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Case Report

Safety of Lutetium-177 prostate-specific membrane antigen-617 (PSMA-617) radioligand therapy in the setting of severe renal impairment: a case report and literature review

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Abstract: Reported here is a case of rapidly progressive metastatic castration-resistant prostate cancer treated with [^{177}Lu]Lu-PSMA-617 in the setting of severe renal impairment and impending ureteric obstruction. PSMA is expressed on renal tubular cells, raising the possibility of radiation-induced nephrotoxicity, and this level of renal impairment would typically exclude the patient from [^{177}Lu]Lu-PSMA-617 therapy. Multidisciplinary input, individualized dosimetry, and patient-specific dose reduction were used to ensure the cumulative dose to the kidneys remained within acceptable limits. He was initially planned for treatment with six cycles of [^{177}Lu]Lu-PSMA-617. However, he had an excellent response to therapy following four cycles of treatment and the last two cycles were omitted. He has been followed for 1-year posttherapy without evidence of disease recurrence. No acute or chronic nephrotoxicity was observed. This case report highlights the utility of [^{177}Lu]Lu-PSMA-617 therapy in severe renal impairment and provides evidence of relative safety in patients who would otherwise not be considered candidates for therapy.

Plain language summary

This report presents a case of a man with aggressive metastatic prostate cancer who received [^{177}Lu]Lu-PSMA-617 therapy, despite having severely reduced kidney function and worsening ureter obstruction. This treatment could have potential side effects on kidney function, but the medical team used a personalized approach to reduce patient risk. The man was initially planned to have six cycles of therapy, but his excellent response to treatment after four cycles meant the last two cycles were not given. The man has been followed for 1 year after treatment and has not experienced any worsening kidney function. This case shows the safe and effective use of [^{177}Lu]Lu-PSMA-617 therapy in a patient with severely reduced kidney function who would not normally qualify for this treatment.

Keywords: PET, predictive biomarker, prostate cancer, PSMA therapy, renal impairment, theranostics

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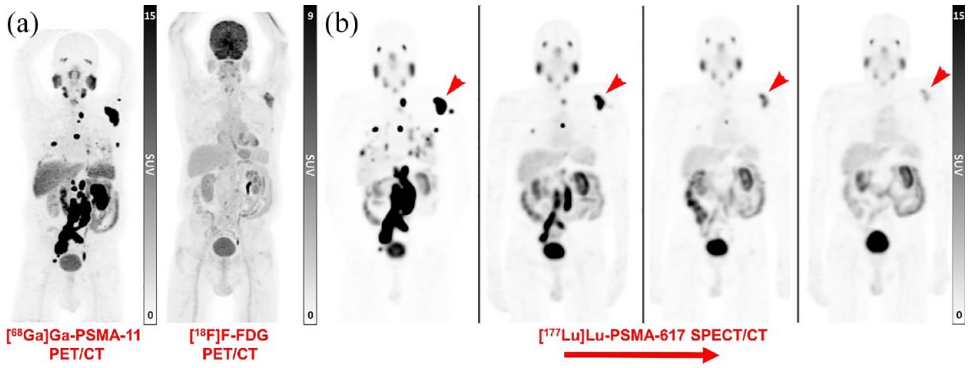

Figure 1. Staging and posttherapy MIP. (a) Staging [^{68}Ga]Ga-PSMA-11 PET/CT study demonstrates intense PSMA uptake in multiple osseous and nodal metastases. There is relatively reduced PSMA uptake in the right kidney, consistent with postobstructive nephropathy. [^{18}F]F-FDG PET/CT study demonstrates no discordant lesions (areas of disease with no significant [^{68}Ga]Ga-PSMA-11 uptake). (b) Posttherapy quantitative [^{177}Lu]Lu-SPECT/CT at 24 h after each cycle of treatment showed a progressive reduction in volume and avidity of multiple PSMA-avid lesions, with many resolving at the fourth posttherapy scan. Most lesions cannot be identified by the fourth cycle, with minimal uptake in the left scapula (red arrowhead).
MIP, maximum intensity projections; PET/CT, Positron emission tomography with computed tomography; PSMA, Prostate-specific membrane antigen.

