ISSN 1738-6217
J Kor Soc Ster Func Neurosurg 2018;14(1):10-13

CASE REPORT

Fractionated Radiosurgical Hypophysectomy for Refractory Pain in Patient with Recurrent Glioblastoma Multiforme

Mi Sun Kim, MD[2], Je Beom Hong, MD[1], Joopyung Kim, MD, PhD[1]

[1]Department of Neurosurgery, CHA Bundang Medical Center, CHA University, Seongnam, Korea
[2]Department of Radiation Oncology, CHA Bundang Medical Center, CHA University, Seongnam, Korea

Intractable cancer pain was apparently managed with hypophysectomy more than five decades ago. However, the procedure was associated with serious postoperative complications including panhypopituitarism, diabetes insipidus, chemical meningitis, visual dysfunction, and hypothalamic insult. As an alternative to surgical or chemical interventions, radiosurgical hypophysectomy has been used to control intractable cancer pain without serious complications. However, in a 50-year-old patient treated with 60Gy concurrent chemoradiotherapy and Gamma knife radiosurgery for recurrent glioblastoma multiforme, the adverse effects of re-irradiation as well as pain control were minimized using fractionated radiosurgical hypophysectomy.

KEY WORDS: Fractionated radiosurgical hypophysectomy · Recurrent glioblastoma multiforme · Opioid-refractory pain.

INTRODUCTION

Eighty to ninety % of cancer patients suffer from severe pain. A fair number of patients in palliative care report refractory pain, which can be very distressing for patients and their families, affecting their overall quality of life.[3)15)16)] The several therapeutic options for cancer pain include pharmacological, neuro-modulatory and intrathecal therapies. However, despite these treatments, a considerable number of patients suffer from intractable pain.

Attempts were first made to treat intractable pain via hypophysectomy more than six decades ago. Luft and Olivecrona[13)] announced the first control of cancer pain using surgical hypophysectomy in patients with breast cancer in 1953. Subsequently, chemical hypophysectomy with alcohol was introduced as a less-invasive treatment.[9)12)] The overall clinical outcomes of surgical and chemical hypophysectomy were favorable with 60 to 70% pain relief. However, the procedure was associated with serious postoperative complications including panhypopituitarism, diabetes insipidus, chemical meningitis, visual dysfunction, and hypothalamic insult. As an alternative to surgical or chemical approaches, radiosurgical hypophysectomy has been used. Backlund and colleagues[1)2)] treated cancer pain with radiosurgical hypophysectomy using the gamma knife system targeting the pituitary gland for the first time in 1972. To avoid complications associated with high-dose radiation, Hayashi and colleagues[5)] reported radiosurgical hypophysectomy using relatively low irradiation doses below 140−160Gy, resulting in control of intractable cancer pain without serious complications.

In case of brain tumor, patients usually receive radiotherapy as a first-line treatment. Although concurrent chemoradiotherapy with temozolomide improves survival outcomes of patients with brain tumor, most patients experience recurrences.[14)] Radiosurgical hypophysectomy in patients manifesting refractory pain associated with recurrent brain tumor is a challenge. We report the effect of fractionated radiosurgical hypophysectomy in a patient with glioblastoma multiforme (GBM).

CASE REPORT

A 50-year-old male presented at another institution with complaints of progressive headache and dizziness. Magnetic resonance imaging (MRI) revealed a brain tumor. The patient underwent tumor removal and was diagnosed with GBM. The treatment included concurrent chemoradiotherapy using 60Gy of radiation and temozolomide in 2006.

