Complications of Gamma Knife Surgery for Parkinson Disease

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Background: Many medical centers throughout the world offer radiosurgery with the gamma knife (GK) for pallidotomy and thalamotomy as a safe and effective alternative to radiofrequency ablative surgery and deep brain stimulation for Parkinson disease (PD). The reported incidence of significant complications varies considerably, and the long-term complication rate remains unknown.

Design: We describe 8 patients seen during an 8-month period referred for complications of GK surgery for PD.

Results: Of the 8 patients, 1 died as a result of complications, including dysphagia and aspiration pneumonia. Other complications included hemiplegia, homonymous visual field deficit, hand weakness, dysarthria, hypophonia, aphasia, arm and face numbness, and pseudobulbar laughter. In all patients, lesions were significantly off target.

Conclusions: The 8 patients with PD seen in referral at our center for complications of GK surgery highlight a spectrum of potential problems associated with this procedure. These include lesion accuracy and size and the delayed development of neurological complications secondary to radiation necrosis. Gamma knife surgery may have a higher complication rate than has been previously appreciated due to delayed onset and underreporting. We believe that the risk-benefit ratio of the GK will require further scrutiny when considering pallidotomy or thalamotomy in patients with PD. Physicians using this technique should carefully follow up patients postoperatively for delayed complications, and fully inform patients of these potential risks.


For editorial comment see page 1970

GK radiosurgery can be safely applied to patients with PD. We describe 8 patients with significant complications following GK radiosurgery for PD seen at our institution during an 8-month period.

Patient 1

A 46-year-old man with a 7-year history of severe tremor-predominant idiopathic PD underwent a right-sided GK thalamotomy (4-mm collimator, 20000 rad [200 Gy] of radiation). Four weeks later, he developed face, arm, and leg numbness on the left side. The tingling and numbness of his upper lip resolved over...
PATIENTS AND METHODS

Eight patients were seen at our movement disorder center for the treatment of complications of GK surgery for PD (surgery was performed at an outside institution). A retrospective review was performed of outside medical records and neuroimaging studies and from our institution's movement disorders center. In the latter cases, patients underwent MRI, and 1 also underwent positron emission tomographic scanning. All MRI scans were obtained on 1.5-T MRI scanners (Philips Medical Systems, North America, Shelton, Conn; or GE Medical Systems, Milwaukee, Wis). In addition, a thorough neuropathological evaluation was performed on the brain of 1 patient (patient 3) who subsequently died.

1 year, but his left arm remained severely numb, with decreased pain and temperature sensation. After the GK procedure (5-6 months), he began experiencing uncontrolable laughter. He felt pressure to laugh even though he interpreted inciting events as not humorous. He experienced no benefit in tremor. A T2-weighted MRI scan showed serial enlargement of a right-sided thalamic/internal capsule lesion during a 21-month period (Figure 1A).

PATIENT 2

A 64-year-old man with idiopathic PD for 11 years and bilateral upper extremity resting tremor and minimal rigidity underwent a right-sided GK thalamotomy (4-mm collimator, 20000 rad [200 Gy]). Improvement in resting tremor of the left arm was noted several months later. Two months following the right-sided GK radiosurgery, he underwent a left-sided GK thalamotomy (4-mm collimator, 20000 rad [200 Gy]). Tremor in his right arm improved, but 1 week after the procedure, he noticed a reduction of voice volume. During the next 3 to 6 months, he developed severe hypophonia. He exhibited mild anosmia, severe dysfluency, and significant hypophonia on examination 1 year postoperatively. A T2-weighted MRI scan showed large lesions bilaterally in the internal capsules (17 mm on the left and 10 mm on the right) and in large regions of the thalamus (Figure 1B).

