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Original Research Article

Spatially fractionated radiotherapy (Lattice SFRT) in the palliative treatment of locally advanced bulky unresectable head and neck cancer

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ABSTRACT

Objectives: Locally advanced bulky unresectable head neck cancer causes significant tumor mass effects, leading to severe symptoms. This study aims to report the safety and outcomes in patients undergoing Lattice spatially fractionated radiotherapy (Lattice SFRT) for locally advanced bulky unresectable head and neck cancer.
Methods: Patients with bulky head and neck cancer received Lattice SFRT between June 2022 and June 2023. Lattice SFRT was administered in 2–3 fractions of 12 Gy (Gy) using 6-megavolt (MV) photon beams through a multileaf collimator (MLC) based on VMAT technology. The primary endpoints were symptomatic and tumor response rates. Secondary endpoints were overall survival, local control, and acute and late toxicity rates.
Results: 19 consecutive patients meeting the study criteria were identified, predominantly with squamous cell carcinoma histology. The median patient age was 62 years (range 39–79 years), and the median tumor volume was 208 cc (cc) (range 48–701 cc). All patients completed radiotherapy. Among all investigated patients, 16 of 19 (84.2 %) patients achieved an objective response, including 10 individuals achieved a partial response (PR), with 3 of them exhibiting regression exceeding 75 %. 17 patients showed symptom improvement to varying degrees. Acute toxicity of Radiation Therapy Oncology Group (RTOG) grade 1 or higher occurred in 5 patients, while no grade 3 adverse events was observed.
Conclusions: Lattice SFRT proves to be a viable treatment option for the palliative management of bulky head and neck cancer. In the palliative setting, Lattice SFRT offers timely symptom relief, enhancing patient quality of life. Treatment toxicity remains within an acceptable range. Continued optimization of Lattice SFRT delivery and patient selection can benefit from further data on the feasibility and efficacy of this radiation modality.

Introduction

Head and neck cancer (HNC) is one of the most prevalent malignancies globally [1]. For advanced head and neck cancer, radiotherapy combined with chemotherapy is recommended treatment model because of the invasion of vital anatomical structures. However, conventional fractionated radiotherapy has been shown to be limited in achieving local control of large bulky tumors (≥6 cm) [2,3]. Hypofractionated palliative radiotherapy is often used and evidence of effectiveness has come from retrospective institutional studies or small phase II trials [4,5]. Due to the unique anatomical position of head and neck cancers, the use of stereotactic body radiotherapy (SBRT) has been limited because of severe toxicity.

Spatially fractionated radiotherapy (SFRT) represents an alternative approach to delivering high-dose radiotherapy, offering the theoretical advantage of safely escalating doses for large tumors [6]. Initial clinical observations on the effectiveness and safety of GRID SFRT, utilizing megavoltage photon beams, were presented by Mohiuddin's group [7], particularly in palliative care for patients with bulky tumors intolerant to or resistant to conventional radiotherapy. Additionally, GRID SFRT has proven successful in both palliative and definitive treatment approaches for large head and neck tumors [8]. From 2007 to 2015, 21 patients with massive head and neck tumors with a median maximum tumor diameter of 9.5 cm were enrolled in this study. GRID SFRT can provide timely symptom management and improve patient quality of life in the palliative setting. While GRID is more widely available, recent advancements in SFRT techniques have led to improved dose distribution compared to GRID. The transition from 2D GRID to a 3D configuration, known as Lattice SFRT, offers potential advantages, especially in large tumors surrounded by crucial organs at risk (OARs)[9,10]. In

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Lattice SFRT plans, a heterogeneous dose distribution is created within the planning target volume (PTV), forming a 3D array where high-dose regions (vertices or hotspots) alternate with low-dose areas (periphery), resembling peaks and valleys. Despite delivering ablative doses to discrete sub-volumes, the valleys serve to minimize treatment-related toxicity [11]. The safety and clinical efficacy of Lattice SFRT have been documented across various voluminous tumors [12–16].

To our knowledge, no clinical studies have been reported using Lattice SFRT for bulky lesion in advanced HNC. We conducted a clinical study reviewing the treatment of advanced HNC with bulky lesions using Lattice SFRT in Sichuan Cancer Hospital. Preliminary outcome and side effects were evaluated in this study.

