Original paper

Knowledge-based plan optimization for prostate SBRT delivered with CyberKnife according to RTOG0938 protocol

Davide Monticelli a,b, Roberta Castriconi b,* , Alessia Tudda a,b, Andrei Fodor c, Chiara Deantoni c, Nadia Gisella Di Muzio c, Paola Mangili b, Antonella del Vecchio b, Claudio Fiorino b,1, Sara Broggi b,1

a Università degli Studi di Milano, Milano, Italy
b Medical Physics Department, IRCCS San Raffaele Scientific Institute, Milano, Italy
c Department of Radiation Oncology, IRCCS San Raffaele Scientific Institute, Milano, Italy

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ABSTRACT

Purpose: To extend the knowledge-based (KB) automatic planning approach to CyberKnife in the case of Stereotactic Body Radiation Therapy (SBRT) for prostate cancer.

Methods: Seventy-two clinical plans of patients treated according to the RTOG0938 protocol (36.25 Gy/5fr) with CyberKnife were exported from the CyberKnife system to Eclipse to train a KB-model using the Rapid Plan tool. The KB approach provided dose-volume objectives for specific OARs only and not PTV. Bladder, rectum and femoral heads were considered in the model. The KB-model was successfully trained on 51 plans and then validated on 20 new patients. A KB-based template was tuned in the Precision system for both sequential optimization (SO) and VOLO optimization algorithms. Plans of the validation group were re-optimized (KB-TP) using both algorithms without any operator intervention and compared against the original plans (TP) in terms of OARs/PTV dose-volume parameters. Paired Wilcoxon signed-rank tests were performed to assess statistically significant differences (p < 0.05).

Results: Regarding SO, automatic KB-TP plans were generally better than or equivalent to TP plans. PTVs V95% was slightly worse while OARs sparing for KB-TP was significantly improved. Regarding VOLO optimization, the PTVs coverage was significantly better for KB-TP while there was a limited worsening in the rectum. A significant improvement was observed in the bladder in the range of low-intermediate doses.

Conclusions: An extension of the KB optimization approach to the CyberKnife system has been successfully developed and validated in the case of SBRT prostate cancer.

1. Introduction

The increasing complexity of radiotherapy treatment planning has made it very challenging in generating consistent and high-quality treatment plans. Even more in the case of Stereotactic Body Radiation Therapy (SBRT), where high-precision delivery of few high-dose fractions with very high dose fall-off around the target is required [1-6].

Automatic plan solutions were largely investigated [7-13] and implemented during recent years in order to make radiation therapy planning optimization more efficient by reducing the time for planning, limiting the intra/inter-operator variability and possibly improving the quality of plans regardless of the planner’s experience [14]. One of the most consolidated solutions for automated planning is the knowledge-based (KB) method. Several approaches for KB-planning applications have been proposed [9]. Good et al. assessed the capability of a mutual information method based on a dataset of treated patient to predict the dose-volume histogram (DVH) [15]. Other studies investigated the feasibility of a principal-component-analysis (PCA) based model to estimate the expected organ at risk (OAR) sparing [16,17]. Nwankwo et al. developed a predicted model based on the geometric position relative to the target [18]. The key characteristic of any KB approach is that for each new patient, the achievable dosimetric features are predicted using a training dataset of delivered clinical plans, considering the individual anatomical characteristics of each specific patient. One of the most consolidated solutions for automated planning is the knowledge-based (KB) method. Several approaches for KB-planning applications have been proposed [9]. Good et al. assessed the capability of a mutual information method based on a dataset of treated patient to predict the dose-volume histogram (DVH) [15]. Other studies investigated the feasibility of a principal-component-analysis (PCA) based model to estimate the expected organ at risk (OAR) sparing [16,17]. Nwankwo et al. developed a predicted model based on the geometric position relative to the target [18]. The key characteristic of any KB approach is that for each new patient, the achievable dosimetric features are predicted using a training dataset of delivered clinical plans, considering the individual anatomical characteristics of each specific patient.
important aspects of any KB approach is the population of the training set. The training set should be as much as possible representative of the clinical scenario and possibly free of sub-optimal plans, in order to avoid the phenomenon of the so-called ‘garbage in - garbage out’. Training a KB model with sub-optimal plans would weaken the performance of the model which is based on the quality of the plans used to train the model. Among several suggested KB approaches, RapidPlan (RP) is the most widespread commercial tool (Varian Medical System, Inc., Palo Alto, USA) incorporated in the Varian Eclipse planning system; RP allows to generate a KB model based on the training of a data set of available clinical plans, thus obtaining a representative model of the planning institute approach. This tool combines PCA and regression techniques to generate an estimated OAR’s DVH range for a new patient [19]. The resulting DVH prediction model may be used to build a template for automatic plan optimization. No PTV’s DVH prediction is available for RP tool.

