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Unresectable Chondrosarcomas Treated With Carbon Ion Radiotherapy: Relationship Between Dose-averaged Linear Energy Transfer and Local Recurrence

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Abstract. *Background/Aim: The local control rate of chondrosarcomas treated with carbon-ion radiotherapy (CIRT) worsens as tumour size increases, possibly because of the intra-tumoural linear energy transfer (LET) distribution. This study aimed to evaluate the relationship between local recurrence and intra-tumoural LET distribution in chondrosarcomas treated with CIRT. Patients and Methods: Thirty patients treated with CIRT for grade 2 chondrosarcoma were included. Dose-averaged LET (LET_d) distribution was calculated by the treatment planning system, and the relationship between LET_d distribution in the planning tumour volume (PTV) and local control was evaluated. Results: The mean LET_d value in PTV was similar between cases with and without recurrence. Recurrence was not observed in cases where the effective minimum LET_d value exceeded 40 keV/μm. Conclusion: LET_d distribution in PTV is associated with local control in chondrosarcomas and patients treated with ion beams of higher LET_d may have an improved local control rate for unresectable chondrosarcomas.*

Carbon ion beams have higher relative biological effectiveness (RBE) than photon and proton beams owing to their high linear energy transfer (LET) (1-4). Generally, between 10 and 100 keV/μm, the RBE increases with increasing LET and reaches a maximum at approximately 100 keV/μm (5). Owing to the higher RBE in the spread-out Bragg peak region than in the entrance region, carbon ion radiotherapy (CIRT) is considered more useful than other radiotherapy (RT) modalities for radioresistant tumours such as sarcomas (6).

Complete resection is the primary definitive treatment for bone and soft tissue sarcomas (7), and RT is an option for unresectable and incompletely resected tumours. Most bone and soft tissue sarcomas are considered resistant to conventional photon RT (8), and therefore, conventional photon RT is usually employed in the neoadjuvant or adjuvant settings (9). Conversely, CIRT is usually employed for the definitive treatment of unresectable axial sarcomas and has demonstrated efficacy in bone and soft tissue sarcomas (10-12), although there is still room for improvement in the oncologic results of CIRT. In the case of chondrosarcomas, for example, the overall 5-year local control (LC) rate in patients treated with CIRT was 53%, and the LC rate was inversely related to the tumour volume (13).

One of the reasons for the poor LC rate in larger chondrosarcomas could be related to the distribution of dose-averaged LET (LET_d) in the tumours. In general, as tumour volumes increase, the LET_d varies more widely in the target. The low LET_d contributions increase with increasing tissue depth, peaking at the distal fall-off region (14). Therefore, the LET_d is high in the distal region of a tumour where the beams stop and low in the proximal region or centre of the tumour where the beams traverse. To compensate for this variation, CIRT beams are generally designed to achieve a uniform biological effect in the tumour in terms of RBE-weighted dose. An RBE-weighted dose is defined as the product of absorbed dose and RBE. The RBE depends on various factors such as LET, particle species, track structure, dose, dose rate, oxygen pressure, endpoint, and tissue type.

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Ideally, all of these factors should be incorporated into the RBE model (15). However, this is difficult owing to the complexities in the biological effect mechanism. In the National Institute of Radiological Sciences (NIRS), the RBE-depth dependence (16) for CIRT is based on the radiosensitivity of the human salivary gland (HSG) tumour cells under normoxic conditions as a reference, irrespective of the tumour type (16-19). However, the suitability of using RBE for the treatment of HSG cells has not yet been evaluated for cases of chondrosarcoma.

Thus, this study aimed to evaluate the appropriateness of using the RBE derived from HSG to cases of chondrosarcomas. Therefore, we investigated the relation between LC in chondrosarcomas and $LET_{d,}$ which is the function of RBE in planning tumour volume (PTV), using a retrospective analysis of patients treated with CIRT for primary chondrosarcomas in which CIRT beams provide a uniform RBE-weighted dose in PTV.

