Progress in Nephron Sparing Therapy for Renal Cell Carcinoma and von Hippel-Lindau Disease

Dominique Joly,* Arnaud Méjean, Jean-Michel Corréas, Marc-Olivier Timsit, Virginie Verkarre, Sophie Deveaux, Paul Landais, Jean-Pierre Grünfeld and Stéphane Richard

From the Faculté de Médicine, Université Paris Descartes (DJ, AM, JMC, MOT, PL, JPG, SR), Services de Néphrologie (DJ, PL, JPG, SR), d'Urologie (AM, MOT), de Radiologie (JMC), de Biostatistique (EA 4067) (PL) and d'Anatomie Pathologique (VV), Assistance Publique-Hôpitaux de Paris and Institut National de la Santé et de la Recherche Médicale U845 (DJ), Hôpital Necker-Enfants Malades, Paris and Centre de Référence Cancers Rares Institut National du Cancer, Prédispositions héréditaires au cancer du rein de l'adulte, Assistance Publique-Hôpitaux de Paris (DJ, AM, JMC, MOT, VV, SD, SR), Service d'Urologie, Hôpital de Bicêtre (DJ, AM, JMC, MOT, VV, SD, SR), Génétique Oncologique Ecole Pratique des Hautes Etudes, Institut National de la Santé et de la Recherche Médicale U753, Institut de cancérologie Gustave Roussy Villejuif (SR) and Faculté de Médecine Paris-Sud (SR), Le Kremlin-Bicêtre, France

Abbreviations and Acronyms

GFR = glomerular filtration rate
NSS = nephron sparing surgery
RCC = renal cell carcinoma
RFA = radio frequency ablation
VHL = von Hippel Lindau

Submitted for publication October 12, 2010.
Supported by grants from the French National Cancer Institute, Rein and Réseau National Prédispositions héréditaires au cancer du rein and French Ligue Nationale contre le Cancer, Comités du Cher, de l'Indre et de l'Allier.

* Correspondence: Service de Néphrologie, Hôpital Necker, 149 rue de Sèvres, 75015 Paris, France (telephone: (33)1-4449415; FAX: (33)1-44495450; e-mail: dominique.joly@nck.aphp.fr).

For another article on a related topic see page 2353.

Purpose: Patients with von Hippel-Lindau disease frequently have early, multiple and recurrent renal cell carcinoma. Renal cell carcinoma treatment, which must prevent metastatic disease and spare nephrons, has changed in the last 2 decades. We evaluated renal cell carcinoma treatments in the long term in a large series of patients with von Hippel-Lindau disease.

Materials and Methods: We retrospectively evaluated the use and results of surgery and radio frequency ablation in patients with von Hippel-Lindau followed at our institution between 1988 and 2009. Renal anatomical survival was analyzed according to 3 periods, including 1) 1988 to 1994—the learning phase of nephron sparing surgery, 2) 1995 to 2003—routine nephron sparing surgery and 3) 2004 to 2009—the emergence of radio frequency ablation.

Results: A first renal cell carcinoma was treated at a mean age of 38 years (range 15 to 67) in 113 patients with von Hippel-Lindau disease. During a median followup of 7.2 years 251 therapeutic procedures were performed in a total of 176 kidneys. We observed a shift of first line renal cell carcinoma treatment with time, that is nephrectomy in 52% of cases in period 1, tumorectomy in 75% in period 2 and radio frequency ablation in 43% in period 3. The shift paralleled improved renal survival. While nephron sparing surgery was primarily done for lesions greater than 30 mm, radio frequency ablation was used to treat less numerous and smaller ipsilateral lesions but they required more frequent intervention. Radio frequency ablation became the most widely used second or third line procedure and allowed renal salvage in 8 patients.

Conclusions: Nephron sparing surgery and more recently radio frequency ablation enable earlier treatment of smaller tumors and are associated with a significant improved renal prognosis in patients with von Hippel-Lindau disease.

Key Words: kidney; carcinoma, renal cell; von Hippel-Lindau disease; catheter ablation; France

Von Hippel-Lindau disease is a rare, autosomal dominant genetic disease (Online Mendelian Inheritance in Man 193300) that is estimated to occur in 1/36,000 live births. *VHL* germline mutation predisposes patients to renal cysts and carcinoma, central nervous system and retina hemangioblastoma,

0022-5347/11/1856-2056/0
THE JOURNAL OF UROLOGY®

Vol. 185, 2056-2060, June 2011
Printed in U.S.A.
DOI:10.1016/j.juro.2011.02.007

pancreatic cysts and neuroendocrine tumors, pheochromocytoma, endolymphatic sac tumors and epididymal or adnexal cystadenoma.[1,2]

