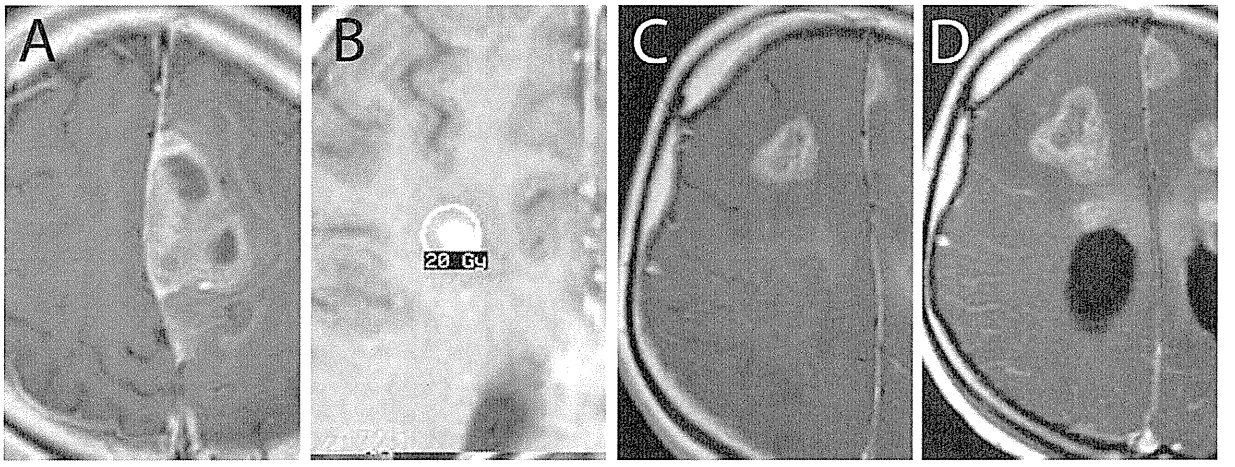

Figure 1. Case 7 in Table 1 is shown: (A) axial gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) at presentation; (B) dose planning of stereotactic radiosurgery for recurrence; (C, D) MRI taken at 1 (C) and 3 months (D) after stereotactic radiosurgery showing tumor progression.

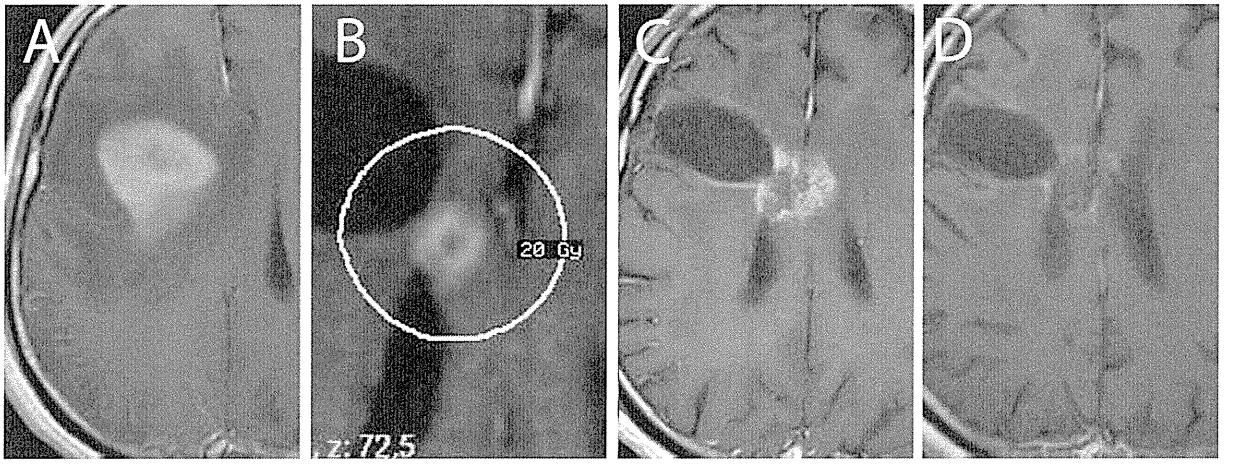

Figure 2. Case 1 in Table 2 is shown: (A) axial gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) at presentation; (B) dose planning of stereotactic radiosurgery for recurrence; (C) MRI taken at 1 month after stereotactic radiosurgery showing diffuse enhancement around treated lesion; (D) MRI taken at 25 months after stereotactic radiosurgery showing no recurrence.

