BACKGROUND: There is little information on long-term outcomes after salvage treatment by either surgery or stereotactic radiosurgery (SRS) for patients with recurrent/residual nonfunctioning pituitary adenomas (NFPAs).

OBJECTIVE: To reappraise the efficacy and safety of SRS for patients with NFPAs touching/compressing the optic apparatus (OA).

METHODS: We studied 27 patients (14 females, 13 males; mean age: 61 [range, 19-85] yr) who underwent SRS between 1998 and 2008 for NFPAs with such condition. The median tumor volume was 4.9 (range, 1.8-50.8) cc. To avoid excess irradiation to the OA, the lower part of the tumor was covered with a 50% or a 60% isodose gradient, ie 49% to 98% (mean, 84%; median, 88%) of the entire tumor received the selected doses. Median doses at the tumor periphery/OA were 7.6/11.0 (interquartile range [IQR], 5.8-9.1/10.1-11.8) Gy.

RESULTS: Seven patients (26%) were confirmed to be deceased due to unrelated diseases at a median post-SRS period of 149 (IQR, 83-158) mo. Follow-up magnetic resonance imaging (MRI) showed tumor growth in 2 patients (7%) at the 11th and 134th post-SRS month; the former underwent surgery and the other SRS. Excluding these 2 patients, the latest follow-up MRI examinations, performed 13 to 238 (median: 168, IQR: 120-180) mo after SRS, showed no size changes in 5 (19%) and shrinkage in 20 (74%) patients. Cumulative incidences of tumor growth control were 96.3% and 91.8% at the 120th and 180th post-SRS month. None of our patients developed subjective symptoms suggesting SRS-induced optic neuropathy or endocrinological impairment.

CONCLUSION: In patients with NFPAs touching/compressing the OA, SRS achieves good long-term results.

KEY WORDS: Radiation therapy, Radiosurgery, Gamma knife, Pituitary adenoma

Abbreviations: CI, confidence interval; CT, computed tomography; fSRT, fractionated stereotactic radiotherapy; IQR, interquartile range; IRB, institutional review board; MR, magnetic resonance; MRI, magnetic resonance imaging; NFPAs, nonfunctioning pituitary adenomas; OA, optic apparatus; SRS, stereotactic radiosurgery

Excellent, achieving high rates of tumor control, neurological improvement, and endocrinological remission, with minimal morbidity and mortality rates. However, recurrence rates are reportedly between 7% and 33% even after complete resection and can reach 75% after incomplete tumor removal.1-4 Salvage surgery is usually performed for patients with recurrent or residual NFPAs after surgery. However, there is surprisingly little information on long-term outcomes after salvage treatment, whether with surgery or stereotactic radiosurgery (SRS).

In the 21st century, either SRS5-12 or fractionated stereotactic radiotherapy (fSRT)13-28 has been used for patients with...
recurrent or residual NFPAs after surgical resection. Our aim is to reappraise long-term imaging follow-up results (median, 13 [maximum, 18; interquartile range [IQR], 10-14.5 yr) of postsurgical salvage SRS for NFPAs touching/compressing the optic chiasm using our database, which includes patients who underwent SRS. Our dose-planning technique is unique, i.e., intentional partial tumor coverage designed to avoid excess irradiation to the optic apparatus (OA), focusing on tumor control and optic nerve preservation.