PATIENT 3

A 69-year-old man with a 7-year history of idiopathic PD who presented with bilateral upper extremity resting tremor and rigidity underwent a left-sided GK thalamotomy (4-mm collimator, 20000 rad [200 Gy]). His right arm tremor resolved several weeks after the procedure, and his Unified Parkinson Disease Rating Scale part 3 score 2 months after the procedure improved from 12.5 to 4.5. Eight months after the left-sided GK thalamotomy, he underwent a right-sided GK thalamotomy (4-mm collimator, 15000 rad [150 Gy]). One month after the second procedure, he began a 5- to 6-month decline, including progressive bilateral extremity weakness, dysarthria, dysphagia, and worsening of gait. He lost more than 13.5 kg because of difficulty swallowing. He developed aspiration pneumonia and subsequently died. A T2-weighted MRI scan showed bilateral radiation-induced changes in the thalamus and the internal capsule (Figure 1C). A positron emission tomographic scan showed decreased metabolism in the basal ganglia and in the left side of the thalamus. The results of a neuropathological examination revealed that the older left-sided lesion involved the external segment of the globus pallidus, the internal capsule, and the lateral aspect of the thalamus (Figure 2A). Areas within the lesion varied in age. There were areas undergoing acute necrosis (Figure 3A), areas exhibiting recent coagulation necrosis (Figure 3B), and older areas of organized necrosis (Figure 3C). The latter consisted of histiocytic accumulation, glial scarring, hemosiderin-laden macrophages, and thick-walled hyalized blood vessels typical of radiation necrosis. The more recent right-sided lesion involved the internal capsule and the adjacent thalamus (Figure 2B). Microscopically, this lesion showed coagulation necrosis (Figure 3D).

PATIENT 4

A 64-year-old man with a 4-year history of idiopathic PD characterized by a right upper extremity resting tremor underwent a left-sided GK thalamotomy (4-mm collimator, 20000 rad [200 Gy]). Shortly after the procedure (2-4 months), his resting tremor improved significantly. Ten months after the procedure, he began to slur his speech. On follow-up examination, he was noted to have dysarthric speech and a decrease in agility of right-sided finger movements with a decrease in grip strength. A T2-weighted MRI scan showed a lesion involving the left side of the thalamus and the left internal capsule (Figure 1D).

PATIENT 5

A 59-year-old man with idiopathic PD for 5 years with only a right upper extremity resting tremor underwent a left-sided GK thalamotomy (4-mm collimator, 20000 rad [200 Gy]). Four months after his surgery, his tremor resolved. Six months after the GK procedure, he developed a headache and a right-sided facial droop. During the following week, he noted weakness in his right hand. He subsequently developed diplopia, which later resolved. During the next 2 months, he developed balance and gait problems. He was administered corticosteroids for 1 month, with only mild improvement in weakness. He then noted right lower extremity weakness and intermittent right-sided face and hand numbness. The results of a follow-up examination revealed right hemiparesis with brisk right-sided deep tendon reflexes, right lower extremity clonus, and a right extensor plantar response. He walked with a hemiplegic gait with circumduction of the right lower extremity and flexion of the right upper extremity. T2-weighted MRI studies showed lesions involving the internal capsule, the thalamus, and the mesencephalon, consistent with radiation necrosis and cerebral edema (Figure 1E).
Table 1. Reported Complications of GK Surgery for PD*

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Pallidotomy†</th>
<th>Thalamotomy†</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindquist et al,16 1991‡</td>
<td>0</td>
<td>2</td>
<td>Transient hemiparesis (n = 1)</td>
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<tr>
<td>Rand et al,6 1993</td>
<td>0</td>
<td>7</td>
<td>None reported</td>
</tr>
<tr>
<td>Pan et al,7 1996</td>
<td>0</td>
<td>8</td>
<td>Limb weakness (n = 1)</td>
</tr>
<tr>
<td>Ohye et al,8 1996</td>
<td>0</td>
<td>6</td>
<td>None reported (all patients underwent previous mapping)</td>
</tr>
<tr>
<td>Friedman et al,9 1996</td>
<td>4</td>
<td>0</td>
<td>Dementia and psychosis (n = 1)</td>
</tr>
<tr>
<td>Bonnen et al,10 1997</td>
<td>1</td>
<td>0</td>
<td>Visual field problem (n = 1)</td>
</tr>
<tr>
<td>Young et al,11 1998</td>
<td>28</td>
<td>27</td>
<td>Visual field problem (n = 1) and hypophonia and a gait problem (n = 1)</td>
</tr>
<tr>
<td>Duma et al,12 1999</td>
<td>18</td>
<td>42</td>
<td>Visual field problems (n = 4), speech/swallowing problems (n = 3), gait problems (n = 3), dysarthria (n = 1), and numbness (n = 1)</td>
</tr>
<tr>
<td>Friedman et al,13 1999</td>
<td>2</td>
<td>15</td>
<td>Slow finger movements (n = 2); action tremor (n = 1); hemiparesis (unrelated infarct) (n = 1); hypophonia/dysphagia (n = 1); severe symptomatic edema (n = 4); and dysarthria, akinesia, and weakness (n = 1)</td>
</tr>
</tbody>
</table>

