ANCER-RELATED pain can be intractable pain that is not relieved completely by any modern methodology. Approximately 38% of patients with cancer experience severe pain. Moreover, in the terminal stages, more than 60% of patients develop intractable pain.\textsuperscript{1,12,13} This pain is too severe to allow patients to experience an acceptable quality of life. To date, various methods have been tried to control this severe pain, including focal irradiation, functional surgery, and medication. Therapeutic success that achieves consistent freedom from pain, however, has proved elusive. This is not only an individual patient problem but also a social problem.

Two or three decades ago, cancer pain could be controlled by surgical or chemical hypophysectomy.\textsuperscript{2,5,6,8,10,11,17} These treatments provided most patients with relief from their severe pain. Severe adverse effects, however, including panhypopituitarism, diabetes insipidus, and visual dysfunction appeared in all of the cases. In patients with terminal disease these complications were more significant than the pain relief.

Gamma knife radiosurgery has been mostly used to treat brain tumors and vascular malformations, although it was originally designed to treat functional disorders such as movement disorders, intractable epilepsy, and pain. Indeed, in 1968 Leksell published the results of a centrum medianum gamma thalamotomy for cancer pain in two patients. He administered a maximum dose of 200 to 250 Gy.\textsuperscript{7} Subsequently, Steiner, et al.,\textsuperscript{14} and Young, et al.,\textsuperscript{15,16} have treated intractable pain, particularly cancer pain related to bone metastasis, with various protocols. Cancer pain has been treated by gamma knife radiosurgery (GKS), targeted to the pituitary gland–stalk, as an alternative new pain control method. The purpose of this study was to investigate a prospective multicenter protocol to prove the efficacy and the safety of this treatment.

Objective. The authors have treated intractable pain, particularly cancer pain related to bone metastasis, with various protocols. Cancer pain has been treated by gamma knife radiosurgery (GKS), targeted to the pituitary gland–stalk, as an alternative new pain control method. The purpose of this study was to investigate a prospective multicenter protocol to prove the efficacy and the safety of this treatment.

Methods. Indications for patient inclusion in this treatment protocol were: 1) pain related to bone metastasis; 2) no other effective pain treatment options; 3) general condition rated as greater than 40 on the Karnofsky Performance Scale; 4) morphine effective for pain control; and 5) no previous treatment with radiation (GKS or conventional radiotherapy) for brain metastasis. The authors at one institution have treated two patients, who suffered from severe cancer pain related to bone metastasis, by using GKS. The target was the pituitary gland. The maximum dose was 160 Gy with one isocenter of an 8-mm collimator, keeping the radiation dose to the optic nerve less than 8 Gy. At another institution two patients were treated in the same way; an additional five patients were treated similarly with targeting of the pituitary gland with two isocenters of 4-mm collimator.

In all nine cases, pain resolved without significant complication. Pain relief was observed within several days, and this effect was prolonged until the day that they died. At a follow up of 1 to 24 months, no recurrences and no hormonal dysfunction were observed.

Conclusions. Despite insufficient experience, the efficacy and the safety of GKS for intractable pain were demonstrated in nine patients. This treatment has the potential to ameliorate cancer-related pain, and GKS will play a more important role in the treatment of intractable pain. More experience and additional refined study protocols are needed to evaluate which parameters are important, to determine what treatment strategy is the best, and to clarify the safest option for patients with intractable cancer pain.

Key Words • gamma knife • radiosurgery • pituitary ablation • cancer pain
also treated intractable pain. Young, et al.,16 reported that a good response (> 50% pain reduction) was observed in 65% of the patients. We have tried an alternative approach to surgical or chemical hypophysectomy4,9 by using GKS to induce a lesion in the stalk of the pituitary gland (maximum dose 150–200 Gy). To date, only a few patients have been treated. The early results, however, have been promising, and the significant side effects notably observed after chemical and surgical hypophysectomy4,9 have been absent.

The mechanism of action of this treatment remains unclear; however, it would seem to have considerable potential for the adequate control of cancer pain with preservation of underlying function. Consequently, it was decided to design a prospective protocol with which to examine the efficacy and safety of the treatment, and to determine how the phenomenon works during the analysis of a multicenter collaborative study.

