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Gamma knife stereotactic radiosurgery as an effective tool in primary CNS lymphoma: Evaluation of stereotactic radiosurgery and methotrexate treatment in a prospective and observational clinical research study

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ABSTRACT

Objective: The purpose of this study was to compare the progression of Primary Central Nervous System Lymphoma (PCNSL) in patients treated with methotrexate (MTX) versus those treated with a combination of Stereotactic Radiosurgery (SRS) and MTX. Progression was measured via brain lesion count and tumor volume.
Methods: This observational and prospective cohort study evaluated the outcome of SRS treatment of PCNSL in one hundred twenty-eight subjects. We analyzed baseline, prospective, and retrospective data of patients enrolled in the brain tumor registry between June 2010 and August 2017. Seventy-three patients were treated exclusively with MTX while the remaining fifty-five patients received a combination of SRS and MTX. Strict inclusion and exclusion criteria were established.
Results: Mean survival rate for patients receiving combined SRS and MTX treatment was significantly higher (52.6 months) compared to the MTX group (19.8 months); $p = 0.0029$. At the 36 months follow-up, patients treated with SRS and MTX also had a lower rate of tumor progression (32.7 %) than the MTX group (95.9 %); $p = 0.00192$. Local tumor control was achieved in all patients treated with SRS. No clinical toxicity was observed in this group.
Conclusions: Clinical results obtained from this observational study highlight the potential effectiveness of SRS in the treatment of PCNSL. Although treatment outcomes have improved in the past years, additional evidence in the clinical design of randomized trials is needed to evaluate the strength of this treatment in specific situations.

1. Introduction

Primary central nervous system lymphoma (PCNSL) is a rare disease and aggressive malignancy accounting for less than 3% of all brain tumors and characterized by a yearly incidence of 0.5 cases per 100,000 people [1–4]. PCNSL presents as either a single or multifocal mass that may infiltrate the cortex and extend into the white and/or gray matter [3,5]. Untreated lesions have a poor prognosis and a low median survival time [6–8]. Currently, there isn't a universally accepted therapeutic approach for patients that have been newly diagnosed with this disease [9,10]. Therefore, the available treatment options remain limited, in large part, due to a lack of empirical evidence to support their efficacy [1,11,12].

The standard treatment (ST) for PCNSL consists of different methotrexate-based chemotherapy regimens associated with whole brain radiotherapy (WBRT) [5,11,13–15]. Unfortunately, the ST requires the application of high doses which can result in a broad range of serious adverse events including methotrexate toxicity, severe neurotoxicity, and cognitive decline. Most PCNSL patients are at least 60 years old and exhibit multiple, complex morbidities [3,4,7–9,14]. For these reasons, researchers are trying to find the best treatment of PCNSL by looking at the outcomes of combining targeted-chemotherapy and focal radiotherapy in order to reduce adverse events [15–19]. Increased interest in stereotactic radiosurgery (SRS) as a treatment for primary CNS

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lymphoma has also occurred [1,3,4,20–24]. Gamma Knife surgery (GKRS) is a non-invasive four-step neurosurgical procedure which includes the positioning (?) of a stereotactic frame to the patient's head, stereotactic image acquisition, treatment planning, and radiation [9, 25–28]. The results of GKRS include rapid and successful outcome rates, improvement in prognosis, and increased quality of life for the patients; however, GKRS has not been approved as a standard treatment for PCNSL [3,4,12,25]. A recent report showed a novel and interesting approach for the treatment of PCNSL with GKRS [24,25]. The present study extends the number of cases analyzed and confirms previous positive outcomes.

2. Materials and methods

We analyzed baseline prospective and retrospective data from subjects who were enrolled in the Brain Tumor Registry study anytime between June 2010 and August 2017. The study was approved by the local ethics committee and informed consent was obtained from all of the study's participants in accordance to STROBE guidelines. Data for the study were collected by a single-blind, post-doctoral researcher using Research Electronic Data Capture (REDCap). Strict inclusion and exclusion criteria were employed (Table 1). Subjects were eligible for the study if they (1) had a PCNSL diagnosis that had been confirmed with a brain biopsy, (2) had a clinical diagnosis of PCNSL, (3) had not received radiotherapy, (4) did not have AIDS or any other immunodeficiency disorders, and (5) were older than 18 years of age.