In 2015, tumor recurrence was detected during a follow-up MRI. The patient underwent re-operation, gamma knife radiosurgery and 8 cycles of temozolomide. Nevertheless, the patient's symptoms deteriorated resulting in

Address for correspondence: Joopyung Kim, MD, PhD
Department of Neurosurgery, CHA Bundang Medical Center, CHA University, 59 Yatap-ro, Bundang-gu, Seongnam 13496, Korea
Tel: +82-31-780-5697, Fax: +82-31-780-5269
E-mail: jpkim@cha.ac.kr

right hemiplegic paralysis and motor aphasia. A second re-operation and ACNU/cisplatin chemotherapy were performed in 2016. During the course of recovery after surgery, cognitive dysfunction, right-sided hypoesthesia (face to foot) and numbness occurred. The patient exhibited allodynia at the right thoracic level 2 to 8 and constant, stedy and shooting and sharp severe pain, with a score of 10 on the visual analog scale, despite the use of narcotics, antidepressants and analgesic drugs. The patient was immobilized because of severe pain. At that time, MRI revealed a nodular enhancement at corpus callosum to right sided splenium and multifocal small nodular enhancements at left parietal and temporal lobe with mild diffusion restriction and showed irregular ring shaped enhancement in left basal ganglia with cental necrosis and noted linear enhancement along ependymal lining of bilateral lateral ventricles, mainly occipital horns (Fig. 1).

The patient received 60Gy concurrent chemoradiotherapy and Gamma knife radiosurgery previously. Therefore, to minimize the adverse effect of re-irradiation such as panhypopituitarism, diabetes insipidus, visual dysfunction, and hypothalamic insult. We planned a fractionated radio-

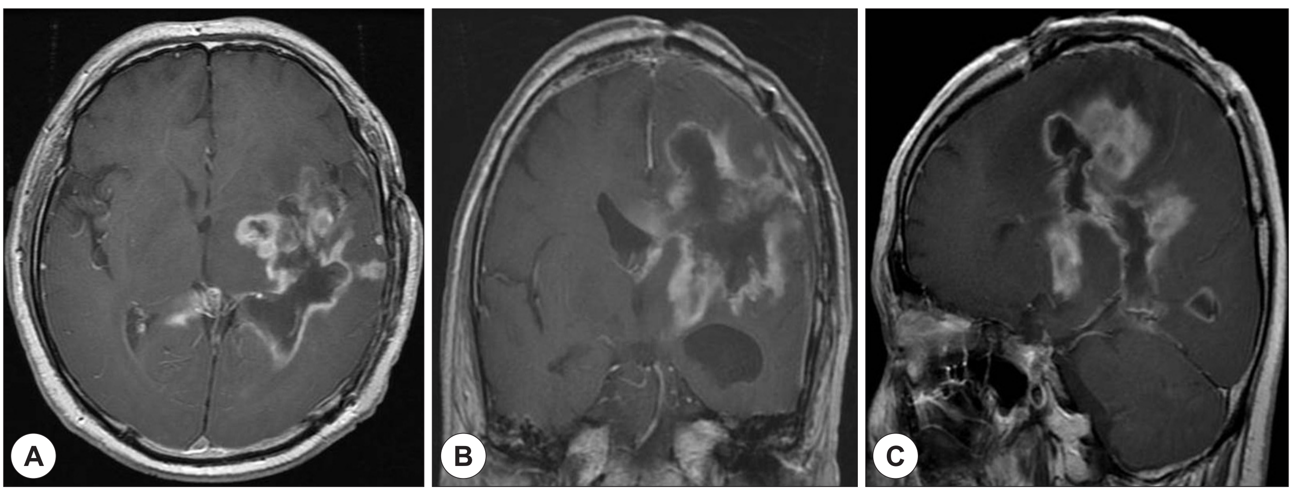

Fig. 1. Preoperative magnetic resonance imaging reveals a nodular enhancement at corpus callosum to right sided splenium and multifocal small nodular enhancements at left parietal and temporal lobe with mild diffusion restriction and show irregular ring shaped enhancement in left basal ganglia with cental necrosis on the Gd-enhanced T1-weighted image (A : Axial, B : Coronal, C : Sagittal planes).