Clinical Material and Methods

Patient Eligibility

Patient eligibility for entry into the trial is presented in Table 1. The most important indication was thought to be the response of the pain to morphine because we suspected that the effect of a GKS-induced lesion on the pituitary stalk might be mediated through triggering the release of endorphins.

Assessment Before and After Treatment

The components of the pretreatment evaluation were: 1) registration of the site of the primary tumor (to determine if it was a lesion with hormonal responsiveness); 2) activity and distribution of the cancer (using tumor markers, echography, bone scintigraphy, and whole-body CT and/or MR imaging); 3) severity of pain level as classified in Table 2; 4) an endocrinological study; 5) visual function analysis including visual acuity, visual field, and eye movements; and 6) brain MR imaging to determine the relationship between the pituitary stalk/gland and surrounding structures. Postoperative assessment was performed with the aforementioned pretreatment evaluations 2, 3, 4, 5, and 6.

Radiosurgery Technique

The Leksell frame was applied to the head parallel with the optic nerves (Fig. 1). Images for dose planning were obtained from both MR imaging and CT scanning. The MR images were T1-weighted 1-mm axial and coronal slices and T2-weighted 2-mm coronal slices. The CT studies consisted of a series of contrast-enhanced 1-mm slices and a series of 1-mm slices using the bone algorithm. The images were exported to GammaPlan (Elekta Instruments AB, Stockholm, Sweden) for dose planning. The target center should be located at the border between the pituitary gland and the stalk. An 8-mm collimator was used. The 50% isodose should cover both the lower part of the pituitary stalk and more than half of the pituitary gland. It was an absolute requirement that the dose to the optic pathway should be kept below a maximum of 8 Gy. If the pituitary stalk is too short to achieve this with the aforementioned shot localization, then the isocenter would be shifted to a lower position to achieve the required degree of protection to the optic pathway. The gamma angle was adjusted to ensure that the upper margin of the 8-Gy containing isodose ran parallel to the optic nerves. In addition, a plugging technique was used to modify the shape of the 8-Gy containing isodose to reduce the dose delivered to the optic pathway further, without modification of the shape of 50% isodose.

Finally, the 3D imaging capability of GammaPlan was used to confirm the relationship between the target (50% isodose) and the surrounding vital structures (Fig. 2 upper) and to determine the relationship between the 8-Gy containing isodose and the optic pathway (Fig. 2 center).

Two patients were treated in Tokyo and two patients were treated in Hong Kong, all four using the aforementioned dose planning method. The Prague team treated five patients, but used two isocenters with the 4-mm collimator helmet. These nine patients have been followed for 1 to 24 months.

Results

Clinical Results

All patients became completely pain free (Class I in Table 2) within a few days after GKS. This effect was maintained as long as they lived, and no recurrence of pain occurred. It made no difference whether the cancer was hormonally sensitive. No patient suffered from any hormonal dysfunction (Group A, Table 2). Specifically, panhypopituitarism and diabetes insipidus were not observed. No patient developed any visual dysfunction. No morphological changes could be detected on the follow-up MR images.

<table>
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<th>TABLE 1</th>
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<td><strong>Indications for GKS-induced pituitary ablation</strong></td>
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<td><strong>Classification of the pain severity after treatment and evaluation of endocrinological status before and after treatment</strong></td>
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<td>Classification</td>
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<tr>
<td>pain severity class</td>
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<tr>
<td>II almost pain free w/ medication (&gt;50% pain reduction)</td>
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<tr>
<td>III partially pain free (&lt;50% pain reduction)</td>
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<tr>
<td>IV no pain relief</td>
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<tr>
<td>endocrinological status group</td>
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<tr>
<td>B partial hypopituitarism (including diabetes insipidus only)</td>
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<tr>
<td>C panhypopituitarism w/out diabetes insipidus</td>
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<td>D panhypopituitarism w/ diabetes insipidus</td>
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J. Neurosurg. (Suppl 5) / Volume 97 / December, 2002

M. Hayashi, et al.
Illustrative Cases

Case 1

This 61-year-old man suffered from hormone-sensitive prostate cancer and harbored a lumbar metastasis. His KPS score was 100%. Nonetheless, he suffered extremely severe pain from the bone metastasis, and neither epidural block nor local irradiation with conventional radiotherapy had an adequate effect. Subsequently, he was given morphine, which in sufficient doses reduced his pain, but at the price of severe constipation. Finally, he was hospitalized in Tokyo to undergo a surgical procedure to relieve his pain. He had no other illnesses such as hypertension or diabetes mellitus. His sole complaint was his prostate cancer.

