

## Renal Cancer

## **TYROSINE KINASE INHIBITORS AS ADJUVANT THERAPY FOR METASTATIC SARCOMATOID RENAL CELL CARCINOMA: THE MCMASTER EXPERIENCE**

*Yang B, Khambati A, Hotte S, Kapoor A*

**ABSTRACT:** Sarcomatoid variant of renal cell carcinoma (RCC) is a uncommon variant of RCC, accounting for up to 13.2% of renal parenchymal tumours. This highly malignant transformation portends a poor prognosis and is associated with high local aggressiveness and metastatic rates. Median survival after diagnosis is dismal, in the order of 3.8 – 6.8 months. However, recent advances in understanding the pathobiology of RCC have led to the identification of novel therapeutic targets for RCC. In particular, a series of emerging anti-angiogenic agents and receptor tyrosine kinase inhibitors (TKI's) appear to be promising. Sunitinib and sorafenib are novel TKI's that have shown significant clinical activity in metastatic clear cell RCC. The activity of sunitinib and sorafenib in sarcomatoid histologies has not been evaluated. Clinical features and outcomes of 12 patients with metastatic sarcomatoid variant RCC treated in our institute from July 2004 – October 2007 were evaluated in a retrospective chart review. ANOVA, Fisher's exact test, Cox regression analysis and Kaplan – Meier methods were used to analyze our patient characteristic and survival data. All patients had radical nephrectomy performed. Seven were treated with adjuvant TKIs, 2 with gemcitabine based regimens and 3 did not receive adjuvant therapy. Median survival of patients in each arm were 6.9, 9.3 and 3.8 months respectively. Our data demonstrates survival on adjuvant TKI's was significantly longer than with surgery alone ( $p=0.017$ ). We did not identify any significant predictors of survival.

## **CO-EXISTENCE OF HIGH LEVELS OF THE PTEN PROTEIN WITH ENHANCED AKT ACTIVATION IN RENAL CELL CARCINOMA**

*He L, Fan C, Gillis A, Feng X, Sanatani M, Hotte S, Kapoor A, Tang D*

**ABSTRACT:** Recruiting Akt to the membrane-bound phosphatidylinositol (3,4,5) trisphosphate (PIP3) is required for Akt activation. While PI3 kinase (PI3K) produces PIP3, PTEN dephosphorylates the 3-position phosphate from PIP3, thereby directly inhibiting Akt activation. PTEN is the dominant PIP3 phosphatase, as knockdown of PTEN results in increases in Akt activation in mice. The PTEN tumor suppressor gene is frequently mutated in a variety of human cancers, consistent with an inverse correlation between levels of the PTEN protein and Akt activation. We have examined PTEN expression and Akt activation in 35 primary clear cell renal cell carcinomas (ccRCCs) and 9 papillary RCCs (pRCCs) and their respective non-tumor kidney tissues. The PTEN protein was reduced in 16 ccRCCs (16/35=45.7%) and 8 pRCCs (8/9=88.9%). In these RCCs, 25.0% (4/16) of ccRCCs and 25.0% (2/8) of pRCCs expressed elevated Akt activation. 19 ccRCCs (19/35=54.3%) expressed comparable or higher levels of PTEN. Of these ccRCCs, 31.6% (6/19) showed increases in Akt activation. As PTEN dominantly inhibits Akt activation, the coexistence of high levels of the PTEN protein with enhanced Akt activation suggests the existence of novel mechanisms which attenuate PTEN function in ccRCC. These mechanisms may reduce PTEN function or increase PIP3 production.

**A PHASE III, RANDOMIZED, 3-ARM STUDY OF TEMSIROLIMUS (TEMSR) OR INTERFERON-ALPHA (IFN) OR THE COMBINATION OF TEMSR + IFN IN THE TREATMENT OF FIRST-LINE, POOR-PROGNOSIS PATIENTS (PTS) WITH ADVANCED RENAL CELL CARCINOMA**

*Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Staroslawska E, O'Toole T, Park Y, Moore L*

**BACKGROUND:** Temsirolimus (TEMSR, CCI-779) is a specific inhibitor of mTOR, a signaling protein that regulates cell growth and angiogenesis. In a single-agent, phase 2 study, TEMSR administration to heavily pretreated patients (pts, n=111) with adv RCC resulted in a median overall survival (OS) of 15.0 mos (Atkins et al., J Clin Oncol 2004). Retrospectively, 49 pts were categorized in a poor-risk group (Motzer et al., J Clin Oncol 2002). The TEMSR-treated pts in this group had a 1.7-fold longer median OS than the first-line, IFN-treated, poor-risk group reported by Motzer et al. In a phase 1 study, the maximum tolerated dose of the combination of TEMSR + IFN in adv RCC pts was TEMSR 15 mg intravenously (IV) once/wk + IFN 6 million units (MU) subcutaneously (SC) 3 times weekly (TIW) (Smith et al., Proc ASCO 2004). Thus, this phase 3 study in first-line, poor-risk adv RCC pts was initiated in July 2003.

