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Case Report

A Case of Diffuse Astrocytoma with 32-year Survival after Boron Neutron Capture Therapy

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A 39-year-old man had received boron neutron capture therapy (BNCT) for a grade II astrocytoma (compatible with diffuse astrocytoma, not otherwise specified in the WHO 2016 criteria). He returned to his previous work after surgery, but, 7 years later, he suddenly developed seizures, and his health condition deteriorated. Therefore, he underwent a second surgery. The mass removed in the second operation was mostly necrotic as a result of previous radiation treatment. He then showed no signs of recurrence and did not require any treatment other than antiepileptic drugs for 25 years. He was able to be employed by a listed company until the age of 65 years for light jobs as a physically handicapped individual. This case suggests the effectiveness of BNCT even for rather low-grade astrocytomas.

Keywords: diffuse astrocytoma, neutron capture therapy, long-term survival

Introduction

The mainstream conditions for which boron neutron capture therapy (BNCT) is used are glioblastomas or other malignant tumors. However, even for patients with low-grade astrocytomas, tumor development might be the primary cause of death,[1,2] since the survival rates of patients with low-grade astrocytomas at 20 years were 22% and 26%. These facts imply surgery alone is insufficient to treat low-grade gliomas and necessitate the addition of medical or radiological treatments. It has been difficult to expand the indications for reactor-based BNCT to low-grade gliomas. Recently, accelerator-based neutron emitters have become available. Therefore, in our opinion, accelerator-based BNCT should be one of the treatments of choice even for diffuse astrocytoma. This case report suggests the effectiveness of BNCT, even for rather low-grade astrocytomas.

Case Report

A 39-year-old man suddenly felt dizzy and had convulsive sensations in the occipital region when he was on a train. He lost consciousness and had left hand convulsions. He did not show any obvious neurological problems on admission to Inagi Municipal Hospital.

CT showed a small low-density area in the left frontal convexity without obvious enhancement (Fig. 1A). MRI (T_1-weighted) showed a distinct low signal area in the left frontal lobe (Fig. 1B).

On Day 25 of admission, he underwent surgery via left frontal craniotomy for a suspected low-grade astrocytoma (Fig. 1C). A pinkish, elastic, well-demarcated tumor was extirpated totally. The pathological diagnosis was astrocytoma grade II, with proliferation of neoplastic astrocytes with abundant nuclear atypia in various-sized round nuclei, but without obvious pleomorphic features (Figs. 1D and 1E).

He was then transferred to University Hospital, and on Day 46 of admission, he received BNCT[3–7] using the previous craniotomy site. Antecedently 5 g (80 mg/kg) of BSH ($Na_2{}^{10}B_{12}H_{11}SH$) was administered via the left internal carotid artery from 20:00 to 20:26 the prior night. Intracarotid administration was the usual method at that time; however, after development of CT and other imaging modalities, we become aware that sufficient delivery of medicaments to the target site is possible via venous administration.[7,8] The 5 g of BSH administered over the course of 26 minutes is equivalent to approximately 48 mg^{10}B/kg. No residual tumors were found in the previous operation site with the naked eye. Thermal neutron irradiation was conducted the afternoon following BSH administration for a total of 5 hours and 39 min. At that time, the thermal neutron fluence on the apex of the left frontal lobe was estimated to be 1.1×10^{13} nvt. Therefore, surface fluence was calculated to be 1.58×10^{13} nvt. This implies delivery of 6–8 Gy-Eq to the normal tissue without ^{10}B, which has an 8–10 times greater radiation effect on the ^{10}B-containing cells than tissue without ^{10}B. For the tissues within the beam, non-thermal neutron effects are 2–4 Gy-Eq and γ-rays are 3–4 Gy-Eq. We did not obtain other information at that time, for example, ^{10}B concentration in the blood.

He was discharged on Day 62 of admission. MRI (T_1-weighted) at 35 days after BNCT showed no residual tumors (Fig. 1F). Approximately 6 months after the first operation, he was able to return to his previous full-time work.