METHODS

Patient Population

This institutional review board (IRB)-approved, retrospective cohort study used this prospectively accumulated database including 106 patients who underwent Gamma Knife (Elekta Instrument AB, Stockholm, Sweden) SRS between 1998 and 2008 for pituitary adenomas (Tokyo Women’s Medical University IRB No. 2071). One of the co-authors (M.Y.) performed every SRS procedure in all 106 patients. Among the 106 patients, there were 28 (26.4%) with recurrent/residual NFPAs, touching/compressing the optic chiasm, after surgery. One of these 28 patients was followed through the 16th post-SRS month with magnetic resonance imaging (MRI), which showed no change in tumor size. However, we have been unable to contact either this patient or his relatives. Therefore, we analyzed the remaining 27 patients for this study. Pre-SRS clinical characteristics are summarized in Table 1. There were 14 female and 13 male patients. Mean and median ages at the time of SRS were 61 and 66 yr with a range of 19 to 85 yr. Although 3 patients were nonsymptomatic, 22 had visual disturbances, and 1 each panhypopituitarism and dizziness at the time of the initial NFPA diagnosis. Pre-SRS surgery was performed once in 17, twice in 8, and 4 times in 2 patients. The median interval between the first surgery and SRS was 14 (IQR: 5-58) mo. One patient who underwent 2 surgical procedures had a partial visual field defect, and 1 each had bilateral blindness, left blindness with right hemianopsia, and bitemporal hemianopsia (Table 2). Also, before SRS, 10 patients had partial and 8 had complete deficiency of anterior pituitary lobe function. Anterior pituitary lobe function was normal in the remaining 9 patients. Hormonal replacement therapy had been administered to 9 patients prior to SRS; hydrocortisone for the one with partial deficiency and hydrocortisone + levotyroxin sodium for all 8 with complete deficiency.

Radiosurgical Technique

The first author (M.Y.) fully explained our treatment strategy to each patient prior to SRS, and written informed consent was obtained from all 27 as well as at least one adult relative. As all 27 patients were referrals to our institution made by their primary neurosurgeons, the decision to undergo SRS had already been made when they first came to our institute. However, the first author (M.Y.) still explained the obvious advantages of surgical removal as compared with SRS to each patient. Nevertheless, 25 of the 27 patients refused repeat surgery. In the other 2 who had each undergone 4 surgical procedures, the referring neurosurgeons informed us that a fifth surgical intervention had essentially been impossible because the tumor was very difficult to access at the time of the fourth intervention.

Prior to June of 2003, all radiosurgical procedures were performed using a Gamma Unit Model B (Elekta Instrument AB) and, thereafter, with a Leksell Model C unit (Elekta). After establishing local anesthesia, a Leksell Model G stereotactic coordinate frame (Elekta Instrument AB) was placed on the patient’s head. Stereotactic gadolinium-enhanced T1-weighted axial and coronal magnetic resonance (MR) images, with a 1 to 2 mm slice thickness depending on tumor size, were obtained for target coordinate determination and dose-planning. We also routinely obtained 3-dimensional constructive interference in steady state axial MR images and computed tomography (CT) axial images without contrast enhancement, allowing identification of bone structures and cranial nerves.

The Leksell GammaPlan system (Elekta Instrument AB) was employed for dose planning. The actual treatment plan, outlining our SRS policy for pituitary adenomas touching/compressing the OA, is presented in Figure 1. To avoid excess irradiation to the OA, i.e., keeping the dose below 12.0 Gy, the superior portion of the target tumor was covered with an isodose gradient of no more than 12.0 Gy in patients whose pre-SRS optic nerve functions were maintained (Figure 1A). As shown in Table 1, although median tumor volume was 4.9 (IQR: 3.0-9.8) cc, planned target volumes ranged from 1.5 to 35.1 (median 4.1, 4.9 Gy.

