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Clinical Cancer Research

Sequential FDG-PET/CT as a Biomarker of Response to Sunitinib in Metastatic Clear Cell Renal Cancer

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Abstract

Purpose: To test the hypothesis that sequential ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) is a correlative marker in metastatic clear cell renal cancer (mRCC), patients were treated with sunitinib. Three sequential scans were conducted to determine whether the timing of the investigation was relevant.

Experimental Design: Forty-four untreated mRCC patients were enrolled into this prospective phase II study. ^{18}F-FDG-PET/CT scans were conducted before ($n = 44$) and after 4 weeks ($n = 43$) and 16 weeks ($n = 40$) of sunitinib given at standard doses. The primary endpoint was to correlate FDG-PET/CT response (20% reduction in SUV_{max}) at 4 and 16 weeks with overall survival (OS).

Results: Forty-three (98%) patients had FDG-PET/CT avid lesions at diagnosis (median $SUV_{max} = 6.8$, range: <2.5–18.4). In multivariate analysis, a high SUV_{max} and an increased number of PET-positive lesions correlated with shorter OS [HR: 3.30 (95% CI: 1.36–8.45) and 3.67 (95% CI: 1.43–9.39), respectively]. After 4 weeks of sunitinib, a metabolic response occurred in 24 (57%) patients, but this did not correlate with progression-free survival (HR for responders = 0.87; 95% CI: 0.40–1.99) or OS (HR for responders = 0.80; 95% CI: 0.34–1.85). After 16 weeks of treatment, disease progression on FDG-PET/CT occurred in 28% ($n = 12$) patients which correlated with a decreased OS and PFS [HR = 5.96 (95% CI: 2.43–19.02) and HR = 12.13 (95% CI: 3.72–46.45), respectively].

Conclusions: Baseline FDG-PET/CT yields prognostic significant data. FDG-PET/CT responses occur in the majority of patients after 4 weeks of therapy; however, it is not until 16 weeks when the results become prognostically significant. *Clin Cancer Res; 17(18); 6021–8. ©2011 AACR.*

Introduction

The introduction of targeted antiangiogenic agents has revolutionized the treatment of metastatic clear cell renal cancer (mRCC; refs. 1–4). Sunitinib prolongs survival and is established as first-line therapy in metastatic disease (1, 2). The majority of patients treated with sunitinib initially obtain a clinical benefit, however, acquired resistance occurs and is associated with a poor outcome (3). Traditional methods of identifying patients who benefit from therapy, such as radiological response by RECIST (Response Evaluation Criteria in Solid Tumors), have not been proved as helpful in renal cancer (5). Correlative biomarkers to identify subsets of patients who benefit from sunitinib therapy are required.

Positron emission tomography (PET), using ^{18}F-fluorodeoxyglucose (FDG), is useful as a diagnostic tool in some tumors as lung cancer; however, results in renal cancer have been less helpful (6, 7). Several studies have also shown that changes in tumor metabolism, measured by FDG-PET/CT, occur early in the course of systemic therapy and may predict outcome (8, 9). Indeed metabolic responses, defined as a greater than 20% reduction in the standard uptake variable (SUV), predict clinical benefit from sunitinib in gastrointestinal stromal tumors (10). However, relatively little is known about the role of FDG-PET/CT for treatment monitoring in renal cancer. Preliminary data suggest that targeted therapies, such as sunitinib, can result in a reduction in tumor metabolic activity in mRCC, but its role as a correlative biomarker in sunitinib-treated patients has not been evaluated (11).