Patients and Methods

Patients. This study included patients with primary chondrosarcomas treated with CIRT between June 2000 and February 2012 at NIRS (12). All patients underwent treatment according to the institutional clinical protocol. The LC rate varies by tumour grade and is generally related to the RBE-weighted dose (13). To focus the influence of LET_d on the LC rate, we selected a homogeneous collective of 45 patients with grade 2 (G2) chondrosarcomas and those who received a dose of 70.4 Gy (RBE) for PTV, as they formed the largest subset of the cohort of all chondrosarcoma patients. Patients with tumours located below the second cervical vertebra (C2) were included in the study, while those with chondrosarcomas at the base of the skull or above C2 were excluded because they were managed using another protocol. All recurrent tumours on the margin of the PTV were defined as marginal recurrences. Generally, the marginal recurrences are strongly caused by the incorrect settings of the CTV and/or PTV. Since this study aimed to investigate the relationship between LET and local recurrence, marginal recurrences were considered to reduce the accuracy of the analysis. Therefore, ten cases with marginal recurrences were excluded from the analysis. Moreover, five cases planned for different types of treatment systems were also excluded. Finally, 30 patients were selected for this study, of whom 11 had local recurrences and 19 had no recurrences. Details of the patients and their tumour characteristics are summarized in Table I. For this retrospective analysis, all patients signed an informed consent form approved by the local institutional review board.

CIRT. Carbon-ion beams were generated at the NIRS using the Heavy Ion Medical Accelerator in Chiba (HIMAC), which is a synchrotron. For treatments, ion beams with accelerated energies of 290, 350, and 400 MeV/n were available for treatment, and beam energies of 350 and 400 MeV/n were used for deep-seated tumours, corresponding to a water-equivalent depth range of 15-28 cm (10). The patients were treated with passive beams using a ridge filter as energy modulator (20). Details of the CIRT technique with the HIMAC for bone and soft tissue malignancies including chondrosarcomas have been described previously (10, 13, 21).

Table I. *Patient characteristics (n=30).*

Characteristics	Value	
	No recurrence n=19	Recurrence n=11
Tumour size [cm^3] (median/range)	344 (38/1398)	485 (206/1709)
Follow-up time [months] (median/range)	49.4 (8.0/112)	52.7 (8.2/135.4)
Fractionation	16 fractions/4 weeks	
Dose/fraction	4.4 Gy (RBE)/fraction	
Number of fields	3	
Fields/day	1	

Treatment planning system. Treatment plans for all the patients were generated using the Heavy Ion Plan (HIPLAN) system (21) at NIRS. Treatment planning was performed with biological treatment plan optimization, which used a clinical RBE of 3 at the depth corresponding to 80 keV/μm (10). The RBE profile was taken from measurements in HSG cells (16). The HIPLAN system has an RBE look-up table as a function of irradiation depth and the width of the spread-out Bragg peak, which is independent of the dose level, instead of individually calculating the RBE in the treatment planning system with the RBE models. Dose calculation was performed with a grid size of 2 mm.

LET_d calculation. Therapeutic carbon-ion beam includes secondary fragment particles due to nuclear interactions (22); therefore, the contributions of various types of ions needed to be utilized to evaluate the biological effect. The biological effect of the therapeutic beam on the tumour results from the total effect of the individual particle of different LET and the dose value at the point. As LET_d is a variable that includes various LET and dose components; it is commonly used for analysis of LET on LC in CIRT (23). The HIPLAN system uses Sihver's model (14) to calculate the LET_d distributions to water, including the contributions of secondary and tertiary particles considering the dose-weighting contribution.

The LET_d distributions at location r $\bar{L}(\boldsymbol{r})$ were calculated according to a previous study (24) and as follows:

$$\bar{L}(\boldsymbol{r}) = \frac{\sum_i [n_i \cdot D_i(\boldsymbol{r}) \cdot L_i(\boldsymbol{r})]}{\sum_i [n_i \cdot D_i(\boldsymbol{r})]}$$

where $D_i(\boldsymbol{r})$ was the physical dose distribution by beam i, n_i was the number of fractionations, and $L_i(\boldsymbol{r})$ was the LET distribution by beam i.

Evaluated indicators. We evaluated the lowest LET_d value and the percentage of the low LET_d region in the PTV based on the hypothesis that chondrosarcomas recurred in the low-LET region. We also evaluated LET_d volume histograms (LVHs) and the mean LET_d value in the PTV (MLP). Treatment plans of controlled and non-controlled tumours were evaluated for the following parameters.