*GK indicates gamma knife; PD, Parkinson disease.
†Data are given as total number of patients undergoing surgery, as reported in each article.
‡Observations were made in 1986.

Figure 1. A, Patient 1, approximately 3 months after a right-sided gamma knife (GK) thalamotomy. An axial fluid-attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) scan shows a large irregular hyperintense lesion in the right side of the thalamus that has enlarged from the scan taken approximately 2 years prior (not shown). The interval enlargement during this extended period is strongly suggestive of radiation change or necrosis. B, Patient 2, approximately 6 months after bilateral GK thalamotomies (procedures performed 1 month apart). An axial FLAIR MRI scan shows bilateral irregular areas of T2 hyperintensity on the left (17 mm) and the right (10 mm). The smaller right-sided lesion is centered in the posterior limb of the right internal capsule. The larger left-sided lesion is centered just posterior to the posterior limb of the left internal capsule. There is linear T2 hyperintensity extending along the white matter tracts of the posterior limbs of the internal capsules bilaterally. The left-sided lesion also involves the anterior thalamus. An axial T2-weighted gradient echo image (not shown) demonstrated a small punctate focus of low signal centrally within the lesion, representing a magnetic susceptibility artifact, consistent with blood products. C, Patient 3, approximately 12 months after a left-sided GK thalamotomy and 4 months after a right-sided GK thalamotomy. An axial FLAIR image shows a small area of hyperintensity in the region of the right side of the globus pallidus medialis and the right internal capsule and a much larger area of abnormal hyperintensity at the site of the older left-sided GK thalamotomy. The abnormal signal involves the anterior left side of the thalamus and the posterior limb of the left internal capsule, and edema can be seen extending anteriorly into the left lamina medialis. Postgadolinium axial T1-weighted images (not shown) demonstrated abnormal enhancement involving both of the thalamotomy lesions, greater on the left. These findings were consistent with bilateral radiation necrosis. D, Patient 4, approximately 4 months after a left-sided GK thalamotomy. An axial proton density–weighted MRI scan shows an area of hyperintensity in the posterior limb of the left internal capsule. E, Patient 5, approximately 7 months after a left-sided GK thalamotomy. An axial FLAIR MRI scan shows extensive involvement of the left side of the thalamus and the left internal capsule. At other levels (not shown), the left cerebral peduncle, the mesencephalon, and the temporal lobe were also involved.
PATIENT 6

A 47-year-old man with a 5-year history of idiopathic PD characterized by tremor, severe motor fluctuations, and levodopa-related dyskinesias of the upper and lower extremities underwent a left-sided GK pallidotomy (4-mm collimator, 15000 rad [150 Gy]). One week after his procedure, he complained of flashes of light occurring in his right visual field. Several days later, the flashes disappeared, and he complained of visual loss with only mild improvement in tremor, rigidity, and dyskinesia. Three months postoperatively, his vision changed dramatically for several days and the results of his ocular examination revealed complete right homonymous hemianopia. A T2-weighted MRI scan showed a lesion involving the globus pallidus, the internal capsule, and the optic tract (Figure 4A).

PATIENT 7

A 68-year-old man with idiopathic PD and mild bilateral upper extremity resting tremor, rigidity, and severe dyskinesias worse in his left upper extremity underwent a right-sided GK pallidotomy (4-mm collimator, 15000 rad [150 Gy]). Mild improvement of the left-sided dyskinesia was observed after several weeks. Several months after the procedure, he developed visual loss. Complete left homonymous hemianopia was found on follow-up examination. A T2-weighted MRI scan demonstrated a large lesion (22 × 14 mm) involving the globus pallidus, the optic tract, and the internal capsule (Figure 4B).