In this prospective study, we test the hypothesis that metabolic response assessed by FDG-PET/CT, defined as a

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Translational Relevance

This study investigates FDG-PET/CT as a surrogate marker of response to sunitinib therapy in metastatic clear cell renal cancer. The results show that the majority of clear cell renal cancers (57%) have a metabolic response (20% reduction in SUV_{max}) to sunitinib after only 4 weeks of therapy. However, these early changes do not correlate with outcome, unlike later scans at 16 weeks, which identified a subgroup of patients with a poor prognosis. This subgroup of patients is worthy of further evaluation with prospective randomized clinical studies, which focus on an early switch to another targeted agent and could be the first step toward individualized therapy. The sequential scans show dynamic metabolic changes, which give us some insight into mechanisms of acquired resistance to sunitinib.

greater than 20% reduction in SUV, correlates with outcome in untreated patients with mRCC treated with sunitinib. FDG-PET/CT was conducted before, after 4, and after 16 weeks of sunitinib treatment to determine whether the timing of imaging influenced the results. The 4-week time point was chosen because FDG-PET/CT is prognostically discriminatory with sunitinib in other tumor types at this time (10). The later 16-week time point was chosen to identify metabolic progression of disease.

Materials and Methods

Study design and patients selection

Forty-four patients with newly diagnosed untreated mRCC participated in a prospective phase II multicenter trial using sunitinib (SUMR NCT01024205; ref. 12). The primary endpoint of the SUMR trial was to assess the clinical benefit of upfront sunitinib in mRCC in Memorial Sloan Kettering Cancer Centre (MSKCC) intermediate- and poor-risk patients who had not had a nephrectomy. Analysis of progression-free survival (PFS) was conducted using RECIST v1.1. The primary endpoint of SUMR was to show a clinical benefit (complete response, partial response, or stable disease by RECIST v1.1) in 70% or more patients after 16 weeks of sunitinib (which was achieved: clinical benefit = 86%). Outcome data were available for both PFS and overall survival (OS) for this study.

All patients participating in the SUMR trial also participated in a FDG-PET/CT imaging study. The sequential FDG-PET imaging aspect of the study was an established secondary endpoint of the trial. This endpoint was to correlate FDG-PET/CT response (20% reduction in SUV_{max}) at 4 and 16 weeks with outcome (PFS and OS). Other exploratory endpoints of the imaging aspects of this study included correlating SUV_{max} and number of FDG-PET–positive lesions at baseline with outcome (PFS and OS). We also compared SUV levels in the metastatic sites and primary renal tumor as an exploratory endpoint. FDG-PET/CT scanning results had no influence on treatment decisions.

Statistics

The OS and PFS were analyzed using the Kaplan–Meier method. Comparison of groups was conducted using the log-rank test. Univariate and multivariate analyses were conducted to identify independent prognostic factors associated with a poor outcome. Factors included in this model included age, gender, Heng risk factors, tumor grade, best response to therapy, and number of metastatic sites. Correlation coefficients were used to compare SUV uptake in the metastatic sites and kidney tumors. Cutoff point analysis was conducted as part of the exploratory analysis to identify levels of most significance. Statistical analysis was conducted using SPSS and STATA 10 software packages. This study was reviewed and approved by the Internal Review Board and had external ethical approval by an appropriate ethics committee.

Treatment

Sunitinib was given for 4 weeks at 50 mg orally followed by a 2-week interval, in repeat cycles. Doses were reduced to 37.5 mg and subsequently to 25 mg in the face of toxicity (grade 3 or more). Second-line therapy was not widely available during this period in the United Kingdom and only 3 patients received further targeted therapy.

FDG-PET/CT imaging

A FDG-PET/CT was conducted [0–14 days (median: 1 day)] before sunitinib therapy. The second scan was conducted 2 to 5 days (median: 2 days) after the last dose of drug on cycle 1 (week 4). The third scan was conducted 1 to 6 days (median 2 days) after the last dose of drug on cycle 3 (week 16).

