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ORIGINAL ARTICLE

The role of 18F-FAZA PET/CT in detecting lymph node metastases in renal cell carcinoma patients: a prospective pilot trial

Umberto Capitanio[1] · Gino Pepe[2] · Elena Incerti[2] · Alessandro Larcher[1] · Francesco Trevisani[1] · Roberta Lucianò[3] · Paola Mapelli[2,4] · Valentino Bettinardi[2] · Cristina Monterisi[2] · Andrea Necchi[5] · Stefano Cascinu[4,6] · Rosa Bernardi[7] · Roberto Bertini[1] · Claudio Doglioni[3,4] · Luigi Gianolli[2] · Andrea Salonia[1,4] · Maria Picchio[2,4] · Francesco Montorsi[1,4]

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Abstract

Background The accurate detection of nodal invasion is an unmet need in the clinical staging of renal cancer. Positron emission tomography (PET) with 18F-fluoroazomycin arabinoside (18F-FAZA), a hypoxia specific tracer, is a non-invasive imaging method that detects tumour hypoxia. The aim of this work was to evaluate the role of 18F-FAZA PET/CT in the identification of lymph node metastases in renal cancer.

Methods A proof-of-concept phase 2 study including 20 kidney cancer patients (ClinicalTrials.gov Identifier: NCT03955393) was conducted. Inclusion criteria were one or more of the following three criteria: (1) clinical tumour size > 10 cm, (2) evidence of clinical lymphadenopathies at preoperative CT scan and (3) clinical T4 cancer. Before surgery, 18F-FAZA PET/CT was performed, 2 h after the intravenous injection of the radiotracer. An experienced nuclear medicine physician, aware of patient's history and of all available diagnostic imaging, performed a qualitative and semi-quantitative analysis on 18F-FAZA images. Histopathological analysis was obtained in all patients on surgical specimen.

Results Fourteen/19 (74%) patients had a non-organ confined renal cell carcinoma (RCC) at final pathology (either pT3 or pT4). Median number of nodes removed was 12 (IQR 7–15). The rate of lymph node invasion was 16%. No patient with pN1 disease showed positive 18F-FAZA PET, thus suggesting the non-hypoxic behaviour of the lesions. In addition, neither primary tumour nor distant metastases presented a pathological 18F-FAZA uptake. No adverse events were recorded during the study.

Conclusions 18F-FAZA PET/CT scan did not detect RCC lymph neither nodal nor distant metastases and did not show any uptake in the primary renal tumour.

Keywords Kidney cancer · Renal cell carcinoma · Lymph node invasion · Imaging · PET · 18F-FAZA · Tumour hypoxia

Clinical trial registrations: ClinicalTrial.gov Identifier: NCT03955393: EudraCT number: 2016-001774-15

Co-last authors are Maria Picchio and Francesco Montorsi

✉ Umberto Capitanio
capitanio.umberto@hsr.it

[1] Unit of Urology, Division of Experimental Oncology, Urological Research Institute (URI), IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy

[2] Unit of Nuclear Medicine, IRCCS San Raffaele Scientific Institute, Milan, Italy

[3] Unit of Pathology, IRCCS San Raffaele Scientific Institute, Milan, Italy

[4] School of Medicine, Vita-Salute San Raffaele University, Milan, Italy

[5] Unit of Oncology, IRCCS Istituto dei Tumori, Milan, Italy

[6] Unit of Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy

[7] Division of Experimental Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy

Introduction

Lymph node invasion (LNI) represents one of the most informative predictors of progression and mortality in the oncological setting. Nonetheless, LNI remains a critical issue for clinical decision-making in patients with renal cell carcinoma (RCC) [1]. Indeed, differently from other malignancies, (a) nodal status imaging, (b) sentinel node technique and (c) standard lymphadenectomy (LND) have been demonstrated inadequate in the staging and management of RCC patients [2]. A novel imaging technique is urgently needed in RCC setting to detect macroscopic and micro nodal invasion, to identify those patients who are at higher risk of having nodal metastases and to accurately plan the best management.