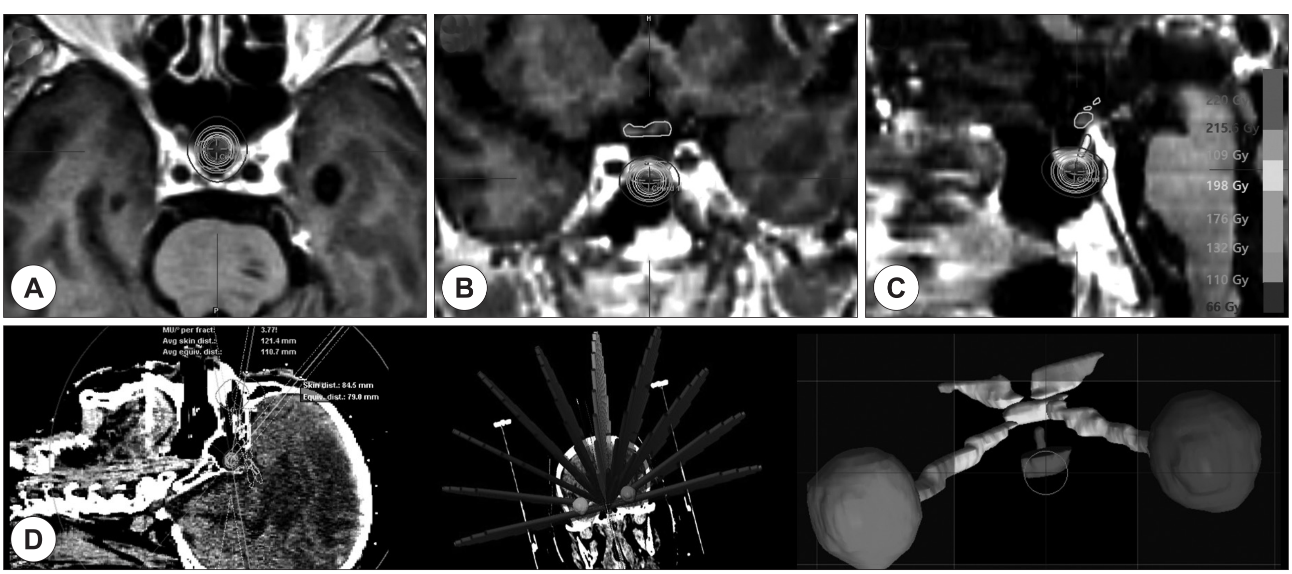

Fig. 2. Radiosurgical hypophysectomy protocol (A-C) Isodose line in magnetic resonance imaging : The 50% isodose (blue line) covers the gland-stalk junction and more than half of the gland. A : Axial, B : Coronal, and C : Sagittal planes, D : 3D dose planning image and optic pathway.

surgical hypophysectomy with Novalis (Varian Medical Systems, Inc., Palo Alto, CA, USA).

Pre-treatment visual and endocrinological function was normal. T1 gadolinium-enhanced and T2 Fluid-Attenuated Inversion Recovery (FLAIR) MRIs with 1-mm slice thickness were performed and combined with simulation computed tomography (CT) images with 1.5-mm slice thickness. The gross target volume (GTV) included gland-stalk junction, without added margin. Dose planning was performed using I-plan (version 4.5.6, Brainlab AG, Munich, Germany) Ten non-coplanar arc beams with a 10.0 mm-diameter circular arc con were used to encompass the GTV. The 50% isodose line covered the GTV (Fig. 2). The fractional dose was 55Gy. A total of 220Gy was administered during four consecutive days. The dosage regimen involved 115Gy in a single fraction equivalent to doses of 2Gy fractions (EQD2). The maximal dose to organ-at-risk was as followed; brainstem 18.59Gy, optic chiasm 20.61Gy, left optic nerve 19.76Gy, right optic nerve 18.12Gy, left optic tract 11.65Gy, and right optic tract 11.18Gy. When these were converted to biologically effective dose with conventional fractionated radiotherapy, maximal doses to organ-at-risk were tolerable (brainstem 28.43Gy, optic chiasm 33.6Gy, left optic nerve 31.38Gy, right optic nerve 27.29Gy, left optic tract 13.78Gy, and right optic tract 12.96 Gy). The patient was immobilized with a relocatable stereotactic frame comprising a thermoplastic mask (ExacTrac frameless system BrainLAB). The patient position was ensured with a 6-direction couch to minimize the geometric deviation. Image guidance was performed with a stereoscopic kilovoltage X-ray system.

