Management of Small Renal Masses

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Abstract

This article presents a review of some of the most recent and most relevant studies in the management of small renal masses.

Keywords: small renal masses (SRM), contrast-enhanced ultrasound (CEUS), laparoscopic partial nephrectomy (LPN), robotic partial nephrectomy (RPN), cryoablation, radiofrequency ablation (RFA), stem cells, anticancer vaccines
Small renal masses (SRM) are currently defined as kidney lesions measuring ≤4 cm in their maximal diameter. The overall incidence of renal masses has risen constantly, reaching a plateau only in recent years. The most accelerated rise has been demonstrated among SRMs. The current incidence is approximately 10.8 per 100,000 in the United States, with localized stage I disease representing >50% of all newly diagnosed renal tumors. Most early stage kidney cancers are renal cell carcinomas (RCCs), and most are diagnosed incidentally by imaging as small renal masses (SRMs). Most of this rise in incidence is due to increased use of imaging techniques (CT, ultrasound).

Ultrasound (US) is highly sensitive in the detection of renal masses(1). However, it may not be able to differentiate benign and malignant lesions in smaller masses. The purpose of a study(1) was to determine the diagnostic efficacy of contrast-enhanced ultrasound (CEUS) for small renal masses. 85 patients underwent CEUS for evaluation of renal masses. Of these patients, CEUS findings were retrospectively analyzed for small renal cell carcinoma (RCC) cases (n=38) and angiomyolipoma (AML) cases (n=11). The tumor echogenicity and enhancement patterns and degrees were evaluated. The diagnostic efficacy of CEUS in differentiating the two diseases was compared. On CEUS, the findings of diffuse heterogeneous enhancement (observed in 78.9% of RCCs and 27.3% of AMLs, p=0.003), washout from hyperenhancement or iso-enhancement to hypoenhancement in late phase (73.7% of RCCs and 18.2% of AMLs, p=0.001), and perilesional rim-like enhancement (57.9% of RCCs and 9.1% of AMLs, p=0.006) were significantly different between AML and RCC cases. The corresponding sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 86.8% (33/38), 63.6% (7/11), 89.2% (33/37), 58.3% (7/12), and 81.6% (40/49), respectively. CEUS could have diagnostic value in the evaluation of small renal mass. CEUS showed a higher diagnostic efficacy than conventional US for differentiating RCC and AML(1).

Small renal masses (SRMs) are defined as radiologically enhancing renal masses of less than 4 cm in maximal diameter(2). The incidence of renal cell carcinoma (RCC) has increased in recent years, which is mainly due to the rise in incidental detection of localized SRMs. However, the cancer-specific mortality rate is not increasing. This discrepancy may be dependent on the indolent nature of SRMs. About 20% of SRMs are benign, and smaller masses are likely to have pathologic characteristics of low Fuhrman grade and clear cell type. In addition, SRMs are increasingly detected in elderly patients who are likely to have comorbidities and are a high-risk group for active treatment like surgery. As the information about the nature of SRMs is improved and management options for SRMs are expanded, the current role of renal mass biopsy for SRMs is also expanding. Traditionally, renal mass biopsy has not been accepted as a standard diagnostic tool in the clinical scenario because of several issues about safety and accuracy. However, current series on SRM biopsy have reported high diagnostic accuracy with rare complications. Studies of modern SRM biopsy have reported diagnostic accuracy greater than 90% with very high specificity. Also, current series have shown very rare morbid cases caused by renal mass biopsy(2).

The perioperative outcomes of RPN were compared with LPN performed for SRMs(3), in a large multi-institutional series. A new composite outcome measure, termed „optimal outcome” for the RPN group has been defined. The Trifecta was defined as negative surgical margin, zero perioperative complications and warm ischemia ≤ 25. The „optimal outcome” was defined as achievement of Trifecta with addition of 90% eGFR preservation and no CKD stage upgrading. Univariable and multivariable analysis were performed to identify factors predicting Trifecta and „optimal outcome” achievement.

A total of 1185 RPN and 646 LPN met the inclusion criteria. Patients in the RPN group were older and had higher median CCI and higher RENAL scores. The RPN group had lower warm ischemia time (18 vs. 26), overall complication rate (16.2 vs. 25.9%), and PSM (3.2% vs. 9.7%). A significantly higher Trifecta rate was observed for RPN (70% vs. 33%). The rate of achievement of „optimal outcome” for RPN group was 38.5%.

In this large multi-institutional series RPN was superior to LPN in terms of peri-operative surgical outcomes measured by Trifecta. Patients in the RPN group had better outcomes for all three components of Trifecta compared to their LPN counterparts. The more strict definition for „optimal outcome” might be a better tool for assessing peri-operative and functional outcomes after minimally invasive partial nephrectomy. This tool needs to be externally validated(3).