Images were acquired 60 minutes following injection of 400 MBq of ^{18}F-FDG. Patients fasted for 6 hours prior to scans. Blood glucose was monitored in all patients prior to administration of ^{18}F-FDG using a glucometer. Patients with high glucose (>8 mmol/L) were not scanned. For all PET-CT examinations, a low-dose free breathing computed tomography (CT) was used for attenuation correction. PET scans were conducted on combined PET-64 slice CT scanners [GE healthcare (n = 36) and Phillips (n = 8)]. Calibrations with a ^{68}Gr or ^{18}F-FDG filled phantoms were conducted on the day of PET-CT examinations to ensure consistency of SUV measurement between scanners. All patients were imaged on the same scanner for sequential PET-CT scans, with identical PET acquisition mode and reconstruction parameters.

FDG-PET/CT images were reviewed on a diagnostic workstation (Advantage 4.4; GE Healthcare) and were quantified for FDG uptake using SUV_{max} in primary and metastatic tumor sites. An SUV_{max} above 2.5 was considered to represent disease activity. Scans were reviewed centrally by 2 observers, a dual certified Nuclear Medicine Physician and Radiologist and Nuclear Medicine Physician. Both observers were blind to the clinical outcomes and not involved in subsequent analysis.

Analysis of ^{18}F-FDG uptake in the primary tumor was made with reference to intravenous contrast-enhanced CT

images to differentiate tumor from physiologic parenchymal and urinary activity. Two-dimensional circular regions of interest were placed over tumor lesions to obtain SUV_{max} values. Both SUV_{max} and number of FDG-avid metastatic sites were correlated with outcome. These 2 parameters were chosen, as they represented the most active disease (SUV_{max}) and burden of disease of active disease (number of PET-avid sites of disease).

Response assessment

FDG-avid tumor lesions were identified at baseline. The most FDG-avid lesion was selected as the target lesion. This was followed prospectively for changes in tumor metabolic activity by measuring SUV. The percentage change in SUV (ΔSUV%) was calculated between baseline and subsequent FDG-PET/CT at 4 and 16 weeks. PET response was stratified by the metabolic response criteria using a greater than 20% reduction in SUV (13). We chose this widely used threshold because a 20% variation in SUV was previously identified to be outside the normal fluctuation of SUVs in test-retest studies. Furthermore, this level has been successfully used to identify patients with a good outcome to sunitinib in other tumors (10). Metabolic progression of disease was defined as presence of new metabolically active lesions or at least 20% increase in SUV from baseline. Changes in SUV between the first and second FDG-PET/CT and first and third FDG-PET/CT were calculated.

Results

Between January 2007 and January 2010, 44 patients with previously untreated mRCC were enrolled onto the study. All patients had MSKCC intermediate- ($n = 34$) or poor-risk disease ($n = 10$) and were treated with sunitinib as per protocol. Patient characteristics are shown in Table 1.

Best response evaluation (by CT RECIST v1.1) showed a partial response in 6 patients (14%), stable disease in 30 patients (68%), and progressive disease in 8 patients (18%). Treatment-associated toxicity (grade 3 or more) occurred in 24 patients (54%) and required a dose reduction. Toxicity was in line with that previously described with sunitinib.

The PFS and OS for all patients was 9.2 months (95% CI: 5.9–21.0 months) and 14.4 months (95% CI: 9.1–NA), respectively. Second-line therapy was given to 3 patients [sorafenib ($n = 1$) and everolimus ($n = 2$)].

Baseline FDG-PET/CT was conducted on all 44 patients. The second FDG-PET/CT did not occur in 1 individual, whereas the third FDG-PET/CT did not occur in 4 individuals because of disease progression. One patient had a negative FDG-PET/CT at baseline and was not included in the sequential PET analysis to assess response.

