A treatment planning study comparing tomotherapy, volumetric modulated arc therapy, Sliding Window and proton therapy for low-risk prostate carcinoma

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Abstract

Background: Comparing radiation treatment plans to ascertain the optimal intensity-modulated radiation technique for low-risk prostate cancer.

Methods: Treatment plans for 20 randomly selected patients were generated using the same dose objectives. A dosimetric comparison was performed between various intensity-modulated techniques, including protons. All treatment plans provided conventional treatment with 79.2Gy. Dosimetric indices for the target volume and organs at risk (OAR), including homogeneity index and four conformity indices were analyzed.

Results: No statistically significant differences between techniques were observed for homogeneity values. Dose distributions showed significant differences at low-to-medium doses. At doses above 50Gy all techniques revealed a steep dose gradient outside the planning target volume (PTV). Protons demonstrated superior rectum sparing at low-to-higher doses (V10-V70, P < .05) and bladder sparing at low-to-medium doses (V10–V30, P < .05). Helical tomotherapy (HT) provided superior rectum sparing compared to Sliding Window (SW) and Rapid Arc (RA) (V10–V70, P < .05). SW displayed superior bladder sparing compared to HT and RA (V10–V50, P < .05). Protons generated significantly higher femoral heads exposure and HT had superior sparing of those.

Conclusion: All techniques are able to provide a homogeneous and highly conformal dose distribution. Protons demonstrated superior sparing of the rectum and bladder at a wide dose spectrum. The radiation technique itself as well as treatment planning algorithms result in different OAR sparing between HT, SW and RA, with superior rectum sparing by HT and superior bladder sparing by SW. Radiation plans can be further optimized by individual modification of dose objectives dependent on treatment plan strategy.

Keywords: Prostate, Helical tomotherapy, Volumetric Modulated Arc Therapy, Sliding Window, Proton treatment, Dosimetric indices
Background
Different radiotherapy techniques and fractionation regimes are currently used for the treatment of localized prostate cancer. Conventionally fractionated intensity modulated radiotherapy (IMRT) is the most frequently applied treatment modality for prostate cancer [1–4]. IMRT can be performed either by static (“step-and-shoot” (SS), Sliding Window (SW)) or rotational approaches (helical tomotherapy (HT) or Volumetric Modulated Arc Therapy (Rapid Arc, RA). Intensity modulated proton therapy (IMPT) is also a well-known treatment modality for localized prostate cancer and is more likely to spare the organs at risk (OAR) due to steep dose gradients outside of the Bragg peak [5–9]. All of these techniques are capable of achieving treatment plans with high conformity, reducing the dose delivered to the surrounding healthy tissue and, consequently, treatment-related toxicities, especially the risk of secondary malignancy. To date there is no consensus on the ”optimal overall” treatment mode [10, 11]. In this study, a statistical analysis of dosimetric parameters between HT, SW, RA and IMPT providing conventionally fractionated radiotherapy was evaluated. Similar dose objectives for PTV and OAR were used in the radiation planning for all techniques. The dosimetric indices were assessed according to the criteria of ICRU Report 83 [12].

Material and methods
Treatment plans were generated for 20 randomly selected patients with low-risk prostate cancer who received definitive HT. The databases of thin-cut 3 mm CT scans were fused with those of 1.5 T MRI scans. The target was made using a scoring system that compared the clinical target volume (CTV) and planning target volume for femoral heads (Table 1) [13]. The following dosimetric indices were assessed: V10, V30, V50, V70 (defined as the percentage of organ volume receiving given radiation dose), Dmax, Dmean, D1cc for rectum and bladder, as well as V50 and D1ccm for femoral heads. A comparison of each patient was made using a scoring system that compared D2 %, D98 % and V95 values. The indices for the 20 patients were averaged to assess the advantages and

| Organ                  | Dose | Volume (in % or in ccm as absolute volume for femoral heads) |
|------------------------|------|-------------------------------------------------------------|
| Rectum [14]            | 10Gy | -a                                                          |
|                        | 30Gy | ≤60 %                                                       |
|                        | 50Gy | ≤50 %                                                       |
|                        | 60Gy | ≤35 %                                                       |
|                        | 65Gy | ≤25 %                                                       |
|                        | 70Gy | ≤20 %                                                       |
|                        | 75Gy | ≤15 %                                                       |
| Urinary bladder [15]   | 10Gy | -a                                                          |
|                        | 30Gy | ≤a                                                          |
|                        | 50Gy | ≤60 %                                                       |
|                        | 65Gy | ≤50 %                                                       |
|                        | 70Gy | ≤35 %                                                       |
|                        | 75Gy | ≤25 %                                                       |
| Femoral heads [13]     | 50Gy | ≤5 %                                                        |
|                        | 40Gy | ≤1ccm                                                       |