Six years and two months later, he had a sudden seizure and showed right hand weakness and slowing of speech. CT findings at that time (Fig. 2A) showed an increase in the size of the edematous area surrounding the calcification. Prednisolone 20 mg daily was started, and this treatment was somewhat effective for decreasing the edematous area.

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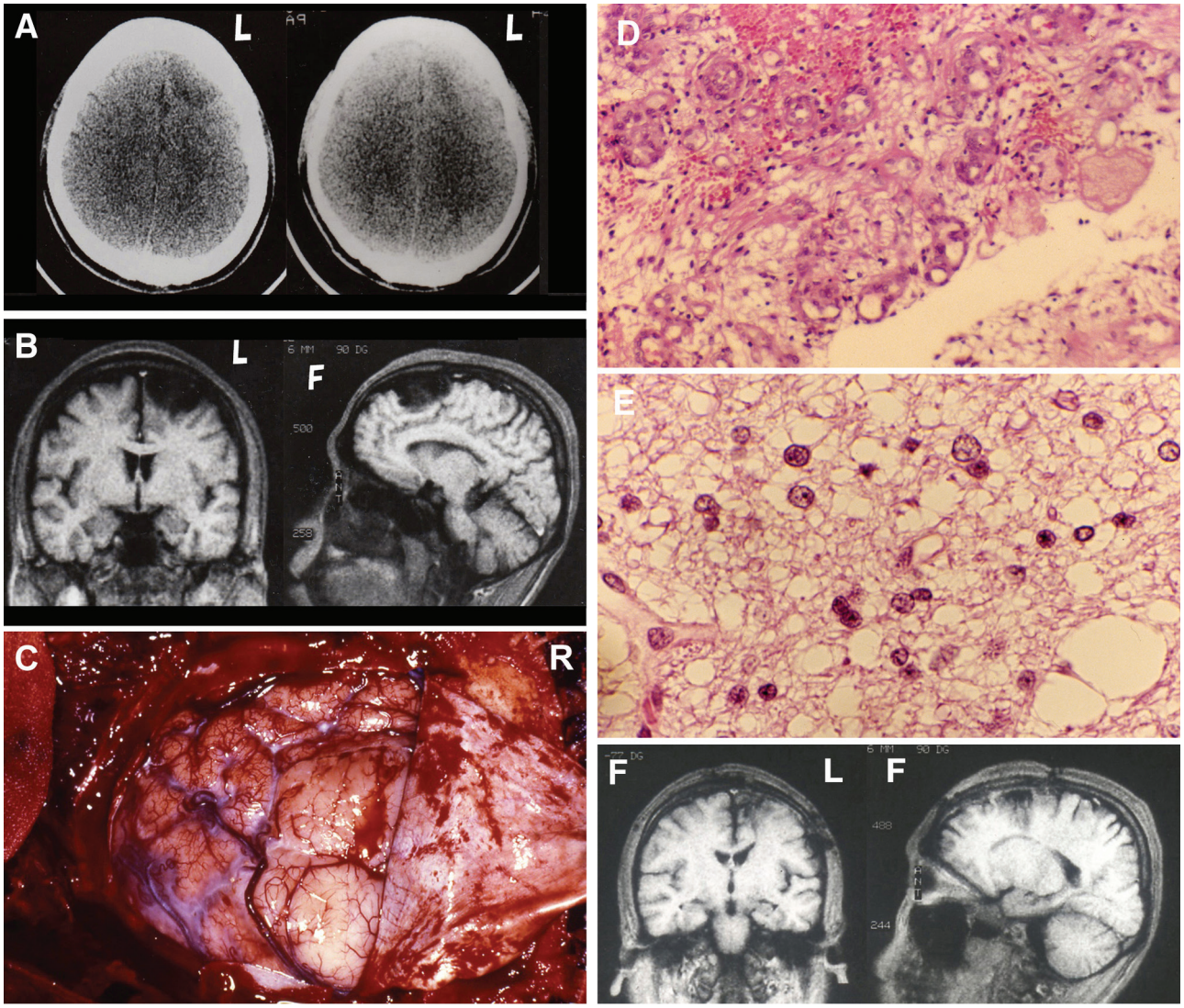

Fig. 1 (**A**) CT on admission. (**B**) MRI (T_1-weighted) CE (-) on Day 15 of admission. (**C**) A view after the left frontal craniotomy and the dura mater was opened. (**D and E**) Histology of the first operation. (**D**) (×100 HE): small stellate tumor cells without obvious pleomorphic features form microcysts with glial fibers. There are many capillaries without endothelial proliferation. (**E**) (×400 HE): In this section, neoplastic astrocytes with round or oval-shaped nuclei proliferate in the white matter forming microcysts with glial fibers. (**F**) MRI (T_1-weighted) CE (-) on Day 88 of admission, 35 days after BNCT.