Patients are at high risk for early multiple and recurrent clear cell RCC.[3] Total nephrectomy was systematically done in the past to prevent the risk of metastatic progression, which led to end stage renal disease requiring dialysis. Preserving normal renal parenchyma emerged as a major therapeutic goal in VHL cases. Since several groups reported that most RCC in VHL cases has low pathological grade,[4,5] grows slowly[6,7] and never becomes metastatic at less than 3 cm,[8] in the early 1990s NSS was developed.[4,5,9] The standard therapeutic procedure for RCC in VHL cases was to monitor small lesions by imaging and perform partial nephrectomy for any RCC that became 2.5 to 3 cm.[10–16] During the last decade percutaneous ablative therapies, such as RFA and cryotherapy, that were developed to treat localized RCC in select patients emerged as a novel nephron sparing therapy applicable to patients with VHL.[17–20]

We report a large series of consecutive patients with VHL treated for RCC at our institution, encompassing 3 decades and 3 therapeutic policies, to evaluate the use and results of radical and partial nephrectomy, and RFA.

MATERIALS AND METHODS

We identified all consecutive patients with VHL referred to our hospital between January 1988 and January 31, 2009. This retrospective cohort comprised 72 men and 104 women with VHL disease from a total of 112 families. All patients or family index cases tested positive for *VHL* germline mutations.

Patient charts were reviewed retrospectively. Data were collected on age, gender, organs affected by VHL and *VHL* mutation type. For each therapeutic procedure we recorded preoperative imaging results, date and type of treatment (nephrectomy, partial nephrectomy or RFA) and results (number, size and Fuhrman grade of treated lesions). At last followup in April 2010 we recorded the last imaging result, cancer status, renal status (modification of diet in renal disease estimated GFR less than 60, less than 30 and less than 15 ml/minute/1.73 m^2, used to define chronic kidney disease stages 3 to 5, respectively), the date of complete anatomical loss of a renal unit (defined as death of a kidney on subsequent renal survival analysis), dialysis or transplantation status, and date and cause of death.

Surgical Management

Between 1988 and 2003 patients were candidates for NSS when 1 or several solid or complex tumors became 2.5 to 3.0 cm in diameter. The surgeon also removed all visible and easily accessible ipsilateral renal lesions. Solid lesions were excised by partial nephrectomy or wedge resection with a rim of normal surrounding renal parenchyma, or by enucleation. Radical nephrectomy was proposed when the kidney contained more than 5 or 6 large tumors (greater than 30 mm), or when large size, difficult kidney site or complex association with cysts precluded sparing surgery. In the early years ex vivo tumor excision followed by autotransplantation was done in 9 cases. This demanding, risky technique was abandoned in 1994 and replaced by in situ procedures[10] that have since been performed routinely. In recent years laparoscopic NSS has been done when possible.

Radio Frequency Ablation

RFA became available at our institution in early 2004. It was preferentially offered as primary treatment for 2 to 3 cm RCC and as a secondary procedure in most cases. During the procedure other adjacent lesions of significant size (greater than 1 cm) were also treated when possible. RFA was not proposed for lesions greater than 4 cm or for some lesions that could not easily be reached by the probe. Prophylactic measures were performed when RCC was adjacent to critical tissue, such as bowel (hydrodissection) or ureter (internal cooling).

As soon as RFA became available, we formalized a monthly meeting dedicated to patients with VHL. All cases were discussed by an oncogeneticist (SR), 1 of 2 urological oncologists (AM or MOT), 1 interventional radiologist (JMC) and 1 of 2 nephrologists (DJ or JPG).

For analysis we arbitrarily defined 3 therapeutic periods, each being related to a different therapeutic policy in patients with VHL with RCC. Period 1 from 1988 to 1994 was related to the initiation of NSS, period 2 from 1995 to 2003 was related to routine NSS and period 3 from 2004 to 2009 was related to RFA emergence.

Statistical Analysis

Results are shown as the number and percent for categorical variables, and as the mean ± SD or median and range for continuous variables. Overall survival was calculated from the date of study inclusion to death or last followup. Survival curves were derived from Kaplan-Meier estimates with $p < 0.05$ considered statistically significant. Statistical analysis was performed with StatView® 5.0.

RESULTS

Patient Clinical Characteristics and Study Cohort

At last followup the 176 patients in the entire VHL cohort were a mean of 39.7 ± 12.1 years old (range 19 to 80.9). Of the patients 63 did not undergo RCC due to no renal lesion in 7 at a mean age of 41 ± 11.3 years, simple renal cysts (Bosniak 1) in 29 at age 42.9 ± 13.9 years, renal microlesions (8 mm or less) in 13 at age 45 ± 12.8 years and small RCC under surveillance in 11 at age 43.2 ± 14 years. Three patients with RCC refused treatment. The remaining 113 patients underwent RCC treatment with the first lesion treated at a mean age of 37.6 ± 11.6 years. Subsequently mean followup of patients with treated RCC was 6.3 ± 5.4 years. During this time frame of 722.8 patient-years 176 of the 225 kidneys in a total of 113 patients were treated for RCC with