**METHODS:** Pts with adv RCC and no prior systemic therapy were enrolled in this open-label study if they had  $\geq 3$  of 6 risk factors (the 5 Motzer criteria and  $>1$  metastatic disease site). Pts were randomized (1:1:1) to arm 1, IFN up to 18 MU SC TIW; arm 2, TEMSR 25 mg IV once/wk; or arm 3, TEMSR 15 mg IV once/wk + IFN 6 MU SC TIW. The primary study endpoint was OS; the study was powered to compare the TEMSR arms with the IFN arm.

**RESULTS:** We report 20 Mar 2006 preliminary data from an interim analysis performed by the IDMC. Of the 626 pts enrolled, 442 deaths occurred. Patients treated with TEMSR had a statistically longer survival than those treated with IFN (Table). OS of patients treated with IFN and TEMSR + IFN were not statistically different. The 3 most frequently occurring adverse events  $\geq$ gr 3 were asthenia (arm 1: arm 2: arm 3, 27%: 12%: 30% pts), anemia (24%: 21%: 39% pts), and dyspnea (8%: 9%: 11% pts).

**CONCLUSIONS:** Single-agent TEMSR significantly increases the OS of first-line, poor-risk adv RCC pts compared with IFN, with an acceptable safety profile.

## **DOES RAPAMYCIN INHIBIT TGF $\beta$ 1 INDUCED PERITONEAL FIBROSIS AND ANGIOGENESIS?**

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**ABSTRACT:** Rapamycin is a novel antirejection agent that has demonstrated anti-angiogenic activity in the setting of tumorigenesis. In order to evaluate the effect of rapamycin on angiogenesis associated with fibrosis, we administered rapamycin in drinking water to mice with peritoneal fibrosis induced by adenovirus mediated gene transfer of transforming growth factor  $\beta$ 1 (AdTGF $\beta$ 1). Forty female C57Bl/6 mice had an intraperitoneal injection with either AdTGF $\beta$ 1 or a control adenovirus (AdDL). Starting on day 4, animals received either rapamycin (Wyeth, Canada) 2 mg/kg/day or vehicle via drinking water. Animals (5/group) were sacrificed on days 10 or 21 after adenovirus administration. Peritoneal tissue was taken for quantitative histology to assess fibrosis (submesothelial thickening) and angiogenesis. AdTGF $\beta$ 1 induced a significant fibrogenic and angiogenic response compared to AdDL. Rapamycin had no significant effect on these parameters at day 10. At day 21, AdTGF $\beta$ 1 / rapamycin treated animals had decreased submesothelial thickness and decreased angiogenic response compared with AdTGF $\beta$ 1 / vehicle treated animals. A prolonged course of rapamycin appears to inhibit TGF $\beta$ 1 induced angiogenesis and fibrosis. Further work will elucidate the mechanism of this inhibition.

## **COST OF ILLNESS OF RENAL CELL CARCINOMA IN CANADA**

*Abugaber A, Lang K, Thompson D, Bhardway T, Kapoor A, Jaszewski B*

**BACKGROUND:** Renal cell carcinoma (RCC) is the most common form of kidney cancer. RCC patients have limited treatment options and low survival rates, particularly for advanced-staged patients. Despite its importance, data on the economic burden of RCC are limited.

**METHODS:** A prevalence-based approach was used to estimate the aggregate annual societal cost burden of RCC in Canada. Key relationships represented in the model include the annual number of patients treated for RCC by age group and cancer stage; utilization of cancer treatments; unit costs; work-days missed, and wage rates.

**RESULTS:** The annual prevalence of RCC in Canada in 2005 was estimated to be 17,845 cases. The associated annual burden of RCC (Canadian \$2005) was approximately \$357 million (\$19,981 per patient). Health-care costs and lost productivity accounted for 65.6% (\$234 million) and 34.4% (\$123 million) of the total, respectively. Reflecting its higher prevalence, the total cost associated with Stage II RCC accounted for the greatest share (67%) followed by Stage I, Stage III, and Stage IV RCC, at 19.8%, 11.6% and 1.6%, respectively.