He was informed of the nature of the treatment being offered and gave his informed consent. We performed the aforedescribed evaluations. The findings were as follows: 1) progressive prostate cancer; 2) significantly raised levels of PAP/PSA and a 3 × 4 × 5–cm primary tumor seen on with echography; 3) Class IV pain (Table 2); 4) Group A pituitary function (Table 2); 5) normal visual function; and 6) normal brain findings on MR images but a short pituitary stalk (only 6 mm).

Before treatment, his general condition declined (KPS score 50%). He became anemic following the development of anorexia and infections. The indications were adequate according to our protocol, and he was treated with a maximum dose of 160 Gy to one isocenter using the 8-mm collimator. The isocenter was placed a little lower in this patient because of his short pituitary stalk. This ensured that the optic pathways did not receive more than 8 Gy. Pain reduction began only a few hours after treatment. On the next day, he was pain free on a dose of morphine of 40 mg/day. By postoperative Day 4 he was completely pain free without any medication. In addition, his anorexia and infections improved and had disappeared by postoperative Day 7. This patient was followed for 3 months. The pain related to the bone metastasis did not recur, and he remained pain free. No reduction in pituitary hormone secretion occurred, and visual function remained normal.
There was, however, a transient increase in serum adrenocorticotropic level 2 weeks later after GKS. The brain MR imaging remained unchanged (Fig. 2 lower). Moreover, the original cancer did not change in size, but the tumor markers (PAP/PSA) transiently decreased 2 weeks after the treatment.

Case 2

This 54-year-old woman suffered from nonhormone-responsive lung cancer and had a right costal metastasis. Her KPS score was 40%. The bone metastasis–related pain was extremely severe, and even a continuous intravenous infusion of morphine could not completely alleviate it. There were no other treatment options for her pain, except for medication, because her prognosis was too poor; her survival was estimated to be approximately 2 months. In addition, she had multiple brain metastases without perifocal edema. They were not, however, considered to have a great deal of influence on her prognosis. In consequence, we decided to treat the severe pain rather than control the brain metastases. She underwent 160-Gy radiotherapy with dose planning performed with a single 8-mm collimator isocenter. Again, the center of the isocenter had to be shifted downward to protect the optic pathways. On the next day, she was pain free with the continuous infusion of morphine, and was transferred to a hospice. She died of lung cancer 1 month later. During this time, she remained pain free. No endocrinological change appeared. We performed MR imaging spectroscopy of the hypothalamus both before and 1 day after the operation. The N-acetyl aspartate had dramatically increased from 80 to 190 within 24 hours. She and her family were very satisfied with the results of the treatment.

Discussion

Control of Cancer Pain Due to Bone Metastases

Any treatment aimed at a symptom rather than a disease should be as conservative as possible. This applies even when the symptom is severe pain in patients with bone metastases. We usually perform local irradiation and/or epidural block for bone metastases. If these measures are ineffective, morphine therapy should be considered. Recently, morphine has become easier to administer in patients with cancer pain. Therefore, morphine can replace the aforementioned options as the first choice of treatment for severe bone metastases–induced cancer pain.

If these less invasive treatments are not effective, however, there are surgical alternatives, which include selective rhizotomy, dorsal root entry zonectomy, percutaneous cordotomy, and stereotactic surgery (thalamotomy). Dorsal root entry zonectomy is usually considered one of the most effective options for control of this kind of pain. This treatment has some potential complications, however, including urinary incontinence and paraparesis. Even if the patients accept these procedures, with their attendant risks the patients still have to suffer considerable physical and mental stress related to the operation.

Surgical and Chemical Hypophysectomy for Control of Cancer Pain

Several decades ago, attempts were made to control cancer pain with hypophysectomy. In 1953, Luft and Olivecrona\(^5\) reported their first experience of the control of cancer pain with hypophysectomy in patients with breast cancer; these patients also suffered severe pain related to bone metastases. The intention was to control the progression of a hormonally sensitive tumor by depriving it of pituitary stimulation. A surprising effect of the operation was the complete relief of the pain from the bone metastases.