PCNSL in all patients was diagnosed via a stereotactic brain tumor biopsy confirmed by an experienced neuropathologist. Furthermore, detailed clinical information was collected from all those qualified through in-person interviews and medical examinations. During clinical assessments, patients were asked to describe their symptoms which helped to establish a PCNSL diagnosis. Examples of the symptoms listed included seizures, neurological symptoms, and headaches. Patients who met all the criteria established were offered both treatment options: (a) methotrexate alone or (b) GKRS in addition to methotrexate. All treatment recommendations were discussed amongst a multidisciplinary CNS tumor committee. Patients received at least one cycle of HD-MTX (3.5 g/m^2) before being evaluated for GKRS.

All patients underwent standard brain tumor MRI protocol including FLAIR, DWI, T2, T2 TSE, SWI and PWI. For the pre-contrast T1-weighted images, MPRAGE sequences were performed. Counting of lesions was based on concurrent evaluation of axial susceptibility-weighted imaging (SWI), a volume acquisition technique, with 1.5 mm reconstructed images and axial T2 gradient echo, 3 mm images. Brain lesions were counted by the neuroradiologist assigned to the study who was blinded to the clinical data. The MRI protocol was implemented to evaluate the tumor size at the six, twelve, and fifty-two-week follow-ups. Primary outcomes were evaluated by measuring tumor sensibility and brain tumor lesion size as noted on MRI and CT scans. These were further assessed using survival rates. Secondary outcomes were assessed by measuring the tumors' reduction in size which was calculated through either MRI and/or CT scans, and response to treatment. Changes in tumor lesion sizes were also evaluated via MRI every three months following radiosurgery.

Table 1
Study Inclusion and Exclusion Criteria.

Inclusion criteria
Diagnosis of primary central nervous system lymphoma confirmed by Histopathology
Age 18 or older
ECOG* performance less than or equal to 0−4
Exclusion criteria
History of cancer
Evidence of lymphoma outside the central nervous system
HIV infection
Metastasis or multiple types of cancer

* Eastern Cooperative Oncology Group (ECOG) Performance Status.

The definition for tumor response to treatment was established upon the modified Response Criteria of the International Collaborative Group PCNSL. The definitions used for this study included: complete response (CR) which represented complete disappearance of all evidence of lymphoma, partial response (PR) which represented a reduction in tumor size of 50 % or more, progressive disease (PD) which represented an increase in tumor size by at least 25 % or the development of new lesions, stable disease (SD) which was used to categorize any patient outcomes that did not meet any of the above-mentioned criteria, and progression-free survival (PFS) which represented the length of time from diagnosis to recurrence or progression.

Subjects were selected as candidates to GKRS when both of the following criteria were met: (1) patient's PCNSL was histologically confirmed and (2) there was no previous history of cancer treatment. The decision for a patient to undergo GKRS following methotrexate chemotherapy was left at the discretion of the patient as well as the treating physicians. The team of health care professionals for every patient included a radiation oncologist, a medical oncologist, and a neurosurgeon. Rescue gamma knife radiosurgery therapy was offered to participants in the MTX group who presented new tumor lesions after 6 months of therapy. Prior to the 1.5-T MRI acquisition with intravenous contrast, participants were fitted to a stereotactic head frame. All subjects were treated at our institution with Leksell Gamma Knife® Perfexion™. The Radiation Technology Oncology Group dosing guidelines were followed; however, doses were decreased depending upon tumor location by the treating radio surgical team. Treatment planning was achieved by fusion of pre-therapy thin-slice MRI (axial slice thickness 1 mm) and simulation CT scan. When T1 imaging was insufficient, fluid-attenuated inversion-recovery sequences were used to demarcate the full extent of tumor cellularity. Based on neuroscience center protocol, targets were prescribed marginal doses ranging from 10 to 20 Gy to minimize adverse radiation effects. Decreasing doses were used as an inverse square function to increase target volume Dose planning was implemented with multiple isocenters to maximize dose-gradient index and was prescribed to a line of 50 % isodose. Statistical analysis was completed to analyze the results using SPSS version 22 (SPSS, Inc., Chicago, IL, USA). Analyses were performed to evaluate the presence of new lesions at the tumor level, GSP, and OS. Secondary endpoints evaluated included assessment of toxicity at the clinical level and comorbidities present. Mann-Whitney tests were used to compare quantitative and ordinal variables. The Kaplan-Meier method was used for the univariate analysis of survival with the evaluation of differences made using the log-rank test. Confidence intervals (CI) for survival times were constructed from the logarithmic transformation of the Kaplan-Meier survival estimator (product limit). All reported p-values were bilateral with values less than 0.05 considered statistically significant.