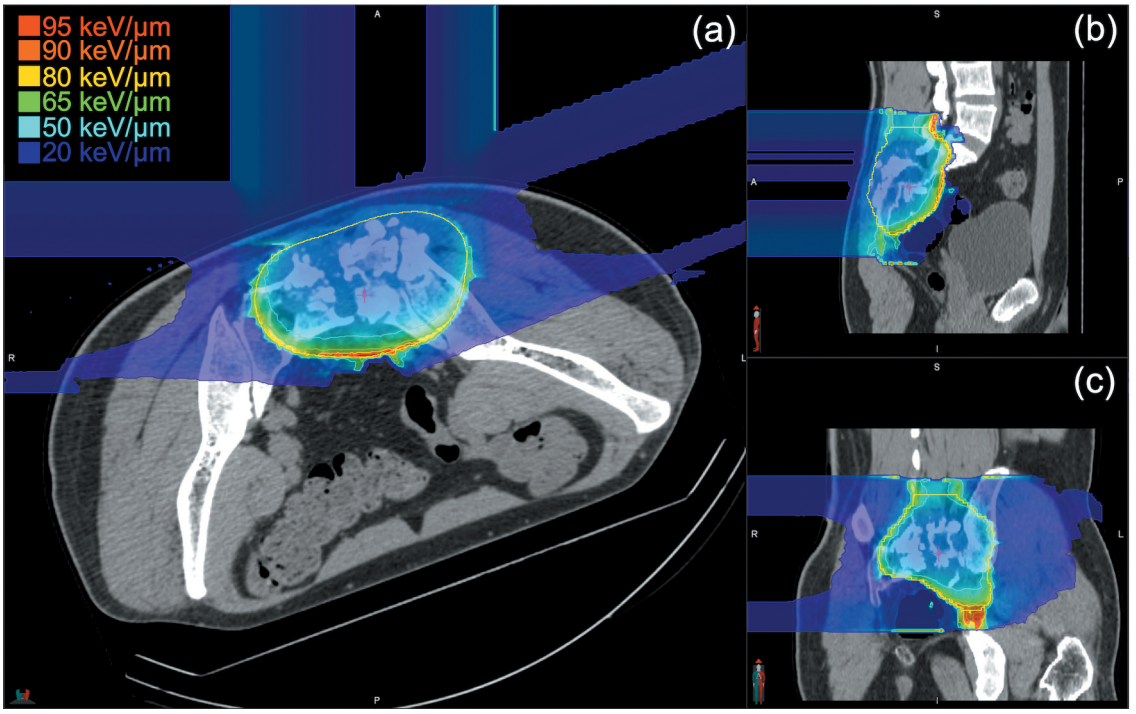

Figure 1. *Dose-averaged linear energy transfer (LET_d) distributions in the planning tumour volume (PTV). The combined LET_d distribution was calculated outside the treatment planning system and then registered with the CT image. (a) Axial view, (b) sagittal view, and (c) coronal view. The image was prepared by fusing the treatment planning image with the image showing the LET_d distribution in a rainbow-colored pattern. The yellow circle shows the PTV edge. The pink cross denotes the iso-centre.*

1. Near-minimum LETd in the PTV. We also selected the near-minimum LET_d in the PTV $L_{1\ ml}$ (the minimum dose to 1 ml of the PTV) as an indicator of recurrence. The 1-ml volume with the lowest LET was excluded due to the uncertainty of the treatment planning program in calculating the minimum LET.

2. Percentage of low LETd region in the PTV. The percentage of the low LET_d region in the PTV was defined as the ratio of the volume in the PTV receiving less than *x* keV/μm to the entire volume of the PTV. In a previous study, the oxygen enhancement ratio (OER) decreased from 50 keV/μm (25); hence, in this study, *x* was set to 50 keV/μm ($V_{50\ keV/\mu m}$).

Statistical analysis. The correlation between $L_{1\ ml}$ and tumour volume was analysed statistically with Spearman's rank-correlation coefficient. *p*-Values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using Python software, version 3.6.5.

Results

LET_d distribution and LVHs. Figure 1 demonstrates a typical example of the LET_d distribution calculated with the HIPLAN system where the LET_d value was high in the distal region of the PTV and low in the centre of the PTV. In this example, the highest LET_d value in the PTV region was 124 keV/μm, while that at the iso-centre was 37 keV/μm.