Methods and materials

Patient selection

Patients with $\geq$ 5 cm masses developing from head and neck cancer are eligible for treatment if the following criteria are met: age $>$ 18 years, clinical classification T4 or N3, ECOG Performance Status $\leq$ 2, a life expectancy $>$ 3 months, and the absence of severe bleeding. Endpoints of interest included tumor response, symptom improvement, treatment tolerance, and adverse events. All patients signed informed consent prior to the delivery of radiation therapy. The present study was approved by Sichuan Cancer Hospital Ethics Committee.

Lattice SFRT

All patients received Lattice SFRT using VMAT technology with a multileaf collimator (MLC) base. The entire gross tumor was designated the gross tumor volume (GTV). Our Lattice SBRT technique set a geometric arrangement of spherical vertices, each with a diameter of 0.4 cm, spaced 2 cm center-to-center, and a 2.0 cm separation between successive axial planes of spheres, using the hexagonal closest packed model. To ensure optimal coverage, all spheres were positioned more than 1 cm away from the tumor edge. The volume of these spheres was defined as the GTV-peak. The Lattice SBRT prescription was formulated with the premise that the GTV should receive 400 cGy per fraction, and the GTV-peak should be dosed at 1200 cGy per fraction. During Lattice SFRT planning, efforts were made to achieve $\geq$ 95 % prescription dose coverage for at least 95 % of both PTV_400 and PTV_1200. Planning directives adhered to OAR constraints consistent with 5-fraction SBRT guidelines published in the American Association of Physicists in Medicine (AAPM) Task Group 101 [17]. Fig. 1 illustrates examples of GTV-peak placement and the corresponding dose distribution. The number of fractions (2–3) administered to each patient depended on factors such as performance status, and tumor size.

All treatment plans were implemented utilizing an Elekta Infinity 6 MV linear accelerator. Upon finalization of Lattice SBRT contouring and treatment planning through the MONACO treatment planning system (version 5.11), plan integrity and deliverability were rigorously assessed according to the standard clinical SBRT QA protocol, involving review by both physicians and physicists. Lattice SBRT sessions were conducted alternate-day, with cone-beam CT (CBCT) obtained immediately before treatment to verify tumor positioning.

Systemic therapy

Chemotherapy and immunotherapy were administered following multidisciplinary discussions, aligning with individual patient conditions.