It has been investigated whether visceral fat (VFA) and or subcutaneous fat (SQF) levels are associated with the tumor phenotype of small renal masses(4). In a subset multivariate analysis of the 81 patients with RCC, increasing VFA was statistically associated with...
worsening Fuhrman grade (p=0.017). VFA may be linked to the pathophysiology of renal function in patients evaluated for renal masses. Additionally, VFA may be associated with worsening tumor grades in patients with small-volume RCC. Interestingly, SQF did not play such a role(4).

A meta-analysis of the literature evaluating comparisons on the peri-operative and oncological outcomes between laparoscopic partial nephrectomy (LPN) and laparoscopic ablation therapy (LAT) in the treatment of small renal masses (SRMs) was conducted(5). Data from 11 studies including 928 patients (525 patients in the LPN group and 403 in the LAT group) were collected. Baseline characteristics were compared and differences were found in age, preoperative renal function and proportion of solitary kidney (p < 0.05 respectively). For peri-operative outcomes, the LPN group had greater estimated blood loss, longer operative duration and length of hospital stay, and more peri-operative complications (p < 0.05, respectively). The LAT group had a significantly higher local recurrence (p < 0.05). There was no significant difference in postoperative change of renal function (p = 0.21). In comparison with LPN, LAT provides better peri-operative outcomes, but has a higher local recurrence rate. LAT does not seem to provide an obvious advantage in protecting renal function(5).

Partial nephrectomy (PN) is the standard therapy for small renal masses(6). Resection margin assessment continues to be a key issue during PN. Biopsy of the residual kidney and intraoperative gross pathological consultations are the most common methods today. Intraoperative imprint cytology (IC) examinations have been successfully used in other tumor entities to assess surgical margins. The diagnostic value of intraoperative IC for surgical margin assessment during PN has been evaluated. In addition to routinely performed frozen-section (FS) analysis, intraoperative IC examinations were performed on 114 tumors, which were resected with PN. These 2 were then matched with final histopathological examination findings. Before FS, roll-off IC slides were obtained, air dried, and stained by Hemacolor quick staining. Both the pathologist and the cytologist were blinded to the findings(6). The study included 29 women and 76 men. Of 331 IC slides, 317 (96%) contained sufficient diagnostic cells. IC revealed 21 tumors with positive resection margins. Of the 21 positive resection margins, 2 were false positives. IC showed a specificity of 98%, sensitivity of 100%, a positive predictive value of 100%, and negative predictive value of 98%. FS examinations revealed positive resection margins in 20 tumors. One of these 20 margins was false positive. Furthermore, FS examination failed to diagnose a positive resection margin in 1 tumor. FS examination showed a specificity of 99% and sensitivity of 98% in assessing surgical margins with a positive predictive value of 95% and negative predictive value 98%. IC examinations exhibit equivalent diagnostic value compared with FS analysis. IC is an inexpensive method with an ability to give rapid and highly accurate information. Like any cytological examination, there is interobserver variability. IC could be considered as an alternative to FS especially when the nature of resection margins is suspected but further investigations are necessary(6). Partial nephrectomy has become the gold standard of treatment for small renal masses(7).

Robotic partial nephrectomy was found to be a safe and efficacious procedure for the treatment of T1b renal tumors with excellent intermediate oncologic and functional outcomes(7). A classification tree to predict the risk of benign disease in small renal masses has been developed to aid the clinician when deciding on treatment strategies for small renal masses(8). Comparative outcomes among matched patients who underwent robotic partial nephrectomy (RPN) or open partial nephrectomy (OPN) by a single surgeon at a single institution are presented(9). There was no significant difference between the 2 cohorts with respect to patient age, BMI, ASA score, preoperative glomerular filtration rate, tumour size and the R.E.N.A.L. nephrometry score. The mean operative time was longer in the RPN group, but there were no significant differences with respect to warm ischemic time and postoperative renal function. The length of hospitalization and use of postoperative analgesics were more favourable in the RPN cohort. There was no significant difference in the mean estimated blood loss, transfusion rate, or complications between the cohorts. Considering the perioperative and postoperative parameters, RPN is a viable option as a nephron-sparing surgical procedure for small renal masses that yields outcomes comparable to those achieved with OPN(9). This study(10) demonstrates that the tension required to cause suture failure is only slightly higher than the tension typically applied during PN and necessary to control bleeding and urine leaks. After reperfusion of the kidney, the tension can increase by ≥29% under hypertensive conditions. Incorporation of sufficient (≥0.5 cm) capsule and avoidance of acute angles of entry or exit during closure of the kidney are likely to reduce suture failure(10). Cryoablation and
Radiofrequency ablation (RFA) show marginally lower oncologic outcomes compared to surgical treatment, balanced by better functional and perioperative outcomes(11). Microwave ablation and high-intensity focal ultrasound are modalities with the potential of creating localized high temperatures. However, difficulties in renal implementation are impairing sufficient ablation results. Irreversible electroporation, although not strictly thermal, is a new technology showing promising results(11). Thermal ablation for small renal masses is a safe procedure for both long-term oncologic and functional outcomes. Thermal ablation continues to be associated with a low risk of residual disease. RFA and cryoablation remain the standard techniques whereas alternative techniques require further studies(11).