Thereafter, surgical hypophysectomy was performed worldwide with variations in technique. Zervas\(^17\) favored a radiofrequency coagulation, Hardy\(^3\) used a transsphenoidal pituitary ablation, and Forrest, et al.,\(^2\) used radioactive implants. Subsequently, chemical hypophysectomy with alcohol injected directly into the pituitary gland was performed as an alternative less invasive treatment by Greco, et al.,\(^3\) Moricca,\(^11\) Lipton, et al.,\(^8\) and Katz and Levin.\(^9\) Overall 64.4% of patients became pain free in the 1101 reported cases; pain-free status in 70% of 334 cases treated with surgical hypophysectomy and 61.9% of 767 cases treated with chemical hypophysectomy.\(^2,3,5,6,8,10,11,17\) There were, however, significant adverse effects in almost all cases after these procedures. Panhypopituitarism was observed in all cases. Diabetes insipidus was observed in half of the cases. Eye movement disorder, visual field defect, hypothalamic insult, and meningitis were also observed in some cases. Thus, although almost all patients experienced substantial relief after surgical/chemical hypophysectomy, all patients developed significant complications. Consequently, hypophysectomy disappeared from the armamentarium of cancer pain treatments.

Pathophysiological Effect of GKS on the Pituitary Stalk

The pathophysiological mechanism by which hypophysectomy can induce complete pain relief in bone metastases has not yet been determined. Intrinsic α-endorphin has been considered to be one of the important factors, because an increase in the level of both α-endorphin and adrenocorticotropic hormone are known to occur after hypophysectomy. The mechanism underlying the increase in level of α-endorphin following hypophysectomy, however, remains unclear.

In this study, we have begun to use GKS-induced pituitary gland–stalk ablation as a new alternative option for the control of cancer pain. The accuracy and the safety of this method are supported by the early results reported in this paper. Gamma knife radiosurgery for pituitary ablation has had surprisingly satisfactory clinical results with an early, complete, and prolonged clinical effect in control of cancer pain, and no important adverse effects.\(^4,9\) The GKS-related mechanism of action for pituitary ablation is not known. Nor is it known if the pain relief produced by this procedure is due to the same mechanism by which pain is relieved following hypophysectomy.

There are some reasons to suspect that GKS for pituitary ablation may not initially trigger a destructive effect in the pituitary gland stalk. This is because there are a number of findings that could indicate a stimulating rather than a destructive effect: 1) there was no evidence of destructive changes, no dysfunction of endocrinological status, and no morphological changes on follow-up MR images; 2) clinical symptoms showed a stimulating effect
Gamma knife pituitary ablation for cancer pain

on the hypothalamus with rapid recovery of appetite loss and general condition; and 3) MR spectroscopy revealed a stimulating effect in the hypothalamus with the level of N-acetyl aspartate, which is related to the activity of neurons, rising remarkably within 24 hours after GKS.

These findings lead us to hypothesize that the initial mechanism of action might be different between surgical/chemical hypophysectomy and GKS for pituitary ablation. Experimental studies in rats are underway to examine these phenomena. In addition, we continue with this prospective clinical study not only to prove the mechanism of GKS for pituitary ablation, but also to evaluate the efficacy and the safety of this treatment as an alternative for the control of cancer pain.

Proposed Prospective Study of GKS for Pituitary Ablation for Cancer Pain

The questions, which will be addressed by the ongoing prospective study, are as follows. 1) Is there a difference in the effect on pain after GKS for pituitary ablation between hormonally responsive and nonhormonally responsive tumors? 2) What is the optimal dose to the pituitary gland—stalk for the efficient, safe, speedy effect of GKS for pituitary ablation? 3) How long can the effect of GKS for pituitary ablation be maintained for the control of the pain? 4) What changes occur in the secretion of intrinsic α-endorphin? 5) Does GKS for pituitary ablation stimulate the hypothalamus?

Conclusions

Early experience in three centers using GKS-induced pituitary ablation has provided lasting pain relief for otherwise intractable pain from bone metastases. The treatment was successful in all nine patients, and no side effects were observed. The mechanism of action of the treatment is unknown and is currently the subject of further studies. More clinical experience is needed to establish the indications and technique of this method to achieve the most consistent long-lasting results.

References


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