Abbreviations: a-the dose-volume limit is not defined in the QUANTEC reports
disadvantages in PTV coverage and OAR sparing of the various radiation techniques.

Based on the recommendations of the ICRU 83 reports and several clinical studies, specific conformal indices were used to describe the dose distribution [12, 16]. Thus, the heterogeneity index (HI) and four conformity indices (CI; these include the ICRU conformity index (CICRU), coverage index (CA), coverage index COV (CACOV), and conformation number (CN)) were calculated (Table 2). These indices refer to the PTV volume, partial PTV volume covered by 95% of prescribed isodose (PTVp), and volume treated by 95% of prescribed isodose (TVp) [16]. The HI characterizes dose heterogeneity inside the PTV and is calculated using the near maximum (D2%), near minimum (D98%), and the mean dose (Dmean): D2%–D98% / Dmean (optimal at 0) [12]. The CN provides complementary information about the irradiation of PTV and healthy tissues, and is calculated as PTVp/PTV x PTVp/TVp; a value of 1 indicates optimal result [17]. The CICRU was described in the ICRU 62 report and is defined as the quotient TVp/PTV (optimal at 1) [18]. The CA quantifies the radiation exposure of the surrounding healthy tissue and is defined as TVp/PTV (optimal at 0) [19]. The CACOV describes the coverage of the target volume by the prescribed isodose and is calculated as PTVp/PTV; ideal PTV coverage is indicated by a value of 1 [20].

A comparison of monitor units and treatment times could not be performed because the current implementation of monitor unit calculation in Eclipse Proton Planning is based on theoretical ideas and has not yet been verified by measurements due to a lack of experimental data (Proton Algorithm Reference Guide, Eclipse™, August 2013, Varian Medical Systems, Inc., Palo Alto).

In the statistical analyses, a non-parametric Wilcoxon signed-rank test was used to assess the differences between two techniques. The threshold for statistical significance was defined as P < .05. All statistical analyses were performed using the SPSS software (IBM SPSS Statistics 22.0).

Treatment plans were created separately by three physicists.

Results

The dosimetric values for PTV and OAR were assessed from the patient-averaged dose-volume histogram (DVH) and are presented in detail in Tables 2 and 3. The D98% and D2% did not significantly vary between the techniques. However, the HT showed inferior dose distribution within the PTV, with the largest interval between D98% and D2% values compared to SW, RA, and IMPT. The IMPT provided significantly superior homogeneity values compared to HT, SW, and RA (Table 2). Comparison of the four CI, which describe the dose distribution within the PTV and the healthy tissue, demonstrated HT showed a tendency toward inferior conformation (Table 2). A paired comparison analysis showed significantly improved CN for RA compared to HT (P = .001), SW (P = .005), and IMPT (P = .001). The IMPT demonstrated superior CN compared to HT (P = .001). The CICRU value of 1.20 obtained by HT reflects a larger coverage volume by the treatment dose than the PTV itself. For RA was found significantly superior CICRU in contrast to HT and IMPT (P = .001), and SW showed superior CICRU compared to HT (P = .001) and IMPT (P = .002). The CA revealed that RA was significantly superior to all other techniques, and that SW was superior to HT and IMPT (P < .05). IMPT showed significantly better CACOV values than other modalities (P < .05) (Table 2).