However, generalized convulsions occurred again, and various anticonvulsants were increasingly added.

Seven years and 5 months after the first surgery, he was re-hospitalized in a wheelchair because his neurological condition had gradually deteriorated. He could hardly walk except for a short distance. He showed anisocoria, right hemiparesis, and dysphasia, and he always complained of sleeplessness. CT findings on the second admission showed a mass effect with midline shift. MRI (T_1-weighted) with Gd enhancement showed several irregular ring enhancements surrounded with the low signal area (Fig. 2B). He underwent a second operation on Day 13 of the second admission. The dura mater was opened, and the craniotomized area was seen to be occupied with an amorphous hard mass, which was totally removed en bloc. The residual hard rim was also carefully removed. In accordance with the CT and MRI findings, the cut surface of the tumor mass was also amorphous and had some calcified parts.

Microscopically (Fig. 2C), most of the mass contained abundant hyaline substance mixed with fibrous connective tissue and scattered calcification. In some small areas, large glial cells with homogeneously eosinophilic cytoplasm and densely condensed small nuclei were observed. These cells were consistent with glioma cells severely damaged by irradiation. These microscopic features were in accordance with grade III damage of Oboshi's criteria for evaluation of the radiation effect.[9]

Postoperatively, his speech disturbance and hemiparesis were rather worse. By Day 25 of the second admission, he had recovered gradually and was able to stand.

On Day 35 of the second admission, he became confused. He was found to have a large cyst with an enhanced round