Introduction

Prostate-specific membrane antigen (PSMA) is a transmembrane protein highly expressed in prostate cancer. Targeted PSMA radioligand therapy, such as [^{177}Lu]Lu-PSMA-617, is a new treatment option for men with metastatic castration-resistant prostate cancer (mCRPC), improving survival and quality-of-life.[1,2] Following intravenous administration of [^{177}Lu]Lu-PSMA-617 into the patient, the drug binds and is internalized by PSMA-expressing prostate cancer cells. Unbound [^{177}Lu]Lu-PSMA-617 is rapidly cleared from the body through renal filtration and secretion. Additionally, PSMA is expressed on renal tubular cells, raising the possibility of radiation-induced nephrotoxicity.[3] Herein, we report the treatment of a patient with rapidly progressive disease, severe renal impairment, and impending ureteric obstruction who was referred for consideration of [^{177}Lu]Lu-PSMA-617. Clinical trials excluded similar patients, and current The United States Food and Drug Administration (FDA)-prescribing information recommends withholding [^{177}Lu]Lu-PSMA-617.[4] We detail multidisciplinary management of this patient from nuclear medicine, medical oncology, and urology perspectives and provide dosimetric and safety data of [^{177}Lu]Lu-PSMA-617 in this setting.

Case presentation

A 78-year-old male with a 15-year history of prostate cancer was referred for consideration of [^{177}Lu]Lu-PSMA-617 radioligand therapy as part of an investigator-initiated, ethics-approved, institutionally sponsored prospective registry (NCT04769817). He originally presented with a baseline prostate-specific antigen (PSA) of 23 µg/L and was treated with radiotherapy to the prostate, as well as commenced on androgen deprivation therapy (ADT) with a PSA nadir of 0.61 µg/L. He responded to ADT for 7 years and subsequently developed biochemical failure, which was treated with the addition of bicalutamide. However, his PSA continued to slowly rise for 3 years. At this time, CT imaging demonstrated metastatic disease with nodal and osseous metastases, and he was started on enzalutamide. After an additional 3 years of therapy, the patient's PSA rose to 555 µg/L, and he was treated with docetaxel reaching a nadir of 60.6 µg/L.

At the time of referral, his prostate cancer was no longer responding to docetaxel with a PSA of 262 µg/L and a PSA doubling time of 1.4 months. Positron emission tomography with computed tomography (PET/CT) demonstrated extensive nodal disease above and below the diaphragm and numerous bony metastases (Figure 1). In addition, he reported right-sided flank pain and treatment-related side effects from docetaxel and steroid use, including peripheral neuropathy and proximal limb weakness. Despite this, he continued to function well with an Eastern Cooperative Oncology Group (ECOG) performance status of 1. Of critical importance, [^{68}Ga]Ga-PSMA-11 PET/CT showed intense uptake at

