or subtraction imaging MRI, was 85% for RFA and 90% for cryoablation at six months post-treatment, but the rate of pathological success, defined as the lack of malignant/atypical cells on post-ablation biopsy or radical nephrectomy histopathologic interpretation, for RFA was 65% and for cryoablation was 94%. For the tumors treated with RFA, a total of six patients (24%) who had no evidence of post-ablation enhancement on six-month imaging follow-up had biopsy interpretation showing viable renal cancer cells, whereas all patients in the post cryoablation group who had no enhancement on six-month imaging had negative contemporary biopsies. However, as was pointed out in an editorial comment following the article, the persistent disease rate of 35% for RFA reported in this paper was not reproduced by later groups reporting much better RFA results, and selection bias may have been a factor in the referral of more technically challenging cases to RFA. There were significantly more centrally-located tumors in the RFA group, half as many in the RFA group had a normal contralateral kidney as did those in the cryoablation group, and there were 17 times more solitary renal remnants in the RFA group. Centrally located neoplasms within kidneys that in some cases may have demonstrated architectural distortion on imaging may have shown limited conspicuity as distinct from the surrounding renal parenchyma. Also, as was true in the study by Rendon,[125] only hematoxylin (H) and eosin (E) staining was used for histopathologic evaluation, and the accuracy of routine staining in the evaluation of post RFA treated tissue for viable cells is unknown.

A study by Raman et al.[132] presented data supporting the reliability of radiologic imaging as an indicator of successful RFA on long term surveillance. Nineteen patients with 20 neoplasms underwent RFA in the

study. Pre-procedure biopsy confirmed renal cell carcinoma in 17 of the 20 tumors and oncocytoma in the remaining three. All 20 of the neoplasms remained radiographically negative (stable in size and without contrast enhancement on CT) on surveillance studies carried out to over one year. Tru-Cut core biopsies of the ablative zone one year or more following the treatment was performed on all 20 neoplasms. Histopathological examination using H and E staining showed "unequivocal tumor eradication" in all cases, with coagulative necrosis, hyalinization, inflammatory cell infiltration and residual ghost cells. Comparing their more promising results with several prior papers that reported both higher frequencies of viable tumor on post-treatment biopsies and failure of imaging to detect these tumors, researchers attributed differences as likely related to false-positive biopsies performed too early in the post-treatment period; tissue "…evaluation at early time points (less than one year) is probably insufficient and even inappropriate for definitively confirming treatment success or failure."

A report by Javadi et al.[133] describing three post-RFA patients in whom the CT imaging findings on follow-up studies were atypical emphasizes the importance of close follow-up and tissue sampling with percutaneous biopsy when post-procedure surveillance imaging findings are not as expected. In one of the cases, soft tissue that was initially felt to represent post-procedure hematoma persisted on a six-month follow-up CT. Despite the absence of contrast enhancement, a CT-guided biopsy yielded minute fragments of renal cell cancer. In one of the other two cases the ablation zone tissue abruptly enlarged with some enhancement that was not the typical crescentic or nodular pattern seen in viable tumor, and in the other case the perinephric fat began to demonstrate an infiltrated appearance containing soft tissue strands, but percutaneous biopsy did not yield viable tumor in either of these cases.

In summary, given the findings of the preceding studies close attention to overall radiographic pattern and morphology of the treated lesion over time, pretreatment verification of tumor, careful reporting of outcomes following ablative procedures, careful description of patient and pretreatment tumor characteristics and further assessment of post treatment biopsy accuracy are needed. **Based on what we know today, findings of concern are growth of the lesion with or without enhancement, new nodularity, failure of regression in size of the treated lesion over time, satellite soft tissue nodules, port site nodularity or enhancement beyond three months from ablation.** Further data to clarify both the histopathologic methodology for detecting viable tumor cells in ablated renal tissue as well as the accuracy of contrast-enhancement or lack thereof on CT or MRI as an indicator of persistent or completely eradicated tumor after renal ablative procedures will be helpful to validate the reliability of post procedural radiologic imaging surveillance protocols.

***Needle biopsy post ablation.*** Please refer back to the background on needle biopsy post-ablation for an in-depth discussion.