**CONCLUSIONS:** The economic burden of RCC in Canada is substantial at a cost of \$357M which represents 2% of the total cost of illness of cancer in Canada (\$16.64B, inflated to \$2005). Interventions to reduce the prevalence of RCC have the potential to yield considerable economic benefits.

## **COST EFFECTIVENESS OF SORAFENIB VERSUS BEST SUPPORTIVE CARE IN ADVANCED RENAL CELL CARCINOMA IN CANADA**

*Jaszweski B, Gao X, Reddy P, Bhardwaj G, Bjarnason A Finelli A, Kapoor A, Abugaber A*

**BACKGROUND:** Results from the Phase III TARGETs study showed that sorafenib plus best supportive care (BSC) significantly prolonged progression-free survival (PFS) compared with BSC alone ( $p < 0.000001$ ) in patients with advanced renal cell carcinoma (RCC). In addition, at a planned interim analysis, overall survival was numerically longer with sorafenib than BSC with a hazard ratio of 0.72. The objective of this study was to evaluate the cost-effectiveness of sorafenib + BSC versus BSC alone in advanced RCC from a US payer perspective.

**METHODS:** A Markov model was developed to project the lifetime survival and costs associated with sorafenib + BSC and BSC alone. The model tracked patients with advanced RCC through three disease states - PFS, progression, and death. Transition probabilities between disease states varied for each 3-month period and were obtained from the TARGETs study. Life-years gained were used as a measure of treatment effectiveness. Resource utilization included drug, administration, physician visits, monitoring, and adverse events. Costs and survival benefits were discounted annually at 3%. All costs were adjusted to 2004 US dollars. Scenario sensitivity analyses were conducted.

**RESULTS:** The lifetime per patient costs were \$85,571 and \$36,634 for sorafenib + BSC and BSC alone, respectively. The life-years gained were higher for sorafenib relative to BSC. The incremental cost-effectiveness ratio (ICER) of sorafenib + BSC versus BSC alone was \$75,354 per life-year gained. The key drivers of the model results were survival after progression and PFS probabilities for both treatment groups. Sensitivity analyses showed that the model results were robust to variance in sorafenib and BSC treatment costs.

**CONCLUSIONS:** The incremental cost-effectiveness ratio was within the established threshold that society is willing to pay (i.e., \$50,000-\$100,000). Therefore, sorafenib + BSC appears to be cost-effective in the management of advanced RCC.

## **MANAGEMENT OF METASTATIC RENAL CELL CARCINOMA (MRCC) WITH TYROSINE KINASE INHIBITION (TKI) SORAFENIB AND SUNITINIB – CLINICAL EXPERIENCE AND TOXICITY MANAGEMENT**

*Kapoor A*

**INTRODUCTION:** The management of mRCC has undergone a fundamental shift towards use of sorafenib (Nexavar®) and sunitinib (Sutent®) since recent Health Canada approval for these agents in this patient population.

**METHODS:** 17 patients were treated with sorafenib 400mg BID po, 5 patients treated with sunitinib 50 mg po x 4 weeks, 2 weeks off, for mRCC from January 2006 to December 2006. Average age for sunitinib-treated patients was 51 (35–62), with metastasis mainly to lung and bone. Average age for sorafenib-treated patients was 62 (50–87), with metastasis mainly to lung and bone. Three patients with brain metastasis (an exclusion criteria for initial trials) were treated with sorafenib. Two patients with sarcomatoid variant RCC (an exclusion criteria for initial trials) were treated with sunitinib.

**RESULTS:** Main toxicities in sorafenib group were increased fatigue (40%), hand-and-foot rash (38%), diarrhea (37%), hypertension (15%). Eight patients (mainly older) were dose reduced to 200 mg BID po because of painful hand-and-foot rash. Two patients discontinued drug due to hand-and-foot rash, and one due to diarrhea, despite dose reduction. Main toxicities in sunitinib group were increased fatigue (40%), diarrhea (40%), hand-and-foot rash (20%), hypertension (20%). Neutopenia, anemia, thrombocytopenia were more common in the sunitinib group. No patient discontinued therapy in the sunitinib group, this group was a smaller and younger cohort. Of 3 patients with mRCC and brain metastases treated with sorafenib, one progressed after 3 months and 2 patients have stable disease currently at 5 months.

**CONCLUSION:** Sorafenib and sunitinib are reasonably well tolerated oral agents for the treatment of mRCC. Toxicity management strategies are crucial to ensure quality of life and targeted dose compliance.

