ORIGINAL PAPER

Relationship between prostate volume changes and treatment duration of neoadjuvant androgen deprivation during intensity-modulated radiation therapy for Japanese patients with prostate cancer

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ABSTRACT

The application of neoadjuvant androgen deprivation (NAD) in prostate cancer leads to a reduction in prostate volume, and the trends in volume reduction differ according to the treatment duration of NAD. A reduction in volume during external beam radiation therapy may lead to the exposure of normal tissues to an unexpected dose. In fact, prostate volume reductions have primarily been reported in European and American institutions. Although the prostate volume of Japanese patients is known to be small, the trends in prostate volume change during radiation therapy remain unclear. In the present study, we aimed to evaluate the changes in prostate volume of Japanese patients during intensity-modulated radiation therapy (IMRT) with NAD. Nineteen Japanese patients with prostate cancer underwent IMRT with NAD. Kilovoltage computed tomography (CT) images were obtained for treatment planning and verification of the treatment position for each treatment fraction. The patients were divided into 3 groups based on the duration of NAD, as follows: NAD < 3 months (short NAD: S-NAD), 3 months ≤ NAD < 6 months (middle NAD: M-NAD), and NAD ≥ 6 months (long NAD: L-NAD). The prostate volume reductions at the 36th treatment fraction, relative to the planning CT, were 7.8%, 2.0%, and 1.7% for the S-NAD, M-NAD, and L-NAD groups, respectively. Prostate volume shrunk greater in the S-NAD group than in the M-NAD and L-NAD groups; this finding was consistent with those of previous studies. The prostate volume changes in Japanese patients were smaller compared to those in European and American patients.

Key Words: prostate cancer, neoadjuvant androgen deprivation, IMRT, IGRT, Japanese patients

INTRODUCTION

Radiation therapy is one of the primary treatment methods for prostate cancer.[1, 2] Compared to radical prostatectomy, an advantage of radiation therapy is the perseveration of sexual and urinary

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functions.[3] Furthermore, given the recent developments of superior dose delivery techniques such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy, a highly conformal dose distribution and steep dose gradient can be achieved.[4, 5] Accordingly, dose escalation can be safely permitted without an increase in normal tissue toxicity.[6] Nevertheless, it is important to understand that high-precision treatment depends upon image guidance for the correction of patient setup errors.[4]

In head and neck radiation therapy, changes in target shape and volume during treatment can lead to the application of inadequate doses to target regions and excessive doses to normal tissue regions.[7, 8] Hence, replanning is generally performed during the course of head and neck treatment.[9] However, the change in prostate volume is not often considered in prostate cancer treatment in most institutions. Hence, in most cases, the initial treatment plan is employed until the end of the treatment, except for cases with large anatomical changes between the treatment planning computed tomography (CT) and the daily pretreatment localization CTs.

In cases of intermediate- and high-risk prostate cancer, some studies have indicated that the treatment results are improved if neoadjuvant androgen deprivation (NAD) is applied in addition to external beam radiation therapy.[10–12] In fact, several previous studies have shown that NAD causes a 25–50% reduction in prostate volume, regardless of the application of radiation therapy.[13–19] Moreover, other studies have indicated a prostate volume reduction of 15% between the initial CT simulation and the end of radiation treatment, based on the presupposition that the initial CT scan was performed within 3 months of NAD.[20, 21] Lilleby *et al.* noted that the reduction was greater during the 3 months after the initiation of NAD than after 3 months.[18] Nevertheless, in previous studies, no consensus was reached whether radiation therapy alone decreased prostate volume.[20, 22–24]

The prostate volumes are known to differ depending on the race.[25] However, most of the previous studies on prostate volume changes are limited to European and American institutions, including those in the United States,[13–16] United Kingdom,[17] Norway,[18] the Netherlands,[19] Italy,[20] and Turkey.[21] Although the prostate volume is known to be small in Asians as compared to Europeans, Americans, and Australians,[26, 27] the characteristics of the changes in prostate volume during radiation therapy with NAD in Japanese patients have not been clarified.

In the present study, we aimed to evaluate the prostate volume changes during IMRT in Japanese patients and to statistically assess the relationship between prostate volume changes and duration of NAD.

