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An original radio-biomimetic approach to synthesize radiometabolites for PET imaging

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Repeat Ablative Therapy in Hereditary or Multifocal Renal Cancer: Functional and Oncological Outcomes

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Abstract

Objectives :

To report managing renal tumors in patients at greater risk of repeated interventions (genetic predisposition, multifocal tumors) with thermoablative treatments (AT). A known significant challenge in these patients is the balance between nephron preservation and oncologic outcome.

Material and methods:

This retrospective, single-center study was based on data from patients treated with one or more AT for hereditary or multifocal renal tumors between 2007 and 2017. All medical records were systematically reviewed, and ten patients meeting inclusion criteria were selected. Six patients had confirmed von Hippel-Lindau disease, one Bird-Hogg-Dubé syndrome, one chromosome 3 translocation and two had a presumed genetic predisposition.

Results:

Median age at cancer diagnosis was 39.5 years (+/- 8.9). Fifty-seven tumors, including 41 de novo tumors that appeared during follow-up, were treated with 32 AT sessions (cryotherapy or radiofrequency) with an average tumor size of 13.5mm (+/- 9 SD) and a median RENAL score of 6 [5 ; 7]. One patient underwent concomitant partial nephrectomy for a 55mm lesion which was close to the bowel. Treatment was unsuccessful in two cases, subsequently managed successfully by retreatment with AT. Median delay of appearance of de novo tumor after the first AT was 18 months [6 ; 24]. One patient had metastatic progression. Overall and cancer specific survival was 90% and 100% respectively, with a mean follow-up of 7.5 years (+/- 4.9). The mean decrease in CKD-EPI estimated glomerular filtration rate at the end of follow-up was 5.5 mL/min/1.73m² (+/- 24).

Conclusion:

This study suggests that AT allows to meet the oncological objectives whilst preserving renal function in patients with renal cancer at greater risk of repeated treatments.

Key words: *ablative therapies; cryotherapy; hereditary renal cancer*

1. Introduction

Genetic predisposition is one of the main risk factors for renal cancer, and a family history is found in about 5-8% of patients with this condition. (1). Hereditary forms of renal cancer are characterized by bilateral, multifocal and early occurring tumors, which may be associated with extrarenal symptoms depending on the predisposition (2). Von Hippel-Lindau disease (VHL) is an autosomal dominant syndrome, with a prevalence of 1/53 000. Affected individuals may develop tumors of the central nervous system, kidneys, adrenal glands, pancreas, epididymis or of the broad ligament (3). Renal tumors in these patients are diagnosed on average at 39 years of age (4).

Since recurrence is frequent in these young patients throughout their lifetime, renal function preservation and optimal oncological outcomes, i. e. preventing metastatic evolution or disease related death, are the major challenges. Maintaining a balance between these two goals makes management complex, requiring close collaboration between urologists and radiologists. In the last two decades, the development of ablative therapies (AT) has modified the management workflow of localized renal tumors. Current AT techniques include cryotherapy, radiofrequency, microwave ablation and irreversible electroporation. These treatments can be applied to the organ directly via an open surgical approach or percutaneously under image guidance, allowing an in situ destruction of the tumor. Focused ultrasound and stereotactic radiotherapy can also be used, either in direct contact or from a distance.

European guidelines suggest AT as an alternative for small renal tumors (i. e. less than three centimeters) in elderly patients with comorbidities, considered unfit for surgery (5). They also recommend renal biopsy prior to AT in the absence of previous histology. For the American Urological Association, AT is a treatment option for tumors smaller than 3 cm, but patients must be informed about the increased risk of incomplete treatment, poorly defined criteria for success and of the potential for difficult salvage surgery if treatment fails (6).

Nevertheless, there are no clear guidelines regarding the decision to re-treat with AT in cases of renal recurrence or development of multifocal lesions.

During routine follow-up of patients with VHL, small renal tumors are closely monitored. Nephron sparing surgery is undertaken if the tumor reaches three centimeters (7). This consensus is extended and applied to inherited diseases with the same renal evolutionary profile such as Birt-Hogg-Dub e syndrome (BHD) or

translocations of chromosome 3 (t(3)) (8). The three centimeter threshold was based on surgical management only (9).