## **REDUCTION OF THE CYTOSOLIC CDK11 PROTEIN EXPRESSION IN CLEAR CELL RENAL CELL CARCINOMA**

*Kapoor A, He L, Gillis A, Fan C, Rybak A, Tang D*

**PURPOSE:** The PITSLRE kinase (Cdk11) is mapped to 1p36.3, a region frequently deleted in solid tumors. To determine how Cdk11 functions in renal tumorigenesis, we examined Cdk11 expression in 34 cases of primary clear cell carcinoma (ccRCC) and their matched non-tumor tissues.

**MATERIALS AND METHODS:** ccRCC and the adjacent non-tumor kidney tissues were obtained after surgery. Both tissues were mounted on the same slide for immunohistochemistry staining for Cdk11 expression. Lysate was prepared from the paired ccRCC and non-RCC tissues and analyzed for the expression of Cdk11 and actin. After being normalized against actin, the levels of the Cdk11 protein in ccRCC were compared to those of Cdk11 in the matched non-RCC kidney tissues.

**RESULTS:** In comparison to the paired non-RCC tissues, 44% of ccRCCs (15/34) and 52.9% of ccRCCs (18/34) contain less than 50% and 60% of the Cdk11p110 protein, respectively, when compared to Cdk11 expression in the paired non-tumor kidney tissues. In non-tumor kidney tissues, Cdk11 is largely expressed in the cytosol and nucleus of the proximal tubule epithelial cells. In ccRCC tissues, Cdk11 is predominantly a nuclear protein, suggesting that the process of ccRCC tumorigenesis results in loss of the cytosolic portion of Cdk11p110. The levels of Cdk11 reduction do not correlate with the tumor sizes and grades of ccRCC.

**CONCLUSIONS:** Reduction in Cdk11 expression and loss of cytosolic Cdk11 occur in ccRCC.

## **THE NATURAL HISTORY OF SMALL RENAL MASSES: A PROSPECTIVE MULTI-CENTER CANADIAN TRIAL**

*Mattar K, Azuero J, Basiuk J, Rendon R, Kapoor A, Jewett M*

**INTRODUCTION:** The incidence of asymptomatic renal masses is increasing, in part due to widespread imaging. This has led to a stage and grade migration in new renal cell carcinomas (RCC) to small, lower grade tumours, which have limited growth potential. To better define the natural history of small renal masses presumed to be RCC, we evaluated

patients newly diagnosed with T1aN0M0 renal tumors who elected conservative management with surveillance.

**METHODS:** Eight Canadian centers prospectively enrolled 100 patients with 121 renal tumors (99 solid and 22 complex cystic masses) from 2002 until 2006. Patients were eligible if elderly, had comorbidity or refused treatment. They were invited to undergo percutaneous biopsy for pathological diagnosis, genomic analysis and tissue banking. Active surveillance with serial imaging was scheduled at 3 months intervals in year 1 and 6 months in year 2 or until progression occurred (increase to 4 cm or volume doubling in <12mo). Pathologically benign tumors were imaged annually. The study endpoints were the time to and rate of tumour progression.

**RESULTS:** The mean tumor diameter at diagnosis was 2.1 cm (range 0.4– 3.9 cm; mean volume 6.4 cm<sup>3</sup>). Forty-four biopsies were performed which confirmed malignancy in 56% of the specimens. Of the remaining 34%, 11 were normal kidney, 2 angiomyolipoma and 1 oncocytoma. Four biopsies were not diagnostic. Over a mean follow-up of 10 months, the average growth rate was 0.14 cm/year, and did not differ statistically from zero growth ( $p=0.07$ ). Two patients met out criteria for tumor progression but continue to be followed conservatively due to the presence of comorbidities. Only one patient died from an unrelated cause, and no patient developed metastatic disease. Molecular studies of prognostic factors for progression are in progress.

**CONCLUSION:** A number of studies have demonstrated that most but not all small renal masses are RCC and most appear to grow slowly and have limited potential for metastases in the short term. This is the first multicentre prospective study and the first to involve routine needle biopsy. Initial active surveillance with serial imaging and delayed surgery for progression appears to be a safe option in short term in our population. Delayed treatment for tumor progression is unlikely to adversely affect long-term outcomes.