3. Results

One hundred and twenty-eight (128) cases of immunocompetent patients were evaluated. Seventy-three (73) patients were treated only with methotrexate and fifty-five (55) patients were treated with a combination of GKRS and methotrexate. Clinical history, MRI reports, and positive histopathological reports for PCNSL were reviewed for each case. The median prescription dose was 11 Gy (range: 10–20 Gy) and the median target volume was 6.4 cm^3 (range: 1.6–22 cm^3) (Table 2). Clinical follow-ups were done after 3 months (n = 128), 6 months (n = 128), one year (n = 120), two years (n = 83), and three years (n = 61). In the first 12 months, 65 patients in the methotrexate group (89 %) and 52 patients in the GKRS plus MTX group (94.6 %) experienced a decrease in tumor volume of more than 75 % (p = 0.192). Eighteen months after the beginning of treatment, 25 patients (34.2 %) in the Methotrexate group did not exhibit new lesions or an increase in old tumor lesions compared to 40 patients (76.9 %) in the GKRS plus MTX group who did (p =

Table 2
Demographic and Preoperative Data of Immunocompetent Patient.

Patient Parameters	Methotrexate	GKRS plus Methotrexate	p-value
Number of Patients	73	55	–
Age	[58.1 ± 15.3]	[56.9 ± 13.3]	0.685
Male	33 (47 %)	26 (47 %)	–
Body mass index (kg / m2)	[24.1 ± 2.6]	[25.2 ± 3.1]	0.39
Pre-albumin (mg / dL)	[18.1 ± 1.3]	[19.1 ± 0.9]	0.347
Albumin (g/dL)	[3.4 ± 0.4]	[3.2 ± 0.4]	0.89
Median survival rate	19.8 months (11.3–29.1)	52.6 months (28.3–59.3)	0.0029

0.0023). At 36-month follow-up (range: 27–39 months), three patients in the methotrexate group (4.1 %) did not present new tumor lesions compared to the 37 patients (67.3 %) in the radiosurgery group (p = 0.00192) who did.

The average survival rate from the time of initial diagnosis was higher in the GKRS + MTX group (52.6 months; range: 28.3–59.3 months) than in the methotrexate group (19.8 months, range 11.3–29.1). Between groups comparison indicated that this result was statistically significant (p = 0.0029). Lesions treated with GKRS showed a complete response which was confirmed through brain magnetic resonance imaging performed within the three to eight weeks following treatment (medium range: 6.3 weeks). A direct relationship was established between a survival rate of at least 24 months and the marginal dose (odds ratio 6.5, p = 0.031, 95 % CI (1.4–18, 57)), the standard dose increase (odds ratio 1.54, p = 0.012, 95 % CI (1.15–2.89)), and the highest dose increase (odds ratio: 1, pretreatment Score Karnofsky (odds ratio 5.13, p = 0.008, 95 % CI (1.55–85.1)). In the methotrexate group, thirteen patients underwent methotrexate therapy and subsequently, in a range of 7–16 months, underwent rescue radiosurgery. Among patients undergoing rescue radiosurgery, ten patients received two or more doses of radiosurgery, at different times, due to the reappearance of lesions. Sixty (60) patients in the methotrexate group (82.1 %) were not treated with radiosurgery during the duration of the study due to heterogeneous reasons such as patient decision, lost at follow-up, or death. The initial tumor volume was a significant predictor for the local control of lesions in the methotrexate group. Larger volumes of lesions were associated with poorer control in both the Cox proportional hazards model and in the log-rank test (Table 3).

