Gamma Knife Pituitary Radiosurgery for Intractable Pain: New Treatment Trial of Thalamic Pain Syndrome

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Abstract

Rationale Cancer pain related to bone metastasis is one of typical pain, and has been controlled well using Gamma knife pituitary radiosurgery (GKPR) without any significant complication. One clinical report notes that central pain such as thalamic pain syndrome can also be controlled with chemical hypophysectomy, although it is accompanied with transiently diabetes insipidus. This historical evidence prompted us to even perform GKPR for control of thalamic pain syndrome with development of the treatment concept for cancer pain.

Material and Method In our institutional experience, we have treated 27 patients suffering from central pain with GKPR. Among them, 22 patients were suffering from thalamic pain syndrome. The target was only the pituitary gland involving the border in between the pituitary stalk and gland. Prescribed maximum dose was 140 to 180Gy. We could evaluate 20 patients with thalamic pain syndrome more than 6 months follow-up.

Results Initial significant pain reduction was observed in 75.0% (15/17). Patients who took pronounced effect experienced pain reduction within 48 hours. Long-term effectiveness (>1 year) was observed in 33.3% (5/15). In other cases, rapid recurrence (< 3 months) was observed in 33.3% (5/15). No any significant postoperative complication was observed excluding two patient who developed transiently diabetes insipidus.
Conclusions Our clinical study protocol is not mandatory. Optimizing this treatment protocol requires more investigation for clinical results of GKPR in the patients with thalamic pain. However, some efficacy and safety have been seen in all cases. We assume that GKPR has a potential to control this kind of intractable central pain. In the near future, it will play an important role in the field of the management of intractable pain.

Key Words: Gamma Knife, pituitary radiosurgery, thalamic pain syndrome

Introduction

Thalamic pain syndrome is one of typical intractable pain, regarded to be incurable. Various protocols such as medication and functional neurosurgery have been used to control the intractable pain, but no sufficient pain control has been observed.

Three or four decades ago, hypophsectomy was used in an attempt to cure intractable pain. In 1953, Luft and Olivecrona \(^{17}\) reported the first experience of cancer pain control with surgical hypophysectomy for the patients with breast cancer. Surgical hypophysectomy was then performed for pain control \(^{3,12,19}\). Subsequently, chemical hypophysectomy using alcohol injection was developed as an alternative lesser invasive treatment \(^{4,13,15,18}\). So far, the overall clinical results of surgical/chemical hypophysectomy achieved 64.4\% of complete pain relief in 1101 reported cases who suffered from cancer pain \(^{3,4,12,13,15,17,19}\). However, majority of the patients developed significant postoperative complications such as panhypopituitarism, severe diabetes insipidus, meningitis, visual dysfunction and hypothalamic insult.

In order to integrate surgical/chemical hypophysectomy to be safer treatment using Gamma knife surgery (GKS), Backlund in 1972 tried to treat cancer pain with GKS, targeted to the pituitary gland with 200-250Gy \(^{1,2}\) as a method of pituitary ablation. This report was the first series of pituitary ablation by GKS to show the efficacy and safer than hypophysectomy. Subsequently, Hayashi et al could also control well cancer pain \(^{5,6,7,8,9,10,11}\) reported that “Gamma knife pituitary radiosurgery” (GKPR) with highly resolution of MRI/CT using relatively lower irradiation dose (160Gy) under the concept of no ablation of the pituitary gland. Additionally, no any significant adverse effect was observed within limited follow-up term (1-24 months). So far, GKPR has been recognized as an effective and safer treatment for control of intractable pain, even though action mechanism has not been elucidated.

In 1983, Levin et al applied chemical hypophysectomy to thalamic pain syndrome and reported their experience of 3 patients’ clinical results \(^{14}\). All cases experienced significant pain reduction within 48 hours, and finally two of them presented complete pain relief. Another one presented much significant pain reduction (>80\%). All cases were accompanied with tempo-
rally secondary effect, panhypopituitarysm and diabetes insipidus. The efficacy lasted 19 - 58 months.

Thus, we have established our protocol and tried to control thalamic pain syndrome with GKPR based on both historical and our own clinical evidence. In this article, we’d like to report our initial experience and clinical results, and demonstrate the potential of GKPR for thalamic pain syndrome.

**Material and Methods**

An indication of thalamic pain syndrome in GKPR is as follows: 1) The pain should be thalamic pain syndrome, 2) No any other effective treatment prior to GKS, 3) High risk patient: impossible to be treated under general anesthesia, 4) Main complaint should be “pain”, not “numbness”.