FDG-PET/CT at baseline

Forty-three patients (98%) had a positive FDG-PET/CT at baseline before starting sunitinib (Table 2). The primary renal cancer was FDG avid in 40 (91%) patients and 39 (89%) had FDG-avid metastatic sites. The SUV_{max} for all tumor sites ranged between less than 2.5 and 18.4 (median $SUV_{max} = 6.8$). There was no difference in the level of FDG uptake observed between the primary tumor (median $SUV_{max} = 5.6$; range: <2.5–18.4) and metastatic sites (median $SUV_{max} = 5.4$; range: <2.5–16.7). The commonest metabolically active metastatic sites were lung ($n = 25$), lymph nodes ($n = 24$), bone ($n = 12$), adrenal ($n = 8$), and liver ($n = 7$). The sensitivity and specificity for FDG-PET/CT compared with contrast-enhanced CT was 87% and 95%, respectively.

Table 1. Patients demographics and characteristics at diagnosis

Number of patients	44
Age	61 (range: 44–78)
Gender	
Male	33 (75%)
Female	11 (25%)
MSKCC prognostic risk	
Intermediate	34 (77%)
Poor	10 (23%)
Prognostic factors present	
Raised calcium	10 (23%)
Anemia	26 (59%)
Raised lactate dehydrogenase	15 (34%)
<1 y to treatment	42 (95%)
Performance status > 1	8 (18%)
Metastatic sites	
Lung	32 (72%)
Liver	7 (16%)
Bone	11 (25%)
Lymph nodes	25 (57%)
Adrenal	8 (18%)
Other	14 (32%)
Clear cell tumor grade	
1–2	23 (52%)
3–4	21 (48%)
Median platelet count	315 (range: 186–688)
Median neutrophil count	6.1 (range: 2.3–10.8)
Median OS, mo	14.4 (95% CI: 9.1–NA)
Median PFS, mo	9.2 (95% CI: 5.9–21.0)

In multivariate analysis, SUV_{max} (above the median) correlated with decreased OS (HR: 3.30; 95% CI: 1.36–8.44; $P < 0.01$; Table 3 and Fig. 1A). Subsequent analysis of SUV_{max} for the renal tumor and the metastatic sites separately showed that both correlated OS ($P < 0.05$). Cutoff point analysis revealed that a SUV_{max} of 7.1 was the most significant level to predict overall survival (HR: 3.33; 95% CI: 1.35–8.53).

The median number of ^{18}F-FDG–avid metastatic sites at diagnosis was also investigated as a potential surrogate marker. The median number of ^{18}F-FDG–avid sites was 7 (range: 0–61). On multivariate analysis, increased number of ^{18}F-FDG–avid sites (above median) was associated with a significantly shorter OS (HR: 3.67; 95%

Table 2. FDG-PET/CT in patients with metastatic RCC prior to sunitinib

Patients with at least 1 FDG-avid lesion	43		
Number of ^{18}F-FDG–avid lesions per patient	6.5 (0–61)		
Median SUV_{max}	6.8 (<2.5–18.4)		
Median SUV_{max} uptake of primary renal	5.6 (<2.5–18.4)		
Median SUV_{max} of metastatic sites	5.4 (<2.5–16.7)		
Sensitivity and specificity of FDG-PET compared with contrast-enhanced CT	Median (SUV_{max})	Sensitivity, %	Specificity, %
Renal tumor	5.6	90	100
Lymph nodes	7.32	88	92
Lung	4.5	78	100
Adrenal	7.25	87	87
Bone	6.55	91	76
Liver	5.4	100	100
Other	6.7	86	86
Total	6.8	87	95
Number of metastatic sites involved	PET avid	CT positive	
0	4 (9%)	0	
1	7 (16%)	11 (25%)	
2	17 (39%)	18 (41%)	
3+	16 (36%)	15 (24%)	
Response to sunitinib after 1 cycle of treatment (compared with baseline PET)	Overall ($n = 42$)	Renal tumor ($n = 40$)	Metastatic sites ($n = 39$)
Partial response	24 (57%)	19 (48%)	23 (58%)
Stable disease	14 (35%)	20 (50%)	14 (36%)
Progressive disease	4 (8%)	1 (2%)	3 (7%)
Response to sunitinib after 3 cycle of treatment (compared with baseline PET)[a]	Overall ($n = 39$)	Renal tumor ($n = 37$)	Metastatic sites ($n = 35$)
Partial response	14 (36%)	17 (46%)	13 (38%)
Stable disease	13 (33%)	19 (54%)	11 (31%)
Progressive disease	12 (31%)	0	11 (31%)

[a]Response rates vary as FDG-PET–negative lesions cannot be considered for response.