When assessing the growth control of tumor lesions with cerebral magnetic resonance in the methotrexate group, it was found that local control in small tumors (<=0.5 mm) was 56.1 %, 42.3 %, and 33.2 %, at three, six, and twelve-month follow-up visits, respectively. In large tumors (> =0.6 mm), local control was 49.7 %, 35.3 % and 22.1 %, at the three, six, and twelve-month follow-up visits, respectively. Age, sex, cerebral side localization, and the presence of Epstein-Barr virus (EBV) were not predictive of local control in the immunocompetent patients that composed the methotrexate group. The size of the treated lesions was not predictive of the outcome either in patients who underwent radiosurgery as a rescue therapy.

Table 3
Neuropathological evaluation.

Methotrexate Only	**Hazard Ratio**	95 % **Confidence Interval**	**P-value**	**Log-Rank**
Age	0.94	0.99 - 1.01	0.166	0.431
Sex	1.29	0.66 - 1.89	0.189	0.211
Epstein Barr	0.25	0.41 - 1.72	0.29	0.386
Tumor Volume (cm^3)	1.22	0.99 - 2.71	0.023	0.021
Dmin (Gy)*	0.64	0.51 - 2.05	0.084	0.097 (Patients who were treated with rescue radiosurgery)

Methotrexate plus Radiosurgery	**Hazard Ratio**	95 % **Confidence Interval**	**P-value**	**Log-Rank**
Age	0.89	0.99 - 1.04	0.197	0.39
Sex	1.21	0.76 - 1.81	0.21	0.291
Epstein Barr	0.29	0.45 - 1.69	0.16	0.298
Tumor volume cm^3	1.35	0.99 - 1.91	0.12	0.171
Dmin (Gy)*	0.71	0.73 - 2.1	0.112	0.097

Dmin: minimum dose prescribed using Gray as the unit of measurement.

Tumor volumes were divided into three groups: small (<0.5 cm^3), medium (0.5 - 2 cm^3), and large (> 2 cm^3). Statistical evaluation revealed that smaller lesions showed significantly better local control when compared to the medium (p = 0.031) or larger (p = 0.021) lesions. Among thirty-one patients who experienced tumor recurrence within the first 6 months after the initiation of methotrexate treatment, nine of them received additional radiosurgery treatment in an average of 7.1 months (range: 4–10 months). On the other hand, twelve patients in the radiosurgery group displayed new lesions in an average of 24.3 months (range: 18.1–27.3 months) and nine patients that received additional radiosurgery treatment had new lesions in an average of 27.1 months (range: 24–29 months) after the initial radiosurgery treatment (Fig. 1). Local tumor control was achieved in all the cases treated with radiosurgery. Results regarding the response to chemotherapy with high doses of methotrexate as the first line therapy are described in Table 4 along with the the associated toxic effects (grade 3–4). In all cases treated with radiosurgery, no clinical or radio-surgical toxicity was observed (Fig. 2). The side effects attributed to gamma knife radiosurgery were entirely mild. Headache was present in 18 % of patients, vertigo (not exceeding seven days) was present in 12 % patients, and drowsiness was reported in 4% of patients. None of the patients reported mental symptoms nor cognitive deterioration.

4. Discussion

In this study, we identified novel factors associated with variability in tumor susceptibility to radiosurgery independently of age in patients with PCNSL. Specifically, we found that an increasing volume of tumor lesion was associated with lower tumor susceptibility. Furthermore, we found that early treatment in multiple lesions and GKRS were associated with lower tumor progression and increased tumor susceptibility in long term. Finally, PCNSL in older adults was associated with presence of multiple tumor lesions and more adverse events related to MTX treatment.

Therapy for primary central nervous system lymphoma is an active and developing field of medical research [3,24,25]. The principal approach to treatment of PCNSL includes an induction phase followed by a consolidation phase [25–28]. The induction phase consists of polychemotherapy involving methotrexate delivered at specific doses [25]. Consolidation therapy consists of WBRT which targets the whole brain, the first two cervical segments of the spinal cord, and the eyes, This kind of approach comes with a high risk of severe neurotoxicity (25–35 % with a related mortality of 30 %) which affects long-term quality of life especially in older adult patients [3–6,25,26]. For this reason, researchers are trying to find a less invasive approach that could offer a high success rate and limit adverse events such as neurocognitive weakness, neurotoxicity, and brain atrophy [14,16–18]. Likewise, stereotactic radiosurgery has proved to be a beneficial option for the treatment of brain tumors consisting of single or multiple brain lesions [11,24,29]. The technique results in a reduction of adverse events and an increased ability to target multiple lesions and achieve local tumor control [11,12]. For patients with relapsed or refractory PCNSL in the palliative setting, this technique showed a good clinical response, improved overall survival, and local tumor control [19]. It is important to emphasize that, in this study, no patient demonstrated cognitive impairment or neurotoxicity, thus, supporting the tolerability of the GKRS approach. Lower tumor lesion volume is associated with improved GKRS response and may also allow higher treatment doses to each