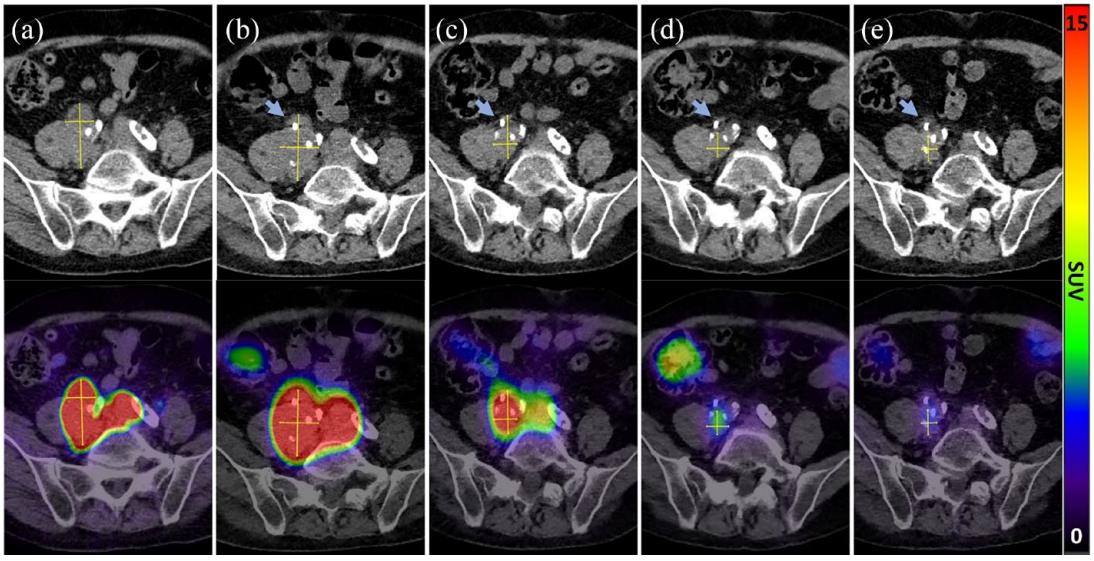

Figure 2. [^{68}Ga]Ga-PSMA-11 PET/CT and posttherapy [^{177}Lu]Lu-SPECT/CT imaging. (a) Staging [^{68}Ga]Ga-PSMA-11 PET/CT study demonstrates an intensely PSMA-avid nodal mass compressing the right ureter. (b–e) Posttherapy quantitative [^{177}Lu]Lu-SPECT/CT at 24 h after each cycle. Between staging and the first posttherapy scan, a right ureteric stent was inserted (light blue arrow on CT images). The patient was treated 6 weeks after staging, and the right-sided nodal mass obstructing the ureter has increased in size. Between the first posttherapy scan and the fourth posttherapy scan, the nodal mass has decreased from 6.0 cm × 3.3 cm to 2.1 cm × 1.4 cm. Posttherapy scans are acquired 24 h after administering [^{177}Lu]Lu-PSMA-617 therapy. However, it can take several weeks for PSMA-avid prostate cancer to respond to [^{177}Lu]Lu-PSMA-617 therapy. As such, a posttherapy scan represents the response to treatment from the prior cycle(s), not the current one. The decrease in size of the nodal mass on the fourth posttherapy scan reflects the last three cycles of therapy.
PET/CT, Positron emission tomography with computed tomography; PSMA, Prostate-specific membrane antigen.

all sites of disease with a maximum standardized uptake value (SUVmax) of 93 and mean SUV (SUVmean) of 17. [^{18}F]F-FDG PET/CT confirmed no discordant disease, defined as metastases of prostate cancer with high [^{18}F]F-FDG-avidity but lacking uptake on [^{68}Ga]Ga-PSMA-11 PET/CT, which would limit [^{177}Lu]Lu-PSMA-617 efficacy.

Staging [^{18}F]F-FDG and [^{68}Ga]Ga-PSMA-11 PET/CT, as well as 24-h posttherapy quantitative [^{177}Lu]Lu-PSMA-617 single photon emission computed tomography with CT (SPECT/CT) studies, demonstrated right renal outflow tract obstruction secondary to a conglomerate nodal mass measuring 5.8 cm × 2.5 cm compressing the ureter (Figure 2) with a volumetric doubling time of 2.3 months. The patient's estimated glomerular filtration rate (eGFR) using the CKD-EPI[5] equation had declined from 41 mL/min/1.73 m^2 to 16 mL/min/1.73 m^2 over 4 months.

Prior to treatment with [^{177}Lu]Lu-PSMA-617, a MAG3 renogram to evaluate renal function demonstrated an obstructed right kidney that contributed 13% to total renal function, and the left kidney contributed the remaining 87% (Supplemental Figure 1). In the urology clinic, the patient was found to be hyperkalemic with a potassium of 6.0 mmol/L and was admitted to the hospital for further management. As the right kidney renal cortex appeared preserved on both [^{18}F]F-FDG and [^{68}Ga]Ga-PSMA-11 PET/CT studies, it was thought that the MAG3 might be underestimating his renal function due to acute obstruction. Therefore, a right-sided nephrostomy tube and subsequent right ureteric stent were placed to optimize renal function prior to [^{177}Lu]Lu-PSMA-617. Consequently, the patient's eGFR improved from 16 mL/min/1.73 m^2 to 24 mL/min/1.73 m^2 over 2 weeks.