Three days after radiosurgical hypophysectomy, most of the intractable pain disappeared, which reduced the need for morphine. No acute complications were detected. The effect of pain control persisted until the follow-up period. Neither visual disturbance nor hormonal dysfunction was detected during the follow-up period.

DISCUSSION

Pituitary gland-stalk irradiation has emerged as an alternative treatment option for the control of cancer pain. Stereotactic radiosurgery (SRS) is effective for the treatment of chronic intractable pain with response rates ranging between 57% and 100% (Table 1).

The main difference between surgical or chemical hypophysectomy and radiation to the pituitary is the absence of severe complications. The advantage of radiation therapy is that no morphological changes were observed as demonstrated in previous studies.[4] Hayashi and colleagues[4-6] suggest two possible mechanisms of pain relief. They hypothesize that a surge in beta-endorphins released via stimulation of the surrounding hypothalamus and a similar effect during surgical ablation contributes to long-term amelioration. Pituitary SRS resulted in hypothalamic hyperactivity and increased the levels of N-acetyl aspartate. They also suggested that a dose regimen of 160Gy for general cancer pain and 140Gy for thalamic pain to minimize or avoid complications.

The patient in this study was previously treated with conventional radiotherapy and radiosurgery for tumor control. We had to consider the tolerance dose of organ-at-risk. In case of single fraction radiosurgery, tolerance dose for optic pathway, such as optic nerve and optic chiasm is 8 − 10Gy with low a/b ratio (≤3Gy).[11)18)19] In conventional radiotherapy, tolerance dose of optic pathway is higher than single fraction radiosurgery.[17] For these late-responding tissues sparing, fractionated radiation than single session radiosurgery is more effective.[8]

We selected a fractionated method to minimize complications and maximize irradiation to pituitary-stalk junction with a dose of 220Gy in four fractions. A single fraction in EQD2 comprised 115Gy. Three days after treatment, the patient showed pain relief and pain control was maintained thereafter.

Neurosurgeons may be uncomfortable with high-dose radiosurgery in a patient with a history of extensive radiotherapy. However, we investigated new ways to treat opioid-refractory pain and found that fractionated radiosurgical hypophysectomy might be an option to maximize the therapeutic effect of SRS while minimizing the complications.

Table 1. Pituitary radiosurgery for intractable cancer pain

Study	Target	Etiology	Max dose (Gy)	Pain relief
Backlund (1972)[1]	Anterior two-thirds of pituitary gland with the 50% isodose	Malignant	200−250	4/7 (57%)
Hayashi (2002)[4]	Junction between pituitary gland and stalk with the 50% isodose	Malignant	150−200	9/9 (100%)
Kwon (2004)[10]	Junction between pituitary gland and stalk with the 50% isodose	Malignant	150−160	7/7 (100%)
Hayashi (2007)[7]	Pituitary gland with the 50% isodose covering the lower stalk	Nonmalignant	140−180	17/24 (71%)

CONCLUSION

Fractionated radiosurgical hypophysectomy was effective and safe for intractable pain in a patient with recurrent GBM. Fractionated radiosurgical hypophysectomy is minimally invasive compared with surgical techniques and resulted in rapid analgesic effect. In addition, the fractionated method was safe in patients with a history of radiation therapy.