Thermal ablative technologies have evolved considerably and are now important components of the treatment of small renal masses(12). Both radiofrequency ablation and cryoablation have intermediate-term oncologic control that rivals surgical options, with favorable complication profiles. Studies comparing cryoablation and radiofrequency ablation show no significant difference in oncologic control or complication profile between the two modalities. Early data from small series with microwave ablation have shown similar promising results. Newer technologies including irreversible electroporation and high-intensity-focused ultrasound have theoretical advantages, but will require further research before becoming a routine part of the ablation armamentarium(12). The purpose of this study(13) was to evaluate the amount of radiation exposure patients with small renal masses undergoing percutaneous cryotherapy (PCA) or percutaneous radiofrequency ablation (PRFA) receive during treatment and follow-up. These relatively high radiation exposures should be included in the informed consent for these procedures. In addition, caution should be employed when applying these technologies in young patients that are most susceptible to long-term radiation damage(13). Treatment for small renal masses continues to be partial nephrectomy mostly involving the clamping of renal blood vessels(14). Although necessary, this technique results in warm renal ischemia and reperfusion injury (IRI) to the afflicted kidney. Hydrogen sulfide (H2S), a novel endogenous gaseous molecule, protects against prolonged cold and short-term warm renal ischemia and reperfusion injury (IRI) H2S treatment improved long-term renal function and decreased long-term inflammation associated with warm IRI, and may offer a novel therapeutic approach to preventing warm IRI-induced renal injury associated with renal surgical procedures(14).

Patient- and tumor-related factors affect treatment decisions greatly(15). With multiple treatment options available, surgeon-specific characteristics and biases may also influence treatment recommendations. There are various factors that influence the management options offered to patients with SRMs. The present study results suggest that surgeon age, personal history of cancer, practice-type and other surgeon-specific variables may affect treatments offered among urologists across Canada(15).

The association between preoperative neutrophil-lymphocyte ratio (NLR) and clinicopathologic characteristics in patients with small renal masses (SRM) has been evaluated(16). In 1001 patients, scientists noted higher mean preoperative NLR in men (3.0 ± 1.4 versus 2.6 ± 1.3 in women, P < 0.01) and Caucasians (2.9 ± 1.4 versus 1.9 ± 0.9 in African Americans, P < 0.01) but no significant differences in patients with low (I-II) versus high (III-IV) American Society of Anesthesiologists (ASA) scores (2.8 ± 1.4 versus 2.9 ± 1.5, P = 0.18) or benign versus malignant pathology (2.9 ± 1.4 versus 2.8 ± 1.3, P = 0.75). Spearman correlation analysis (p) showed preoperative NLR significantly correlated with age (p = 0.15, P < 0.01) and preoperative serum creatinine (Crea) [p = 0.13, P < 0.01]. On multivariable linear regression analysis older age, male gender, Caucasian race, and preoperative Crea were predictive of higher preoperative NLR, but ASA score and tumor pathology were not. Conclusions. In patients with SRM, we found no association between preoperative NLR and tumor pathology(16).

A meta-analysis of observational studies on perioperative complications and oncological outcomes of partial nephrectomy (PN) and radiofrequency ablation (RFA) has been performed(17).

Patients who underwent RFA were significantly older (P < 0.001). In the subanalysis of stage T1 tumors, the major complication rate of PN was greater than that of RFA (laparoscopic partial nephrectomy (LPN)/robotic partial nephrectomy (RPN): 7.2%, open partial nephrectomy (OPN): 7.9%, RFA: 3.1%, both P < 0.001). Minor complications occurred more frequently after RFA (RFA: 13.8%, LPN/RPN: 7.5%, OPN: 9.5%, both P < 0.001). By multivariate analysis, the relative risks for minor complications of RFA, compared with LPN and OPN, were 1.7-fold and 1.5-fold greater (both P < 0.01), respectively. Patients treated with RFA had a greater local progression rate than those treated by PN (RFA:...
The association of baseline health and gender with small renal mass pathology has been investigated as approximately 20% of those masses are benign and women are twice as likely as men to have benign pathology(18). Patients with renal masses ≤ 4 cm who underwent partial and radical nephrectomy were included in this study. Multivariable logistic regression analysis was performed to determine demographic and clinicopathologic factors associated with malignant pathology.