PATIENT 8

A 42-year-old man with a 7-year history of idiopathic PD characterized by tremor, rigidity, and levodopa-related dyskinesias underwent a left-sided GK pallidotomy (4-mm collimator, 10000 rad [100 Gy]). Several weeks after the procedure, he noticed a decrease in dyskinesias and was able to reduce the dosages of his antiparkinsonian medications. During the next several months, he developed right-sided facial, arm, and leg weakness; dysarthric speech; and a hemiparetic gait. The results of an MRI examination 5 months postoperatively were identical to those of the preoperative examination, showing no changes despite strong clinical evidence of evolving radiation-induced damage. He was subsequently admitted to the hospital 9 months postoperatively for worsening right-sided weakness. His MRI study (Figure 4C) at that time showed subtle T2 hyperintensity of the left external segment of the globus pallidus and the internal capsule.
Lars Leksell originally developed radiosurgery in the 1950s as a noninvasive way to perform functional neurosurgery. The first prototype of the GK was developed in 1968 and was used to produce thalamic lesions for tremor. The target was determined by pneumoencephalography. The original stereotactic frame was too large to introduce a collimator to control the radiation target size, which led to larger than expected lesions. In the mid-1980s, stereotactic MRI localization was introduced, and an 8-mm collimator helmet was used to control the lesion volume. In 1986, the GK was used to deliver radiation using an 8-mm collimator, but the volume of the resulting lesion was too large, and the patient experienced transient hemiparesis. Investigators have since switched to a 4-mm collimator in an effort to limit the intended target to a 4-mm size. The GK has been used in the treatment of arteriovenous malformations, tumors, chronic pain, trigeminal neuralgia, anxiety disorders, obsessive-compulsive disorder, and epilepsy.

Benefits and complications from radiosurgical procedures are delayed by approximately 1 to 12 months from the time of treatment. To our knowledge, no long-term studies have been performed to fully evaluate the time course of improvement of symptoms or occurrence of complications. The delayed benefit for patients with PD undergoing radiosurgery is due to the time it takes for the radiation to functionally damage or destroy the tissue targeted. Lesions can expand over time and cause delayed adverse effects due to extension into adjacent structures. In this series, we observed considerable spread into adjacent structures, as evidenced by the incidence of neurological complications that occurred. Complications were delayed in all 8 patients and included swallowing difficulty with aspiration pneumonia and eventual death (n=1), homonymous visual field deficits (n=2), weakness (n=3), numbness and pseudobulbar laughing (n=1), and hypophonia with thalamic aphasia (n=1) (Table 2).
PROBLEMS WITH TARGETING

One of the concerns with GK procedures is accurate targeting. Even with the best image-guided targeting techniques, the intended target has been shown to be off the anatomical target by an average of 1.5 mm (range, 0-4 mm). Magnetic resonance imaging and patient-specific distortions can add several millimeters to the localization error. A few millimeters of error may result in involvement of structures adjacent to the intended target and in injury to the internal capsule or the optic tract; little, if any, therapeutic benefit may occur. The GK procedure also does not allow for microelectrode recordings to aid in target identification. The 8 patients studied show significant problems with accurate targeting of thalamic and pallidal regions.

PROBLEMS WITH LESION SIZE

Control of lesion size with the GK represents another problem. Two major factors contribute to this problem: the size of the collimator and the potentially progres-