The patient was discussed in our multidisciplinary meeting including members from medical oncology, urology, nuclear medicine, radiology, and radiation oncology.[6] Given the imaging findings, rapidly progressive disease, and prior toxicity to chemotherapy, treatment with [^{177}Lu]Lu-PSMA-617 was recommended despite the low eGFR. A 20% dose reduction using our

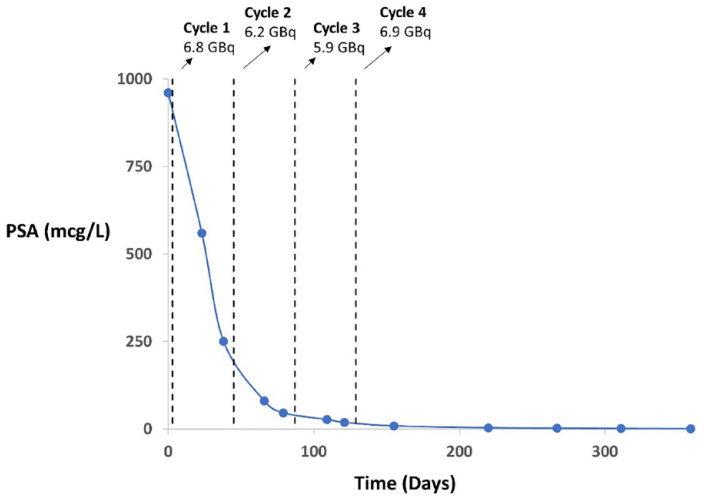

Figure 3. PSA response to [^{177}Lu]Lu-PSMA-617 therapy. Interval decline in PSA with response to four cycles of therapy. The patient has been followed for 1 year without evidence of disease recurrence. Actual PSA measurements are denoted by blue circles.
PSA, prostate-specific antigen.

standard protocol adapted from the TheraP trial[1] was recommended. Treatment with [^{177}Lu]Lu-PSMA-617 was preferred over cabazitaxel, given persistent peripheral neuropathy from prior docetaxel and steroid-induced proximal limb weakness. The possible risk of nephrotoxicity was explained to the patient. He consented to receive [^{177}Lu]Lu-PSMA-617 acknowledging that alternatives of best supportive care would likely result in rapid death. In addition, we obtained informed consent from the patient to publish his clinical information and imaging in this case report.

On the day of [^{177}Lu]Lu-PSMA-617 administration, he was prehydrated with 500 mL of normal saline and advised to maintain good oral hydration (⩾1.5 L per day). No diuretics were administered on the day of therapy. SPECT/CT studies were acquired 24 and 96 h post [^{177}Lu]Lu-PSMA-617 to define accurate renal dosimetry.[7] The mean absorbed dose for metastatic prostate cancer was 26.1 Gy, while the mean renal absorbed dose was 1.8 Gy for the left kidney and 1.2 Gy for the right kidney and provided reassurance that further cycles could be safely administered (Supplemental Figure 2). Critically, no significant change in eGFR was observed over four cycles of [^{177}Lu]Lu-PSMA-617 therapy. The average absorbed dose received by the left and right parotid glands was 2.2 Gy and 2.1 Gy, respectively. Although the accepted limit for salivary gland absorbed dose tolerance has not yet been established,[8] observations from External beam radiation therapy (EBRT) suggest that toxicity risks are minimal when the mean absorbed dose to both parotid glands remains below 10 Gy, and a proposed absorbed dose limit of 20 Gy.[9] Due to the lack of serial plasma samples, it is not possible to accurately estimate the toxicity in the bone marrow/blood from the SPECT/CT scans taken after therapy. Nevertheless, the absence of hematologic toxicity suggests that the dose to the marrow was indeed not harmful.