In 1726 patients, compared to patients with benign pathology, those with malignant pathology included a higher proportion of men (64.3% versus 42.7%, p < 0.01) and high American Society of Anesthesiologists class (43.8% versus 37.3%, p = 0.04), and had higher preoperative serum creatinine levels (1.1 mg/dL versus 1.0 mg/dL, p < 0.01) and larger tumors (2.5 cm versus 2.2 cm, p < 0.01). Gender-specific multivariable logistic regression analysis showed that in women factors associated with malignant pathology were high American Society of Anesthesiologists class (OR 1.57, 95% CI 1.07-2.32, p = 0.02) and tumor size (OR 1.46, 95% CI 1.19-1.79, p < 0.01). In men, factors associated with malignant pathology were tumor size (OR 1.33, 95% CI 1.06-1.67, p = 0.01) and age (OR 0.97, 95% CI 0.95-0.99, p < 0.01). Male gender and larger tumor size are significantly associated with malignant small renal masses(18). In addition, poor baseline health as represented by a high American Society of Anesthesiologists class is significantly associated with malignant pathology in women(18).

142 patients with cT1aN0M0 lesions were treated with laparoscopic radical nephrectomy (LRN) and partial nephrectomy (PN)(19). 68 of these subjects were treated with LRN and 74 were treated with laparoscopic PN (LPN). The clinicopathological characteristics of the two groups of patients, including diameter-axial-polar (DAP) nephrometry and RENAL nephrometry score (RENO-NS), operative results, and outcomes, were analyzed. A multivariate logistic regression analysis for the selection of PN as the treatment showed that tumor size, DAP nephrometry, RENAL-NS and imperative condition were all independent factors. The area under the curve receiver operating characteristics (ROC-AUC) of DAP and RENAL-NS for performing LPN were 0.897 and 0.825, respectively(19). Although LRN was performed in patients with a high nephrometry score in this study, open partial nephrectomy (OPN) should be considered for patients with a high nephrometry score in T1a renal cell carcinoma (RCC) because of better functional and similar oncological outcomes. Based on ROC analysis, when DAP is 6 or less, LPN should be considered and when DAP is 7 or more, OPN should be considered(19).

Understanding the degree of phenotypic heterogeneity within a small renal mass (SRM) may have implications for interpreting renal mass biopsy (RMB) data(20). In this study the authors(20) sought to quantify the nuclear grade heterogeneity within SRMs. The renal mass database was queried for patients with T1a (<4cm) renal masses, stratified by the following criteria: imaging diameter <2 cm or > 2 cm, clear cell or papillary histology, low-grade (LG; Fuhrman 1-2) or high-grade (HG; Fuhrman 3-4) with tissue available for review. Four consecutive specimens were chosen from each of the 8 strata for a total of 32. All specimens were reanalyzed and the highest Fuhrman grade present in each 10x-powered field was recorded. A case was classified as heterogeneous if multiple grades were present and classified as discordant if the highest Fuhrman grade was present in less than 50% of the specimen(20). A median of 5 slides (IQR 3.5-7.5) and 59 10x powered fields (IQR 34-109) were examined per patient. Overall, 26 samples (81.3%) were heterogeneous, including 15 of 16 (93.8%) HG specimens. Among all cases, 10 (31.3%) were discordant, and among HG specimens, 4 (25%) were discordant. The median fraction of LG tissue in HG specimens was 38.9% (IQR 12.2 - 57.2). The majority of SRMs demonstrated considerable nuclear grade heterogeneity. The greatest degree of heterogeneity and discordance was observed in HG tumors. One should consider these findings when interpreting RMB data as the risk of under sampling HG tumors may not be insignificant(20).

An alternative to conventional laparoscopy when looking for virtually scarless surgery is mini-laparoscopy, a reproducible technique that preserves the triangulation concept(21). A drawback of this approach is
the poor image quality provided by mini-scopes. The introduction of the SPIEs technology, a novel endoscopic camera allowing for better visualisation of anatomic details even with 3-mm optics, has boosted the use of mini-laparoscopy in a centre for laparoscopic partial nephrectomy (LPN) to treat low-complexity renal masses. Allowing for inclusion criteria, 10 consecutive patients who satisfied inclusion criteria were enrolled in our prospective study undergoing clampless mini-retroperitoneoscopic LPN performed by a single surgeon with laparoscopic expertise. Preliminary data show that the approach seems to be safe and effective, with comparable outcomes to conventional LPN. Larger sample size and comparative studies are needed to confirm these findings. The evaluation of cosmetic results will be the focus of further studies(21).