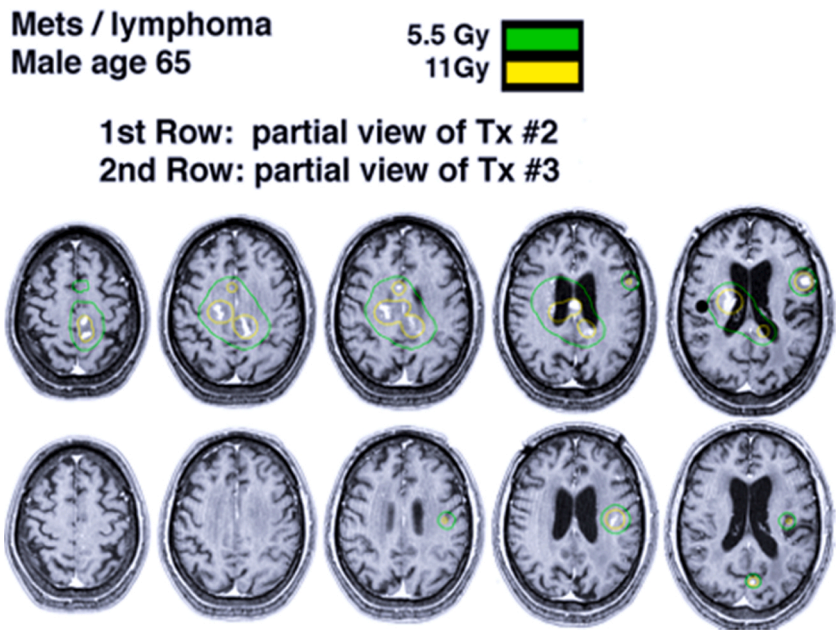

Fig. 1. Brain MRI for gamma knife surgical plan. The image shows total tumor control in brain MRI follow-ups. Gamma Knife surgery should be performed for tumor control as a part of the initial treatment of PCNSL. It is noninvasive, safe, and its effects occur rapidly. Its use improves prognosis and enhances the patient's quality of life.

Table 4
Response to first-line chemotherapy and associated toxic effects by group.

	Methotrexate (*n* = 73)	**Methotrexate + Radiosurgery (*n* = 55)**
Total HIV negative patients studied	73	55
Complete response to 6 months of treatment (CR)	29	44
Partial response (PR)	12	9
Stable disease (SD)	4	46
Progressive disease (PD)	14	3
Recurrence or new tumors	44	11
Death in initial therapy	6	1
Unknown	5	3
Thrombocytopenia	46	39
Leukopenia	42	37
Infections	29	24
Anemia (Hemoglobin < = 11.0)	32	21
Elevation of aminotransferases	14	9
Stomatitis	6	2
Urea or creatinine elevation	5	1
Altered consciousness	12	7
Peripheral neuropathy	3	1
Dizziness	61	47
Hearing loss (temporary)	1	0

lesion, which is another parameter that is associated with better survival.

However, the main concern with whole brain radiotherapy, particularly in young patients and in those with a more favorable prognosis, is the negative impact on neurocognitive function and quality of life [30,31]. In this study, a cohort of more than ten immunocompetent patients in the methotrexate group was diagnosed with progressive disease after twelve months of starting treatment. Many patients subsequently underwent treatment using a radiosurgery-based rescue regimen. Compared to other treatments available for recurrent PCNSL, two of these patients achieved favorable long-term results and had no recurrence 24 months after treatment with radiosurgery. Four patients continued with follow-up visits every three months and underwent ongoing prophylactic treatment with methotrexate. Thereby suggesting the presence of chemosensitivity that was maintained despite prior exposure to the drug. These clinical results may suggest that the addition of radiosurgery is clinically safe and allows for better tumor lesion control.