Generally, RP-based optimization was found to be able to generate acceptable plans, at least comparable to previously optimized clinical plans [9,20-27]. There are also few examples showing that the KB model trained with plans based on a certain delivery technique can be efficiently adapted to another one [28,29] or that RP can also be trained within the Varian environment with plans optimized and delivered using other technologies, such as helical tomotherapy [30,31]. However, there are no available commercial solutions regarding automated planning for the CyberKnife system. Furthermore, to our knowledge, there are no examples in literature about KB-model applied to the CyberKnife system in the prostate district. Few papers investigated the use of KB-model for SBRT treatments in districts other than the prostate. Foy et al. [32] validated the use of fully automated VMAT plans for spinal metastasis, Visak et al. [33,34], Snyder et al. [35] and Delaney et al. [36] investigated the use of a KB-model for early-stage lung cancer while Hardcastle et al. [37] reported the results of prospective use of KB-model for real-time quality assurance of treatment plan quality in the kidney district. The aim of the present work was to extend the KB-planning approach using RP to CyberKnife in the case of SBRT prostate treatment.

2. Methods and materials

2.1. Clinical protocol and planning optimization

Current study considered patients treated at our institute between 2017 and 2021 for prostate cancer with CyberKnife, according to the RTOG0938 protocol [38]. The dose prescription is 36.25 Gy to PTV delivered in 5 fractions normalized at the peripheral isodose (range 75%-84%), so that 100% of the prescribed dose covers at least the 95% of the PTV volume, satisfying in the meantime dose-volume constraints for the OAR. Table 1 shows the constraints of the protocol for OARs. The PTV was defined as the CTV expanded by 3 mm in all directions. In our clinical practice no dose – volume constraints were considered in planning optimization for the urethra.

| Table 1 |
| Dose-volume constraints according to the RTOG0938 protocol. For ‘Maximum point dose’ we considered a point that is 0.03 cc in size. * In our clinical practice no-dose-volume constraints were considered in planning optimization for the urethra. |

<table>
<thead>
<tr>
<th>Organ</th>
<th>Volume</th>
<th>Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTV</strong></td>
<td>Minimum dose received by 95% of</td>
<td>≥ 36.25</td>
</tr>
<tr>
<td></td>
<td>PTV</td>
<td>100% of prescription dose</td>
</tr>
<tr>
<td>Minimum dose received by 100% of</td>
<td>95% of prescription dose</td>
<td>≤ 38.78</td>
</tr>
<tr>
<td><strong>Urethra</strong></td>
<td>Maximum point dose</td>
<td>107% of prescription dose</td>
</tr>
<tr>
<td><strong>Rectum</strong></td>
<td>Maximum point dose</td>
<td>≤ 38.06</td>
</tr>
<tr>
<td></td>
<td>≤ 3 cc</td>
<td>34.40</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>32.625</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>≤ 29</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>≤ 18.125</td>
</tr>
<tr>
<td><strong>Bladder</strong></td>
<td>Maximum point dose</td>
<td>≤ 38.06</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>≤ 32.625</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>≤ 18.125</td>
</tr>
<tr>
<td><strong>Penile Bulb</strong></td>
<td>Maximum point dose</td>
<td>≤ 100% prescription dose</td>
</tr>
<tr>
<td></td>
<td>≤ 3 cc</td>
<td>20</td>
</tr>
<tr>
<td><strong>Femoral Heads</strong></td>
<td>Maximum point dose</td>
<td>≤ 81% of prescription dose</td>
</tr>
<tr>
<td></td>
<td>≤ 10 cc</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54% of prescription dose</td>
</tr>
</tbody>
</table>

The majority of the plans were optimized with the multileaf collimator (MLC) while 15/72 plans were optimized with the IRIS collimator.