The objectives of a study (22) were to analyze specific comorbidities associated with survival and actual causes of death for patients with small renal masses, and to suggest a simplified measure associated with decreased overall survival specific to this population. Congestive heart failure, chronic kidney disease, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes and cerebrovascular disease were associated with decreased overall survival among Medicare beneficiaries with small renal masses. The cardiovascular index could serve as a clinically useful prognostic aid when advising older patients that are borderline candidates for surgery or active surveillance(22).

For small renal masses (SRMs), open partial nephrectomy represents the therapeutic standard of care, and laparoscopic partial nephrectomy (LPN) has provided encouraging outcomes(23). Laparoscopic renal cryoablation (LRC) could be regarded as an alternative to surgical excision in selected patients, if perioperative complication rates and oncologic results are comparable. However, the short- and long-term outcomes of LRC versus LPN have not been adequately assessed. This study evaluated the safety and efficacy of LRC compared with LPN in the treatment of SRMs(23).

Nine eligible trials (555 cases and 642 controls) assessing LRC versus LPN were identified, including two prospective and seven retrospective studies. Patients undergoing LRC were significantly older (weighted mean difference [WMD], 6.48 years; 95% confidence interval [CI], 3.12-9.83; P<.001) and had a higher solitary kidney rate (odds ratio [OR]=3.76; 95% CI, 2.05-6.92; P<.001). Although LRC was associated with shorter operative time (WMD, -54.28 minutes; 95% CI, -83.79 to -24.78; P<.001), less blood loss (WMD, -111.75 mL; 95% CI, -147.96 to -75.53; P<.001), lower risk of conversion (OR=0.17; 95% CI, 0.05-0.60; P=.005), and fewer overall complications (OR=0.53; 95% CI, 0.29-0.98; P=.04), especially the rate of intraoperative complications (OR=0.20; 95% CI, 0.07-0.58; P=.003) and major complications (OR=0.45; 95% CI, 0.25-0.81; P=.008), patients having LPN might still benefit from a significantly lower local recurrence rate (OR=13.03; 95% CI, 4.20-40.39; P<.001) and lower distant metastasis rate (OR=9.05; 95% CI, 2.31-35.51; P=.002).

Compared with LPN, LRC was associated with reliable perioperative safety, comparable renal function, and fewer complications; however, LRC may still result in a higher risk of tumor progression. Therefore, our meta-analysis suggested that LRC was associated with worse oncological outcomes than LPN but that LRC may be indicated in selected patients with significant comorbidity(23).

The pathologic outcomes and associations with MRI features in small renal masses measuring up to 20mm were evaluated(24) 86 patients (61 ± 13 years; 45 M/41F) with 92 renal masses measuring up to 20mm that underwent MRI prior to tissue diagnosis were included. Two radiologists independently evaluated all masses for microscopic lipid, hemorrhage, T2-hyperintensity, T2-homogeneity, cystic/necrotic areas, hypervascularity, enhancement homogeneity, circumscribed margins, and predominantly exophytic location. These MRI features, as well as patient age, gender, and history of RCC, were compared with pathologic findings using Fisher’s exact test, unpaired t-test, and multivariate logistic regression(24).

26.1% (24/92) of masses under 2 cm were benign, only 32.6% (30/92) were clear-cell RCC, and only 7.6% (7/92) were high-grade. Among 16 masses measuring up to 1cm, only 12.5% (2/16) were clear-cell RCC, and none was high-grade. Within the entire cohort, no MRI or clinical feature showed a significant difference between benign and malignant lesions (p ≥ 0.053). However, for both readers, clear-cell RCC exhibited a significantly higher frequency of T2-hyperintensity, cystic/necrotic areas, and hypervascularity, and a significantly lower frequency of hemorrhage, T2-homogeneity, and enhancement homogeneity (p<0.001-0.036). Hypervascularity was a significant independent predictor of clear-cell RCC for both readers (p=0.002-0.007), as was T2-hyperintensity for reader 2 (p=0.007). A substantial fraction of small renal masses were benign, and when malignant, largely exhibited indolent pathologic char-
acteristics, particularly when measuring under 1 cm. Although small benign and malignant masses could not be differentiated on MRI, hypervascularity showed a significant independent association with clear-cell RCC in comparison with other lesions (24). The incidental renal mass represents a heterogeneous group that contains both benign and malignant pathologies (25). The majority of renal cell carcinomas are discovered incidentally, without the presence of symptoms directly related to the mass, and are closely associated with the term small renal masses because of the discovery before the onset of symptoms. In general, small renal masses are defined as 4 cm or smaller, and may account for greater than half of renal cell carcinoma diagnosis. The use of renal mass biopsy may offer additional pathological information but the clinician must be reminded of the technical and diagnostic limitations of renal mass biopsy. Patient-dependent factors, such as life expectancy and comorbidities, guide the management of small renal masses, which include active surveillance, partial nephrectomy, radical nephrectomy, and ablative techniques (cryoablation and radiofrequency ablation). Partial nephrectomy has demonstrated durable oncologic control for small renal masses while preserving renal function and, if feasible, is the current treatment of choice. In the other extreme of the renal cell carcinomas spectrum and in the presence of metastatic disease, the removal of the renal primary tumor is termed cytoreductive nephrectomy. Two randomized trials (SWOG 8949 and EORTC 30947) have demonstrated a survival benefit with cytoreductive nephrectomy before the initiation of immunotherapy. These two studies have also been the motivation to perform cytoreductive nephrectomy in the targeted therapy era. Currently, there are two ongoing randomized prospective trials trying to investigate the timing and relevance of cytoreductive nephrectomy in the contemporary setting of targeted therapy (25).