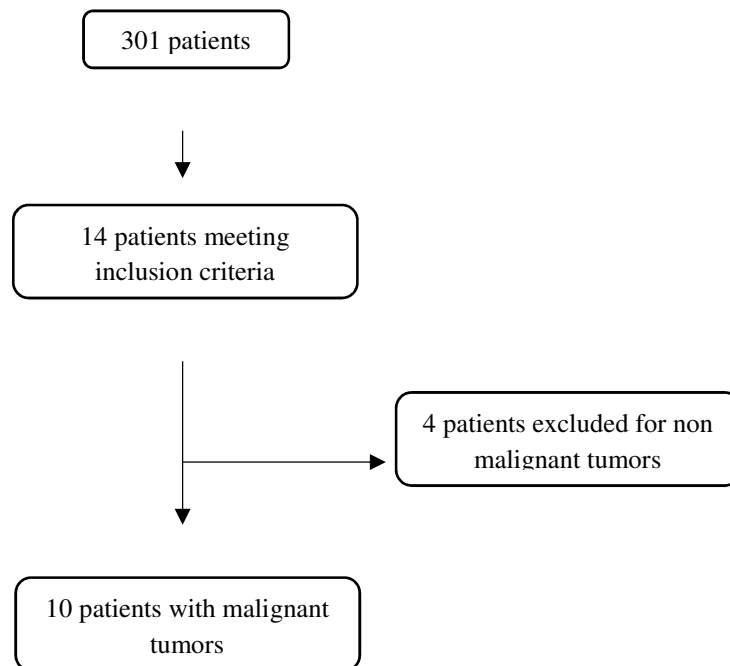
The objective of this study was to report managing of renal tumors in patients at greater risk of repeated interventions with AT.

2. Material and Methods

This was an observational, descriptive, retrospective, unicentric study.

2.1 Study population:

Between 2007 and 2017, 301 patients underwent at least one percutaneous renal thermo-ablative intervention for a renal tumor. Their medical records were systematically reviewed, and 14 patients with a history of bilateral, multifocal or early occurring renal tumors (before 60 years of age) were selected. Among these 14 patients, 4 underwent AT for non-malignant angiomyolipoma secondary to tuberous sclerosis, and were excluded. Within the 10 remaining patients, 8 had a confirmed genetic diagnosis of renal cancer predisposition (6 VHL, 1 BHD and 1 t(3)), and 2 had bilateral recurrent tumors before the age of 45, with negative genetic testing.



Flow Chart

2.2 Procedure:

Patients were advised to undergo AT based on a decision following multidisciplinary discussion. Ablative therapy was proposed if feasible, i. e. when the tumor size was 1 cm or more. The objective was to treat all solid masses present at the time of decision. All procedures were performed by a consultant interventional radiologist, under general anesthesia on an inpatient basis with a hospital stay of at least one night post-procedure. Imaging modalities included computed tomography (CT) or magnetic resonance imaging (MRI), depending on visibility of tumor on pre procedural cross sectional imaging as well as scanner availability. The interventional radiologist determined the number of probes required in order to cover the entire lesion with the iceball, whilst maintaining a safety margin of 5mm (10). A minimum of 2 probes were utilised, and separated by at least 15mm from one another. As recommended, cryoablation was performed with a dual-freeze protocol (11,12).

2.3 Post-procedure follow-up

Initial imaging follow-up included an MRI exam at one or three months post-procedure. If normal, the next MRI was performed at nine months post-procedure and then annually thereafter. Biochemical and clinical follow-up was performed by the referring urologist, at their discretion.

De novo tumor was defined as new pathological contrast enhancement, followed by increase in size. Incomplete treatment was defined as persistent pathological contrast enhancement on the AT scar on the first post-procedure scan.

2.4 Data Collection and Analysis

Primary endpoint was the overall survival (OS). Secondary endpoints were the cancer specific survival (CSS), the metastatic-free survival (MFS), the safety of ablative therapy and the post-ablative renal function. The hypothesis was that AT allows to meet the oncological objectives whilst preserving renal function in the management of renal tumors at greater risk of repeated interventions.

For each patient, data collection included age at renal cancer diagnosis, body mass index (kg/m²), hypertension, diabetes, smoking, previous renal surgery, renal function before the first AT, at the day following the last AT session, and last known value (creatinine values were collected, the estimated GFR was then manually calculated using the CKD-EPI formula), duration of clinical and biochemical follow-up, MFS, OS and CSS. For each procedure, data collection included size of the treated tumor(s), the RENAL nephrometry score (13), immediate

and delayed complications according to the Clavien Dindo classification (14), length of hospital stay, imaging follow-up, incomplete treatment and its management.