CI: 1.43–9.39; $P < 0.05$; Table 3 and Fig. 1B). Cutoff point analysis revealed that 8 or more PET-positive lesions were the most significant level to predict OS (HR: 3.78; 95% CI: 1.47–9.82; $P < 0.05$).

Metabolic response after cycle 1 of therapy

Forty-two patients underwent FDG-PET/CT after the first cycle of sunitinib therapy (week 4). The percentage reduction in total SUV (metastatic and renal lesions) was 26% (range: 72% to +76%). The median reduction in SUV_{max} of the most metabolically active tumor lesion was 22% (range: −67 to +80%). A metabolic response in the SUV_{max} lesion occurred in 24 of 42 patients (57%). This metabolic response was not associated with prolonged PFS (HR for responders = 0.87; 95% CI: 0.40–1.99) or OS (HR for responders = 0.80; 95% CI: 0.34–1.85; Fig. 2A and B). Further cutoff point analysis could not identify any specific threshold for reduction in tumor metabolic activity (SUV_{max}) which was associated with outcome.

The median reduction in SUV_{max} for the primary tumor was 23% (range: 67% reduction to 80% increase) and for metastatic sites was 14% (60% reduction to 31% increase). Metabolic response was not associated with a prolonged PFS or OS in either the primary tumor or metastatic sites ($P > 0.05$ for each). There was a positive correlation between metabolic response in the primary tumor and metastatic sites ($P < 0.001$).

Responding patients with a high and low initial SUV were compared for outcome. The initial SUV (below median vs. above median) in PET responders had no effect on survival although the numbers were small ($P > 0.05$).

Metabolic response after cycle 3 of therapy

Thirty-nine patients had a third FDG-PET/CT after 16 weeks of therapy. When compared with baseline, the percentage reduction in total SUV (metastatic and renal lesions) was 16% (−66% to +104%). The median reduction in SUV_{max} between baseline and the third cycle of therapy was 13% (range: −72% to +94%; Fig. 2C). Overall 14 (36%) patients had a metabolic response in the SUV_{max} lesion, 13 (36%) had stable disease and 12 (28%) had

Table 3. Univariate and multivariate analyses at diagnosis

	Results of univariate analysis		Results of multivariate analysis	
	HR	95% CI	HR	95% CI
MSKCC prognostic score (good vs. int. vs. poor)	2.32[a]	1.01–6.26	2.49[a]	1.02–6.26
Male gender	1.07	0.51–9.46	N.S.	
Increased number of metastatic sites[b]	2.01	0.80–5.51	N.S.	
Raised neutrophil count[b]	2.22[a]	0.91–5.38	N.S.	
Raised platelet count[b]	1.41	0.58–3.43	N.S.	
Increased number of PET-positive lesions[b]	4.24[a]	1.43–12.59	3.67[a]	1.43–9.39
High SUV at diagnosis[b]	3.40[a]	1.25–9.30	3.30[a]	1.36–8.44
Grade (1 and 2 vs. 3 and 4)	1.28	0.67–2.33	N.S.	

Abbreviation: N.S., not significant.
[a]Significance level of less than 0.05.
[b]Comparing above and below median.

disease progression. Metabolic progression of disease was associated with decreased OS (HR: 5.96; 95% CI: 2.42–19.02; $P < 0.01$; Fig. 2D). Subsequent univariate and multivariate analyses were conducted at the 16-week time point.