LVHs were drawn in all cases to compare the LET_d distributions in cases with and without recurrence (Figure 2). Representative values are shown as $L_{50\%}$ values, which denote the median LET_d values in the PTV. The $L_{50\%}$ of the cases with and without recurrence ranged from 37.8 to 46.8 keV/μm and 38.5 to 70.6 keV/μm, respectively. No recurrence was observed in patients with an $L_{50\%}$ higher than 46.8 keV/μm.

MLP. Figure 3 demonstrates MLP as a function of tumour volume. The figure presents MLP as inversely correlated with the tumour volume. The MLP of the cases with and without recurrence ranged from 38.7 to 52.2 keV/μm and 41.4 to 72.3 keV/μm, respectively.

$L_{1\ ml}$. Figure 4 demonstrates $L_{1\ ml}$ as a function of tumour volume. The $L_{1\ ml}$ of the cases with and without recurrence ranged from 24.7 to 54.9 keV/μm and 22.4 to 36.3 keV/μm, respectively. Recurrences were not observed in cases with $L_{1\ ml}$ values of 36.3 keV/μm or higher. $L_{1\ ml}$ and tumour volume showed the correlation of $L_{1\ ml}$ with tumour volume (r=–0.90, $p<0.01$).

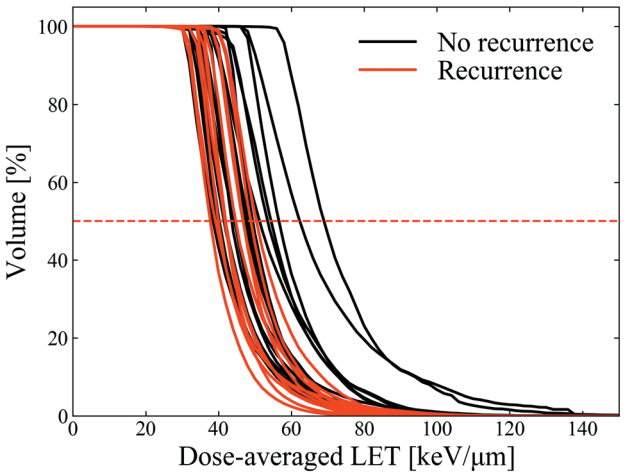

Figure 2. *Dose-averaged linear energy transfer (LET_d) volume histograms in the planning tumour volume (PTV). The red and black lines show recurrent and non-recurrent cases, respectively. Representative values are shown across the red dashed line as L50% values, which indicate the median LET_d values in the PTV. The L50% of the cases with and without recurrence ranged from 37.8 to 46.8 keV/μm and 38.5 to 70.6 keV/μm, respectively.*

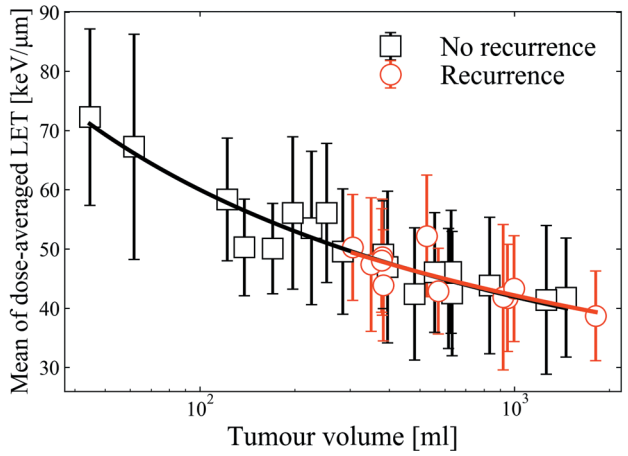

Figure 3. *Mean dose-averaged linear energy transfer (LET) values in the planning tumour volume (PTV) (MLP). The black squares and red circles denote the MLP in non-recurrent and recurrent cases, respectively.*