***Guideline Statement 19.***

***A urologist should be involved in the clinical management of all patients undergoing renal ablative procedures including percutaneous ablation. (Expert Opinion)***

**Discussion:** The Panel considers urologists to be the experts in the evaluation, management and follow-up of both the small renal mass as well as renal cancer and the treatment associated complications. Urologists should be involved in the care of the patient whether or not they perform the actual procedure. They should be active partners of interventional radiologists, and participation in the percutaneous procedure is encouraged.

***Guideline Statement 20.***

***The Panel recommends that all patients undergoing ablation procedures for a renal mass undergo a pretreatment diagnostic biopsy. (Recommendation; Evidence Strength: Grade C)***

**Discussion:** The Panel considers renal mass biopsy to be of benefit in post-procedure risk stratification and counseling of the ablation patient. A diagnostic biopsy (whether benign or malignant) will help refine the post-operative follow-up, may allow reduction of the burden of surveillance imaging in patients with benign tumor histology and prevent empirically labeling a patient as having renal cancer. Conversely, patients who do not undergo biopsy or have indeterminate results on biopsy should be followed as a renal cell cancer patient, which carries the potential burdens of unnecessary surveillance. Percutaneous biopsy carries minimal risk for post procedure complications and tumor spillage and metastatic disease.

***Guideline Statement 21.***

***The standardized definition of "treatment failure or local recurrence" suggested in the Clinical T1 Guideline document should be adopted by clinicians. This should be further clarified to include a visually enlarging neoplasm or new nodularity in the same area of treatment whether determined by enhancement of the neoplasm on post-treatment contrast imaging, or failure of regression in size of the treated lesion over time,***

***new satellite or port site soft tissue nodules or biopsy proven recurrence. (Clinical Principle)***

**Discussion:** Utilization of a standardized definition of failure may reduce delivery of inappropriate follow-up care, help with future comparative outcomes studies and support new knowledge in the understanding of response to ablative treatments.

***Guideline Statement 22.***

***The Panel recommends that patients undergo cross-sectional scanning (CT or MRI) with and without intravenous (IV) contrast unless otherwise contraindicated at three and six months following ablative therapy to assess treatment success. This should be followed by annual abdominal scans (CT or MRI) thereafter for five years. (Recommendation; Evidence Strength: Grade C)***

**Discussion:** This recommendation is based on a 5-10% failure rate of ablative therapy and places a high value on the early detection by scanning (CT or MRI) to direct potential retreatment. Close attention to overall pattern and morphology, with respect to growth/ shrinkage and nodularity of the neoplasm over time, as well as contrast enhancement on serial follow-up scanning is advised. Patients who cannot receive IV contrast for imaging related to renal dysfunction or allergies should still undergo cross sectional MRI or CT to assess for regression of the treated lesion and to monitor for nodularity or growth. As previously stated any growth in size of the treated lesion, lack of regression in size of the lesion over time, new nodularity, satellite soft tissue nodules, port site nodularity or enhancement beyond three months from ablation would be concerning and should prompt a biopsy.

Further data to clarify both the histopathologic methodology for detecting viable tumor cells in RFA-treated renal tissue as well as the accuracy of contrast-enhancement or lack thereof on CT or MRI as an indicator of persistent or completely eradicated tumor after renal RFA will be helpful to validate the reliability of post procedural radiologic scanning surveillance protocols. Until there is long-term data showing equivalence to surgery in terms of efficacy, a five-year follow-up period is warranted for patients undergoing ablative therapy.

Patients who have undergone ablative treatment of renal tumors are subsequently followed with radiologic scanning using CT or MRI. Immediate post-procedural imaging of the ablated tumor generally shows the tumor to be larger than its pre-treatment size for RFA due to ablation of a peripheral margin of normal tissue, and for cryoablation due to extension of the iceball beyond the original tumor margin. Radiological evolution of cryoablated tumors is characterized by significant shrinkage and loss of contrast enhancement on CT. Tumors successfully treated with RFA demonstrate no IV contrast enhancement but with minimal shrinkage on CT.[123]

On MRI, the imaging hallmark of successful renal tumor ablation is lack of tumor enhancement at gadolinium-enhanced imaging. Rim enhancement, believed to represent reactive change, may occasionally be seen at early postprocedural MR scanning after RFA or cryoablation, which later resolves.

