Original Study

Radiofrequency Ablation for Renal Cancer in Von Hippel–Lindau Syndrome Patients: A Prospective Cohort Analysis

Marco Allasia,[1] Francesco Soria,[1] Antonino Battaglia,[1] Carlo Gazzera,[2] Marco Calandri,[2] Mirko Parasiliti Caprino,[3] Barbara Lucatello,[3] Andrea Velrti,[5] Mario Maccario,[3] Barbara Pasini,[4] Andrea Bosio,[1] Paolo Gontero,[1] Paolo Destefanis[1]

Abstract

Management of renal-cell carcinoma (RCC) in Von Hippel–Lindau syndrome (VHL) patients represents a clinical challenge. Radiofrequency ablation (RFA) is currently used in selected cases for treatment of small-size RCC. The aim of this study was to evaluate the safety and complication rate of RFA in treating RCC in VHL patients. The treatment did not impair renal function and resulted in complete oncologic control.

Introduction: Management of renal-cell carcinoma (RCC) in patients with Von Hippel–Lindau syndrome (VHL) represents a clinical dilemma: the oncologic outcomes must be weighed against preservation of renal function. Radiofrequency ablation (RFA) is currently used in selected cases for treatment of small-size RCC. The aim of this study was to evaluate the safety, complications, and functional and oncologic outcomes of RFA in the treatment of RCC in VHL patients. **Patients and Methods:** RCCs were treated with ultrasound-guided RFA or with laparoscopic RFA. Clinical and radiologic response, disease recurrence, and survival outcomes were evaluated during follow-up. Early and late complications were recorded and graded. **Results:** Nine RCC patients underwent RFA. The median number of RCCs per patient was 3 (interquartile range, 2-4). Among these 9 patients, a total of 20 RCCs were treated by RFA (19 ultrasound-guided RFA and 1 laparoscopic procedure). Median RCC size was 2.5 cm (interquartile range, 2.0-3.0). RFA did not impair renal function ($P = .35$). In 2 cases disease persisted, and in 1 case disease recurred after 18 months. These patients were retreated with ultrasound-guided RFA with complete response and no renal function impairment. RFA treatment was overall well tolerated and safe. No complications were recorded. Postoperative stay was no longer than 1 day. **Conclusion:** RCC occurred in about two-thirds of VHL patients, who had young age at presentation; it was frequently multifocal and recurrent. The use of RFA, with extended indications, could represent a tailored treatment for VHL patients, reducing the risk of renal failure and resulting in satisfying oncologic results.

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Introduction

Von Hippel–Lindau syndrome (VHL) is a rare inherited autosomal-dominant syndrome that affects 1 in 36,000 live births.[1-4] It is characterized by a high incidence of benign and malignant highly vascularized tumors and cysts in different organs.[1-3,5,6] VHL results from a germ-line mutation of the oncosuppressor gene, *VHL*, which is localized on the short arm of chromosome 3 (3p25-26).[7] This mutation leads to an up-regulation of the hypoxia-inducible

[1]Division of Urology, Department of Surgical Science
[2]Department of Interventional Radiology and Diagnostic Imaging
[3]Division of Endocrinology, Diabetology, and Metabolism
[4]Department of Preventive and Predictive Medicine, Unit of Medical Genetics, A. O. Città della Salute e Della Scienza di Torino—presidio Molinette, University of Turin, Turin, Italy
[5]Department of Diagnostic Imaging, San Luigi Gonzaga University Hospital, Orbassano, Torino, Italy

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Address for correspondence: Marco Allasia, MD, Division of Urology, Department of Surgical Science, A. O. Città della Salute e Della Scienza di Torino—presidio Molinette, University of Turin, C.so Bramante 88, Torino 10126, Italy
Fax: +00390116336577; e-mail contact: marc.allasia@gmail.com

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factors 1 and 2 (HIF1, HIF2), which are involved in the cellular anoxia responding processes. HIFs enhance glucose uptake and increase expression of angiogenic, growth, and mitogenic factors.[3,5]

Renal-cell carcinoma (RCC) is the most common malignant lesion affecting VHL patients.[2] The lifetime risk of developing RCC in these patients is estimated to be up to 50%.[1-3] These malignancies usually show peculiar clinical and pathologic features, such as young age at presentation and multifocality. Moreover, they are almost all clear-cell RCCs and are usually diagnosed at early stages.[1,2] Nevertheless, metastatic RCC represents the first cause of death in VHL patients.[4]

As a result of the high probability of multiple de novo RCC development, the management of these patients represents a clinical dilemma. Oncologic outcomes must be weighed against the need to preserve renal function. Therefore, conservative treatments should be offered whenever possible. Historically, nephron-sparing surgery has represented the standard treatment, even if to date there are no published high-volume and/or prospective trials evaluating long-term functional and oncologic outcomes. Because of the lack of high-level trials in this field, recommendations for RCC treatment in VHL are lacking.[8,9]

The development of new minimally invasive treatments for small renal masses may represent a therapeutic opportunity in this category of patients. Radiofrequency ablation (RFA) is nowadays extensively used in selected cases for the treatment of small-size RCCs, with reported favorable outcomes.[10-14] RFA has been also tested in VHL patients with small-size RCCs, with some initial promising results reported.[15-18] Nevertheless, almost all the published trials enrolled only a small number of patients.