Following four cycles of [^{177}Lu]Lu-PSMA-617 therapy, the patient's PSA level declined sharply, with a 97% reduction in the serum PSA (Figure 3) and a corresponding 61% reduction in measurable tumor volume (Table 1), by RECIST 1.1 criteria. Additionally, functional imaging with [^{177}Lu]Lu-PSMA-617 showed a marked reduction in size and avidity of multiple PSMA-avid lesions, many of which were no longer identified (Figure 1 and 2). He was reviewed at the multidisciplinary meeting after the fourth dose, and a pause in treatment was felt appropriate, given the paucity of remaining PSMA-avid targetable disease. Throughout therapy and 12 months of follow-up, his eGFR remained between 24 and 30 mL/min/1.73 m^2 with no evidence of [^{177}Lu]Lu-PSMA-617-induced acute or chronic nephrotoxicity (Supplemental Figure 3). His only treatment-related side-effect was transient grade 1 dry mouth. He has had a durable response to therapy, with the latest follow-up PSA value measuring 0.84 mcg/L, representing his nadir at 12 months since the administration of the first dose of [^{177}Lu]Lu-PSMA-617.

As part of our prospective registry, he completed quality-of-life questionnaires using the standard EORTC QLQ-C30 and Brief Pain Inventory Short Form (BPI-SF) survey every 3 weeks (Supplemental Figure 4).[10] Importantly, with treatment, the patient experienced resolution of pain, and improvement in his family interactions, social activities, ability to care for his own needs, as well as his self-reported overall health and quality-of-life. One year after therapy, he continues to remain asymptomatic and has no limitations in any of these fields.

Discussion and implications for clinical care

This case highlights the effectiveness of [^{177}Lu]Lu-PSMA-617 radioligand therapy in a complex patient with rapidly progressive end-stage disease

and severe renal impairment secondary to obstructive lymphadenopathy. Importantly, it highlights how multidisciplinary input was critical to various aspects of patient outcomes. The FDA-approved product monograph recommends not proceeding with [^{177}Lu]Lu-PSMA-617 in patients with eGFR lower than 30 mL/min until improvement.[4] However, this case report demonstrates the relative safety of [^{177}Lu]Lu-PSMA-617 treatment despite poor renal function. In this scenario, the eGFR during treatment was as low as 24 ml/min/1.73 m^2. Despite this, we demonstrated renal dose from [^{177}Lu]Lu-PSMA-617 therapy to be approximately in line with existing literature on patients with normal renal function, 0.92 Gy/GBq.[11] This is different than other radionuclide treatments, such as peptide receptor radionuclide therapy with [^{177}Lu]Lu-DOTATATE[12] or [^{90}Y]Y-DOTATATE[13] where the renal dose is substantially increased in the setting of renal impairment. The European Association of Nuclear Medicine procedural guideline for PSMA-based radionuclide therapy reports a renal tolerance of between 28 and 40 Gy depending on risk factors and recommends weighing the benefit-to-risk ratio if the cumulative absorbed dose approaches 40 Gy in a patient expected to live greater than 1 year.[14] Importantly, follow-up in our patient demonstrated stable renal function over a 1-year posttherapy period.

On one hand, several studies have demonstrated stable or improved renal function following [^{177}Lu]Lu-PSMA-617. In a prior study evaluating the renal safety of [^{177}Lu]Lu-PSMA-617 patients with reduced baseline renal function ($\leq$60 mL/min), Rosar *et al.*[3] concluded that there was no deterioration of renal function following treatment. Rather, more than half of the study patients experienced both an improvement in renal function (GFR $\geq$ 20%) and clinical status. Unfortunately, the presence of hydronephrosis and obstructive uropathy was not discussed. In a separate paper by Zhang *et al.*,[15] [^{177}Lu]Lu-PSMA-617 was shown to be well tolerated in the setting of a solitary kidney. Importantly, Zhang *et al.* reported that 50% (8/16) of patients had evidence of hydronephrosis, though no response of this hydronephrosis to therapy was included in the study. In our patient, the insertion of a stent and subsequent improvement in renal function from 16 to 24 mL/min/1.73 m^2 prior to therapy combined with shrinkage retroperitoneal nodes with [^{177}Lu]Lu-PSMA-617 therapy likely contributed to this improvement, whereas critical obstruction leading to death would likely have occurred without intervention.

Table 1. Response assessment to [^{177}Lu]Lu-PSMA-617 therapy using RECIST 1.1 criteria.