Fluorine-18 labelled fluoroazomycin arabinoside (18F-FAZA) is a highly selective PET radiotracer of hypoxia, which has been recently developed and tested in several other oncological settings [3–5]. 18F-FAZA is a sugar-coupled 2-nitroimidazole derivate with low lipophilicity, fast body clearance and a favourable tumour/background (T/B) ratio. 18F-FAZA distribution is overlapping with carbonic anhydrase IX (CAIX) antigen allocation, which is highly over-expressed in RCC tissue and, therefore, is expected to show superimposable selectivity for RCC [6]. Moreover, 18F-FAZA has been demonstrated to be a marker of hypoxia and pathological metabolic patterns, which are common to all renal cancers [3–5] [6]. Moreover, Chapman et al. [7] showed in a RCC mouse model that 18F-FAZA PET could be used to monitor drug response during Sunitinib therapy and may guide combination therapies based on the tumour's hypoxia status. For all these reasons, we decided to test this radiotracer with the aim to identify lymph nodal and metastatic disease in RCC patients.

In the current prospective phase 2 trial, we propose to test the performance of 18F-FAZA PET/CT in detecting nodal metastases in RCC patients. Secondary endpoints included the assessment of the performance of 18F-FAZA PET/CT in characterizing primary RCC and detecting distant metastases.

Patients and methods

Patients' characteristics

A prospective pilot phase 2 study involving 20 patients (mean age: 64 years, range 33–85 years) was performed from April 2017 to February 2019 (ClinicalTrials.gov Identifier: NCT03955393). The study complied with the guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The local Ethical Committee approved the study (EudraCT number: 2016-001774-15). All patients gave written informed consent prior to study participation. Twenty patients resulted candidates to nephrectomy and extended LND according to one or more of the following three clinical criteria: (1) tumour size > 10 cm and/or (2) evidence of lymphadenopathies at preoperative CT scan (defined as lymph node diameter > 10 mm) and/or (3) clinical T4 cancer. Further eligibility criteria included age of at least 18 years, ECOG performance status 0–1 and expected survival time of at least 3 months; female patients of childbearing age were requested to have a negative pregnancy test. Exclusion criteria included other medical conditions that might limit the amount of tracer to be administered: New York Heart Association (NYHA) Classification III/IV cardiac disease [8], history of autoimmune hepatitis, unavailability or immunological, and clinical follow-up assessments. No patient received neoadjuvant medical treatment.

18F-FAZA PET imaging technique

18F-FAZA was administered intravenously. The mean injected activity dose to the 20 patients was 381 MBq (range: 338–438 MBq). Imaging was performed 2 hours after injection and was acquired on a Discovery 690 PET/CT scanner (GEMS, Wakesha, Wisconsin, USA). Before each emission imaging session, a whole-body low-dose CT scan was acquired for attenuation correction (120 kV, AutomA: 30-150 mA). The acquisition time for each scan was 3 min per bed position. PET data were acquired in three-dimensional mode and were reconstructed with an ordered-subset-expectation minimization (OSEM) algorithm, also accounting for attenuation, scatter, random, point-spread function, and time-of-flight model. The specific parameters of the reconstructed protocol were subsets = 18, iterations = 3, transaxial filter Gaussian full width half maximum = 4 mm, and axial filter = standard. PET images were analysed by an expert nuclear medicine physician (G.P.) aware of patients' medical history and other performed imaging modalities. Both a qualitative (positive/negative) and semi-quantitative analysis (maximum and mean standardized uptake value—SUV_{max} and SUV_{mean}) were performed. Hypoxic volume on 18F-FAZA PET images was defined as a region with a T/B ratio greater than or equal to 1.2 [9]. The tumour value corresponded to the maximum of the 18F-FAZA uptake within either the primary renal cancer or lymph nodal involvement, delineated on CT images, while the background value corresponded to the 18F-FAZA uptake in the aorta (ascending aorta and aortic arch).