MATERIALS AND METHODS

Patient characteristics

In this study, we retrospectively evaluated the data of 19 Japanese patients who underwent IMRT with NAD for prostate cancer at our institution from October 2008 to February 2010. This study was approved by the Institutional Review Board of Nagoya University Hospital, and all patients provided written informed consent. All patients had biopsy-proven prostate carcinoma (T1c–T4), without any distant metastases (M0); the nodal status was N0 or N1. The median patient age was 70 years (range, 61–78 years).

To allow comparison with previous European and American studies,[20, 21] we divided patients into three groups according to the duration of NAD as in those studies: NAD < 3 months (short NAD: S-NAD), 3 months ≤ NAD < 6 months (middle NAD: M-NAD), and NAD ≥ 6 months (long NAD: L-NAD). The duration of NAD was defined as the interval between NAD initiation and the time of planning CT; the median duration from the planning CT to the first treatment

day was 8 days (range, 4–16 days).

All patients had received maximum androgen blockade (MAB) with luteinizing hormone-releasing hormone agonist and anti-androgen. Patients who discontinued NAD owing to drug-induced hepatitis during the treatment were excluded from the analysis.

Prescription methods

IMRT was performed using a treatment planning system (TPS; Eclipse ver. 8.9, Varian Medical Systems, USA) and a linear accelerator (CLINAC 2100CD, Varian Medical Systems, USA). A total prescription dose of 74 Gy (2 Gy per fraction; Monday to Friday) was delivered using 10 MV photon beams. All treatment fractions were conducted using image-guided radiation therapy (IGRT) to correct positional errors for target and critical organs. The median duration of the IMRT (from the start to the end of treatment) was 55 days (range, 50–61 days).

Acquisition of CT images and measurement of prostate volume

All patients underwent CT scans by using the CT-on-rails system (GE HiSpeed NX/i, General Electric, USA) that was installed in the treatment room. Kilovoltage CT images were obtained for treatment planning and verification of the pretreatment position, referred to as IGRT, for the 1st, 6th, 11th, 16th, 21st, 26th, 31st, and 36th treatment fraction. The CT scans were performed with the following parameters: field of view, 500 mm; slice thickness, 2 mm; and X-ray tube voltage, 120 kV. For obtaining treatment planning CT scans, we used an auto-mA technique to control X-ray tube current. In contrast, with regard to pretreatment position verification, we set the X-ray tube current at approximately 100 mA to ensure that the patient is exposed to a low dose.

A radiation oncologist, who was blinded to the NAD duration and CT timing, delineated the prostate in the obtained CT images on the TPS. The prostate volumes were measured using a software tool on the TPS. The intra-observer variability in the delineating process was evaluated by repeated delineation in 9 patients who were randomly chosen.

Statistical analysis

Statistical analysis was performed with SPSS (IBM SPSS Statistics 22, IBM, USA). The average prostate volume at planning CT was assessed using one-way analysis of variance (ANOVA) to compare the differences among the groups based on the NAD duration. Friedman's test was used to compare prostate volume changes in each group during IMRT. The null hypothesis stated that prostate volume would not change during treatment. A significance level of 0.05 was used to reject the null hypothesis.

RESULTS

Patient characteristics are summarized in Table 1. A total of 5, 8, and 6 patients were assigned to the S-NAD, M-NAD and L-NAD groups, respectively. Before the experiments, we evaluated the intra-observer variability in the delineation process of prostate volume, and observed that the median percentage variation in prostate volume was approximately 4.0%.

The relationship between the NAD duration and the prostate volume at the planning CT is illustrated in Figure 1. A logarithmic curve was applied ($R^2 = 0.30$). The trends in prostate volume over the course of IMRT in each group have been shown in Figure 2a–c. In the S-NAD group, the median absolute and percentage variation in prostate volume over the course of treatment, compared to those at the planning CT, were –0.8 cm^3 (range, –6.1 to 0.7 cm^3) and –3.4% (range, –20.0% to 3.2%), respectively. Similarly, in the M-NAD and L-NAD groups, the

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median absolute variations were –0.3 cm³ (range, –0.8 to 0.6 cm³) and –0.3 cm³ (range, –1.0 to 0.3 cm³), and the median percentage variations were –1.4% (range, –4.7% to 3.3%) and –2.0% (range, –9.2% to 2.7%), respectively. A temporary increase in prostate volume (3.5 cm³) was