2.2. KB Model setting

The clinical plans of 72 previously treated patients were available. All plans, including DICOM 3D dose distributions, computed tomography images and geometric structures, were exported from the CyberKnife system (Accuray Precision v 3.3) to Eclipse (Varian v.13.6).

Fifty-two randomly chosen plans were selected to train a KB-model using the RapidPlan tool and the remaining twenty plans were used to build an external validation cohort. 9/52 plans of the training set and 6/20 plans of the validation set were clinically optimized with IRIS while most plans were optimized with MLC. All plans were calculated with the Ray Tracing algorithm using high resolution for the dose calculation grid.

Each plan was linked to a virtual arc plan consisting of two fully reverse arcs with a collimator inclination angle of 15° and with field size of 10x10 cm, in order to assess the association between the dosimetric and the geometric features. The prescribed dose was normalized at the same peripheral isodose defined in the CyberKnife treatment planning system. It is important to notice that the geometry setting between model training cohort and validation test set for DVH prediction should be the same, especially when dose distributions come from other TPS and/or delivery modalities. As the same geometry for configuration is used for the DVH prediction in a new patient, the relationship between geometric and dosimetric features has been maintained. Hence, the same virtual arc geometry used for the training of the model was adapted also for the DVH prediction of the validation patients set.

The OARs considered for the model were the bladder, the rectum and the femoral heads. In the model, femoral heads were considered as a paired structure even if left and right femoral heads were separately contoured in the original plan. The penile bulb was also included in the
model for the trained plans where the structure was contoured; however, due to the limited number of plans with the penile bulb drawn (only 21 plans), we decided to avoid the use of the resulting prediction due to the poor statistics and related problem of estimate robustness [43,44]. Of note, the dose received by the penile bulb was always very small (mean dose range: 2.81–18.83 Gy), being this OAR always not overlapped and relatively far from PTV.

The training-model process is well explained in literature [45,46]. The result was the generation of a set of coefficients for each OARs providing an evaluation of the principal component scores of the DVH based on the geometric and anatomic characteristics of OARs and PTV. The tuning of the model was performed by using statistical tools available in the RP system and the so-called ‘Model Analytic platform’, that permit to evaluate and eliminate potential outliers. The latter are expected to deviate from the general trend of the model because they do not meet the clinical goal of dosimetric parameters (dosimetric outliers) or show a geometry that largely differs from the rest of the training set (geometric outliers). The second category should not be removed from the model since it represents a scarcely present, but still possible geometry. In total one plan and some OAR structures were excluded from the model. In particular the Cook’s distance, which describes influential data points in a regression model, and the DVH prediction for each OAR structure, have been of primary importance to discriminate potential outliers.

After the tuning of the model, an internal and external validation should be performed [20,22,47,48].

2.3. Validation tests

Regarding the internal validation, for each OAR structure trained in the model, the residual and regression plots in terms of principal component parameters were considered. Moreover, a KB prediction on selected dose-volume parameters was made and the prediction was compared with the respective clinical plan parameter, checking if the planned clinical value fell within the estimated range. The dose-volume parameters considered were: V95%, V90%, V80%, V50% for the rectum, V90% and V50% for the bladder. Of note, Vx% means the volume (in cc or % as specified in brackets) receiving at least the ‘x’ percentage of the prescribed dose.

Concerning the external validation, a KB prediction on randomly twenty plans not included in the model was performed to assess the goodness of the model. The dose-volume parameters considered were the same as the internal validation. Dose-volume parameters for the femoral heads were not considered both for internal and external validation because they were far below the V54% constraint of the protocol.