### Table 1. Patient, Prior Surgery, Clinical Characteristics, and Radiosurgical Parameters

<table>
<thead>
<tr>
<th>Categories</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients (%) Median IQR</td>
</tr>
<tr>
<td>Age [yr]</td>
<td>66 (50-70)</td>
</tr>
<tr>
<td>Sex, female</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Male</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Prior surgery, once</td>
<td>17 (63)</td>
</tr>
<tr>
<td>Twice</td>
<td>8 (30)</td>
</tr>
<tr>
<td>Four times</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Months between 1st surgery and SRS</td>
<td>14 (5-58)</td>
</tr>
<tr>
<td>Presentation, visual disturbance</td>
<td>22 (81)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>1 (4)</td>
</tr>
<tr>
<td>No/incidental</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Tumor volume (TV) [cc]</td>
<td>4.9 (3.0-9.8)</td>
</tr>
<tr>
<td>Planning target volume (PTV) [cc]</td>
<td>4.1 (2.7-7.0)</td>
</tr>
<tr>
<td>Coverage (PTV/TV) [%]</td>
<td>88 (81-95)</td>
</tr>
<tr>
<td>Minimum dose to PTV [Gy]</td>
<td>15.0 (12.0-18.0)</td>
</tr>
<tr>
<td>Mean dose of TV [Gy]</td>
<td>16.4 (14.7-18.5)</td>
</tr>
<tr>
<td>Minimum dose of TV [Gy]</td>
<td>7.6 (5.8-9.1)</td>
</tr>
<tr>
<td>Maximum dose of TV [Gy]</td>
<td>25.0 (20.0-30.0)</td>
</tr>
<tr>
<td>Maximum dose of OA [Gy]</td>
<td>11.0 (10.1-11.8)</td>
</tr>
<tr>
<td>OA volume (cu mm) receiving &gt;8 Gy</td>
<td>114 (69-197)</td>
</tr>
<tr>
<td>OA volume (cu mm) receiving &gt;10 Gy</td>
<td>10 (2-49)</td>
</tr>
<tr>
<td>OA volume (cu mm) receiving &gt;12 Gy</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>Imaging f/u months after SRS</td>
<td>156 (120-174)</td>
</tr>
<tr>
<td>Clinical f/u months after SRS</td>
<td>157 (139-174)</td>
</tr>
<tr>
<td>&gt;10 yr of the above</td>
<td>21 (78)</td>
</tr>
</tbody>
</table>

btwn, between; SRS, stereotactic radiosurgery; OA, optic apparatus; f/u, follow-up
TABLE 2. Changes in Tumor Sizes and Visual and Pituitary Functions After SRS (SRS)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-SRS</th>
<th>Post-SRS results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients (%)</td>
<td>No. of patients (%)</td>
</tr>
<tr>
<td>Tumor size</td>
<td>Reduced 20 (74)</td>
<td>Increased 2 (7)*</td>
</tr>
<tr>
<td></td>
<td>Unchanged 5 (19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased 2 (7)*</td>
<td></td>
</tr>
<tr>
<td>Pre-SRS visual field</td>
<td>Normal 10 (37)</td>
<td>Unchanged 10 (37)</td>
</tr>
<tr>
<td></td>
<td>Unchanged 1 (4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bitemporal hemianopsia 1 (4) Normalized 1 (4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial visual field defect 14 (52) Improvedb 4 (11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unchanged 8 (22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Worsened 2 (7)*</td>
<td></td>
</tr>
<tr>
<td>Pre-SRS pituitary function</td>
<td>Normal 9 (33)</td>
<td>Normal 9 (33)</td>
</tr>
<tr>
<td></td>
<td>partial anterior deficiency 10 (37) unchanged 10 (37)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complete anterior deficiency 8 (30) unchanged 8 (30)</td>
<td></td>
</tr>
</tbody>
</table>

*aThese 2 patients underwent salvage treatment (see text). 
bPartial visual field defect showed improvement but not normalization.

IQF: 3.0-9.8) cc. Thus, 49% to 98% (median 88%, IQF: 81%-95%) of the entire tumor received irradiation with a median planned target dose of 15.0 (IQR: 12.0-18.0) Gy, while the median dose at the tumor periphery was 7.6 (IQR: 5.8-9.1) Gy. The OA was delineated using T1-weighted and/or 3-dimensional constructive interference in steady state axial MR images. The OA doses, ie maximum dose and OA volumes receiving >8 Gy, >10 Gy, and >12 Gy, were determined using a dose-volume histogram (Table 1).

Rationale of Our Dose Planning Policy

The widely accepted and now well-established SRS dose planning policy for benign tumors is that the tumor should be totally covered with a prescribed dose. However, as we reported elsewhere, intentional partial coverage is considered to be reasonable when preservation of cranial nerve functions is an important consideration.29 The earliest Gamma Knife (Elekta) experiences at the Karolinska Hospital group in the 1970s, when neither CT nor MRI was available, involved the placement of only one irradiation target with a 4-/8-mm collimator at the center of the pituitary tumor. This strategy achieved effects, ie tumor shrinkage, in some patients. Therefore, we assumed that partial coverage of pituitary adenomas would have modest effects, at least.30