Surgery

Upfront laparotomy was performed in all the cases. At the time of nephrectomy, LND included, for left tumours, paraaortic and preaortic nodes from the crus of the diaphragm to the inferior mesenteric artery and, on the right, paracaval, retrocaval and precaval nodes from the adrenal vein to the level of the inferior mesenteric artery. Interaortocaval nodes were removed, as well. All the cases were reviewed by two dedicated expert uro-pathologists (C.D. and R.L.). Primary

Table 1 Patients' clinical and pathological characteristics

	Clinical characteristics											Pathological characteristics						
Number	Age	Gender	Tumour side	Tumour size (mm)	Tumour size > 10 cm	cT4	cN1	cM1	Renal vein involvement	IVC involvement	FAZA PET	Histology	pT	pN	G	Number of removed nodes	Number of positive nodes	Location of positive nodes
1	77	F	Left	70	No	Yes	Yes	0	0	0	neg	ccRCC	pT1b	0	3	22	0	NA
2	77	M	Left	95	No	Yes	Yes	0	1	0	neg	pap2RCC	pT4	1	4	23	19	Paraaortic (16), interaoortacaval (1), hilar (2)
3	85	M	Right	112	Yes	Yes	No	0	0	0	neg	ccRCC	pT3a	0	4	10	0	NA
4	66	M	Right	110	Yes	Yes	Yes	0	1	1	neg	pap2RCC	pT3b	0	3	8	0	NA
5	68	F	Right	65	No	Yes	No	1	0	0	neg	UTUC	NA	NA	NA	NA	0	NA
6	33	F	Left	120	Yes	No	No	0	0	0	neg	ccRCC	pT2b	0	2	1	0	NA
7	80	M	Right	70	No	Yes	Yes	1	1	1	neg	ccRCC	pT3b	0	3	10	0	NA
8	46	M	Left	90	No	No	Yes	0	0	0	neg	ccRCC	pT3a	0	3	23	0	NA
9	71	M	Right	75	No	Yes	Yes	0	1	1	neg	ccRCC	pT3b	0	2	14	0	NA
10	61	F	Left	128	Yes	No	Yes	1	0	0	neg	ccRCC	pT3a	1	4	17	5	Paraaortic (5)
11	68	M	Right	140	Yes	Yes	Yes	0	0	0	neg	ccRCC	pT4	0	4	13	0	NA
12	84	M	Right	120	Yes	No	No	1	0	0	neg	ccRCC	pT3a	0	3	8	0	NA
13	64	F	Left	105	Yes	No	No	0	0	0	neg	ccRCC	pT3a	0	3	4	0	NA
14	60	M	Right	102	Yes	No	No	0	1	1	neg	ccRCC	pT3b	0	2	13	0	NA
15	57	M	Left	125	Yes	No	No	0	0	0	neg	ccRCC	pT2a	0	2	6	0	NA
16	49	F	Right	75	No	Yes	Yes	0	0	0	neg	ccRCC	pT3a	0	4	16	0	NA
17	60	F	Right	95	No	No	Yes	0	0	0	neg	ccRCC	pT3a	1	4	4	2	Interaortacaval (1), Retrocaval (1)
18	54	M	Right	57	No	No	Yes	0	0	0	neg	ccRCC	pT1b	0	2	11	0	NA
19	62	M	Right	140	Yes	No	Yes	0	0	0	neg	ccRCC	pT2a	0	3	7	0	NA
20	61	M	Right	145	Yes	No	Yes	0	0	0	neg	ccRCC	pT3a	0	3	12	0	NA

ccRCC clear cell renal cell carcinoma, *pap2RCC* papillary type 2 renal cell carcinoma, *UTUC* upper tract urothelial cancer, *NA* not applicable