Table 1 Patient characteristics

Parameter	Stratification	S-NAD[a] group	M-NAD[b] group	L-NAD[c] group
Tumor stage	T1	2	5	
	T2	3	1	1
	T3		2	4
	T4			1
Gleason score	6	2	1	
	7	3	6	3
	8		1	1
	9			2
PSA[d] (ng/ml)	Median (range)	10.9 (4.6–17)	12.1 (4.3–26)	53.6 (19–290)

a) S-NAD = short-term neoadjuvant androgen deprivation, b) M-NAD = middle-term neoadjuvant androgen deprivation, c) L-NAD = long-term neoadjuvant androgen deprivation, d) PSA = prostate-specific antigen.
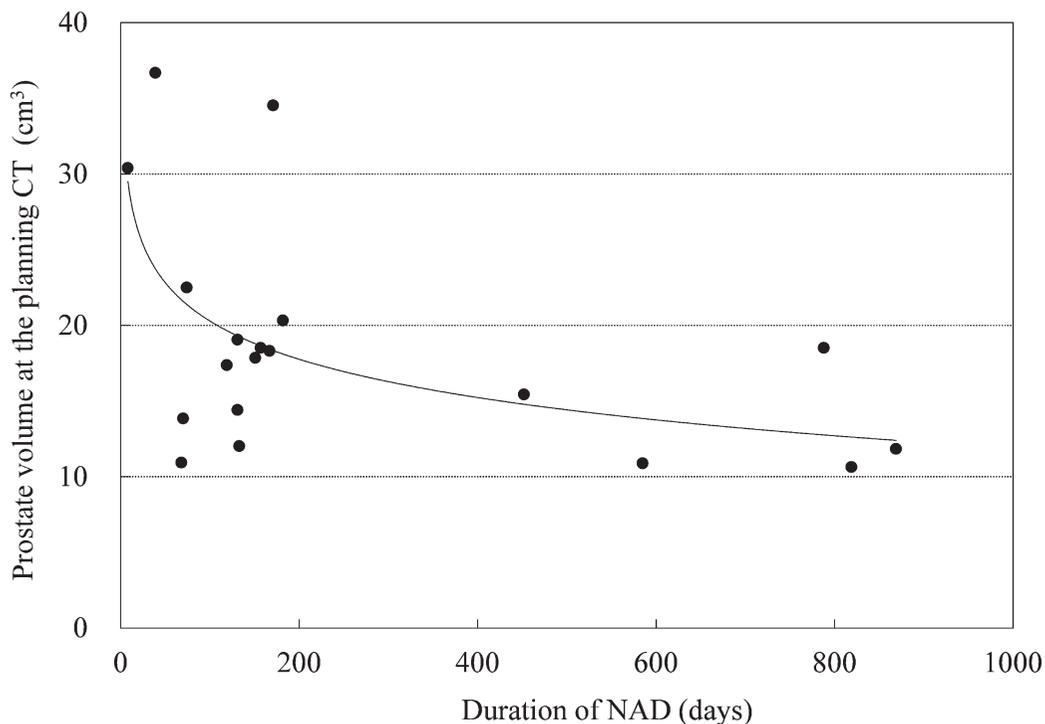