2.4. Automatic KB plan optimization

Selected DVH constraints may be extracted from the KB prediction model to generate an individually optimized template for plan optimization. The generated constraints were based on the lower band’s value predicted by RP. The translation of the DVH prediction into an optimized template is not an easy task and requires an adequate fine-tuning. For this reason the process was carried out by two expert planners of our institute. All the plans of the external validation set were re-optimized based on the KB-templates (supplementary materials: table S1 and table S2) both with SO and VOLO optimization algorithms, using MLC type collimator. Automatic plans (KB-TP) were compared against the original clinical plans (TP) in terms of selected OARs and target dose-volume parameters. In particular, V100% and V95% were considered for PTV and CTV, V95%, V90%, V80%, V50% and V100% for the rectum, V90%, V50% and V10 Gy for the bladder, V30% and V10% for the femoral heads even though these parameters had not a clinical impact. Paired Wilcoxon signed-rank tests were performed to assess statistically significant differences (p < 0.05). Of note, all original clinical plans were optimized with SO and the same isodose normalization was maintained also with the VOLO re-optimized plans, in order to consistently compare the plans.

Moreover, one more template was tuned both for SO and VOLO by considering urethra sparing, based on RTOG protocol, useful for the optimization of treatment patients where the urethra delineation is available. A hard maximum dose constraint for urethra was added in SO (Table S3); a target goal was added for the overlap urethra region (overlap between the planning urethra and the PTV) together with a dose maximum critical goal for the urethra (Table S4). The ‘urethra sparing’ template was tested on five extra-patients for which urethra delineations were available and compared with the plans optimized with the original template.

3. Results

3.1. Validation tests

3.1.1. Internal Validation

After the fine-tuning, the final KB-model consisted of 51 trained plans and as many as 50 OAR structures for the rectum, 48 for the bladder and 52 for the femoral heads. The average PTV was 96.3 ± 24.9 cm³ (range: 42.6–166.6 cm³) for the patients in the training group. The distribution of PTV and OARs volumes are shown in supplementary materials (Figure S2). The trend line (dash lines) and the two standard deviations (SD) of the plot (straight lines) were reported. The correlation R² values for both regression and residual plots are shown in Table 2 for the respective organ. Of note, even if the penile bulb showed the highest value for both the correlation parameters (probably due to an overfitting of the model), we decided to avoid the use of the resulting prediction considering the poor number of plans available for this structure (only 21). The size of the training sets is an issue. As well reported by Cagni et al. [44], training sets with ≤ 30 plans need to be avoided also for the considered highly consistent treatment plans (panto-optimale like). Based on this analysis, training sets with ≥ 45 plans resulted in accurate DVH predictions.

Moreover, the KB prediction on selected dose-volume parameters of the clinical plans used to train the model, are shown in supplementary materials (Figure S2).

3.1.2. External Validation

Figure S3 shows the comparison between rectum and bladder volumes of the validation and the training cohort sets; no significant differences were observed.

Fig. 2 shows the dose-volume parameters for the rectum and the bladder, analyzed for the twenty validation plans, in terms of clinical DVH values and model estimated lower and upper bands. Regarding the rectum, 6/20, 5/20, 5/20, 4/20 clinical plans are lower than the estimated DVH bands (meaning the clinical are better than the estimated), when considering V95%, V90%, V80% and V50% dose-volume points, respectively. Generally, the lower estimated bands and the clinical plans were within the constraints (black lines, Fig. 2), except for the V95% parameter, where six plans are slightly above the limit even if they are inside the predicted bands. This is the case also in some clinical situations because of the small volumes that receive more than 95% of the prescribed dose and the compromise with the target coverage.

Regarding the bladder, 6/20 and 5/20 clinical plans are out of the estimated DVH bands, respectively for V90% and V50% dose-volume points. Three out of twenty plans for both parameters are lower than the estimated bands and only a few points are over the constraints.
3.2. KB Optimization

Several fine-tuning tests based on repetitive planning of five sample patients were done, testing the impact of the position of DVH constraints and their weights. The best templates were chosen. Once the KB-based templates were tuned, the automatic re-optimization of the twenty validation plans was successfully carried out both for SO and VOLO optimization and acceptable clinical plans were obtained.

Fig. 3 shows the mean DVH of the original clinical plans (TP) and automatic KB plans (KB-TP) for the validation set referring to SO (A) and VOLO optimization (B). Fig. 4 shows the average percentage differences of volumes (TP values minus KB-TP values) as a function of the dose for both OARs and PTV for SO (A) and VOLO optimization (B). The dose ranges corresponding to statistically significant differences are filled (p < 0.05). Quantitative analyses are shown in Table 3.