A greater difference in dose distribution between the techniques was found at the low-to-medium dose ranges compared to the higher doses (Figs. 1 and 2). The patient-averaged DVH revealed IMPT had statistically superior rectum sparing at low-to-higher doses compared to all other techniques (V10–V70, P < .05), with the exception of HT at V70 (Fig. 3, Table 3). Significantly lower rectum exposure was provided by HT at

| Table 2 | Averaged dosimetric values for PTV and conformal indexes |
|---------|---------------------------------------------------------|
|         | HT Mean ± SD | SW Mean ± SD | RA Mean ± SD | Protons Mean ± SD | Pairs with statistically significant differences (P = . < .05)/Technique with best result (mean values) |
| PTV     |              |              |              |                  |                                                       |
| PTV coverage (%) | 98.2 ± 1.4 | 98.6 ± 0.8 | 98.3 ± 0.8 | 99.6 ± 0.2 | Pr > HT, Pr > SW, Pr > RA / Pr > SW > RA > HT |
| D2 (%)  | 103.3 ± 0.5 | 102.5 ± 0.4 | 102.4 ± 0.3 | 102.5 ± 0.4 | RA > HT, SW > HT, Pr > HT / RA > SW = Pr > HT |
| D98% (%)| 95.3 ± 1.9 | 95.5 ± 0.6 | 95.3 ± 0.6 | 96.7 ± 0.4 | Pr > HT, Pr > SW, Pr > RA / Pr > SW > RA > HT |
| Homogeneity index, HI | 0.08 ± 0.02 | 0.07 ± 0.01 | 0.07 ± 0.01 | 0.06 ± 0.01 | Pr > HT, Pr > SW, Pr > RA / Pr > SW = RA > HT |
| Conformation number, CN | 0.81 ± 0.04 | 0.89 ± 0.02 | 0.91 ± 0.03 | 0.88 ± 0.02 | SW > HT, RA > HT, RA > SW, RA > Pr, Pr > HT / RA > SW > Pr > HT |
| ICRU Conformity index, CICRU | 1.20 ± 0.1 | 1.09 ± 0.03 | 1.07 ± 0.04 | 1.13 ± 0.03 | SW > HT, SW > Pr, RA > HT, RA > Pr, Pr > HT / RA > SW > Pr > HT |
| Coverage index, CA | 0.22 ± 0.1 | 0.11 ± 0.03 | 0.08 ± 0.03 | 0.13 ± 0.03 | RA > HT, RA > SW, RA > Pr, Pr > HT / RA > SW > Pr > HT |
| Coverage index COV, CACOV | 0.98 ± 0.01 | 0.99 ± 0.01 | 0.98 ± 0.01 | 1.00 ± 0.00 | Pr > HT, Pr > SW, Pr > RA / Pr > SW > RA = HT |

Abbreviations: HT helical tomotherapy; SW Sliding Window; RA Rapid Arc; Pr Protons; SD standard deviation; > dosimetric superiority
Table 3: Averaged dosimetric values for organs at risk