Post-SRS MR Imaging Follow-up

MR imaging follow-up is generally performed at 3-mo intervals for the initial 18 mo after SRS, after which 6-mo intervals through the 36th post-SRS month and, thereafter, 12-mo intervals are recommended. The follow-up MR imaging in 13 (48.1%) of the 27 patients was performed at our facility. Regarding tumor growth control, diameter ≥110% relative to the pretreatment diameter was regarded as “growth,” diameter <90% was taken as “shrinkage,” all other observations as “no change.” As to the endpoint, failures were regarded as events, any others as censored. At each MRI follow-up examination, patients were carefully interviewed to assess whether any subjective symptoms suggesting SRS-induced optic neuropathy or endocrinological impairment had developed. Also, ophthalmological and endocrinological examinations, including baseline serum levels of the 6 anterior pituitary hormones as well as visual acuity and field testing, are recommended at a several-year interval. These examinations were entrusted to each patient’s primary neurosurgeon.

Statistical Analysis

We employed the intention-to-treat principle for analyzing all data. Summary statistics were constructed, for the baseline variables, based on frequencies and proportions for categorical data, while the median, IQR, and ranges were used for continuous variables. A competing risk analysis was applied for time-to-event outcome analyses of our study endpoints because death is a competing risk for these endpoints.31,32 A statistician (Y.S.) using SAS software version 9.4 (SAS Institute, Cary, North Carolina) and the R statistical program, version 3.10, performed all statistical analyses. Prior to the statistical analyses, the database was cleaned by another co-author (Y.H.). Neither of these authors was involved in any aspect of SRS treatment or follow-up of the patients. A P-value of less than .05 was considered to be statistically significant.

RESULTS

Among the 27 patients, as of February of 2018, 7 (26%) were confirmed to be deceased with a median post-SRS period of 149 (IQR: 83-168) mo; median age at the time of death was 85 (IQR, 82-90) yr. Causes of death were confirmed to involve emaciation associated with aging in 5 patients, while 1 each had died of an infectious pulmonary disease and heart disease. Among the 20
surviving patients, median post-SRS clinical observation period to date is 168 (IQR: 158-184, maximum: 238) mo.

Tumor Growth Control

Follow-up MRI showed tumor growth in 2 patients (7%) at the 11th and 134th post-SRS months (Table 2). Excluding these 2 patients, the latest follow-up MRI examinations, which were performed 13 to 238 (median, 168; IQR, 120-180) mo after SRS, showed no size changes in 5 patients (19%) and shrinkage in 20 (74%, illustrative cases are shown in Figures 1 and 2), ie the crude incidence of tumor growth control was 92.6% and cumulative incidences of tumor growth-free survival estimated with a competing risk analysis were 96.3% (95% confidence interval [CI], 99.7%-83.8%), 96.3% (95% CI, 99.7%-83.8%), and 91.8% (95% CI, 98.7%-76.4%) at the 60th, 120th, and 180th post-SRS month. Among pre-SRS clinical and radiosurgical factors, univariable analysis demonstrated none to significantly correlate with tumor growth. In the 2 patients with MRI-demonstrated tumor growth, salvage treatment was performed because their visual fields had gradually narrowed; one underwent surgery at the 11th and the other re-SRS at the 134th post-SRS month (Figure 3). The former patient who underwent 2 surgical procedures and external beam radiotherapy before SRS has remained free of tumor growth for 151 mo, to date, since the last, ie the third, surgery. The post-re-SRS follow-up period was short (less than 20 mo) in the 1 patient who underwent re-SRS, with neither tumor enlargement nor additional neurological/endocrinological deficiencies having been identified, thus far.

