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ORIGINAL ARTICLE

Prostate Cancer

^{68}Ga-PSMA ligand PET/CT integrating indocyanine green-guided salvage lymph node dissection for lymph node metastasis after radical prostatectomy

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To efficiently remove all recurrent lymph nodes (rLNs) and minimize complications, we developed a combination approach that consisted of ^{68}Gallium prostate-specific membrane antigen (PSMA) ligand positron emission tomography (PET)/computed tomography (CT) and integrated indocyanine green (ICG)-guided salvage lymph node dissection (sLND) for rLNs after radical prostatectomy (RP). Nineteen patients were enrolled to receive such treatment. ^{68}Ga-PSMA ligand PET/CT was used to identify rLNs, and 5 mg of ICG was injected into the space between the rectum and bladder before surgery. Fluorescent laparoscopy was used to perform sLND. While extensive LN dissection was performed at level I, another 5 mg of ICG was injected via the intravenous route to intensify the fluorescent signal, and laparoscopy was introduced to intensively target stained LNs along levels I and II, specifically around suspicious LNs, with ^{68}Ga-PSMA ligand PET/CT. Next, both lateral peritonea were exposed longitudinally to facilitate the removal of fluorescently stained LNs at levels III and IV. In total, pathological analysis confirmed that 42 nodes were rLNs. Among 145 positive LNs stained with ICG, 24 suspicious LNs identified with ^{68}Ga-PSMA ligand PET/CT were included. The sensitivity and specificity of ^{68}Ga-PSMA ligand PET/CT for detecting rLNs were 42.9% and 96.6%, respectively. For ICG, the sensitivity was 92.8% and the specificity was 39.1%. At a median follow-up of 15 (interquartile range [IQR]: 6–31) months, 15 patients experienced complete biochemical remission (BR, prostate-specific antigen [PSA] <0.2 ng ml^{-1}), and 4 patients had a decline in the PSA level, but it remained >0.2 ng ml^{-1}. Therefore, ^{68}Ga-PSMA ligand PET/CT integrating ICG-guided sLND provides efficient sLND with few complications for patients with rLNs after RP.

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INTRODUCTION

Prostate cancer (PCa) is the most commonly observed solid organ malignancy affecting aging men worldwide.[1] In recent years, the incidence of this disease in China has increased rapidly. According to statistics, more than 50% of patients with PCa in China have locally advanced or metastatic tumors at the time of diagnosis due to prostate-specific antigen (PSA) screening and geographical variables.[2] Radical prostatectomy plus extensive pelvic lymphadenectomy (RP + ePLND) is one of the standard treatments for patients with locally advanced PCa.[3] Furthermore, multidisciplinary treatment, including androgen ablation, chemotherapy, and radiation therapy, has been given to these patients before or after RP. However, 35% to 50% of patients with locally advanced PCa experience biochemical recurrence (BCR) within 5 years after surgery.[4] Approximately 25% of BCR patients develop recurrent lymph nodes (rLNs).[5] The prognosis of patients with rLNs alone is better than that of those with bone or visceral organ metastasis.[6,7] Salvage lymph node dissection (sLND) refers to surgery performed on the pelvic-retroperitoneal region due to potential LN metastasis and is more time-consuming and has a higher rate of complications than radiation therapy.[8,9] Recently, ^{68}Gallium prostate-specific membrane antigen (PSMA) ligand positron emission tomography (PET)/computed tomography (CT) was used to identify rLNs in patients with low levels of PSA, and robotic sLND was accordingly used to perform sLND.[10] Furthermore, Manny *et al.*[11] reported that indocyanine green (ICG) could be used to target stained pelvic LNs during RP. Consequently, rLNs were definitely included in fluorescent nodes. Moreover, Boscolo-Berto *et al.*[12] described that apart from the ascending ducts from the cranial gland leading to the external iliac nodes and the lateral ducts leading to the hypogastric nodes, lymphatic ducts from the posterior surface of the prostate were directed to the pararectal lymphatic plexus, leading to the lymphatic network around the common iliac artery and aorta. Notably, we previously performed a comparative study between ePLND and ICG-guided PLND and confirmed that ICG-guided PLND was able to provide a two-year metastasis-free survival rate of 100%, whereas conventional ePLND was able to provide a rate of 86%.[13]

In this study, we incorporated ICG-guided PLND into the sLND approach. In total, we identified 19 patients with rLNs using ^{68}Ga-

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PSMA ligand PET/CT test who accordingly underwent laparoscopic sLND via the ICG guidance approach and achieved 78.9% (15/19) PSA complete biochemical remission (BR) over a median follow-up time of 15 months and reduced the incidence of perioperative complications.