which temozolomide at a dose of 200 mg/m^2 using the 5 of 28-day regimen was initiated. After the third cycle of temozolomide, eruption and thrombocytopenia were observed, so chemotherapy was switched to nimustine hydrochloride (100 mg/dose), which was administered intravenously once a month thereafter. Although complete remission was maintained until 17 months after the onset, a recurrent lesion 10 mm in diameter was observed near the resection cavity in the right frontal lobe. Extended field SRS was applied to this lesion. The clinical target volume was set as the gadolinium-enhanced lesion plus a 1-cm–wide margin, and 20 Gy was prescribed at the margin of this wide target (Fig. 2B). One month after the SRS, diffuse enhancement around the irradiated area was observed (Fig. 2C). As radiation necrosis was suspected, oral prednisolone at a dose of 30 mg daily was initiated, and the area of enhancement ceased to expand thereafter. At 25-month follow-up after the SRS, the treated lesion had been locally controlled, and no new recurrence was noted (Fig. 2D).

A 27-year-old man (case 2 in Table 2) presented with right hemiparesis. MRI revealed a homogeneously enhanced mass in the right frontal lobe (Fig. 3A). Stereotactic biopsy was performed, and the diagnosis of glioblastoma was obtained. He received 60-Gy external beam radiotherapy followed by adjuvant temozolomide at a dose of 200 mg/m^2 using the 5 of 28-day regimen. Complete remission was achieved and maintained until 39 months after the onset, when a recurrent lesion (maximal diameter, 15 mm) was noted in the right frontal lobe