## **EXPRESSION OF VARIOUS DRUG RESISTANCE PROTEINS IN WILMS' TUMOR**

*Pinthus JH et al.*

**PURPOSE:** The multidrug resistance-related protein (MRP-1), lung resistance-related protein (LRP) and topoisomerase-II (TOPO-II) are associated with drug resistance against various chemotherapeutics and protect cells against toxic compounds. Their expression in cancer cells may result in altered membrane transport (MRP-1, LRP) and altered enzymatic activity (TOPO-II). The aim of this study was to evaluate the extent of MDR-related protein expression in Wilms' tumor (WT) using tissue microarray (TMA) technique.

**MATERIAL AND METHODS:** TMA paraffin embedded block was constructed from normal renal tissue, 14 samples of WT from different patients, and from xenografts derived thereof. Each tumoral sample was presented in the block by several cores, 0.06 mm in diameter. After serial slicing, of 4  $\mu$ m thickness, the histological slides were stained with hematoxylin & eosin (H&E) and immunostained with antibodies against MRP-1, LRP and TOPO-II. The immunostaining was graded semi-quantitatively by the percentage of the stained cells and the intensity of stain.

**RESULTS:** All the normal kidney tissue samples expressed MRP-1, mainly in the proximal tubules, and were weakly stained or negative for LRP and TOPO-II. No staining was seen in normal renal glomeruli. Samples of WT were universally stained for MRP-1 (only in the tubular component of the tumor), no expression of LRP was detected and various distribution of TOPO-II was observed. The xenografts varied regarding MRP-1 and TOPO-II expression and exhibited weak / negative staining of LRP.

**CONCLUSIONS:** Our study presents the expression of various multidrug resistance proteins in WT, indicating that only MRP-1 might have a potential clinical role. The differences between the expressions of those proteins in the authentic tumors and in their related xenografts might explain differences in response to chemotherapy comparing original tumors and related animal models.

**MULTIPLE IMPRINTED AND STEMNESS GENES PROVIDE LINK BETWEEN NORMAL AND TUMOR PROGENITOR CELLS OF THE DEVELOPING HUMAN KIDNEY**

*Dekel B, Metsuyanin S, Schmidt-Ott KM, Fridman E, Jacob-Hirsch J, Pinthus JH et al.*

**ABSTRACT:** Wilms' tumor (WT), the embryonic kidney malignancy, is suggested to evolve from a progenitor cell population of uninduced metanephric blastema, which typically gives rise to nephrons. However, apart from blastema, WT specimens frequently contain cells that have differentiated into renal tubular or stromal phenotypes, complicating their analysis. We aimed to define tumor-progenitor genes that function in normal kidney development using WT xenografts (WISH-WT), in which the blastema accumulates with serial passages at the expense of differentiated cells. Herein, we did transcriptional profiling using oligonucleotide microarrays of WISH-WT, WT source, human fetal and adult kidneys, and primary and metastatic renal cell carcinoma. Among the most significantly up-regulated genes in WISH-WT, we identified a surprising number of paternally expressed genes (PEG1/MEST, PEG3, PEG5/NNAT, PEG10, IGF2, and DLK1), as well as Meis homeobox genes [myeloid ecotropic viral integration site 1 homologue 1 (MEIS1) and MEIS2], which suppress cell differentiation and maintain self-renewal. A comparison between independent WISH-WT and WT samples by real-time PCR showed most of these genes to be highly overexpressed in the xenografts. Concomitantly, they were significantly induced in human fetal kidneys, strictly developmentally regulated throughout mouse nephrogenesis and overexpressed in the normal rat metanephric blastema. Furthermore, in vitro differentiation of the uninduced blastema leads to rapid down-regulation of PEG3, DLK1, and MEIS1. Interestingly, ischemic/reperfusion injury to adult mouse kidneys reinduced the expression of PEG3, PEG10, DLK1, and MEIS1, hence simulating embryogenesis. Thus, multiple imprinted and stemness genes that function to expand the renal progenitor cell population may lead to evolution and maintenance of WT.