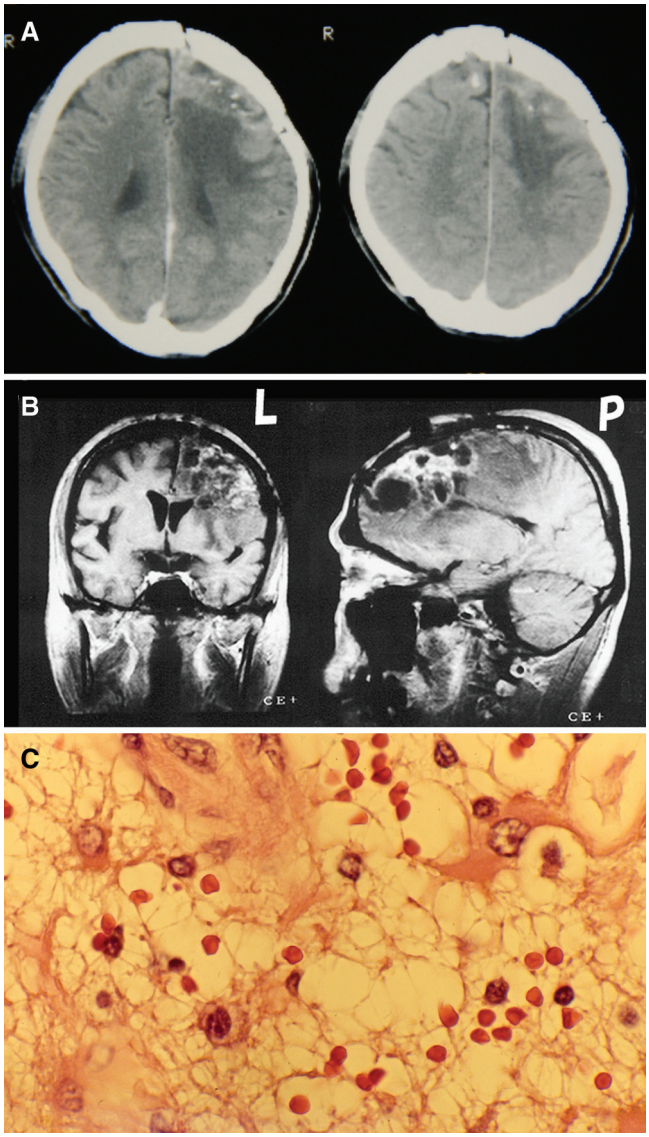

Fig. 2 (**A**) CT findings CE (+) at 6 years and 2 months after BNCT, when the patient became sick. (**B**) MRI (T_1-weighted) CE (+) at 7 years and 6 months after BNCT. Before the second operation. (**C**): Histology of the 2nd operation (×400, HE). Most of the tumor contained abundant hyaline substance mixed with fibrous connective tissue and scattered calcification. In some small areas, large glial cells with homogeneously eosinophilic cytoplasm and densely condensed small nuclei were observed.

rim at the previous tumor site on CT (Fig. 3A). Cyst tapping was done, and a xanthochromic viscous fluid was obtained. The laboratory results showed pleocytosis (4834/mm^3) and an abundance of protein (4.3 g/L). No bacilli were detected on specimen culture. Therefore, the cyst punctures were repeated four times until Day 56 of the second admission. These procedures were effective. He became more active and energetically received physical therapy and trained by himself.

On Day 270 of the second admission, he was discharged because he had gradually shown improvement in motor activity and speech. His Kernohan's Performance Status had recovered to 70. He returned to full-time employment for a while, but he could not keep working because of the language disorder. He could walk slowly using a simple cane. His speech was halting, but not aphasic.

He maintained this condition for several years. MRI showed that the tumor sites were replaced with the enlarged anterior horn of the left lateral ventricle. Eleven years and twelve years after the second surgery, MRI findings showed improvement, with reduced size of the residual cysts (Figs. 3B and 3C), and the apparent diffusion coefficient of the cyst content was comparable to that of the ventricular fluid (Fig. 3D).

He had difficulty finding a new employer for several years, but finally he was employed by a listed company as a physically handicapped person for 9 years until his retirement at age 65 years. His commute to the office consisted of an approximately 20-minute walk and a 15-minute train ride. Follow-up MRI 20 years after the second surgery showed no interval changes, except the bone flap had been removed by a plastic surgeon to repair the scalp defect. Despite seizures being well controlled with carbamazepine (200 mg b.i.d.) until 22 years after his second operation, the seizures increased in frequency, and they were then controlled with levetiracetam (500 mg b.i.d.). At that time, MRI appeared to show some increased enhancement at the frontal convexity, but there were no remarkable changes after that time (Fig. 4). He did not want to have an exploratory incision. He could visit as an ambulatory outpatient with a 20-minute walk using only a simple cane.

Discussion

In this case, the patient had a rather well-defined, low-grade tumor. The development of a space-occupying lesion was noticed 7 years after treatment. The period of reoperation was comparable to the reported progression-free time (5.3–5.5 years) of astrocytoma grade II.[10,11] From a histological viewpoint, the pathological findings of the specimen taken at the second operation were mostly in accordance with grade III of Oboshi's criteria for evaluation of the therapeutic effects of radiation,[9] which are used at the Japan National Cancer Research Center Hospital. Grade III corresponds to the efficacy of radiation therapy, that is, the tissue shows a markedly altered appearance, in which presumably non-viable tumor cells are present singly or in small clusters, and viable cells are hardly seen.

Hatanaka and Nakagawa reported a tumor-to-blood ratio of about 2:1 at 17.5 h after the end of an intracarotid infusion of BSH in 39 patients treated in Japan.[5] Gabel et al.[12] reported that the average value for the tumor-to-blood ratio ranged from 1.3:1 to 2:1 in the BSH results from four centers in Europe. These relatively low tumor-to-blood ratios suggest that passive diffusion from blood through an incomplete blood–brain barrier (BBB) is the primary mode of accumulation of BSH in tumor. In BNCT, the ionization energy from $^{10}B(n,\alpha)^7Li$ reaction that reaches the vascular endothelial cells is the cause of the radiation necrosis, as the smallest capillaries in the brain have an internal diameter of about 8 μm and wall thickness of 0.1 to 0.3 μm. Especially, as in the present case in which the tumor was totally removed, adjacent tissues might be involved due to endothelial damage.[12,13]

