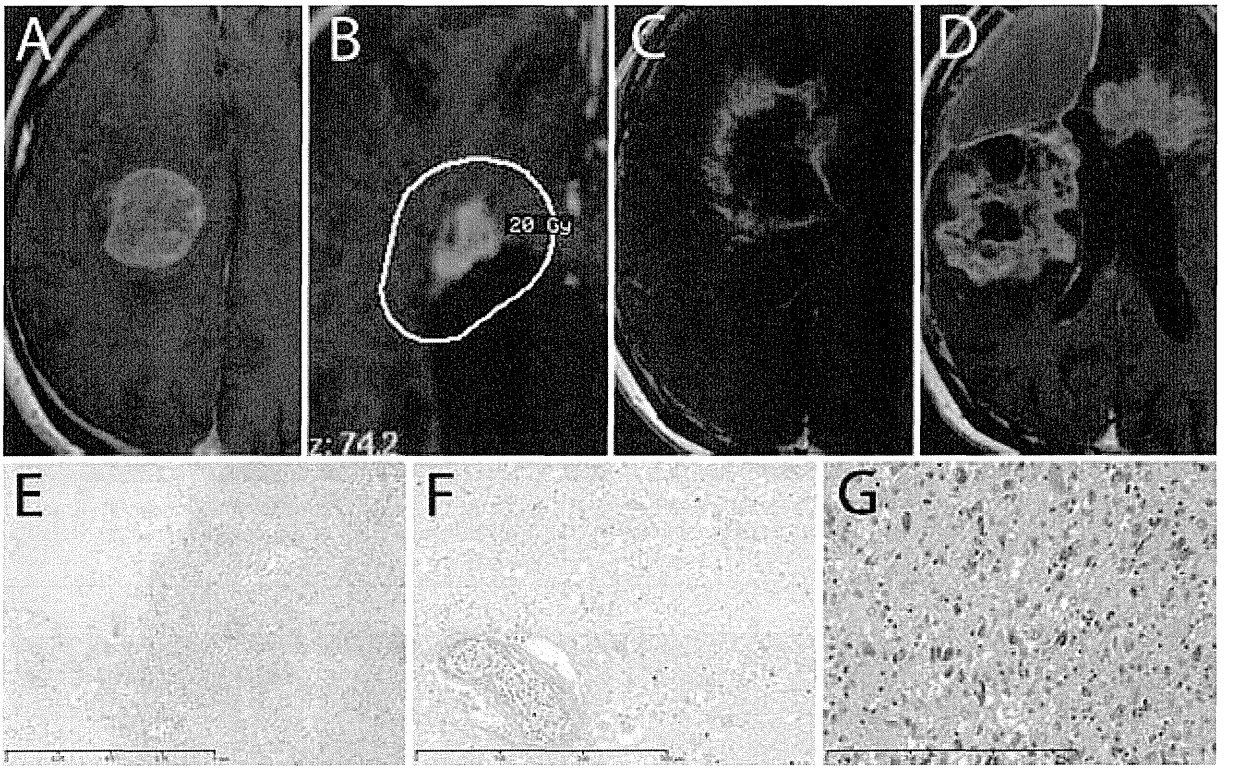

Figure 3. Case 2 in Table 2 is shown. (A) Axial gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) at presentation is shown. (B) Dose planning of stereotactic radiosurgery for recurrence. (C) MRI taken at 5 month after stereotactic radiosurgery revealed progression of enhancing lesion around 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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REFERENCES

1. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. World Health Organization Histological Classification of Tumours of the Central Nervous System. 4th ed. Lyon, France: International Agency for Research on Cancer; 2007.
2. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352:987-996.
3. Dirks P, Bernstein M, Muller PJ, Tucker WS. The value of reoperation for recurrent glioblastoma. *Can J Surg.* 1993;36:271-275.
4. Larson DA, Suplica JM, Chang SM, et al. Permanent iodine 125 brachytherapy in patients with progressive or recurrent glioblastoma multiforme. *Neuro Oncol.* 2004;6:119-126.
5. Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol.* 1999;17:2572-2578.
6. Chang SM, Parney IF, Huang W, et al. Patterns of care for adults with newly diagnosed malignant glioma. *JAMA.* 2005;293:557-564.
7. Hau P, Baumgart U, Pfeifer K, et al. Salvage therapy in patients with glioblastoma: is there any benefit? *Cancer.* 2003;98:2678-2686.
8. Kano H, Niranjan A, Kondziolka D, Flickinger JC, Lunsford LD. Outcome predictors for intracranial ependymoma radiosurgery. *Neurosurgery.* 2009;64:279-287.
9. Kinoshita M, Izumoto S, Kagawa N, Hashimoto N, Maruno M, Yoshimine T. Long-term control of recurrent anaplastic ependymoma with extracranial metastasis: importance of multiple surgery and stereotactic radiosurgery procedures—case report. *Neurol Med Chir (Tokyo).* 2004;44:669-673.
10. Endo H, Kumabe T, Jokura H, Shirane R, Tominaga T. Stereotactic radiosurgery for nodular dissemination of anaplastic ependymoma. *Acta Neurochir (Wien).* 2004;146:291-298.
11. Kano H, Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD. Stereotactic radiosurgery for pilocytic astrocytomas part 1: outcomes in adult patients. *J Neurooncol.* 2009;95:211-218.
12. Koga T, Morita A, Maruyama K, et al. Long-term control of disseminated pleomorphic xanthoastrocytoma with anaplastic features by means of stereotactic irradiation. *Neuro Oncol.* 2009;11:446-451.
13. Larson DA, Gutin PH, McDermott M, et al. Gamma knife for glioma: selection factors and survival. *Int J Radiat Oncol Biol Phys.* 1996;36:1045-1053.
14. Souhami L, Seiferheld W, Brachman D, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. *Int J Radiat Oncol Biol Phys.* 2004;60:853-860.
15. Kondziolka D, Flickinger JC, Bissonette DJ, Bozik M, Lunsford LD. Survival benefit of stereotactic radiosurgery for patients with malignant glial neoplasms. *Neurosurgery.* 1997;41:776-783.
16. Chamberlain MC, Barba D, Kormanik P, Shea WM. Stereotactic radiosurgery for recurrent gliomas. *Cancer.* 1994;74:1342-1347.
17. Kong DS, Lee JI, Park K, Kim JH, Lim DH, Nam DH. Efficacy of stereotactic radiosurgery as a salvage treatment for recurrent malignant gliomas. *Cancer.* 2008;112:2046-2051.
18. Combs SE, Widmer V, Thilmann C, Hof H, Debus J, Schulz-Ertner D. Stereotactic radiosurgery (SRS): treatment option for recurrent glioblastoma multiforme (GBM). *Cancer.* 2005;104:2168-2173.
19. Mehta MP, Masciopinto J, Rozental J, et al. Stereotactic radiosurgery for glioblastoma multiforme: report of a prospective study evaluating prognostic factors and analyzing long-term survival advantage. *Int J Radiat Oncol Biol Phys.* 1994;30:541-549.
20. Masciopinto JE, Levin AB, Mehta MP, Rhode BS. Stereotactic radiosurgery for glioblastoma: a final report of 31 patients. *J Neurosurg.* 1995;82:530-535.
21. Wallner KE, Galicich JH, Krol G, Arbit E, Malkin MG. Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma. *Int J Radiat Oncol Biol Phys.* 1989;16:1405-1409.
22. Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. *Neurology.* 1980;30:907-911.
23. Massager N, Maris C, Nissim O, Devriendt D, Salmon I, Levivier M. Experimental analysis of radiation dose distribution in radiosurgery. II. Dose fall-off outside the target volume. *Stereotact Funct Neurosurg.* 2009;87:137-142.
24. Schiffer D, Cavalla P, Dutto A, Borsotti L. Cell proliferation and invasion in malignant gliomas. *Anticancer Res.* 1997;17:61-69.
25. Brandes AA, Tosoni A, Franceschi E, et al. Recurrence pattern after temozolomide concomitant with and adjuvant to radiotherapy in

newly diagnosed patients with glioblastoma: correlation with MGMT promoter methylation status. *J Clin Oncol.* 2009;27:1275-1279.
26. Milano MT, Okunieff P, Donatello RS, et al. Patterns and timing of recurrence after temozolomide-based chemoradiation for glioblastoma. *Int J Radiat Oncol Biol Phys.* 2010;78:1147-1155.
27. Pouratian N, Crowley RW, Sherman JH, Jagannathan J, Sheehan JP. Gamma Knife radiosurgery after radiation therapy as an adjunctive treatment for glioblastoma. *J Neurooncol.* 2009;94:409-418.
28. Shrieve DC, Alexander E III, Black PM, et al. Treatment of patients with primary glioblastoma multiforme with standard postoperative radiotherapy and radiosurgical boost: prognostic factors and long-term outcome. *J Neurosurg.* 1999;90:72-77.
29. Sarkaria JN, Mehta MP, Loeffler JS, et al. Radiosurgery in the initial management of malignant gliomas: survival comparison with the RTOG recursive partitioning analysis. Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys.* 1995;32:931-941.
30. Grosu AL, Weber WA, Franz M, et al. Reirradiation of recurrent high-grade gliomas using amino acid PET (SPECT)/CT/MRI image fusion to determine gross tumor volume for stereotactic fractionated radiotherapy. *Int J Radiat Oncol Biol Phys.* 2005;63:511-519.
31. Gutin PH, Iwamoto FM, Beal K, et al. Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys.* 2009;75:156-163.
32. Vordermark D, Kolbl O, Ruprecht K, Vince GH, Bratengeier K, Flentje M. Hypofractionated stereotactic re-irradiation: treatment option in recurrent malignant glioma. *BMC Cancer.* 2005;5:55.
33. Todo T. Oncolytic virus therapy using genetically engineered herpes simplex viruses. *Front Biosci:* 2008;13:2060-2064.