PATIENTS AND METHODS

Patients

Nineteen patients who experienced BCR and whose rLNs were identified by ^{68}Ga-PSMA ligand PET/CT were enrolled to receive ICG-guided sLND in The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, between March 2017 and December 2019. During the initial RP period, ^{68}Ga PSMA ligand PET/CT was not a routine preoperative examination; instead, bone emission computed tomography (ECT) combined with pelvic magnetic resonance imaging (MRI) was a more common preoperative combination for detecting the presence of tumor metastasis. Thirteen patients underwent RP + PLND surgery, and 6 patients had pathologically positive lymph nodes. A total of 192 lymph nodes were dissected during the RP + PLND surgery, of which 27 lymph nodes were confirmed to be pathologically positive. Fifteen of the 19 patients with postoperative BCR received androgen deprivation therapy (ADT; 78.9%). The clinical characteristics of these 19 patients at the time of RP surgery are described in **Table 1**. This study was approved by the Ethics Committee of The Third Affiliated Hospital of Sun Yat-sen University (batch number: Medical Ethics of The Third Affiliated Hospital of SYSU [2017]2-142), and all patients signed informed consent forms. Clinical evaluation included PSA, and ^{68}Ga-PSMA ligand PET/CT examinations were introduced to determine rLNs without bone and visceral metastases. The following data were collected: clinicopathological characteristics, adjuvant ADT or radiotherapy (RT), site and number of positive nodes identified by imaging and at final pathology, perioperative blood loss (ml), operative time (min), and length of hospital stay (day). All patients were confirmed to have no allergy to iodine prior to surgery. Fluorescent laparoscopes used in the surgeries were produced by the Opmandi Company (OPTO-CAM2100) in Foshan, China. All 19 patients underwent ICG-guided sLND surgery within 1–2 weeks after ^{68}Ga-PSMA ligand PET/CT examination. All surgeries were performed by the same senior surgeon (XG).

Table 1: Characteristics and outcomes of patients at the time of radical prostatectomy and indocyanine green-guided salvage lymph node dissection

Characteristic	*Value (n=19)*
Age at sLND (year), median (IQR)	71 (65–76)
PSA at sLND (ng ml^{-1}), median (IQR)	2.67 (1.36–13.28)
Pathologic T stage, *n* (%)	
pT2	6 (31.6)
pT3	10 (52.6)
pT4	3 (15.8)
Gleason grade group, *n* (%)	
<3	4 (21.1)
4	8 (42.1)
5	7 (36.8)
Pathologic N stage, *n* (%)	
pN0	7 (36.8)
pN1	6 (31.6)
pNx	6 (31.6)
Lymph nodes removed at RP, median (IQR)	9 (6–19)
ADT before sLND, *n* (%)	15 (78.9)
Months from RP, median (IQR)	33 (14–136)
Operative time (min), median (IQR)	108 (75–143)
Blood loss (ml), median (IQR)	50 (40–120)
Length of stay (day), median (IQR)	5.8 (4–12)
Follow-up (month), median (IQR)	15 (6–31)
PSA <0.2 ng ml^{-1}, *n* (%)	15 (78.9)
PSA >0.2 ng ml^{-1}, *n* (%)	4 (21.1)
Postoperative complications (Clavien-Dindo classification)	3 (level I/II)
Lymphatic leakage, *n* (%)	1 (5.3)
Intestinal tympanites, *n* (%)	2 (10.5)

RP: radical prostatectomy; sLND: salvage lymph node dissection; IQR: interquartile range; PSA: prostate-specific antigen; ADT: androgen deprivation therapy