Continuous variable was represented as median (IQR). Categorical variable was represented as number and frequency.

3. Results

3.1 Study population

Mean age at diagnosis of renal cancer was 39.5 (+/-8.9 SD, from 24 to 55). Seven patients had previous history of surgery (4 patients with previous partial nephrectomy, 1 patient with radical nephrectomy and 2 patients with PN and RN). Mean follow-up was 7.5 +/-4.9 years. Patients' characteristics are listed in **Table A.1**.

3.2 Treatment outcome

Thirty-two ablative treatments were performed, with an average of 3.2 AT per patient (24 cryotherapy and 8 radiofrequency). The treatments were performed percutaneously under radiological control, with the exception of one case performed by laparotomy. Fifty-seven lesions were treated, mean treated tumor size was 13.5 +/- 9mm. The median RENAL nephrometry score, which was available for 42 of the 57 treated lesions, was of 6 [5 ; 7], and 2 tumors had a high complexity score (>9). Treatment of these 2 highly complex tumors was not linked to post-operative complication nor to incomplete treatment.

Length of stay (LOS) after treatment was less than 48 hours in 84% (27/32) of cases.

Incomplete treatment was observed after two procedures, both managed with successful retreatment by cryoablation. The first incomplete treatment was noted after a challenging radiofrequency ablation of a 10mm median upper pole lesion of the left kidney, close to the stomach. The one-month post-procedure MRI showed a persistent centimetric focus of pathological contrast enhancement of the AT scar, which was closely monitored until it reached 35mm at retreatment, 4 years after the initial AT. The second incomplete treatment occurred after cryoablation of an 18mm lateral, inferior pole lesion in the left kidney. In this case, a 6mm focus of pathological contrast enhancement of the AT scar was noted at one-month post-procedure, with growth to 18mm at retreatment, one year post-procedure.

Only one patient had no de novo tumor during follow up after the first AT, the radiological recurrence-free survival at the end of follow-up was 10% (1/10). Forty-one de novo tumors appeared during follow-up, after a median delay of 18 [6 ; 24] months. Forty of them were treated with AT, with a median delay between appearance of the de novo tumor and its treatment of 3 [1 ; 6] months. One de novo tumor was treated with partial nephrectomy due to its large size (55mm) and close proximity to bowel.

Metastatic progression was observed in one patient, involving the liver. The only reported death was related to a pneumonia with no relation to the AT procedure or renal cancer status. The overall and specific survival was 90% and 100% respectively.

Treatment outcomes are demonstrated in **Table A.2**.

3.3 Complications

Two minor immediate complications (urinary tract infection, severe post-operative pain) required conservative treatment or observation (graded I to II according to Clavien-Dindo classification), and one major delayed complication (tumoral spread along the cryotherapy path) required a follow up cryotherapy procedure (grade IIIb).

3.4 Functional outcomes

The mean glomerular filtration rate (GFR) estimated with the Chronic Kidney Disease – Epidemiological Collaboration equation (CKD-EPI) before the first AT was 95,8 (+/-27.3) mL/min. The mean decrease GFR the day after the last AT and at the end of follow-up was respectively 15,5 (+/-17.8) mL/min and 5.5 (+/-24.1) mL/min. The mean biological follow-up of 80 +/-50.8 months. Functional outcomes are listed in **Table A.1**.

4. Discussion

Conservative treatment by PN has become the standard treatment for T1 localized kidney tumors (5), due to equivocal oncological outcomes (15) and better functional outcomes (16), compared to RN. When possible, PN and RN are discussed based on tumor characteristics. However, more often than not, conservative treatment is imposed on patients for whom RN is at high risk of leading to dialysis (single kidney, chronic renal insufficiency, bilateral tumors, ...). In this challenging setting, AT may also be proposed (17).

In a cohort of patients with kidney tumors, in the critical setting and out of genetic context, Long et al. (18) showed in a retrospective comparative study that ATs significantly decreased the risk of transfusion, complications and LOS despite patients having a higher comorbidity index and higher ASA score. The decrease in renal function (12.5% for the PN group vs 11.1% for the AT group) and metastatic-free survival rate at 5-year (89% vs 85% respectively) were similar in both groups, whereas the recurrence-free survival rate at 5 years was significantly superior in the PN group (92% vs 74% respectively, $p < 0.001$). Nevertheless, according to Johnson et al, repeat PN is accompanied by a decrease of the renal function (95.3mL / min pre-operative vs 84.6mL / min postoperative, $p < 0.05$) and exposes to an increased risk of postoperative complications (22 complications for 51 procedures, with 6 major complications, where 3 patients required hemodialysis) (19).