Table 2. Delayed Gamma Knife Surgery Complications in 8 Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Intended Site</th>
<th>Actual Lesion Site</th>
<th>Complication</th>
<th>Length of Benefit/Complication</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Th</td>
<td>Th and IC</td>
<td>Numbness</td>
<td>None/1 mo</td>
</tr>
<tr>
<td>2</td>
<td>Th (bilateral)</td>
<td>Th and IC</td>
<td>Pseudobulbar laughter</td>
<td>None/5 mo</td>
</tr>
<tr>
<td>3</td>
<td>Th (bilateral)</td>
<td>Th and IC</td>
<td>Hypophonia and aphasia</td>
<td>1-2 mo/3 mo</td>
</tr>
<tr>
<td>4</td>
<td>Th</td>
<td>Th and IC</td>
<td>Dysarthria, dysphagia, aspiration, and death</td>
<td>Weeks/4 mo</td>
</tr>
<tr>
<td>5</td>
<td>Th</td>
<td>Th, IC, and Md</td>
<td>Hemiparesis</td>
<td>4 mo/6 mo</td>
</tr>
<tr>
<td>6</td>
<td>GPi</td>
<td>GPe, Gpi, IC, and OT</td>
<td>Visual field loss</td>
<td>Weeks/3 mo</td>
</tr>
<tr>
<td>7</td>
<td>GPi</td>
<td>GPe, Gpi, IC, and OT</td>
<td>Visual field loss</td>
<td>Weeks/months</td>
</tr>
<tr>
<td>8</td>
<td>GPi</td>
<td>GPe and IC</td>
<td>Hemiparesis and dysarthria</td>
<td>Weeks/months</td>
</tr>
</tbody>
</table>

*Th indicates thalamus; IC, internal capsule; Md, mesencephalon; Gpi, globus pallidus medialis; GPe, globus pallidus lateralis; and OT, optic tract.

Figure 4. A, Patient 6, approximately 9 weeks after a left-sided gamma knife (GK) pallidotomy. An axial T1-weighted 3-dimensional gradient echo magnetic resonance imaging (MRI) scan demonstrates an abnormal hypointense signal extending anteromedially into the left side of the optic tract (arrow), which is mildly enlarged. The right side of the optic tract is normal. B, Patient 7, approximately 10 months after a right-sided GK pallidotomy. A coronal postgadolinium T1-weighted MRI scan demonstrates abnormal enhancement at the pallidotomy site that measures approximately 12 mm. The abnormal enhancement is consistent with radiation necrosis. C, Patient 8, approximately 9 months after a GK pallidotomy. An axial T2-weighted MRI scan reveals a subtle area of hyperintensity (also on multiple cuts not shown) at the left side of the external segment of the globus pallidus and the internal capsule (arrow). There was no abnormality on an MRI scan obtained 6 months after the GK pallidotomy (not shown) despite an evolving clinical deficit.
sive nature of radiation-induced tissue injury. Modern GK procedures are limited by the size of the collimator. Gamma knife treatment is restricted to standard-size collimators of 4, 8, 14, or 18 mm. If a desired lesion size is between 5 and 7 mm, an 8-mm collimator must be used, resulting in a larger than expected lesion. Early lesions, made with the 8-mm collimator for GK pallidotomy and thalamotomy, were larger than expected; therefore, most groups switched to the 4-mm size. Even with a 4-mm collimator, there are many examples in the literature of larger than expected volumes of tissue affected after GK pallidotomy or thalamotomy. Most of the described patients stated that there was no clinical correlation or deficit associated with the MRI changes. Early lesions, made with the 8-mm collimator for GK pallidotomy and thalamotomy, were larger than expected; therefore, most groups switched to the 4-mm size. Even with a 4-mm collimator, there are many examples in the literature of larger than expected volumes of tissue affected after GK pallidotomy or thalamotomy. Most of the described patients stated that there was no clinical correlation or deficit associated with the MRI changes.6,11,12,15 The 8 patients described herein cast some doubt on these conclusions in that lesions involving the structures adjacent to the intended target correlated with the neurological complications exhibited by the patients. Lesion sizes on T1- and T2-weighted images after radiofrequency pallidotomy generally should not exceed 6 to 7 mm in diameter or 100 to 150 mm³ in volume.20 Thalamotomy lesions require at least 40 to 60 mm³ of volume for tremor relief. The GK technology cannot achieve a target volume this small.8 Smaller, more focused, collimators have yet to be developed. A series of 4 patients who underwent GK pallidotomy, described by Friedman et al,9 revealed highly variable lesion sizes. In other studies,13,14 T2-weighted lesions varied from 6 to 22 mm in diameter. In a series by Friehs et al,21 140 lesions produced with the GK for PD, pain, or other disorders varied in size from undetectable to 4000 mm³ (collimator sizes for all studies were 4 mm). It has been previously reported,16 as in patient 8, that MRI changes with the GK may be absent even in the presence of a clinical deficit. The unpredictable tissue response to ionizing radiation represents a second complicating factor that contributes to the variability of lesion size following GK procedures. Endothelial cells are believed to be the principle locus of vulnerability following radiation exposure and their damage leads to fibroinoid vascular necrosis with resultant ischemic coagulative necrosis of the neuronal and glial elements (Figure 3). The characteristic thick-walled hyalinized vessels most likely represent the primary nature of the endothelial-vascular damage. The problem with this type of physical injury is that, in some individuals, the necrotizing process is not self-limited and can progress and expand over months to years. In patient 3, the earlier left-sided thalamic lesion clearly exhibited areas of old and fresh necrosis approximately 1 year after the procedure was performed (Figure 3).