Fig. 1 Relationship between the duration of NAD and prostate volume at the planning CT. Abbreviations: NAD = neoadjuvant androgen deprivation; CT = computed tomography.
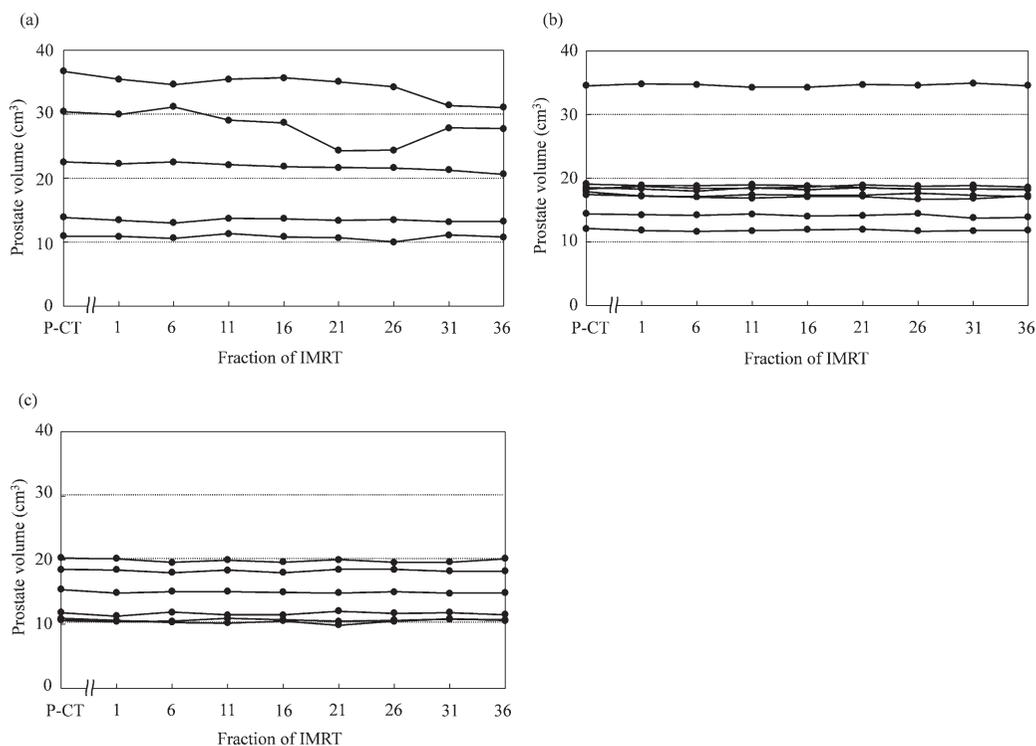
(a)

(b)

(c)

Fig. 2 Trends in prostate volume over the course of intensity-modulated radiation therapy (IMRT) in each group. (a) short-term neoadjuvant androgen deprivation (S-NAD) group, (b) middle-term neoadjuvant androgen deprivation (M-NAD) group, (c) and long-term neoadjuvant androgen deprivation (L-NAD) group. Abbreviation: P-CT = planning computed tomography.

Table 2 Prostate volume changes over the course of IMRT.

Group	Treatment planning	Prostate volume (cm^3)							
		Treatment fraction							
		1st	6th	11th	16th	21st	26th	31st	36th
S-NAD [a]	22.9 ± 10.9	22.4 ± 10.5	22.4 ± 10.7	22.3 ± 10.2	22.1 ± 10.3	21.0 ± 9.7	20.7 ± 9.6	20.9 ± 8.9	20.7 ± 8.8
M-NAD [b]	19.0 ± 6.7	18.9 ± 6.9	18.7 ± 6.9	18.8 ± 6.7	18.8 ± 6.7	18.9 ± 6.8	18.8 ± 6.8	18.7 ± 7.0	18.7 ± 6.8
L-NAD [c]	14.6 ± 4.1	14.3 ± 4.2	14.2 ± 4.0	14.4 ± 4.2	14.2 ± 4.0	14.3 ± 4.3	14.3 ± 4.0	14.4 ± 3.9	14.4 ± 4.1

a) S-NAD = short-term neoadjuvant androgen deprivation, b) M-NAD = middle-term neoadjuvant androgen deprivation, c) L-NAD = long-term neoadjuvant androgen deprivation.

observed in one patient in the S-NAD group between the 26th and 31st treatment fraction points.