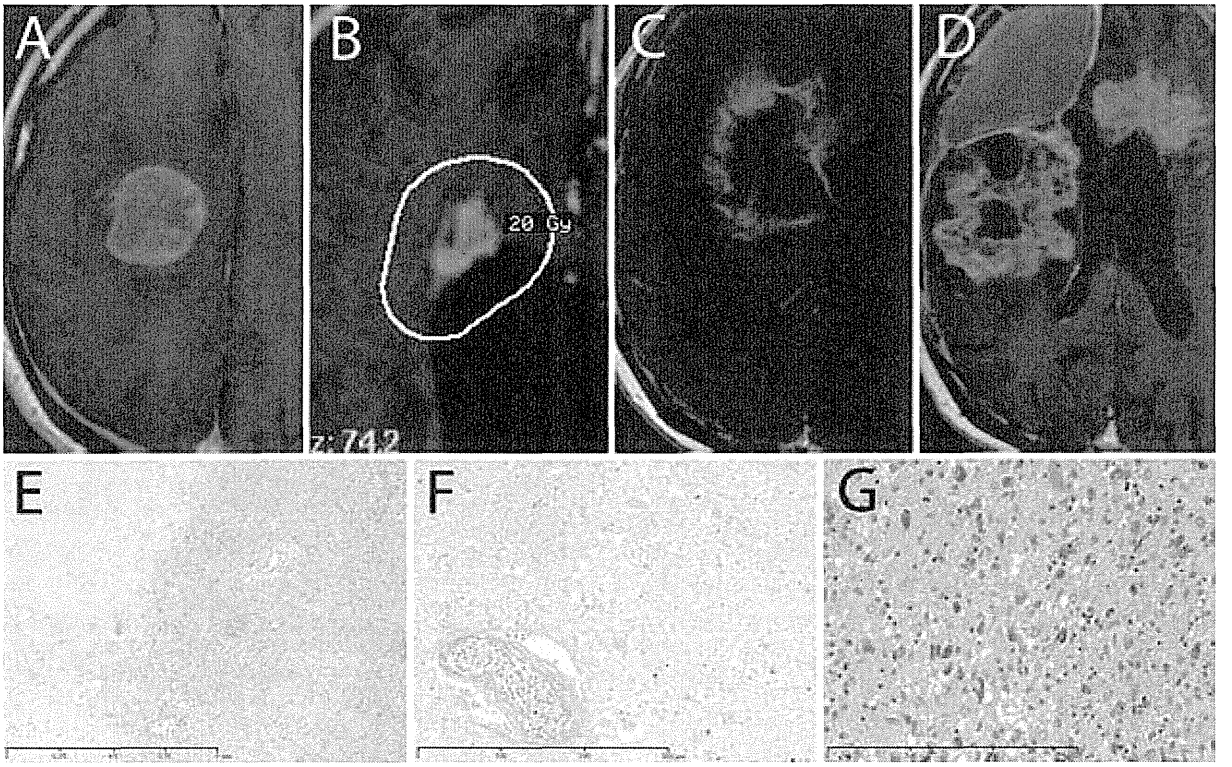

Figure 3. Case 2 in Table 2 is shown. (A) Axial gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) at presentation is shown. (B) Dose planning of stereotactic radiosurgery for recurrence. (C) MRI taken at 5 month after stereotactic radiosurgery revealed progression of enhancing lesion around the treated area. (D) MRI taken at 12 months after stereotactic surgery revealed continued tumor growth. (E-G) Hematoxylin and eosin staining of a surgical specimen at recurrence (E) revealed focuses of radiation necrosis (F) surrounded by an area of tumor with high cellularity (G).

beneath the wall of the right lateral ventricle. This recurred lesion was treated by extended field SRS targeting the gadolinium-enhanced lesion plus a 1-cm–wide margin. Prescribed margin dose was 20 Gy (Fig. 3B). Heterogeneous enhancement appeared at the irradiated site 1 month after the SRS and continued to grow despite the use of oral prednisolone. Frontal lobectomy was performed 5 months after the SRS to decrease the tumor mass that caused deterioration of the consciousness level (Fig. 3C). Recurrence of glioblastoma was confirmed by a histological examination, and the tumor continued to grow diffusely after the surgery. The patient died of tumor progression 12 months after the SRS for recurrence (Fig. 3D). Histologically, the surgical specimens at recurrence (Fig. 3E) consisted of focal areas of radiation necrosis (Fig. 3F) surrounded by areas of viable tumors with high cellularity consistent with glioblastoma (Fig. 3G).

DISCUSSION

Our results showed that extended field SRS potentially provided improved local control of isolated recurrence of glioblastoma without causing uncontrollable symptomatic radiation necrosis. In several studies analyzing patients treated with radiation and temozolomide, 72% to 92% of recurrence was revealed as local relapse,[25,26] the most frequent pattern of glioblastoma recurrence.[6] Local control is also important for recurrent lesions, but treatment with SRS led to local progression in 65% to 90%,[14,27-29] which was in line with our result with conventional SRS targeting only the gadolinium-enhanced area. The logical assumption regarding the reason for this lack of efficacy is that SRS, owing to its characteristic feature of steep dose falloff, is unable to kill tumor cells infiltrating the tissue outside the irradiated field.[20,27] When we extended the irradiation field with the intent to include as many tumor cells invasive to the surrounding tissue as possible, we achieved a high local control rate of 93%. This result showed that extended field SRS was highly effective in controlling recurrent glioblastoma for selected patients found with small lesions. One limitation of this treatment is that it is not applicable to lesions larger than approximately 20 mm in diameter. Adding a sufficient margin to a large lesion results in a large prescribed isodose volume, and may cause uncontrollable radiation-

induced adverse events. A close radiological follow-up after the initial treatment is necessary to detect such small recurrent lesions for this treatment to be suitable for an extended field SRS application. Stereotactic fractionated radiotherapy may be 1 treatment option for larger recurrent lesions. By using 11-C-methionine positron emission tomography for targeting, stereotactic fractionated radiotherapy was reported to have achieved the median survival time of 9 months.[30] Although the incidence of radiation necrosis after SRS was not significantly different between conventional and extended field SRS, all patients who developed radiation necrosis after extended field SRS required steroid administration. This risk of eventual necessity of steroid administration may be another limitation of this approach.

Whereas extended field SRS achieved a high local tumor control rate, it did not show a significant survival benefit compared with conventional SRS in our study. All patients treated with extended field SRS received external beam radiation therapy and temozolomide before SRS. The majority of patients treated with extended field SRS died of remote recurrences within the brain. Because the rates of new recurrences in patients treated with temozolomide and radiation are quite high to begin with, 25% at 1 year and 66% at 2 years,[26] the role of extended field SRS for the occurrence of remote recurrences is unclear. Obviously, radiation therapy, including SRS, and temozolomide are not sufficient to control the disease. New approaches are underway, including monoclonal antibodies that target specific molecules, for example, bevacizumab,[31,32] and oncolytic viruses that replicate selectively in tumor cells.[33]

In conclusion, extended field SRS was well tolerated and superior to conventional SRS in the local control of small recurrent lesions of glioblastoma, although a further device to suppress remote recurrences may be necessary to improve survival.

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The authors made no disclosures.

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