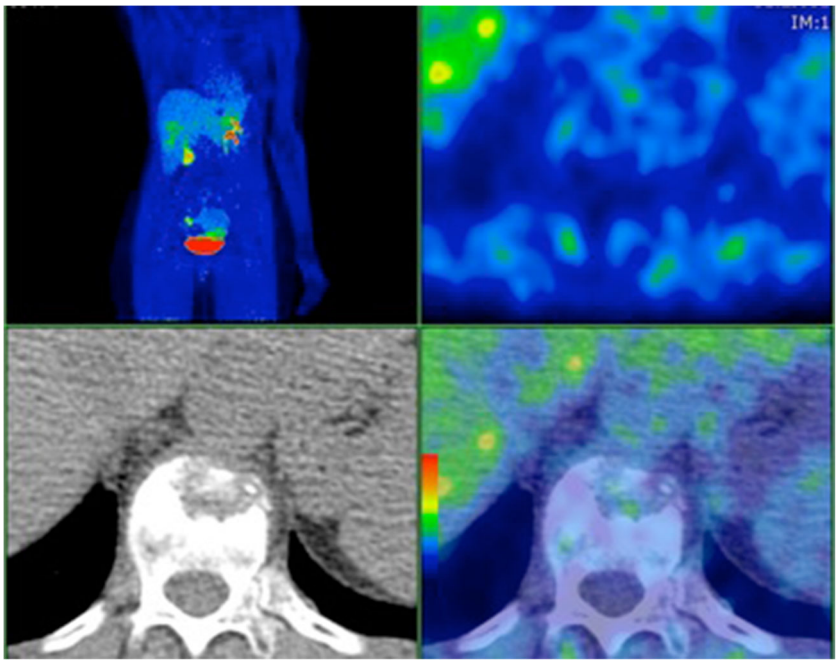

Fig. 1 Female patient with transitional cell carcinoma. 18F-FAZA PET/CT did not show any tracer uptake nor in the kidney neither in the lytic areas of the vertebra

tumours and lymph nodes were fixed in 4% formalin, paraffin embedded, cut into 5-μm thick sections and stained with haematoxylin and eosin according to standard protocols.

Results

Table 1 reports the clinical and pathological characteristics of the patients' cohort. Figures 1, 2, 3 and 4 depict three different cases included in the current trial. Sixty-five percent of the patients were male. Patients were included for 1 vs. 2 vs. 3 inclusion criteria in 45% vs. 45% vs. 10% of the cases, respectively (Table 1).

At final pathological report, clear cell RCC (ccRCC) was diagnosed in 17 cases (85%). High-grade disease (G3–4) was found in 14 cases (70%). Fourteen/19 (74%) patients resulted non-organ confined (either pT3 or pT4). Median number of nodes removed was 12 (IQR 7–15). The rate of lymph node invasion was 16%.

18F-FAZA PET/CT was well tolerated in all patients, with no adverse events were observed. The qualitative evaluation of the 18F-FAZA PET/CT images showed no increased

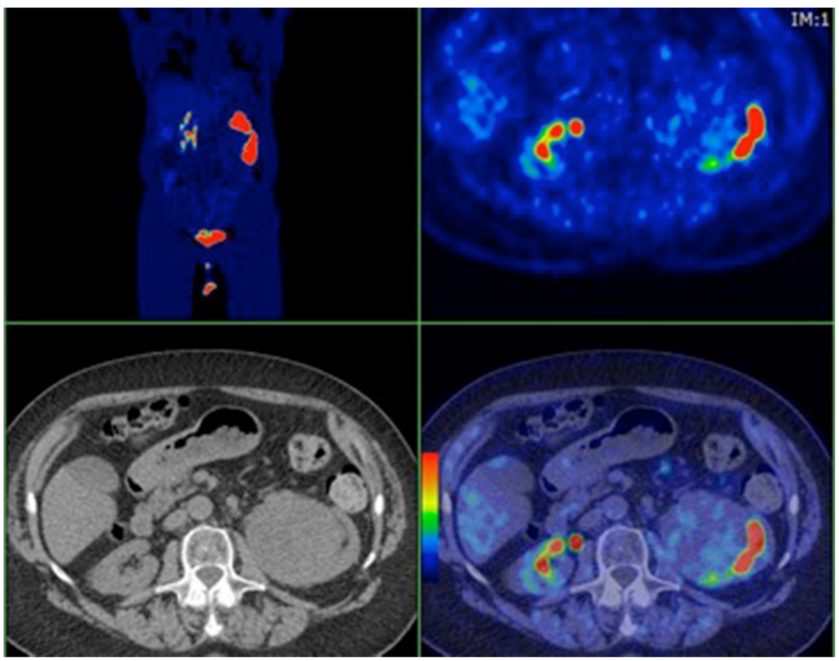

Fig. 2 Female patient with clear cell RCC (pT1bpN0). 18F-FAZA PET/CT did not show any tracer uptake in the left kidney