|                | HT Mean ± SD | SW Mean ± SD | RA Mean ± SD | Protons Mean ± SD | Pairs with statistically significant differences (P = .< 05)/Technique with best result (mean values) |
|----------------|--------------|--------------|--------------|-------------------|------------------------------------------------------------------------------------------------|
| Urinary Bladder|              |              |              |                   |                                                                                                 |
| V10 (%)        | 42.0 ± 23.8  | 39.3 ± 23.3  | 46.8 ± 23.2  | 30.2 ± 18.5       | Pr > HT, Pr > SW, Pr > RA, SW > HT, SW > RA / Pr > SW > HT > RA                                  |
| V30 (%)        | 26.2 ± 18.6  | 23.5 ± 16.4  | 27.0 ± 19.1  | 21.2 ± 14.7       | Pr > HT, Pr > SW, Pr > RA, SW > HT, SW > RA / Pr > SW > HT > RA                                  |
| V50 (%)        | 16.8 ± 12.5  | 15.6 ± 11.6  | 17.0 ± 13.3  | 15.3 ± 11.5       | SW > HT, SW > RA, Pr > RA, Pr > HT / Pr > SW > HT > RA                                      |
| V70 (%)        | 6.0 ± 4.9    | 5.4 ± 4.8    | 6.4 ± 4.8    | 5.3 ± 4.7         | Pr > SW, Pr > RA, Pr > HT / Pr > SW > HT > RA                                              |
| Dmean (Gy)     | 17.4 ± 10.1  | 15.8 ± 9.6   | 17.9 ± 10.1  | 13.8 ± 9.1        | Pr > HT, Pr > SW, Pr > RA, SW > HT, SW > RA / Pr > SW > HT > RA                               |
| Dmax (Gy)      | 82.5 ± 2.8   | 80.0 ± 2.8   | 80.9 ± 3.1   | 80.9 ± 1.7        | SW > HT, RA > HT, Pr > HT / SW > Pr > RA > HT                                               |
| D1ccm (Gy)     | 76.3 ± 8.2   | 76.2 ± 6.3   | 76.3 ± 8.1   | 76.2 ± 6.0        | SW > HT, Pr > HT / Pr > SW > RA > HT                                                      |
| Rectum         |              |              |              |                   |                                                                                                 |
| V10 (%)        | 59.1 ± 17.9  | 62.7 ± 16.6  | 69.0 ± 18.7  | 24.6 ± 9.2        | Pr > HT, Pr > SW, Pr > RA, HT > SW, HT > RA, SW > RA / Pr > HT > SW > RA                    |
| V30 (%)        | 24.8 ± 7.6   | 32.8 ± 5.7   | 41.7 ± 13.3  | 15.7 ± 5.8        | Pr > HT, Pr > SW, Pr > RA, HT > SW, HT > RA, SW > RA / Pr > HT > SW > RA                    |
| V50 (%)        | 12.8 ± 4.0   | 17.3 ± 2.5   | 23.5 ± 7.5   | 9.3 ± 3.8         | Pr > HT, Pr > SW, Pr > RA, HT > SW, HT > RA, SW > RA / Pr > HT > SW > RA                    |
| V70 (%)        | 1.1 ± 0.7    | 1.5 ± 0.8    | 3.4 ± 1.8    | 1.0 ± 0.8         | Pr > RA, Pr > SW, HT > SW, HT > RA, SW > RA / Pr > HT > SW > RA                            |
| Dmean (Gy)     | 17.3 ± 3.9   | 20.3 ± 3.4   | 24.5 ± 5.3   | 9.0 ± 3.4         | Pr > HT, Pr > SW, Pr > RA, HT > SW, HT > RA, SW > RA / Pr > HT > SW > RA                    |
| Dmax (Gy)      | 78.3 ± 1.8   | 75.9 ± 1.2   | 77.3 ± 1.5   | 76.4 ± 2.2        | Pr > HT, Pr > RA, SW > HT, SW > RA, SW > Pr / SW > Pr > RA / HT > HT                       |
| D1ccm (Gy)     | 67.5 ± 4.1   | 68.9 ± 2.4   | 71.5 ± 2.5   | 65.9 ± 4.2        | HT > SW, HT > RA, SW > RA, Pr > HT, Pr > SW, Pr > RA / Pr > HT > SW > RA                   |
| Femoral head, right | 18.0 ± 2.9   | 32.0 ± 6.2   | 28.1 ± 5.3   | 35.2 ± 3.9        | HT > SW, HT > RA, HT > Pr, RA > SW, RA > Pr / HT > RA > SW > Pr                        |
| Femoral head, left | 18.1 ± 2.9   | 31.9 ± 5.1   | 26.6 ± 5.0   | 35.5 ± 2.5        | HT > SW, HT > RA, HT > Pr, RA > Pr, RA > SW / HT > RA > SW > Pr                         |

Abbreviations: HT helical tomotherapy; SW Sliding Window; RA Rapid Arc; Pr Protons; PTV planning target volume; SD standard deviation; Dx (Gy) dose (Gy) absorbed by certain percentage (%) or absolute volume (ccm) of the contoured structure; Vx percentage of organ volume exposed to certain radiation dose; > dosimetric superiority

Fig. 1: Treatment plans for tomotherapy (HT), Sliding Window (SW), Rapid Arc (RA), and protons (IMPT). Representative dose distribution with V10 (yellow), V30 (green), V50 (blue), and V70 (orange) isodoses. The prostate is delineated in red, rectum in brown, urinary bladder in yellow.
compared to SW and RA at low-to-higher doses (V10–V70, P < .05) (Fig. 3, Table 3). A statistical difference in Dmean values was found in all tested pairs, with lower absolute values for protons and a maximum of absolute values for RA. Lowest Dmax value was achieved by SW, and D1ccm values revealed the lowest radiation exposure and RA produced the greatest coverage (Table 3).