Thus, the greater risk of requiring repeated treatments is an important parameter to consider in patients with hereditary renal cancer. According to Shuin et al., repeated surgery has an impact on patients' quality of life (20). Repeated kidney surgery also indirectly decreases life expectancy, considering the high risk of hemodialysis in the long-term. In an epidemiological study of newly hemodialyzed patients between 2002 and 2011 in France, the probability of survival at 5 years after beginning dialysis was 70.3% [69.4; 71.2] for patients aged from 45 to 64 years (21).

A few studies have focused on hereditary renal cancer managed by AT, and they exclusively assessed VHL patients (22,23). The largest study of renal tumors treated with AT in VHL patients included 33 tumors in 14 patients (24). No significant decline in renal function was observed. With an average follow-up of 37.6 months, 4 patients presented with a suspicion of recurrence, and 3 of them underwent reprocessing. The overall and specific survival after this follow-up was 92% and 100% respectively, which parallels in similarity to our study.

The data from these studies are retrospective and on small populations with limited hindsight. The majority of the tumors treated had an average size of less than 3 cm. The consensus of the 3 cm threshold prior to surgical

treatment of recurrence in VHL patients, mentioned by Duffey et al. (7) does not seem to apply to a management strategy by AT.

In our cohort, the de novo tumors that appeared during follow-up were treated before reaching 3 cm in size, without prior renal biopsy. This is also common practice in other series' in the literature, where characteristic radiological appearances negate the need for repeat biopsy (25).

Postoperative surveillance consisted of a routine MRI, performed at 1-month post-treatment. In case of incomplete treatment, the retreatment was delayed (4 and 1 year in our study). Yet, in the first few months post-treatment, distinguishing tumor recurrence in the scar from inflammation secondary to the intervention is diagnostically problematic (26).

This management strategy seems adaptable to patients with hereditary or multifocal renal tumors in our experience. Despite the high rate of repeat ablations (3,2 AT sessions per patient), only one patient presented with metastatic progression out of the 10 patients included, and no deaths were linked to renal cancer. Renal function may be decreased the day after the last AT, but was not clinically significant at the end of follow-up, even with the important decrease of patient n°6 (-61mL/min). The last known value of the creatinine of this patient was during the septic shock due to pneumonia which caused his death. Because the mean change in GFR is not clinically significant at the end of follow-up, he was included in the analysis.

Limitations of our study included its retrospective and monocentric nature, as well as the small population and the heterogeneity of genetic predispositions. This limits our ability to retain a robust management strategy for AT in patients with renal cancer at greater risk of repeated treatments. In addition, the ablation techniques were inconsistent, with both cryotherapy and radiofrequency being utilised. Our contribution consists of expanding the data of existing studies on this topic, where management was only based on several small retrospective series'. For higher levels of evidence, national networks (for example UroCCR in France) should be utilized to collect data prospectively and with more patients affected by this oncological therapeutic challenge.

5. Conclusion:

Through adopting an early treatment strategy for de novo tumors in our cohort, with a high rate of reprocessing, AT allows to meet the oncological objectives whilst preserving renal function in patients with renal cancer at greater risk of repeated treatments. However, we cannot definitively conclude on these data alone because of the low level of evidence. For a higher level of scientific evidence, it would be necessary to perform a prospective randomized study comparing surgery and ATs in the hereditary or multifocal renal tumor population.

6. Authors contributions:

V Gaillard : project development, data collection, management and analysis, manuscript writing and editing

T Tricard : project development, data analysis, manuscript writing

J Garnon: data management, data analysis, manuscript writing

RL Cazatto: data collection, manuscript writing

D Dalili: manuscript writing and editing

A Gangi: project development, data collection

H Lang: project development, data analysis, manuscript writing and editing

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Table A.1 : Patients characteristics and functional outcome