Since 2000, at our tertiary-care referral center, we began using RFA for the treatment of small-size RCCs in VHL patients. The aim of our study was to evaluate the safety, complication rate, and functional and oncologic outcomes of RFA in the treatment of RCC in VHL patients during the 15 years of experience at our center.

Materials and Methods

In this single-center retrospective study, we included all patients with VHL referred to our multidisciplinary VHL care unit starting from January 1, 2000. The unit is made up of a multidisciplinary team, which includes a geneticist, neurologist, neurosurgeon, oncologist, ophthalmologist, endocrinologist, and urologist. The team aims to treat and follow VHL patients. Patient data have been included in our VHL database since the team was created. Usually every patient who is suspected to have VHL or who has a family history of VHL is referred to the VHL care unit.

Management and Follow-up

Every patient referred to VHL unit undergoes a genetic evaluation in order to confirm the clinical diagnosis. A magnetic resonance imaging (MRI) and/or computed tomography (CT) of the abdomen and pelvis, X-ray, and/or a CT of the chest and a MRI of the brain are usually performed at baseline and annually thereafter. If further symptoms appear, other imaging examinations are performed accordingly.

The management of renal masses is guided by many factors such as age, comorbidity rate, renal function, tumor size, location, history of RCC, and, when available, pathology report of tumor biopsy results. Figure 1 shows the flowchart adopted in our unit for RCC management in VHL.

Lesions less than 1 cm in size are usually eligible for active surveillance, which consists of urologic evaluation and imaging of the abdomen every 3 or 6 months (using MRI and ultrasound [US], or, alternatively, contrast-enhanced US). Conversely, lesions larger than 1 cm are usually eligible for active treatment. In this case, the first choice is usually percutaneous ablation with US-guided RFA. The feasibility of RFA is established considering RCC volume and location. The cutoff diameter for RFA eligibility is 4 cm.[19] Cystic lesions are not considered a contraindication for RFA. RFA is performed percutaneously whenever possible and is assisted by laparoscopy only in selected cases.

RCCs larger than 4 cm are usually treated with laparoscopic or open partial nephrectomy. Radical nephrectomy is considered only as the last choice.

Follow-up after treatment usually consists of MRI and/or CT scan of the abdomen, and X-ray or CT scan of the chest every 3 months for the first year, every 6 months for the second year, and annually thereafter.

In case of images suspicious for RCC persistence or recurrence, location and time of onset are taken as the most valuable variables to guide the treatment decision process. Generally lesions occurring in previously treated areas are considered as local disease recurrence if they occurred after at least imaging evidence of complete response. Lesions in the treated area at first image control are considered disease persistence. Conversely, lesions occurring in different areas of the kidneys are usually considered as de novo RCC.

The management of disease persistence, local disease recurrence, and de novo RCC that we adopted was the same as that of the first appearance of RCC (Figure 1).

RFA Technique

All the RFA US-guided procedures (Esaote; MyLab Twice, Genoa, Italy) were performed by 2 experienced interventional radiologists as previously described.[20]

All ablative procedures were performed under local anesthesia (1% lidocaine at the insertion site) and analgosedation.

RFA was performed using a 17-gauge electrode multitined needle (Med-Italia, Medolla, Italy).

Treatment time varied between 8 and 30 minutes, depending on the size of the lesion and the tissue impedance, and was automatically recorded by the RFA generator (RF 3000, 200 W capacity; Boston Scientific, Marlborough, MA) during the ablation. This generator utilizes impedance as a procedural end point. As proteins denature and tissue desiccates, the resistance to the passage of electrical current (impedance) increases. Two cycles of ablation were always performed in each procedure in order to perform a complete ablation and lesion destruction.

The needle trajectory was chosen with the aim of ensuring the best treatment coverage, minimizing the amount of normal parenchyma crossed, and avoiding damage to vascular structures. In case of poorly vascularized parenchymal nodules, to obtain better visualization, contrast-enhanced US (SonoVue, Bracco, Milan, Italy) was performed while inserting the electrodes.