Patient eligibility was critically performed. Among all, the most important subject is that main complaint should be “pain”, not “numbness”. In our limited experience, no clinical improvement of numbness was observed after GKPR. At the time of preoperative evaluation, we had to confirm all patients of a normal visual and endocrinological function.

Leksell frame is applied on the head with parallel to the optic pathway. We perform MRI (T1WI axial 1.0mm slices / T2WI coronal 2.0mm slices/ 3D heavily T2WI axial 0.5mm slices) and CT (plain axial 1.0mm slices/ bone 1.0 mm slices). We use Gamma Plan (ELEKTA Instrument AB) to make dose planning for this treatment. A center of the isocenter should be located on the pituitary gland. Additionally, fifty percent isodose area (8mm collimator) should involve the border of between the pituitary gland and lower

![Figure 1: Dose Planning on 3D image (50% isodose): This figure showed the target, which was 50% isodose area (80Gy) and the anatomical relationship between the target and the optic pathway, carotid artery, pituitary gland, stalk, and brain stem.](image)
part of the pituitary stalk. We normally use 140 to 180Gy at maximum dose. Subsequently, we should take into account the delivered irradiation dose to the optic pathway to be kept less than 10Gy at maximum. If the length of pituitary stalk is too short, we have to move the isocenter to be lower in order to reduce the excessive irradiation dose to the optic pathway. We have to modify gamma angle from 90 degrees to 75-85 degrees to make the 10Gy isodose line parallel to the optic pathway. Then we use beam plugging technique to modify the shape of 10Gy line to reduce the delivered dose to the optic pathway, without modification of 50% isodose line.

Finally, we examine it by using 3D images to confirm the relationship between the target (50% isodose line) and the surrounding vital structures on the display of Gamma Plan [Fig.1] to know the relationship between 10Gy line and the optic pathway [Fig.2].

In our institutional experience, we treated 22 patients with post-stroke thalamic pain syndrome. Twenty cases were available with the followed-up period of more than 3 months (3-24 months).

**Results**

_Clinical Data and Dose/Energy Calculation in Patients with Thalamic Pain Syndrome_

We have treated 22 patients (14 men and 8 women) with thalamic pain syndrome. The average age was 64.7 years old. All cases were suffering from cerebral vascular disease: 16 thalamic hemorrhage, 5 thalamic infarction, and 1 malignant lymphoma which was treated by radiosurgery. The mean

![Figure 2: Dose Planning on 3D image (5% isodose): This figure showed the 5% isodose area (8Gy) to know the anatomical relationship between the area and the optic pathway. We have to avoid excessive irradiated dose to the optic pathway.](image)
duration between onset and treatment was 91.2 months.

We checked dose / energy calculation in every patient. The mean length of the pituitary stalk was 9.1 mm, the mean maximum and the average dose of the pituitary stalk were 136.2 Gy and 45.9 Gy respectively. The mean unit energy (energy (mJ) per volume (cm$^3$)) of the pituitary stalk was 29.4 mJ/cm$^3$. The mean maximum and average dose of the pituitary gland were 146.2 Gy and 110.2 Gy. The mean unit energy of the pituitary gland was 111.7 mJ/cm$^3$.

Clinical Results of Patients with Thalamic Pain Syndrome after GKPR

Most cases had both severe pain and numbness at the time of preoperative evaluation. Initially, pain reduction was observed in 75.0% (15/20) within 48 hours after GKPR. Long-term effectiveness (more than 1 year) was observed in 33.3% (5/15). However, the effectiveness lasted only for three months (rapidly recurrence) in 33.3% (5/15) and the other 33.3% (5/15) within 6 months. Severe numbness never improved since GKPR, because the severity of numbness worsened in spite of significant pain reduction. No secondary effect of hormonal insufficiency was observed excluding two transiently slight DI. No patient developed visual dysfunction. No any morphological change on MRI was demonstrated within limited follow-up [Fig.3].