Regarding SO, on average, the reported cases show slightly lower PTV coverage in the range of V95% and V100% due to a better sparing of the rectum and the bladder (Fig. 3A and 4A). All dose-volume parameters considered both for the rectum and the bladder are significantly better in KB-TP plans (Table 3). The femoral heads are worse for KB-TP plans in the range of V20% and V50%. Of note, only one constraint on the maximum dose was added in the template and no prediction was considered. Regarding PTV there is a significant positive difference in the V95%-V100% range (Fig. 4A) meaning that the coverage is better for the TP plans as said before.

Concerning VOLO optimization, on average, the reported cases show greater target coverage in the V95% and V100% range while the rectum is significantly worse in the region of higher doses due to the soft nature of the objectives in the template (Fig. 4B), although the differences are small and of likely null clinical meaning. The femoral heads, similar to the SO, are worse for the KB-TP plan in the range V20%-V50%. Of note, V95%, V90%, V80% for the rectum are significantly worse in KB-TP plans, while V10Gy is significantly better. For the bladder, V50% and V10Gy are significantly better in KB-TP plans whereas V90% is worse but with no significance (Table 3). Regarding PTV there is a significant negative difference in V95%-V100% range meaning that the coverage is better for KB-TP plans (Fig. 4B). VOLO optimization allows a decrease of treatment time; the average KB-VOLO delivery time was 18.55 ± 1.70 min compared to 36.05 ± 7.91 min of clinical TP and 34.10 ± 2.59 min of the SO automatic plan.

In Figs. S4 and S5 the mean DVHs for extra five patients automatically optimized with "urethra sparing" and "no urethra sparing" templates were compared, respectively for SO and VOLO optimization approach. The urethra maximum dose constraint (≤38.8 Gy) is well
respected in both approaches. No significant differences were reported for all considered OARs (rectum, bladder and femoral head), while there is an expected slight decrease in the mean dose delivered to the PTV with the urethra-sparing approach. However, the PTV V95% is still comparable (97% with SO and 100% with VOLO).

4. Discussion

The present work represents the first attempt of implementing a KB approach to automate the plan optimization process in the prostate district using the CyberKnife system. Two algorithms implemented in the treatment planning system were considered: the sequential and the VOLO optimization. Optimized planning templates based on the KB-
model were able to generate high-quality automatic plans for both modalities, at least comparable to clinical plans, without any further intervention of the planner. In order to use the KB-predicted DVH to automatically optimize treatment plans, selected DVH constraints were extracted from the KB-prediction model to generate an individually optimized template. The generated constraints were based on the lower band values predicted by the KB model. The translation of the DVH prediction into an optimized template requires an adequate fine tuning. Several fine-tuning tests based on repetitive planning of five sample patients were done, testing the impact of several DVH constraints and relative weights. The template that was able to automatically generate clinical acceptable plans satisfying all the dose-volume constraints was chosen as the definitive.

Regarding SO, OARs sparing was significantly better, mostly at lower doses. On the other hand, on average, the target coverage was slightly lower than the TP even if it was still acceptable. To solve this problem, a user intervention could improve PTV coverage to make it comparable with that one of manual plans.

Concerning VOLO optimization, the coverage was significantly better than TP while for the rectum there was significant, although limited, worsening mostly at higher doses. Instead, the bladder was better spared than TP, especially at low and intermediate doses. A plan re-normalization could improve the OARs sparing, by keeping acceptable PTV coverage. A limit of this work is that the VOLO KB-model was created based on manual CyberKnife plans optimized with the sequential algorithm. A proper KB-model, based on plans originally optimized with VOLO, could in principle give different and better results for the automatic optimization. Further investigations are needed concerning this issue. The biggest advantages of VOLO optimization consist in the reduction of the delivery time [49], which makes it more suitable to the clinical implementation. In fact, the average KB-VOLO delivery time was 18.55 ± 1.70 min compared to 36.05 ± 7.91 min of clinical TP and 34.10 ± 2.59 min of the SO automatic plan.