**INHIBITION OF FIBROBLAST TO MYOFIBROBLAST TRANSITION IN PROSTATE CANCER AND WILMS' TUMOR XENOGRAFTS ENABLE REDUCTION IN TREATMENT BURDEN**

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**ABSTRACT:** Stromal myofibroblasts play an important role in tumor progression. The transition of fibroblasts to myofibroblasts is characterized by expression of smooth muscle genes and profuse synthesis of extracellular matrix proteins. We evaluated the efficacy of targeting fibroblast-to-myofibroblast transition with halofuginone on tumor progression in prostate cancer and Wilms' tumor xenografts. In both xenografts, low doses of halofuginone treatment, independent of the route of administration, resulted in a trend toward inhibition in tumor development. Moreover, halofuginone synergizes with low dose of docetaxel in prostate cancer and vincristine and dactinomycin in Wilms' tumor xenografts, resulting in significant reduction in tumor volume and weight comparable to the effect observed by high doses of the respective chemotherapies. In prostate cancer and Wilms' tumor xenografts, halofuginone, but not the respective chemotherapies, inhibited the synthesis of collagen type I,  $\alpha$ -smooth muscle actin, transgelin, and cytoglobin, all of which are characteristics of activated myofibroblasts. Halofuginone, as the respective chemotherapies, increased the synthesis of Wilms' tumor suppressor gene product (WT-1) and prostate apoptosis response gene-4 (Par-4), resulting in apoptosis/necrosis. These results suggest that targeting the fibroblast-to-myofibroblast transition with halofuginone may synergize with low doses of chemotherapy in achieving a significant antitumoral effect, avoiding the need of high-dose chemotherapy and its toxicity without impairing treatment efficacy.

**COMPUTERIZED TOMOGRAPHY MEASUREMENT OF VISCERAL ADIPOSITY PREDICTS PLASMA ADIPONECTIN LEVELS AND PRESENCE OF METASTATIC DISEASE IN PATIENTS WITH CLEAR CELL RENAL CELL CARCINOMA**

*Chatterjee S, Kleinman N, Kapoor A, Khambati A, Pinthus JH*

**INTRODUCTION:** Obesity is a risk factor for renal cell carcinoma (RCC). We have recently shown that plasma levels of adiponectin, a hormone secreted solely by adipocytes, inversely correlates to adverse prognostic factors in clear cell RCC, but not with body mass index (BMI). The purpose of this study was to develop a quantitative method of measuring visceral obesity and to correlate it to adiponectin levels and disease characteristics.

**METHODS:** Blood samples were collected pre-operatively from a cohort of 25 patients (11 with metastatic disease) confirmed to have clear cell RCC (stage T1-T3). Visceral and peripheral fat content was measured using pre-operative CT. Three representative slices were analyzed, the top of L2 vertebral body, umbilicus and the anterior superior iliac spine. Tissue at fat density was digitally extracted from each image, separated into subcutaneous and visceral components and then the number of pixels was summed across three slices to create a surrogate score of visceral and peripheral fat. This score was correlated to plasma adiponectin levels, tumour size, grade, presence of metastasis and BMI.

**RESULTS:** Using linear regression analysis, plasma adiponectin correlated inversely with the size of the tumor ( $P < 0.01$ ) but not with BMI. BMI correlated strongly with CT total fat and peripheral fat measurements ( $P < 0.01$ ) but not visceral fat measurement. Similarly, visceral obesity correlated inversely with plasma adiponectin levels ( $p = 0.04$ ) and with the presence of metastasis ( $p = 0.03$  by logistic regression) but not with other prognostic factors.

**CONCLUSION:** Using a novel and easily reproducible method to quantify adiposity we have shown that visceral obesity correlates with aggressive disease and lower levels of plasma adiponectin in RCC.

**LOWER PLASMA ADIPONECTIN LEVELS ARE ASSOCIATED WITH LARGER TUMOR SIZE AND METASTASIS IN CLEAR CELL CARCINOMA OF THE KIDNEY**  
*Pinthus JH, Kleinmann N, Tisdale B, Chatterjee S, Lu JP, Aubrey G, Hamlet T, Singh G, Farrokhyar F, Kapoor A*

**OBJECTIVES:** To examine a possible relationship between plasma adiponectin levels and renal cell carcinoma (RCC). Adiponectin, a cytokine secreted by adipocytes, is a potent antiangiogenic factor. Plasma levels of adiponectin in patients with RCC and tumor adiponectin receptors R1 and R2 (AdipoR1&2) expression levels were measured and correlated with disease characteristics.

**METHODS:** Preoperative plasma samples from 42 patients were analyzed in triplicate for adiponectin levels with a specific ELISA assay. All patients had clear-cell RCC, including 15 with metastatic disease. Diabetic patients were excluded; all had normal renal function. The RCC and surrounding normal renal tissue were comparatively analyzed for AdipoR1&2 expressions (immunoblotting) in 15 patients.