REFERENCES

1. Backlund EO, Rahn T, Sarby B, De Schryver A, Wennerstrand J: *Closed stereotaxic hypophysectomy by means of 60 Co gamma radiation. Acta Radiol Ther Phys Biol 11:545-555, 1972*
2. Backlund EO: *Gamma hypophysectomy. J Neurosurg 100:1133-1134; author reply 1134, 2004*
3. Elsayem A, Swint K, Fisch MJ, Palmer JL, Reddy S, Walker P, et al: *Palliative care inpatient service in a comprehensive cancer center: clinical and financial outcomes. J Clin Oncol 22:2008-2014, 2004*
4. Hayashi M, Taira T, Chernov M, Fukuoka S, Liscak R, Yu CP, et al: *Gamma knife surgery for cancer pain-pituitary gland-stalk ablation: a multicenter prospective protocol since 2002. J Neurosurg 97:433-437, 2002*
5. Hayashi M, Taira T, Chernov M, Izawa M, Liscak R, Yu CP, et al: *Role of pituitary radiosurgery for the management of intractable pain and potential future applications. Stereotact Funct Neurosurg 81:75-83, 2003*
6. Hayashi M, Taira T, Ochiai T, Chernov M, Takasu Y, Izawa M, et al: *Gamma knife surgery of the pituitary: new treatment for thalamic pain syndrome. J Neurosurg 102:38-41, 2005*
7. Hayashi M, Chernov MF, Taira T, Ochiai T, Nakaya K, Tamura N, et al: *Outcome after pituitary radiosurgery for thalamic pain syndrome. Int J Radiat Oncol Biol Phys 69:852-857, 2007*
8. Hoban PW, Jones LC, Clark BG: *Modeling late effects in hypofractionated stereotactic radiotherapy. Int J Radiat Oncol Biol Phys 43: 199-210, 1999*
9. Katz J, Levin AB: *Treatment of diffuse metastatic cancer pain by instillation of alcohol into the sella turcica. Anesthesiology 46:115-121, 1977*
10. Kwon KH, Nam TK, Im YS, Lee JI: *Pituitary irradiation by gamma knife in intractable cancer pain. J Korean Neurosurg Soc 36:286-290, 2004*
11. Leber KA, Bergloff J, Pendl G: *Dose-response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. J Neurosurg 88:43-50, 1998*
12. Lipton S, Miles J, Williams N, Jones NB: *Pituitary injection of alcohol for widespread cancer pain. Pain 5:73-82, 1978*
13. Luft R, Olivecrona H: *Experiences with hypophysectomy in man. J Neurosurg 10:301-316, 1953*
14. Patel M, Siddiqui F, Jin JY, Mikkelsen T, Rosenblum M, Movsas B, et al: *Salvage reirradiation for recurrent glioblastoma with radiosurgery: radiographic response and improved survival. J Neurooncol 92:185-191, 2009*
15. Portenoy RK: *Treatment of cancer pain. Lancet 377:2236-2247, 2011*
16. Rhondali W, Tremellat F, Ledoux M, Ciais JF, Bruera E, Filbet M: *Methadone rotation for cancer patients with refractory pain in a palliative care unit: an observational study. J Palliat Med 16:1382-1387, 2013*
17. Scoccianti S, Detti B, Gadda D, Greto D, Furfaro I, Meacci F, et al: *Organs at risk in the brain and their dose-constraints in adults and in children: a radiation oncologist's guide for delineation in everyday practice. Radiother Oncol 114:230-238, 2015*
18. Stafford SL, Pollock BE, Leavitt JA, Foote RL, Brown PD, Link MJ, et al: *A study on the radiation tolerance of the optic nerves and chiasm after stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 55:1177-1181, 2003*
19. Tishler RB, Loeffler JS, Lunsford LD, Duma C, Alexander E, 3rd, Kooy HM, et al: *Tolerance of cranial nerves of the cavernous sinus to radiosurgery. Int J Radiat Oncol Biol Phys 27:215-221, 1993*