Table 2 shows the average prostate volume and standard deviation for each group at planning CT and at each radiation treatment time point. The changes in volume relative to that at planning CT were plotted on Figure 3; the error bar with standard deviation was excluded in the graph to avoid overlaps. The average prostate volumes at planning CT were 22.9 cm^3 (range, 10.9 to 36.7 cm^3), 19.0 cm^3 (range, 12.0 to 34.5 cm^3), and 14.6 cm^3 (range, 10.6 to 20.3 cm^3) in the S-NAD, M-NAD, and L-NAD groups, respectively. ANOVA showed that there was no significant difference between any of the groups based on the duration of NAD. Compared to
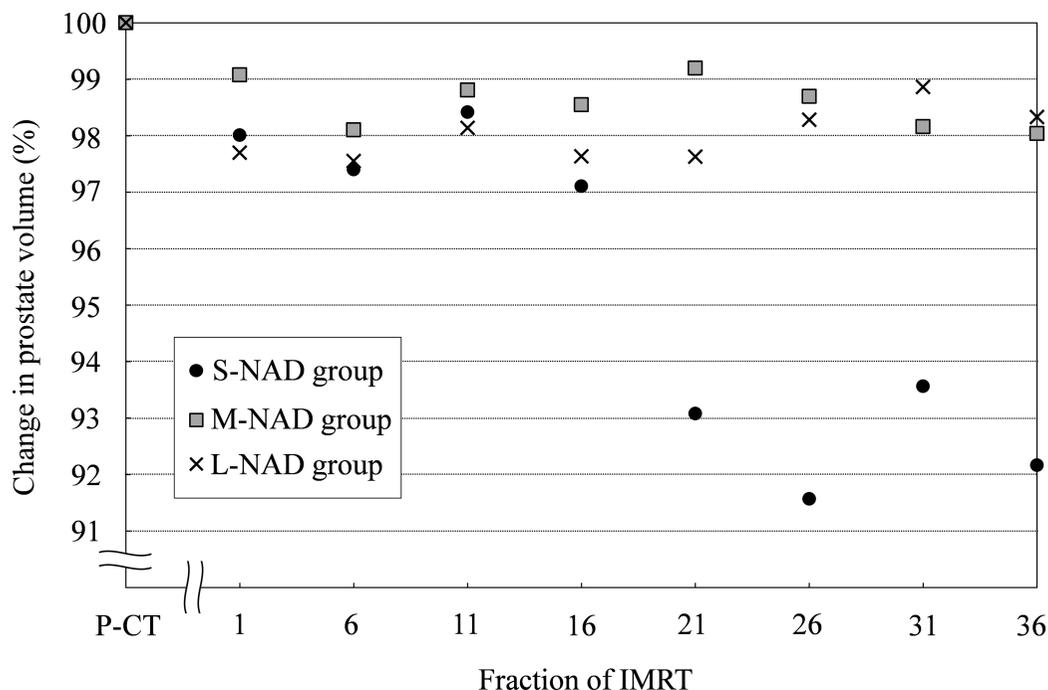
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Fig. 3 Averaged percentage change in prostate volume in each group over the course of intensity-modulated radiation therapy (IMRT). The error bars with standard deviation were abbreviated to avoid overlap among the groups. Abbreviations: S-NAD = short-term neoadjuvant androgen deprivation, M-NAD = middle-term neoadjuvant androgen deprivation, L-NAD = long-term neoadjuvant androgen deprivation, P-CT = planning computed tomography.

that at planning CT, the percentage reductions in prostate volume at the 36th treatment fraction point were 7.8% (2.2 cm³), 2.0% (0.3 cm³), and 1.7% (0.2 cm³) in the S-NAD, M-NAD, L-NAD groups, respectively. Friedman's test, as a nonparametric ANOVA, indicated significant differences in prostate volume during the course of treatment in the S-NAD and M-NAD groups (S-NAD group: $p = 0.004$, M-NAD group: $p = 0.049$). In contrast, no significant difference in prostate volume was observed during the radiation treatment in the L-NAD group ($p = 0.298$).

DISCUSSION

With regard to the intra-observer variability in the process of delineating the prostate, the median percentage variation in prostate volume was 4.0%. A previous study has indicated that the variability in delineating the prostate and seminal vesicles ranged from 1.5% to 9% (average, 5%).[28] Thus, the intra-observer variability in present study was similar to that reported in the previous study, and accordingly, we believe that such a value was suitable.

Sanguineti *et al.* reported that the short-term NAD group (<3 months) showed a prostate volume reduction of 14.2% over the course of three-dimensional conformal radiation therapy (3DCRT) for prostate cancer.[20] Similarly, Onal *et al.* indicated that the prostate volume reduced by 14.1% in the short-term NAD group over the course of 3DCRT.[21] In the present study, the average percentage reduction in prostate volume was 7.8% (2.2 cm³) in the S-NAD group. Thus,

the change in prostate volume during IMRT in Japanese patients, as noted in the present study, is small as compared to that reported in other studies.