Functional Outcomes

As summarized in Table 2, among the 17 patients with disturbed visual functions, bitemporal hemianopsia showed normalization in 1 and partial visual field defects were remarkably improved in 4, while symptoms were unchanged in 8. In the 2 remaining patients, as described above, gradual narrowing of their visual fields had occurred in parallel with tumor growth. The confrontation test was used as a visual field assessment in 24 (92.3%) of the 26 patients (excluding 1 patient with bilateral blindness) at the time of MRI follow-up. Among these
FIGURE 2. Four illustrative cases (cases 1, 2, 3, and 4). A to D, Before radiosurgery. E, 19.8 yr. F, 10 yr. G, 13 yr, and H, 15 yr after radiosurgery. One patient (case 2) underwent pacemaker placement 10.5 yr after radiosurgery and, therefore, CT rather than MRI was used for evaluation at the 14th postradiosurgical year, which showed no tumor growth. This patient died due to heart disease at age 82 yr, 14.5 yr after radiosurgery. Another patient (case 3) died due to gastric cancer at age 83 yr, 14.2 yr after radiosurgery. The other 2 patients are still being followed.
This case illustrates treatment failure. A, Dose planning at the time of the first radiosurgery. Yellow line: 18 Gy, green lines: 15 Gy, 12 Gy, 9 Gy, 6 Gy, and 3 Gy from the center. B, Dose planning for this patient at the time of the second radiosurgery 134 mo after the first radiosurgery. Note: Tumor regrowth can be seen in the portions of the tumor irradiated with lower doses (arrows).

DISCUSSION

Because the majority of patients with a recurrent/residual NFPA touching/compressing the OA underwent salvage surgery, our herein-reported small cohort may be a rather exceptional subset. Nevertheless, the present study suggested that, using our novel irradiation technique, ie intentional partial coverage to avoid excessive irradiation of the OA, longer progression-free survival on MRI (shrinkage and no change) could be expected. Furthermore, to date, none of our patients have experienced either subjective symptoms or optic and endocrinological dysfunctions indicative of SRS-related deterioration.

Postsalvage Surgery for Recurrent/Residual Tumors

There are no reports describing sufficiently long-term follow-up results after salvage surgery performed for recurrent/residual NFPA. Although Rudnik et al,30 Cavallo et al,31 Hwang et al,32 Tajudeen et al,33 and Alamadi et al34 reported salvage surgery on recurrent NFPA, they did not describe long-term follow-up results after reoperation. Benveniste et al35 and Matteo et al36 reported that, although their study subjects included patients with functional and nonfunctional tumors, postoperative regrowth occurred in 15% and 23% during the median follow-up periods of 32 (range, 1-109) mo and 30 (range, 3-63) mo after the second surgery, respectively. Recently, based on 2 studies of 29 and 24 subjects, including patients with functional and nonfunctional tumors, postoperative regrowth rates were 3.1% and 0%, respectively.37,38 However, postoperative observation periods were not sufficiently long, with a median of 17 (range; 12-108) mo in the former and a mean of 39 (range, 3-135) mo in the latter investigation. Most recently, Bakhsheshian et al39 reported surgical treatment outcomes of 268 NFPA patients with a mean follow-up time of 38 (range, 3-235) mo. Among their 268 patients, 57 underwent salvage surgery. At the 2-yr follow-up examination, progression-free survival as demonstrated by MRI was 95.4% after salvage surgery. Nevertheless, their median observation period after surgery was only 2 yr. In the present study, however, the median imaging follow-up period after salvage SRS was far longer, 156 mo, than those of the above-mentioned studies, 17 to 38 mo. Nevertheless, cumulative incidences of recurrence were acceptably low, ie 3.7% and 8.2% at the 120th and 180th post-SRS months.

Previous Publications on Gamma Knife SRS for NFPA

Previous studies on Gamma Knife SRS (Elekta AB) for patients with NFPA, which were relatively small with the entire tumor...
having been covered with optimal doses in most cases, are listed in Table 3,5-12 Crude rates of tumor control ranged from 83.4% to 97.6% and cumulative rates were 76% to 87% at the 10th post-SRS year. Our results, crude and post-10-yr cumulative rates of 93% and 96%, were considered to be favorable, even for patients in whom relatively large tumors had been treated. It is noteworthy that the median imaging follow-up period after SRS, 156 mo, in our study was far longer than those in other series, ie the next longest reported period was a median of 93 mo as reported by Gopalan et al.9 Furthermore, during the long-term clinical observation period (maximum, 238; median, 168; IQR, 152-180 mo), none of our patients developed subjective symptoms suggesting SRS-induced optic neuropathy or endocrinological impairment.