Imaging

Imaging examination was performed by the whole-body PET/CT imaging (GE Discovery Elite PET/CT, Boston, MA, USA), which has the characteristics of fast acquisition time and high resolution. It can quickly and accurately detect millimeter-level lesions and evaluate the therapeutic effect with ligand of ^{68}Ga-PSMA (radiochemical purity 92%–98%; provided by Guangzhou Atom Hi-Tech Isotope Pharmaceutical Co., Ltd., Guangzhou, China). PET/CT imaging range is from the middle of the femur to the top of the head, 1 min and 40 s per bed. The CT acquisition conditions are as follows: the voltage of 120 kV, the electric current is automatically adjusted according to the machine's software (70–220 mA), the scan thickness is 3.75 mm, reconstruction of the attenuation correction sequence and the standard soft tissue algorithm sequence. The VUE Point FX algorithm (GE Healthcare, Boston, MA, USA) is used for obtaining transverse, coronal, and sagittal tomographic images and maximum intensity projection (MIP) images. On the GE AW 4.6 workstation (GE Healthcare), the standard phase and diuretic delay phase PET/CT fusion images are used to delineate the region of interest (ROI) of the lymph node lesions.

Surgical technique

Preoperatively, ^{68}Ga-PSMA ligand PET/CT was used to identify the positions of rLNs in the pelvis and retroperitoneum. Under ultrasound guidance, 5 mg of ICG (Dalian Bell Pharmaceutical Co., Ltd., Dalian, China) was injected into the space between the posterior wall of the bladder and the anterior wall of the rectum 60 min before the operation. Given that regular lymphatic drainage was altered after RP plus PLND, the repertoire of ICG-guided sLND started at level I. Five trocars were placed in the abdomen, and extensive LN dissection was carried out to cover the pelvic region, focusing on the inguinal and hypogastric arteries. After completing level I dissection, another 5 mg of ICG was injected via the intravenous route, and the laparoscope was switched to fluorescence mode to search for residual LNs at level I. Subsequently, the fluorescent LNs along the presacral and common iliac arteries were identified and removed, while fluorescently unstained LNs were not dissected at level II. Forceps were then used to retract the ascending or descending colon. The lateral peritoneum was then exposed longitudinally to examine ICG-stained LNs along the abdominal aorta until the upper border of the renal vessel. At levels III and IV, only ICG-stained LNs were dissected; otherwise, LN dissection was not performed (**Figure 1**). The intraoperative fluorescent LN data were matched to the preoperative ^{68}Ga-PSMA ligand PET/CT imaging data to confirm that the suspicious rLNs were included (**Figure 2**). All fluorescently stained (levels I, II, III, and IV) and unstained (level I) LNs were sent for pathologic analysis.

Follow-up

Perioperative complications were classified according to the Clavien–Dindo classification and recorded during the hospital stay.[14]

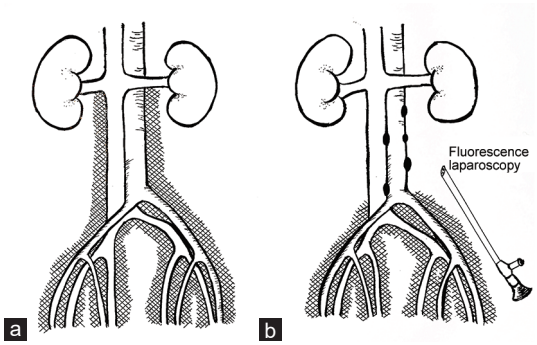

Figure 1: General sLND and ICG-guided sLND schematic diagrams. (**a**) General sLND involves the pelvic and retroperitoneal regions. (**b**) The repertoire of ICG-guided sLND started at level I, and only ICG-stained LNs were dissected at levels II, III, and IV. ICG: indocyanine green; LNs: lymph nodes; sLND: salvage lymph node dissection.