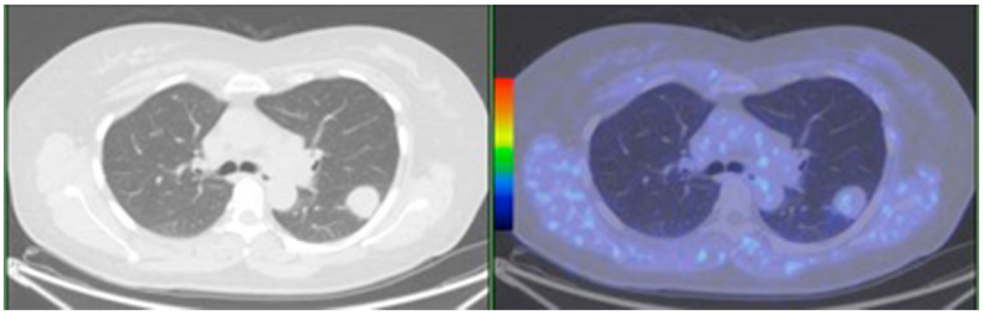

Fig. 3 Female patient with clear cell RCC (pT3apN0). 18F-FAZA PET/CT did not show any tracer uptake nor in the right kidney neither in the left pulmonary nodule

pathological uptake in correspondence of metastatic lymph nodes, thus suggesting the non-hypoxic behaviour of the lesions. Standardized uptake value (SUVmean and SUVmax) therefore were not calculated as well as T/B ratio. In addition, neither primary tumour nor distant metastases presented a pathological 18F-FAZA uptake.

Statistical analysis in terms of sensitivity, specificity and accuracy were also not assessable because of the negative findings observed on 18F-FAZA PET/CT.

Discussion

RCC represents the third most frequent cancer in urological setting, after bladder and prostate tumours [10]. In this context, lymph node metastasis detection and treatment are critical issues in daily clinical decision-making for many reasons. Firstly, no imaging technique allows accurately detecting and staging lymph node invasion in RCC setting [11]. The smallest size for lymph node metastasis detection is 5 mm at best, with a false-negative rate of 10%—a rate that becomes even higher in the presence of micrometastases [12]. Indeed, the available imaging technologies showed a false-positive rate of up to 60%, mainly because of reactive inflammation [12]. Moreover, sentinel node technique is currently investigational in RCC setting due to the unpredictable lymphatic drainage system out of the kidney [13]. Beside such anatomical unpredictability of lymphatic outflow, an additional confounder consists in the predilection of RCC for early haematogenic dissemination without lymph node infiltration [14]. Indeed, 57% of metastatic RCC patients treated with cytoreductive nephrectomy and LND has no evidence of LNI [14]. Although LND represents the most accurate and reliable staging and therapeutic procedure for the detection of lymph node invasion in bladder and prostate cancer patients, the value of LND in RCC still remains controversial [1]. To date, no data clearly demonstrated which candidates should be submitted to LND and which template should be used. Therefore, a novel, accurate, standardized imaging technique is urgently needed in RCC setting to detect nodal invasion. With the development of novel imaging strategies, the non-negligible percentage of patients with false-negative nodal staging at preoperative conventional imaging may benefit from a novel diagnostic/staging tool as regards prognosis (staging) and therapy (LND vs. neoadjuvant vs. adjuvant therapy vs. metastasectomy) [1, 2, 15].