### Safe SRS Doses for the OA

Debate continues as to what is a safe SRS-dose for the OA. According to the historic report by Tishler et al,40 a safe dose, assuming visual preservation, is not more than 8 Gy with SRS. However, in their study, doses were measured using only CT, making the dose estimations less than optimal as compared to current data, routinely obtained with MRI. According to recently published studies on SRS for sellar or parasellar tumors, no optic neuropathy occurred in patients whose OA was irradiated with doses of 14 to 16 Gy or less.7,41-44 As described herein, none of our patients, even the 7 in whom irradiation doses exceeded 12.0 Gy (maximum 12.9 Gy), developed SRS-induced optic neuropathy.

Nowadays, the factors influencing radiation-induced optic neuropathy are considered to be not only the absolute dose but also the volume of the high-dose irradiation delivered to the OA.33 Furthermore, we speculate that the state of the OA itself might be another important factor. An OA with a well-preserved anatomic structure might be more tolerant of higher irradiation doses. In contrast, when the OA is markedly compressed or fragmented, it is theoretically more vulnerable to the effect of irradiation. Vernimmen and Slabbert44 reported that meaningful alpha–beta values could not be determined for the optic chiasm.

### Is fSRT Safer than SRS?

In recent years, fSRT has been recommended as a means of avoiding radiation-induced complications involving the OA.13-28 While fSRT might theoretically be safer than SRS, Nishioka et al45 analyzed the histopathological changes in pituitary adenoma specimens after either SRS or fSRT and found that SRS-treated specimens showed more intense histological changes, including hyaline deposition and central necrosis. Very recently, Barber et al28 reported crude incidences of tumor control to be 0% to 7.4% based on their own results and a comprehensive review of 8 published series. However, radiation-induced optic neuropathy and endocrinopathy occurred in 1.9% and 33.3% of treated cases, respectively. Furthermore, solid evidence indicating whether fSRT is truly safe, based on long-term studies, is as yet lacking. According to the review by Barber et al,28 the longest median follow-up period was only 48 (range, 12-132) mo, which is too short to allow meaningful conclusions to be drawn regarding the efficacy and safety of fSRT.28

Furthermore, all of the studies quoted by Barber et al28 included patients with functioning tumors and/or

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**TABLE 3.** Studies of Gamma Knife Radiosurgery for NFPA (Since 2000)

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>No. of patients</th>
<th>Median (mean) dose (Gy) at the tumor periphery [ranges]</th>
<th>Median (mean) tumor volume (cc) [ranges]</th>
<th>Median (mean) dose (Gy) at the OA [ranges]</th>
<th>Median (mean) imaging f/u months [ranges]</th>
<th>Optic neuropathy (%)</th>
<th>Crude control rates (%)</th>
<th>Actuarial control rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheehan et al (2002)6</td>
<td>42</td>
<td>(16.2) [10.0-34.0]</td>
<td>NA</td>
<td>(7.0) [2.5-9.0]</td>
<td>(31) [6-102]</td>
<td>2.4</td>
<td>97.6</td>
<td>NA</td>
</tr>
<tr>
<td>Iwai et al (2005)8</td>
<td>34</td>
<td>14.0 [8.0-20.0]</td>
<td>2.5 [0.7-36.2]</td>
<td>8.0 [2.0-11.0]</td>
<td>60 [30-108]</td>
<td>None</td>
<td>87.1</td>
<td>93/5 yr</td>
</tr>
<tr>
<td>Gopalan et al (2011)9</td>
<td>48</td>
<td>(18.4) [8.0-25.0]</td>
<td>(5.1) [0.9-27.0]</td>
<td>(3.6) [0.9-10.0]</td>
<td>93 [50-215]</td>
<td>6.3</td>
<td>83.4</td>
<td>80/10 yr</td>
</tr>
<tr>
<td>Park et al (2011)10</td>
<td>125</td>
<td>13.0 [10.0-25.5]</td>
<td>3.5 [0.4-28.1]</td>
<td>7.7 [3.0-11.0]</td>
<td>62 [NA-228]</td>
<td>0.8</td>
<td>89.6</td>
<td>76/10 yr</td>
</tr>
<tr>
<td>El-Shehaby et al (2012)11</td>
<td>21</td>
<td>12.0 [12.0-12.0]</td>
<td>(4.8) [0.5-11.8]</td>
<td>(7.9) [3.2-12.5]</td>
<td>(44) [24-90]</td>
<td>None</td>
<td>95.2</td>
<td>NA</td>
</tr>
<tr>
<td>Starke et al (2012)12</td>
<td>140</td>
<td>(18.0) [5.0-25.0]</td>
<td>(5.6) [0.6-35.0]</td>
<td>(4.0) [0-13.0]</td>
<td>50 [6-204]</td>
<td>None/12.8a</td>
<td>90</td>
<td>87/10 yr</td>
</tr>
<tr>
<td>Present study (2018)</td>
<td>27</td>
<td>7.6 [3.2-10.9]</td>
<td>4.9 [1.8-50.8]</td>
<td>11.0 [8.7-12.9]</td>
<td>156 [11-216]</td>
<td>None/7.4a</td>
<td>92.6</td>
<td>91.8/15 yr</td>
</tr>
</tbody>
</table>