The research study and metanalysis reported by Kasenda et al. [4] found that older adult PCNSL patients benefit from HD-MTX-based therapy and that more aggressive HD-MTX protocols do not improve overall outcomes. Furthermore, it concluded that even though WBRT may improve outcome, it is associated with an increased risk for severe neurological side-effects. Given the trade-off between a potentially small survival benefit and the risk of neurological side-effects, the authors urged caution regarding the interpretation of WBRT being a superior treatment in addition to HD-MTX [33]. Radiosurgery treatment within the first month of diagnosis prompted a decline in neurological symptoms without the side effects associated with conventional radiotherapy and complete brain radiotherapy after three months of treatment. In all immunocompetent patients treated with radiosurgery, a higher 36-month survival rate was found when compared to studies previously published [4,21,23,24,32,33]. Our study results are consistent with others' experience using radiosurgery for PCNSL with respect to high rates of local tumor control. For instance, in reports by Palmer et al. [24], none of the primary CNS lymphoma patients treated at various stages with GKRS were noted to have a local tumor recurrence at thirty-six months follow-up. Notably, tumor response rates to radiosurgery were also high with greater than 85 % of lesions disappearing on MRI follow-up, thus resulting in better overall outcomes.

The study limitations include a heterogenous population and the biases associated with the prospective but non-randomized nature of our clinical analysis, such as selection bias. This remained a problem even on the prospective comparative analysis given that the evidence was limited to being prospective, but non-randomized, cohort. In addition, we were unable to determine factors like immunotherapy, new generations of chemotherapy, or targeted therapy used for salvage.

5. Conclusion

The results obtained from this clinical study demonstrate the value of GKRS as a non-invasive, safe, and useful technology in the treatment of PCNSL. GKRS may be clinically recommended as part of an effective

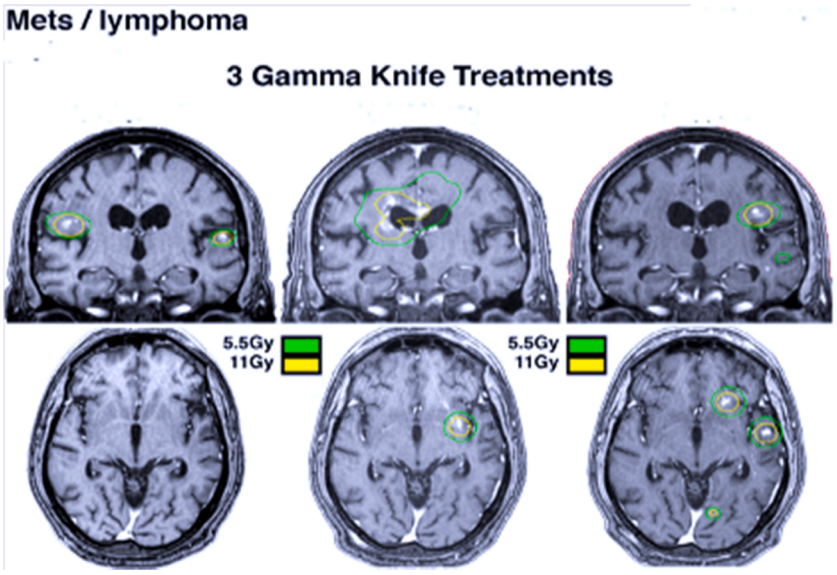

Fig. 2. Stereotactic radiosurgery plan, three months, and six-months follow-up. No radiation necrosis is visible in the brain MRI following treatment.

treatment modality in immunocompetent patients. Consequently, there is an enormous need for prospective, randomized clinical studies using GKRS therapy as part of the first-line treatment scheme or combined with new validated therapies for cancer, such as immunotherapy, to assess, compare, and analyze the success rate of current treatment options for this rare brain tumor.

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CRediT authorship contribution statement

Andres M. Alvarez-Pinzon: Conceptualization, Visualization, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Aizik Wolf:** Visualization, Investigation, Methodology. **Jose E. Valerio:** Conceptualization, Methodology, Investigation, Writing - original draft. **Matteo Borro:** Software, Validation, Writing - original draft. **Daniela Herrera:** Writing - review & editing. **Jose Ramon Alonso:** Supervision, Visualization, Investigation, Writing - original draft.

Declaration of Competing Interest

None.

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