In this regard, PET/CT is a leading imaging modality for many types of solid tumours. The ability to non-invasively characterize molecular processes during a relatively fast whole-body scan is the major advantage of this technology. With the use of specific hypoxia tracers, PET allows non-invasive in-vivo imaging and quantification of tissue hypoxia, being potentially useful to assess the intratumoural distribution of regional tumour hypoxia. Several hypoxia-specific tracers have been proposed for tumour hypoxia imaging [16]. The most extensively studied tracer is 18F-FMISO, which has less favourable biokinetics compared to other hypoxia radiotracers. Next-generation nitroimidazole tracers, such as 18F-FAZA, have been developed to achieve faster clearance by reducing lipophilicity. An oxygenation-dependent

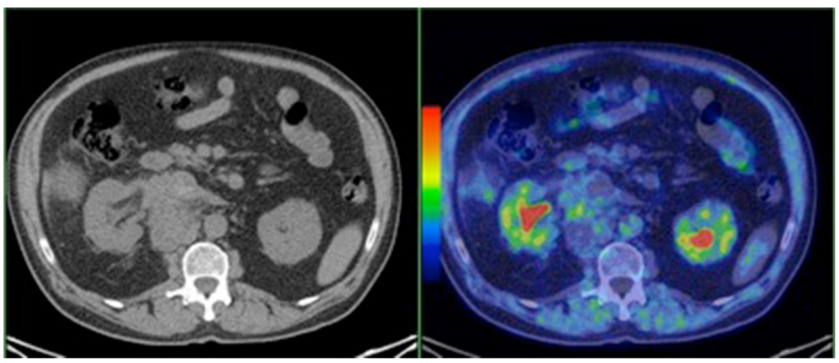

Fig. 4 Female patient with papillary type 2 RCC (pT3bpN0). 18F-FAZA PET/CT did not show any tracer uptake in the right kidney. No uptake was detected in retroperitoneal adenopathies

uptake mechanism for 18F-FAZA as well as superior biokinetics of 18F-FAZA compared with 18F-FMISO was demonstrated [17, 18].

18F-FAZA has not been tested yet in the clinical field for the detection of lymph node or distant metastases in RCC. 18F-FAZA showed higher uptake in perinecrotic areas and low uptake in areas positive for Hoechst 333342 (marker of neoangiogenesis) [16, 19], thus being a promising marker of both necrosis and hypoxia. Moreover, a recent translational study relying on a RCC mouse model suggested the use of 18F-FAZA for monitoring hypoxia status and drug response during sunitinib therapy [7].

The aim of the present study was to evaluate if the assessment of hypoxic tissue by using 18F-FAZA PET/CT could be of help in identifying lymph nodal metastases in RCC patients. Moreover, since in other oncological settings (e.g. head and neck) it has been emphasized the importance of investigating both the primary tumour and lymph nodes (because the hypoxia in a lymph node might not be representative for the oxygenation status of the primary tumour [20]), we secondarily analysed the tracer performance also on both primary tumour and distant metastases [21–23].

In our population of patients, no nodal metastasis showed positive 18F-FAZA PET, thus suggesting the non-hypoxic behaviour of the lesions. In addition, neither primary tumour nor distant metastases presented 18F-FAZA uptake. Indeed, we can speculate that hypoxia was probably not the most represented biological mechanism in this cohort of locally advanced RCC and that the presence of a neoangiogenetic process within RCC, instead of a hypoxic metabolism, might have hampered and negatively conditioned 18F-FAZA uptake.

Although safe and with no adverse event recorded, the current pilot phase 2 trial demonstrated null accuracy of the tracer in detecting primary tumour, LNI and distant metastases. Nonetheless, although with negative results, the current paper increases the knowledge in the setting of RCC imaging and detection of LNI. Indeed, in the last years, more than 40% of the negative phase 3 RCTs in oncology were conducted without a supporting phase 2 trial [24], which might have led to a different or an alternative trial design. Therefore, the current negative results are needed for future trial design and for focusing researches' efforts where needed. Finally, further translational researches are on-going—relying on the same study cohort—to furthermore analyse the hypoxia pathways and why a hypoxia tracer could not increase the diagnostic and staging accuracy in RCC.

Conclusions

18F-FAZA PET/CT scan did not detect RCC lymph neither nodal nor distant metastases and did not show any uptake in the primary kidney tumour, confirming the absence of detectable hypoxia in these tissues.

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Compliance with ethical standards

Conflict of interest Dr. Umberto Capitanio received grants/research supports, honoraria or consultation fees by the following: Ipsen, IBSA, Recordati, Konpharma.

Prof. Maria Picchio received GE Healthcare travel meeting support not related to the work.

The other authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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