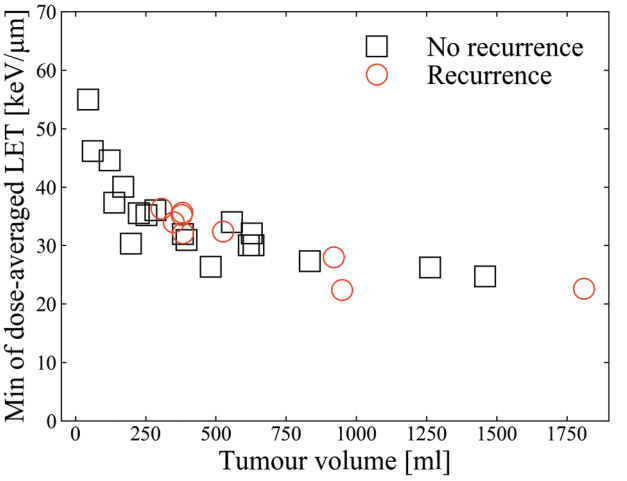

Figure 4. *Relationship between L1 ml and tumour volume. The black squares and red circles denote the L1 ml in non-recurrent and recurrent cases, respectively.*

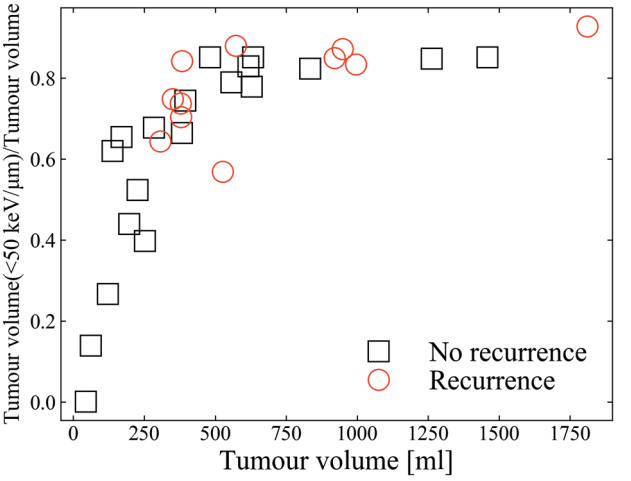

Figure 5. *Tumour volume ratios in the low LET_d region. Black open squares and red open circles denote non-recurrent and recurrent cases, respectively.*

V50 $_{keV/\mu m}$. Figure 5 shows $V_{50\ keV/\mu m}$ as a function of tumour volume. The $V_{50\ keV/\mu m}$ of the cases with and without recurrence ranged from 0.56 to 0.92 and 0.00 to 0.85, respectively. Recurrences were not observed in cases where $V_{50\ keV/\mu m}$ was less than 0.56. The correlation between $V_{50\ keV/\mu m}$ and the tumour volume was analysed statistically with Spearman's rank-correlation coefficient. The result showed the correlation of the $V_{50\ keV/\mu m}$ with tumour volume (r=0.86, p<0.01).

Discussion

In this analysis, the group having more than 36.3 keV/μm in $L_{1\ ml}$ or 0.56 or less in $V_{50\ keV/\mu m}$ showed no recurrence. Moreover, $L_{1\ ml}$ and $V_{50\ keV/\mu m}$ showed a close correlation

with tumour volume. These findings suggest that the current HSG-based RBE model does not completely describe the true variation of the RBE with LET of chondrosarcoma, particularly at the low and medium LET range appearing at the central region of the large PTV where hypoxia often develops.

This may be explained by the development of hypoxic areas at the centre of the tumour when there is an imbalance between cell proliferation and vascularization (26). Radiosensitivity is reduced in this hypoxic environment owing to the longer persistence of free radicals (27). This phenomenon is known as the oxygen effect, and its degree is indicated by the OER (28). The value of the OER estimated by *in vitro* study is approximately 3 for photon beams. According to Furusawa *et al*., in the case of carbon-ion beams, the OER begins to decline from 50 keV/μm, attaining a value of 2 at 50 keV/μm and 1 at 100 keV/μm (25). Tinganelli *et al*. also obtained similar findings (29). However, in the treatment of patients, the change in OER was not explicitly taken into account in the RBE model because the background HSG response was measured under normoxic conditions.

Imai *et al*. reported that the LC rate decreases with increasing tumour volume (13). Our study showed that LET_d at the centre of the PTV diminished with an increase in tumour volume, and patients with local failure had lower $L_{1\ ml}$ and $V_{50\ keV/\mu m}$ within the PTV. These results may provide supportive evidence for Imai's report. Therefore, the RBE-weighted dose calculations in the low LET region using the current RBE model may be imperfect. Also, local recurrences after RT may be reduced by using higher LET radiation, particularly at the central region of the PTV.