The whole urinary bladder also experienced the best shielding using IMPT at lower-to-higher doses (V10–V70, P < .05) (Fig. 3, Table 3). SW demonstrated significantly lower bladder exposure in a wide dose spectrum than HT and RA (V10–V50, P < .05) (Fig. 3, Table 3). Dmean values were significantly different between all tested pairs, except for HT/RA, with lower absolute values for IMPT and higher absolute values for RA. Significantly lower Dmax values were gained for RA. D1ccm values revealed nearly the same bladder exposure for all techniques (Table 3).

D1ccm values indicated femoral heads experienced the highest exposure from protons and superior sparing from HT (Table 3). V50 revealed femoral heads received very small coverage volume (<1 %) for all techniques.

Discussion
This study performed a statistical dosimetric comparison between different IMRT techniques using conventional fractionation to treat low-risk prostate cancer. IMRT was found to provide a conformal dose distribution, allowing dose escalation in the prostate and inferior OAR toxicity compared to 3-D conformal radiotherapy (3-D CRT) [21–24]. A dosimetric comparison between different IMRT techniques has already been performed in several series of studies [1–4, 25–32]. Tsai et al. found that HT provided superior conformity and OAR sparing compared to VMAT and static IMRT [2]. Hermann et al. demonstrated comparable homogeneity, CN values and OAR dosimetric values between VMAT, SS and SW [26]. The dosimetric comparison between static and rotational IMRT in this trial revealed superior rectum sparing by HT and superior bladder sparing by SW at low-to-higher doses (Table 3, Fig. 3). However, no accentuated priority for rectum sparing in HT plans or for bladder sparing in SW plans was made by the plans’ assessment. In our opinion, the Tomo Planning System is more sensitive to dose constraints than the Eclipse planning system. This increased sensitivity can result in greater rectum sparing in HT plans while using the same dose objectives in the Eclipse planning system for SW and RA. In addition, the high sensitivity of the Tomo Planning System can result in larger SD values for homogeneity and the conformity indices in HT plans compared to other IMRT techniques, as shown in Table 2. A higher radiation exposure for OAR at low doses was found for RA compared to HT and SW. Despite the use of two incomplete arcs intended to protect the rectum, RA demonstrated greater rectum exposure in a wide dose spectrum (Table 3). However, most of the conformity values were statistically superior for RA compared to SW and HT. Thus, assuming same dose objectives for treatment planning, differences in dose distribution within PTV and OAR can be explained both by impact of radiation technique itself and by use of different dose calculation algorithms.

Superior sparing of OAR by protons is expected due to extremely steep dose gradients outside of the Bragg peak. As demonstrated by Vargas et al. for localized
prostate carcinoma, protons provided improved rectum sparing at 10–80Gy and bladder sparing at 10–35Gy compared to the IMRT techniques [5]. On the contrary, a comparable sparing of rectum, bladder and femoral heads for IMPT and VMAT techniques was observed by Georg et al. [6]. In agreement with the results found by Schwarz et al., IMPT revealed similar homogeneity values and significantly inferior conformity values compared to HT. Rectum exposure for both techniques above 65Gy was equivalent, and superior sparing of bladder and penile bulb was obtained for protons in a wide dose spectrum [7]. A recent SEER-Medicare based study observed a lower rate of gastrointestinal toxicity by IMRT-treated patients compared to proton-treated patients, and similar outcomes were observed for urinary toxicity and erectile dysfunction [9]. Based on normal tissue complication probability (NTCP) estimates, Schwarz et al. demonstrated very similar probabilities of late gastrointestinal complications for HT and IMPT [7]. Thus, the current data do not permit a definitive conclusion about the dosimetric superiority and therapy tolerance of protons compared to IMRT. In this study, IMPT showed an improved homogeneity value compared to the other techniques, and lower conformity values compared to SW and RA (Table 2), although the planning software did not allow for a robust optimization of the proton therapy. In accordance with the findings of Vargas et al., the protons demonstrated statistically superior rectum and bladder sparing at low-to-higher doses (Table 3, Fig. 3). In the case of highly curative low-risk prostate carcinoma, it is critical both to perform homogeneous prostate coverage in order to achieve a long-term local tumor control, and to minimize the risk of chronic toxicities and secondary malignances. The steep dose gradient to the rectum and bladder, even at the lowest doses, leads to the assumption of decreased risk of secondary malignancy after proton treatment. However, the clinical relevance of the higher exposure of the femoral heads through the opposing right and left lateral beams used by protons is unknown. Thus, the incidence of late toxicity, including secondary malignancy, after proton treatment should be further evaluated in long-term trials.