The prostate clinical plans used to train and then to validate the KB model were based on RTOG0938 protocol (36.25 Gy / 5fr), excluding the maximum dose constraint (≤38.8 Gy) to the urethra. In our clinical practice the maximum dose constraint to the urethra region was considered too much restrictive, supported by Fuller et al. [50,51] experience giving a limit of 45.6 Gy in 4 fractions to Dmax, as well as D50% < 39.9 Gy. Therefore, for all patients treated at our institute based on RTOG protocol (5 fractions) included in this study, the urethra delineation wasn’t considered in planning optimization, differently from patients treated in 4 fractions (Fuller approach), where the urethra region is delineated and included in the planning optimization. To try to generalize and make useful our approach to be fully compliant with the RTOG protocol (including the urethra constraints), two different optimization templates were defined, both for SO and VOLO optimization algorithms. In the original template, based on our clinical experience, no urethra sparing was considered; in the generalized template, the sparing of the urethra region was included and optimized. To take urethra sparing into account, the original template was slightly modified. In SO approach a hard dose maximum constraint to the urethra was added. While a target goal for the overlap urethra region (overlap between the planning urethra and the PTV) together with a dose maximum critical goal for the urethra were added in VOLO approach. Even with available urethra contours, the urethra DVH prediction with KB model approach could not have considered. Rapid Plan doesn’t perform DVH prediction of target structures and the urethra sparing should be considered a trade-off between the maximum dose constraint and the PTV coverage; for this reason, the adding of “ad-hoc” urethra/PTV constraints should be considered the optimal choice for the planning optimization approach.

Few experiences are reported in literature regarding the implementation of automatic planning for SBRT approaches [32-36,52]. Moreover, there are not yet specific commercial solutions able to automatize treatment plans for the CyberKnife system. The possibility to extend the use of the RapidPlan tool and to apply RP models to other techniques and delivery machines is not new and has been already demonstrated in the tomotherapy environment [30,31,53]. Currently, there are no studies in literature about KB-models applied to CyberKnife in the prostate district. Importantly, the Erasmus MC Cancer Institute group has proposed different fully automated planning solutions using Multicriteria Optimization implemented in the “Erasmus-iCycle” software [54,55], showing significant improvements compared to previously delivered clinical plans. Their results cannot be directly compared with our findings due to the different aims of the two approaches. In fact, the major aim of any KB approach is to “translate” the past experience into a model, with possibly only little quality improvement; the autoplan approach followed by the Rotterdam group was explicitly intended to improve plan quality based on an optimized template set to find the “best” Pareto solution.

It will be interesting to test our KB-model performance outside our institutions. While plan quality may vary between planners of the same institute, larger variations may be expected among different institutions mainly due to possible differences in planning technique, dose prescription, contouring and sparing OARs approach. The implementation of a model outside the institution where has been generated requires a careful evaluation, often adaptation to the local situation, and extensive validation. This issue will be focused within an ongoing project for large-scale implementation of automatic KB plan optimization (MIKAPOco, Multi-Institutional Knowledge-based Approach to Plan Optimization for
Fig. 4. The mean differences of the volume as a function of the dose for OARs and target for SO (A) and VOLO (B); in green is highlighted the portion of graph where the differences are statistically significant ($p < 0.05$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
the Community). Tudda et al. [56], in this context, investigated the inter-variability of KB-models for right breast cancer patients treated with tangential field whole breast irradiation. Results showed limited inter-institute variability of plan prediction models translating in high inter-institute interchangeability, except for one institute.

5. Conclusions

In conclusion, a fully automatic extension of the KB-approach to the CyberKnife system has been successfully proved. Even though automatic plans were generally better than, or equivalent to manual planning, the clinical impact was “low” in the majority of cases, especially at higher doses. This is expected, being that the KB approach based on the past experience, so dramatic improvements in plan quality were not expected. On the other hand, optimization time was dramatically reduced: although a careful quantitative estimate was not possible because the time spent for manual planning was not previously registered, typical values of the time necessary for planning such patients with CK (with both SO and VOLO) are in the range of 2–4 h. This operator time may in principle be almost completely spared once the system is run to automatically generate the KB plan.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmp.2023.102606.

References