Discussion

Hypophysectomy and α-endorphin

The action mechanism that hypophysectomy caused in complete pain relief has not yet been elucidated. Majority of the patients with cancer pain have been treated by morphine and have experienced pain reduction. Therefore, as one of action mechanisms, it is supposed that hypophysectomy may trigger an intrinsic morphine-like effect. β-endorphin, whose precursor (pre pro-opiomelanocortin: PPOMC) exists in the pituitary gland and the arcuate

Figure 3: Postoperative changes of MRI findings: These MRI (sagittal T2 WI), which were obtained at pre GKPR(a), 4 day(b), 1 week(c), 1 month(d), and 2 months(e) later, showed no morphological change at the pituitary gland-stalk.
nucleus in the hypothalamus, is well known to control this kind of severe pain like morphine. There are several reports about the increase of the level of \( \alpha \)-endorphin after hypophysectomy in both blood and cerebrospinal fluid (CSF) of the patients. Hypophysectomy, ablation of the pituitary gland and stalk, is supposed to trigger the release PPOMC in excessive quantity into the blood and CSF. From endocrinological and morphological point of view, on the other hand, GKPR does not make apparent damage to the pituitary gland/stalk. We presume that \( \alpha \)-endorphin contributes in this action mechanism to reduce the pain severity.

**What is Action Mechanism of GKPR for Thalamic Pain Syndrome?**

Recently, pituitary gland-stalk irradiation with gamma knife has been adopted as a new alternative for cancer pain control. GKPR has provided surprising and satisfactory clinical results. Compared with those of tumor / vascular anomaly radiosurgery (20-30 mJ/cm\(^3\)), we used extremely high irradiation average dose and unit energy like 110.2 Gy and 117.2 mJ/cm\(^3\). The results were surprising. It has immediate, complete and long-lasting clinical effect in controlling cancer pain without any significant secondary effects. We summarize the effect of GKPR according to our clinical experience as follows; 1) There is no evidence of destructive changes: no dysfunction of endocrinological status and no morphological change of MRI findings\(^{5,6,8,10,11}\) and 2) Clinical symptoms show hyper-function of the hypothalamus after GKPR: rapidly recovering appetite loss and general condition\(^{5,6}\). GKPR has provided pain reduction just as hypophysectomy does, but severe secondary effect was never seen in the cases of GKPR\(^{5,6}\). Therefore, we strongly suppose that the action mechanism by GKPR may provide something new “biological differential effect” (BDE) to the hypothalamus-thalamus, not our expected “destructive effect” to the pituitary gland/stalk by hypophysectomy. That should be a new “neuromodulating effect” to the central nervous system by Gamma knife radiosurgery\(^{2,5,6,7,8,9,10,11}\). We suppose that this kind of BDE might provide efficacy to thalamic pain syndrome. We have just started to investigate MR Spectroscopy in the area of hypothalamus and thalamus to show BDE as hyperfunction of the hypothalamus-thalamus, especially the level of NAA/Cr ratio, which is related to the activity of neuron cells.

**Rationale and Future Work of GKPR for Thalamic Pain Syndrome**

Levin’s experience prompted us to establish one sophisticated idea that thalamic pain syndrome could also be controlled with GKPR as cancer pain treatment. In 2002, we developed new treatment protocol for thalamic pain syndrome based on our experience of cancer pain\(^{7,8,9,10,11}\). We defined the
maximum dose as 140Gy, which was smaller than 160Gy for cancer pain, because we had to consider the risk of secondary effect for these patients who were expected to have long life span. According to the initial clinical results of 8 cases, 7 cases (87.5%) experienced initial pain reduction, majority of cases (71.4%) presented real recurrence within 6 months without any secondary effect. GKPR provides temporally efficacy, but this biological phenomenon prompts us to develop the new treatment indication. The only remaining problem is the duration of effectiveness. We are beginning to think that the maximum dose should be shifted from 140Gy to 160-180Gy as equal to the treatment protocol for cancer pain with GKPR. More experience and longer duration of follow-up are essential to evaluate the efficacy and safety. However, GKPR has apparently provided significant pain reduction to many patients without any secondary effect. We believe that GKPR has a great possibility to control this kind of medically refractory severe pain in the very near future.

Conclusions

In our institutional experience, we have treated 39 consecutive patients with intractable (12 patients with cancer pain related to the bone metastasis and 27 patients with intractable central pain). Both two subgroups had a good indication of the treatment with GKS targeted to the pituitary gland/stalk (GKPR) and were treated safely. Majority of the patients experienced significant pain reduction.

So far, our experience is still limited. In addition, some modification is needed, especially for patients with thalamic pain syndrome. However, the efficacy and the safety were seen in majority of the patients. We believe that this treatment has a potential to control the intractable severe pain, and GKPR will play a much important role in the field of pain control. We’d like to have more experience and make an optimal protocol by evaluating which parameters is the most important, know what treatment strategy is the best. By doing so, we would be able to prove the efficacy and safety, and contribute to the development of this treatment.

References