It is unclear whether refinement of the GK procedure with an improved smaller collimator and/or a decreased radiation dose may improve outcome. For these reasons, and the collimator issues previously discussed, the GK approach does not appear to be optimal for delivery of the discrete and precisely located lesions required for palliation of PD symptoms and minimization of adverse effects. In addition, there does not seem to be any way to predict which patients may develop delayed onset of progressive complications.

To our knowledge, safe radiation doses for GK thalamotomy and pallidotomy have not been defined. Doses used by most investigators6,11-15 have ranged from 12000 to 20000 rad (120-200 Gy). One report4 found a significant difference between high dose (16000 rad [160 Gy]) and low dose (12000 rad [120 Gy]) in terms of improvement in clinical symptoms (78% vs 56%), but only a few patients were studied. It has been suggested that lesion size is associated with radiation dose, and that doses of 16000 rad (160 Gy) or higher lead to larger lesion volumes.21 The variability of lesion sizes and the occurrence of radiation necrosis has resulted in many neurosurgeons discontinuing the use of multiple isocenters for lesioning, which may increase radiation exposure and lesion volume.13,14 All thalamotomy procedures reported herein, with the exception of 1, were done using 20000 rad (200 Gy) (1 was done with 15000 rad [150 Gy]), and the 3 pallidotomy procedures were done with 15000, 15000, and 10000 rad (150, 150, and 100 Gy), respectively. (all with a single isocenter). We suspect that the doses, especially in the thalamotomy group, were too high, but a systematic study to determine the significance of dose remains to be performed.

CONCLUSIONS

This report documents major complications associated with the use of GK radiosurgery for PD in 8 patients referred to our institution during an 8-month period. Although the complication rate for the GK procedure remains uncertain, we suspect it is higher than the limited data suggest, considering the paucity of published studies. The lack of long-term follow-up could also lead to underestimation of the morbidity and mortality associated with this technique. We cannot generalize the results in this article, given that the complications reported in these 8 patients were all from a single center, and the total number of radiosurgical procedures performed remains unknown. Not all centers may experience the same incidence of complications as reported herein.

Problems with the accuracy of targeting, the variability of lesion size, and delayed complications make the use of the GK for ablative procedures requiring a high degree of accuracy better suited to those patients who are unable to undergo conventional radiofrequency lesioning or deep brain stimulation. Radiation from the GK can lead to tissue necrosis, significant morbidity, and even death. A study of appropriate radiation doses and their contribution to adverse effects has yet to be performed. The incidence of significant complications of non-GK radiofrequency pallidotomy and thalamotomy is between 1% and 2%.4,24 Although we do not know the total number of procedures performed during this short period, the significant complication rate would likely be greater than 1% to 2%.

It has already been suggested that radiosurgery may not be appropriate for pallidotomy.9,13 Considering the limited benefits of thalamotomy for PD symptoms other than tremor, we believe that radiosurgery has limited applications in patients with PD. Caution should also be exercised when considering other targets, such as the subthalamic nucleus. We believe it is incumbent on physicians performing radiosurgery for the treatment of PD to inform patients fully of potential complications of the
REFERENCES


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