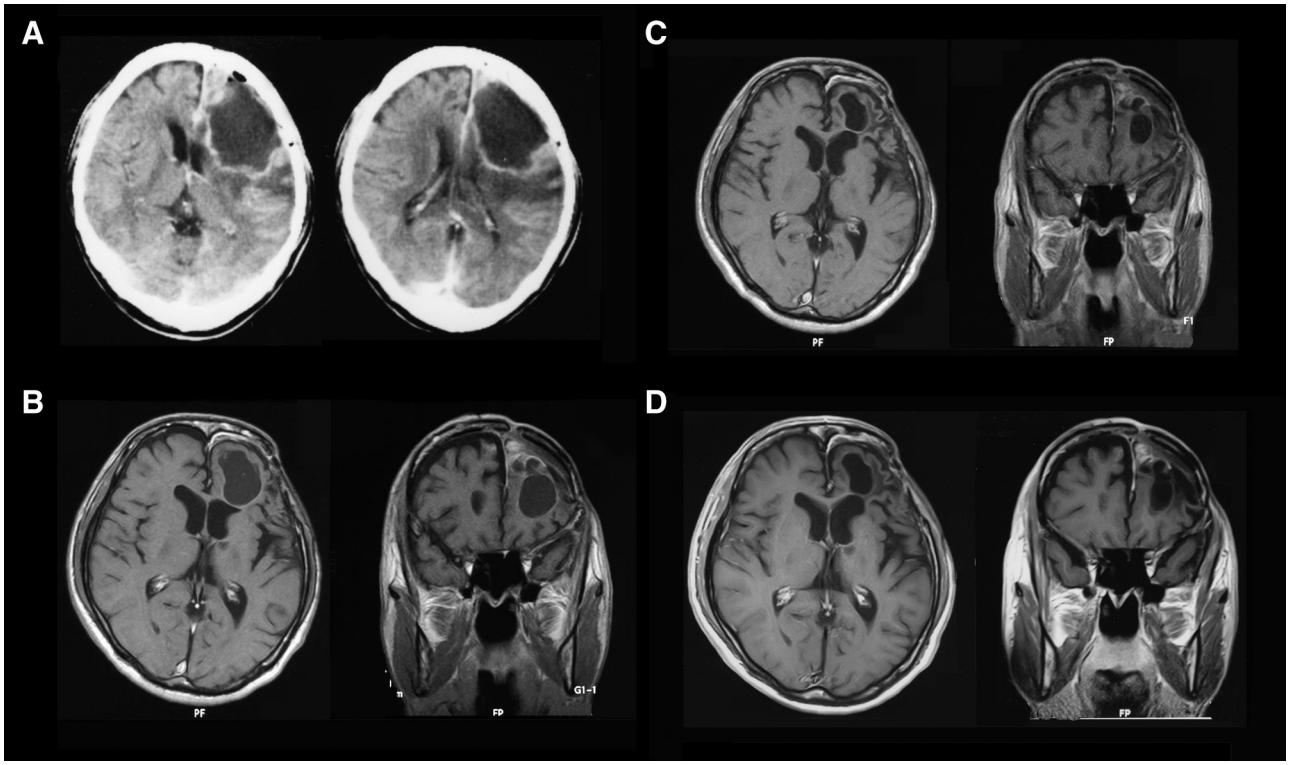

Fig. 3 (**A**) CT on Day 35 after the second operation shows a large cyst with an enhanced round rim at the previous tumor site. The laboratory results of the cyst content showed pleocytosis (4834/mm^3) and an abundance of protein (4.3 g/L). No bacilli were detected in specimen culture. (**B**) MRI (T_1-weighted) CE (+) at 14 years and 2 months after BNCT. (**C**) MRI (T_1-weighted) CE (+) at 17 years and 8 months after BNCT. (**D**) MRI (T_1-weighted) CE (+) at 18 years and 11 months after BNCT.