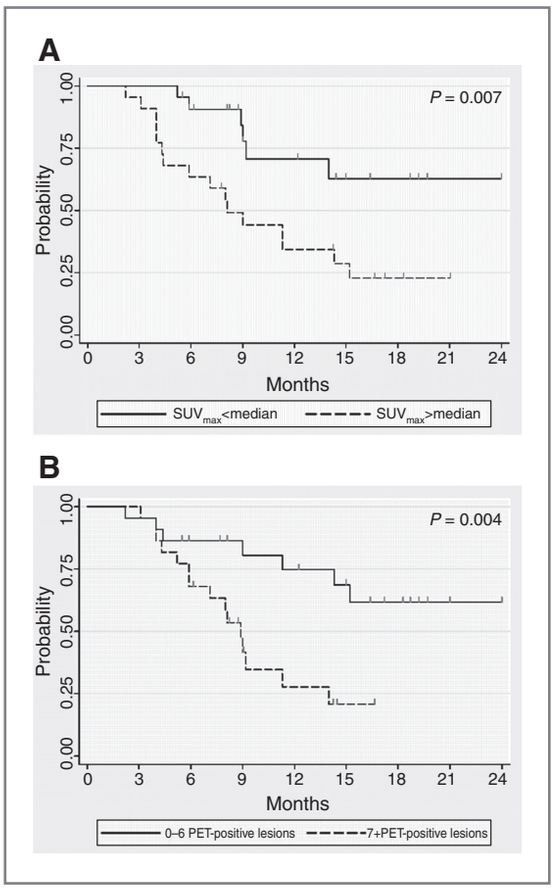

Figure 1. A, OS based on SUV_{max} at diagnosis. B, OS based on the number of FDG-avid metastatic lesions at diagnosis.

This analysis included best response to therapy on CT (RECIST) and PET response at 16 weeks (as well as the other factors at baseline). Multivariate analysis showed only FDG-PET progression and MSKCC prognostic score at diagnosis were significant for OS [(HR: 3.2; 95% CI: 1.97–7.49; $P < 0.01$) and (HR: 4.49; 95% CI: 1.29–15.64; $P = 0.02$), respectively].

Further analysis of these patients with metabolic progression revealed they had a significantly higher SUV at baseline (median SUV = 7.1; range: 3.2–16.7)] than metabolic nonresponders (median SUV = 4.4; range: <2.5–15.3; $P < 0.05$; Fig. 3A). In addition, 10 of the 12 metabolic progressors (82%) had an initial FDG-PET/CT response to therapy at the 4 weeks. Potentially explaining why the 4-week scan was not of prognostic significance.

There was no correlation between FDG-PET response and dose reduction of sunitinib ($n = 24$) at 4- or 16-week time point ($P > 0.05$). A comparison of the second and third FDG-PET/CT revealed only 2 patients achieved a further response to therapy in the third scan. Overall, the median change in SUV_{max} between these second and third scans was a 4% increase.

Discussion

This work evaluates the role of sequential FDG-PET/CT in untreated mRCC patients who received sunitinib. To our knowledge, it is the first to address this issue. Although the majority of patients had a metabolic response after 4 weeks of therapy, it did not correlate with outcome. Instead FDG-PET/CT at a later time point (16 weeks) was prognostically significant. Indeed FDG-PET/CT progression at this time point occurred in a significant proportion of patients who subsequently did poorly. These patients with FDG-PET/CT progression at 16 weeks had more metabolically active disease at baseline and the majority initially had a metabolic