In the M-NAD and L-NAD groups, the average percentages of prostate volume reduction over the course of IMRT were 2.0% (0.3 cm^3) and 1.7% (0.2 cm^3), respectively. However, a significant difference in prostate volume change was only observed during the course of IMRT in the M-NAD group and not the L-NAD group, even though the reduction level was the same. Sanguineti *et al.* reported that the percentage of prostate volume reduction was 1.1% (0.7 cm^3) in the group of patients receiving NAD for 3–6 months[20]; the authors also indicated that the reduction in this group was significantly smaller as compared to that in the short-term NAD group. The results of our study are consistent with those of Sanguineti *et al.*

The average prostate volume at the planning CT was 45.2 cm^3 and 60.3 cm^3 in the studies of Sanguineti *et al.* and Onal *et al.*, respectively.[20, 21] In contrast, the average prostate volume in our study was 22.9 cm^3 in the S-NAD group. Langenhuijsen *et al.* evaluated the reduction in prostate volume following MAB treatment while considering the prostate volume before treatment.[19] Based on their findings, the large prostate group (>60 cc) showed a greater reduction as compared to the small prostate group (≤60 cc). Hence, we believe that the reduction in prostate volume induced by NAD was small for Japanese patients with a smaller prostate, even in the S-NAD group. This is the first report on prostate volume reduction during radiation therapy with NAD among Asians.

A temporary increase in prostate volume was observed in one patient in the S-NAD group. Such a finding may be associated with the intra-observer variability of prostate delineation[28, 29] or side-effects caused by inflammation due to radiation therapy.[30]

A previous study indicated that the reduction in prostate volume with NAD treatment influenced the exposure of the surrounding normal tissue to high radiation doses in 3DCRT.[15] Another study indicated that an additional treatment planning session during the course of 3DCRT may be beneficial for preventing unnecessary dose-limiting organ exposure, as a result of prostate volume reduction.[21] Sanguineti *et al.* also suggested that planning CT scans should be obtained at 2–3-month intervals after the initiation of NAD, as a large change in prostate volume immediately after NAD may lead to an unexpected increase in the percentage of the rectal wall exposed to intermediate doses.[20] However, the percentages of prostate volume reduction in those reports were greater than those observed in the present study. In Japanese patients with smaller prostates, the reduction in prostate volume may have only a small effect on the dose distributions as compared to that mentioned in other reports. The effect of such a reduction in volume on the dose distribution will serve as a topic of future investigations.

Our study has several limitations. First, as the sample size was small, the statistical analysis methods that could be used were limited. Although the study participants had varying tumor stage, prostate-specific antigen levels, and Gleason scores, Langenhuijsen *et al.* reported that these factors are not associated with prostate volume reduction.[19] Moreover, the small patient numbers might have caused major study bias and intergroup disproportion in the architectures of the prostatic gland, causing difference in the sensitivity of NAD. In addition, the vast majority of patients with low-risk prostate cancer that did not require NAD were treated by surgery and interstitial brachytherapy in our institution. Hence, most of the patients who received external beam radiation therapy and NAD belonged to the intermediate- or high-risk groups. This protocol conforms to the National Comprehensive Cancer Network guideline.[31] Therefore, we could not acquire the data of control patients who received external beam radiation therapy with no NAD. Second, we could not acquire CT images at the initiation of NAD. Therefore, any difference in the prostate volume among the three groups at NAD initiation was not detected and we could not obtain prostate volume reduction from NAD initiation to the planning CT. Third, the delineation

in present study was performed by a single radiation oncologist. Hence, we evaluated only intra-observer variability, but not inter-observer variability. Nakamura *et al.* reported that the prostate volume definition varies widely (23.8–98.3 cm³) among Japanese radiation oncologists.[32] Hence, this study could potentially be influenced by the delineation process of the oncologist. Finally, the treatment planning CT images were acquired by using an auto-mA technique. In contrast, the daily pretreatment localization CT images were acquired by using an mA value that was as low as possible. Such a discrepancy in the CT parameters may lead to differences in image quality, and could consequently affect the delineation of the prostate.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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