The association of tumor size, renal nephrometry systems (RNSs), including RENAL, centrality index (C-index), preoperative aspects and dimensions used for anatomical, and diameter-axial-polar scoring, and individual categories of these RNSs with warm ischemia time (WIT) has been evaluated (26). A single surgeon’s series of robotic partial nephrectomy patients for whom RNS was available were identified. Spearman’s correlation was used to evaluate associations between the RNSs and individual categories and WIT. Analysis was performed based on 69 patients with a median tumor size of 3.5 cm (interquartile range 2.6-4.2). Overall, each scoring system and tumor size were found to have a statistically significant association with the WIT, with the C-index system exhibiting the strongest correlation (coefficient: -0.609, P < 0.001), which was confirmed in the series beyond the surgeon’s learning curve. In the subgroup of relatively small renal masses (<3 cm), there was a statistically significant association between the C-index, preoperative aspects and dimensions used for anatomical, and diameter-axial-polar systems with WIT. However, for tumors >3 cm, none of the RNSs was found to have a statistically significant correlation with WIT, except for the tumor size (coefficient: 0.354, P = 0.027). For subcategories, axial scoring was found to have a consistent statistically significant correlation with WIT. Overall, each RNS and tumor size strongly correlated with WIT in patients undergoing robotic partial nephrectomy. However, the RNS outperformed tumor size in small (<3 cm) renal masses with an optimal discriminating power, whereas for relatively larger (>3 cm) tumors, WIT was significantly dependent on tumor size, and every centimeter may count (26). Growth rate and tumor size are factors shown to be predictive of tumor biology (27). The doubling times (DTs) of untreated RCC at the primary site were calculated. The tumor volume was calculated at two points in time using images yielded by the CT imaging. The DT for the entire population was 460.01 days (range 174-913 days) (27). The diagnostic accuracy of in-bench core biopsies (CBs) from renal masses, and the interobserver and intraobserver variability in pathological subtyping of renal tumors were assessed (28). Routine hematoxylin-eosin (HE)-stained sections from each CB were evaluated by five pathologists on two occasions. The surgical specimen was the reference standard. Diagnostic accuracy and the generalized kappa for intraobserver and interobserver agreement were calculated. Five tumors were benign and 57 malignant. Eight percent to 16% of the CBs were considered inadequate for diagnosis. In 0-8% of the cases, the pathologist could not discriminate between a benign or malignant tumor. Overall accuracy ranged from 77% to 90%. Sensitivity (79-100%) and positive predictive value (100%) were high with narrow 95% confidence interval (95%CI). Specificity (100%) was high but negative predictive value (29%-100%) varied, with wide 95% CI. Interobserver agreement was fair to almost perfect (kappa=-0.010 to 0.830) for the different subtypes. In 64-81% of the CBs, the subtype was correctly classified. Intraobserver agreement was substantial (mean kappa=0.628) for all pathologists. Diag-
The use of percutaneous biopsy of renal masses has not been traditionally widely used because of concerns about safety, accuracy and sampling errors(30). The current gold standard of treatment for localized renal tumors is partial or radical nephrectomy(30). Many small masses are benign tumors or low-grade renal cell carcinomas (RCCs). RCCs can be managed with active surveillance or with minimally invasive ablative technologies. Percutaneous needle core biopsy of renal masses is a safe and accurate diagnostic procedure. Bleeding is very rare and no case of RCC seeding along the needle tract has been observed in the last decade(30).