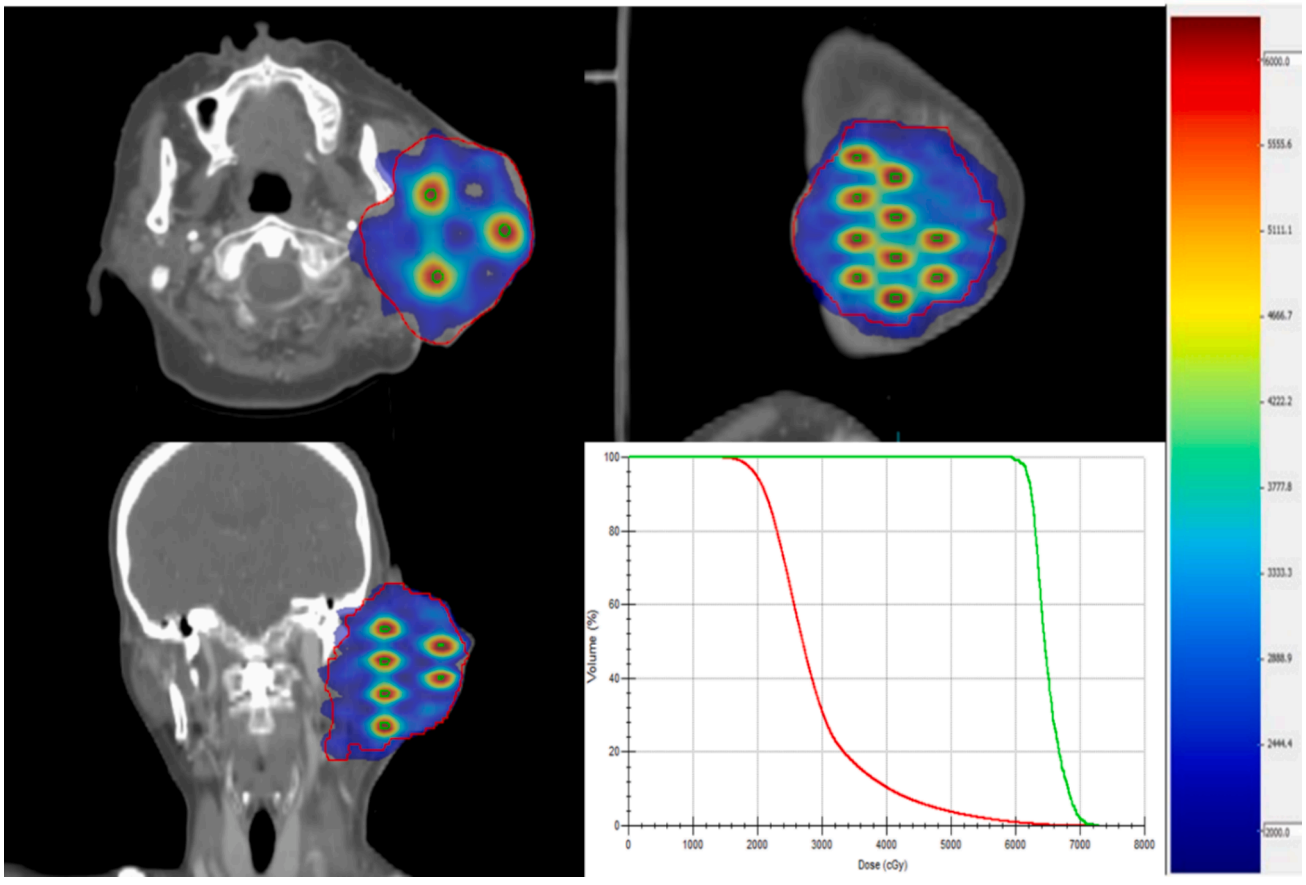

Fig. 1. The delineation of GTV-peak and the dose distribution diagram of a patient of parotid gland cancer.

Patient follow-up

Patients underwent acute toxicity assessments during SFRT and also for 90 days post-radiotherapy completion. Clinical evaluations occurred at baseline, once during therapy, and at 14, 30, and 90 days. Contrast-enhanced CT/MRI scans were conducted 30- and 90-days post-radiotherapy completion. The assessment included treatment response, encompassing changes in tumor size, symptom improvement, and local control. Improvement in symptoms was measured by VAS questionnaire score. Toxicity evaluations followed the criteria outlined by the Radiation Therapy Oncology Group (RTOG) and the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Acute toxicity was characterized by reactions occurring 90 days after irradiation completion or when acute symptoms persisted beyond this period. Symptomatic response referred to the subjective improvement of symptoms, such as pain, moderate bleeding, and swelling.

Results

Between June 2022 and June 2023, a total of 19 patients were enrolled in the study (refer to Table 1). The predominant tumor histology was squamous cell carcinoma, 1 patient was angiosarcoma, and 1 patient was adenosquamous carcinoma. The median age of patient was 62 years (range 39–79 years). Among the patients, 9 presented with local T4 lesions, while 10 had large cervical masses. 13 patients had previously received at least first-line treatment. In particular, 6 patients had received primary radiotherapy. The tumors exhibited a median volume of 208 cc (range 48–701 cc). Radiotherapy was conducted with alternate-day irradiation, and all patients successfully completed the radiotherapy sessions. Refer to Table 2 for details on the number of radiotherapy fractions and treatment characteristics. Concurrent chemotherapy was administered to 10 patients. 8 patients received cisplatin-based regimens and 2 patients were treated with capecitabine, and 3 patients received immunotherapy (PD-1 inhibitor).

Table 1
Patient and tumor characteristics.

Age(years)	
Median	62
Rang	39–79
Sex	
Male	10
Female	9
Stage	
T4	9
N3	10
Location of primary tumor	
Paranasal sinus	2
Oropharynx	2
Hypopharynx	3
Parotid gland	3
Thyroid	2
Oral cavity	3
Other	4
Histology	
Squamous cell carcinoma	17
Other	2
Number of treatment lines	
First-line treatment	6
2 lines or more	13
Systemic Therapy	
Chemotherapy	10
Immunotherapy	3
None	6
Gross Tumor Volume, cc	
Median	208
Rang	48–701

According to imaging evaluation at 1 month after SFRT radiotherapy, tumor regression was observed in 16 of 19 patients. Among the patients, 10 individuals achieved a clinical and radiological partial response (PR), with 3 of them exhibiting regression exceeding 75 %. Figs. 2 and 3 present the effect of tumor regression and two typical cases. However, 3 patients experienced tumor lesion progression after SFRT. In terms of symptom improvement, 17 patients showed improvement to varying degrees.