A previous study provided adequate evidence regarding the efficacy of optimizing radiation quality using various charged particles to improve the biological effect (30). To address the issue of the low LET region, Bassler *et al*. (31) proposed an advanced technique, namely, LET painting, to redistribute the high LET of carbon-ion beams to a certain region of the tumour, using field arrangements. A previous in-silico study showed that LET painting increases the tumour control probability in hypoxic tumours by directing the high LET region to the hypoxic compartment of the tumour (32). Inaniwa *et al*. also proposed the use of a LET painting technique for treatment using two or more ion species in one treatment session, known as intensity-modulated composite particle therapy (IMPACT) (33). Since IMPACT provides a uniform LET distribution in large tumours, we propose the use of IMPACT for treating chondrosarcomas with regions of low LET_d. Adjusting the LET_d in the PTV of chondrosarcomas, based on the results of this study, may serve to improve LC rates with clinically meaningful outcomes.

This study has several limitations. First, the number of candidates in this study was small because of the clinical setting to enrol chondrosarcoma patients into CIRT. Most of chondrosarcoma patients receive surgery, and patients treated with CIRT were judged as medically unresectable cases. Furthermore, chondrosarcoma is a rare malignancy. These factors make it difficult to collect a large number of patients treated with definitive CIRT. Second, the relationship between patient outcome data and LET_d distribution was retrospectively analysed and therefore, might have inevitably biased the results. Tumour volume itself may be a confounding factor in the analysis of LC rate. However, one of the reasons of poor LC rate of larger chondrosarcomas could relate with LET distribution. We exclusively selected G2 chondrosarcomas to ensure uniformity in the nature of the tumour being analysed. We also showed that the LET distribution was affected by the tumour volume and LET_d may be related to the LC rate.

Third, the LET_d distribution was calculated using the HIPLAN system. The system analytically calculates and employs the broad-beam algorithm, ignoring the divergence of the beams (21); therefore, uncertainties may be present in the calculation results. However, a previous study reported good agreement between the measurement and calculation results of the LET_d on the central axis of the beams (14). Since this analysis focused on the PTV, the influence of the lateral divergence of the beam was low, with less uncertainty in the calculation results.

Forth, the RBE increases with increasing LET_d up to 100 keV/μm. Beyond this LET_d value, the RBE begins to fall (5). Therefore, in the region receiving more than 100 keV/μm, the relation between LET and RBE may be lost. However, this study evaluated the shortfall of LET_d in the PTV, and the range of values was under 100 keV/μm. Therefore, this evaluation may provide useful information regarding recurrence in chondrosarcomas.

In conclusion, this study revealed that the LET_d within the PTV may be associated with LC in chondrosarcomas. Our results suggest that CIRT outcomes may be improved by utilizing LET painting techniques such as IMPACT to provide optimal dose and LET_d distributions within the PTV.

Conflicts of Interest

Dr. Kanematsu reports personal fees from Mitsubishi Electric Corporation, personal fees from Elekta, Inc., personal fees from Osaka International Cancer Treatment Foundation, outside the submitted work; In addition, Dr. Kanematsu has a patent JP6383429 issued, a patent JP5954705 with royalties paid to Mitsubishi Electric Corporation, Elekta, Inc, and RaySearch Laboratories, a patent JP5521225 with royalties paid to Mitsubishi Electric Corporation, Elekta, Inc, and RaySearch Laboratories, a patent JP4456045 with royalties paid to Mitsubishi Electric Corporation, a patent JP3531453 issued, and a patent JP Application 2018-177593 pending. Dr. Inaniwa reports grants from the Japan Society for Promotion of Science (JSPS), during the conduct of the

study; personal fees from TOSHIBA Corporation, personal fees from Mitsubishi Electric Corporation, personal fees from Elekta, Inc., personal fees from Osaka Heavy Ion Therapy Center, outside the submitted work.

Authors' Contributions

Shinnosuke Matsumoto: Investigation, writing - original draft. Sung Hyun Lee and Mai Fukahori: Investigation. Reiko Imai: Resources, Writing – review & editing, conceptualization. Taku Inaniwa, Naruhiro Matsufuji, and Ryosuke Kohno: Software. Shunsuke Yonai and Noriyuki Okonogi: Project administration, writing – review & editing. Shigeru Yamada and Nobuyuki Kanematsu: Supervision.

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