f/u: follow-up, NA: not available
aOptic neuropathy due to tumor growth (see text).
bDetermined by a competing risk analysis.

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The optimal dose for functioning tumors would be higher than that for NFPAs. Furthermore, the treatment goals differ markedly between functioning and nonfunctioning tumors. Therefore, this heterogeneity in patient populations may weaken the conclusions drawn in these earlier studies.

Optimal doses for tumor growth control of NFPAs are considered to be 12.0 to 14.0 Gy at the tumor periphery with SRS. As described above, the OA dose of 12.0 to 14.0 Gy is not dangerously high, which means that fSRT is unnecessary in most patients. Furthermore, as reported herein, if the dose is decreased at the tumor margin facing the OA, long-term tumor growth control rates do not differ from previously reported results in which the tumors were totally covered with the selected doses. Even when the entire tumor is not covered with an optimal dose, as described herein, irradiating the lower part of the tumor may decrease the blood supply to this part of the tumor enough to produce growth control or even shrinkage of the tumor.

Factors Impacting Tumor Growth Control

We identified neither pre-SRS factors nor radiosurgical parameters as correlating with tumor growth control, probably due to our small sample size having insufficient statistical power. Larger tumor volume and lower peripheral dose are reportedly unfavorable factors for tumor control. Recently, Gopalan et al. reported that, based on 48 patients with NFPAs treated with Gamma Knife SRS (Elekta), the rate of tumor control was significantly lower in those with tumor volumes greater than 5 cc than in those with tumor volumes of 5 cc or less. They also noted a decrease in the tumor control rate for NFPA treated with low irradiation doses, ie less than 12 Gy. Park et al. reported that, based on 125 NFPA patients undergoing Gamma Knife SRS, tumor volume less than 4.5 cc and one recurrence (vs 2 or more recurrence) were factors significantly favoring better tumor control.

Weaknesses of our Study

The most significant weakness of our study is likely the use of a retrospective cohort, given the obvious heterogeneity of clinical factors. There were probably some biases in patient selection and observation. The second major weakness stems from all patients having been performed and their methods varied because the procedures were conducted by the patients’ primary neurosurgeons in other facilities. No patients underwent hormone loading tests after treatment. The fourth weakness is that tumor volumes were not determined on follow-up MRI, with only linear measurements having been performed.

CONCLUSION

We must always keep in mind that surgical removal is far better than SRS or fSRT for managing patients with postoperatively recurrent/residual NFPAs touching or even compressing the optic chiasm. However, some patients with these conditions have contraindications for surgical removal and/or refuse surgery. In such cases, Gamma Knife SRS (Elekta) can achieve good long-term results. The opinion that fSRT is the only appropriate option is thus, in our experience, unwarranted.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