Target lesions	Baseline size	Fourth posttherapy scan size
Lymph Node 1 Right common iliac nodal mass	6.0 × 3.3 cm	2.1 × 1.4 cm
Lymph Node 2 Left para-aortic node	3.0 × 2.1 cm	1.7 × 0.7 cm
Sum of diameters	5.4 cm	2.1 cm
	% Reduction	61%
	Response	Partial response

On the other hand, a single-center retrospective trial conducted by Widjaja *et al.* evaluated 46 mCRPC patients and found that having an abnormal pretherapeutic eGFR (<90 mL/min/1.73 m^2) was the strongest predictor of worsening CKD.[16] The risk of kidney injury is also supported by a phase II prospective study by Violet *et al.*[17] where grade 1–2 renal injury was observed in 10% of patients as measured by an 11.7 mL/min reduction in renal function using [^{51}Cr]Cr-ethylenediaminetetraacetic acid (EDTA) between pretherapeutic and 3-month follow-up assessment. Our patient demonstrated no worsening of his baseline renal dysfunction, and this was likely related to optimization of his renal function with ureteric stenting, personalized dosimetry, adequate hydration during treatment, and reducing the number of [^{177}Lu]Lu-PSMA-617 cycles from six to four given his excellent response to therapy. Large-scale trials in patients with severe renal impairment are unlikely to be undertaken. Nevertheless, this case report should only be regarded as preliminary evidence, and further experience and reports are needed to assess renal risk in patients undergoing lutetium-PSMA.

Another teaching point of this case report is the favorable response to therapy. Several factors can account for this response, including tumor biology and inherent sensitivity to radiation. In a recent paper by Buteau *et al.*,[18] high PSMA uptake within the total tumor burden on pretreatment PSMA PET/CT, measured by a SUVmean $\geq$10, predicts

a higher likelihood of favorable response to [^{177}Lu]Lu-PSMA-617. In the case of our patient, the metastatic prostate cancer is significantly PSMA avid on staging [^{68}Ga]Ga-PSMA-11 PET/CT (SUVmean 17), which is a marker for high accumulation of the therapeutic radionuclide. The elevated retention is likely a combination of the sink-effect[19] where tumor uptake in extensive metastatic disease with reduced accumulation in normal tissue and possibly poor renal functionlimitingurinaryclearanceof[^{177}Lu]Lu-PSMA-617. The longer residence time of the radiopharmaceutical in the patient provides more opportunity for a therapeutic dose of radiation to interact with the cancer. In addition, no worsening of hematologic parameters was observed during treatment or in the follow-up period.

To conclude, this case report describes an excellent response to [^{177}Lu]Lu-PSMA-617 in a patient with mCRPC and poor renal function where current clinical guidelines would caution proceeding with treatment.[4] Multidisciplinary input, individualized dosimetry, as well as patient-specific dose reduction was used to ensure the cumulative dose to the kidneys remained within acceptable limits. No nephrotoxic or hematologic toxicity was observed during therapy or in 1 year of follow-up. In patients with significantly reduced renal function, a personalized approach, including the use of dosimetry, and assessment for underlying obstructive ureteric pathology, should be considered.

Declarations

Ethics approval and consent to participate

The patient was treated under an ethics-approved, institutionally sponsored prospective registry (NCT04769817). The patient provided consent to receive [^{177}Lu]Lu-PSMA-617.

Consent for publication

The patient provided written informed consent to publish his clinical information, and imaging in this case report.

Author contribution(s)

Duncan E. K. Sutherland: Conceptualization; Formal analysis; Investigation; Software; Writing – original draft; Writing – review & editing.

Raghava Kashyap: Conceptualization; Formal analysis; Investigation; Software; Writing – original draft; Writing – review & editing.

Price Jackson: Formal analysis; Software; Writing – original draft; Writing – review & editing.

James P. Buteau: Conceptualization; Formal analysis; Investigation; Software; Writing – original draft; Writing – review & editing.

Declan G. Murphy: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

Brian Kelly: Investigation; Supervision; Writing – review & editing.

Lavinia Spain: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

Shahneen Sandhu: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

Arun A. Azad: Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

Elizabeth Medhurst: Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Grace Kong: Conceptualization; Formal analysis; Investigation; Writing – review & editing.

Michael S. Hofman: Conceptualization; Formal analysis; Funding acquisition; Investigation; Project administration; Writing – original draft; Writing – review & editing.

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Competing interests

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Availability of data and material

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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