The subtypes of renal cell carcinoma were diagnosed on needle core biopsies using a combination of histopathology and a molecular diagnostic algorithm(31). Core biopsies were taken of renal tumors following nephrectomy. RNA was extracted and quantitative real-time polymerase chain reaction was performed for 4 gene products to differentiate among renal cell carcinoma subtypes. Histopathological diagnosis was achieved on a second core before and after obtaining the molecular diagnostic algorithm results. Based on the nephrectomy diagnosis 6 of 77 renal masses were nonneoplastic and 71 were tumors, including 65 renal cell carcinoma/oncocytomas. The overall diagnostic accuracy using histology and a molecular diagnostic algorithm combined was 90.0% (70 of 77). Side by side comparison of histology vs molecular diagnostic algorithm was feasible for 60 classifiable renal cell carcinoma/oncocytomas (31 clear cell, 14 papillary renal cell carcinoma, 6 chromophobe renal cell carcinoma, 2 mucinous tubular and spindle cell carcinoma, and 7 oncocyto). In this group histology correctly predicted the final histological subtype in 83.3% (50 of 60) of cores. Addition of the molecular diagnostic algorithm to histology improved the subtyping accuracy to 95% (57 of 60), whereas the molecular diagnostic algorithm alone was accurate in 50 of 60 cases (83.3%). Dividing these 60 specimens into clear cell and nonclear cell neoplasms, the addition of the molecular diagnostic algorithm improved the sensitivity for the diagnosis of clear cell carcinoma from 87.1% (27 of 31) to 100% and the negative predictive value from 87.5% to 100%. Core biopsies of renal tumors provide adequate material for diagnosing and subtyping renal cell carcinoma. The addition of a molecular diagnostic algorithm to histology improved the diagnostic accuracy of core biopsies of renal masses(31). To better understand the molecular mechanisms that underlie the tumorigenesis and progression of clear cell renal cell carcinoma (ccRCC), the gene expression profiles of 29 ccRCC tumors obtained from patients with diverse clinical outcomes were studied by using 21,632 cDNA microarrays(32). Gene expression alterations that were common to most of the ccRCC were identified and also those unique to clinical subsets. There was a significant distinction in gene expression profile between patients...
with a relatively nonaggressive form of the disease versus patients with a relatively aggressive form. Approximately 40 genes most accurately make this distinction, some of which have previously been implicated in tumorigenesis and metastasis(32).

Genes specific to each cancer subtype were found(33). In order to establish the use of some of these genes as novel subtype markers, we four genes were selected and immunohistochemical analysis has been performed on 40 cases of primary kidney tumors. The results were consistent with the gene expression microarray data: glutathione S-transferase alpha was highly expressed in clear cell RCC, alpha methylacyl racemase in papillary RCC, carbonic anhydrase II in chromophobe RCC and K19 in TCC. In conclusion, it has been demonstrated that molecular profiles of kidney cancers closely correlated with their histological subtypes. Also, in these subtypes differentially expressed genes have been identified that could have important diagnostic and therapeutic implications(33).

The expression patterns of 7075 genes were analyzed in four conventional (clear cell) renal cell carcinomas (RCC), one chromophobe RCC, and two oncocytomas using cDNA microarrays(34). Expression profiles were compared among tumors using various clustering algorithms, thereby separating the tumors into two categories consistent with corresponding histopathological diagnoses. Specifically, conventional RCCs were distinguished from chromophobe RCC/oncocytomas based on large-scale gene expression patterns. Chromophobe RCC/oncocytomas displayed similar expression profiles, including genes involved with oxidative phosphorylation and genes expressed normally by distal nephron, consistent with the mitochondrion-rich morphology of these tumors and the theory that both lesions are related histogenetically to distal nephron epithelium. Conventional RCCs underexpressed mitochondrial and distal nephron genes, and were further distinguished from chromophobe RCC/oncocytomas by overexpression of vimentin and class II major histocompatibility complex-related molecules(34). Novel, tumor-specific expression of four genes-vimentin, class II major histocompatibility complex-associated invariant chain (CD74), parvalbumin, and galectin-3-was confirmed in an independent tumor series by immunohistochemistry. Vimentin was a sensitive, specific marker for conventional RCCs, and parvalbumin was detected primarily in chromophobe RCC/oncocytomas. In conclusion, histopathological subtypes of renal epithelial neoplasia were characterized by distinct patterns of gene expression. Expression patterns were useful for identifying novel molecular markers with potential diagnostic utility (34).