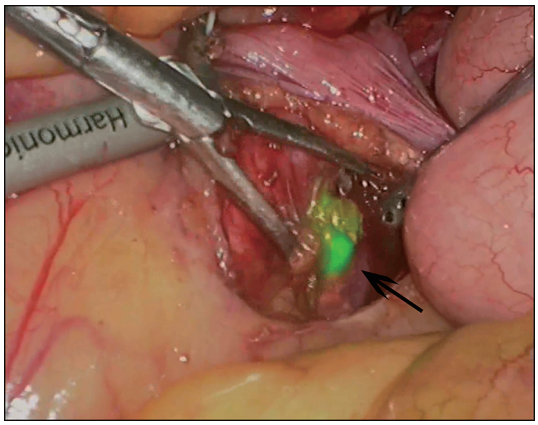

Figure 2: Intraoperative picture of ICG-guided sLND (ICG-stained LNs were dissected). ICG: indocyanine green; LNs: lymph nodes; sLND: salvage lymph node dissection.

All patients were followed up by outpatient clinic visits or telephone interviews at 1 month, 3 months, 6 months, 9 months, and 12 months after the operation. Patients were then followed up every 6 months for 1 year and then yearly thereafter. Follow-up visits included examinations for surgical complications, serum PSA levels, urinary control function, BCR, rLNs, and distant systemic metastases.

Statistical analyses

SPSS version 23 statistical software (IBM, Armonk, NY, USA) was used to process the data and for statistical analyses. Continuous data are presented as the median and interquartile range (IQR) and were compared with the Student's *t*-test. Categorical data are expressed as the number and percentage and were compared with the Chi-square test or Fisher's exact test, as appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

The median age of the 19 patients was 71 (IQR: 65–76) years, the median PSA level at sLND was of 2.67 (IQR: 1.36–13.28) ng ml^{-1}, and the median Gleason score at previous RP was 8.2 (IQR: 7–10); the total number of suspicious LNs identified with ^{68}Ga-PSMA ligand PET/CT was 24. During the perioperative period, the median operation time was 108 (IQR: 75–143) min, and the median blood loss was 50 (IQR: 40–120) ml. The complication rate of sLND was 15.8%. The median follow-up time was 15 (IQR: 6–31) months. Fifteen patients had a complete BR (PSA <0.2 ng ml^{-1}). In the remaining 4 patients, the serum PSA level declined after surgery but remained >0.2 ng ml^{-1}. In accordant, those patients received ADT plus abiraterone (ABT). During the follow-up, 2 cases had PSA response (<0.2 ng ml^{-1}) and another 2 presented a rising PSA and subsequently underwent ^{68}Ga-PSMA ligand PET/CT again. Above-mentioned examination found new metastasis site: 1 case at sacroiliac joint on the right, and the other case at 4th lumbar vertebra. Therefore, radiation therapy was performed. By update visit, PSA level of these two patients was <0.2 ng ml^{-1} and ADT was discontinued. Detailed information on the characteristics of the 19 patients is provided in **Table 1**.

Pathologically malignant rLNs were recorded in all 19 patients. Of 216 resected LNs, 145 were fluorescently stained, and 42 of the stained LNs were confirmed to be malignant by the pathologist. Twenty-four rLNs were identified by ^{68}Ga-PSMA ligand PET/CT preoperatively and 145 fluorescently stained LNs were dissected during the operation. Of the 42 rLNs detected by the pathologist, 7 (16.7%) pathologically positive lymph nodes are located in the retroperitoneal area. Detailed information on rLNs before, during, and after sLND is shown in **Table 2**. The sensitivity and specificity of ^{68}Ga-PSMA ligand PET/CT for identifying rLNs were 42.9% and 96.6%, respectively. The sensitivity and specificity of ICG fluorescence-targeted localization for detecting rLNs were 92.8% and 39.1%, respectively (**Table 3**).