Pt No.	Gender	Age at cancer diagnosis (years)	Predisposition	Body Mass Index (kg/m ²)	Hypertension	Diabetes	Smoking	Previous hystory of surgery (PN/RN)	Follow-up (years)	Renal function before first AT (mL/min, CKD-EPI)	Renal function changes the day after last AT (mL/min, CKD-EPI)	Renal function changes at end of follow-up (mL/min, CKD-EPI)
1	W	24	VHL	21,48	0	0	0	0/0	4,5	126	-54	+12
2	W	48	VHL	21,30	1	0	0	0/0	9,75	72	-16	-11
3	W	44	VHL	20,96	1	0	0	1/0	15,5	70	-9	+18
4	W	55	VHL	33,76	0	1	0	1/1	2,25	112	-17	-15
5	W	36	VHL	36,33	0	0	0	0/0	1,9	108	-1	+16
6	M	32	VHL	27,17	0	0	1	1/0	9,25	136	-36	-61
7	M	38	BHD	19,66	0	0	0	0/1	2	91	-12	+1
8	M	34	t(3)	35,57	0	0	0	4/0	9	105	+1	+11
9	M	44	Presumed	23,88	1	0	1	2/1	14	47	+5	-25
10	W	40	Presumed	35,56	1	0	1	5/0	7,5	91	-16	-1
Mean (SD)		39,5 (+/- 8.9)		27.6 (+/-7)					7,5 (+/- 4.9)	95,8 (+/-27.3)	-15,5 (+/-17.8)	-5,5 (+/- 24)

Table A.2 : Treatment outcome

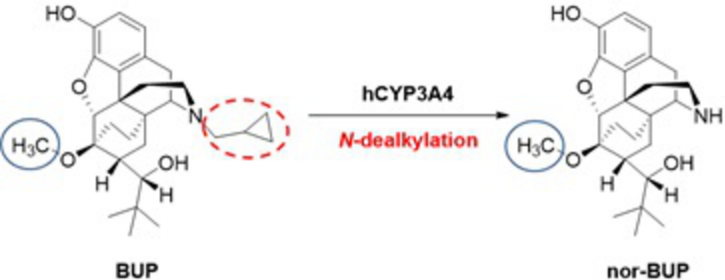
Pt. No.	No. AT sessions (CA/RF)	No. Tumors (mm)	No. Residual Tumors	LOS > 48 hours
1	1 (1/0)	3 (3 - 15)	0	0
2	2 (1/1)	4 (10 - 25)	1	0
3	4 (4/0)	4 (10 - 32)	0	1*
4	2 (1/1)	3 (4 - 15)	0	1*
5	2 (2/0)	2 (11 - 45)	0	0
6	7 (7/0)	13 (5 - 44)	1	0
7	2 (2/0)	5 (7 - 25)	0	1*
8	2 (2/0)	2 (10 - 25)	0	0
9**	8 (2/6***)	17 (2 - 15)	0	2*
10	2 (2/0)	4 (7 - 13)	0	0
Total	32 (24/8)	57	2	5
Mean (SD)		13,5 +/- 9		
Median RENAL score		6 [5 ; 7]		

CA = cryoablation, RF = radiofrequency ablation

*In order: 1 surveillance for severe pain, 1 surveillance at the request of the patient (anxiety), 1 post-operativ urinary tract infection, 1 surveillance after AT performed by laparotomy, 1 surveillance for anticoagulant therapy

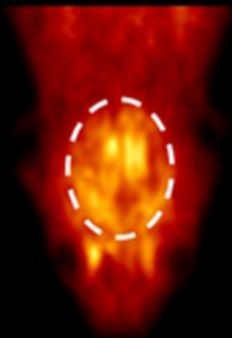
**Only patient who had hepatic metastatic evolution 16 years after the first AT, and who died of a pneumopathy

***One RF was performed by laparotomy

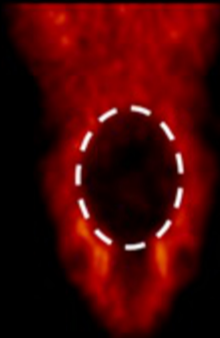


Isotopic labelling with carbon-11

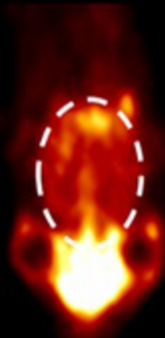
A

 $[^{11}\text{C}]\text{BUP}$  $0.436 \pm 0.054 \text{ \%ID/cm}^{-3}$

B

 $[^{11}\text{C}]\text{nor-BUP}$  $0.067 \pm 0.023 \text{ \%ID/cm}^{-3}$

C

 $[^{11}\text{C}]\text{nor-BUP} + \text{TQD}$  $0.557 \pm 0.077 \text{ \%ID/cm}^{-3}$ 