Morphologic distinction among clear cell, papillary, and chromophobe types of renal cell carcinoma (RCC) can be difficult, as is the diagnostic distinction between oncocytoma and RCC(35). Whether these renal tumors can be distinguished by their mRNA expression profile of a few selected genes was examined. The expression of four genes in renal tumor was evaluated by quantitative reverse transcription-PCR: carbonic anhydrase IX (CA9), methylacyl-CoA racemase (AMACR), parvalbumin (PVALB), and chloride channel kb (CLCNKB). CA9 expression was highest in clear cell carcinoma and lowest in chromophobe RCC and oncocytoma. AMACR expression was highest in papillary RCC, and CLCNKB was highest in chromophobe RCC/oncocytoma. PVALB was highest in chromophobe RCC, variable in oncocytoma, and low in clear cell and papillary types. Similar findings were observed in fresh-frozen and formalin-fixed specimens. The mRNA expression ratios among these genes (i.e., CA9/AMACR and AMACR/CLCNKB ratios) further accentuate the gene expression differences among these tumors, and a molecular diagnostic algorithm was established. This algorithm accurately classified 31 fresh-frozen tumors into 14 clear cell, 5 papillary, 6 chromophobe, and 6 oncocytomas. In the formalin-fixed group, the molecular criteria accurately classified the cases into 15 clear cell, 16 papillary, and 32 in the chromophobe/oncocytoma group but could only separate some, but not all, oncocytomas from chromophobe RCC. RNA expression ratios based on the four-gene panel can accurately classify subtypes of RCC as well as help distinguish some oncocytomas from chromophobe RCC(35). Gene expression microarray studies have demonstrated distinct molecular signatures for different types of renal neoplasms based on overall gene expression patterns (36). However, in most of these studies the investigators use renal tumors with defined histology. Others analyze a test set of renal tumors in double-blind fashion using recently established molecular profiles of renal tumors as benchmarks.

Neoplasms were subjected to gene expression profiling using cDNA chips containing 21,632 genes. Analysis was clustered with previously established molecular profiles of 91 histologically defined kidney neoplasms and comparative genomic microarray analysis while blinded to tumor histology and clinical information (36).
The molecular diagnosis and classification of unknown renal neoplasms is possible. Molecular diagnosis appears to be reliable and comparable to the standard of urological pathology. This molecular method may be a potentially useful test for establishing an accurate diagnosis that can impact clinical management(36).

Several biomarkers are being investigated in renal cell carcinoma, of which many relate to pathogenic molecular changes that are currently therapeutic targets(37). Carbonic anhydrase IX is a von Hippel-Lindau mediated enzyme that is expressed in most renal cell carcinoma cases. High (greater than 85%) expression of this marker indicates favorable prognosis and may predict the response to interleukin-2 therapy. B7-H1 expression in renal cell carcinoma cells/lymphocytes may indicate worse survival, possibly through impaired host antitumor immunity(37).

The number of renal masses, both benign and malignant, discovered only at autopsy is declining, possibly because of better detection before death(38). However, the rate of occult kidney cancer per 100 autopsies did not change significantly between the two periods, 1955-60 and 1991-2001, suggesting a true increase in the frequency of clinically detected kidney cancer in the USA(38). The aggressive potential of small renal cell carcinoma increases dramatically beyond a tumor diameter of 3 cm. Given the difficulty in measuring tumor diameters reliably with sequential imaging studies, the threshold for selecting patients for a surveillance strategy should be set well under this parameter(39).

The recent popularization of laparoscopic radical nephrectomy may beget underuse of partial nephrectomy(40). Despite more frequent application during the last 2 decades, nationwide use of PN remains relatively uncommon, even for the smallest renal masses. Recognizing the favorable outcomes associated with preservation of renal parenchyma, findings identify a possible quality of care concern that should be addressed by the urological community(40). Laparoscopic radical nephrectomy, partial nephrectomy in the presence of normal contralateral kidney and ablative surgery for small renal masses are living options for the treatment of located RC(41). For metastatic RC cyto/reductive nephrectomy is the standard of care before immunotherapy or combined treatment with tumor vaccines.

We can conclude that on the horizon are: laparoscopic partial nephrectomy for localized disease and allogeneic dendritic cells - autologous tumor cells - hybrid vaccines - like non-toxic tumor vaccines. Several experimental therapies involving orientation RC cells using specific markers, such as G250, are under investigation(41). In two previous articles we (42,43) have proposed some anticancer therapies (42) and we have discussed the concept of anticancer vaccines(43). Intimate understanding of the molecular mechanisms of kidney cancer have led us to propose some new approaches to small renal masses (SRM) such as chemotherapy, combination chemotherapy and anticancer vaccines (43), the use of stem cells to destroy cancer cells and repair impaired chemotherapy and post-operatively, the development of DNA vaccines based on inactivated renal tissue both pre-operatively,