Radiation-associated mucosal and cutaneous toxicities was evaluated during SFRT and 90 days post-radiotherapy completion. Acute toxicities were identified in five patients: 3 with G2 mucositis, 2 with G1 skin toxicity, and 1 with G2 dysphagia due to radiation effects on the oral mucosa. No grade three or higher acute toxicities were observed. Table 3 provides a summary of treatment responses and radiation toxicities. The absence of late toxicities was not reported in this initial analysis due to the limited duration of follow-up.

Discussion

Most of patients with locally advanced HNC lose the opportunity for surgery, and concurrent chemoradiotherapy is the only curative treatment [18,19]. However, in patients with bulky lesions, curative chemoradiotherapy possibly leads to severe side effects, which significantly reducing the patients' quality of life. In addition, approximately 40 % patients will develop a regional recurrence within 5 years after definitive treatment [19]. Previous studies [20,21] have shown that severe late complications from treatment reach to 30 % in patients with locally recurrent HNC received reirradiation.

At present, with the development of high conformal radiotherapy technologies such as intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), stereotactic body radiation therapy (SBRT), image-guided radiation therapy (IGRT), as well as protons or heavy ions, reirradiation is becoming increasingly common. It has been reported that tumor volume is closely related to efficacy and side effects in patients with locally recurrent HNC treated by SBRT, the remission rate significantly declines and treatment toxicity significantly increases with tumor volume increases [22–24]. Moreover, brachytherapy has been reported that treating HNC with a 1-year local control rate of 54 %-77 %, but the acute toxicity of grade 3/4 was more than 30 %[25–27]. Recently, the use of proton or heavy ions radiation therapy technology in treating HNC has become more widespread, and studies have reported a local control rate of over 70 % at 1 year [28–32]. But the dose of treatment is highly variable, meanwhile, poor access to treatment due to lack of equipment. The special radiotherapy technology, SFRT has been reported in research on bulky tumors [8,11–15,7,33–35]. The results showed it to be a safe and effective palliative treatment measure for patients with large volume tumors (mainly in the trunk and limbs). Choi et al [8] reported on the use of GRID SFRT in combination with IMRT for extremely advanced HNC patients, 54.5 %(6/11) of patients received variable degree of palliation. With the development of radiotherapy equipment, the clinical application of 3D Lattice technology has gradually increased. This technology made very high doses more focus of radiotherapy within the spherical or cylindrical area of tumors (known as vertices). At the same time, it helps maintain a regular dosage around the tumor, protecting peripheral organs from exceeding their tolerance. Studies of this technology [11–13,15,16] have reported significant efficacy in treating large volume tumors and protecting surrounding organs, but reports on its use in HNC is few.

In our study, all patients were treated using the new Lattice SFRT technology. 13 of them had failed first treatment, 5 had recurrent

Table 2
Physical parameters of radiotherapy.

Target Patient	Site	Gross tumor volume, cm^3	Lattice volume, cm^3	Peak volume ratio	Fraction	*GTV after SFRT, cm^3
1	paranasal sinus	101	1.78	1.76	2	43 (43 %)
2	paranasal sinus	215	20.9	9.74	2	66 (31 %)
3	oral cavity	78	2.21	2.8	2	63 (81 %)
4	Right neck	443	19.1	4.32	2	483 (109 %)
5	Left neck	112	4.26	3.78	2	81 (72 %)
6	Right neck	359	22.5	6.27	3	123 (34 %)
7	Left neck	48	2.44	5.13	2	35 (73 %)
8	Left neck	223	11	4.93	2	43 (19 %)
9	Left neck	376	19.9	5.3	3	59 (16 %)
10	Left parotid	281	12.8	4.4	2	59 (21 %)
11	Thyroid	246	12.7	5.15	3	150 (61 %)
12	Left neck	189	6.07	3.21	3	116 (61 %)
13	Right neck	117	13.5	11.5	2	141 (120 %)
14	Right neck	68	2.75	4.04	3	74 (109 %)
15	Left parotid	116	11.4	9.82	2	40 (34 %)
16	Nasopharynx	159	5.38	3.38	2	129 (81 %)
17	Thyroid	62	2.25	3.59	2	45 (73 %)
18	Right neck	701	14.1	2.01	3	268 (38 %)
19	Left neck	52	1.91	3.67	3	38 (73 %)

*The volume of GTV after 1 month of SFRT.