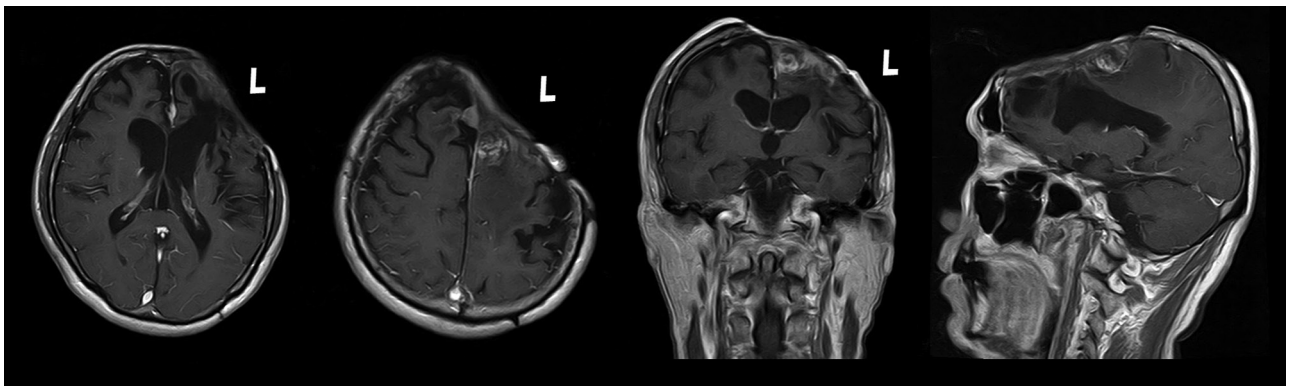

Fig. 4 MRI (T_1-weighted) CE (+) at 31 years and 7 months after BNCT.

The patient has shown no sign of recurrence in the last 25 years. His CT or MRI findings have remained stable for tumor growth, and the tumor sites and areas of radiation necrosis have been replaced with cysts of protein-rich fluid and the enlarged anterior horn of the left lateral ventricle. Moreover, the size of the largest cyst had diminished, and the concentration of protein within it appeared to be decreased in the recent examinations. Compared to the penetrating ability of X-rays or γ-rays, the penetration depth of thermal or epithermal neutron rays is limited. Careful selection of radiation doses to limit exposure to within the area containing tumor cells is mandatory.

The case presented here shows some histological effects of radiation necrosis. On the other hand, Scerrati et al.[14] reported that the extent of surgical excision is important, and they achieved a median survival of 12 years for supratentorial WHO grade II gliomas. Recently, survival rates over 26% at 15 years were reported with multimodality treatment.[15–17] Survival rates of 22% and 26% at 20 years have also been reported, but even for patients with low-grade astrocytomas, tumor development might be the primary cause of death.[1,2] A report on the EORTC 22845 randomized trial suggested that early radiotherapy after surgery lengthens

the period without progression but does not affect overall survival. Radiotherapy can be deferred for patients with low-grade glioma who are in a good condition, provided they are carefully monitored.[18] Therefore, although the present patient was not an extraordinarily long survivor, this is still a report of a rare case as the longest survivor after BNCT.

Recent reports on BNCT are limited to glioblastomas and malignant meningiomas,[19–21] though the results are quite limited. Kageji et al.[22] reported that, in newly diagnosed glioblastoma patients, median survival time (MST) was 19.5 months and 2-, 3-, and 5-year survival rates were 31.8%, 22.7%, and 9.1%, respectively.[22] Miyatake et al. reported that the MST for patients with newly diagnosed glioblastoma treated with surgery and BNCT followed with XRT boost was 23.5 months, compared to 15.6 months for surgery with BNCT alone and 10.3 months for the historical controls.[21]

Currently, accelerator-based neutron sources have been developed as neutron sources in hospital settings.[23,24] For treatment of diffuse astrocytoma, as almost all patients eventually succumb to their disease, BNCT could be one of the choices for treatment, and precedent surgical removal of the tumor as much as possible is essential.

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Conflicts of Interest Disclosure

All authors have no conflict of interest.

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