DISCUSSION

Currently, sLND is the mainstay therapy in the setting of rLNs after RP and includes radiation and surgical management.[15,16] sLND involves the pelvic and retroperitoneal regions, but ^{68}Ga-PSMA ligand PET/CT provides the potential for the early diagnosis of rLNs. Therefore, we aimed to efficiently remove rLNs and minimize complications using a combination approach integrating ^{68}Ga-PSMA ligand PET/CT with ICG-guided sLND. Our study indicated that patients with less than 3 PSMA ligand PET-positive spots experienced a good outcome after sLND, and ICG binding to rLNs produced high sensitivity but low specificity, while ^{68}Ga-PSMA ligand PET/CT produced low sensitivity but high specificity regarding rLNs; moreover, the detection rate of ^{68}Ga-PSMA ligand PET/CT depended on the level of PSA recurrence and size of rLN.[17,18] This is in accordance with our results. In our study, the sensitivity of ICG fluorescence-targeted localization for detecting rLNs and the specificity of ^{68}Ga-PSMA ligand PET/CT for identifying rLNs were 92.8% and 96.6%, respectively (**Table 3**). In particular, Manny *et al.*[11] completed ICG-guided PLND in 50 patients and confirmed that of all fluorescently stained LNs, metastatic nodes were definitely detected, while negative nodes were not. Therefore, we incorporated the high sensitivity of ICG with the high specificity of ^{68}Ga-PSMA ligand PET/CT with respect to the identification of rLNs pre- and intraoperatively, and the initial results of this study demonstrated that our combination approach for sLND could increase the efficacy in both oncological and surgical outcomes. Over the median follow-up time of 15 months, among the 19 patients in this study, 15 (78.9%) achieved complete BR, while according to PET/CT- and MRI-directed extended salvage radiotherapy, 7/25 (28.0%) with rLNs achieved BR.[19] Meanwhile, the rate of early clinical recurrence (eCR) in our patients was 21.1%, similar to that in the robotic sLND cohort.[20] According to the evaluated number of rLNs before and after surgery in this study, the median number of ^{68}Ga-PSMA-positive spots per patient before surgery was less than 3. Further, ICG-guided sLND revealed 145 fluorescently stained LNs, and 42 rLNs were identified by a pathologist, confirming all 19 patients with rLNs, including 3 with >3 rLNs. In addition, the median operative time of ICG versus open versus

Table 2: Data on lymph nodes identified and removed via indocyanine green-guided salvage lymph node dissection

Level of the lymph node removed	*^{68}Ga-PSMA ligand PET/CT (+), n*	*ICG (+), n*	*Pathological results (+), n*
Level I	15	92	23
Level II	6	40	12
Level III	3	10	4
Level IV	0	3	3
Total lymph nodes removed	24	145	42

ICG: indocyanine green; ^{68}Ga-PSMA: ^{68}Gallium prostate-specific membrane antigen; PET: positron emission tomography; CT: computed tomography

Table 3: Sensitivity and specificity of ^{68}Gallium prostate-specific membrane antigen ligand positron emission tomography/computed tomography and fluorescent indocyanine green for the detection of recurrent lymph nodes

Predictor	*Pathological rLNs (+), n*	*Pathological rLNs (–), n*	*Detection capability (%)*
^{68}Ga-PSMA ligand PET/CT			
Positive	18	6	Sensitivity (42.9)
Negative	24	168	Specificity (96.6)
ICG			
Positive	39	106	Sensitivity (92.8)
Negative	3	68	Specificity (39.1)

ICG: indocyanine green; ^{68}Ga-PSMA: ^{68}Gallium prostate-specific membrane antigen; PET: positron emission tomography; CT: computed tomography; rLNs: recurrent lymph nodes

robotic was 108 min versus 150 min versus 150 min, and the median complication rates among ICG versus open versus robotic were 15.8% versus 42.7% versus 20.0%, indicating that the combination approach not only removes the rLNs identified by ^{68}Ga-PSMA ligand PET/CT but also targets more rLNs by ICG, avoiding unnecessary injury.[15,21]

Another important question in ICG-guided sLND is where and when to inject ICG during the sLND operation. There are four main methods of ICG injection in ICG-guided robotic RP + PLND surgery: percutaneous robot guided, transrectal ultrasound (TRUS) guided, cystoscope guided, and level IV injection. Techniques were selected based on relative ease of use, efficiency, ability to evenly diffuse dye into the lymph nodes, and avoidance of spillage. Percutaneous robotic-guided ICG injection proved to be superior to cystoscope or transrectal delivery.[11] As first surgery (RP + ePLND) can result in extensive adhesion in the pelvic region, which blocks regular lymphatic drainage relating to the lymphatic network of PCa.[22] Boscolo-Berto *et al.*[12] reviewed the literature and experimentally dissected a human corpse with prostatic lymphatic drainage. Based on their study, there is a pararectal lymphatic plexus relating to the prostate in the direction of the lateral sacral lymph nodes, finally arriving at the common iliac and aortic lymphatic plexuses. We took advantage of this anatomical route, and after injecting 5 mg of ICG into the space between the bladder and rectum before surgery, ICG reached the level of the common iliac artery and the renal artery within 60 min, triggering ICG fluorescent guidance on rLN dissection.[23] While managing rLNs at level II or above, we injected another 5 mg of ICG via intravenous to intensify the rLN-targeting ability of ICG using its oncological affinity.[23,24] There has been a lot of discussion about the dosage and timing of ICG injection in the literature. Most surgeons considered that administration of 2.5–5 mg per ICG approximately 30 min before surgery is ideal for achieving reliable intraoperative staining. The false-positive rate of ICG accumulation may be high with excess dose and may lead to false and unnecessary resections.[11,25]