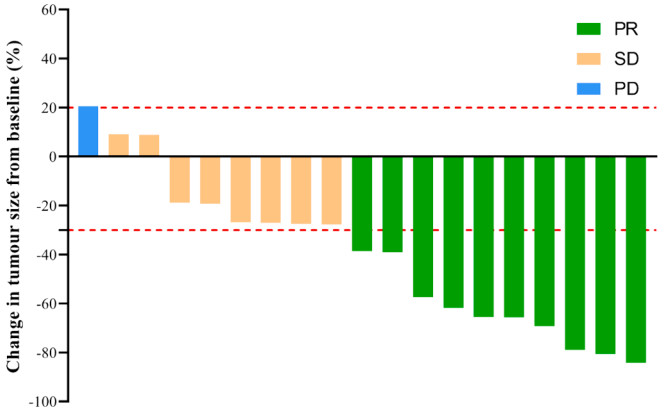

Fig. 2. Best change in the target lesion volume compared with that at baseline (n = 19).

disease after curative radiotherapy, and 8 had progressed after induction chemotherapy. The research results showed that over 80 % (16/19) of the patients had tumor regression and 17 patients had symptom improvement. This result was superior to the previous study of 2D grid SFRT [8], which data showed 42 %(5/12) of the patients had tumor regression with palliative intent. The possible reason for the small number fractions but high tumor response rate of SFRT may be attributed to its unique biological effect (bystander effect)[36,37]. Additionally, no definitive or potential grade 3 or higher-level toxicity was observed, the dose protection effect of Lattice SFRT on the organs at risk around the tumor was confirmed in our study. The safety was significantly improved compared with other studies [8,24,25], such as SBRT, 2D grid SFRT and brachytherapy etc. Combine evidence above, our results suggested that Lattice SFRT is one of the potential effective treatments for this type of cancer.

For systemic treatment, agents typically deemed suitable for standard-fractionation radiotherapy in cases of HNC, such as platinum-based chemotherapy, taxanes, and cetuximab, are deemed acceptable in a clinical trial context [38]. Nevertheless, consensus guidelines typically advise against the administration of systemic therapy during SFRT [39]. Interestingly, 10 patients received concurrent chemotherapy during SFRT in our study, and no serious side effects were observed. The concurrent use of immunotherapy during SFRT has been documented in the literature [40], while consensus on the application of SFRT combined with immunotherapy for treating HNC remains to be established. In our study, 3 patients were administered immunotherapy during SFRT, and there were no observed adverse events of grade 3 or above. This provides valuable insights that may support further clinical studies in establishing the efficacy of such combined therapeutic approaches.

The recently published GRID physics and dosimetry white paper [41] outlined the standardization of GRID dose prescription, underscoring the necessity for a defined peak dose. This involved explicating both the dosimetric and geometric characteristics of heterogeneous dose distribution, including specific parameters such as dose volume histogram characteristics (D10, D50, D90) and peak-to-peak distance. However, many studies on Lattice SFRTs have not provided clear details on these parameters. One study [11] described a method of delineating spheres using a geometric arrangement of spherical vertices, each with a diameter of 1.5 cm, a center-to-center spacing of 6 cm, and a separation of 3.0 cm between successive axial planes of spheres. However, this method may not necessarily be applicable for head and neck tumors, which typically have a relatively smaller volume. In our study, we implemented a sphere arrangement with a diameter of 4 mm and a spacing of 2 cm for SFRT irradiation of head and neck tumors. This finding offers valuable insights for future studies establishing the feasibility of this radiotherapy technique and lays the groundwork for subsequent clinical research.