**RESULTS:** Mean, median, and range of plasma adiponectin levels were 6.33, 5.84, and 1–25.2µg/ml, respectively. A strong inverse correlation was found between plasma adiponectin levels and tumor size with significantly lower levels of adiponectin in tumors  $\geq 4$ cm ( $p < 0.01$ ). The median adiponectin levels in metastatic and nonmetastatic patients were 4.08 and 7.4µg/ml, respectively ( $p = 0.029$ ). A trend toward significant lower adiponectin levels in high versus low Fuhrman grade (3 and 4 vs. 1 and 2) was noted ( $p = 0.057$ ). Expression of AdipoR1&R2 was found to be lower in tumor tissue compared with the patient's normal surrounding kidney tissues in 40% of the cases. Metastatic tumors expressed lower levels of AdipoR2. Body mass index was not inversely correlated with adiponectin levels.

**CONCLUSIONS:** Lower blood levels of adiponectin are positively associated with clear-cell RCC aggressiveness and could potentially be used as a biomarker.

## RADIOFREQUENCY ABLATION AND CRYOABLATION OF RENAL TUMOURS

Kwan KG, Matsumoto ED

**INTRODUCTION:** With widespread utilization of noninvasive cross-sectional abdominal imaging, small solid renal masses are being found with increasing frequency 1. These small tumours are often discovered incidentally by abdominal ultrasound or computer tomography (CT). These incidentally discovered renal tumours are generally slower growing, are detected at an earlier stage, and are localized to the kidney 2,3. The triad of pain, hematuria, and palpable mass is now more the exception than the rule. Many patients now treated for renal cell carcinoma (RCC) are asymptomatic at presentation. The radical nephrectomy has been the “gold standard” for the treatment of clinically localized RCCs, but a shift has occurred toward treating small, incidentally found renal neoplasms in a nephron-sparing manner. Nephron-sparing techniques have been shown to offer oncologic and functional outcomes that are equivalent to those with radical nephrectomy for patients with renal tumours 4 cm or smaller in size 4–6. Since the mid 1990s, the movement toward minimally invasive alternatives has meant the replacement of open surgery (radical or partial nephrectomy) with laparoscopic techniques and now with *in situ* ablative technologies 7,8. Ablative techniques offer advantages over extirpative techniques by reducing perioperative morbidity, shortening the hospital stay, promoting faster recovery, and importantly, potentially treating patients who are poor surgical candidates while preserving renal parenchyma 9,10. Several ablative technologies have been investigated, among them, cryoablation (CA), radiofrequency ablation (RFA), microwave 11, high-intensity focused ultrasound 12,13, laser interstitial thermotherapy 14, microwave thermotherapy, and radiosurgery. The current outcomes with RFA and CA are promising, but long-term studies are ongoing to validate their oncologic efficacy and durability. This overview briefly outlines advances in energy- ablative techniques for RCC and provides a synopsis of recent clinical studies of RFA and CA.

## **RADIOFREQUENCY ABLATION OF RENAL TUMORS: INTERMEDIATE-TERM RESULTS**

*Park S, Anderson JK, **Matsumoto ED**, Lotan Y, Josephs S, Cadeddu JA*

**BACKGROUND AND PURPOSE:** Needle ablative therapies are being offered to patients presenting with small renal masses, but long-term outcomes are currently unavailable. We report our intermediate-term results (1–4 years) after radiofrequency ablation (RFA) of small (<4-cm) renal masses.

**PATIENTS AND METHODS:** At our institution, all renal tumors treated using RFA since May 2001 have been recorded in a prospective database. During this time, 94 tumors (mean size 2.4 cm; range 1–4.2 cm) in 78 patients were treated using a temperature-based RFA generator by either a percutaneous (59%) or a laparoscopic approach. The patients followed with imaging at 6 weeks, 3 and 6 months, and every 6 months thereafter. Only patients with at least 12 months of follow-up were eligible for this analysis; the mean follow-up was 25 months.

**RESULTS:** Of the 89% of masses that were biopsied, 77% were renal-cell carcinomas (RCC), of which 66% were Fuhrman grade 1, 31% were grade 2, and 3% were grade 3. Three recurrences were noted, for an overall recurrence-free rate of 96.8%. In this patient population with numerous comorbid conditions, there were six deaths but only one related to renal cancer, for a cancer-specific survival rate of 98.5% and an overall survival rate of 92.3%.

**CONCLUSION:** In the intermediate term (1–4 years), the oncologic effectiveness of RFA appears comparable to that of traditional treatments offered for small renal masses. Further studies of larger numbers of patients with longer follow-up are needed.