The dose objectives for the rectum and urinary bladder met the criteria laid out by the QUANTEC reports [14, 15]. Current dose constraints are primarily generated from 3-D CRT datasets [22]. The advanced IMRT techniques, including protons, all provide highly conformal dose distribution, performing superior OAR sparing than 3-D CRT. For this reason, dose objectives should be derived from the datasets of these advanced radiotherapy technologies.

For each radiation technique, a corresponding planning system is used to determine dose calculation algorithms. Moreover, radiation plans can be optimized by individual modification of dose objectives for each treatment case. These arguments can diminish the relevance of the obtained results, despite the use of similar dose
objectives in radiation planning. Thus, the selection criteria for dosimetric comparison of treatment plans should be further optimized.

De Meerleer et al. demonstrated that static IMRT plans had a superior ratio of tumor control probability (TCP)/normal tissue complication probabilities (NTCP) compared to 3-D CRT plans. As a result, IMRT techniques provide improved tumor control without a corresponding increase in radiation toxicities [33]. The clinical relevance of dosimetric differences between various advanced IMRT techniques should be further analyzed in relation to NTCP parameters, including risk of secondary malignancy, as already described by Hall in several reviews [34, 35].

And finally, late-responding organs that have a low $\alpha/\beta$ ratio such as the prostate are more sensitive to high fraction doses [36, 37]. Several retrospective studies demonstrated the dosimetric feasibility, clinical outcomes, and local tumor control of hypofractionated radiotherapy in the treatment of localized prostate carcinoma [38–41]. Our ongoing research will focus on evaluating dose objectives for various advanced radiation techniques, including the Cyber Knife technique, in order to simultaneously provide homogeneous prostate coverage and conformal dose distribution through the delivery of a large fraction dose.

Conclusion
The major findings to emerge from this study are as follows: (i) All techniques revealed a homogeneous and high conformal dose distribution with more explicit differences at the low-to-medium dose ranges. At the dose above 50Gy all techniques demonstrated a steep dose gradient outside the PTV, implying a similar frequency and severity of acute toxicities. (ii) When using the same dose objectives during planning, IMPT revealed superior rectum and bladder sparing in a wide dose spectrum. This trend was more relevant at the low-to-medium doses. The superior OAR sparing by IMPT was concordant with results of Vargas et al, while did not match the results of Georg et al [5, 6]. In contrast to findings of Schwarz et al., IMPT revealed conformity values comparable to SW and RA techniques and even superior to HT [7]. (iii) While the slight advantage in bladder sparing by SW can be explained by the use of different dose calculation algorithms during the treatment plan optimization process, the highly significant superior rectum sparing by HT can only be partially explained by the algorithm and is assumed to be a result of the HT treatment technique. Of course, the radiation plans can be further optimized by individual modification of dose objectives in dependence of treatment plan strategy.

Additional file

Abbreviations
3-D CRT: 3-dimensional conformal radiotherapy; CICRU: CRU conformity index; CN: conformation number; CT: computed tomography; CTV: clinical target volume; CA: coverage area; CA_COV: coverage index COV; DVH: dose-volume histogram; HI: homogeneity index; HT: helical tomotherapy; ICRU: International Commission on Radiation Units and Measurements; IMRT: intensity modulated proton therapy; IMRT: intensity modulated radiotherapy; LINAC: linear accelerator; MLIC: multileaf collimator; MRI: magnetic resonance imaging; NTCP: normal tissue complication probabilities; OAR: organ at risk; PTV: planning target volume; QUANTEC: Quantitative Analyses of Normal Tissue Effects in the Clinic; RA: Rapid Arc; RTOG: Radiation Therapy Oncology Group; SW: Sliding Window; TCP: tumor control probability; VMAT: Volumetric Modulated Arc Therapy

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Availability of data and materials
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All authors participated in patient treatment and were involved in the preparation of the manuscript. All authors reviewed and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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