Nonetheless, our study has some limitations. Firstly, it's a single-center retrospective study, that overlooks the heterogeneity of tumor pathology and the variation in concurrent treatment plans. Additionally, given the relatively short follow-up period for patients, only short-term toxic effects were observed. Long-term follow-up to identify potential late toxicities is crucial, which will provide the basis for the future application of SFRT technology. We will conduct prospective clinical studies to further ascertain the efficacy and toxic effects of Lattice SFRT in combination with immunotherapy for bulky HNC.

Conclusions

Lattice SBRT represents a novel strategy for administering escalated doses of radiation to large tumors, potentially overcoming the constraints associated with conventional fractionation. Both clinically and technically, our approach has demonstrated feasibility and is currently undergoing thorough evaluation in more robust clinical trials. This research is specifically targeted at patients dealing with substantial, unresectable head and neck cancer, aiming to provide valuable insights and advancements in treatment efficacy. In the future, LRT should be combined with conventional fractionated radiotherapy and immunotherapy for better results.

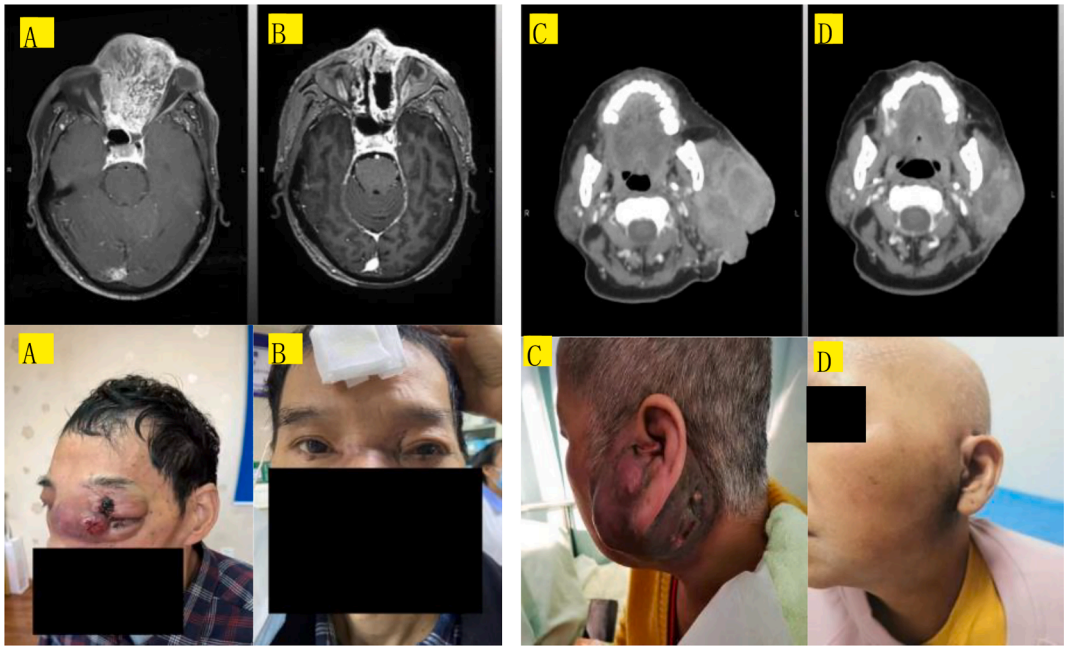

Fig. 3. Representative images of two patients with bulky tumor of head and neck who were treated with Lattice SFRT. Both patients were treated with LRT combined with chemotherapy. LRT was performed in 2 fractions with 4 Gy/f GTV and 12 Gy/f GTV-peak. A&C: before SFRT B&D: 1 month after SFRT.

Table 3
Response to treatment and radiation toxicities.

Treatment evaluation	
Tumor regression	16
SD or PD	3
Symptomatic Benefit after Irradiation	
Yes	17
No	2
Acute Toxicity	
None	14
Mucositis	2
Skin	2
Dysphagia	1

Author contributions

Peng Xu, Jinyi Lang, Shun Lu contributed to the conception of the study;
Shuo Wang, Jie Zhou, Ke Yuan performed the experiment;
Xianliang Wang contributed significantly to analysis and manuscript preparation;
Peng Xu, Shun Lu performed the data analyses and wrote the manuscript;
Lintao Li helped perform the analysis with constructive discussions.

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.

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