## **LAPAROSCOPIC MANAGEMENT OF ADVANCED RENAL CELL CARCINOMA WITH LEVEL I RENAL VEIN THROMBUS**

*Kapoor A, Nguan C, Al-Shaiji TF, Hussain A, Fazio L, Omar MA, Luke PW*

**OBJECTIVES:** To present our series of laparoscopic radical nephrectomy in patients with level I tumor thrombus. The existence of renal vein tumor thrombus presents a technical challenge in securing hilar control during the resection of a renal mass. To our knowledge, this experience represents one of the largest series of laparoscopic nephrectomy for renal cell carcinoma associated with a macroscopic renal vein thrombus.

**METHODS:** From April 2002 to June 2004, 12 patients (8 men and 4 women) were diagnosed with renal masses. In addition to computed tomography, cavography and magnetic resonance imaging were used to determine the levels of tumor thrombi preoperatively in those who had suspicious involvement of the renal vein on computed tomography.

**RESULTS:** Laparoscopic nephrectomy was performed in a standard fashion. Hand-assisted laparoscopic nephrectomy was used in 6 cases involving large tumors with bulky hilar adenopathy. All renal veins were stapled using an endoscopic vascular stapler. Intraoperative laparoscopic ultrasonography was used to delineate the extent of the vein thrombus in 4 cases to enable proper stapler positioning. No intraoperative complications occurred, and 2 cases were electively converted to open nephrectomy. The postoperative narcotic requirements and hospitalization times were low. Pathologic examination of the tumor specimens demonstrated negative resection margins in all patients.

**CONCLUSIONS:** In carefully selected patients, laparoscopic resection of renal masses with level I renal vein thrombi is feasible. Because of technical considerations that may be identified intraoperatively, early conversion to open nephrectomy should be anticipated. Long-term results regarding oncologic control continue to be assessed.

## **TEMSIROLIMUS, INTERFERON, OR THE COMBINATION OF INTERFERON PLUS TEMSIROLIMUS FOR PATIENTS WITH ADVANCED RENAL CELL CARCINOMA AND POOR RISK FEATURES**

*Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A et al.*

**BACKGROUND:** Interferon alfa is widely used for metastatic renal-cell carcinoma but has limited efficacy and tolerability. Temsirolimus, a specific inhibitor of the mammalian target of rapamycin kinase, may benefit patients with this disease.

**METHODS:** In this multicenter, phase 3 trial, we randomly assigned 626 patients with previously untreated, poor-prognosis metastatic renal-cell carcinoma to receive 25 mg of intravenous temsirolimus weekly, 3 million U of interferon alfa (with an increase to 18 million U) subcutaneously three times weekly, or combination therapy with 15 mg of temsirolimus weekly plus 6 million U of interferon alfa three times weekly. The primary end point was overall survival in comparisons of the temsirolimus group and the combination-therapy group with the interferon group.

**RESULTS:** Patients who received temsirolimus alone had longer overall survival (hazard ratio for death, 0.73; 95% confidence interval [CI], 0.58 to 0.92;  $P=0.008$ ) and progression-free survival ( $P<0.001$ ) than did patients who received interferon alone. Overall survival in the combination-therapy group did not differ significantly from that in the interferon group (hazard ratio, 0.96; 95% CI, 0.76 to 1.20;  $P=0.70$ ). Median overall survival times in the interferon group, the temsirolimus group, and the combination-therapy group were 7.3, 10.9, and 8.4 months, respectively. Rash, peripheral edema, hyperglycemia, and hyperlipidemia were more common in the temsirolimus group, whereas asthenia was more common in the interferon group. There were fewer patients with serious adverse events in the temsirolimus group than in the interferon group ( $P=0.02$ ).

**CONCLUSIONS:** As compared with interferon alfa, temsirolimus improved overall survival among patients with metastatic renal-cell carcinoma and a poor prognosis. The addition of temsirolimus to interferon did not improve survival.

**TREATMENT OF ADULT RHABOID RENAL CELL CARCINOMA WITH SORAFENIB**

*Kanaroglou N, Tutino R, Kapoor A*

**TRANSFORMING GROWTH FACTOR B1 OVER EXPRESSION IN THE RODENT KIDNEY – A NON-INFLAMMATORY MODEL OF CHRONIC ALLOGRAFT NEPHROPATHY**

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**CORRELATION OF COMPUTERIZED TOMOGRAPHY MEASUREMENT OF VISCERAL ADIPOSITY WITH PLASMA ADIPONECTIN LEVELS AND PRESENCE OF METASTATIC DISEASE IN PATIENTS WITH CLEAR CELL RENAL CELL CARCINOMA**

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