***Guideline Statement 23.***

***Patients may undergo further scanning (CT or MRI) beyond five years based on individual patient risk factors. (Option; Evidence Strength: Grade C)***

**Discussion:** A limitation of the current ablative literature is the dearth of long term outcomes studies with confirmed histology. Initial ablative series mostly focused on elderly patients with poor surgical risk and multiple medical co-morbidities. However, with increasing utilization of ablative modalities on younger patients, longer term follow up will likely become a more significant issue. Long term follow up of patients who have undergone ablative therapy should be carried out with the same clinical principles as patients treated by extirpative modalities of similar size/histology.

***Guideline Statement 24.***

***Patients undergoing ablative procedures who have either biopsy proven low risk renal cell carcinoma, oncocytoma, a tumor with oncocytic features, nondiagnostic biopsies or no prior biopsy should undergo annual chest x-ray (CXR) to assess for pulmonary metastases for five years. Imaging beyond five years is optional based on individual patient risk factors and the determination of treatment success. (Expert Opinion)***

**Discussion:** Most patients undergoing ablative procedures have small masses <4cm with no obvious radiographic signs of non-organ confined disease and, therefore, fall into the low risk (cT1, N0, Nx) category for surveillance. Although the potential burdens and risks of over-surveillance should be borne in mind, it was the Panel's opinion that these patients should be followed with the assumption that the tumor is renal cell carcinoma, given the risk of metastatic progression even in Clinical T1a renal masses and the yet unknown long term (five years and beyond) oncologic efficacy for ablative procedures.

***Guideline Statement 25.***

***The Panel recommends against further radiologic scanning in patients who underwent an ablative procedure with pathological confirmation of benign histology at or before treatment and who have radiographic confirmation of treatment success and no evidence of treatment related complications requiring further imaging. (Recommendation; Evidence Strength: Grade C)***

**Discussion:** Given the low biological potential of benign renal masses, routine follow-up scanning after the six month postprocedural mark other than to confirm treatment success or to monitor complications should be avoided.

***Guideline Statement 26.***

***The alternatives of observation, repeat treatment and surgical intervention should be discussed, and repeat biopsy should be performed if there is radiographic evidence of treatment failure within six months if the patient is a treatment candidate. (Expert Opinion)***

**Discussion:** Salvage therapy in ablative failures may be complex, and depending on the size and location of the area of recurrence, options including re-ablation, salvage partial and radical nephrectomy may be considered when feasible. Salvage partial nephrectomy may be particularly challenging in the post ablative setting, and reports of this in the literature are rare. [106,134] Given the high risk surgical status of many of the patients who undergo ablation, the risks of extirpative therapy must be carefully weighed against potential benefits.

***Guideline statement 27.***

***A progressive increase in size of an ablated neoplasm, with or without contrast enhancement, new nodularity in or around the treated zone, failure of the treated lesion to regress in size over time, satellite or port side lesions, should prompt lesion biopsy. (Expert Opinion)***

**Discussion:** Given the dearth of long term (five year and beyond) oncologic efficacy of ablative procedures and the slow natural history of renal cell cancer in terms of growth rate, findings such as increasing size, new nodularity, satellite lesions, or failure of the treated lesion to regress over time even in the absence of enhancement should prompt lesion biopsy. The Panel has chosen to include non-contrast enhanced imaging findings based on reports of recurrence even in the absence of imaging enhancement, and in recognition of the fact that in circumstances of declining renal function, contrast enhanced studies are contraindicated, and, therefore, non-contrast enhanced imaging is the only form of radiologic surveillance available.