Regarding the surgical skill required for ICG-guided sLND, special dissection of the inguinal artery and adjacent to the hypogastric artery was performed with a harmonic scalpel. Subsequently, a laparoscopic probe was used to intensively examine the lateral sacral and common iliac artery rLNs and to specifically dissect fluorescently stained rLNs. Finally, the lateral peritoneum was exposed, and ICG-guided sLND at levels III and IV was performed according to the manipulation at level II. Based on our experience and literature reports, if tumor invasion is found in the bilateral seminal vesicles or adjacent to the rectum, rLNs at level II, level III, or possibly level IV might be present.[26] ICG-guided laparoscopy should be used to examine these areas carefully during surgery. By combining intraoperative ICG fluorescence positivity with preoperative ^{68}Ga-PSMA ligand PET/CT data, we found that sLND can be performed faster, more accurately, and with a shorter operation time.

In addition, it is necessary to select appropriate patients with rLNs for sLND.[27] The European Association of Urology (EAU) prostate cancer guidelines revealed that the sLND management of rLNs has been studied by several retrospective analyses; however, the real efficacy of this salvage procedure and the impact on survival are still unproven.[28] Our initial experience of sLND patient selection is based on whether the seminal vesicles were invaded and the internal iliac artery area was dissected at first RP surgery, and ^{68}Ga-PSMA ligand PET/CT imaging revealed rLNs following BCR. If ^{68}Ga-PSMA ligand PET/CT indicates rLNs and patients with long life expectancy, sLND may be considered. ICG-guided sLND will remove the micro-metastases LN that cannot be detected by imaging studies. Literature reports have shown that preoperative factors that significantly correlate with the prognosis of patients who undergo sLND are ^{68}Ga-PSMA ligand PET/CT showing no extrapelvic rLNs and a preoperative PSA level <4 ng ml^{-1}. Postoperative predictive factors are a small number of positive rLNs after sLND, complete BR (PSA <0.2 ng ml^{-1}), and the exclusion of extrapelvic rLNs.[15,29] In this study, the number of suspicious rLNs per patient was 1.26, the number of removed ICG-stained LNs per patient was 7.63, and the number of pathological LNs, including 7 extrapelvic rLNs, was 2.21 per patient, which were attributed to the success of the combined approach. Of the 4 patients who did not achieve BR, 3 had extrapelvic rLNs, and all of these patients received adjunct therapy with a good response at the updated visit.

CONCLUSIONS

sLND, either by radiation or by minimally invasive surgery, is currently the major effective therapy for rLNs after RP. PET/CT- and MRI-directed sLND therapy for rLNs is a new updated strategy that can significantly delay PCa progression and potentially cure PCa recurrence. We integrated ^{68}Ga-PSMA ligand PET/CT and ICG fluorescence-guided sLND in 19 patients with rLNs, and the initial results demonstrated that this combined approach is effective in treating BCR patients who develop rLNs, and unnecessary complications can be avoided. Of note, the combined approach is specifically applicable to patients with extrapelvic rLNs. The ICG injection route for sLND and long-term survival warrant further validation.

AUTHOR CONTRIBUTIONS

TCL participated in the study design, surgery, acquisition of data, coordination and drafted the manuscript. YW participated in the surgery and follow-up. CTX, MZL, XPL, and WTH participated in the follow-up, and LYL and KL performed the statistical analyses. XQW and JMD participated in the study design and data analysis. XG conceived the study, participated in the study design, and edited the final manuscript for publication. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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