This series reports on 27 patients with residual/recurrent nonfunctioning pituitary macroadenomas (NFA) touching the optic chiasm who were treated with single-fraction stereotactic radiosurgery (SRS). The authors report excellent local control of >90% at 10–15 years despite systematically undercovering portions of the tumor to limit dose to the optic apparatus (OA). Dose maximum to the OA were >12 Gy in 7 of 27 patients and at most 12.9 Gy with no noticeable radiation-induced optic neuritis (RION). This has 2 implications: First, undercovering small portions of the tumor may not affect local control. It is unclear if substantial portions of the target were significantly underdosed. With a mean marginal prescription dose of 15 Gy and a series maximum of 12.9 Gy on the OA it is conceivable that most of the adenomas treated will have seen 12 Gy, a dose that can achieve 85% control of NFAs at 10 years.1 A small-volume cold spot may indeed be of little significance for overall tumor control. Second, this series provides long-term data on the risk of RION, the fear of which typically limits dose to the optic chiasm to 8–10 Gy. Although it is hard to believe that neuropathy of the optic tracts would have been missed, rigorous ophthalmoalogical assessments were not done, and the sample is small. Doses <12 Gy may nevertheless confer an acceptable risk of toxicity if the volume remains small. Finally, the authors discuss and compare single fraction SRS to conventionally fractionated radiotherapy in 1.8-2 Gy per fraction. We add a third alternative which is emerging: fractionated SRS on the Gamma Knife ICON (Elekta). The
that are even in contact with the AVP. In the present study, 27 patients with residual/recurrent non-functioning pituitary adenomas were selected for SRS because of comorbidities that were thought to pose a significant risk to the majority of the tumor was covered with an “optimal” dose while delivering high dose per fraction to slow growing tumors for which the alpha/beta ratio is likely low.

Horia Vulp
Tony J.C. Wang
New York, New York


One of the primary considerations in deciding whether or not a patient with a parasellar tumor is safe to treat with single-fraction stereotactic radiosurgery (SRS) is the relationship of the tumor to the anterior visual pathways (AVP). Historically, tumors approaching the optic nerves or chiasm (<2 mm) were frequently referred for fractionated radiation treatments because it was believed that the risk of radiation-induced optic neuropathy (RION) after single-fraction SRS would be too great. However, numerous reports have shown that the radiation tolerance of the AVP is clearly greater than 8 Gy and the anterior visual pathways (AVP) were 96% and 92%, respectively. Importantly, no patient developed a subjective or objective (Goldman testing, n = 16) decline in their vision after single-fraction SRS. Although more stringent ophthalmologic follow-up would strengthen the authors’ conclusions, this paper adds further support that adherence to the AVP radiation tolerance guidelines developed 25 years ago (8 Gy) limits the applicability and effectiveness of single-fraction SRS for patients with tumors in the para-sellar region.

Christopher S. Graffeo
Bruce E. Pollock
Rochester, Minnesota


In this small series of SRS for recurrent or residual non-secretory pituitary tumors the main value is the extended follow-up and the demonstration of tumor control even in patients with optic apparatus compression. Despite initial surgery at the time of SRS, all patients had imaging evidence of contact with optic system. Tumor regression was seen in many. The authors selected the radiosurgical dose so that the majority of the tumor received a dose of >15 Gy, while the margin dose and therefore the optic chiasm dose was kept low (8-10 GY). The patients were selected for SRS because of comorbidities that were thought to pose risks for a second microsurgical or endoscopic approach. It is difficult to determine both the true incidence of new optic neuropathy as well as new endocrinopathy because that data was not available in most patients prior to their SRS procedure. At least 1 patient was already blind. For those with existing endocrine or visual deficits, no additional injuries were reported after SRS. Tumor control rates after SRS for pituitary tumors are in the range of 90% at 10 years. For those patients with no pre-SRS endocrine deficits prior reports suggest that approximately 30% will develop at least 1 new anterior endocrine axis deficiency over long-term follow-up. Because of its low risk, SRS is an important option in elderly or ill patients thought high risk for repeat surgery. Optimizing the treatment plan to keep the tumor dose high while perhaps by using lower isodoses at the dorsal tumor margin, or even specifically reducing dose in a component of the tumor near critical structures may be sufficient to maintain tumor control while reducing endocrine and optic nerve risks.

L. Dade Lunsford
Pittsburgh, Pennsylvania