**FUTURE DIRECTIONS**

In this clinical practice guideline document, the Panel applied the AUA's rigorous and systematic approach to guideline development. This approach pairs a systematic review of the current best evidence with the Panel members' clinical judgment to address the most pertinent questions relating to the appropriate extent and timing of follow-up in patients with a history of a renal mass. Addressing these questions in this context required an integration of different study types related to diagnosis, prognosis and therapy. In addition, it required the Panel members to make judgments about the appropriate level of certainty by which we hope to rule in or rule out a given condition, for example local or distant recurrence, to ultimately arrive at measured recommendations about an appropriate follow-up regimen. Additional considerations were concerns about the potential long-term risk of cumulative radiation posed by frequent imaging.

Most of the guideline statements in this document are based on low quality evidence, which is reflective of the literature and the need for continuing high quality and transparent research that will have an important impact in the follow-up of patients with renal neoplasms. We have identified the following areas of priority:

1. There is a critical need for high quality, prospectively defined cohort studies to better define the prognosis of various renal masses and to establish prognosticators of important patient outcomes, such as overall survival, disease specific survival, cardiovascular and metabolic sequelae and quality of life. These trials need to include either hypothesis generating or hypothesis testing analyses of laboratory, tissue based or circulating biomarkers. An important first step in these trials is the application of standardized specimen collection algorithms (including blood, urine and tumor tissue) to create a bank of material that makes future investigation of this patient population possible. All studies relating to the prognosis and management of renal masses should include a standardized data set of patient and tumor demographics as well as treatment details to allow a meaningful interpretation of its results. When feasible, rates of oncological outcomes for patients with localized and metastatic disease should be provided separately. Reporting should include measures of estimates' precision (i.e. standard errors or confidence intervals), sites and timing of recurrences/metastases, information about the completeness of follow-up and ideally be based on consecutive patients.

2. Given the potential burden of long-term follow-up of renal masses, randomized trials of different surveillance regimens (i.e. high versus low intensity) should be conducted in order to better tailor follow-up to the patients' needs. Embedded in such trials could be studies that evaluate the impact of new and resource-intense imaging modalities, such as PET. While those trials are not conducted, oncological outcomes by surveillance imaging modalities should be reported in order to assess their detection accuracy and potential utility.

3. There is a need for better prospectively designed studies to define the diagnostic accuracy of renal biopsies to define the underlying pathology, natural history and need for treatment.

4. There is a need for better prospectively designed studies to define the diagnostic accuracy of renal biopsies following ablative therapies to define the treatment response, natural history and need for further treatment.

5. There is a need for better prospectively designed studies to examine the utility of tissue, plasma, or tumor markers or existing markers of systemic inflammation/immune response, in predicting survival, recurrence or metabolic sequelae.

6. In light of the expanding use of ablative therapies for renal masses there is need for a uniform definition of treatment success and failure. For the purposes of this document a local tumor recurrence following ablative therapy was defined as **" as any localized disease remaining in the treated kidney at any point after the first ablation, as determined by a tumor with contrast enhancement after ablation, a visually enlarging lesion in the same area of treatment with or without the presence of contrast enhancement, the failure of an ablated lesion to regress in size over time, and or the development of new satellite or port site soft tissue nodules."** We suggest that this definition should be employed in future studies.

7. There is a need for better prospectively designed studies to define the risk of positive microscopic and gross margins in patients undergoing nephron sparing surgery in terms of the risk of a local or distant recurrence and the timing and pattern of recurrences to guide future surveillance efforts.

8. There is an important need for the stringent application of well-defined criteria for reporting treatment related harm that should be part of any report. Examples of such systems should include the Martin Criteria, a formal validated grading system such as the Dindo-Clavien grading system for rating complications, and a standardized reporting methodology such as that recommended by the EAU (European Association of Urology) guideline panel assessment in 2012.[135]

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**CONFLICT OF INTEREST DISCLOSURES**

All panel members completed COI disclosures. Relationships that have expired (more than one year old) since the panel's initial meeting, are listed. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received.

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This document was written by the Follow-up for Renal Cancer Guidelines Panel of the American Urological Association Education and Research, Inc., which was created in 2009. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the committee included urologists as well as other clinicians with specific expertise on this disorder including pathology, oncology and radiology. The mission of the committee was to develop recommendations that are analysis-based or consensus -based, depending on Panel processes and available data, for optimal clinical practices in the follow-up of renal cancer**.**

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**While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated.** As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (‘off label‘) that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

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