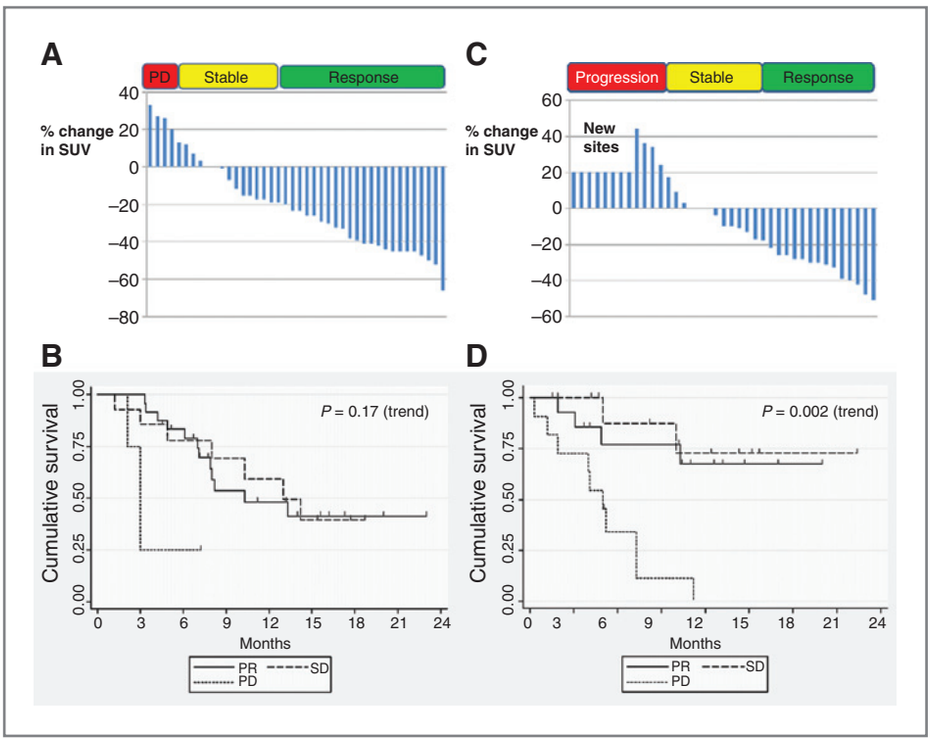

Figure 2. A, waterfall plot showing PET response (SUV_{max}) after 4 weeks of sunitinib ($n = 42$). B, OS based on metabolic FDG-PET response at 4 weeks. C, waterfall plot showing PET response (SUV_{max}) after 4 weeks of sunitinib ($n = 39$). D, OS based on metabolic FDG-PET response at 16 weeks. PR, partial response; SD, stable disease; PD, progressive disease.

response to sunitinib (Fig. 3A). This shows the dynamic nature of the tumor and helps us understand why the initial response at 4 weeks did not correlate with outcome. It also gives us some clues about the occurrence of sunitinib resistance. For example, early repeat tumor biopsy at 4 weeks may be too soon to identify molecular markers responsible for the development of resistance.

The subgroup of patients with FDG-PET/CT progression at 16 weeks are potentially worthy of further evaluation with prospective randomized clinical studies.

The observation that the timing of functional imaging is relevant in predicting outcome may explain why previous angiogenic imaging studies with dynamic contrast–enhanced (DCE) MRI and ultrasound in this field have been contradictory (14, 15). Future work comparing FDG-PET/CT and DCE MRI/ultrasound at sequential time points would help clarify these issues. Ideally sequential biopsies taken from multiple sites for molecular analysis at the same time as functional imaging would be invaluable although ethically challenging.

In contrast to our data, FDG-PET/CT responses in gastrointestinal stromal tumors at 4 weeks are prognostically significant. This underlines the inherent molecular differences between the 2 tumor types (10, 16, 17).

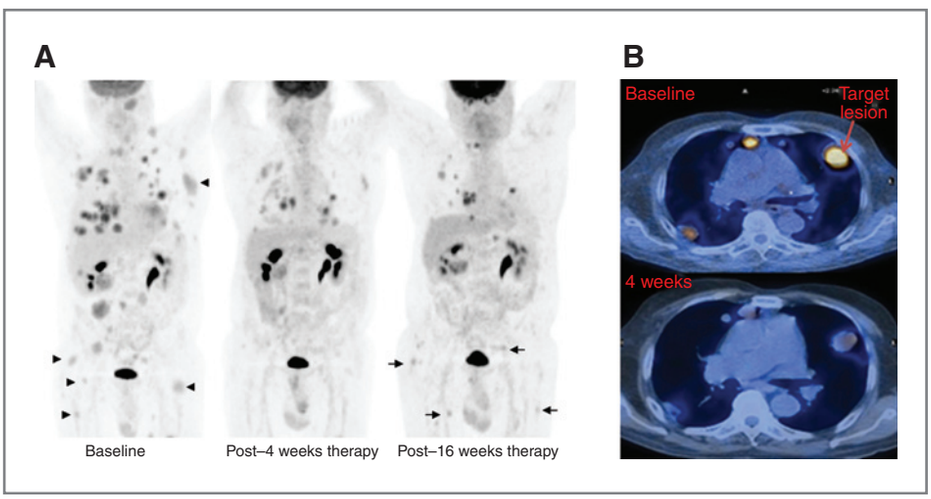

Figure 3. A, maximum intensity projection images of sequential whole body PET scans. Baseline scan shows widespread FDG-avid metastatic lesions including multiple muscle deposits (arrowheads). The 4-week scan shows a response in SUV_{max}. The 16-week therapy scan shows new FDG-avid muscle deposits consistent with progression. B, comparison of axial-fused PET-CT images at identical level through the chest at baseline and 4 weeks postcommencement of therapy showing a response to therapy.

FDG-PET has not been widely used in metastatic renal cancer, as it was not initially thought to add to standard diagnostic procedures (18). Our works show that FDG-PET/CT at diagnosis has a relatively high sensitivity and specificity compared with previous smaller reports (7). We speculate that this is because our series consisted of patients with widespread aggressive disease (compared with previous reports). Nevertheless, for diagnostic purposes, these results should be interpreted in conjunction with CT or MRI. Our results also show FDG-PET/CT gives additional prognostic information in that high SUV_{max} and an increased number of PET positive lesions are both associated with a poor outcome in multivariate analysis. This information potentially helps further define a subgroup of patients with a poor outcome and could be the basis for clinical studies in the future (19).

This work has a number of shortcomings. The phase II clinical study (SUMR), from which this work was derived, was powered to address the efficacy of upfront sunitinib (the primary endpoint) and therefore, the prespecified sequential PET analysis, which was the focus of the translational aspect of the study, was exploratory in nature. Nevertheless, the sequential scans delivered significant findings which can be taken forward. Also, sequential PET scans were only preformed in patients who had not progressed clinically or radiologically, and a small proportion of patients with a very poor outcome were not available at the 4-week (2%) and 16-week (9%) time points, which may have affected the results. The FDG-PET scans were conducted at specific time points within sunitinib cycles (day 30). This time point was chosen as patients were off sunitinib (48 hours), reducing any direct effect caused by the drug and hopefully making the sequential scans more comparable with the baseline scan. However, it is not clear whether these results apply at different time points within the cycles and stopping the sunitinib may result in tumor rebound influencing the results (20). Finally, the absence of second-line therapy in the United Kingdom may affect the OS results. However, this lack of further therapy reduces the potentially confounding impact these treatments may have on the prognostic significance of sunitinib in this setting, supporting OS as an endpoint in this work.

Overall this study showed that the majority of mRCC tumors have increased metabolic activity, which is of prognostic significance. The timing of FDG-PET/CT is relevant in predicting outcome. We speculate that the early metabolic responses are associated with a pharmacodynamic effect of drug and it is not until later that identification of subgroups with acquired resistance occurs. These findings may be the basis for further translational research and clinical trials.

Disclosure of Potential Conflicts of Interest

T. Powles has Honoraria from Speakers Bureau and is a consultant/advisory board member of Pfizer. Pfizer supplied an educational grant to support this work to QMUL (the sponsor).

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